

BRIEFING

⟨1059⟩ **Excipient Performance.** This proposal is based on the version of the chapter official as of May 1, 2018. It is proposed to revise the chapter as follows based on the Excipient Performance ⟨1059⟩ Expert Panel's recommendations:

1. Change the chapter layout. Because one functional category can be used in multiple dosage forms, remove the dosage form titles under which the functional categories were grouped. Under each functional category create a section titled Dosage Forms that contains a list of dosage forms in which the functional category is generally used.
2. Align types of dosage forms listed in the Dosage Forms sections with those described in [Pharmaceutical Dosage Forms ⟨1151⟩](#).
3. Divide the *pH Modifier (Acidifying/Alkalizing/Buffering Agent)* functional category into two functional categories, [Acidifying and Alkalizing Agent](#) and [Buffering Agent](#), respectively.
4. Revise the category title *Adhesive* to [Adhesive \(Pressure Sensitive\)](#).
5. Combine the *Capsule Shell* and *DPI Capsule Shell* categories under [Capsule Shell](#).
6. Add 29 new *NF* functional categories: [Air Displacement](#), [Alcohol Denaturant](#), [Antifoaming or Defoaming Agent](#), [Antitack Agent](#), [Biodegradable Polymer](#), [Cationic Dendrimer](#), [Crystallization Inhibitor](#), [Desiccant](#), [Drag-Reducing Agent](#), [Emulsifying Agent](#), [Filtering Aid](#), [Gelling Agent](#), [Humectant](#), [Liposome-Forming Agent](#), [Muco-adhesive](#), [Opacifier](#), [Permeation Enhancer](#), [Physical Form Stabilizer](#), [Physical-Chemical Identifier](#), [Polymeric Membrane](#), [Printing Ink Component](#), [Solvent](#), [Sorbent](#), [Stabilizer](#), [Sugar-Coating Agent](#), [Surfactant](#), [Vehicle](#), [Viscosity-Lowering Agent](#), and [Water-Repelling Agent](#).
7. Revise the existing functional categories to update any outdated or missing information.

Additionally, it is proposed to revise the [USP and NF Excipients, Listed by Functional Category](#) reference table, in conjunction with this chapter to reflect the proposed changes to the chapter and to provide a list of excipients grouped on the basis of their functional categories. In addition to updating the current list of excipients under existing functional categories and adding excipients under new functional categories, it is proposed to rearrange the reference table to remove references to the dosage forms in which these excipients are commonly used. The reference table is an extension of this chapter and is a useful tool for the reader to navigate through the list of functional categories and dosage forms in search of a suitable excipient. The revision of the reference table has been conducted in parallel with the revision of the chapter and will appear in *PF* for public comment. See the *Briefing* for [USP and NF Excipients, Listed by Functional Category](#) and for [Description and Relative Solubility](#) published elsewhere in this *PF*. Interested parties are encouraged to comment. The comment period for this revision ends March 31, 2020.

(EXC1: G. Holloway.)

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⟨1059⟩ EXCIPIENT PERFORMANCE

Change to read:

INTRODUCTION

~~Excipients are used in virtually all drug products and are essential for product manufacturing and performance. Thus, the successful manufacture of a robust product requires the use of well-defined excipients and manufacturing processes that consistently yield a quality product. Excipients used in drug products typically are manufactured and supplied in compliance with compendial standards. However, the~~

effects of excipient properties on the critical quality attributes (CQAs) of a drug product are unique for each formulation and process and may depend on properties of excipients that are not evaluated in *USP* or *NF* monographs. The effects of variations in excipient material attributes depend on the role of an excipient in a formulation and the CQAs of the drug product. This general chapter provides a framework for applying Quality by Design (QBD) principles to excipient quality and performance.

An excipient may be used in different ways or for different purposes in a formulation and may therefore require different material attributes to achieve the desired performance. Excipient functional categories are broad, qualitative, and descriptive terms for the purpose an excipient serves in a formulation. A list of excipients grouped by functional category is included in *NF* under *Front Matter, Excipients*, which summarizes some of the more common purposes that excipients serve in drug products. Also important are the material attributes of the ingredients that must be identified and controlled to ensure the excipient performs its intended function in a drug product. A critical material attribute (CMA) is a physical, chemical, biological, or microbiological property of a material that must be within an appropriate limit, range, or distribution to ensure that drug product CQAs are maintained throughout the product life cycle. Most, but not all, CMAs become tests in a compendial monograph. In some applications, excipient suppliers and users will need to identify and control material attributes in addition to monograph specifications. Identification of CMAs requires a thorough understanding of drug product CQAs; the manufacturing process(es); and the physical, chemical, biological, or microbiological properties of each ingredient. Manufacturers should anticipate lot-to-lot and supplier-to-supplier variability in excipient properties and should have in place appropriate control measures to ensure that CMAs are maintained within the required limits. Prior knowledge, experimental designs, and risk assessment tools can be used to prioritize and identify CMAs of excipients as well as critical process parameters. A CMA of an excipient may not be related to the major component of the excipient because, for example, the presence of minor components (e.g., peroxides, elemental impurities, or microbiological content) may affect product stability or quality. Good product development practices, which at times are termed QBD principles, require understanding excipient CMAs that contribute to consistent performance and are the foundation of a control strategy that accommodates excipient variability, consistently achieving final product CQAs.

This informational general chapter provides an overview of the key functional categories of excipients and tests or procedures that can be used to monitor and control CMAs.¹

In this chapter, the functional categories have been organized by their most typical use in common pharmaceutical dosage forms. However, functional categories can apply to multiple dosage forms. The association of a functional category with a particular dosage form does not limit the use of an excipient to a single type of dosage form or delivery system. Each functional category includes a general description; the mechanisms by which excipients achieve their function; physical properties common to these excipients; chemical properties; and a list of *USP* general chapters that can be useful in the development of specific tests, procedures, and acceptance criteria to ensure that CMAs are adequately monitored and controlled. Because of the complex nature and interplay of formulation ingredients, processing, and dosage form performance requirements, the information provided in this chapter should not be viewed as either restrictive or completely comprehensive.

Change to read:

TABLETS AND CAPSULES

Functional Category: Diluent

DESCRIPTION

Diluents are components that are incorporated into tablet or capsule dosage forms to increase dosage form volume or weight. Sometimes referred to as fillers, diluents often compose a large portion of the dosage form, and the quantity and type of diluent selected often depend on its physical and chemical

properties. Thus, successful and robust manufacturing and dosage form performance depend on the measurement and control of the CMAs.

FUNCTIONAL MECHANISM

Among the most important functional roles diluents play is their ability to impart desirable manufacturing properties (e.g., powder flow, tablet compaction strength, wet or dry granule formation, or homogeneity) and performance (e.g., content uniformity, disintegration, dissolution, tablet integrity, friability, or physical and chemical stability). Some diluents (e.g., microcrystalline cellulose) occasionally are referred to as "dry binders" because of the high degree of tablet strength they impart to the final compressed tablet.

PHYSICAL PROPERTIES

The primary physical properties relevant to tablet/capsule diluents are those that can have a direct effect on diluent and formulation performance. These include: 1) particle size and size distribution, 2) particle shape, 3) bulk/tapped/true density, 4) specific surface area, 5) crystallinity, 6) moisture content, 7) powder flow, 8) solubility, 9) crystal form, and 10) compaction properties for tablet dosage forms.

CHEMICAL PROPERTIES

Tablet diluents comprise a large and diverse group of materials that include inorganics (e.g., dibasic calcium phosphate or calcium carbonate), single-component organic materials (e.g., lactose monohydrate or mannitol), and multicomponent (e.g., silicified microcrystalline cellulose or sugar spheres), or complex organics (e.g., microcrystalline cellulose or starch). They may be soluble or insoluble in water, and they may be neutral, acidic, or alkaline in nature. These chemical properties can have a positive or negative effect on the drug substance physical or chemical stability and on performance. Appropriate selection of excipients with desirable physical and chemical properties can enhance the physical and chemical stability as well as the performance of the drug substance and dosage form. The detailed composition of an excipient may be important because excipient function could be influenced by the presence of minor concomitant components that are essential for proper performance. Pharmaceutical scientists may find it necessary to control the presence of undesirable components (e.g., elemental impurities or peroxides) to ensure adequate dosage form stability and performance.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in diluent functions: [Light Diffraction Measurement of Particle Size \(429\)](#), [Bulk Density and Tapped Density of Powders \(616\)](#), [Crystallinity \(695\)](#), [Characterization of Crystalline Solids by Microcalorimetry and Solution Calorimetry \(696\)](#), [Density of Solids \(699\)](#), [Loss on Drying \(731\)](#), [Optical Microscopy \(776\)](#), [Particle Size Distribution Estimation by Analytical Sieving \(786\)](#), [Powder Fineness \(811\)](#), [Specific Surface Area \(846\)](#), [Water Determination \(921\)](#), and [Powder Flow \(1174\)](#).

Functional Category: Wet Binder

DESCRIPTION

Tablet and capsule binders are incorporated into formulations to facilitate the agglomeration of powder into granules during mixing with a granulating fluid such as water, hydroalcoholic mixtures, or other solvents. The binder may be either dissolved or dispersed in the granulation liquid or blended in a dry state, and other components and the granulation liquid may be added separately during agitation. Following evaporation of the granulation liquid, binders typically produce dry granules that achieve the desired properties such as granule size, size distribution, shape, content, mass, and active content. Wet granulation facilitates the further processing of the granules by improving one or more of the granule properties such as flow, handling, strength, resistance to segregation, dustiness, appearance, solubility, compaction, or drug release.

FUNCTIONAL MECHANISM

Binders are soluble or partially soluble in the granulating solvent or, as in the case of native starches, can be made soluble. Concentrated binder solutions also have adhesive properties. Upon addition of liquid, binders typically facilitate the production of moist granules (agglomerates) by altering interparticle adhesion. They also may modify interfacial properties, viscosity, or other properties. During drying they may produce solid bridges that yield improved residual dry granule strength.

PHYSICAL PROPERTIES

Dispersion or dissolution of a binder in the granulation liquid depends on its physical properties: depending on the application, then surface tension, particle size, size distribution, solubility, and viscosity are among the important properties. Homogeneous incorporation of a binder into a dry blend also depends on its physical properties such as particle size, shape, and size distribution. Viscosity often is an important property to consider for binders: for polymers, viscosity is influenced by the nature of the polymer structure, molecular weight, and molecular weight distribution. Polymeric binders may form gels.

CHEMICAL PROPERTIES

Tablet and capsule binders can be categorized as: 1) natural polymers, 2) synthetic polymers, or 3) sugars. The chemical nature of polymers—including polymeric structure, monomer properties and sequence, functional groups, degree of substitution, and cross-linking—influences the complex interactions that can occur during granulation. Natural polymers in particular may exhibit greater variation in their properties because of variations in their sources and therefore their composition.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in binder functions: [Bulk Density and Tapped Density of Powders \(616\)](#), [Chromatography \(621\)](#), [Crystallinity \(695\)](#), [Density of Solids \(699\)](#), [Loss on Drying \(731\)](#), [Particle Size Distribution Estimation by Analytical Sieving \(786\)](#), [Specific Surface Area \(846\)](#), [Viscosity—Capillary Methods \(911\)](#), and [Powder Flow \(1174\)](#).

Functional Category: Disintegrant

DESCRIPTION

Disintegrants are functional components that are added to formulations to promote rapid disintegration into smaller units and to allow a drug substance to dissolve more rapidly. Disintegrants are natural, synthetic, or chemically modified natural polymeric substances. When disintegrants come in contact with water or stomach or intestinal fluid, they function by absorbing liquid and start to swell, dissolve, or form gels. This causes the tablet structure to rupture and disintegrate, producing increased surfaces for enhanced dissolution of the drug substance.

FUNCTIONAL MECHANISM(S)

The ability to interact strongly with water is essential to the disintegrant function. Three major mechanisms describe the function of the various disintegrants: volume increase by swelling, deformation, and capillary action (wicking). In tablet formulations, the function of disintegrants is best described as a combination of two or more of these effects. The onset and degree of the locally achieved actions depend on various parameters of a disintegrant, such as its chemical nature and its particle size distribution and particle shape, as well as some important tablet parameters such as hardness and porosity.

PHYSICAL PROPERTIES

The primary physical properties relevant to a disintegrant are those that describe the product's particle structure as a dry powder or its structure when in contact with water. These properties may include: 1) particle size distribution; 2) water absorption rate; 3) swelling ratio or swelling index; and 4) the characterization of the resulting product, whether it is still a particulate or a gel is formed.

CHEMICAL PROPERTIES

Polymers used as disintegrants are either nonionic or anionic with counterions such as sodium, calcium, or potassium. Nonionic polymers are natural or physically modified polysaccharides such as starches,

celluloses, pullulan, or cross-linked polyvinylpyrrolidone. The anionic polymers mainly are chemically modified starches, cellulose products, or low-cross-linked polyacrylates. These chemical properties should be considered in the case of ionic polymers. Disintegration performance is affected by pH changes in the gastrointestinal tract or by complex formation with ionic drug substances.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in disintegrant functions: [Light Diffraction Measurement of Particle Size \(429\)](#), [Optical Microscopy \(776\)](#), [Particle Size Distribution Estimation by Analytical Sieving \(786\)](#), and [Powder Flow \(1174\)](#).

Functional Category: Lubricant

DESCRIPTION

Lubricants typically are used to reduce the frictional forces between particles and between particles and metal-contact surfaces of manufacturing equipment such as tablet punches and dies used in the manufacture of solid dosage forms. Liquid lubricants may be absorbed into the granule matrix before compaction. Liquid lubricants also can be used to reduce metal-metal friction on manufacturing equipment.

FUNCTIONAL MECHANISM

Boundary lubricants function by adhering to solid surfaces (granules and machine parts) and by reducing the particle-particle friction or the particle-metal friction. The orientation of the adherent lubricant particles is influenced by the properties of the substrate surface. For optimal performance, the boundary lubricant particles should be composed of small, plate-like crystals or stacks of plate-like crystals. Fluid film lubricants melt under pressure and thereby create a thin fluid film around particles and on the surface of punches and dies in tablet presses, which helps to reduce friction. Fluid film lubricants resolidify after the pressure is removed. Liquid lubricants are released from the granules under pressure and create a fluid film. They do not resolidify when the pressure is removed but are reabsorbed or redistributed through the tablet matrix over the course of time.

PHYSICAL PROPERTIES

The physical properties that are important for the function of boundary lubricants include particle size, surface area, hydration state, and polymorphic form. Purity (e.g., stearate:palmitate ratio) and moisture content also may be important. The physical properties of possible importance for fluid film lubricants are particle size and solid state/thermal behavior. Purity also may be important.

CHEMICAL PROPERTIES

Lubricants can be classified as boundary lubricants, fluid film lubricants, or liquid lubricants. Boundary lubricants are salts of long-chain fatty acids (e.g., magnesium stearate) or fatty acid esters (e.g., sodium stearyl fumarate) with a polar head and fatty acid tail. Fluid film lubricants are solid fats (e.g., hydrogenated vegetable oil, type 1), glycerides (glyceryl behenate and distearate), or fatty acids (e.g., stearic acid) that melt when subjected to pressure. Liquid lubricants are liquid materials that are released from granules under pressure.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in lubricant functions: [Light Diffraction Measurement of Particle Size \(429\)](#), [Crystallinity \(695\)](#), [Characterization of Crystalline Solids by Microcalorimetry and Solution Calorimetry \(696\)](#), [Loss on Drying \(731\)](#), [Optical Microscopy \(776\)](#), [Particle Size Distribution Estimation by Analytical Sieving \(786\)](#), [Specific Surface Area \(846\)](#), [Thermal Analysis \(891\)](#), [Water Determination \(921\)](#), and [Characterization of Crystalline and Partially Crystalline Solids by X-Ray Powder Diffraction \(XRPD\) \(941\)](#).

ADDITIONAL INFORMATION

Certain lubricants, particularly those used in effervescent dosage forms, do not fall into the chemical categories defined above. These materials are used in special situations, and they are not suitable for universal application. Talc is an inorganic material that may have some lubricant properties. It is generally used in combination with fluid film lubricants to reduce sticking to punches and dies.

Functional Category: Glidant and/or Anticaking Agent

DESCRIPTION

Glidants and anticaking agents are used to promote powder flow and to reduce the caking or clumping that can occur when powders are stored in bulk. In addition, glidants and anticaking agents reduce the incidence of bridging during the emptying of powder hoppers and during powder processing.

FUNCTIONAL MECHANISM

Glidants are thought to work by a combination of adsorption onto the surface of larger particles and reduction of particle-particle adhesive and cohesive forces, thus allowing particles to move more easily relative to one another. In addition, glidants may be dispersed among larger particles and thus may reduce friction between these particles. Anticaking agents may absorb free moisture that otherwise would allow the development of particle-particle bridges that are implicated in caking phenomena.

PHYSICAL PROPERTIES

Primary physical properties of potential importance for glidants and anticaking agents are particle size, particle size distribution, and surface area. They may be slightly hygroscopic.

CHEMICAL PROPERTIES

Glidants and anticaking agents typically are finely divided inorganic materials. Typically they are insoluble in water. Some of these materials are complex.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in glidant or anticaking agent functions: [Light Diffraction Measurement of Particle Size \(429\)](#), [Loss on Drying \(731\)](#), [Particle Size Distribution Estimation by Analytical Sieving \(786\)](#), [Specific Surface Area \(846\)](#), and [Water Determination \(921\)](#).

Functional Category: Coloring Agent

DESCRIPTION

Coloring agents are incorporated into dosage forms to produce a distinctive appearance that may serve to differentiate a product from others that have a similar physical appearance or, in some instances, to protect photolabile components of the dosage form. These substances are subdivided into dyes (water-soluble substances), lakes (insoluble forms of a dye that result from its irreversible adsorption onto a hydrous metal oxide), inorganic pigments (substances such as titanium dioxide or iron oxides), and natural colorants (colored compounds not considered dyes per se, such as riboflavin). Coloring agents are subject to federal regulations, and consequently the current regulatory status of a given substance must be determined before its use.

The Federal Food, Drug, and Cosmetic Act defines three categories of coloring agents:

- FD&C colors: those certifiable for use in coloring foods, drugs, and cosmetics
- D&C colors: dyes and pigments considered safe in drugs and cosmetics when in contact with mucous membranes or when ingested
- Ext. D&C colors: colorants that, because of their oral toxicity, are not certifiable for use in ingestible products but are considered safe for use in externally applied products.

FUNCTIONAL MECHANISM

Water-soluble dyes usually are dissolved in a granulating fluid for use, although they also may be adsorbed onto carriers such as starch, lactose, or sugar from aqueous or alcoholic solutions. These latter

products often are dried and used as formulation ingredients. Because of their insoluble character, lakes almost always are blended with other dry excipients during formulation. For this reason, direct-compression tablets often are colored with lakes.

PHYSICAL PROPERTIES

Particle size and size distribution of dyes and lakes can influence product processing times (blending and dissolution), color intensity, and uniformity of appearance. A coloring agent should be physically nonreactive with other excipients and the drug substances.

CHEMICAL PROPERTIES

The most important properties of a coloring agent are its depth of color and resistance to fading over time. Substances can be graded on their efficiency in reflecting desired colors of visible light, as well as on their molar absorptivities at characteristic wavelengths. A coloring agent should be chemically nonreactive with other excipients and the drug substances. The quality of a coloring agent ordinarily is measured by a determination of its strength, performance, or assay. The impurity profile is established by measurements of insoluble matter, inorganic salt content, metal content, and organic impurities.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected coloring agent functions: [Light Diffraction Measurement of Particle Size \(429\)](#) and [Color—Instrumental Measurement \(1061\)](#). Instrumental methods should be used to determine the absolute color of a coloring agent.

ADDITIONAL INFORMATION

Coloring agents are subject to federal regulations, and consequently the current regulatory status of a given substance must be determined before it is used.

Functional Category: Capsule Shell

DESCRIPTION

The word "capsule" is derived from the Latin *capsula*, which means a small container. Among other benefits, capsules enable pharmaceutical powders and liquids to be formulated for dosing accuracy, as well as ease of transportation. The capsule material should be compatible with all other ingredients in the drug product. Hard capsules typically consist of two parts: both are cylindrical, and one part is slightly longer than the other and is called the body. The cap fits closely on the body to enclose the capsule. In contrast, the soft capsule is a one-piece unit that may be seamed along an axis or may be seamless. The capsule material may be derived from hydrolysis of collagen that originates from porcine, bovine, or fish sources, or it can be of nonanimal origin, e.g., cellulosic or polysaccharide chemical entities. The capsule shell also contains other additives such as plasticizers, colorants, and preservatives. In some cases, capsule shells are sterilized to prevent microbial growth. The capsule shell is an integral part of the formulation, and therefore robust manufacturing and formulation performance depends on the measurement and control of CMAs. Capsules can be used to administer drugs by oral, rectal, vaginal, or inhalation routes.

FUNCTIONAL MECHANISM

Capsules can enclose solid, semisolid, or liquid formulations. Capsules have a variety of benefits: masking unpleasant taste, facilitating blinding in clinical studies, promoting ease of swallowing, and presenting a unique appearance. Conventional capsule shells should dissolve rapidly at 37° in biological fluids such as gastric and intestinal media. However, the solubility properties of the shell can be modified (e.g., with enteric and controlled-release polymers) to control the release of the capsule contents.

PHYSICAL PROPERTIES

The primary physical properties relevant to the capsule shell are those that can have a direct effect on product performance: 1) moisture content, 2) gas permeability, 3) stability on storage, 4) disintegration, 5) compactness, and 6) brittleness. The moisture content varies with the type of capsule. Hard gelatin capsules typically contain 13%–16% water compared to hypromellose (hydroxypropyl methylcellulose or

HPMC) capsules that typically contain 4%–7% water content. Moisture content has an important effect on capsule brittleness. Soft gelatin capsules contain 5%–15% water. Equilibrium water content also may be crucial to dosage form stability because water migration can take place between the shell and capsule contents. Gas permeability may be important and generally is greater for HPMC capsules than for gelatin capsules because of the presence of open structures in the former. Unlike HPMC capsules, which do not cross-link, gelatin capsules have the potential to cross-link due to environmental and chemical exposure. Gelatin capsules may undergo cross-linking upon storage at elevated temperature and humidity [e.g., 40°(75% RH)]. Gelatin shell material is also well known to cross-link due to exposure to aldehydes, ketones, and certain dyes in shell formulations. Thus, presence of these materials in excipients should be considered for gelatin encapsulated products. Cross-linking slows in vitro dissolution and often necessitates introduction of enzymes in the test medium. Gelatin capsules should disintegrate within 15 min when exposed to 0.5% hydrochloric acid at 36°–38° but not below 30°. HPMC capsules can disintegrate below 30°.

CHEMICAL PROPERTIES

Gelatin is a commercial protein derived from the native protein, collagen. The product is obtained by partial hydrolysis of collagen derived from skin, white connective tissue, and bones of animals. Type A gelatin is derived by acid treatment, and Type B gelatin is derived from base treatment. The common sources of commercial gelatin are pigskin, cattle hide, cattle bone, cod skin, and tilapia skin. The gelatin capsule shell also typically contains coloring agents, plasticizers such as polyhydric alcohols, natural gums and sugars, and preservatives such as sodium metabisulfite and esters of *p*-hydroxybenzoic acid. The more commonly used nongelatin capsules today are made from HPMC. Different capsule types contain different moisture levels and may thus influence drug product stability. The detailed composition of an excipient may be important because the shell function can be influenced by small amounts of impurities in the excipients (e.g., peroxides in oils or aldehydes in lactose and starches) that can cause capsule cross-linking. The presence in capsule shells of undesirable materials, such as metals, odorants, water-insoluble substances, and sulfur dioxide, should be evaluated to ensure stability and performance.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected capsule shell functions: [Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests \(61\)](#), [Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms \(62\)](#), [Arsenic \(211\)](#), [Elemental Impurities—Limits \(232\)](#) and [Elemental Impurities—Procedures \(233\)](#), [Residue on Ignition \(281\)](#), [Disintegration \(701\)](#), [Dissolution \(711\)](#), [Water Determination \(921\)](#), and [Color—Instrumental Measurement \(1061\)](#).

ADDITIONAL INFORMATION

In addition to the general chapters listed above, useful information for ensuring consistency in selected capsule shell functions may be found in [Gelatin, Gel Strength \(Bloom Value\)](#).

Functional Category: Coating Agent

DESCRIPTION

Oral tablets may be coated using compression coating, sugar coating, or film coating. Compression coating (effectively making a tablet within a tablet) typically uses the same ingredients as a conventional tablet and thus is outside the scope of this section. The term “sugar coating” refers to a process and does not require that sucrose be part of the formulation. Oral capsules can be coated using film coating procedures. Reasons for coating pharmaceutical dosage forms include masking unpleasant tastes or odors, improving ingestion and appearance, protecting active ingredients from the environment, and modifying the release of the active ingredient (e.g., controlled-release or gastrointestinal targeting). Materials used as coating agents differ depending on the coating process used. Sugar coating was the original coating process. However, today for technical and economic reasons, sugar coating largely has been replaced by

film coating. Sugar coating is a complex process that typically involves the application of several different coats including a seal coat, key coat, subcoat, smoothing coat, color coat, and polishing coat. The coating solutions or suspensions are slowly poured or otherwise applied in aliquots onto a bed of tablets in a slowly rotating pan. The coating process typically takes an extended period (potentially several days) and results in a substantial increase in tablet weight. In contrast, film coating generally is a simpler process in which coating solution or suspension is sprayed onto tablets either in a rotating pan or in a fluid-bed apparatus and results in only a modest increase in capsule or tablet weight. The materials used in both sugar coating and film coating include natural, semisynthetic, and synthetic materials. These may be solutions, suspensions, or colloidal dispersions (latexes or pseudolatexes) that can be applied as either aqueous or nonaqueous systems. In addition, waxes and lipids can be applied as coatings in the molten state without the use of solvents. They also can be applied in the solid state as a polishing coat on top of sugar coating or film coating.

FUNCTIONAL MECHANISM—SUGAR COATING

The seal coat is used to seal the surface of the tablet cores to prevent water in the coating solutions or suspensions from causing the tablet cores to disintegrate during coating. The seal coat typically is a polymer (e.g., shellac) that is insoluble in water and is applied as a thin coat from a solution in a nonaqueous solvent. The key component of the majority of sugar coating solutions or suspensions is a solute, typically sucrose, that is highly soluble in water and forms a sticky, viscous solution (a syrup) at very high concentration. Other materials can be dissolved or suspended in the solution, depending on the stage during the coating process. As the coating dries, the dissolved coating material adheres to the surface of the tablets. The coating solution or suspension typically is applied in incremental steps, followed by drying, until the requisite coating has been achieved. The key coat is composed of another thin coat that is designed to adhere to the seal-coated cores to provide a base for the subcoat so the latter can adhere to the tablet surface. The subcoat typically contains a high concentration of suspended solids and is designed to increase the weight of the tablets comparatively quickly. The smoothing coat is designed to provide a smooth surface, and the color coat provides the final color if required. Finally, the tablets may be transferred to a polishing pan and polished using a mixture of waxes to provide a high-gloss finish.

FUNCTIONAL MECHANISM—FILM COATING

Film-coating agents are composed of film-forming materials (see *Functional Category: Film-Forming Agent*) that impart desirable pharmaceutical properties such as appearance and patient acceptance (e.g., taste masking and ease of swallowing). Film-coating agents also can serve other functional purposes such as providing a barrier against undesirable chemical reactions or untimely release of a drug from its components. After ingestion, the film coating may dissolve by processes such as hydration, solubilization, or disintegration, depending on the nature of the material used. Enteric coatings are insoluble in acidic (low pH) media but dissolve readily in neutral pH conditions. However, most common film-coating polymers do not have pH-specific solubility. The thickness of the film may vary by application and the nature of the coating agents. In the coating process, the polymer chains spread out on the core surface and coalesce into a continuous film as the solvent evaporates. Polymer solutions or dispersions with a low viscosity and high pigment-binding capacity reduce the coating time and facilitate relatively simple and cost-effective manufacturing. Plastic polymers, waxes, and lipid-based coatings can be applied without solvents by melting and atomization. When molten fluid droplets strike the surface of the fluidized drug particles, they spread and resolidify to form film layers. Therefore, film-coating materials generally have the ability to form a complete and stable film around the substrate. The film coating typically is applied uniformly and is carefully dried to ensure that a consistent product is produced. Suitable plasticizers may be required to lower the minimum film-forming temperature of the polymer, and formulators should consider their potential effect on drug release.

PHYSICAL PROPERTIES

Sugar coating is a lengthy, complex process. The physical properties of the seal-coating polymer and solution are important. The physical properties of the syrup component in the subsequent layers and any dissolved or suspended solids also are important, and coating agents must be sufficiently stable during use.

Film coating is a complex process, and the characteristics of the film-forming polymer are important. The particle size of colloidal dispersions varies with their composition and manufacture (latex, pseudolatex, or redispersed powder) and can have an effect on film formation. The surface tension of coating preparations can influence the spray pattern in the manufacturing process. The film should possess sufficient elasticity and mechanical strength to withstand the stresses during coating and packaging operations. For coatings that are applied in a molten state without solvents (plastic polymers, waxes, and lipid-based coatings), melting range and melt viscosity are the primary properties that formulators must consider.

CHEMICAL PROPERTIES

Coating components can be of natural, semisynthetic, or synthetic origin and also can be available in different chemical grades. They comprise a diverse variety of different chemical materials. Formulators must consider the nature of the material and its intended use when they identify and quantitate chemical CMAs to ensure consistent performance.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected coating agent functions: [Fats and Fixed Oils \(401\)](#), [Light Diffraction Measurement of Particle Size \(429\)](#), [Dissolution \(711\)](#), [Tensile Strength \(881\)](#), [Thermal Analysis \(891\)](#), [Viscosity—Capillary Methods \(911\)](#), [Viscosity—Rotational Methods \(912\)](#), and [Viscosity—Rolling Ball Method \(913\)](#). In addition, the general chapters listed under *Functional Category: Film-Forming Agent* (below) also may be appropriate for the evaluation of film-coating polymers.

ADDITIONAL INFORMATION

Additives often are included in a coating formulation. Fillers (e.g., sugar alcohols, microcrystalline cellulose, calcium carbonate, and kaolin) may be added to increase the solids content of the coating agent without increasing viscosity. Stearic acid can be used to improve the protective function/moisture barrier of a coating. Coloring agents (e.g., titanium dioxide and iron oxides) may be added to modify appearance.

Functional Category: Plasticizer

DESCRIPTION

A plasticizer is a low molecular weight substance that, when added to another material—usually a polymer—makes the latter flexible, resilient, and easier to handle. Plasticizers are key components that determine the physical properties of polymeric pharmaceutical systems such as tablet film coatings and capsule shells.

FUNCTIONAL MECHANISM

Plasticizers function by increasing the intermolecular and intramolecular mobility of the macromolecules that comprise polymeric materials. They achieve this by interfering with the normal intermolecular and intramolecular bonding mechanisms in such systems. The most effective plasticizers exert their effect at low concentrations, typically less than 5% w/w. Plasticizers commonly are added to film coatings (aqueous and nonaqueous systems) and capsule shells (hard and soft varieties) to improve their workability and mechanical ruggedness. Without the addition of plasticizers, such materials can split or fracture prematurely. Plasticizers also are added to semisolid pharmaceutical preparations, such as creams and ointments, to enhance their rheological properties.

PHYSICAL PROPERTIES

The most common plasticizers are low molecular weight (<500 Da) solids or liquids. They typically have low melting points (<100°) and can be volatile (i.e., exert an appreciable vapor pressure) at ambient temperature. Plasticizers can reduce the glass transition temperature (T_g) of the system to which they are added.

CHEMICAL PROPERTIES

Many modern plasticizers are synthetic esters such as citrates and phthalates. Traditional pharmaceutical plasticizers include oils, sugars, and their derivatives.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected excipient functions: [Residual Solvents \(467\)](#), [Melting Range or Temperature \(741\)](#), [Refractive Index \(831\)](#), [Specific Gravity \(841\)](#), [Thermal Analysis \(891\)](#), and [Water Determination \(921\)](#).

ADDITIONAL INFORMATION

The choice of an appropriate plasticizer often is guided by reference to its solubility parameter, which is related to its cohesive energy density. Solubility parameter values for many common materials are tabulated in standard reference texts. To ensure maximum effectiveness, the solubility parameter of the plasticizer and the polymeric system being plasticized should be matched as closely as possible.

Functional Category: Film-Forming Agent

DESCRIPTION

Film-forming agents typically are polymers that can be used to prepare polymer films to coat tablets or capsules for oral administration, to modify appearance, to modify drug release, or to serve other purposes such as melt-in-the-mouth formulations. Polymeric materials used as film-forming agents can be derived from natural, semisynthetic, or synthetic sources, and they can be supplied as powders, granules, pre-prepared solutions, or colloidal dispersions. Colloidal dispersions may contain other components such as plasticizers, surface-active agents, preservatives, or stabilizers. Film-forming agents can be applied as colloidal dispersions (latexes or pseudolatexes) or as aqueous, hydroalcoholic, or nonaqueous polymeric solutions.

FUNCTIONAL MECHANISM

Film-forming agents typically are composed of polymeric materials that possess the ability to form films after solvent evaporation from a solution of the polymer or from the continuous phase of a colloidal dispersion. Thus, the polymer alone must be a solid at ambient temperature and humidity. Some polymers can form films without the inclusion of added components, but other polymers may require the use of additional components such as plasticizers.

PHYSICAL PROPERTIES

Many polymeric film-forming agents are available in a variety of physical grades that typically are based on the nominal viscosity of the particular grade. The physical properties of the polymer usually are those of a solid, and many polymers are available as powders and granules. In addition to the normal properties of bulk powders and granules, other important physical properties of a polymeric film-forming agent are the molecular weight distribution, which is linked to the nominal viscosity of the grade, and the glass transition temperature (T_g). If the film-forming agent is provided as a pre-prepared solution or dispersion, the viscosity of the solution or dispersion can affect performance and should be monitored.

CHEMICAL PROPERTIES

Film-forming agents comprise a diverse group of materials, including natural, semisynthetic, and synthetic materials as discussed above. They may have ionizable functional groups that impart pH-dependent properties and also can be available in different chemical grades (e.g., with different degrees of chemical substitution). Pharmacopeial monographs often describe classes of polymeric materials that allow

a considerable range of composition. Formulators should consider these factors when they identify critical material attributes and establish specifications to ensure consistent performance.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected film-forming agent functions: [Fats and Fixed Oils \(401\)](#), [Light Diffraction Measurement of Particle Size \(429\)](#), [Bulk Density and Tapped Density of Powders \(616\)](#), [Chromatography \(621\)](#), [Density of Solids \(699\)](#), [Dissolution \(711\)](#), [Optical Microscopy \(776\)](#), [pH \(791\)](#), [Tensile Strength \(881\)](#), [Thermal Analysis \(891\)](#), [Viscosity—Capillary Methods \(911\)](#), [Viscosity—Rotational Methods \(912\)](#), [Viscosity—Rolling Ball Method \(913\)](#), [Bulk Powder Sampling Procedures \(1097\)](#), [Near-Infrared Spectroscopy—Theory and Practice \(1856\)](#), (CN 1-May-2020), [Raman Spectroscopy \(1120\)](#), [Pharmaceutical Dosage Forms \(1151\)](#), [Powder Flow \(1174\)](#), and [Scanning Electron Microscopy \(1181\)](#).

Functional Category: Flavor and Fragrance

DESCRIPTION

A flavor is a single chemical entity or a blend of chemicals of natural or synthetic origin that has the ability to elicit a taste or aroma (i.e., fragrance) response when orally consumed or smelled. The primary purpose of flavor that is added to a pharmaceutical preparation is to provide all or part of the taste and aroma of the product taken into the mouth. Flavors commonly are used in pharmaceutical oral disintegrating tablets, oral solutions, and oral suspensions to mask objectionable drug taste and to make the formulation more palatable, thus promoting patient compliance.

FUNCTIONAL MECHANISM

Chemicals dissolved in saliva excite chemoreceptors on taste buds that reside primarily on the tongue and thus arouse taste perception. Dissolution also releases volatile chemicals that reach the olfactory receptors, triggering aroma perception. The total of taste and odor responses constitutes flavor. Humans can distinguish among five components of taste: sourness, saltiness, sweetness, bitterness, umami (savory), and a wide range of specific odors. Flavor enhancers and taste modifiers can be used to modify the sweetness profile of a sweetening agent or to mask off flavors. For example, organic acids, such as aspartic and glutamic acids, are known to reduce bitterness.

PHYSICAL PROPERTIES

Taste perception depends on physicochemical, physiological, and psychological factors. Physical properties such as particle size, solubility, humectancy, texture, and color all influence the senses. In addition to flavor, the sensory attributes of sight (e.g., appealing color), sound (e.g., crunch of a chewable tablet), and mouth feel (e.g., viscous, slimy, chalky, cloying, or watery) also contribute to and influence the overall sensory experience.

CHEMICAL PROPERTIES

Chemicals that provide one of the five basic tastes possess a wide variety of structures, functional groups, and molecular weights. Chemicals used to flavor pharmaceuticals by providing both odor and taste tend to have low molecular weights (<250 Da) and polar functional groups such as esters, ketones, aldehydes, amines, or alcohols. To increase the stability of the flavor(s) in a solid dosage form and to minimize flavor-drug interactions, formulators can add flavors in an encapsulated or spray-dried form.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in flavor functions: [Light Diffraction Measurement of Particle Size \(429\)](#), [Chromatography \(621\)](#), [Congealing Temperature \(651\)](#), [Loss on Drying \(731\)](#), [Melting Range or Temperature \(741\)](#), [Optical Rotation \(781\)](#), [Particle Size Distribution Estimation by Analytical Sieving \(786\)](#), [Refractive Index \(831\)](#), and [Specific Gravity \(841\)](#).

Functional Category: Release-Modifying Agents

Release-modifying agents are used to control drug release in extended-release formulations (also referred to as prolonged-release or controlled-release formulations). Sustained-release and enteric-coating agents are included under *Functional Category: Coating Agent*.

DESCRIPTION

Release-modifying agents change a medicinal product's drug-release pattern to achieve the desired drug plasma profile for a given time. The majority of release-modifying agents are polymers that differ in solubility, ease of erosion, rate of swelling, or sensitivity to the biological environment in which they are placed. These polymers have been used to fabricate matrix- or membrane-based drug delivery systems for oral, parenteral, transdermal, and other routes of administration. Matrix-controlled-release drug delivery systems can be classified as hydrophilic-eroding matrices, hydrophilic noneroding matrices, or hydrophobic matrices. In membrane-controlled-release drug delivery systems, the drug reservoir is coated by a rate-controlling polymeric membrane that may consist of a blend of polymers to control release. Such devices may take the form of tablets, capsules, microspheres, vesicles, fibers, patches, and others. In addition to polymers, certain lipid-based excipients also can be used as release-modifying agents in hydrophobic matrix devices and other types of modified-release systems. Typically, these lipid-based materials are fats and waxes or related materials with melting ranges above 45°.

FUNCTIONAL MECHANISM

Upon contact with a biological fluid, release-controlling polymers may undergo a variety of physical changes such as swelling, gelling, dissolution, or erosion, each of which can be triggered by simple aqueous exposure or can be modulated by pH, osmotic stress, or interactions with bile or other intestinal contents. In addition to physical changes, polymers may undergo chemical degradation by acids, bases, enzymes, water, heat, and others. Any or all of these mechanisms may act in concert to control the rate at which the drug is released from the delivery system.

For hydrophilic matrices in which drug diffusion dominates release rate, the rate of drug release depends on the properties of the polymer gel and the nature of the continuous phase in the interstices of the gel influences the dissolution and diffusion rates of the drug. In the case of eroding matrices, the gel erodes because of the mechanical action of the gastrointestinal tract as the water uptake increases, and the gel becomes more dilute, thus reducing the diffusion distance or releasing drug particles that subsequently dissolve. Hydrophobic matrix-forming materials are not soluble. Drug release from such systems is governed by drug diffusion through the tortuous pores that remain as soluble components dissolve.

Membrane-based drug delivery systems include polymer-coated tablets, capsules, and microspheres. Drug-release mechanisms from such systems are complex and depend on physicochemical characteristics of the drug and polymers or lipids used as well as biological factors in the case of biocompatible and biodegradable systems. Most commonly, drug release from such systems is governed by drug diffusion through the hydrated rate-controlling membrane.

Other modified-release systems for parenteral use include solid lipid nanoparticles and liposomes. The release mechanisms for these systems often involve a complicated interplay with biological processes such as potential clearance through the reticulo-endothelial system, targeted delivery, and cellular uptake.

Osmotic pump devices are a special case of membrane delivery systems. The rate-controlling polymer is insoluble and semipermeable—i.e., it will allow water but not drug molecules—to diffuse through the membrane. Release is controlled by the osmotic pressure of the core components and the viscosity of the resulting solution or suspension. The drug, either in solution or as a suspension, is forced out of a hole in the membrane, which is typically drilled by a laser during product manufacture.

PHYSICAL PROPERTIES

The physical properties of the release-controlling excipient depend on the chemical type: hydrophilic polymer, hydrophobic polymer, semipermeable polymer blends, or lipid, wax, or biodegradable polymer (which can be hydrophilic or hydrophobic).

Hydrophilic polymers gel in contact with water or aqueous media. Because they should provide resistance to the mechanical action of the gastrointestinal tract during passage, they typically are higher molecular weight grades of the polymers. At the concentrations typically used during in vivo release, these high molecular weight polymers often do not exhibit Newtonian properties except in very dilute solution (if they are soluble). Formulators should monitor the kinetic and viscoelastic properties of the gels formed in the release medium.

Hydrophobic polymers are insoluble in water, and their solution properties are determined in nonaqueous solutions. The polymers used in the preparation of semipermeable membranes in osmotic pump devices also are insoluble in water, and similarly their solution properties are determined in nonaqueous solutions. Similarly, hydrophobic lipid-based materials are insoluble in water.

CHEMICAL PROPERTIES

Release-controlling agents have many different types and origins and are available in a range of grades that reflect the considerable variation in their chemical structures and properties. Formulators must consider these variables during any chemical investigation and when they consider the effects of chemical structure on excipient performance. Properties of interest may include chemical composition for copolymers and cellulosic derivatives, degree of ionization, molecular weight, degree of cross-linking, or, for lipids, fatty acid composition. Residual impurities from the manufacturing process, e.g., monomers, initiators, quenching agents, peroxides, and aldehydes, may affect drug substance stability and should be monitored.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected functions of release-modifying agents: [Fats and Fixed Oils \(401\)](#), [Light Diffraction Measurement of Particle Size \(429\)](#), [Crystallinity \(695\)](#), [Characterization of Crystalline Solids by Microcalorimetry and Solution Calorimetry \(696\)](#), [Dissolution \(711\)](#), [Loss on Drying \(731\)](#), [Melting Range or Temperature \(741\)](#), [Nuclear Magnetic Resonance Spectroscopy \(761\)](#), [Optical Microscopy \(776\)](#), [Particle Size Distribution Estimation by Analytical Sieving \(786\)](#), [Specific Surface Area \(846\)](#), [Mid-Infrared Spectroscopy \(854\)](#), and [Ultraviolet-Visible Spectroscopy \(857\)](#), [Tensile Strength \(881\)](#), [Thermal Analysis \(891\)](#), [Viscosity—Capillary Methods \(911\)](#), [Viscosity—Rotational Methods \(912\)](#), [Viscosity—Rolling Ball Method \(913\)](#), [Water Determination \(921\)](#), [Characterization of Crystalline and Partially Crystalline Solids by X-Ray Powder Diffraction \(XRPD\) \(941\)](#), [Powder Flow \(1174\)](#), and [Scanning Electron Microscopy \(1181\)](#).

ADDITIONAL INFORMATION

Some release-modifying agents may include additives such as an antioxidant or an anticaking agent.

Change to read:

ORAL LIQUIDS

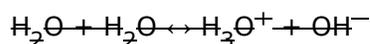
Functional Category: pH Modifier (Acidifying/Alkalizing/Buffering Agent)

DESCRIPTION

The hydrogen ion concentration, $[H^+]$, in an aqueous solution is expressed as $pH = -\log(H^+)$. The pH of pure water is 7 at 25°. An aqueous solution is acidic at $pH < 7$ and alkaline at $pH > 7$. An acid can be added to acidify a solution. Similarly, a base can be used to alkalize a solution. A buffer is a weak acid (or base) and its salt. When a buffer is present in a solution, the addition of small quantities of strong acid or base leads to only a small change in solution pH. Buffer capacity is influenced by salt/acid (or base/salt) ratio and total concentration of acid (or base) and salt. The pH of pharmaceutical solutions typically is controlled using acidifying/alkalizing and buffering agents to: 1) maintain a pH close to that of relevant body fluid to avoid irritation, 2) improve drug stability where it is found to be pH dependent, 3) control equilibrium solubility of weak acids or bases, and 4) maintain a consistent ionization state of molecules during chemical analysis, e.g., high-performance liquid chromatography.

FUNCTIONAL MECHANISM

The ionization equilibria of weak bases, weak acids, and water are the key to the functions of acidifying, alkalizing, and buffering agents. The autoprotolytic reaction of water can be expressed as:



The autoprotolysis constant (or ion product) of water is $K_w = 1 \times 10^{-14}$ at 25° and varies significantly with temperature. Because the concentrations of hydrogen and hydroxyl ions in pure water are equal, each has the value of approximately 1×10^{-7} mol/L, leading to the neutral pH of 7 at 25°. When an acid, base, or salt of a weak acid (or base) is added, the ionization equilibrium of water is shifted so that $[\text{H}^+][\text{OH}^-]$ remains constant, thus resulting in a solution pH that is different from 7.

PHYSICAL PROPERTIES

pH modifiers typically are dissolved in liquid dosage forms. Physical properties may be important and should be considered because they may influence processing requirements (e.g., particle size may influence mixing time required to dissolve a pH modifier).

CHEMICAL PROPERTIES

Buffers and pH modifiers influence solution pH, buffer capacity, osmolality, osmolarity, and water conductivity. When used in chemical analysis, buffers must be chemically compatible with the reagents and test substance. Buffers used in physiological systems should not interfere with the pharmacological activity of the medicament or the normal function of the organism.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected pH modifier or buffering agent functions: [Water Conductivity \(645\)](#), [Osmolality and Osmolarity \(785\)](#), and [pH \(791\)](#).

Functional Category: Wetting and/or Solubilizing Agent

DESCRIPTION

Solubilizers can be used to dissolve otherwise insoluble molecules. They function by facilitating spontaneous phase transfer to yield a thermodynamically stable solution. A number of solubilizers are available commercially. Acceptable solubilizers for pharmaceutical applications have been fully evaluated in animals for safety and toxicology. Wetting agents increase the spreading and penetrating properties of a liquid by lowering its surface tension.

FUNCTIONAL MECHANISM

Wetting and solubilizing agents comprise a variety of different chemical structures or classes. Some solubilizers have unique chemical structures. For example, a hydrophilic moiety may be tethered with a hydrophobic moiety to yield distinct micelle shapes and morphologies in water, thus facilitating solubilization. The mechanism of solubilization often is associated with a favorable interaction of the insoluble agent and the interior core of the solubilizer assembly (e.g., micelles). In other cases, unique hydrophobic sites that are capable of forming inclusion complexes are present. Other types of solubilizers use a range of polymeric chains that interact with hydrophobic molecules to increase solubility by dissolving the insoluble agent into the polymeric chains.

PHYSICAL PROPERTIES

Wetting and solubilizing agents are typically solid, liquid, or waxy materials. Their physical properties depend on their chemical structures. The physical properties and performance of the wetting agents and solubilizers, however, depend on the surface-active properties of the solubilizers and on the hydrophilic-lipophilic balance (HLB). Materials with lower HLB values behave as emulsifiers, whereas those with higher HLB values typically behave as solubilizing agents. For example, the commonly used wetting and solubilizing agent sodium lauryl sulfate (HLB 40) is hydrophilic and highly water soluble and, upon

dispersion in water, spontaneously reduces surface tension and forms micelles that function to solubilize lipophilic materials.

The unique hydrophilicity and hydrophobicity properties of solubilizers can be characterized by their chemical structures, aggregate numbers, or critical micelle concentrations (CMCs). The CMC value is unique to an individual solubilizer that bears hydrophilic, lipophilic, and/or hydrophobic chains. CMC is a measure of the concentration at which the surface-active molecules aggregate. These molecular aggregates can solubilize the solute by incorporating part into the hydrophobic interior. Such interactions with the insoluble molecule further stabilize the molecules in the entire assemblies without precipitation.

CHEMICAL PROPERTIES

The chemical and surface-active properties depend on the structures of the solubilizers. Because of the complex nature of solute-solvent-solubilizer interactions, pharmaceutical scientists must carefully consider, identify, and control the CMAs of solubilizers.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected solubilizing agent functions: [Fats and Fixed Oils \(401\)](#), [Light Diffraction Measurement of Particle Size \(429\)](#), [pH \(791\)](#), [Specific Gravity \(841\)](#), [Specific Surface Area \(846\)](#), [Mid-Infrared Spectroscopy \(854\)](#), and [Ultraviolet-Visible Spectroscopy \(857\)](#), [Thermal Analysis \(891\)](#), [Viscosity—Capillary Methods \(911\)](#), [Viscosity—Rotational Methods \(912\)](#), [Viscosity—Rolling Ball Method \(913\)](#), and [Scanning Electron Microscopy \(1181\)](#).

Functional Category: Antimicrobial Preservative

DESCRIPTION

Antimicrobial preservatives are used to kill or prevent growth of bacteria, yeast, and mold in the dosage form.

FUNCTIONAL MECHANISM

Preservatives work by a variety of mechanisms to control microbes. Most work at the cell membrane, causing membrane damage and cell leakage. Other modes of action include transport inhibition, protein precipitation, and proton-conducting uncoupling. Some preservatives are bactericidal (kill bacteria or yeast and mold); some are bacteriostatic (inhibit growth of microorganisms); and others are sporicidal (kill spores). Several of the preservatives can act synergistically (e.g., combinations of parabens).

PHYSICAL PROPERTIES

Antimicrobials generally are soluble in water at concentration ranges at which they are effective. The vapor pressure of these agents is important, especially if the dosage form is intended for lyophilization or spray drying. Several of these agents are flammable. Understanding an excipient's partition coefficient is important because partitioning of a preservative into an oil phase can diminish the preservative's concentration in the aqueous phase, which in turn can reduce its value as a preservative.

CHEMICAL PROPERTIES

Phenolic preservatives can undergo oxidation and color formation. Incompatibilities of preservatives (cationic and anionic mixtures, adsorption to tubes or filters, or binding to surfactants and proteins) should be taken into account during product development.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected antimicrobial functions: [Injections and Implanted Drug Products \(1\)](#), [Antimicrobial Effectiveness Testing \(51\)](#), [Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests \(61\)](#), [Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms \(62\)](#), and [Antimicrobial Agents—Content \(341\)](#).

ADDITIONAL INFORMATION

Safety and labeling requirements regarding the use of antimicrobial preservatives should be considered.

Functional Category: Chelating and/or Complexing Agents

DESCRIPTION

Chelating agents form soluble complex molecules with certain metal ions (e.g., copper, iron, manganese, lead, and calcium) and essentially remove the ions from solution to minimize or eliminate their ability to react with other elements and/or to precipitate. The agents are used in pharmaceuticals (oral, parenteral, and topical formulations), cosmetics, and foods to sequester ions from solution and to form stable complexes. Chelating agents also are referred to as chelants, chelators, or sequestering agents.

Complexing agents form soluble complex molecules (e.g., inclusion complexes) with other solutes (e.g., drug substances) and can influence physical and chemical properties such as solubility and stability.

FUNCTIONAL MECHANISM

Chelating agents are used to sequester undesirable metal ions from solution. The chemical structure of chelating agents allows them to act as a "claw" to associate with the metal atom by forming a heterocyclic ring structure. Complexing agents function similarly but mechanistically and do not (by definition) require a two-point claw structure because they can associate via one or more binding sites. All chelating agents are complexing agents, but not all complexing agents are chelating agents. Chelating agents are used as antioxidant synergists, antimicrobial synergists, and water softeners. By sequestering metal ions from solution, chelating agents reduce the propensity for oxidative reactions. Chelating agents also have the ability to enhance antimicrobial effectiveness by forming a metal-ion-deficient environment that otherwise could feed microbial growth.

Complexing agents generally form soluble complex molecules with solutes (e.g., drug molecules) that can influence physical, chemical, and drug delivery properties. Complexing agents that form inclusion complexes typically contain a hydrophobic cavity into which a drug substance can enter and an outer, more hydrophilic region.

PHYSICAL PROPERTIES

Chelating and complexing agents generally are soluble in water and typically are dissolved in liquid dosage forms. Physical properties may be important and should be considered because they may influence processing requirements (e.g., particle size may influence mixing time required to dissolve). Chelating and complexing agents exhibit different degrees of hygroscopicity. Because chelating agents are used in low levels, particle size distribution can be important to enable acceptable dosage form content uniformity.

CHEMICAL PROPERTIES

Chelating agents complex with metal ions via any combination of ionic and covalent bonds. Dilute aqueous solutions may be neutral, acidic, or alkaline. Edetic acid and its salts are incompatible with strong oxidizers, strong bases, and polyvalent metal ions (e.g., copper and nickel). Specific agents are selected for a formulation based on their solubility, affinity for the target metal ion, and stability. Edetate salts are more soluble than the free acid. Unlike other edetate salts and the free acid, edetate calcium disodium does not sequester calcium and therefore is preferred to prevent hypocalcemia. It is also preferred to chelate metals with the release of calcium ions. Alternatively, disodium edetate can be used to treat hypercalcemia. Edetic acid will decarboxylate if heated above 150°.

Complexing agents generally form molecular complexes with drug substances that are dependent on complexing agent physical and chemical properties. The ability of a solute to form an inclusion complex is dependent on complexing agent molecular weight, chemical structure, and the dimensions of the hydrophobic cavity.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected chelating and complexing functions: [Antimicrobial Effectiveness Testing \(51\)](#), [Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests \(61\)](#), [Elemental Impurities—Limits \(232\)](#), and [Elemental Impurities—Procedures \(233\)](#), [Iron \(241\)](#), [Lead \(251\)](#), [Antimicrobial Agents—Content \(341\)](#), [Light Diffraction](#)

Functional Category: Antioxidant

DESCRIPTION

This category applies to antioxidants used as in vitro stabilizers of pharmaceutical preparations to mitigate oxidative processes. Antioxidants used for their biological activity in vivo may be regarded as active ingredients with therapeutic effects and are not discussed. Antioxidants delay the onset of and/or significantly reduce the rate of complex oxidative reactions that could otherwise have a detrimental effect on the drug substance. Antioxidants also can be considered for protecting nonactive components such as unsaturated oils, pegylated lipids, flavors, and essential oils. Thus, antioxidants preserve the overall integrity of the dosage form against oxidative stress. Antioxidants are most effective when incorporated in the formula to prevent or delay the onset of chain reactions and to inhibit free radicals and hydroperoxides from engaging in the cascading processes described above. Effective application of antioxidants and evaluation of their efficacy necessitate an understanding of oxidative mechanisms and the nature of the byproducts they generate. Autoxidation is initiated when oxygen reacts with a substrate to form highly reactive species known as free radicals ($RH \rightarrow R\cdot$). After "initiation" the free radicals in the presence of oxygen can trigger chain reactions ($R\cdot + O_2 \rightarrow ROO\cdot$ and $ROO\cdot + RH \rightarrow R\cdot + ROOH$) to form peroxy radicals, hydroperoxides, and new alkyl radicals that can initiate and then propagate their own chain reactions. The cascading reactions during the propagation phase can be accelerated by heat, light, and metal catalysts. In the presence of trace amounts of metal catalysts (Cu^+ , Cu^{2+} , Fe^{2+} , and Fe^{3+}), hydroperoxides (ROOH) readily decompose to $RO\cdot$ and $ROO\cdot$ and subsequently can trigger reactions with the API and/or the excipients (e.g., hydrocarbons) to form hydroxyl acids, keto acids, and aldehydes that can have further undesirable effects. Note that hydroperoxides are not solely the reaction products of oxidative mechanisms within a formulation. Residual amounts of hydroperoxides also can be found in commonly used excipients like polyethylene glycols, polyvinylpyrrolidone, and polysorbates. The initiation phase generally is slow and has a limited effect on the quality of the finished product. The propagation phase, in contrast, involves rapid, irreversible degradation of chemical species.

FUNCTIONAL MECHANISM

Antioxidants can be grouped by their mode of action. Phenolic antioxidants that block free radical chain reactions also are known as true or primary antioxidants. This group consists of monohydroxy or polyhydroxy phenol compounds with ring substitutions. They have very low activation energy to donate hydrogen atom(s) in exchange for the radical electrons that are rapidly delocalized by free radicals. By accepting the radical electrons, they stabilize free radicals. The reaction yields antioxidant free radicals that also can react with lipid free radicals to form other stable compounds. Thus, they can block oxidative chain reactions both in the initiation and propagation stages. Because of their solubility behavior, phenolic antioxidants are most effective in protecting oils and oil-soluble actives against oxidative stress. Reducing agents generally are water-soluble antioxidants (e.g., L-ascorbic acid) with lower redox potential than the drug or the excipient they are protecting. They delay the onset and the rate of oxidative reactions by sacrificially reacting with oxygen and other reactive species. The oxygen-scavenging potential of the reducing agents may be sensitive to pH and also can be negatively affected in the presence of trace elements. Chelating agents bind with free metals (Cu^+ , Cu^{2+} , Fe^{2+} , and Fe^{3+}) that may be present in trace amounts in the formulation. The newly formed complex ions are nonreactive. Chelating agents therefore remove the capacity of the metal catalysts to participate in oxidative reactions that occur during the propagation stage.

The utility of antioxidants can be maximized by synergistic use of one or two primary antioxidants along with reducing and chelating agents. The combined effect often is greater than the sum of the individual effects of each antioxidant (synergistic effect).

PHYSICAL PROPERTIES

Solubility of the antioxidant should be greatest in the formulation phase (oily, aqueous, or emulsion interface), where the drug substance is most soluble. The temperature at which the antioxidant decomposes is critical for autoclaved preparations, where loss of antioxidant activity may occur. Stability of the antioxidant also must be considered and may be a function of pH and processing conditions. Metal ions may react with propyl gallate to form colored complexes. At alkaline pH, certain proteins and sodium salts may bring about discoloration of *tert*-butylhydroquinone.

CHEMICAL PROPERTIES

Activation energy, oxidation-reduction potential, and stability at different formulation (e.g., pH) and processing (e.g., heat) conditions are important chemical properties. If the dosage form's expected shelf life depends on the antioxidant's function, the concentration must be factored in and periodically assessed to ensure that a sufficient amount of antioxidant remains throughout the product shelf life.

GENERAL CHAPTERS

The following general chapters may be useful for assessing selected excipient antioxidant functions: [Iron \(241\)](#), [Chromatography \(621\)](#), [Crystallinity \(695\)](#), [Melting Range or Temperature \(741\)](#), [Specific Surface Area \(846\)](#), and [Water Determination \(921\)](#).

Functional Category: Sweetening Agent

DESCRIPTION

Sweetening agents are used to sweeten oral dosage forms and to mask unpleasant flavors. See *Functional Category: Flavor and Fragrance* for more details.

FUNCTIONAL METABOLISM

Sweetening agents bind to receptors on the tongue that are responsible for the sensation of sweetness. The longer the sweetener molecule remains attached to the receptor, the sweeter the substance is perceived to be. The standard for sweetness is sucrose.

PHYSICAL PROPERTIES

The primary physical properties relevant to sweeteners relate to their compatibility with the other ingredients in the formulation (e.g., acidic ingredients), processing conditions (e.g., heating), particle size and distribution, moisture content, isomerism, sweetness, and taste-masking capability. These properties may be formulation dependent.

CHEMICAL PROPERTIES

Sweeteners can be divided into three main groups: sugars (which have a ring structure), sugar alcohols (sugars that do not have a ring structure), and artificial sweeteners. All sweeteners are water soluble. The stability of many sweeteners is affected by pH and other ingredients in the formulation. Some sweeteners may catalyze the degradation of some active ingredients, especially in liquids and in cases in which the manufacturing processes involve heating.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected sweetening functions: [Light Diffraction Measurement of Particle Size \(429\)](#), [Loss on Drying \(731\)](#), [Melting Range or Temperature \(741\)](#), [Optical Rotation \(781\)](#), and [Water Determination \(921\)](#).

ADDITIONAL INFORMATION

Products that contain aspartame must include a warning on the label stating that the product contains phenylalanine. Sugar alcohols have a glycemic index well below that of glucose. However, sorbitol is slowly metabolized to fructose and glucose, which raises blood sugar levels. Sugar alcohols in quantities generally greater than 20 g/day act as an osmotic laxative, especially when they are contained in a liquid formulation. Preservative systems should be carefully chosen to avoid incompatibility with the sweetener, and some sweeteners are incompatible with certain preservatives.

SEMISOLIDS, TOPICALS, AND SUPPOSITORIES

Functional Category: Suppository Base

DESCRIPTION

Suppository bases are used in the manufacture of suppositories (for rectal administration) and pessaries (for vaginal administration). They can be hydrophobic or hydrophilic.

FUNCTIONAL MECHANISM

Suppositories should melt at just below body temperature (37°), thereby allowing the drug to be released either by erosion and partition if the drug is dissolved in the base or by erosion and dissolution if the drug is suspended in the base. Hard fat suppository bases melt at approximately body temperature. Hydrophilic suppository bases also melt at body temperature and typically also dissolve or disperse in aqueous media. Thus, release takes place via a combination of erosion and dissolution.

PHYSICAL PROPERTIES

The important physical characteristic of suppository bases is melting range. In general, suppository bases melt between 27° and 45°. However, individual bases usually have a much narrower melting range within these temperature boundaries, typically 2°–3°. The choice of a particular melting range is dictated by the influence of the other formulation components on the melting range of the final product.

CHEMICAL PROPERTIES

Hard fat suppository bases are mixtures of semisynthetic triglyceride esters of longer chain fatty acids. They may contain varying proportions of mono- and diglycerides and also may contain ethoxylated fatty acids. They are available in many different grades that are differentiated by melting range, hydroxyl number, acid value, iodine value, solidification range, and saponification number.

Hydrophilic suppository bases are mixtures of hydrophilic semisolid materials that in combination are solid at room temperature and yet release the drug by melting, erosion, and dissolution when administered to the patient. Hydrophilic suppository bases have much higher levels of hydroxyl groups or other hydrophilic groups than do hard fat suppository bases. Polyethylene glycols that show appropriate melting behavior are examples of hydrophilic suppository bases.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected suppository base functions: [Fats and Fixed Oils \(401\)](#), [Congealing Temperature \(651\)](#), [Melting Range or Temperature \(741\)](#), and [Pharmaceutical Dosage Forms \(1151\)](#).

ADDITIONAL INFORMATION

Some materials included in suppositories based on hard fats have much higher melting ranges. These materials typically are microcrystalline waxes that help stabilize molten suspension formulations. Suppositories also can be manufactured from glycerinated gelatin.

Functional Category: Suspending and/or Viscosity-Increasing Agents

DESCRIPTION

Suspending and viscosity-increasing agents are used in pharmaceutical formulations to stabilize dispersal systems (e.g., suspensions or emulsions), to reduce the rate of solute or particulate transport, or to decrease the fluidity of liquid formulations.

FUNCTIONAL MECHANISMS

A number of mechanisms contribute to the dispersion stabilization or viscosity-increasing effect of these agents. The most common is the increase in viscosity—because of the entrapment of solvent by macromolecular chains or clay platelets—and the disruption of laminar flow. Other mechanisms include gel formation via a three-dimensional network of excipient molecules or particles throughout the solvent continuum and steric stabilization wherein the macromolecular or mineral component in the dispersion

medium adsorbs to the surfaces of particles or droplets of the dispersed phase. The latter two mechanisms increase formulation stability by immobilizing the dispersed phase.

PHYSICAL PROPERTIES

Each of the mechanisms—increased viscosity, gel formation, or steric stabilization—is a manifestation of the rheological character of the excipient. Because of the molecular weights and sizes of these excipients, the rheological profiles of their dispersions are non-Newtonian. Dispersions of these excipients display viscoelastic properties. The molecular weight distribution and polydispersity of the macromolecular excipients in this category are important criteria for their characterization.

CHEMICAL PROPERTIES

The majority of the suspending and viscosity-increasing agents are: 1) hydrophilic carbohydrate macromolecules (acacia, agar, alginic acid, carboxymethylcellulose, carrageenans, dextrin, gellan gum, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, maltodextrin, methylcellulose, pectin, propylene glycol alginate, sodium alginate, starch, tragacanth, and xanthan gum); and 2) noncarbohydrate hydrophilic macromolecules, including gelatin, povidone carbomers, polyethylene oxide, and polyvinyl alcohol. Minerals (e.g., attapulgit, bentonite, magnesium aluminum silicate, and silicon dioxide) comprise the second largest group of suspending and viscosity-increasing agents. Aluminum monostearate is the one non-macromolecular, nonmineral excipient in this functional category. It consists chiefly of variable proportions of aluminum monostearate and aluminum monopalmitate.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected viscosity-increasing functions: [Viscosity—Capillary Methods \(911\)](#), [Viscosity—Rotational Methods \(912\)](#), and [Viscosity—Rolling Ball Method \(913\)](#).

Functional Category: Ointment Base

DESCRIPTION

An ointment is a viscous semisolid preparation used topically on a variety of body surfaces. An ointment base is the major component of an ointment and controls its physical properties.

FUNCTIONAL MECHANISM

Ointment bases serve as vehicles for topical application of medicinal substances and also as emollients and protective agents for skin.

PHYSICAL PROPERTIES

Ointment bases are liquids with a relatively high viscosity so that solids can be suspended as a stable mixture.

Ointment bases are classified as: 1) oleaginous ointment bases that are anhydrous, do not absorb water readily, are insoluble in water, and are not removable by water (e.g., petrolatum); 2) absorption ointment bases that are anhydrous and absorb some water but are insoluble in water and are not water removable (e.g., lanolin); 3) emulsion ointment bases that are water-in-oil or oil-in-water emulsions and are hydrous, absorb water, and are insoluble in water (e.g., creams of water, oils, waxes, or paraffins); and 4) water-soluble ointment bases that are anhydrous and absorb water and are soluble in water and are water removable (e.g., polyethylene glycol).

CHEMICAL PROPERTIES

Ointment bases are selected to be inert and chemically stable.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected ointment base functions: [Congealing Temperature \(651\)](#), [Viscosity—Capillary Methods \(911\)](#), [Viscosity—Rotational Methods \(912\)](#), and [Viscosity—Rolling Ball Method \(913\)](#).

Functional Category: Stiffening Agent

DESCRIPTION

A stiffening agent is an agent or a mixture of agents that increases the viscosity or hardness of a preparation, especially in ointments and creams.

FUNCTIONAL MECHANISM

In general, stiffening agents are high melting point solids that increase the melting point of ointments or increase the consistency or body of creams. Stiffening agents can be either hydrophobic (e.g., hard fat or paraffin) or hydrophilic (e.g., polyethylene glycol, high molecular weight).

PHYSICAL PROPERTIES

The primary physical property relevant to stiffening agents is their high melting point or melting range. Typical melting ranges for stiffening agents range from 43° to 47° (cetyl esters wax), 53° to 57° (glyceryl distearate), 69° to 74° (glyceryl behenate), and 85° to 88° (castor oil, hydrogenated).

CHEMICAL PROPERTIES

Stiffening agents comprise a diverse group of materials that include glycerides of saturated fatty acids, solid aliphatic alcohols, esters of saturated fatty alcohols and saturated fatty acids, saturated hydrocarbons, blends of fatty alcohols and a polyoxyethylene derivative of a fatty acid ester of sorbitan, and higher ethylene glycol polymers.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected stiffening agent functions: [Congealing Temperature \(651\)](#), [Melting Range or Temperature \(741\)](#), [Viscosity—Capillary Methods \(911\)](#), [Viscosity—Rotational Methods \(912\)](#), and [Viscosity—Rolling Ball Method \(913\)](#).

ADDITIONAL INFORMATION

Some of the materials included as stiffening agents increase the water holding capacity of ointments (e.g., petrolatum) or function as co-emulsifiers in creams. Examples include stearyl alcohol and cetyl alcohol.

Functional Category: Emollient

DESCRIPTION

Emollients are excipients used in topical preparations to impart lubrication, spreading ease, texture, and softening of the skin and to counter the potentially drying/irritating effect of surfactants on the skin.

FUNCTIONAL MECHANISM

Emollients help form a protective film and maintain the barrier function of the epidermis. Their efficacy may be described by three mechanisms of action: protection against the delipidizing and drying effects of surfactants, humectancy due to occlusion (by providing a layer of oil on the surface of the skin, emollients slow water loss and thus increase the moisture retention capacity of the stratum corneum), and lubricity, adding slip or glide to the preparation.

PHYSICAL PROPERTIES

Emollients impart one or more of the following attributes to a pharmaceutical preparation: spreading capacity, pleasant feel to the touch, softness of the skin, and indirect moisturization of the skin by preventing transepidermal water loss.

CHEMICAL PROPERTIES

Emollients are either oils or are derived from components of oils as esters of fatty acids. Depending on the nature of its fatty acid ester, an emollient may be liquid, semisolid, or solid at room temperature. Generally, the higher the molecular weight of the fatty acid moiety (carbon chain length) the richer the feel and softness of the touch. Fluidity generally is imparted by shorter chain length and higher degree of

unsaturation in the fatty acid moiety. The degree of branching of ester bonds also influences the emollient properties.

GENERAL CHAPTER

The following general chapter may be useful in ensuring consistency in selected emollient functions: [Fats and Fixed Oils \(401\)](#).

PARENTERALS

Functional Category: Pharmaceutical Water

DESCRIPTION

Water is used as a solvent, vehicle, diluent, or filler for many drug products, especially those supplied in liquid form. These may include injectable drugs, ophthalmic drugs, inhalation solutions, and others. Water also is a vehicle for buffers and antimicrobial agents and is a volume expander for infusion solutions.

USP includes monographs for eight grades of pharmaceutical waters. Water for Injection is intended for use in the preparation of parenteral solutions. Where used for the preparation of parenteral solutions subject to final sterilization, use suitable means to minimize microbial growth, or first render the Sterile Water for Injection and, thereafter, protect it from microbial contamination. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render the Sterile Water for Injection and, thereafter, protect it from microbial contamination. Do not use Purified Water in preparations intended for parenteral administration. Where used for sterile dosage forms other than for parenteral administration, process the article to meet the requirements under [Sterility Tests \(71\)](#), or first render the Sterile Purified Water and, thereafter, protect it from microbial contamination. USP also contains references to other types of water, such as distilled water, deionized water, and others according to specific use as summarized in general information chapter [Water for Pharmaceutical Purposes \(1231\)](#).

FUNCTIONAL MECHANISM

A solvent is able to dissolve materials because it is able to disrupt the intermolecular attractive forces and to allow the individual molecules to become dispersed throughout the bulk solvent. Water is a favored solvent and vehicle in the majority of applications because it is easy to handle, safe, and inexpensive.

PHYSICAL PROPERTIES

Water is liquid at normal temperature and pressure. It forms ice at the freezing temperatures of 0° or lower, and it vaporizes at a normal boiling temperature of 100°, depending on atmospheric pressure. Vaporized water in the form of steam is used for sterilization purposes because the latent heat of steam is significantly higher than that of boiling water.

CHEMICAL PROPERTIES

Water in its pure form is neutral in pH and has very low conductivity and total organic carbon (TOC). However, pH, conductivity, and TOC are affected by storage conditions and exposure to gases in the air. Exposure to atmospheric carbon dioxide lowers water's pH. Storage in plastic containers may increase the TOC content of water over time. Water stored in glass containers may result in an increase in pH and conductivity over time.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected pharmaceutical water functions: [Injections and Implanted Drug Products \(1\)](#), [Bacterial Endotoxins Test \(85\)](#), [Total Organic Carbon \(643\)](#), [Water Conductivity \(645\)](#), [Water for Hemodialysis Applications \(1230\)](#), and [Water for Pharmaceutical Purposes \(1231\)](#).

Functional Category: Bulking Agent

DESCRIPTION

Bulking agents used in lyophilized pharmaceuticals, also referred to as freeze-dried products, include various saccharides, sugar alcohols, amino acids, and polymers. The primary function of bulking agents is to provide a pharmaceutically elegant freeze-dried cake with noncollapsible structural integrity that will reconstitute rapidly before administration. In addition, bulking agents are selected to prevent product loss caused by blow-out during freeze drying, to facilitate efficient drying, and to provide a physically and chemically stable formulation matrix. Complementary combinations of bulking agents, e.g., mannitol and a polymer, frequently are used to improve performance.

FUNCTIONAL MECHANISM

A bulking agent that readily crystallizes during lyophilization helps maintain the structural integrity of the cake formed during primary drying, thereby preventing macroscopic collapse and maintaining pharmaceutical elegance. Microscopic collapse of amorphous components in the formulation can still occur (with some potentially undesirable results) but does not result in macroscopic collapse or "meltback" if the bulking agent's properties and concentration are adequate. The bulking agent also should possess a high eutectic melting temperature with ice to permit relatively high primary drying temperatures with commensurate rapid and efficient drying and subsequent rapid reconstitution upon usage. Functional cake-forming excipients, such as mannitol, frequently are used because they crystallize during freezing, thereby allowing efficient drying and the formation of a structurally robust and stable cake. Amino acids and cosolvents also have been used to achieve this effect. Most biopolymer active ingredients remain amorphous upon freeze-drying, and bulking agents such as disaccharides can function as lyoprotectants by helping to maintain a stable amorphous phase during freezing and drying to prevent denaturation. Solubility enhancement of an insoluble crystalline active ingredient sometimes is achieved with the use of a biopolymer that enhances solubility or prevents crystallization during lyophilization or subsequent reconstitution. Bulking agents also are selected on the basis of biocompatibility, buffering capability, and tonicity-modifying properties.

Lyoprotectant properties of bulking agents (i.e., those that protect the drug substance during lyophilization) typically are achieved by the formation of a highly viscous glassy phase that includes the biopolymer drug substance in combination with low molecular weight amorphous saccharides such as sucrose, trehalose, or certain amino acids. A typical approach for protein pharmaceutical formulation is to combine a sugar alcohol that readily crystallizes and an amorphous diluent. This mixture acts as a lyoprotectant.

PHYSICAL PROPERTIES

Bulking agents are dissolved in aqueous solution before lyophilization. Therefore, chemical purity and the absence of bioburden and pyrogenic materials are essential properties of the excipient. However, the physical form and particle properties of the excipient generally are not relevant to the final properties of the lyophilized formulation. The solubilization process and the drying process can be facilitated by the use of volatile cosolvents such as ethanol or tertiary butyl alcohol.

The physical properties that are essential to product performance during and after lyophilization include the glass transition temperature (T_g) of the amorphous frozen concentrate before drying, the glass transition temperature of the final dried formulation cake, and the eutectic melting temperature of the crystalline bulking agent with ice. The glass transition temperature (T_g) of the formulation depends on the glass transition temperatures of the individual components, concentrations, and interactions. Although approximations can be made based on reported transition temperatures for individual components, current practice includes the measurement of formulation glass transition temperatures by thermal analysis or freeze-drying microscopy.

The physical states of the bulking agent during and after lyophilization are important physical properties. Both formulation composition and processing parameters play roles in determining whether the bulking agent is amorphous or takes a specific crystalline form. Rate of freezing, drying temperatures, and

annealing are among the important process parameters used to control the physical state of the formulation and its components. Moisture retention and adsorption after lyophilization also can contribute to formulation instability and poor reconstitution.

CHEMICAL PROPERTIES

Reactivity of the bulking agent with other formulation components, especially the active ingredient, may be critical. Reducing sugars are well known to react with aromatic and aliphatic amines. Glycols may contain trace peroxide levels that can initiate oxidative degradation. The ability of saccharides and polyhydric alcohols to form hydrogen bonds to biopolymers may play a role in their lyoprotection effects.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selecting bulking agent functions: [Injections and Implanted Drug Products \(1\)](#), [Crystallinity \(695\)](#), [Characterization of Crystalline Solids by Microcalorimetry and Solution Calorimetry \(696\)](#), [Thermal Analysis \(891\)](#), [Pharmaceutical Dosage Forms \(1151\)](#), and [Water-Solid Interactions in Pharmaceutical Systems \(1241\)](#).

Functional Category: Tonicity Agent

DESCRIPTION

To avoid crenation or hemolysis of red blood cells and to mitigate pain and discomfort if solutions are injected or introduced into the eyes and nose, solutions should be made isotonic. This requires that the effective osmotic pressure of solutions for injection must be approximately the same as that of blood. When drug products are prepared for administration to membranes, such as eyes or nasal or vaginal tissues, solutions should be made isotonic with respect to these tissues.

FUNCTIONAL MECHANISM

Tonicity is equal to the sum of the concentrations of the solutes that have the capacity to exert an osmotic force across a membrane and thus reflects overall osmolality. Tonicity applies to the impermeant solutes within a solvent—in contrast to osmolarity, which takes into account both permeant and impermeant solutes. For example, urea is a permeant solute, meaning that it can pass through the cell membrane freely and is not factored when determining the tonicity of a solution. In contrast, sodium chloride is impermeant and cannot pass through a membrane without the help of a concentration gradient and, therefore, contributes to a solution's tonicity.

PHYSICAL PROPERTIES

Solutions of sodium chloride, dextrose, and Lactated Ringer's are common examples of pharmaceutical preparations that contain tonicity agents. Not all solutes contribute to the tonicity, which in general depends only on the number of solute particles present in a solution, not the kinds of solute particles. For example, mole for mole, sodium chloride solutions display a higher osmotic pressure than glucose solutions of the same molar concentration. This is because when glucose dissolves, it remains one particle, but when sodium chloride dissolves, it becomes two particles: Na^+ and Cl^- . Several methods are available to calculate tonicity.

CHEMICAL PROPERTIES

Tonicity agents may be present as ionic or nonionic types. Examples of ionic tonicity agents are alkali metal or earth metal halides such as calcium chloride (CaCl_2), potassium bromide (KBr), potassium chloride (KCl), lithium chloride (LiCl), sodium iodide (NaI), sodium bromide (NaBr) or sodium chloride (NaCl), sodium sulfate (Na_2SO_4), or boric acid. Nonionic tonicity agents include glycerol, sorbitol, mannitol, propylene glycol, or dextrose. Sodium or potassium chloride and dextrose commonly are added to adjust tonicity.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected tonicity agent functions: [Injections and Implanted Drug Products \(1\)](#), [Osmolality and Osmolarity \(785\)](#), and [Pharmaceutical Calculations in Pharmacy Practice \(1160\)](#).

AEROSOLS

Functional Category: Propellant

DESCRIPTION

Propellants are compounds that are gaseous under ambient conditions. They are used in pharmaceuticals (nasal sprays and respiratory and topical formulations), cosmetics, and foods to provide force to expel contents from a container.

FUNCTIONAL MECHANISM

Propellant substances are low boiling point liquids or compressed gases that are relatively inert toward active ingredients and excipients. They can be characterized by three properties: whether they form a liquid phase at ambient temperatures and useful pressures, their solubility and/or miscibility in the rest of the formulation, and their flammability. Their performance is judged by their ability to provide adequate and predictable pressure throughout the usage life of the product.

Propellants that have both a liquid and gas phase in the product provide consistent pressures as long as there is a liquid phase present—the pressure in the headspace is maintained by the equilibrium between the two phases. In contrast, the pressure provided by propellants that have no liquid phase may change relatively rapidly as the contents of the container are expelled. As the headspace becomes larger, the pressure within the container falls proportionately. Propellants that have no liquid phase but have significant pressure-dependent solubility in the rest of the formulation have performance characteristics between those of the other two systems. In such cases, as the headspace increases the propellant comes out of solution to help to maintain the pressure of the system.

In metered-dose inhalers, the propellant has a liquid phase that is an integral part of the dispensed pharmaceutical product. Actuating the metering valve dispenses a defined volume of the liquid contents. The propellant spontaneously boils and provides atomizing and propulsive force. A predictable change in active concentration occurs from the beginning to the end of the container life cycle as the liquid phase of the propellant vaporizes to reestablish the equilibrium pressure of the system as the headspace increases.

PHYSICAL PROPERTIES

Propellants have boiling points well below ambient temperatures. A propellant's density for disperse systems and its solubility properties may be significant considerations when one selects a propellant. Apropellants (butane, isobutane, and propane) and dimethyl ether have liquid-phase densities that are less than that of water.

CHEMICAL PROPERTIES

Propellants typically are stable materials. The hydrocarbon propellants (butane, isobutene, and propane) and dimethyl ether are all flammable materials. Apropellants, carbon dioxide, nitrogen, and norflurane are nonflammable. Nitrous oxide is not flammable but supports combustion. Chlorofluorocarbon propellants are considered to be ozone-depleting substances. Their use in foods, drugs, devices, or cosmetics is regulated by 21 CFR 2.125. Albuterol metered-dose inhalers formulated with chlorofluorocarbon propellants have not been available in the United States since January 1, 2009.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected propellant functions: [Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests \(601\)](#), [Chromatography \(621\)](#), and [Water Determination \(921\)](#).

DRY POWDER INHALERS

Dry powder inhalers (DPIs) commonly contain few functional excipients. For example, DPIs may contain a carrier and may use a capsule shell. Other useful excipients include glidants to improve flow during manufacture of the active-carrier mix. A discussion of the use of a lubricant can be found in the tablet or capsule sections above in addition to the carrier properties discussed below.

Functional Category: Carrier

DESCRIPTION

Carriers are used to help deposit the active ingredient in the lung and may have a secondary role in diluting the active to ensure that dosages can be properly metered.

FUNCTIONAL MECHANISM

The carriers are used to promote drug deposition into the lungs for better penetration or absorption in the appropriate lung location. In addition, the carrier is used to decrease the concentration of the active so the latter is adequately dosed in a uniform manner.

PHYSICAL PROPERTIES

The physical properties of carriers include appropriate morphology, hydration state, flowability, surface energy, and particle size distribution.

CHEMICAL PROPERTIES

Carriers must have suitable purity, including low microbial content and no extraneous proteins or impurities, to avoid interactions with the patient's immune system.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected carrier functions: [Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests \(61\)](#), [Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms \(62\)](#), [Elemental Impurities—Limits \(232\)](#) and [Elemental Impurities—Procedures \(233\)](#), [Light Diffraction Measurement of Particle Size \(429\)](#), [Nitrogen Determination \(461\)](#), [Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests \(601\)](#), [Bulk Density and Tapped Density of Powders \(616\)](#), [Crystallinity \(695\)](#), [Characterization of Crystalline Solids by Microcalorimetry and Solution Calorimetry \(696\)](#), [Density of Solids \(699\)](#), [Loss on Drying \(731\)](#), [Optical Microscopy \(776\)](#), [Particle Size Distribution Estimation by Analytical Sieving \(786\)](#), [Powder Fineness \(811\)](#), [Mid-Infrared Spectroscopy \(854\)](#) and [Ultraviolet-Visible Spectroscopy \(857\)](#), [Water Determination \(921\)](#), [Characterization of Crystalline and Partially Crystalline Solids by X-Ray Powder Diffraction \(XRPD\) \(941\)](#), and [Powder Flow \(1174\)](#).

Functional Category: DPI Capsule Shells

DESCRIPTION

Capsule shells sometimes are used in DPIs. The capsule shell is used to contain the dosage amount and safeguard the inhalable powder in a DPI.

FUNCTIONAL MECHANISM

The use of capsule shell may speed pharmaceutical development because it does not require a complex device and can use premeasured drug substance or formulation. A capsule shell must not fragment into inhalable portions and should remain intact after the shell breaks to expose the powder for inhalation.

PHYSICAL PROPERTIES

Capsule shell composition generally is dictated by the drug substance's moisture content, brittleness, and electrostatic interactions with the inhalable powder.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected DPI capsule shell functions: [Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests \(61\)](#), [Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms \(62\)](#), [Arsenic \(211\)](#),

[Elemental Impurities—Limits \(232\)](#), and [Elemental Impurities—Procedures \(233\)](#), [Residue on Ignition \(281\)](#), [Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests \(601\)](#), [Disintegration \(701\)](#), [Dissolution \(711\)](#), [Loss on Drying \(731\)](#), [Optical Microscopy \(776\)](#), [Particle Size Distribution Estimation by Analytical Sieving \(786\)](#), [Uniformity of Dosage Units \(905\)](#), [Water Determination \(921\)](#), [Color—Instrumental Measurement \(1061\)](#), and [Water—Solid Interactions in Pharmaceutical Systems \(1241\)](#).

additional information

In addition to the general chapters listed above, useful information for ensuring consistency in selected capsule shell functions may be found in [Gelatin, Gel Strength \(Bloom Value\)](#).

OPHTHALMIC PREPARATIONS

Functional Category: Antimicrobial Preservatives

DESCRIPTION

The preservative system acts as a safeguard to kill or inhibit the growth of microorganisms that may be inadvertently introduced in the product after the manufacturing process either during storage or use.

FUNCTIONAL MECHANISM

Antimicrobial preservatives work by a number of mechanisms. Quaternary ammonium compounds affect microbial cell membranes via charge interactions with phospholipids, leading to disruption of the cell membrane. Parabens also disrupt cell membrane integrity. Alcohols such as chlorbutanol and benzyl alcohol work via lipid (membrane) solvation and protein denaturation. *N*-[3-(Dimethylamino)propyl]tetradecanamide has greater antimicrobial effectiveness toward fungi and protozoa than do quaternary ammonium compounds. Similar to quaternary ammonium compounds, it disrupts plasma membrane integrity. Sorbic acid works by reduction of the sulfhydryl groups of proteins. Hypochlorite is a strong oxidizing agent. Reactions of chloramines with the amine groups of proteins can cause changes in conformation and thus loss of protein activity. Chlorine released by these reactions can react with cellular constituents, such as proteins and lipid. Polyaminopropyl biguanide accumulates in the cell membrane, blocking the entry of nutrients.

PHYSICAL PROPERTIES

To serve as an ophthalmic antimicrobial preservative, a compound should be at least sparingly soluble in water, thus providing an appreciable range of usable concentrations.

CHEMICAL PROPERTIES

A preservative must be compatible with the active and inactive ingredients of the finished product. For example, quaternary ammonium compounds are incompatible with anionic surfactants. Benzyl alcohol is incompatible with oxidizing agents. Chlorbutanol is incompatible with some nonionic surfactants. Compatibility between compounds varies with the pH of the formula. The preservative should be stable in solution at the formulation pH, usually from 5 to 8. Formulation pH can affect preservative activity by influencing how the preservative partitions between the formulation and microbes and how the preservative interacts with the target sites of the microbial cell. For example, preservatives that must pass through cell membranes before exerting activity should be formulated at a pH at which the preservative is mainly in its un-ionized state.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistent functions of selected antimicrobial preservatives: [Antimicrobial Effectiveness Testing \(51\)](#), [Sterility Tests \(71\)](#), [Bulk Density and Tapped Density of Powders \(616\)](#), [Chromatography \(621\)](#), [Density of Solids \(699\)](#), [Loss on Drying \(731\)](#), [Pharmaceutical Dosage Forms \(1151\)](#), [Powder Flow \(1174\)](#), [Sterility Assurance \(1211\)](#), and [Validation of Microbial Recovery from Pharmacopeial Articles \(1227\)](#).

Functional Category: Polymers for Ophthalmic Use

DESCRIPTION

Polymers are used in ophthalmic preparations to enhance the retention of active ingredients by reducing the amount of product that is lost from the eye when the patient blinks. In addition, polymers also can be components of artificial tears. Most water-soluble polymers commonly used as film-forming agents in ophthalmic preparations can be categorized as follows: 1) cellulose-based substances, 2) biologically produced gums, and 3) synthetically produced substances.

FUNCTIONAL MECHANISM

Film-forming agents for ophthalmic preparations can enhance the retention of active ingredients in the eye by a number of mechanisms. They can be used as simple viscosity-modifying agents to reduce the flow of the product, thereby slowing the rate of product loss after administration. They also can be used to form films on the surface of the eye so the drug remains deposited on the eye after the liquid portion of the product has been expelled or has evaporated. These agents can be formulated to produce a film or a gel when the product warms to body temperature (upon contacting the surface of the eye), mixing with the tear film, and/or evaporating. Some polymers have shown bio-adhesive properties on the cornea and can increase drug retention.

PHYSICAL PROPERTIES

To serve as an ophthalmic film-forming agent, a polymer typically must be at least slightly soluble in water, thus providing an appreciable range of usable concentrations. Such polymers often increase viscosity or exhibit film- or gel-forming properties when warmed to body temperature, when exposed to the pH or solute composition and ionic strength of the tear film, or when the product evaporates.

CHEMICAL PROPERTIES

The finished product viscosity range that can be obtained with a film-forming agent is related to its chemical structure and molecular weight. Functional groups such as the pyruvate and acetate groups of xanthan gum can affect the relationship between viscosity and solution pH and ionic strength and also can determine film- and gel-forming properties. Polymer charge can influence interactions with the mucous layer of the eye. Molecular conformation, chain mobility, and degree of cross-linking also can affect the degree of swelling and thus performance.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistent functions of polymers for ophthalmic use: [Bulk Density and Tapped Density of Powders \(616\)](#), [Chromatography \(621\)](#), [Density of Solids \(699\)](#), [Loss on Drying \(731\)](#), [Particulate Matter in Ophthalmic Solutions \(789\)](#), [Viscosity—Capillary Methods \(911\)](#), [Viscosity—Rotational Methods \(912\)](#), [Viscosity—Rolling Ball Method \(913\)](#), [Pharmaceutical Dosage Forms \(1151\)](#), and [Powder Flow \(1174\)](#). In addition, the general chapters listed under *Functional Category: Film-Forming Agents* also may be appropriate for the evaluation of polymers for ophthalmic use.

TRANSDERMALS AND PATCHES

Functional Category: Adhesive

DESCRIPTION

Topical drug delivery systems (e.g., transdermals or skin patches) require the use of adhesives to maintain contact between the applied drug delivery system and the skin. Adhesives can be intercalated as a separate layer between the formulation matrix and the skin surface, incorporated as a part of the formulation matrix itself, or applied to the periphery of the topical delivery system.

FUNCTIONAL MECHANISM

Adhesion is the tendency of dissimilar surfaces to adhere to one another as a result of one or more types of interactions. For topical drug delivery systems, these adhesive interactions generally are chemical (primarily electrostatic) or dispersive (van der Waals and/or hydrogen bonding) in nature, although there is the possibility of mechanical interaction via the interlocking of microscopic asperities.

PHYSICAL PROPERTIES

In general, the adhesives used in transdermals or skin patches are pressure-sensitive materials whose performance is best characterized by physical test methods for tackiness and viscoelasticity of the adhesive per se and viscosity of a solution of the adhesive.

CHEMICAL PROPERTIES

In transdermals, the most widely used pressure-sensitive adhesives are acrylic, rubber, and silicone polymers. Acrylic polymer adhesives include various esters of acrylic or methacrylic acid, acrylamide, methacrylamide, *N*-alkoxyalkyl, or *N*-alkyl acrylamides. Polyisobutylenes and polysiloxanes are among the most common rubber-based and silicone-based adhesives, respectively. The molecular weight and compositional distribution of the polymers are critical to the replication of the adhesive's efficacy from batch to batch.

GENERAL CHAPTERS

The following general chapters may be useful in evaluating the suitability of adhesives used in transdermals: [Tensile Strength \(881\)](#) and [Viscosity—Capillary Methods \(911\)](#).

Functional Category: Film-Forming Agent

DESCRIPTION

Film-forming agents used as the formulation matrix of topical drug delivery systems (e.g., transdermals or skin patches) or in conjunction with such systems comprise a flexible, nontacky but adherent film, in whole or in part, applied to the skin surface.

FUNCTIONAL MECHANISM

Film formation results from the progressive loss of solvent (or dispersion medium) from a solution (or dispersion) of a film-forming agent, whether in particulate or molecularly dispersed form. Solvent (or dispersion medium) loss leads to closer molecular or particulate packing and increased interaction among the film-forming agent molecules or particles. Ultimately, a continuous film is formed as a result of increased molecular entanglement or particulate sintering.

PHYSICAL PROPERTIES

Properties critical to successful film formation include the film-forming agent's glass transition temperature (T_g), the viscosity of the solution or dispersion, and the surface characteristics of the substrate. Viscoelastic properties such as elastic modulus, viscous modulus, and intrinsic or complex viscosity describe functional characteristics, such as adhesion, for a pressure-sensitive adhesive component. Adhesion to a substrate and tack and shear tests can be used for batch release.

CHEMICAL PROPERTIES

Typical film-forming agents are thermoplastic or thermosetting high molecular weight polymers or copolymers, often in the form of aqueous dispersions or latex compositions. Cellulosic polymers, vinyl polymers and copolymers, and acrylic and methacrylic acid polymers and copolymers frequently are used in topical delivery systems as film-forming agents.

GENERAL CHAPTERS

The following general chapters may be useful in evaluating the suitability of film-forming agents used in transdermals and patches: [Thermal Analysis \(891\)](#), [Viscosity—Capillary Methods \(911\)](#), [Viscosity—Rotational Methods \(912\)](#), and [Viscosity—Rolling Ball Method \(913\)](#).

RADIOPHARMACEUTICALS

Radiopharmaceuticals commonly contain categories of excipients that also are used in conventional drugs. For example, radiopharmaceutical capsules may contain diluents and necessarily use a capsule shell, and parenteral radiopharmaceuticals may contain pharmaceutical water, diluents, tonicity agents, pH modifiers, antimicrobial preservatives, chelating and/or complexing agents, and antioxidants. Many

radiopharmaceuticals differ from conventional drugs, however, because their preparation (reconstitution) involves one or more chemical reactions that require unusual excipients. Furthermore, the self-absorption of emitted radiation may result in the radiolytic decomposition of many radiopharmaceuticals. Hence, several excipients are used predominately in radiopharmaceutical formulations, although they occasionally may be used for other drugs.

Functional Category: Reducing Agent

DESCRIPTION

Reducing agents generally are required for technetium Tc-99m radiopharmaceuticals. Technetium Tc-99m, in the chemical form of sodium pertechnetate (+7 oxidation state), must be reduced to a lower oxidation state so that it can be chelated or otherwise complexed by the intended ligand to form the final Tc-99m radiopharmaceutical. The reducing agent, typically a stannous salt, generally is formulated in the kit for the preparation of the technetium Tc-99m radiopharmaceutical.

FUNCTIONAL MECHANISM

The reducing agent (e.g., stannous ion) must be present in sufficient quantity to reduce all of the technetium atoms to the intended oxidation state but must not produce undesired reduction products or other impurities (e.g., stannous hydroxide precipitates).

PHYSICAL PROPERTIES

Reducing agents (e.g., stannous salts) must be readily soluble in water.

CHEMICAL PROPERTIES

Reducing agents (e.g., stannous salts) are sensitive to oxidation by atmospheric oxygen and oxidizing species in solution. Hence, lyophilized contents of kit vials must be filled with a nonoxidative gas such as nitrogen or argon. The reducing agent also must be stable at the intended pH of the formulated product.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected reducing agent functions: [Chromatography \(621\)](#) and [Radioactivity \(821\)](#).

Functional Category: Transfer Ligand

DESCRIPTION

In the preparation of certain radiopharmaceuticals, the radiometal (e.g., stannous-reduced technetium Tc-99m) is first chelated by a relatively weak chelating ligand and then is transferred to the principal chelating ligand or complexing moiety. Examples of such transfer ligands include citrate, gluconate, and tartrate.

FUNCTIONAL MECHANISM

Transfer ligands typically undergo rapid reactions with reduced technetium to form weak chelates, thus keeping the reduced technetium in a soluble form until it is transferred to the principal ligand. This procedure is especially useful when the kinetics of complexation with the principal ligand is slow or when a heating step is necessary to expose chelating groups on the principal ligand.

PHYSICAL PROPERTIES

Transfer ligands must be readily soluble in water.

CHEMICAL PROPERTIES

Transfer ligands must have rapid complexation kinetics and must form relatively weak chelates compared to complexation with the principal ligand.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected transfer ligand functions: [Chromatography \(621\)](#) and [Radioactivity \(821\)](#).

Functional Category: Colloid Stabilizing Agent

DESCRIPTION

Lyophobic colloids tend to clump together and form large aggregates to minimize their surface-area-to-volume ratio. Colloid stabilizing agents are relatively large lyophilic molecules that coat the surface of each individual colloid particle and prevent or inhibit clumping. Examples of colloid stabilizing agents include gelatin and dextran.

FUNCTIONAL MECHANISM

The colloid stabilizing agent coats the surface of the lyophobic colloid particles, making them appear lyophilic. Additionally, the colloid stabilizing agent may be charged, thus causing the coated colloid particles to repel one another.

PHYSICAL PROPERTIES

Colloid stabilizing agents must be readily soluble in water.

CHEMICAL PROPERTIES

Colloid stabilizing agents must be capable of coating the lyophobic colloid particles, e.g., by electrostatic attraction of an opposite charge.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected colloid stabilizing agent functions: [Chromatography \(621\)](#) and [Radioactivity \(821\)](#).

Functional Category: Free Radical Scavenger

DESCRIPTION

Radiation interactions with water and other molecules frequently produce free radicals. Free radical scavengers preferentially interact with oxidative or reductive free radicals that otherwise would result in degradation of formulation components. In the case of radiopharmaceuticals, free radical scavengers can be used to enhance radiochemical purity. Examples of free radical scavengers include methylene blue and aminobenzoic acid.

FUNCTIONAL MECHANISM

Free radical scavengers preferentially interact with radiolytically produced free radicals before these free radicals can interact with the radiopharmaceutical and produce radiochemical impurities.

PHYSICAL PROPERTIES

Free radical scavengers must be readily soluble in water.

CHEMICAL PROPERTIES

Free radical scavengers must be capable of preferentially interacting with free radicals without causing other effects.

▲INTRODUCTION

The purpose of this chapter is to explain how excipients may be used in formulations and how they relate to compendial specifications, performance-related properties (PRPs), critical material attributes (CMAs), and quality by design (QbD) principles that aid in their selection and control. Excipients are used in virtually all drug products and are essential for drug product manufacturing and performance. To ensure robust drug products with consistent quality, the excipients must be well characterized, qualified, and appropriately specified. Excipients used in drug products typically are manufactured and supplied in compliance with compendial standards. However, the effects of excipient properties on the quality and performance of a drug product may be unique for each formulation and process, and could depend on properties of excipients that are not evaluated in *USP* or *NF* monographs, and which may vary from supplier to supplier and batch to batch (see [General Notices, 4.10 Monographs](#)). The impact of excipient properties and their variability depends on the role of an excipient in a formulation and the critical quality attributes (CQAs) of the drug product.

An excipient may be used in different ways or for different purposes in a formulation and may therefore require different material properties to achieve the desired performance. Excipient functional categories are broad, qualitative, and descriptive terms for the purpose an excipient serves in a formulation. There may be specific limitations related to dosage forms and patient populations (pediatric, geriatric, etc.). A list of excipients grouped by functional category is included in [*USP and NF Excipients, Listed by Functional Category*](#).

Minimum quality requirements for an excipient are specified in an excipient monograph. Additional performance-related properties (PRPs) described in this chapter may also be identified as critical material attributes (CMAs).

A PRP is a physical, chemical, biological, or microbiological property of an excipient anticipated to potentially impact finished product quality and performance, dependent on the application. For example, excipient particle size distribution would be a PRP for oral solid dose forms as this property can impact flow, compactability, and active pharmaceutical ingredient (API) content uniformity. In contrast, if the excipient is dissolved in a liquid dosage form, the particle size distribution may not be a PRP. PRPs are typically assessed during development and when critical to product quality, acceptance criteria should be established. Those properties determined to be CMAs may be adequately controlled through excipient supplier specifications and by grade selection in consultation with the excipient suppliers. PRPs are often the properties that differentiate multiple grades of an excipient.

A CMA is a product-specific physical, chemical, biological, or microbiological property of an excipient intended to control finished product quality and performance. CMAs are properties not necessarily specified by either the supplier or the excipient monograph. Good product development practices, which at times are termed QbD principles, require understanding of how excipient properties contribute to consistent finished drug product performance and are the foundation of a control strategy.

CMAs must be within appropriate limits or used to control the process and/or composition to ensure that the CQAs are consistently met for a particular drug product and maintained throughout the product life cycle. CMAs may be identified during development, scale-up, and life cycle management and require a thorough understanding of drug product CQAs; the manufacturing process(es); the formula; the physical, chemical, biological, or microbiological properties of the excipient; and the interaction between them. Prior knowledge, experiments, and risk assessment tools can also be used to identify potential CMAs. Drug product manufacturers should anticipate batch-to-batch and supplier-to-supplier variability in excipient properties. CMAs should be agreed upon with suppliers to ensure the limits are within the excipient process capability and to ensure alignment on methods for characterization. CMAs are not always related to the major component. The presence of minor components (e.g., peroxides, elemental impurities, or microbiological content) may affect finished product manufacturability, stability, or quality.

Excipient specifications should be based on the monograph requirements and the identified CMAs. In cases where there are no functionality related concerns, tests without acceptance criteria in the monograph may be monitored without imposing limits. In such cases, the drug product manufacturer may employ additional methods to monitor supplier consistency, compare multiple suppliers, and provide further application-specific insight but need not impose their own limits especially if multiple methods are employed across the supplier base.

Functional categories can apply to multiple dosage forms. Each functional category includes a general description; physical properties common to these excipients; chemical properties; the mechanisms by which excipients achieve their function; dosage forms; performance-related properties; and a list of *USP* chapters that can be useful in conducting specific tests and procedures, and in establishing acceptance criteria to ensure that material properties are adequately monitored and controlled. Because of the complex nature and interplay of formulation ingredients, processing, and dosage form performance requirements, the information provided in this chapter should not be viewed as restrictive or comprehensive.

ACIDIFYING OR ALKALIZING AGENT

Description

Acidifying and alkalizing agents may be liquid or solid. They are used to adjust the pH of pharmaceutical drug products to a desired value or range. Acidifying agents lower the pH and alkalizing agents increase the pH. Examples of acidifying agents include hydrochloric acid, phosphoric acid, acetic acid, and citric acid. Examples of alkalizing agents include ammonia solution, sodium hydroxide, potassium hydroxide, and sodium bicarbonate. Measurement of pH is described in [pH \(791\)](#). A related functional category is *Buffering Agent*.

Physical Properties

Particle size may be important if it affects dissolution during the preparation, manufacture, or finished product performance.

Chemical Properties

Acidifying and alkalizing agents influence the pH of the drug product but may not have adequate buffer capacity (See *Buffering Agent*). Acidifying and alkalizing agents used in physiological systems should not interfere with the pharmacological activity of the active ingredient. Multifunctional acidifying or alkalizing agents may have multiple ionization equilibria (pK_a), which influence pH titration.

Functional Mechanism

The pK_a of acidifying and alkalizing agents in aqueous media are key to pH modification. Their strength is a function of the pK_a . Strong acids have a lower pK_a and strong alkali have a higher pK_a . The properties of acidifying and alkalizing agents may vary significantly with temperature.

Dosage Forms

Acidifying and alkalizing agents are typically added to or dissolved in liquid dosage forms, including solutions, injections, irrigations, shampoos, soaps, suspensions, sprays, and liquids to adjust solution pH. These agents may also be incorporated into solid or semisolid dosage forms in the undissolved state for the same purpose upon exposure to aqueous media.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include particle size and solubility. Particle size may be important where dissolution of an acidifying and alkalizing agent may be critical to assuring consistent properties and performance. The presence of insoluble particulates may present problems in the preparation of sterile products. Particle size may influence content uniformity and powder flow properties when incorporated as a solid form.

General Chapters

The following general chapters may be useful in ensuring consistency in selected acidifying functions: [\(791\)](#), [Elemental Impurities \(232\)](#), [Particle Size Distribution by Analytical Sieving \(786\)](#), and [Light Diffraction Measurement of Particle Size \(429\)](#).

ADHESIVE (PRESSURE SENSITIVE)

Description

Pressure sensitive adhesives are excipients designed to maintain contact between the applied drug delivery system and biological membranes. Some adhesives may be available as solutions in organic solvents or water. In these instances, the properties and tests described below refer to the dry adhesive after any cross-linking and removal of the solvent and/or water. Adhesives can be intercalated as a separate layer between the formulation matrix and the skin surface (adhesive used in reservoir patches), incorporated as a part of the formulation matrix itself (adhesive used in matrix patches), or applied to the periphery of the topical delivery system (rim adhesive). Adhesives in systems must permit easy removal of the release liner before use, adhere properly to human skin upon application, maintain adhesion to the skin during the prescribed period of use, and permit easy removal of the dosage form at the end of use without

leaving a residue or causing damage to the skin or other undesirable effect(s). Additionally, adhesives must be able to maintain the performance of the dosage form throughout the shelf life of the drug product. A related functional category is *Muco-Adhesive*.

Physical Properties

In general, pressure sensitive adhesives are viscoelastic materials that can adhere to various surfaces such as skin upon application of light contact pressure and leave no residue upon removal.

Chemical Properties

The most commonly used pressure sensitive adhesives are composed of acrylic, rubber, or silicone polymers. Acrylic polymer adhesives include various esters of acrylic or methacrylic acid, acrylamide, methacrylamide, *N*-alkoxyalkyl, or *N*-alkyl-acrylamides. Polyisobutylenes and polysiloxanes are among the most common rubber- and silicone-based adhesives, respectively.

Functional Mechanism

Adhesion is the tendency of dissimilar surfaces to adhere to one another as a result of one or more types of interactions.

For topical drug delivery systems, adhesive interactions generally are chemical (primarily electrostatic) or dispersive (van der Waals and/or hydrogen bonding) in nature, although there is the possibility of mechanical interaction via the interlocking of microscopic asperities.

Dosage Forms

Pressure sensitive adhesives are typically used in transdermal systems to maintain contact between the applied drug delivery system and the skin. They are also used in adhesive dressings and bandages.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include peel adhesion, release liner peel, tack (quick stick), cold flow, and shear (cohesive strength). The peel adhesion, release liner peel, and tack tests measure the adhesion properties of the dosage form. Each of these tests measures the force required to separate the dosage form from another surface. The cold flow and shear tests measure the cohesive properties of the dosage form. These latter tests measure the resistance to flow of the adhesive matrix.

However, direct peel adhesion, tack, and shear measurements may not be true material properties of the adhesive because they depend on substrate, backing material, and test parameters; therefore, measures of adhesive viscoelastic properties should be considered.

In addition, viscosity of an adhesive solution (if available as a solvent solution) can often be used as a critical material attribute in the processing of the dosage form.

Other potential performance-related properties may include adhesive molecular weight, molecular weight distribution, and cross-link density.

General Chapters

The following general chapters may be useful in evaluating the suitability of adhesives used in transdermals: [Topical and Transdermal Drug Products—Product Quality Tests \(3\)](#), [Tensile Strength \(881\)](#), [Viscosity—Capillary Methods \(911\)](#), and [Viscosity—Rotational Methods \(912\)](#).

Additional Information

The following references are provided for additional information on this topic.

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AIR DISPLACEMENT

Description

Air displacement excipients are inert gases (e.g., nitrogen and argon) used to replace atmospheric air in dosage forms that are liable to interact with gases commonly present in such an environment.

Physical Properties

Air displacement excipients are gaseous, colorless, odorless, and tasteless materials. Their physical properties depend on their chemical structures. Moisture content of the air displacement agents should be considered.

Chemical Properties

Air displacement excipients are inert substances.

Functional Mechanism

Oxygen present in atmospheric air may react with materials that are highly prone or sensitive to oxidation. Air displacement excipients will simply replace atmospheric air in the contents of containers or the container headspace. These oxidation sensitive materials may be drug substances or excipients that may directly or indirectly oxidize and lead to further degradation of the drug substance or excipient. For instance, polysorbates may oxidize upon relatively long exposures to atmospheric air and generate reactive oxygen species, which, in turn, may destabilize drug substances or excipients. For this reason, nitrogen is commonly used to displace atmospheric air in the headspace of packages of polysorbates intended to be used as excipients. In other cases, air displacement may be required to protect the dosage form itself.

Dosage Forms

Oxidation-sensitive materials in solid state are usually less reactive. Therefore, air displacement excipients are more likely to be used in solution dosage forms, including injections and solutions. Because certain packaging materials may be permeable to gases (i.e. certain rubber types), appropriate selection of

packaging material and packaging processes are necessary to ensure drug product stability during shelf life. Minimizing container headspace may also further support the control strategy for the drug product.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include attributes related to impurities (i.e. presence of other gases and/or water). In particular, presence of water may lead to degradation (i.e. hydrolysis) of moisture sensitive drug substances.

General Chapters

The following general chapters may be useful in ensuring consistency in selected air displacement functions: [Impurities Testing in Medical Gases \(413\)](#), [Medical Gases Assay \(415\)](#), [Elastomeric Closures for Injections \(381\)](#), [Packaging and Storage Requirements \(659\)](#), [Package Integrity Evaluation—Sterile Products \(1207\)](#), [Package Integrity Testing in the Product Life Cycle—Test Method Selection and Validation \(1207.1\)](#), [Package Integrity Leak Test Technologies \(1207.2\)](#), and [Package Seal Quality Test Technologies \(1207.3\)](#).

ALCOHOL DENATURANT

Description

Alcohol denaturants are typically very bitter substances that are added to alcohol (e.g., ethanol, methanol, and isopropyl alcohol) or other personal care products such as nail polish remover to deter accidental or intentional consumption. The legally permitted alcohol denaturants may vary from country to country. In some countries, but not the United States, denatured alcohol may be required to be colored (e.g., aniline dye).

Physical Properties

Alcohol denaturants are sufficiently soluble in both alcohol and water to provide a bitter taste when ingested. They may be solids or liquids.

Chemical Properties

Alcohol denaturants are a very diverse group of chemical substances. Examples of alcohol denaturants include denatonium benzoate, methyl isobutyl ketone, and sucrose octaacetate. Additional denaturants also may also include ethyl acetate, brucine, denatonium saccharide, and quassin (the bitter component from quassia tincture). The addition of pyridine or methanol makes alcohol poisonous.

Functional Mechanism

Alcohol denaturants interact with the "bitter" taste buds in the mouth to produce a very unpleasant taste. Denaturants are typically incorporated at low concentrations.

Dosage Forms

Denatured alcohol may be useful in topical dosage forms such as creams, lotions, rinses, shampoos, solutions for topical use, sprays for topical use, ointments, or cosmetics depending upon its application, but such products would not be suitable for ingestion or injection. Sucrose octaacetate is also used in preparations to prevent nail biting.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include producing a very bitter taste at a sufficiently low concentration.

General Chapters

None

Additional Information

Refer to 27 CFR §21 for additional details regarding denaturants.

ANTIFOAMING OR DEFOAMING AGENT

Description

Additives that prevent or eliminate liquid foams. Defoaming implies breaking, rapid knockdown, and control of preexisting foam. Antifoaming or foam inhibition indicates preventing the foam from forming in the first place. Applications may require both the prevention and control of foam. The same types of materials are often used for both antifoaming and defoaming.

Physical Properties

In general, ideal antifoaming agents are insoluble in the foaming medium and have as low a surface and interfacial tension as possible in order to promote spreading of the foam films or foam-stabilizing properties. Typically, they have low viscosity, surface active properties, and spread rapidly on foamy surfaces. Antifoaming agents have an affinity to the air-liquid surface where they destabilize foam lamella.

Chemical Properties

Commonly used antifoaming agents include: silicone derivatives (e.g., poly(dimethylsiloxane), simethicone, and simethicone emulsions) and saturated fatty acids (e.g., lauric acid and myristic acid).

Functional Mechanism

Antifoaming agents function at the air-liquid surface to destabilize foam lamellas, rupture bubbles, break down surface foam, and/or compete at surface with foam-generating moieties.

Dosage Forms

Antifoaming agents are typically added at low levels to liquid formulations, including solutions, liquids and suspensions to prevent or eliminate foaming. As most antifoaming agents are insoluble oils or silicone derivatives, the miscibility of the additive can be improved by emulsification or addition of surfactant. In addition, they are used for foam suppression during bottle-filling operations where foaming is a problem. Antifoaming agents also have a clinical use (atypical active) in certain antacid preparations.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include viscosity, molecular weight, specific gravity, melting temperature, acid value, water content, and iodine and peroxide values.

General Chapters

The following general chapters may be useful in ensuring consistency in performance of antifoaming agents: [Fats and Fixed Oils \(401\)](#), [Procedures, Acid Value, Fats and Fixed Oils \(401\)](#), [Procedures, Iodine Value, Fats and Fixed Oils \(401\)](#), [Procedures, Peroxide Value, Congealing Temperature \(651\)](#), [Refractive Index \(831\)](#), [Specific Gravity \(841\)](#), [\(911\)](#), [\(912\)](#), and [Water Determination \(921\)](#).

ANTIMICROBIAL PRESERVATIVE

Description

Antimicrobial preservatives are used to kill or prevent growth of bacteria, yeast, and mold in the dosage form. They can show limited protection against viral contamination. Use of preservatives to counter microorganisms that may be inadvertently introduced during manufacture does not reduce the need to minimize bioburden in accordance with current good manufacturing practice regulations. Preservatives are also mandatory for multidose liquid products with potential for in-use contamination.

Physical Properties

Antimicrobials generally must be present in the aqueous phase at an effective concentration. Understanding an excipient's partition coefficient is important because partitioning and/or adsorption of a preservative into an oil phase, processing equipment, or packaging can diminish the preservative's effective concentration in the aqueous phase, which, in turn, can reduce its value as a preservative. Volatile preservatives such as alcohols may not be suitable for lyophilization or spray drying processes, for which solid antimicrobials should be added.

Chemical Properties

A preservative must be compatible with the active and inactive ingredients of the finished product. For example, benzyl alcohol is incompatible with oxidizing agents. Chlorobutanol is incompatible with some nonionic surfactants. Others may interact with peptides and proteins. Compatibility among compounds may vary with the pH of the formula. The preservative should be stable in solution at the pH of the formulation. Individual preservative efficacies may be pH-dependent.

Functional Mechanism

Preservatives work by a variety of mechanisms. Most work at the cell wall or cytoplasmic membrane, causing membrane damage and cell leakage. Other modes of action include transport inhibition, protein precipitation, and proton-conducting uncoupling. Some preservatives are bactericidal (kill bacteria or yeast and mold); some are bacteriostatic (inhibit growth of microorganisms); and others are sporicidal (kill spores). Several of the preservatives can act synergistically (e.g., combinations of parabens). Quaternary ammonium compounds affect microbial cell membranes via charge interactions with phospholipids, leading to disruption of the cell membrane. Parabens also disrupt cell membrane integrity. Alcohols such as chlorobutanol and benzyl alcohol work via lipid (membrane) solvation and protein denaturation. Sorbic acid works by reduction of the sulfhydryl groups of proteins. Although not preservatives per se, sugars such as sucrose or sorbitol at high concentrations may inhibit growth due to high osmotic pressure. When using high concentrations of sucrose as a preservative, the increased risk of dental caries should be considered.

Dosage Forms

Preservatives may be used in aqueous liquid dosage forms, including solutions, liquids, irrigations, shampoos, soaps, suspensions, sprays, and multiuse injections. Other dosage forms in which antimicrobial preservatives are often included are creams, lotions, and solid formulations intended for reconstitution as liquids. Choice of preservatives may be dictated by the route of administration, and there may be specific requirements such as a potential for ocular irritancy.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include aqueous solubility, partitioning, organoleptic properties, and particle size where speed of dissolution is critical in a powder or tablet presentation for reconstitution.

General Chapters

The following general chapters may be useful in ensuring consistent functions of selected antimicrobial preservatives: [Antimicrobial Effectiveness Testing \(51\)](#), [Sterility Tests \(71\)](#), [Bulk Density and Tapped Density of Powders \(616\)](#), [Chromatography \(621\)](#), [Density of Solids \(699\)](#), [Loss on Drying \(731\)](#), [Pharmaceutical Dosage Forms \(1151\)](#), [Powder Flow \(1174\)](#), [Sterility Assurance \(1211\)](#), and [Validation of Microbial Recovery from Pharmacopeial Articles \(1227\)](#).

ANTIOXIDANT

Description

Antioxidants are used to mitigate oxidative processes and to stabilize drug product formulations. Antioxidants such as butylated hydroxyanisole, butylated hydroxytoluene, ascorbic acid, methionine, and tryptophan delay the onset of and/or significantly reduce the rate of complex oxidative reactions that could otherwise have a detrimental effect on the drug substance. Antioxidants also can be considered for protecting the sensitive components of a formulation such as unsaturated oils, pegylated lipids, flavors, and essential oils. Thus, antioxidants preserve the overall integrity of the dosage form against oxidative stress.

Physical Properties

Solubility of the antioxidant should be greatest in the formulation phase (oily, aqueous, or emulsion interface), where the drug substance or sensitive formulation components are most soluble. The

temperature at which the antioxidant decomposes is critical for autoclaved preparations, where loss of antioxidant activity may occur. Stability of the antioxidant also must be considered and may be a function of pH and processing conditions. Metal ions may react with propyl gallate to form colored complexes. At alkaline pH, certain proteins and sodium salts may bring about discoloration of *tert*-butylhydroquinone.

Chemical Properties

Activation energy, oxidation–reduction potential, and stability at different formulation (e.g., pH) and processing (e.g., heat) conditions are important chemical properties. If the dosage form's expected shelf life depends on the function of the antioxidant, the concentration must be considered and periodically assessed to ensure that a sufficient amount of antioxidant remains throughout the product shelf life.

Functional Mechanism

Autoxidation is initiated when oxygen reacts with a substrate to form highly reactive species known as free radicals ($RH \rightarrow R \cdot$). After "initiation" the free radicals in the presence of oxygen can trigger chain reactions ($R \cdot + O_2 \rightarrow ROO \cdot$ and $ROO \cdot + RH \rightarrow R \cdot + ROOH$) to form peroxy radicals, hydroperoxides, and new alkyl radicals that can initiate and then propagate their own chain reactions. The cascading reactions during the propagation phase can be accelerated by heat, light, and metal catalysts. In the presence of trace amounts of metal catalysts (Cu^+ , Cu^{2+} , Fe^{2+} , and Fe^{3+}), hydroperoxides (ROOH) readily decompose to $RO \cdot$ and $ROO \cdot$ and subsequently can trigger reactions with the API and/or the excipients (e.g., hydrocarbons) to form hydroxyl acids, keto acids, and aldehydes that can have further undesirable effects. Antioxidants can be grouped by their mode of action. Phenolic antioxidants that block free radical chain reactions also are known as true or primary antioxidants. This group consists of monohydroxy or polyhydroxy phenolic compounds with ring substitutions. They have very low activation energy to donate hydrogen atom(s) in exchange for the radical electrons that are rapidly delocalized by free radicals. By accepting the radical electrons, they stabilize free radicals. The reaction yields antioxidant free radicals that also can react with lipid free radicals to form other stable compounds. Thus, they can block oxidative chain reactions both in the initiation and propagation stages. Because of their solubility behavior, phenolic antioxidants are most effective in protecting oils and oil-soluble actives against oxidative stress. Reducing agents generally are water-soluble antioxidants (e.g., L-ascorbic acid) with lower redox potential than the drug or the excipient they are protecting and delay the onset and rate of oxidative reactions by sacrificially reacting with oxygen and other reactive species. The oxygen-scavenging potential of the reducing agents may be sensitive to pH and also can be negatively affected in the presence of trace elements. Chelating agents bind with free metals (Cu^+ , Cu^{2+} , Fe^{2+} , and Fe^{3+}) that may be present in trace amounts in the formulation. The newly formed complex ions are nonreactive. Chelating agents therefore remove the capacity of the metal catalysts to participate in oxidative reactions that occur during the propagation stage.

The utility of antioxidants can be maximized by synergistic use of one or two primary antioxidants along with reducing and chelating agents. The combined effect often is greater than the sum of the individual effects of each antioxidant (synergistic effect).

Dosage Forms

Antioxidants have been used in a wide range of medicinal products for various administration routes including oral, topical, and injectable. Typical dosage forms containing antioxidants are injections, creams, lotions, foams, and liquids. They can also be used in tablets and in other solid dosage forms.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include purity, aeration, heat, and moisture content. These vary with the type of antioxidant, its physico-chemical nature, the effect it exerts on the active, excipient(s), formulation as a whole, and/or the drug container. The CQA-impacting antioxidant activities are purity and mode of action, which determine how, where, and when the antioxidant may be added in the manufacturing process to ensure content uniformity in the formulation. Process

conditions such as aeration, heat, and moisture that stand to exhaust antioxidant efficacy must be identified and measured for impact on the final outcome, in part for stability. Further stability testing to ensure that a sufficient amount of antioxidant remains to protect the medicinal product throughout its entire shelf life and during the proposed in-use conditions should be undertaken.

General Chapters

The following general chapters may be useful for assessing selected excipient antioxidant functions: [Iron \(241\)](#), [\(621\)](#), [Crystallinity \(695\)](#), [Melting Range or Temperature \(741\)](#), [Specific Surface Area \(846\)](#), and [\(921\)](#).

Additional Information

Unless necessary and justified, the inclusion of antioxidants in medicinal products, notably in pediatrics, is to be avoided. When justified, antioxidants should be used at the lowest feasible concentration levels, sufficient for exerting the intended function. Taking into consideration the safety and allowable intake limits, the usage levels should be carefully considered and justifiable. Antioxidants are most effective when incorporated in the formula to prevent or delay the onset of chain reactions and to inhibit free radicals and hydroperoxides from engaging in the cascading processes described above. Effective application of antioxidants and evaluation of their efficacy necessitate an understanding of oxidative mechanisms and the nature of the byproducts they generate. Note that hydroperoxides are not solely the reaction products of oxidative mechanisms within a formulation. Residual amounts of hydroperoxides also can be found in commonly used excipients such as polyethylene glycols, polyvinylpyrrolidone, and polysorbates. The initiation phase generally is slow and has a limited effect on the quality of the finished product. The propagation phase, in contrast, involves rapid, irreversible degradation of chemical species.

ANTITACK AGENT

Description

Antitack agents are used to reduce surface tackiness and the incidence of tablets sticking together during coating and consequently improve process efficiency, coating uniformity, and appearance, particularly for coatings such as enteric coatings, which often have a low glass transition temperature (T_g). These materials can be incorporated into the coating dispersion or loaded directly into the coating pan during or following the coating process. A related functional category: *Glidant and/or Anticaking Agent*.

Physical Properties

Primary physical properties of potential importance for antitack agents are particle size distribution, particle morphology, and surface area. For waxes, glass transition temperature is important.

Chemical Properties

The chemical nature of antitack agents is varied. Examples include talc, glyceryl monostearate, mono- and diglycerides, carnuba wax, beeswax, and polyvinyl alcohol. Agents such as talc are finely divided inorganic materials and are insoluble in water.

Functional Mechanism

Agents such as talc and waxes function primarily by adsorption onto the surface of tablets and reduction of tackiness. Alternatively, waxes and surfactants may be incorporated into the coating dispersion to increase the slip factor, thereby reducing tablet adhesion during coating and downstream processing.

Dosage Forms

Antitack agents are used mainly in coated tablets, capsules, and multiparticulate beads and granules.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include primarily particle size distribution, particle morphology, surface area, and T_g of the antitacking agent.

General Chapters

The following general chapters may be useful in ensuring consistency in antitack agent functions: [\(429\)](#), [Particle Size Distribution Estimation by Analytical Sieving \(786\)](#), [\(846\)](#), [Thermal Analysis \(891\)](#), [\(921\)](#), and [Scanning Electron Microscopy \(1181\)](#).

BIODEGRADABLE POLYMER

Description

Biodegradable polymers are used to control and sustain drug release from injected particles (generally described as microspheres or microcapsules) or implants. They are used as carriers for small molecules, peptides, and proteins. Commonly used biodegradable polymers include synthetic polymers such as poly(D,L-lactide-co-glycolide) (PLGA), poly(D,L-lactic acid) (PLA), derivatives of PLGA, and polyanhydride. Natural polymers such as collagen, gelatin, alginate, cyclodextrins, chitosan, dextran, agarose, and hyaluronic acid may be used in the formulation of sustained release products.

Physical Properties

The physical properties of biodegradable polymers depend mainly on the nature of monomers, type of linkage, and molecular weight of the polymer. The polymer molecular weight is an important physical property. The other important physical properties include crystallinity, T_g , melting point, and solubility. PLGA particles and implants are generally amorphous. The morphology (amorphous or crystalline) affects the rate of degradation and the mechanical properties of PLGA particles or implants. PLA and PLGA polymers containing less than 50% glycolic acid units are soluble in common organic solvents, whereas PLGA polymers containing more than 50% glycolic acid units are insoluble in common organic solvent. In the case of natural polymers, the main physical properties may include molecular weight and viscosity. Mechanical properties (strength, toughness, and elasticity) of biodegradable polymers may be important for the manufacturing of drug products.

Chemical Properties

Biodegradable polymers are generally polyesters of lactic and glycolic acids.

Functional Mechanism

The performance of a biodegradable polymer such as PLGA is mainly linked to the rate of biodegradation, which can be controlled by properties such as chemical composition (lactide/glycolide ratio) and stereochemistry (composition of L- or DL-lactide). Although PLGA polymers are generally hydrophobic polymers, the PLGA polymer with higher content of lactic acid units is less hydrophilic with lower water absorption property, resulting in slower degradation. The hydrophilicity of the polymer depends on type of linkage, monomers, and chemical composition. PLGA derivatives, PLGA-glucose, or polyethylene glycol (PEG)-PLGA have hydrophobic chains and hydrophilic groups (glucose or PEG). The end structure of polymer can also affect its degradation.

Drugs are loaded into carrier particles or implants during or after formation in a manufacturing process and are distributed throughout the polymer matrix or encapsulated as a core inside the particles. The drug release profile depends on the nature of biodegradable polymers, the nature of drug, and the structure of the carrier. Drug release may be due to a combination of mechanisms such as erosion or degradation of the polymer, diffusion through water-filled pores, diffusion through the polymer, or osmotic pumping. Factors affecting drug release profile other than the physical and chemical properties of biodegradable polymers include the interaction of functional groups between drug and polymers, the shape and size of particles, and other excipients.

Dosage Forms

Biodegradable polymers are used as carriers for small molecules, peptides, and large molecules. The dosage forms of biodegradable polymer-based formulations are mainly lyophilized injections. Solid particles or implants may be generally administered by intramuscular or subcutaneous injections.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include viscosity, solubility, molecular weight distribution, T_g , crystallinity, composition ratio (in the case of PLGA), loss on drying, elemental impurities, and identity.

General Chapters

The following general chapters may be useful in ensuring consistency in selected biodegradable polymers: [Injections and Implanted Drug Products](#) (1), (71), [Bacterial Endotoxins Test](#) (85), (621), (695), (731), (891), (911), (912), [Viscosity—Rolling Ball Method](#) (913), (1151), [Water-Solid Interactions in Pharmaceutical Systems](#) (1241), and [Rheology](#) (1911).

BUFFERING AGENT

Description

A buffering agent is a weak acid or weak base and a conjugate protonated species, typically a salt. Examples of conjugate acid-base pairs include acetic acid and sodium acetate or ammonia solution and ammonium phosphate. When a buffer is present in a solution, the addition of small quantities of acid or base leads to only a small change in solution pH. Buffer capacity is the ability of the buffering agent to minimize pH change and is determined by the ratio of conjugate base to conjugate acid and total concentration of buffering agent.

The pH of pharmaceutical solutions typically is controlled using buffering agents to: 1) improve drug stability where it is found to be pH-dependent, 2) control equilibrium solubility of weak acids or bases, or 3) maintain a pH close to that of relevant physiological pH to avoid irritation. Measurement of pH is described in (791), and [Pharmaceutical Calculations in Pharmacy Practice](#) (1160) provides background information on pH, pH buffers, buffer solutions, and buffer capacity calculations. A related functional category is *Acidifying or Alkalizing Agent*.

Physical Properties

Physical properties such as particle size of the buffering agent may be important in preparing pharmaceutical solutions as it may influence processing requirements such as the mixing time required to dissolve a buffering agent.

Chemical Properties

Buffers influence solution pH, buffer capacity, osmolality, and water conductivity. When used in chemical analysis, buffers must be chemically compatible with the reagents and test substance. Buffers used in physiological systems should not interfere with the pharmacological activity of the medicament. The relationship between solution pH, the buffering agent pKa, and the ratio of ionized to nonionized buffer species is given by the Henderson-Hasselbach equation:

$$\text{For weak acid: } \text{pH} = \text{pKa} + \log \left(\frac{[A^-]}{[HA]} \right)$$

$$\text{For weak base: } \text{pH} = \text{pKa} + \log \left(\frac{[B]}{[BH^+]}\right)$$

Buffer capacity is at its maximum when solution pH is equal to the pKa of the buffering species and decreases as pH deviates from the pKa. Buffer capacity is also dependent upon total buffering agent concentration (C). Buffer capacity, β , may be estimated by the Van Slyke equation:

$$\beta = 2.3C \left(\frac{K_a(H^+)}{K_a + (H^+)^2} \right)$$

Functional Mechanism

The ionization equilibria of weak bases, weak acids, and water are key to the function of buffering agents. The pKa of buffers may vary significantly with temperature.

Dosage Forms

Buffering agents are typically dissolved in liquid dosage forms to control the pH of a solution. Buffering agents may be incorporated into solid or semisolid dosage forms in the undissolved state for the same purpose upon exposure to aqueous media. Typical dosage forms include injections, suspensions, sprays, liquids, emulsions, and ointments.

For injectable products the range of acceptable buffers is limited. Certain buffers may cause pain upon injection or are sensitive to light; thus, the selection of the buffer should be carefully considered. Where freezing may be a step in the process, pH shifts with certain buffers can occur and should be evaluated (e.g., crystallization of phosphate salts). In the case of biological formulations, the buffer species may also play a role in the physical or chemical stability of the protein.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include purity and particle size where dissolution of the buffering agent may be critical to assuring consistent product properties and performance. The presence of insoluble particulates may present problems in the preparation of sterile products. Particle size may influence content uniformity and powder flow properties when incorporated as a solid form.

General Chapters

The following general chapters may be useful in ensuring consistency in buffering agent functions: [Osmolality and Osmolarity \(785\)](#), [\(791\)](#), [\(232\)](#), [\(786\)](#), and [\(429\)](#).

BULKING AGENT

Description

Bulking agents are excipients that provide body and structure to lyophilized (freeze-dried) formulations and include various saccharides, sugar alcohols, amino acids, and polymers.

Physical Properties

Bulking agents are dissolved in aqueous solution before lyophilization. Hence, the physical form and particle properties of the bulking agent are generally not relevant to the final properties of the lyophilized formulation.

The physical properties that are essential to product performance during and after lyophilization include the glass transition temperature (T_g) of the amorphous frozen concentrate before drying, the glass transition temperature of the final dried formulation cake, and the eutectic melting temperature of the crystalline bulking agent with ice. The T_g of the formulation depends on the glass transition temperatures of the individual components, concentrations, and molecular interactions. Although approximations can be made based on reported transition temperatures for individual components, current practice includes the measurement of glass transition temperature of formulation by thermal analysis or freeze-drying microscopy.

The physical states of the bulking agent during and after lyophilization are important physical properties. Both formulation composition and lyophilization processing parameters play roles in determining whether the bulking agent is amorphous or takes a specific crystalline form. Rate of freezing, drying temperatures, and annealing are among the important process parameters used to control the physical state of the formulation and its components.

For protein formulations, the selection of bulking agents requires careful consideration as proteins generally present complex biophysical stability problems. The bulking agent should effectively inhibit

protein unfolding and protect the protein during the lyophilization cycle while also providing a strong cake structure. Disaccharides (i.e. sucrose and trehalose) that remain amorphous in the lyophilization process have been found to be effective stabilizers for protein formulations, by immobilizing the protein in an amorphous glassy sugar matrix inhibiting protein unfolding. In the selection of bulking agents for protein formulations, the T_g of the bulking agent should be considered. Above T_g , the molecular mobility in the system increases, allowing for increased reactivity that can potentially impact storage stability of the protein. Sugars with glass transition temperature significantly above room temperature (i.e. sucrose and trehalose) can provide for good storage stability for protein formulations by restricting molecular mobility in the system during shelf storage of the product. The residual moisture in a lyophilized product can reduce the T_g and thus needs careful evaluation during product development to maximize shelf stability. For some proteins and peptides, bulking agents that can crystallize (i.e. mannitol and glycine) generally do not protect the protein during the lyophilization process, but when mixed in the appropriate ratio with a sugar that stays amorphous (i.e. sucrose) can provide for a stable lyophilized formulation. A potential advantage of such mixed crystalline/amorphous systems is that the primary drying can be conducted at higher temperatures, reducing lyophilization cycle times. The design of such mixed systems can pose challenges and needs careful evaluation during development of the lyophilized product.

Chemical Properties

The control of the chemical purity of the bulking agent is especially critical as any reactive impurities may potentially lead to chemical degradation in small molecules and proteins or aggregation/inactivation of proteins.

A group of sugars that should be avoided as bulking agents for proteins and small molecules are reducing sugars (glucose, lactose, maltose) as they may lead to a Maillard reaction between the carbonyls of the sugar and free amino group on the active ingredient. Low levels of reducing sugars can also be present as an impurity in some sugars that can lead to stability issues. In addition, the presence of trace metals such as Cu^{2+} and Fe^{2+} in bulking agents can cause metal catalyzed oxidation of proteins and small molecules.

Functional Mechanism

A bulking agent that readily crystallizes during lyophilization helps maintain the structural integrity of the cake formed during primary drying, thereby preventing macroscopic collapse and maintaining pharmaceutical elegance. Microscopic collapse of amorphous components in the formulation can still occur (with some potentially undesirable results) but does not result in macroscopic collapse or "meltback" if the properties and concentration of the bulking agent are adequate. The bulking agent also should possess a high eutectic melting temperature with ice to permit relatively high primary drying temperatures with commensurate rapid and efficient drying and subsequent rapid reconstitution upon usage. Functional cake-forming excipients such as mannitol are frequently used because they crystallize during freezing, thereby allowing efficient drying and the formation of a structurally robust and stable cake.

Proteins and many of the biopolymer active ingredients such as nucleic acids remain amorphous upon lyophilization. Bulking agents such as disaccharides can function as lyoprotectants by helping to maintain a stable amorphous phase during freezing and drying that immobilizes the protein in the amorphous glassy sugar matrix. Bulking agents also are selected based on synergistic functionality for biocompatibility, buffering capability, and tonicity-modifying properties.

Dosage Forms

Bulking agents are used in lyophilized formulations for use in injections.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include the T_g of the bulking agent and impurities (reducing sugars, reactive impurities that can interact with proteins, peroxides, and trace metals).

General Chapters

The following general chapters may be useful in ensuring consistency in selecting bulking agent functions: [\(1\)](#), [\(695\)](#), [Characterization of Crystalline Solids by Microcalorimetry and Solution Calorimetry \(696\)](#), [\(785\)](#), [\(891\)](#), [\(1151\)](#), and [\(1241\)](#).

Additional Information

Bulking agents are used in lyophilized formulations of both small molecules and proteins. Bulking agents are included in lyophilized drug products to provide various functions. A lyophilized drug product can contain a single bulking agent or a complementary combination of bulking agents to improve performance. In general, the primary function of the bulking agent is to provide a pharmaceutically elegant cake with noncollapsible structural integrity that will reconstitute rapidly for administration. In addition, bulking agents are selected to prevent product loss caused by blow out during lyophilization, to facilitate rapid and efficient drying, and to provide a stable formulation matrix. In the case of protein drug products that are lyophilized, the bulking agent selected should effectively inhibit protein unfolding and protect the protein and its activity during the lyophilization process. The selected agent should also provide a good cake structure while maintaining chemical and physical stability of the protein, both during lyophilization and on reconstitution.

CAPSULE SHELL

Description

Capsules enable pharmaceutical powders and nonaqueous liquids to be formulated via encapsulation for dosing accuracy as well as ease of transportation. The capsule material should be compatible with all other ingredients in the drug product.

Hard capsules typically consist of two parts: both are cylindrical, the capsule body, which is slightly longer, and the cap, which fits closely over the body to close the capsule. Hard capsule shells may also be used in dry powder inhalers (DPIs). The capsule shell is used to contain the dosage amount and protect the inhalable powder while in the DPI. Traditionally, hard capsules have been manufactured from gelatin derived from the hydrolysis of bovine, porcine, or fish collagen. Type A gelatin is derived by acid treatment, and Type B gelatin is derived from alkali treatment. The common sources of commercial gelatin are pigskin, cattle hide, cattle bone, cod skin, and tilapia skin. In recent years, hard capsules also have been manufactured from substituted celluloses and other polysaccharides, alone or in combination.

In contrast, the soft capsule is a one-piece unit that may be seamed along an axis or may be seamless. Traditionally, soft capsules have been manufactured using a combination of gelatin and a plasticizer, typically, glycerin or sorbitol. Nongelatin soft capsules are now available.

Physical Properties

The primary physical properties relevant to the capsule shell are those that can have a direct effect on product performance: 1) moisture content, 2) gas permeability, 3) physical stability on storage (e.g., increase in brittleness and propensity for cross-linking), 4) disintegration, 5) compactness, and 6) brittleness. The moisture content varies with the type of capsule. Hard gelatin capsules typically contain 13%–16% water compared to hypromellose (hydroxypropyl methylcellulose or HPMC) capsules that typically contain 4%–7% water content. Soft gelatin capsules contain 5%–15% water. Moisture content has an important effect on capsule brittleness. Equilibrium water content also may be crucial to dosage form stability and filling performance because water migration can take place between the shell and capsule contents, and if the capsules are in a brittle state during filling they can break. Gas permeability may be important and generally is greater for HPMC capsules than for gelatin capsules because of the presence of open structures in the former. Unlike HPMC capsules, which do not cross-link, gelatin capsules have the potential to cross-link in an autocatalytic reaction due to environmental and chemical exposure. Gelatin capsules may undergo cross-linking upon storage at elevated temperature and humidity (e.g., 40° 75% RH). Cross-linking slows in vitro dissolution and often necessitates introduction of enzymes in the test

medium, see [Dissolution \(711\)](#) and [Disintegration and Dissolution of Dietary Supplements \(2040\)](#). Gelatin capsules should disintegrate within 15 min when exposed to 0.5% hydrochloric acid at 36°–38° but not below 30°. HPMC capsules can disintegrate below 30°. Gelatin capsules are easier to close after filling than capsules manufactured from other materials.

Chemical Properties

Gelatin is a protein and has all of the characteristic chemical reactions of protein. Gelatin shell material is also known to cross-link due to exposure to aldehydes, ketones, and certain dyes in shell formulations. Thus, presence of these materials in excipients should be considered for gelatin encapsulated products. Cross-linking may also be induced by exposure to high relative humidity, which can be affected by the viscosity of the gelatins used to manufacture the capsule shell.

The capsule material may be derived from processing of collagen that originates from porcine, bovine, or fish sources, or it can be of nonanimal origin, e.g., cellulosic or polysaccharide chemical entities. Gelatin is a commercial protein derived from the native protein, collagen. The product is obtained by partial hydrolysis processing of collagen derived from skin, white connective tissue, and bones of animals. See the [Gelatin](#) monograph for further details. The gelatin capsule shell also typically contains coloring agents, plasticizers such as polyhydric alcohols, natural gums and sugars, and preservatives such as sodium metabisulfite and esters of *p*-hydroxybenzoic acid.

The more commonly used nongelatin capsules are made from hypromellose. In addition to hypromellose “veggie” alternative capsule shells have been developed from pullulan, starch and starch derivatives, iota and kappa carrageenan, and polyvinyl alcohols. To date, gelatin and hypromellose have had the most commercial success. Different capsule types contain different moisture levels and may thus influence drug product stability. The detailed composition of capsule shell may be important because the shell function can be influenced by small amounts of impurities in the excipients (e.g., peroxides in oils or aldehydes in lactose and starches) that can cause capsule cross-linking. The presence in capsule shells of undesirable materials such as metals, odorants, water-insoluble substances, and sulfur dioxide should be evaluated to ensure stability and performance. In some cases, capsule shells are sterilized to prevent microbial growth such as for DPIs.

Functional Mechanism

Capsules function in several ways: containing the dose of the active ingredient, masking unpleasant taste, facilitating blinding in clinical studies, promoting ease of swallowing, and aiding in identification of the drug product. Conventional capsule shells should dissolve rapidly at 37° in biological fluids such as gastric and intestinal media. Traditionally, modified release was achieved by coating the capsule shell with either a disintegration delaying polymer or a rate controlling polymer; however, there are capsule shells available in which the release-modifying polymer is incorporated into the capsule shell (e.g., with enteric and controlled-release polymers) to modify the release of the capsule contents.

Hard capsule shells are also used as unit dose containers in some DPI devices. In addition, the capsule may be opened, and the contents may be added to food or liquid.

Dosage Forms

Capsules are primarily used in oral dosage forms that can enclose solid, semisolid, or nonaqueous liquid formulations. However, capsules can also be used to administer drugs by rectal, vaginal, or inhalation routes.

Performance-Related Properties

Potential performance-related properties include: moisture content, gelling temperature, melt viscosity, mechanical properties, gas permeability, potential to cross-link (gelatin capsules), stability, disintegration, and brittleness.

General Chapters

The following general chapters may be useful in ensuring consistency in selected capsule shell functions: [Microbial Enumeration Tests \(61\)](#), [Tests for Specified Microorganisms \(62\)](#), [Arsenic \(211\)](#), [Residue on Ignition \(281\)](#), [Disintegration \(701\)](#), [\(711\)](#), [\(921\)](#), [Color—Instrumental Measurement \(1061\)](#), [Capsules—Dissolution Testing and Related Quality Attributes \(1094\)](#), [\(2040\)](#), [\(911\)](#), [\(912\)](#), [\(913\)](#), [Viscosity—Pressure Driven Methods \(914\)](#), [\(1911\)](#), and [\(891\)](#).

CARRIER

Description

Carriers are used to help deposit the active ingredient in the lung and may have a secondary role in diluting the active to ensure that dosages can be accurately metered.

Physical Properties

The physical properties of carriers include appropriate morphology, hydration state, flowability, surface energy, and particle size distribution. Carriers must have low microbial content.

Chemical Properties

Carriers must have suitable purity and impurity profiles and no extraneous proteins or impurities to avoid interactions with the patient's immune system.

Functional Mechanism

Carriers may be used to promote drug deposition into the lungs for better penetration or absorption in the appropriate lung location. The carrier may be used to decrease the concentration of the active ingredient so the latter is adequately dosed in a uniform manner. An appropriate balance of adhesive and cohesive forces between the carrier and active ingredient is necessary to produce a stable formulation that permits release of active ingredient at the desired site, improve powder flow, facilitate manufacturing, and improve dosing accuracy.

Dosage Forms

Carriers are used in aerosols dosage forms as a mechanism to transport the drug product into the lung.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include: particle size distribution, flowability, surface energy, particle morphology, amorphous content, impurity profile, water content, microbial load, etc.

General Chapters

The following general chapters may be useful in ensuring consistency in selected carrier functions: [\(61\)](#), [\(62\)](#), [\(232\)](#), [Elemental Impurities—Procedures \(233\)](#), [\(429\)](#), [Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests \(601\)](#), [\(616\)](#), [\(695\)](#), [\(696\)](#), [\(699\)](#), [\(731\)](#), [Optical Microscopy \(776\)](#), [\(786\)](#), [Powder Fineness \(811\)](#), [Mid-Infrared Spectroscopy \(854\)](#), [Ultraviolet-Visible Spectroscopy \(857\)](#), [\(921\)](#), [Characterization of Crystalline and Partially Crystalline Solids by X-Ray Powder Diffraction \(XRPD\) \(941\)](#), and [\(1174\)](#).

CATIONIC DENDRIMER

Description

Cationic dendrimers are a type of well defined globular macromolecule with multibranching three-dimensional structure. They are generally synthesized by precise stepwise introduction of branching points onto a core molecule by either a convergent approach or divergent approach. Cationic dendrimers mainly consist of an internal core, layers of branches, and a multivalent peripheral shell. They are commonly used as nucleic acid carriers, which form stable complexes with nucleic acid and protect them from degradation before reaching the action site. Commonly used dendrimers include polyamidoamine (PAMAM) dendrimers, poly(propyleneimine) (PPI) dendrimers, poly(L-lysine) dendrimers, and their derivatives.

Physical Properties

Because of their well defined, highly branched molecular architecture, cationic dendrimers demonstrate some unique physical properties such as their solubility and viscosity. Dendrimers usually present a tightly packed state in solutions that greatly influence their rheological properties. Generally, dendrimer solutions have lower viscosity than linear polymers. The dendrimer generation, branches, and the molecular weight have important influence on their viscosity. The solubility of dendrimers is strongly influenced by the surface groups. Dendrimers terminated in hydrophilic groups are commonly soluble in polar solvents, whereas dendrimers terminated in hydrophobic end groups are generally soluble in nonpolar solvents. The dendrimer generation and branches significantly influence the flexibility, the charge density, and buffer capacity of the dendrimers, thus influencing the zeta potential, size distribution, stability, and endosome escape ability of formed nucleic acid complexes.

Chemical Properties

Cationic dendrimers can provide high density and a precise number of multivalent functional groups. They generally possess different types of amines, which can be protonated under different pH conditions and given a positive charge formulation. For example, PAMAM dendrimers and PPI dendrimers both contain primary amine groups that can be protonated at a pH of 7.4 to facilitate nucleic acid complexation and tertiary amine that can be protonated in the endosomal pH range to mediate endosome escape.

Functional Mechanism

Under neutral pH conditions, cationic dendrimers are positively charged, whereas nucleic acids are normally negatively charged. Thus, cationic dendrimers such as PAMAM dendrimers, PPI dendrimers, and poly(L-lysine) dendrimers all can form complexes with nucleic acids through electrostatic interaction. Moreover, some of these cationic dendrimers such as PAMAM and PPI, which have a large number of secondary and tertiary amines in the interior, are protonatable under endosomal pH conditions and can mediate efficient endosome escape. Because the preparation of the nucleic acid-dendrimer complex cannot withstand terminal sterilization, dendrimers should be prepared sterile and with low endotoxin.

Dosage Forms

Cationic dendrimers are used together with nucleic acid in injections to form stable complexes, thereby eliminating nucleic acid degradation in blood circulation.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include properties related to identity, viscosity, solubility, buffer capacity, molecular weight distribution, loss on drying, and elemental impurities.

General Chapters

The following general chapters may be useful in ensuring consistency in selected cationic dendrimer functions: [\(1\)](#), [\(71\)](#), [\(85\)](#), [\(621\)](#), [\(695\)](#), [\(731\)](#), [\(891\)](#), [\(911\)](#), [\(912\)](#), [\(913\)](#), [\(1151\)](#), [\(1241\)](#), and [\(1911\)](#).

COLLOID-STABILIZING AGENT

Description

Colloid-stabilizing agents, or protecting agents, are used in lyophobic particulate radiopharmaceuticals to coat the surface of individual colloid particles and prevent or inhibit clumping.

Physical Properties

Colloid-stabilizing agents must be readily soluble in aqueous solution.

Chemical Properties

Colloid-stabilizing agents must be lyophilic and capable of coating the lyophobic colloid particles, e.g., by electrostatic attraction of an opposite charge. Examples of colloid-stabilizing agents include gelatin and dextran.

Functional Mechanism

Lyophobic colloid particles can form aggregates to minimize their surface area-to-volume ratio. Colloid-stabilizing agents are lyophilic molecules that coat the surface of individual colloid particles, making them appear lyophilic. Additionally, the colloid-stabilizing agent may be charged, thus causing the coated colloid particles to repel one another. The net result is the prevention or inhibition of aggregation of colloid particles.

Dosage Forms

Colloid-stabilizing agents are used primarily in radiopharmaceutical suspension dosage forms intended for injection.

Performance-Related Properties

The potential performance-related properties for colloid-stabilizing agents are: solubility, lyophilicity, molecular size or mass, and electrostatic charge at the intended pH.

General Chapters

The following general chapters may be useful in ensuring consistency in selected colloid stabilizing agent functions: [\(621\)](#), [Radioactivity \(821\)](#), [Capillary Electrophoresis \(1053\)](#), and [Solubility Measurements \(1236\)](#).

COLORING AGENT

Description

A coloring agent is any dye, pigment, or substance that when added to a drug or to the human body will impart a color. Coloring agents are incorporated into dosage forms to produce a distinctive appearance that may serve to differentiate a product from others that have a similar physical appearance or, in some instances, to protect photolabile components of the dosage form. These substances are subdivided into soluble dyes, lakes (insoluble forms of a dye that result from its irreversible adsorption onto a hydrous metal oxide), inorganic pigments (substances such as titanium dioxide or iron oxides), and natural colorants (colored compounds not considered dyes per se, such as riboflavin).

Physical Properties

Particle size distribution of dyes and lakes can influence product processing times (blending and dissolution), color intensity, and uniformity of appearance. For lakes and pigments, the color intensity and uniformity of appearance can be influenced by their particle morphology. The color intensity may vary from lot to lot and can influence the consistency of the color of the product. The most important properties of a coloring agent are its depth of color and resistance to fading over time. Substances can be graded on their efficiency in reflecting desired colors of visible light as well as on their molar absorptivities at characteristic wavelengths.

Chemical Properties

This is a very broad group of substances with no apparent common chemical properties. Examples of coloring agents include talc, titanium dioxide, β -carotene, calcium carbonate, ferric ferrocyanide, caramel, iron oxide, triarylmethane dye, and others.

Functional Mechanism

Pigment is an insoluble fine powder that creates colors by its own spectral absorption and its reflection to specific spectral light. Dye is a chemical substance dissolved in the solution that alters colors through the ion or chemical reactions.

Dosage Forms

Coloring agents are used mainly for oral (solid and liquid) dosage forms such as tablets, capsules, gums, pills, solutions, and suspensions to enhance patient compliance and aid in product identity. For tablets, an opaque coating may protect photolabile active ingredients.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include particle size, color intensity, and color uniformity.

General Chapters

The following general chapters may be useful in ensuring consistency in selected coloring agent functions: [\(429\)](#) and [\(1061\)](#). Instrumental methods should be used to determine the color of a coloring agent that is typically compared with a reference standard for the desired color.

Additional Information

Coloring agents are subject to federal regulations, and consequently the current regulatory status of a given substance must be determined before its use.

The Federal Food, Drug, and Cosmetic Act defines three categories of coloring agents:

- FD&C colors: those certifiable for use in coloring foods, drugs, and cosmetics
- D&C colors: dyes and pigments considered safe in drugs and cosmetics when in contact with mucous membranes or when ingested
- External D&C colors: colorants that, because of their oral toxicity, are not certifiable for use in ingestible products but are considered safe for use in externally applied products

Federal regulations state the maximum daily intake allowed.

Patients may be allergic to certain dyes and lakes [such as tartarazine (FD&C Yellow 5), FD&C Red 40] and should be considered in formulating products.

For tablets where the color is desired to be distributed throughout the tablet, water-soluble dyes usually are dissolved in a granulating fluid for use, although they also may be adsorbed onto carriers such as starch, lactose, or sugar from aqueous or alcoholic solutions. These latter products often are dried and used as formulation ingredients. Because of their insoluble character, lakes and pigments almost always are blended with other dry excipients during formulation. For this reason, direct compression tablets are colored with lakes and pigments when the color is desired to be present throughout the dosage form.

Most tablets today are colored by the coating applied to the tablet. Dyes, lakes, and pigments are combined with a polymer and typically a plasticizer, even though in rare cases, water can be used as a plasticizer.

COMPLEXING AGENT

Description

A complexing agent is a compound that associates with metal ions or another compound in solution to form an adduct. The degree of association is less than covalent and greater than that of counterions and is mediated via charge transfer or hydrophobic interactions.

The term ligand is used for a compound that forms one or more coordinate bonds with a metal atom. Chelating agents are multidentate ligands that form soluble complex molecules with certain metal ions (e.g., copper, iron, manganese, lead, and calcium). If the complexing agent reduces the ability of the ion or other compound to react or precipitate, then it is known as a sequestering agent.

Hydrophobic interactions predominate with associations between larger organic molecules, for example, cyclodextrin-drug inclusion complexes.

Physical Properties

Complexing agents generally are soluble in water and typically are dissolved in liquid dosage forms. Physical properties such as particle size of the chelating agent are not normally critical in solution applications but may influence processing requirements such as the mixing time required to dissolve.

Chemical Properties

Complexing agents generally associate with metal ions via charge transfer and with larger organic molecules via hydrophobic interactions.

The hexadentate edetic acid and its salts are representative of agents that complex with and sequester metal ions. Polydentate ligands are key to the functionality of chelating agents that form stronger complexes than with the corresponding number of monodentate ligands. Edetate calcium disodium does not sequester calcium and therefore is preferred to prevent hypocalcemia. Sequestration may be pH-dependent.

Cyclodextrins are representative of complexing agents that function by hydrophobic interaction. Their hydrophobic cavities can accommodate a hydrophobic portion of a drug molecule. Steric effects can interfere as illustrated by β -cyclodextrin, which has the optimum cavity size to house aromatic groups.

Polymeric excipients in general, including carbohydrates and proteins, may form complexes with ions and organic molecules due to their polydentate nature and/or regions of hydrophobicity.

Complexing agents should be chemically compatible with the active ingredient and other formulation components. When used in chemical analysis, they must be chemically compatible with the reagents and test substance.

Functional Mechanism

In addition to ionic interactions, charge transfer can result from lone pair electrons, hydrogen bonding, and aromaticity (π -delocalization) resulting in a degree of association between the complexing agent and target greater than the interaction with simple counterions in solution. Association is greater for multidentate ligands that statistically are less likely to simultaneously dissociate. For example, ethylenediamine binds metals more strongly than methylamine.

Hydrophobic complexes in aqueous solution result from the energetically favored tendency for hydrophobes to associate and exclude water. The greater the number of hydrophobic groups and the better the steric fit, the greater the degree of association.

Dosage Forms

Complexing agents are typically dissolved in liquid dosage forms, including suspensions, liquids, and solutions, or incorporated into solid dosage forms such as powders, tablets, capsules, and pills to deliver the same benefits on subsequent dissolution such as reduced water hardness, reduced catalysis of drug degradation, synergistic antioxidant/antimicrobial effects, and/or increased drug solubility or stability. Specific complexing agents are selected for a formulation based on their functionality (benefit and affinity for target), solubility, and stability.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include particle size, where dissolution of the chelating agent is critical, or to assure content uniformity or flow properties when incorporated in powder mixes.

General Chapters

The following general chapters may be useful: [Water Conductivity](#) (645), (785), (791), (786), (429), and [Particulate Matter in Injections](#) (788).

CRYSTALLIZATION INHIBITOR

Description

Crystallization inhibitors are those molecules that prevent the nucleation and crystal growth of APIs in any dosage form. It applies to all drug classes and formulation dosages where there is risk of solvent mediated phase transition or need for stabilization of an amorphous form. These molecules are primarily polymers, or solubilizers that inhibit crystallization or crystal growth (e.g., Ostwald ripening) of APIs in the desired dosages by maintaining them in original suspensions, solutions, or amorphous solid dispersions.

Nucleation, if not prevented, can lead to a decrease in dissolution and bioavailability of drugs, which may lead to recall of marketed drugs. This is more challenging with amorphous solid dispersions.

Physical Properties

Excipients that behave as crystallization inhibitors are selected based upon the nature of the interaction between the drug and inhibitor molecules. Physical properties that can influence the inhibition of crystallization in liquid dispersions include surface activity and adsorption (for polymeric excipients, folding, unfolding, or re-arrangement of the polymeric chains). For solid dispersions, the ability to increase the glass transition temperature of the dispersion is most important.

Chemical Properties

This is a very broad group of substances with no apparent common chemical properties. Examples of polymeric crystallization inhibitors include povidone, copovidone, hypromellose acetate succinate, polysorbates and polycaprolactam/polyvinyl acetate/polyethylene glycol copolymers. Examples of non-polymeric crystallization inhibitors include sorbitol.

Functional Mechanism

Nucleation inhibitors interact with drug molecules to prevent the formation of crystals from aqueous solution. Crystal growth inhibitors occupy suspended drug crystal surfaces and discourage further crystal growth by hindering the deposition of additional drug molecules from solution. The ability of the excipients to increase the glass transition temperature (T_g) of solid dispersions provides increased stability in addition to inhibition of nucleation and crystal growth. The stronger the intermolecular interactions between the drug and excipients, the stronger the inhibitory effects.

Dosage Forms

Crystallization inhibitors may be used in many dosage forms, including tablets, capsules, other oral solid dosage forms, and suspensions.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include polymeric chain lengths, surface adsorption, and critical micelle concentration (CMC), if applicable.

General Chapters

[\(1911\)](#), [Viscosity \(911\)](#), [\(741\)](#), [\(695\)](#), and [\(891\)](#).

DESICCANT

Description

Desiccants are hygroscopic substances that are used in packaging of pharmaceutical products to reduce and maintain a low level of moisture in the product and humidity inside the container. Examples of most popular desiccants include silica gel, molecular sieve, and calcium oxide.

Physical Properties

Desiccants are typically available in solid form with a high surface area and porosity to increase adsorption. Desiccants may be packaged in a semipermeable package, most commonly packets or canisters to minimize contact with packaging and pharmaceutical product, or they may be incorporated into the container-closure system such as in the cap for a bottle of tablets.

Chemical Properties

Desiccants contain functional groups that interact favorably with water. The properties of desiccants vary with temperature and relative humidity. Desiccants may be coated with or contain a moisture-sensitive indicator. Cobalt dichloride should be avoided as a moisture-sensitive indicator due to contact allergies in some individuals. Desiccants must be compatible with packaging and pharmaceutical products.

Functional Mechanism

Desiccants typically function by physical adsorption rather than chemical absorption of water. However, some desiccants such as calcium oxide chemically react with water.

Dosage Forms

Desiccants may be used in pharmaceutical packaging of solid dosage forms (tablets, capsules, gums, granules, pellets, and pills) to adsorb moisture and maintain a low relative humidity. However, caution must be exercised when using desiccants with gelatin capsules as it may lead to brittleness and cross-linking of the gelatin capsule shells.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include moisture content, specific surface area, adsorption capacity, and particle size for desiccants used in solid form. Adsorption capacity is the mass of water adsorbed per mass of desiccant and depends on time, relative humidity, temperature, and physical and chemical properties of the desiccant.

General Chapters

The following general chapters may be useful in ensuring consistency in selected desiccant functions: [\(429\)](#), [\(731\)](#), [\(786\)](#), [\(811\)](#), [\(921\)](#), [\(1241\)](#), and [\(891\)](#).

Additional Information

In addition to compatibility of the desiccant with the drug product, the packaging material of the desiccant unit must also be taken into consideration. The methods found in [\(891\)](#) can be used to measure dehydration.

DILUENT

Description

Diluents are components that are used to increase solid dosage form volume or weight. Sometimes referred to as fillers or bulking agents, diluents often comprise a large portion of the dosage form, and the quantity and type of diluent selected often depend on its physical and chemical properties.

Physical Properties

The primary physical properties relevant to diluents are those that can have a direct effect on diluent and formulation performance. These include particle size and size distribution, particle shape, bulk/tapped/true density, specific surface area, crystallinity, moisture content, powder flow, solubility, crystal form, and compaction properties for tablets.

Chemical Properties

Tablet diluents comprise a large and diverse group of materials that include inorganics (e.g., dibasic calcium phosphate or calcium carbonate), single-component organic materials (e.g., lactose monohydrate or mannitol), and excipient blends and coprocessed excipients such as silicified microcrystalline cellulose or sugar spheres, or complex organics (e.g., microcrystalline cellulose or starch). They may be soluble or insoluble in water, and they may be neutral, acidic, or alkaline in nature. These chemical properties can have a positive or negative effect on the drug substance physical or chemical stability and on performance. Appropriate selection of excipients with desirable physical and chemical properties can enhance the physical and chemical stability as well as the performance of the drug substance and dosage form. The detailed composition of an excipient may be important because excipient function could be influenced by the presence of minor concomitant components that are essential for proper performance. Pharmaceutical scientists may find it necessary to control the presence of impurities (e.g., elemental impurities or peroxides) to ensure adequate dosage form stability and performance.

Functional Mechanism

Among the most important functional roles diluents play is their ability to impart desirable manufacturing properties (e.g., powder flow, tablet compaction strength, wet or dry granule formation, or homogeneity),

performance (e.g., content uniformity, disintegration, dissolution, tablet integrity, friability, or physical and chemical stability), and adjust the overall dosage form weight. Some diluents (e.g., microcrystalline cellulose) occasionally are referred to as "dry binders" because of the high degree of tablet strength they impart to the final compressed tablet.

Dosage Forms

Diluents are used in every type of solid dosage form such as tablets, capsules, granules, pellets, pills, ointments, creams, and gels.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include particle size and size distribution, particle shape, bulk/tapped/true density, specific surface area, crystallinity, moisture content, powder flow, solubility, crystal form, and compaction properties for tablet dosage forms.

General Chapters

The following general chapters may be useful in ensuring consistency in diluent functions: [\(429\)](#), [\(616\)](#), [\(695\)](#), [\(696\)](#), [\(699\)](#), [\(731\)](#), [\(776\)](#), [\(786\)](#), [\(811\)](#), [\(846\)](#), [\(921\)](#), [\(941\)](#), [Tablet Compression Characterization \(1062\)](#), [\(1174\)](#), and [\(1181\)](#).

DISINTEGRANT

Description

Disintegrants are functional components that are added to solid formulations to promote rapid disintegration into smaller units and to allow a drug substance to dissolve more rapidly. Disintegrants are natural, synthetic, or chemically modified natural polymeric substances. When disintegrants come in contact with water or gastric or intestinal fluid, they function by absorbing liquid and start to swell, dissolve, or form gels. This causes the dosage form structure to rupture and disintegrate, producing increased surfaces for enhanced dissolution of the drug substance. Potent disintegrants, commonly called superdisintegrants, are effective at lower levels in the final formulation, typically less than 10% (w/w).

Physical Properties

The primary physical properties relevant to a disintegrant are those that describe the product's particle structure as a dry powder or its structure when in contact with water. These properties may include particle size distribution, water absorption rate, porosity, swelling ratio or swelling index, and whether a gel is formed.

Chemical Properties

Polymers used as disintegrants are either nonionic or anionic with counterions such as sodium, calcium, or potassium. Nonionic polymers are natural or physically modified polysaccharides such as starches, celluloses, pullulan, or nonpolysaccharides such as croscopolvidone. The anionic polymers mainly are chemically modified starches, cellulose products, or low cross-linked polyacrylates. The chemical properties of the drug or other ingredients should be considered in the case of ionic polymers where interactions may occur. Disintegration performance is affected by pH changes in the gastrointestinal tract or by complex formation with ionic drug substances. Depending on the manufacturing process, cellulose derived disintegrants may retain residual acid, resulting in instability for acid-labile drugs.

Functional Mechanism(s)

The ability to interact strongly with water is essential to the disintegrant function. Three major mechanisms describe the function of the various disintegrants: volume increase by swelling, deformation, and capillary action (wicking). The function of disintegrants is best described as a combination of two or more of these effects. The onset and degree of the locally achieved actions depend on various parameters of a disintegrant such as its chemical nature and its particle size distribution and particle shape as well as some important tablet parameters such as hardness and porosity. For disintegrants that gel, excessive

levels in the formulation may actually slow disintegration, particularly for capsules, as gelling may hinder dispersion of the capsule contents in the stomach or intestinal fluid.

Dosage Forms

Disintegrants are used in solid dosage forms such as tablets, capsules, granules, pellets, and pills to promote rapid disintegration.

Performance-Related Properties

The potential performance-related properties are particle size distribution, water content, and swelling ratio or swelling index.

General Chapters

The following general chapters may be useful in ensuring consistency in disintegrant functions: [\(429\)](#), [\(731\)](#), [\(776\)](#), [\(786\)](#), [\(921\)](#), and [\(1174\)](#).

DRAG-REDUCING AGENT

Description

Drag-reducing agents are excipients that increase the fluidity and/or decrease the turbulence of pharmaceutical liquids (i.e. solutions and dispersions) flowing through narrow channels (in nasal sprays, aerosol-metering valves, etc.), thereby enhancing spray patterns and improving the uniformity of formulation delivery.

Physical Properties

The primary physical property exhibited by drag-reducing agents is high extensional (elongational) viscosity at low solution concentrations. Surfactants that form worm-like micelles have also demonstrated drag-reducing functionality.

Chemical Properties

This is a very broad group of substances, thereby precluding a description of chemical properties. Typical drag-reducing agents are high molecular weight polymers such as polyethylene oxides, PEGs, and polyacrylamides. Worm-like micelle formation and concomitant drag reduction or increased fluidity has also been demonstrated with cationic, anionic, and nonionic surfactants.

Functional Mechanism

Drag reduction by polymers is a boundary layer effect resulting in a significant reduction in turbulent energy losses during flow. The mechanism entails the uncoiling and stretching of polymer molecules under the stress that the fluid exerts on them in flow. Surfactants that form worm-like micelles or shear-induced gels increase wall slippage as the micelles or gels break when deformed too much at too large of a shear.

Dosage Forms

Drag-reducing agents have been incorporated in formulations of aerosols, sprays, and injections.

Performance-Related Properties

The rheological properties of solutions of drag-reducing agents, particularly at low concentrations, are essential to the functioning of these agents. Accordingly, rheological methods that are applicable to dilute solution measurements—particularly, the measurement of extensional (elongational) viscosity—would be especially helpful in formulating dosage forms with these components. Given the polydispersity of polymeric excipients in commerce and the multicomponent nature of most surfactants, size exclusion or gel phase chromatography would help to ensure manufacturing replicability.

General Chapters

The following general chapters may be useful in ensuring consistency in selected drag reduction functions: [\(912\)](#), [\(1911\)](#), and [\(621\)](#).

Additional Information

Even though USP does not currently provide for the measurement of elongational or extensional viscosity, this is the most relevant physical parameter. As such, a formulator would be advised to seek out instrumentation that would enable this property to be measured.

EMOLLIENT

Description

Emollients are excipients used to impart lubrication, spreading ease, texture, pleasant feel, indirect moisturization of the skin by preventing transepidermal water loss, softening of the skin, and to counter the potentially drying/irritating effect of surfactants on the skin.

Physical Properties

Emollients may be liquid, semisolid, or solid at room temperature and which can be spread on the skin using light to moderate pressure.

Chemical Properties

Emollients are either oils or are derived from components of oils as esters of fatty acids, fatty alcohols, or liquid hydrocarbons of requisite molecular weight.

Functional Mechanism

Emollients help form a protective film and maintain the barrier function of the epidermis. Their efficacy may be described by three mechanisms of action: protection against the delipidizing and drying effects of surfactants, humectancy due to occlusion (by providing a layer of oil on the surface of the skin, emollients slow water loss and thus increase the moisture-retention capacity of the stratum corneum), and lubricity, adding slip or glide to the preparation.

Generally, the higher the molecular weight of the fatty acid or fatty alcohol moiety (carbon chain length), the richer the feel and softness of the touch. Fluidity generally is imparted by shorter chain length and a higher degree of unsaturation in the fatty acid moiety.

Dosage Forms

Emollients are typically used in topical formulations such as creams, emulsions, gels, soaps, ointments, lotions, and foams to impart lubrication, spreading ease, texture, and to counter the potentially drying/irritating effect of surfactants on the skin. Emollients can also be included in suppository formulations.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include carbon chain length, rheology, coefficient of friction, dropping point, film forming, melting point, melting range, and sensorial aspects such as slip, tackiness, etc.

General Chapters

The following general chapters may be useful in ensuring consistency in selected emollient functions: [\(401\)](#), [\(741\)](#), [\(891\)](#), [\(911\)](#), [\(912\)](#), [\(913\)](#), [\(914\)](#), and [\(1911\)](#).

EMULSIFYING AGENT

Description

Emulsifying agents are excipients generally used to stabilize two or more immiscible liquid phases that would not normally mix, such as oil and water. Emulsifying agents help stabilize an emulsion to prevent coalescence of the globules of the dispersed phase. Emulsions may be water-in-oil or oil-in-water and both will require emulsifying agents.

Physical Properties

Emulsifying agents are amphiphilic molecules having both lipophilic and hydrophilic properties in the same molecule. On the other hand, finely divided solid particles that stabilize emulsions tend not to be

amphiphilic.

Chemical Properties

The chemical properties of emulsifying agents vary considerably as these excipients may be anionic, cationic, amphoteric, or nonionic in nature. Nonionic emulsifying agents are often classified according to their hydrophilic/lipophilic balance (HLB), although strictly speaking, the HLB approach to surfactant classification and utilization was developed for nonionic ethoxylated surfactants. Furthermore, emulsifying agents may be synthetic, semisynthetic, or natural in origin. Regardless of their classification, all emulsifying agents must be chemically stable in the system as well as nontoxic and nonirritant.

Functional Mechanism

Emulsifying agents act by reducing the interfacial tension between two phases and forming a stable interfacial film. Soluble emulsifying agents tend to concentrate at the oil-water interface to provide a protective film around the dispersed droplets. In addition to this protective layer, such emulsifying agents stabilize the emulsion by reducing the interfacial tension of the system. Some emulsifying agents enhance emulsion stability by imparting a charge to the droplet surface, thus reducing the physical contact between adjacent droplets and thereby decreasing the potential for coalescence. Finely divided solids do not lead to appreciable changes in interfacial tension nor is their emulsion stabilization necessarily affected by the extent of droplet surface coverage.

Dosage Forms

Potential dosage forms include creams, emulsions, injections, foams, solutions, and suspensions. Emulsifying agents may be used in the following routes of administration: oral, parenteral, and topical.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include the ratio of the HLB of the molecule.

General Chapters

The following general chapters may be useful in ensuring consistency in selected emulsification functions: [\(3\)](#), [\(401\)](#), [\(741\)](#), [\(791\)](#), and [\(1151\)](#).

FILM-FORMING AGENT

Description

Film-forming agents are polymeric materials that form a film when spray coated, solvent cast, or hot melt extruded (HME). They have two categories of use: 1) a film coating on a dosage form such as a tablet and capsule and 2) as a structural matrix in film products. Note that sugar coating is addressed separately.

Film coating can serve multiple purposes, including masking unpleasant tastes or odors, improving ingestion and appearance, protecting active ingredients from the environment, providing a distinguishing appearance, and modifying the release of the active ingredient (e.g., controlled-release or gastrointestinal targeting). Materials used as coating agents differ depending on the purpose of the coating. Protective coatings tend to be hydrophilic, whereas controlled release coatings tend to be more hydrophobic. Hypromellose and polyvinyl alcohol are commonly used in film coating.

Film-forming agents may be added to a film formulation to form a structural matrix, allowing the film to be placed or inserted at the administration site, typically a mucosal tissue such as in the mouth, eye, or vagina. Film-forming agents are natural, semisynthetic, or synthetic polymers and are usually the main component of a film. Hydroxypropyl cellulose is a popular choice for films.

Physical Properties

The primary physical properties that affect the performance of a film-forming agent are its mechanical strength, solution viscosity, thermal properties such as T_g , melt viscosity (particularly for HME), water absorption, and drug permeation properties. For mucosal films, bioadhesion is a critical property.

Film coating is a complex process and the characteristics of the film-forming polymer are critical. The resulting film should possess sufficient elasticity and mechanical strength to withstand the stresses during coating and downstream packaging operations. The particle size of colloidal polymer dispersions varies with composition and manufacture (latex, pseudolatex, or redispersed powder) and significantly impacts the coating dispersion and influences the spray pattern during the manufacturing process. For coatings applied in a molten state without solvents (plastic polymers, waxes, and lipid-based coatings), melting range and melt viscosity are the primary properties to consider, as well as water uptake, permeability, and drug diffusion rate through the coating. For drugs prone to oxidation, oxygen permeability is important. The diffuse reflectance properties of the coating may be important if the coating is designed to hide the substrate, although this is primarily accomplished through the addition of an opacifier.

Chemical Properties

Coatings comprise a wide variety of different chemical materials. Coating components can be of natural, semisynthetic, or synthetic origin and may be available in different chemical grades. Polymers used as film-forming agents may be ionic or nonionic or, for those with bioadhesive properties, are typically anionic or neutral charge, with anionic polymers generally having stronger adhesion to mucosal membranes. Common film-forming agents include hypromellose, carboxymethylcellulose, hydroxypropyl cellulose, povidone, polyvinyl alcohol, polyethylene oxide, pullulan, pectin, chitosan, sodium alginate, carrageenan, polyacrylates, and gelatin.

Functional Mechanism

The mechanisms of film-forming agents can be divided into two categories: 1) those that affect performance in the patient and 2) those that affect the manufacturing process. Patient performance mechanisms include mechanical strength, which is necessary for handling and administration and affects tactile response (e.g., mouth feel). Water interaction is critical for controlled-release coatings as a key mechanism of release is the absorption of water and subsequent swelling of the matrix and drug diffusion. Sometimes the release mechanism is the erosion of the polymer from the surface of the film, allowing the release of drug from the core.

Film-coating systems are comprised primarily of film-forming agents that impart desirable pharmaceutical properties such as appearance and patient acceptance (e.g., taste masking and ease of swallowing). Film coating also can serve other functional purposes such as providing a barrier against undesirable chemical reactions or untimely release of a drug from its components. After ingestion, the film coating may dissolve by processes such as hydration, solubilization, or disintegration, depending on the nature of the material used. Enteric coatings are insoluble in acidic (low pH) media but dissolve readily in the neutral pH conditions of the intestines. Some film coatings are insoluble in aqueous solution but permeable to APIs upon contact with water due to the existence of pore forms in the coating. The pore formers could be small molecules or water-soluble polymers. The film-coating process may be applied with or without organic solvents. In the solvent-coating process, the polymer chains spread out on the core surface and coalesce into a continuous film as the solvent evaporates. Polymer solutions or dispersions with a low viscosity and high pigment-binding capacity reduce the coating time and facilitate relatively simple and cost-effective manufacturing. The thickness of the film may vary by application and the nature of the coating agents. Plastic polymers, waxes, and lipid-based coatings can be applied without solvents by melting and atomization. When molten fluid droplets strike the surface of the fluidized drug particles, they spread and congeal to form film layers. Thus, film-coating materials generally have the ability to form a complete and stable film around the substrate. The film coating is applied uniformly and carefully dried to ensure that a consistent product is produced. Suitable plasticizers may be required to lower the minimum film-forming temperature of the polymer, and formulators should consider their potential effect on drug release.

In addition, solution viscosity is a key attribute when solvent casting or spraying onto a surface. In addition, films can also be made by hot melt extrusion, and melting temperature and melt viscosity are critical to film formation. In addition, because solvent casting is commonly used, water is often the solvent

of choice so water interactions are important as it must be removed during drying, and some materials such as HPMCs tightly bind water, so this affects drying and packaging needs.

Dosage Forms

Film-forming agents are used to coat tablets and capsules or to provide a structural matrix in sublingual, buccal, vaginal, and other films. They are also used in ocular, topical, and vaginal delivery systems.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include solution viscosity, water absorption rate, water content, mechanical film strength, bioadhesive properties, plasticizer compatibility, polymer-dissolving rate, T_g or melting point, and residual solvents.

General Chapters

The following general chapters may be useful in ensuring consistency of film-forming agents: [\(401\)](#), [\(429\)](#), [Residual Solvents \(467\)](#), [\(711\)](#), [\(731\)](#), [\(881\)](#), [\(891\)](#), [\(911\)](#), [\(912\)](#), [\(913\)](#), [\(921\)](#), and [\(1911\)](#).

Additional Information

Additives often are included in a coating formulation. Fillers (e.g., sugar alcohols, microcrystalline cellulose, calcium carbonate, and kaolin) may be added to increase the solids content of the coating agent without increasing viscosity. Stearic acid can be used to improve the protective or moisture barrier function of a coating. Opacifiers and coloring agents may be added to modify appearance. Additionally, products manufactured using solvents for film formation should meet the requirements for that solvent as listed in the Code of Federal Regulations.

- Karki S, Kim H, Na SJ, Shin D, Jo K, Lee J. Thin films as an emerging platform for drug delivery. *Asian J. Pharm. Sci.* 2016;11(5):559–574. doi: <https://doi.org/10.1016/j.ajps.2016.05.004>.

FILTERING AID

Description

Filtering aids are finely divided purified siliceous earth or powdered cellulose. Purified siliceous earth is a finely divided powder consisting of the skeletons of diatoms that have been purified by calcining. Powdered cellulose is mechanically abraded cellulose pulp. The filtering aid should be compatible with the materials being filtered.

Physical Properties

Filtering aids are generally insoluble, particularly in the solvent being filtered.

Chemical Properties

Purified siliceous earth has the general properties of silica. Powdered cellulose has the properties of cellulose. They are generally inert.

Functional Mechanism

Filtering aids are used to aid in the filtration of solutions and liquors containing small amounts of undesirable solid particles. The filtering aid improves filtering efficiency by acting as a depth filter and allows the entrapment of any suspended particles above a certain size with reduced risk of filter blockage compared with a membrane filter.

Dosage Forms

Filtering aids may be used in the nonsterile processing of liquid dosage forms such as solutions, suspensions, and liquids. They also may be used in the production of drug substances. The filtering aid should not be present in the final drug dosage form.

Performance-Related Properties

Potential performance-related properties for filtering aids include particle size, particle size distribution, specific surface area, and filtering characteristics.

General Chapters

The following general chapters may be useful in ensuring consistency in filtering aid function: [\(429\)](#), [\(616\)](#), [\(786\)](#), [\(811\)](#), and [\(846\)](#).

FLAVOR AND FRAGRANCE

Description

A flavor or fragrance is a single chemical entity or a blend of chemicals of natural or synthetic origin, which has the ability to elicit a taste or aroma response when orally consumed or smelled. These materials often come in constellations of ingredients: for example, the perception of a flavor and its match to the flavor name by a patient is a function of the color, taste, and aroma that make up a flavor system. The primary purpose of a flavor system is to improve patient compliance especially in pediatric patients. The flavors and fragrances do this by providing all or part of the taste and aroma of the product taken into the mouth.

Physical Properties

Taste perception depends on physicochemical, physiological, and psychological factors. Physical properties such as particle size, solubility, humectancy, texture, and color all influence the senses. In addition to flavor, the sensory attributes of sight (e.g., appealing color), sound (e.g., crunch of a chewable tablet), and mouth feel (e.g., viscous, slimy, chalky, or watery) also contribute to and influence the overall sensory experience. In addition, the volatility affects retention in the dosage form. Flavor solubility in saliva fluids can affect aftertaste; for example, some artificial sweeteners have an unpleasant aftertaste due to precipitation on the tongue.

Chemical Properties

Chemicals that provide one of the five basic tastes possess a wide variety of structures, functional groups, and molecular weights. Chemicals used to flavor pharmaceuticals by providing both odor and taste tend to have low molecular weights (<250 Da) and polar functional groups such as esters, ketones, aldehydes, amines, or alcohols. To increase the stability of the flavor(s) in a solid dosage form and to minimize flavor-drug interactions, formulators can add flavors in an encapsulated or spray-dried form.

Functional Mechanism

After being released from the dosage form, chemicals dissolved in saliva excite chemoreceptors on taste buds that reside primarily on the tongue and thus arouse taste perception and the perception of aroma in the nasal cavity. Dissolution also releases volatile chemicals that reach the olfactory receptors, triggering aroma perception. The total of taste and odor responses constitutes flavor. Humans can distinguish among five components of taste: sourness, saltiness, sweetness, bitterness, umami (savory), and a wide range of specific odors; however, for drugs, sweetness and bitterness are most important. Flavor enhancers and taste modifiers can be used to modify the sweetness profile of a sweetening agent or to mask off-flavors. For example, organic acids such as aspartic and glutamic acids are known to reduce bitterness.

Dosage Forms

Flavors commonly are used in pharmaceutical oral dosage forms such as chewable tablets, orally disintegrating tablets, oral solutions, and oral suspensions to mask objectionable drug tastes and to make the formulation more palatable, thus promoting patient compliance. One example is that of a peppermint or cherry flavor to mask bitter tastes in oral dosage forms.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include molecular weight, particle size, solubility, mouth feel, flavor, and color.

General Chapters

The following general chapters may be useful in ensuring consistency in flavor functions: [\(429\)](#), [\(621\)](#), [\(651\)](#), [\(731\)](#), [\(741\)](#), *Optical Rotation* [\(781\)](#), [\(786\)](#), [\(831\)](#), and [\(841\)](#).

Additional Information

Products that contain aspartame must include a warning on the label stating that the product contains phenylalanine. Sugar alcohols have a glycemic index well below that of glucose. However, sorbitol is slowly metabolized to fructose and glucose, which raises blood sugar levels. Sugar alcohols in quantities generally greater than 20 g/day (adults) act as an osmotic laxative, especially when they are contained in a liquid formulation. Preservative systems should be carefully chosen to avoid incompatibility with the sweetener, and some sweeteners are incompatible with certain preservatives.

FREE RADICAL SCAVENGER

Description

Free radical scavengers are used in radiopharmaceuticals to preferentially interact with radiation-produced oxidative or reductive free radicals that otherwise would result in degradation of formulation components. Free radical scavengers are also used to maintain radiochemical purity over a longer period of time.

Physical Properties

Free radical scavengers must be readily soluble in aqueous solution.

Chemical Properties

Free radical scavengers must be capable of preferentially interacting with free radicals without causing other undesirable effects on the radiopharmaceutical. Examples of free radical scavengers include ascorbic acid, methylene blue, cobaltous chloride, and aminobenzoic acid.

Functional Mechanism

Radiation emitted from radiopharmaceuticals interact with water and other molecules to produce free radicals. Free radical scavengers preferentially interact with these free radicals minimizing deleterious interactions with the radiopharmaceutical that would result in radiochemical impurities.

Dosage Forms

Free radical scavengers are used primarily in liquid radiopharmaceutical dosage forms intended for injection.

Performance-Related Properties

Potential performance-related properties for free radical scavengers are solubility, appropriate oxidizing/reducing properties and ability to scavenge radiation-produced free radicals.

General Chapters

The following general chapters may be useful in ensuring consistent functions of selected free radical scavengers: [\(621\)](#) and [\(821\)](#).

GELLING AGENT

Description

Gelling agents are excipients used to turn a liquid phase into a semisolid. Some gelling agents form a cross-linked network, whereas others achieve gelation by physical entanglement of macromolecular chains.

Physical Properties

Gelling agents are ingredients that undergo a high degree of cross-linking or association when dissolved or dispersed in the appropriate media. Structural properties based on differences in composition, linkage

types/and patterns, chain shapes, and degree of polymerization can dictate such physical properties as solubility, flow behavior (thixotropic), gelling potential, and/or surface and interfacial properties.

Typical physical properties imparted by gelation may include thermal sensitivity and rheological behavior such as thixotropy and/or viscoelasticity.

Other factors that can influence gelling agent properties include: temperature, pH, polymer concentration, cross-linker concentration, and the presence of metal cations.

Chemical Properties

Some of the most common gelling agents used in pharmaceutical formulations include the following: 1) hydrophilic polymers such as cellulose derivatives, alginates, acacia, tragacanth, xanthan gums, carbomers, poloxamers, polysorbates, and polyvinyl alcohol; and 2) clays and other inorganic materials such as colloidal silicon dioxide.

Polymer type, functionality, degree of substitution, degree of polymerization, pH, and metal cations can all have an influence on replication of the gelation properties from batch to batch.

Functional Mechanism

The cross-linking or association of gelling agents, when dissolved or dispersed in the appropriate media, result in an increase in viscosity and gelation as a function of structure, temperature, and concentration.

Dosage Forms

Gelling agents are used in formulations for oral administration such as suspensions and pastes to improve handling and use and to modify drug release from solid oral dosage forms. Gelling agents are also used in topical and transdermal formulations such as creams, lotions, gels, and ointments to increase their viscosity.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include degree of polymerization, degree of substitution, functionality, metal cations, loss on drying, and viscosity.

General Chapters

The following general chapters may be useful in ensuring consistency in selected gelation functions: [\(3\)](#), [Spectroscopic Identification Tests \(197\)](#), [\(731\)](#), [\(791\)](#), [\(911\)](#), [\(912\)](#), and [\(1911\)](#).

GLIDANT AND/OR ANTICAKING AGENT

Description

Glidants are used to promote powder flow, whereas anticaking agents are used to reduce the caking or clumping that can occur when powders are stored in bulk. Often, these excipients can serve both purposes. In addition, glidants and anticaking agents reduce the incidence of bridging during the emptying of powder hoppers and during powder processing. Examples include talc and colloidal silicon dioxide.

Physical Properties

Primary physical properties of importance for glidants and anticaking agents are particle size distribution, particle morphology, and surface area. They may be slightly hygroscopic. Although these agents typically comprise a small portion of the formulation, due to their large surface area, the release of the drug may be affected due to adsorption.

Chemical Properties

Glidants and anticaking agents typically are finely divided inorganic materials and are insoluble in water.

Functional Mechanism

Glidants are thought to work by a combination of adsorption onto the surface of larger particles and reduction of particle-particle adhesive and cohesive forces, thus allowing particles to move more easily relative to one another. In addition, glidants may be dispersed among larger particles and reduce friction

between these particles. Anticaking agents absorb free moisture that otherwise would allow the development of particle–particle bridges that are implicated in caking.

Dosage Forms

Glidants and anticaking agents are used in all types of solid dosage forms as tablets, capsules, granules, and pellets to promote particle flow and reduce caking or clumping that can occur during processing or storage of the bulk materials.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include primarily particle size distribution, moisture content, and surface area.

General Chapters

The following general chapters may be useful in ensuring consistency in glidant or anticaking agent functions: [\(429\)](#), [\(731\)](#), [\(786\)](#), [\(846\)](#), [\(921\)](#), and [\(1181\)](#).

HUMECTANT

Description

Humectants are hygroscopic substances that function to retain water or prevent moisture loss in a product or application site (e.g., skin or hair).

Physical Properties

Humectants may be in liquid or solid form.

Chemical Properties

Humectants may be of natural or synthetic origin. They typically contain hydrophilic groups such as hydroxyl, carboxyl or esterified groups, or amines that interact favorably with water through hydrogen bonding. Examples of humectants include propylene glycol, glycerin, polyethylene glycol, and hyaluronic acid.

Functional Mechanism

Humectants attract and retain moisture due to interactions between water, polar functional groups, and hydrogen bonding. Moisture retention is typically by absorption. Humectants are typically hygroscopic. Humectants may have emollient properties.

Dosage Forms

Humectants may be used in topical dosage forms such as ointments, creams, and emulsions to facilitate the incorporation and retention of moisture into the dosage form. Humectants can increase skin hydration in topical preparations and may be used in shampoos with ingredients that otherwise may have a drying effect.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include particle size in solid form, moisture content, water activity, and hygroscopicity.

General Chapters

The following general chapters may be useful in ensuring consistency in selected humectant functions depending on physical state (solid or liquid form): [\(731\)](#), [\(921\)](#), and [Application of Water Activity Determination to Nonsterile Pharmaceutical Products \(1112\)](#).

LIPOSOME-FORMING AGENT

Description

Liposomes are closed spherical vesicles consisting of an aqueous core surrounded by one or more bilayer membranes consisted of liposome-forming agents. They can be used as a carrier for drugs. These bilayer

membranes are composed of lipid molecules (e.g., phospholipid or egg lecithin), cholesterol, and other additives that modify the lamellarity and release of drug.

Physical Properties

Phospholipids are amphiphilic, surface-active molecules with a high tendency to aggregate both in the dry state and when fully hydrated. Egg lecithins, which also contain phospholipids, are soluble in aliphatic and aromatic hydrocarbons, halogenated hydrocarbons, mineral oil, and fatty acids. They are practically insoluble in cold vegetable and animal oils, polar solvents, and water. When mixed with water, however, phospholipids and lecithins hydrate to form emulsions.

Cholesterol and its derivatives have the function to build and maintain membranes and modulate the membrane fluidity of liposomes. The hydroxyl group on cholesterol interacts with the polar heads of the membrane phospholipids, whereas the bulky steroid rings and the hydrocarbon chain are embedded in the membrane, alongside the nonpolar fatty acid chains of other lipids. Through the interaction with the phospholipid fatty acid chains, cholesterol increases membrane packing, which both alters membrane fluidity and maintains membrane integrity of liposomes. The physical properties of cholesterol and derivatives include density, dielectric constant, viscosity, melting point, solubility, and specific rotation.

Chemical Properties

Phospholipid molecules comprise a polar head group coupled to fatty acid tails. The head group, in turn comprises either a base such as choline, a sugar molecule such as inositol, or an amino acid such as serine linked via a phosphate group to glycerol. The two fatty acid tails are also linked to the glycerol residue. The chemical properties will be governed by the nature of the fatty acid substituents (saturated or unsaturated) and the type of polar head group.

Cholesterol, as the name suggests has a steroid four-ring structure with a hydroxy substituent on the A-ring, two methyl substituents, and a methylheptyl substituent on the D-ring.

Other saturated or unsaturated lipid materials may also be incorporated into the liposomal membrane.

The lipid composition information includes the percentage of each lipid and fatty acid, positional specificity of acyl side chains, and degree of fatty acid unsaturation. In the case of naturally sourced lipid mixtures (e.g. egg lecithin), the lipid composition as a range of percentages for each stated lipid present in the mixture and its fatty acid composition should be determined.

Additional chemical properties of liposome-forming agents include molecular weight, elemental impurities, trans fatty acids, etc.

Functional Mechanism

Liposome-forming agents form liposomes by self-arrangement into bilayer vesicles when they are exposed to an aqueous environment at the appropriate lipid-to-water ratio and temperature. The tetracyclic ring structure of cholesterol contributes to the fluidity of the liposome membrane, as the molecule is in a trans conformation, making all but the side chain of cholesterol rigid and planar.

Dosage Forms

Liposome-forming agents may be used in injections, topical creams, tablets, and capsules.

Performance-Related Properties

Solubility, viscosity, isoelectric point, saponification value, melting point, CMC, and temperature of transition (T_m) are important properties for phospholipids. CMC is used to indicate the tendency of micelle formation. T_m is the temperature of transition from crystalline to mesomorphic (liquid crystalline) state. Other properties that may be important for excipient performance in a dosage form include properties related to identity, HLB value, molecular weight distribution, loss on drying, and elemental impurities.

General Chapters

The following general chapters may be useful in ensuring consistency in selected liposome-forming agent functions: [\(1\)](#), [\(71\)](#), [\(85\)](#), [\(621\)](#), [\(695\)](#), [\(731\)](#), [\(891\)](#), [\(911\)](#), [\(912\)](#), [\(913\)](#), [\(1151\)](#), [\(1241\)](#), and [\(1911\)](#).

LUBRICANT

Description

Lubricants typically are used to reduce the frictional forces between particles, particles and metal contact surfaces, and metal-to-metal contact surfaces of manufacturing equipment. In solid dosage forms, lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule-filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall. Common minerals such as talc or silica, fatty acid esters, and fats (e.g., vegetable stearin, magnesium stearate, or stearic acid) are the most frequently used lubricants in tablets or hard gelatin capsules.

There are two main types of lubricants: boundary and fluid film. Boundary (solid) lubricants are agents added in small quantities to tablet and capsule formulations to improve certain processing characteristics and do not melt under pressure. Fluid film lubricants may be solids that melt under pressure (e.g., stearic acid or hydrogenated vegetable oil) or liquid (e.g., vegetable oils, light mineral oil, or glycerin). Fluid film lubricants are used in a variety of other applications including equipment lubrication.

Physical Properties

The physical properties that are important for the function of boundary lubricants include particle size, surface area, hydration state, polymorphic form, and solid state/thermal behavior for solid lubricants. For metal stearates, the stearate:palmitate ratio, polymorph, hydrate state, and moisture content may be important. Boundary lubricants are salts of long-chain fatty acids (e.g., magnesium stearate) or fatty acid esters (e.g., sodium stearyl fumarate) with a polar head and fatty acid tail. Fluid film lubricants are solid fats (e.g., hydrogenated vegetable oil, type 1), glycerides (glyceryl dibehenate and distearate), or fatty acids (e.g., stearic acid) that melt when subjected to pressure.

Chemical Properties

Boundary lubricants are metal salts, and the properties of the counterion, e.g., magnesium or sodium, may impact drug substance stability. Fluid film lubricants, either solid or liquid, are typically saturated fatty acids or fatty acid esters. However, they may contain trace levels of unsaturated fatty acids that are prone to oxidation (rancidity). Hydrocarbon lubricants, e.g., light mineral oil, are chemically inert, provided that no unsaturated bonds exist.

Functional Mechanism

Boundary lubricants function by adhering to solid surfaces (granules and machine parts) and by reducing the particle-particle friction or the particle-metal friction. The orientation of the adherent lubricant particles is influenced by the properties of the substrate surface. For optimal performance, the boundary lubricant particles should be composed of small, plate-like particles or stacks of plate-like particles. Fluid film lubricants melt under pressure and thereby create a thin fluid film around particles and on the surface of punches and dies in tablet presses, which helps to reduce friction. Fluid film lubricants resolidify after the pressure is removed. Liquid lubricants are released from the granules under pressure and create a fluid film. They do not resolidify when the pressure is removed but are reabsorbed or redistributed through the tablet matrix over the course of time.

Dosage Forms

Lubricants are typically used in solid dosage forms such as tablets, capsules, granules, and pellets to reduce friction between the particles and the metal-contact surface such as the contact that can occur between the punch/die and the formulation during tableting. Liquid lubricants may be used on manufacturing equipment (e.g., light mineral oil) to reduce metal-to-metal friction.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include particle size, surface area, hydration state, polymorphic form, purity, and moisture content. Viscosity may be an important

property of liquid lubricants.

General Chapters

The following general chapters may be useful in ensuring consistency in lubricant functions: [\(429\)](#), [\(695\)](#), [\(696\)](#), [\(731\)](#), [\(776\)](#), [\(786\)](#), [\(846\)](#), [\(891\)](#), [\(911\)](#), [\(912\)](#), [\(913\)](#), [\(914\)](#), [\(921\)](#), and [\(941\)](#).

Additional Information

Certain lubricants, particularly those used in effervescent dosage forms, do not fall into the chemical categories defined above. These materials are used in special situations, and they are not suitable for universal application. Talc is an inorganic material that may have some lubricant properties. It is generally used in combination with fluid film lubricants to reduce sticking to punches and dies.

MUCO-ADHESIVE

Description

Muco-adhesives are temporary adhesives designed to maintain contact between the applied drug delivery system and a mucosal surface. A related functional category is *Adhesive (Pressure Sensitive)*.

Physical Properties

Muco-adhesives are hydrophilic, viscoelastic materials that adhere to mucosal membranes upon application of light contact pressure.

Chemical Properties

Muco-adhesive polymers often have numerous hydrophilic groups, such as hydroxyl, carboxyl, amide, and sulfate. Common muco-adhesives include PEG, polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylic acid, polyhydroxyethyl methacrylate, and chitosan.

Functional Mechanism

Muco-adhesives attach to mucus or the cell membrane by various interactions such as the following:

- Nonspecific, noncovalent interactions that are primarily electrostatic in nature
- Hydrogen bonding with similar groups on a biological surface
- Binding to specific receptor sites on the cell or mucus surface (lectins and thiolated polymers)

Muco-adhesive polymers often swell in water and thus expose the maximum number of adhesive sites and allow for polymer chain flexibility, thereby facilitating adhesiveness. Other mechanisms may be involved depending on the polymer.

Dosage Forms

Muco-adhesives are primarily used in tablets, ointments, gels, and systems and are often delivered via buccal, oral, nasal, ocular, vaginal, and rectal routes. The buccal and sublingual routes are considered as the most commonly used routes.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include tensile strength and resistance to shear, which can be affected by a number of factors, including hydrophilicity, amphiphilicity, molecular weight, cross-linking, swelling, pH, and concentration of active polymer.

General Chapters

The following general chapters may be useful in evaluating the suitability of muco-adhesive: [\(3\)](#), [Mucosal Drug Products—Product Quality Tests \(4\)](#), [\(881\)](#), [\(912\)](#), [\(1911\)](#), and [\(791\)](#).

Additional Information

Shaikh R, Singh TRR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. *J. Pharm. Bioallied Sci.* 2011;3(1):89–100

OINTMENT BASE

Description

Ointment bases are viscous semisolids comprising the major component of a final ointment product, thereby controlling the physical properties of the ointment. Ointment bases are classified as: 1) oleaginous ointment bases [that are anhydrous, do not absorb water readily, are insoluble in water, and are not removable by water (e.g., petrolatum)]; 2) absorption ointment bases [that are anhydrous and absorb some water but are insoluble in water and are not water removable (e.g., lanolin)]; 3) emulsion ointment bases [that are water-in-oil or oil-in-water emulsions and are hydrous, absorb water, and are insoluble in water (e.g., creams of water, oils, waxes, or paraffins)]; and 4) water-soluble ointment bases [that are anhydrous and absorb water and are soluble in water and are water removable (e.g., PEG)].

Physical Properties

Ointment bases have relatively high viscosities because of the amount of solid or semisolid material dispersed throughout the product/preparation.

Chemical Properties

Ointment bases, in some cases, are selected for their inert properties, the improved stability of active ingredients dispersed in them, ability to repel water, decrease transepidermal water loss, and increase skin hydration. As described above, ointment bases may comprise oleaginous mixtures, water-soluble anhydrous polymers, or high viscosity relatively hydrophobic emulsions that contain surfactants to facilitate their formation and stability.

Functional Mechanism

Ointment bases serve as vehicles for topical application of medicinal substances. They are also used as emollients and cutaneous protectives.

Dosage Forms

Ointment bases are heavily utilized, primarily in topical formulations. Ointment bases may also be used in a variety of other dosage forms such as suppositories, medicated sticks, and formulations that are administered to the eye, ear, rectum, and nose.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include hydrocarbon chain length, rheology, fatty acid or fatty alcohol composition, hydrophilicity, and hydrophobicity.

General Chapters

The following general chapters may be useful in ensuring consistency in selected ointment base functions: [\(651\)](#), [\(911\)](#), [\(912\)](#), [\(913\)](#), and [\(401\)](#).

Additional Information

The type of ointment base utilized in a formulation has a major impact on the delivery of a drug substance. Some bases produce a local drug substance effect on or in the tissue to which it is applied. Examples of local therapeutic treatment might be minor topical infections, itching, burns, diaper rash, insect bites, athlete's foot, corns, dandruff, hemorrhoids, and psoriasis. Other bases may deliver a drug substance such that it has a systemic effect as a result of percutaneous absorption. Examples of systemic therapeutic treatments are be found in pain relief, cardiology, hormone replacement, smoking cessation, and hypertension.

OPACIFIER

Description

Opacifiers are excipients that are added to film-forming agents, hard capsule shells, and tablet matrices. Opacifiers may also be added to soft shell capsules, but this is less common, and opacifiers are also

commonly used in sunscreens and cosmetics. In the case of capsule shells and coatings, the goal is to make the film opaque to hide or protect the internal contents from light. Opacifiers can make the product more stable in the case of drugs prone to photodegradation or improve the product appearance: for example, to hide spots or improve a mottled appearance. The key property is a high refractive index, which increases light scattering and makes the coating opaque to the eye. Opacifiers such as titanium dioxide are typically used in the 10%–30% dry weight range and in the 5%–25% range in the coating dispersion.

Physical Properties

Key physical properties that are relevant to opacifier performance are the factors that affect light scattering and distribution in the film or coating. These include particle size, refractive index, reflectiveness, water content, pH (changes in pH can affect physical form of some opacifiers), and density. For some opacifiers such as titanium dioxide, the index of refraction depends upon physical form; for example, the anatase form has a different refractive index from the rutile form of titanium dioxide, which can affect the light scattering properties and hence appearance of a coating or dosage form. Because of differences in whiteness, the anatase form is more commonly used even though the rutile form is the most stable. Examples of opacifiers include titanium dioxide, zinc oxide, zinc acetate, and sometimes calcium carbonate. Most opacifiers are inorganic material that have a high refractive index. Oxidation state and ferric oxides can change color as their oxidation state changes from yellow to red to black.

Chemical Properties

Opacifiers are substances that have a high refractive index. Typically, opacifiers have a particle size that is in the nanometer range. Many opacifiers do not change color or structure when exposed to light for long periods of time or intense light over a short period of time (e.g., light chamber testing).

Functional Mechanism

Opacifiers are materials with high refractive index and thus scatter light and make the film opaque, i.e. light cannot pass through the film without scattering, thus, making the film opaque to light.

Dosage Forms

Opacifiers are used in film coatings, so dosage forms that are coated often use opacifiers, including tablets and both hard and soft capsule shells. They can sometimes be used in tablet matrices and in some liquid preparations (e.g., suspensions) but this is not typical.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include particle size, particle morphology, specific surface area, refractive index, opacity, polymorphic form, color, and color stability. Other factors such as pH sensitivity can be important, for example, sometimes opacifiers such as aluminum oxide are used to make lakes that reduce the solubility of dyes, but at extreme pH, the dye and carrier can dissociate and cause problems with coating stability.

General Chapters

The following general chapters may be useful in ensuring consistency in opacifier function: [\(429\)](#), [\(786\)](#), [\(776\)](#), [Color and Achromicity \(631\)](#), and [\(831\)](#).

PERMEATION ENHANCER

Description

Permeation enhancers play a vital role in drug absorption, thus increasing the bioavailability of poorly absorbed drugs. Permeation enhancers are used especially for transdermal drug delivery by facilitating drug penetration into and through the skin.

Physical Properties

Some physical properties that are desired in a permeation enhancer include good solvent properties for the drug, skin permeation enhancement, and cosolvency.

Chemical Properties

Some chemical properties that are desired in a permeation enhancer include compatibility with drugs and excipients and chemical stability.

Examples of common skin permeation enhancers include alcohols, amides, esters, glycols, fatty acids and fatty alcohols, pyrrolidones, sulfoxides, surfactants (cationic, anionic and non-ionic), ureas, and phospholipids.

Functional Mechanism

Penetration enhancers facilitate drug permeation through the skin by decreasing the impermeability of the skin. In principle, an enhancer may act on skin so that drug diffusivity or drug solubility in the skin—or a combination of both—is modified, leading to an increase in transport of the drug. They may act by one or more of three main mechanisms: 1) disruption of the highly ordered structure of stratum corneum lipid; 2) interaction with intercellular protein; and 3) improved partitioning of the drug, co-enhancer, or solvent into the stratum corneum.

Dosage Forms

Permeation enhancers are most generally used in topical and transdermal systems.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include solubility, partition coefficient, and rheological behavior.

General Chapters

The following general chapter may be useful in ensuring consistency in selected permeation enhancer functions: [\(3\)](#), [\(197\)](#), and [\(1911\)](#).

Additional Information

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PHARMACEUTICAL WATER

Description

Water is used as a solvent, vehicle, diluent, or filler for many drug products, especially those supplied in liquid form.

Physical Properties

Water is liquid at normal temperature and pressure. It forms ice at freezing temperatures of 0° or lower, and it vaporizes at a normal boiling temperature of 100°, depending on atmospheric pressure. Vaporized

water in the form of steam is used for sterilization purposes because the latent heat of steam is significantly higher than that of boiling water.

Chemical Properties

Water in its pure form is neutral in pH and has very low conductivity and total organic carbon (TOC). However, pH, conductivity, and TOC are affected by storage conditions and exposure to gases in the air. Exposure to atmospheric carbon dioxide lowers the pH of water. Storage in plastic containers may increase the TOC content of water over time. Water stored in glass containers may result in an increase in pH and conductivity over time.

Functional Mechanism

A solvent is able to dissolve materials because it is able to disrupt the intermolecular attractive forces and to allow the individual molecules to become dispersed throughout the bulk solvent. Water is a favored solvent and vehicle in the majority of applications because it is easy to handle, safe, and inexpensive.

Dosage Forms

Pharmaceutical water is typically used in creams, emulsions, films, foams, gels, injections, irrigations, liquids, lotions, ointments, rinses, shampoos, solutions, sprays, and suspensions for parenteral, oral, topical and transdermal, mucosal, and radiopharmaceutical drug products in various manners. It is primarily used as a solvent, vehicle, diluent, or filler in the formulations. Pharmaceutical water is also frequently used as a processing aid, e.g., during wet granulation of solid dosage forms. *USP* includes monographs for multiple grades of pharmaceutical water.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include pH, conductivity, and TOC.

General Chapters

The following general chapters may be useful in ensuring consistency in selected pharmaceutical water functions: [\(1\)](#), [\(85\)](#), [Total Organic Carbon \(643\)](#), [\(645\)](#), [\(791\)](#), [Water for Hemodialysis Applications \(1230\)](#), and [Water for Pharmaceutical Purposes \(1231\)](#).

PHYSICAL-CHEMICAL IDENTIFIER

Description

Physical-chemical identifiers are added to pharmaceutical products to unambiguously identify the product for the purposes of anticounterfeiting. Although typically used with solid oral dosage forms, physical-chemical identifiers can be used in other dosage forms such as oral liquids or topical preparations. The amount used in the product is usually very small so as to not affect the performance of the product. Physical-chemical identifiers are typically used with products that are of high value and have a high susceptibility to counterfeiting. This group does not include radioactive compounds or physical devices such as miniature tracking devices but rather includes items that can be incorporated into the formulation of the product. As a best practice, the inclusion of physical-chemical identifiers should be part of a complete program to readily identify the product as genuine.

Physical-chemical identifiers can be incorporated into the product in many ways. For solid and liquid oral dosage forms, they may be a part of the formulation. Coating or printing onto solid dosage forms are possible as well with the introduction of high definition printing and alternative coating systems.

There are many substances that can be used as physical-chemical identifiers. One group consists of simple stable inert compounds typically referred to as taggants or tracers that are incorporated into the product, which are not visible or detectable without the use of analytical technology. These would be substances that would be added in small quantities and uniquely identifiable or substances that are a part of the formulation that has a unique property only known to the manufacturer such as differences in

isotopic distribution of an element in the substance or differences in physical forms of the substance. Unique identifiers may also include inert molecular taggants.

Another group would be physical-chemical identifiers that form a visible but unrecognizable or unknown pattern that can be printed on the tablet or capsule such as a Quick Response (QR) code. Other visible physical-chemical identifiers would include coatings that are unique colors not readily replicated such as pearlescent coatings.

Physical Properties

Due to the large number of physical-chemical identifiers and their unique properties, there is no specific physical property common to all physical-chemical identifiers. However, the physical properties of the physical-chemical identifiers should be compatible with the dosage form such as adequate solubility in an oral liquid where precipitation or "salting out" of one or more ingredients or change in color could occur during storage. As it is possible that a physical property is the key to the uniqueness of the physical-chemical identifier, it is important to maintain the consistency of the unique physical property from batch to batch.

Chemical Properties

Due to the large number of physical-chemical identifiers and their unique properties, there is no specific chemical property common to all physical-chemical identifiers. However, the chemical properties of the physical-chemical identifiers should be compatible with the dosage form. As it is possible that a chemical property is key to the uniqueness of the physical-chemical identifier, it is important to maintain the consistency of the unique chemical property from batch to batch.

Functional Mechanism

The functional mechanism of physical-chemical identifiers is based on the ability to be detected for authentication purposes but not detectable to the patient or others who do not possess the expertise to determine the physical-chemical identifier and/or its identifiable characteristic that makes it unique. Examples include vanilla, titanium dioxide, ferric oxide, and magnesium aluminum silicates, but a multitude of other examples exist.

Dosage Forms

Physical-chemical identifiers are used primarily in solid oral or liquid oral dosage forms.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include the physical or chemical property that imparts the uniqueness to the product. Physical-chemical identifiers function in a diverse number of ways that uniquely identify the product. Therefore, an important CMA would be that the physical-chemical identifier functions as expected for the shelf life of the product. The physical-chemical identifier should be generally accepted as safe or listed in the Inactive Ingredient Database.

General Chapters

None

Additional Information

General chapters related to how the physical-chemical identifier functions in the dosage form may be useful in ensuring consistency. It should be noted that the excipients can impart the unique characteristic for each product in a diverse number of ways, and therefore the appropriate chapter should reflect the specific attributes or properties important for this functionality. Other sources of information may include the CFR and the document FDA Guidance for Industry "Incorporation of Physical-Chemical Identifiers into Solid Oral Dosage Form Drug Products for Anticounterfeiting".

PHYSICAL FORM STABILIZER

Description

Physical form stabilizers are used to keep an ingredient in a dosage form in the desired physical state, typically the amorphous state. There are a number of excipients that can work as a physical form stabilizer such as povidones, povidone derivatives, polyoxylglycerides, polyethylene glycols, tocopherols, surfactants, plasticizers, hypromellose, hypromellose derivatives, water-soluble cellulose esters, polyhydric alcohols (e.g., sorbitol), hydrophilic synthetic polymers, and a combination of the excipients. See *Stabilizer* for a related functional category.

Physical Properties

The key physical property of physical form stabilizers is the ability to keep the target ingredient in the desired physical state during the manufacturing and shelf life of the product. This can be assessed by measuring the T_g or melting point or amorphousness/crystallinity of the excipient(s) used as a physical form stabilizer. Other excipients may require tests to show that the excipient will function as expected, e.g., determination of CMC for surfactants and hydroxypropyl and methoxy content for hypromellose using nuclear magnetic resonance.

Other physical properties include being a solid at room temperature, solubility in aqueous media, compatibility with pharmaceutical processing such as solvent spray drying or the hot melt extrusion process, and compatibility with the bulk drug to form an amorphous drug excipient dispersion.

Chemical Properties

The physical form stabilizer must be compatible with the other ingredients, including the active ingredient in the product.

Physical form stabilizers typically are rich in hydroxyl groups. As such they may form esters with organic acids or amides with primary or secondary amines. They may also contain groups that provide for differences in solubility at different pHs.

Functional Mechanism

Physical form stabilizers typically work by one or more of the following mechanisms: elevation of T_g , reduction in molecular mobility, favorable intermolecular interactions with the drug, and establishment of phase equilibrium with the drug (minimization of free energy). Some stabilizers may work by solubilizing the drug and prevent the formation of hydrates.

Additionally, amorphous bulk drugs or intermediates are frequently used to advantage in the oral delivery of poorly water-soluble drug products. As high energy forms of the bulk drug, amorphous forms of a drug are often prone to crystallization to a more stable, but less soluble form, particularly in the presence of free moisture. Conversion to a crystalline (lower energy) form will result in a consequent loss of dissolution and bioavailability. Physical form stabilizers are able to combine with the amorphous drug at a molecular level and prevent or retard conversion to a crystalline form. Nevertheless, conversion to a crystalline form is possible, particularly in the presence of free moisture and/or higher relative humidity, and the use of moisture vapor-impervious packaging and desiccants may be required.

Dosage Forms

Physical form stabilizers are used primarily in tablets (e.g., hot melt extrusion, spray-dried dispersions), but can be used in pellets, capsules, suspensions, and granules.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include melting point, glass transition temperature (T_g), free moisture content, molecular weight, and molecular weight distribution.

General Chapters

The following general chapters may be useful in ensuring consistency in selected physical stabilizer functions: [\(695\)](#), [\(741\)](#), [Nuclear Magnetic Resonance Spectroscopy \(761\)](#), [\(854\)](#), [\(891\)](#), [\(941\)](#), [\(921\)](#), [\(1112\)](#), [Near-Infrared Spectroscopy \(1119\)](#), and [Raman Spectroscopy \(1120\)](#).

PLASTICIZER

Description

A plasticizer is a low molecular weight substance that, when added to another material (usually a polymer) imparts flexibility, resilience, and ease of handling. Plasticizers are key components that determine the physical properties of polymeric pharmaceutical systems.

Physical Properties

The most common plasticizers are low molecular weight (<500 Da) solids or liquids. They typically have low melting points (<100°) and can be volatile (i.e., exert an appreciable vapor pressure) at ambient temperature. Plasticizers can reduce the T_g of the system to which they are added.

Chemical Properties

Many modern plasticizers are synthetic esters such as citrates and phthalates. Traditional pharmaceutical plasticizers include oils, polyethylene glycols, sugars, and their derivatives. Other commonly used plasticizers include water and triacetin. Plasticizers typically do not react with other components of drug dosage forms.

Functional Mechanism

Plasticizers function by increasing the intermolecular and intramolecular mobility of the macromolecules that comprise polymeric materials. They achieve this by affecting the normal intermolecular and intramolecular interactions and bonding mechanisms in such systems. The most effective plasticizers exert their effect at low concentrations, typically less than 5% (w/w).

Dosage Forms

Plasticizers are used in solid drug products (tablets, capsules, pills, granules, and pellets), creams, ointments, films, systems, and mucosal drug products to enhance the flexibility and resilience of the formulation and improve handling. Plasticizers commonly are added to film coatings (aqueous and nonaqueous systems) and capsule shells (hard and soft varieties) to improve their workability and mechanical ruggedness. Without the addition of plasticizers, such materials can split or fracture prematurely or hinder dissolution. Plasticizers also are added to semisolid pharmaceutical preparations such as creams and ointments to enhance their rheological properties. The use of phthalates should be considered carefully as the use of certain phthalates as excipients in Center for Drug Evaluation and Research (CDER)-regulated products is limited.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include composition, rheology, molecular weight, melting points, compatibility with the excipients, drug substance, and method of manufacture.

General Chapters

The following general chapters may be useful in ensuring consistency in selected excipient functions: [\(401\)](#), [\(467\)](#), [\(741\)](#), [\(831\)](#), [\(841\)](#), [\(891\)](#), [\(921\)](#), [\(911\)](#), [\(912\)](#), [\(913\)](#), and [\(914\)](#).

Additional Information

The choice of an appropriate plasticizer often is guided by reference to its solubility parameter, which is related to its cohesive energy density. Solubility parameter values for many common materials are tabulated in standard reference texts. To ensure maximum effectiveness, the solubility parameter of the plasticizer and the polymeric system being plasticized should be matched as closely as possible.

POLYMERIC MEMBRANE

Description

Polymeric membranes may be used to control the rate of diffusion of the drug out of a dosage form or delivery system to the absorption site.

Physical Properties

Examples of physical properties of a polymer membrane include: hydrophilic-hydrophobic character, polymer composition, molecular weight, molecular weight distribution, and membrane thickness.

Chemical Properties

Polymer membrane excipients are a very diverse group of materials and can have a range of different chemical properties, including polymer backbone and functional chemical groups. Examples of common polymer membranes use in transdermal delivery systems include ethylene vinyl acetate copolymers, microporous polypropylene, *n*-vinyl pyrrolidone copolymers, microporous polyethylene, polyurethanes, and silicone elastomers.

Functional Mechanism

Reservoir-type drug delivery systems contain an inert membrane enclosing an active agent that diffuses through the membrane at a finite, controllable rate. The release rate-controlling membrane can be nonporous so that the drug is released by diffusing directly through the material, or the material may contain fluid-filled micropores—in which case the drug may additionally diffuse through the fluid, thus filling the pores. In the case of nonporous membranes, the rate of passage of drug molecules depends on the solubility of the drug in the membrane and the membrane thickness. By varying the composition and thickness of the membrane, the dosage rate per area of the device can be controlled.

Dosage Forms

Polymeric membranes are most generally used in tablets, capsules, transdermal systems, and ophthalmic ointments and solutions.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include polymer type, permeability, membrane porosity, and membrane thickness.

General Chapters

The following general chapters may be useful in ensuring consistency in selected permeation enhancer functions: [\(3\)](#) and [\(881\)](#).

Additional Information

For capsule dosage forms, the capsule shell can function as a polymeric membrane. A distinct difference from the polymeric membranes or coatings covered by this functional category, however, is that the capsule shell typically dissolves or disperses at the administration site (e.g., the gut) so that its effect on drug release is short-lived. On the other hand, if the capsule shell is enteric-coated, it can persist in the gut and continue to affect drug release.

Terahertz (THz) spectroscopy can be used to determine membrane or coating thickness. Permeability of a membrane can be determined using a diffusion cell. However, dissolution testing is often used to evaluate membrane permeability and drug release from controlled release formulations.

The following reference is provided for additional information on this topic.

- Kandavilli S, Nair V, Panchagnula R. Polymers in transdermal drug delivery systems. *Pharm Tech*. 2002;26(5)62–81.

POLYMER FOR OPHTHALMIC USE

Description

Polymers are used in topical ophthalmic preparations to enhance the retention of active ingredients on the surface of the eye. In addition, polymers also can be components of artificial tears. Most water-soluble

polymers commonly used as film-forming agents in ophthalmic preparations can be categorized as follows: cellulose-based polymers, natural or biologically produced gums, and other synthetic polymers.

Physical Properties

To serve as an ophthalmic film-forming agent, a polymer typically must be at least slightly soluble in water, thus providing an appreciable range of usable concentrations. Such polymers often increase viscosity or exhibit film- or gel-forming properties when warmed to body temperature, when exposed to the pH or solute composition and ionic strength of the tear film, or when the product evaporates.

Chemical Properties

The finished product viscosity range that can be obtained with a film-forming agent is related to its chemical structure and molecular weight. Functional groups such as the pyruvate and acetate groups of xanthan gum can affect the relationship between viscosity and solution pH and ionic strength and also can determine film- and gel-forming properties. Polymer charge can influence interactions with the mucous layer of the eye. Molecular conformation, chain mobility, and degree of cross-linking also can affect the degree of swelling and thus performance.

Functional Mechanism

Film-forming agents for ophthalmic preparations can enhance the retention of active ingredients in the eye by a number of mechanisms. They can be used as simple viscosity-modifying agents to reduce the flow of the product, thereby slowing the rate of product loss after administration. They also can be used to form films on the surface of the eye so the drug remains deposited on the eye after the liquid portion of the product has been expelled or has evaporated. These agents can be formulated to produce a film or a gel when the product warms to body temperature (upon contacting the surface of the eye), mixing with the tear film, and/or evaporating. Some polymers have shown bioadhesive properties on the cornea and can increase drug retention. These polymers may also aid in reducing eye irritation by forming a lubricating layer on the surface of the cornea.

Dosage Forms

These polymers are typically used in ophthalmic ointments and solutions.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include solubility, rheology, degree of cross-linking, polymer molecular weight, and degree of substitution.

General Chapters

The following general chapters may be useful in ensuring consistent functions of polymers for ophthalmic use: [731](#), [Particulate Matter in Ophthalmic Solutions](#) ([789](#)), ([911](#)), ([912](#)), ([913](#)), ([1151](#)), ([1911](#)), ([401](#)), ([429](#)), ([467](#)), ([711](#)), ([881](#)), ([891](#)), and ([921](#)).

PRINTING INK COMPONENT

Description

Printing inks are mixtures of colorants and volatile solvents that are used to print various characters, shapes, and logos on tablets and capsule shells with various colors. Printing inks are used as a method of uniquely identifying a product where other means of identification may not be acceptable or workable. For example, tablets that have many coating layers or a coating layer containing an active ingredient would be a candidate for printing. Capsule shells, if marked, are printed with a unique printing to identify the product. Printing inks may be used to uniquely identify products for different markets even though the remainder of the formulation is the same.

Physical Properties

Printing inks are a mixture of colors and a solvent system to suspend the pigments where the solvent system quickly dries after application to prevent smudging or running. The properties of the mixture must

be compatible with the substrate to which the ink is being applied and must allow the colorants to remain on the dosage form from the printing unit process to the end user. Printing inks are usually suspensions and must be agitated to ensure uniform coloring and intensity from unit to unit and batch to batch. The ingredients in the printing ink must be combined in such a manner that the color meets the acceptance criteria from batch to batch. This would be dependent on the particle size, particle shape, color intensity, color, viscosity, and particle morphology. Printing inks when dry should contain low levels of organic solvents.

Although evaporation is a desired attribute of the printing ink formulation, the evaporation of the solvent during the printing process will cause the density and viscosity of the printing ink system to increase, leading to smearing and other undesired effects. A compatible solvent system diluent that can be added to decrease the viscosity and density to allow the printing ink application and drying to occur more consistently throughout the printing process should be formulated for use during the printing process.

Chemical Properties

Typically, inks contain solvents or solvent system to suspend the ink components and allow the solvents to evaporate quickly upon application along with the ink (coloring components). These ingredients must be compatible with each other and the ingredients of the surface onto which the ink is applied.

Functional Mechanism

Printing inks contain ingredients that during drying do not smear or run but can deposit the ink in place upon printing with the liquid components evaporating during drying leaving an imprint that is resilient. The suspending agents in printing inks should be compatible with the substrate (e.g., hypromellose for aqueous film-coated tablets) as this will assure maximum interaction with the substrate.

Dosage Forms

Printing inks are used primarily in tablets and capsule dosage forms.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include solubility, color, particle size of insoluble ingredients, viscosity, and dispersibility of insoluble ingredients.

General Chapters

The following general chapters may be useful in ensuring consistency in selected printing ink component functions: [§911](#), [§912](#), [§913](#), and [§914](#), [§61](#), [§62](#), [§631](#), [§429](#), [§232](#), [§233](#), and [§841](#).

Additional Information

Ingredients in the printing ink should comply with 21 CFR §206, Imprinting of Solid Oral Dosage Form Drug Products for Human Use, even though some ingredients comply with the *USP* and *NF* monographs. Further assurance for ingredients not listed in the *USP-NF* can be obtained by demonstrating compliance with the *Food Chemical Codex* and/or relevant European Union directives.

PROPELLANT

Description

Propellants are compounds that are gaseous under ambient conditions. They provide force to expel contents from a container.

Physical Properties

Propellants have boiling points well below ambient temperatures. A propellant's density for disperse systems and its solubility properties may be significant considerations when one selects a propellant. Aflurane and norflurane have liquid phase densities that are greater than that of water. Hydrocarbon propellants (butane, isobutane, and propane) and dimethyl ether have liquid phase densities that are less than that of water.

Chemical Properties

Propellants typically are stable materials. The hydrocarbon propellants (butane, isobutane, and propane) and dimethyl ether are all flammable materials. Aflurane, carbon dioxide, nitrogen, and norflurane are nonflammable. Nitrous oxide is not flammable but supports combustion. Hydrofluoroalkanes, which are not ozone-depleting substances (ODS), have replaced chlorofluorocarbon propellants, that are ODS and no longer permitted in foods, drugs, devices, or cosmetics by 21 CFR §2.125, Use of Ozone-Depleting Substances in Foods, Drugs, Devices, or Cosmetics.

Functional Mechanism

Propellant substances are low boiling point liquids or compressed gases that are relatively inert toward active ingredients and excipients. They can be characterized by four properties: existence in a liquid phase at ambient temperatures and useful pressures; solubility and/or miscibility in the rest of the formulation; density; and flammability. Their performance is judged by their ability to provide adequate and predictable pressure throughout the shelf life of the product.

Propellants that have both a liquid and gas phase in the product provide consistent pressures as long as there is a liquid phase present—the pressure in the headspace is maintained by the equilibrium between the two phases. In contrast, the pressure provided by propellants that have no liquid phase may change relatively rapidly as the contents of the container are expelled. As the headspace becomes larger, the pressure within the container falls proportionately. Propellants that have no liquid phase but have significant pressure-dependent solubility in the rest of the formulation have performance characteristics between those of the other two systems. In such cases, as the headspace increases the propellant comes out of solution to help to maintain the pressure of the system.

In metered-dose inhalers, the propellant has a liquid phase that is an integral part of the dispensed pharmaceutical product. Actuating the metering valve dispenses a defined volume of the liquid contents. The propellant spontaneously boils and provides atomizing and propulsive force. A predictable change in active concentration occurs from the beginning to the end of the container shelf life, as the liquid phase of the propellant vaporizes to reestablish the equilibrium pressure of the system as the headspace increases.

Dosage Forms

Propellants are used in pharmaceuticals (inhalation aerosols, nasal aerosols, and topical aerosols) to provide force to expel contents from a container.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include solubility, water content, density, boiling point, purity, impurity profile (related and unrelated), and high-boiling residues.

General Chapters

The following general chapters may be useful in ensuring consistency in selected propellant functions: [\(601\)](#), [\(621\)](#), [\(921\)](#), and [Propellants \(602\)](#).

REDUCING AGENT

Description

Reducing agents, or reductants, are used in the preparation of some radiopharmaceuticals to reduce the oxidation state of certain radiometals such as sodium pertechnetate (+7 oxidation state) to a lower oxidation state, so that they can be chelated or otherwise complexed by the intended ligand to form the final radiopharmaceutical.

Physical Properties

Reducing agents must be readily soluble in aqueous solution.

Chemical Properties

Reducing agents are sensitive to oxidation by atmospheric oxygen and oxidizing species in solution. Hence, lyophilized contents of kit vials must be filled with a nonoxidative gas such as nitrogen or argon. The

reducing agent also must be stable at the intended pH of the formulated product. A common example of a reducing agent is stannous ion in the form of salts (e.g., chloride, fluoride, and tartrate).

Functional Mechanism

The reducing agent must be present in sufficient quantity to reduce all of the radiometal atoms to the intended oxidation state but must not produce undesired reduction products or other impurities (e.g., stannous hydroxide precipitates).

Dosage Forms

Reducing agents are used primarily in liquid radiopharmaceutical dosage forms intended for injections.

Performance-Related Properties

Potential performance-related properties for reducing agents are water solubility and stability in the formulated environment.

General Chapters

The following general chapters may be useful in ensuring consistency in selected reducing agent functions: [\(621\)](#) and [\(821\)](#).

RELEASE-MODIFYING AGENT

Description

Release-modifying agents are used to alter the rate and/or time of release of the drug substance compared with that observed or anticipated for an immediate-release product. There are two types of modified release formulations, i.e. delayed-release formulations (also referred to as enteric-coated or gastroresistant formulations) and extended-release formulations (also referred to as prolonged-release, controlled-release, or sustained-release formulations).

For delayed-release, commonly used enteric polymers include methacrylic acid copolymers and cellulose acetate phthalate. For extended-release, hydrophilic polymers such as cellulose derivatives, hypromellose, and hydroxyl propyl cellulose are widely used in hydrophilic matrix drug delivery systems. Hydrophobic polymers such as ethyl cellulose can be used to achieve extended-release along with water-soluble pore formers. Other ingredients commonly combined with release-modifying ingredients, such as plasticizers, surfactants, colorants, fillers, and buffers are discussed in corresponding functional categories.

Physical Properties

The majority of release-modifying agents are polymers that differ in solubility, ease of erosion, rate of swelling, or sensitivity to the biological environment in which they are placed. An understanding of the functional mechanism of the release-modifying agent is necessary to identify potential important physical and chemical properties. The physical properties of the release-controlling excipient depend on the chemical type: hydrophilic polymer, hydrophobic polymer, semipermeable polymer blends, or lipid, wax, or biodegradable polymer (which can be hydrophilic or hydrophobic).

Hydrophilic polymers gel in contact with water or aqueous media. Because they should provide resistance to the mechanical action of the gastrointestinal tract during passage, they typically are higher molecular weight grades of the polymers. At the concentrations typically used during in vivo release, these high molecular weight polymers often do not exhibit Newtonian properties except in very dilute solution (if they are soluble). Formulators should monitor the kinetic and viscoelastic properties of the gels formed in the release medium.

Hydrophobic polymers are insoluble in water, and their solution properties are determined in nonaqueous solutions. The polymers used in the preparation of semipermeable membranes in osmotic pump devices also are insoluble in water, and similarly their solution properties are determined in nonaqueous solutions. Similarly, hydrophobic lipid-based materials are insoluble in water.

Chemical Properties

Release-modifying agents are composed of many different types and origins and are available in a range of grades that reflect considerable variation in their chemical structures and properties. Many of those agents are cellulose derivatives, such as water-soluble hypromellose and hydroxyl propyl cellulose, water-insoluble ethylcellulose, and the pH-sensitive polymer cellulose acetate phthalate. Synthetic polymers include methacrylate ester polymers, polyethylene oxide, etc.

Formulators must consider these variables during any investigation and consider the effects of chemical structure on excipient performance. Properties of interest may include chemical composition for copolymers and cellulosic derivatives, degree of ionization, molecular weight, degree of cross-linking, or, for lipids, fatty acid composition. Residual impurities from the manufacturing process, e.g., monomers, initiators, quenching agents, peroxides, and aldehydes, may affect drug substance stability and should be monitored.

Functional Mechanism

Upon contact with a biological fluid, release-modifying polymers may undergo a variety of physical changes such as swelling, gelling, dissolution, or erosion, each of which can be triggered by simple aqueous exposure or can be modulated by pH, osmotic stress, or interactions with bile or other intestinal contents. In addition to physical changes, polymers may undergo chemical degradation from the influence of acids, bases, enzymes, water, heat, and other factors. Any or all of these mechanisms may act in concert to control the rate at which the drug is released from the delivery system.

For hydrophilic matrices in which drug diffusion dominates release rate, the rate of drug release depends on the properties of the polymer gel and the nature of the continuous phase in the interstices of the gel that influences the dissolution and diffusion rates of the drug. In the case of eroding matrices, the gel erodes because of the mechanical action of the gastrointestinal tract as the water uptake increases, and the gel becomes more dilute, thus reducing the diffusion distance or releasing drug particles that subsequently dissolve. Hydrophobic matrix-forming materials are not soluble. Drug release from such systems is governed by drug diffusion through the tortuous pores that remain as soluble components dissolve.

Membrane-based drug delivery systems include polymer-coated tablets, capsules, and microspheres. Drug-release mechanisms from such systems are complex and depend on physicochemical characteristics of the drug and polymers or lipids used as well as biological factors in the case of biocompatible and biodegradable systems. Most commonly, drug release from such systems is governed by drug diffusion through the hydrated rate-controlling membrane. The drug release rate can often be modulated by plasticizer, surfactants, or water-soluble pore formers.

Delayed-release can be achieved via enteric coatings, which are insoluble in acidic (low pH) media but dissolve readily in neutral pH conditions. Those pH-sensitive polymers usually have acidic groups that can be ionized at neutral pH, resulting in the breakdown of coating and the release of drug substance. The triggering pH value could be fine-tuned by the variation of acidic groups and hydrophobic groups such as acetate groups.

Other modified-release systems for parenteral use include solid lipid nanoparticles and liposomes. The release mechanisms for these systems often involve a complicated interplay with biological processes such as potential clearance through the reticuloendothelial system, targeted delivery, and cellular uptake.

Osmotic pump devices are a special case of membrane delivery systems. The rate-controlling polymer is insoluble and semipermeable—i.e. it will allow water but not drug molecules—to diffuse through the membrane. Release is controlled by the osmotic pressure of the core components and the viscosity of the resulting solution or suspension. The drug, either in solution or as a suspension, is forced out of a hole in the membrane, which is typically drilled by a laser during product manufacture.

Dosage Forms

Polymers have been used to fabricate matrix-based or membrane-based drug delivery systems for oral, parenteral, transdermal, and other routes of administration. Such devices may take the form of tablets, capsules, systems, and others.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage for release-modifying agents are dependent upon the release-modifying mechanism and include: viscosity, substitution, solubility, particle size, elasticity and plasticity, kinetic and viscoelastic properties of gel, and mechanical strength.

General Chapters

The following general chapters may be useful in ensuring consistency in selected functions of release-modifying agents: [\(401\)](#), [\(429\)](#), [\(695\)](#), [\(696\)](#), [\(711\)](#), [\(731\)](#), [\(741\)](#), [\(761\)](#), [\(776\)](#), [\(786\)](#), [\(846\)](#), [\(854\)](#), [\(857\)](#), [\(881\)](#), [\(891\)](#), [\(911\)](#), [\(912\)](#), [\(913\)](#), [\(921\)](#), [\(941\)](#), [\(1174\)](#), and [\(1181\)](#).

Additional Information

Some release-modifying agents may include additives such as an antioxidant or an anticaking agent.

SOLVENT

Description

Solvents and cosolvents are used to dissolve the active ingredient(s) and excipients in liquid, semisolid, and solid drug products. The most common solvent is water. This section of the chapter will focus on organic solvents. Frequently, the hydrophobicity of active ingredients precludes their simple dissolution in a volume of water appropriate for the intended dosage form. Amphiphilic solvents and cosolvents can be used to improve the solubility or stability of lipophilic or insoluble active ingredients.

Physical Properties

Solvents or cosolvents need be in the appropriate state (liquid, semisolid, or solid) at the intended storage temperature of the drug product. The solvents' and cosolvents' dielectric constant and solubility parameters must ensure complete dissolution of the active ingredient and, if applicable, miscibility with water.

Chemical Properties

Solvents and cosolvents can be categorized into the following three classes: nonpolar solvents such as oils of plant origin; polar protic solvents such as ethanol, propylene glycol, or polyethylene glycols; and polar aprotic organic solvents such as dimethyl sulfoxide, benzyl benzoate, *N,N*-dimethylacetamide, 2-pyrrolidone, and *N*-methyl-2-pyrrolidone.

Functional Mechanism

The intermolecular interactions between solute-solute, solvent-solvent, and solute-solvent control the solubility of the active ingredient(s) in a solvent system. Dissolution is most appropriately viewed as an entropically driven process rather than an enthalpically driven one as solute molecules in solution are more randomly distributed than in the pure solid or liquid bulk phase. Solubility of the solute in a solvent or solvent system depends on the solvation ability of the solvent and the intrinsic ability of a solute molecule to interact with the solvent and thereby separate from the solute phase and transfer into the solvent phase.

Dosage Forms

Typical dosage forms that use solvents are aerosols, creams, films, foams, gels, irrigations, liquids, lotions, ointments, rinses, shampoos, soaps, solutions, sprays, and suspensions.

The parenteral use of solvents and cosolvents entails more restrictions than their use in oral drug products. In addition to the high standards of purity and sterility required, the formulator has to consider safety and tolerability of the (co-)solvent, as well as potential hypertonicity if the cosolvent is present at a high enough concentration.

For topical or mucosal routes of administration, the (co-)solvent might affect the structure or integrity of the epithelium, influencing permeation and release kinetics. Special care should be exercised if the drug product is intended to be applied to a diseased or compromised epithelium.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include attributes related to identity and impurities. The performance-related properties of the raw materials must enable the final drug product to comply with the relevant monographs (e.g., [\(1\)](#)). Solvents and cosolvents can interact with primary packaging and influence the level of leachables present in the drug product.

General Chapters

The following general chapters may be useful in ensuring consistency in selected solvents and cosolvents: [\(1\)](#), [Oral Drug Products \(2\)](#), [\(4\)](#), [\(5\)](#), [Ophthalmic Products—Quality Tests \(771\)](#), [\(1094\)](#), [\(1231\)](#), [Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems \(1663\)](#), [Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems \(1664\)](#), and [Orally Inhaled and Nasal Drug Products \(1664.1\)](#).

SORBENT

Description

Sorbents are materials that function to attract and hold other molecules. Sorbents are classified into two categories: absorbents and adsorbents. Absorbents are used to take up liquids or gases and are characterized by the volume of the substance being absorbed. Adsorbents take up liquids or gases by interacting with the surface of the adsorbing material and forming surface layers. Adsorbents are characterized by the surface interactions that occur.

Sorbents can be used as a rapid-release or modified-release or sustained-release agent for an active ingredient or to adsorb/absorb undesirable compounds like water, solvent molecules, or gas molecules (e.g., oxygen). Additional uses include adsorption of active ingredients to assist the manufacturing process (e.g., content uniformity, stability, minimization of the effects of the deleterious physical properties of the active ingredient on the manufacturing unit processes).

Examples of absorbents include cellulosic compounds, gums, fibers (e.g., cotton, rayon, and polyester), and sugars. Examples of adsorbents include activated charcoal, silica gel, zeolite, crospovidone, titanium dioxide, sodium carbonate, sodium chloride, and ascorbic acid.

Physical Properties

One property of sorbents is high surface area. High surface area is more important for adsorbents than absorbents in their function. It should be noted that the surface area should be controlled especially for adsorbents where effects on the performance of the product may occur (e.g., hindering the rate and extent of dissolution).

Chemical Properties

For adsorbents, the chemistry and consistency of the surface with respect to the molecular structures predominating at the surface is a key property. Adsorbents with highly active surfaces may interact with other parts of the dosage form including the active ingredient or even substances in the environment (e.g., water or gases) and not function as expected. In some cases, the adsorbent/absorbent may undergo a chemical reaction on interacting with a gas or liquid such as iron to ferrous/ferric oxide, ascorbate to dehydroascorbic acid, and calcium oxide to calcium hydroxide.

Functional Mechanism

Sorbents function via one of two mechanisms: absorption or adsorption. The absorption mechanism is one related to the volume of the absorbent where the substance interacts with the mass of the absorbent. Absorption involves the processes of dissolution or diffusion.

In contrast, the mechanism of adsorption involves the interaction of a gas or liquid or solid with the surface of the adsorbent particles with the substance-forming layers on the surface.

Dosage Forms

Sorbents are used in solid dosage forms (tablets, capsules, gums, pills, pellets, and granules) and transdermal products (creams, lotions, and ointments).

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include surface area, particle size, morphology, density, potential interactions with other ingredients in formulation, specificity in adsorption/absorption, and absorptive/adsorptive capability. Adsorption/desorption kinetics may be important.

General Chapters

The following general chapters may be useful in ensuring consistency in selected sorbent functions: [\(921\)](#), [\(846\)](#), [\(429\)](#), [\(776\)](#), [Loss on Ignition \(733\)](#), [\(232\)](#), [\(233\)](#), [\(786\)](#), [\(776\)](#), [\(811\)](#), [\(699\)](#), and [\(1241\)](#).

STABILIZER

Description

Stabilizers are used to prevent or retard a change in a system or individual component in a dosage form. The stabilization of pharmaceutical products may occur via numerous mechanisms including: sequestration, antioxidants, neutralizing agents, viscosity modifying agents, the presence or absence of a particular ion or functional group, or charge-modifying agents (e.g., flocculants). Examples of types of stabilizers include antioxidants (e.g., alkylated phenols, butylated hydroxytoluene, metabisulfites, gallates), sequestrants (e.g., edetates, disodium ethylenediaminetetraacetate), light stabilizers (e.g., ferric oxide and titanium dioxide), emulsion stabilizers [e.g., proteins, polysaccharides, cellulose, starches, surfactants, charged inorganic, and organic compounds (flocculants)]. See *Physical Form Stabilizer* for a related functional category.

Physical Properties

A stabilizer must be compatible with the state of the system in which it is being used (e.g., liquids are typically not a good fit for tablets). Further considerations include other aspects of physical stability such as solubility, precipitation ("salting out"), discoloration, organoleptic properties, flow properties, processing, microbial activity, amorphous or crystalline form stabilization, suspendibility, emulsion stabilization (breaking or inversion), viscosity, or micelle breakdown/formation.

Chemical Properties

A stabilizer should be chemically compatible with the system intended for use. Knowledge of the mechanism of stabilization is key to understanding the important chemical properties. Other considerations include compatibility with the active ingredient and other ingredients, stability of stabilizer function, and initiation of other unintended chemical reactions.

Functional Mechanism

The functional mechanisms of stabilizers are numerous and are dependent on both the stabilizer and the product. Stabilizers may have a direct effect on the stability of the product or an indirect effect (e.g., use of a chelating agent to reduce microbial activity). Mechanisms include, but are not limited to, viscosity change, zeta potential change (charge modification), sequestration, electron scavenging, photon energy dissipation, chemical reaction, neutralization, and absence or dilution of an offending ion or functional group.

Dosage Forms

Stabilizers are used in tablets, capsules, liquids, gels, ointments, creams, injections, emulsions, suspensions, lotions, pastes, solutions, and granules.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include solubility and physical and chemical compatibility. Performance-related properties are unique to each application and can be wide and varied in important attributes.

General Chapters

The following general chapters may be useful in ensuring consistency in selected stabilizer functions: [\(232\)](#), [\(233\)](#), [\(776\)](#), [\(695\)](#), [\(1181\)](#), [\(846\)](#), [Porosimetry by Nitrogen Adsorption-Desorption \(268\)](#), [Porosimetry by Mercury Intrusion \(267\)](#), [\(1174\)](#), [\(61\)](#), [\(62\)](#), [\(51\)](#), [\(71\)](#), [Globule Size Distribution in Lipid Injectable Emulsions \(729\)](#), [\(429\)](#), and [\(891\)](#).

STIFFENING AGENT

Description

A stiffening agent is an agent or a mixture of agents that increases the consistency of a nonaqueous or biphasic preparation. Stiffening agents can be either hydrophobic (e.g., hard fat or paraffin) or hydrophilic (e.g., polyethylene glycol, high molecular weight).

Physical Properties

The primary physical property relevant to stiffening agents is their high melting point or melting range, thus their ability to raise the melting point of the dosage form. Typical melting ranges for stiffening agents range from 43° to 47° (cetyl esters wax), 53° to 57° (glyceryl distearate), 69° to 74° (glyceryl behenate), and 85° to 88° (castor oil, hydrogenated).

Chemical Properties

Stiffening agents comprise a diverse group of materials that include glycerides of saturated long-chain fatty acids, solid aliphatic alcohols, esters of saturated fatty alcohols and saturated fatty acids, saturated hydrocarbons, blends of fatty alcohols and a polyoxyethylene derivative of a fatty acid ester of sorbitan, waxes, and higher ethylene glycol polymers.

Functional Mechanism

In general, stiffening agents are high melting point solids that increase the melting point of ointments or increase the consistency or body of creams. They may also modify the microstructure of the ointment cream or suppository and thus change its rheological properties.

Dosage Forms

Stiffening agents are used for mucosal, topical, and dermal dosage forms as a means to increase the viscosity or hardness of a preparation. Stiffening agents are especially useful in ointments and creams. They are also used in the formulation of suppositories.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include melting point/melting range and viscosity.

General Chapters

The following general chapters may be useful in ensuring consistency in selected stiffening-agent functions: [\(651\)](#), [\(741\)](#), [\(911\)](#), [\(912\)](#), [\(1911\)](#), and [\(913\)](#).

Additional Information

Some of the materials included as stiffening agents increase the water-holding capacity of ointments (e.g., petrolatum) or function as co-emulsifiers in creams. Examples include stearyl alcohol and cetyl alcohol. Some stiffening agents may act as auxiliary suspending agents in the formulation of suppositories.

SUGAR-COATING AGENT

Description

Three methods for coating are compression coating, sugar coating, or film coating. Compression coating (effectively making a tablet within a tablet) typically uses the same ingredients as a conventional tablet and thus is outside the scope of this section. The term "sugar coating" refers to a process and does not require that sucrose be part of the formulation. Sugar coating was the original coating process. However, today for technical and economic reasons, sugar coating largely has been replaced by film coating. The reasons for

sugar coating pharmaceutical dosage forms include masking unpleasant tastes or odors, improving patient acceptance (especially in pediatric patients) and appearance, and protecting active ingredients from the environment. Materials used as sugar-coating agents differ depending on the coating stages (i.e. seal coating, key coating, subcoating, smoothing coat, color coating, and polishing coat). For the sealing step, polymers such as shellac and zein are used to water-proof and harden the tablet core to prevent damage during subcoating. Subcoating is the main step to gain weight (30%–50% of the weight of tablet core), and typical materials used are bulking agents such as calcium carbonate or talc in combination with sucrose solution. The smoothing step is usually completed by applications of plain 70% (w/w) syrup. The color-coating step originally used water-soluble dyes, but water-insoluble pigments including aluminum lakes have gained popularity in the past decades. Finally, waxes, such as carnauba and beeswax in organic solvent or dispersion with aid of surfactants, are applied to the tablet as a final polishing step.

Physical Properties

The viscosity, spreadability, and adherence to substrate of each coating layer are important physical properties. The solids content of the coating suspensions is important because it influences the quality of finished tablets and the speed of processing.

Chemical Properties

Sugar coating comprises a diverse variety of different excipients depending on coating stages. Coating components can be of natural, semisynthetic, or synthetic origin. Typical coating agents are shellac, zein, or other proteins for seal coating; minerals such as talc or calcium carbonate for subcoating; sucrose for smoothing coat; pigments/dyes for color coating; and natural wax for polishing coat.

Functional Mechanism

The coating layers and their functions are as follows, in order of application:

- Seal coat: harden and water-proof the core
- Key coat: adhesion of the subcoat to the seal coat, if required
- Sub coat: bulking, rounding, and shaping
- Smoothing coat: create smooth appearance
- Color coat: provides final color
- Polishing coat: provides surface gloss

Dosage Forms

Sugar-coating agents are used on tablets to enhance the visual appearance, mask bad taste, increase the hardness of the formulation, and provide a unique product identity.

Performance-Related Properties

Because sugar coating is a multicomponent system, properties that may be important for excipient performance for each component will depend on its function in the coating.

General Chapters

The following general chapters may be useful in ensuring consistency in selected coating agent functions: [\(401\)](#), [\(429\)](#), [\(891\)](#), [\(911\)](#), [\(912\)](#), and [\(913\)](#).

Additional Information

Refer to other functional categories within this chapter, such as *Film-Forming Agent* and *Coloring Agent*. Other tests that may be useful in ensuring consistency in the coating agent functions are: tackiness, dynamic mechanical analysis, and glossimetry.

SUPPOSITORY BASE

Description

Suppository bases are hydrophobic or hydrophilic semisolid materials that are solid at room temperature but release the drug product by melting, erosion, and/or dissolution when administered to the patient.

Physical Properties

The important physical characteristic of suppository bases is melting range. In general, suppository bases melt between 27° and 45°. However, individual bases usually have a much narrower melting range within these temperature boundaries, typically 2°–3°. The choice of a particular melting range is dictated by the influence of the other formulation components on the melting range of the final product.

Chemical Properties

Hard fat suppository bases are mixtures of semisynthetic triglyceride esters of longer chain fatty acids. They may contain varying proportions of mono- and diglycerides as well as additives. They are available in different grades that are differentiated by melting range, hydroxyl number, acid value, iodine value, solidification range, and saponification number.

Hydrophilic suppository bases are mixtures of hydrophilic semisolid materials that in combination are solid at room temperature and yet release the drug by melting, erosion, and/or dissolution when administered to the patient. Hydrophilic suppository bases have much higher levels of hydroxyl groups or other hydrophilic groups than do hard fat suppository bases. Polyethylene glycols that show appropriate melting behavior are examples of hydrophilic suppository bases.

Functional Mechanism

Suppositories should melt at just below body temperature (37°), thereby allowing the drug to be released either by erosion and partition if the drug is dissolved in the base or by erosion and dissolution if the drug is suspended in the base. Hard fat suppository bases melt at approximately body temperature. Hydrophilic suppository bases also melt at body temperature and typically dissolve or disperse in aqueous media. Thus, release takes place via a combination of erosion and dissolution.

Dosage Forms

Suppository bases are used in the manufacture of suppositories (for rectal administration) and inserts (pessaries for vaginal administration).

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include melting range, hydrocarbon chain length, hydroxyl value, and iodine value.

General Chapters

The following general chapters may be useful in ensuring consistency in selected suppository base functions: [\(401\)](#), [\(651\)](#), [\(741\)](#), and [\(1151\)](#).

Additional Information

Some materials included in suppositories based on hard fats have much higher melting ranges. These materials typically are microcrystalline waxes that help stabilize molten suspension formulations. Suppositories also can be manufactured from glycerinated gelatin.

SURFACTANT

Description

Surfactants are amphiphilic molecules that lower the surface (or interfacial) tension at solid-liquid, liquid-liquid, and/or gas-liquid interfaces. As such, they comprise both hydrophilic moieties and lipophilic moieties in the same molecule. Surfactants play a significant role in stabilizing proteins from aggregation and/or particulate formation upon interfacial and shear stresses. The most commonly used surfactants in protein solutions are polysorbates 80 and 20. Poloxamer 188 is also used in a few cases. Given the multifunctionality of surfactants, see also the functional category *Wetting and/or Solubilizing Agent* for more details in their use with small molecules.

Physical Properties

Surfactants are typically solid, liquid, or waxy materials. Their physical properties depend on their chemical structures. Surfactants are usually used in concentrations above their CMCs. CMC is a measure of the concentration at which the surfactant molecules aggregate. By using concentrations above CMC, surfactant levels are believed to be at a sufficient level to saturate interfaces.

Chemical Properties

The chemical properties depend on the structures of the surfactants. As a critical excipient to mitigate particulate formation upon interfacial stress in protein solutions, it is important to understand surfactant stability for each drug product. For example, polysorbates are known to be hydrolyzed by residual enzymes (i.e. lipases) co-concentrated during the protein purification process. The ester hydrolysis leads to separation of the lipophilic and hydrophilic portions of the surfactant molecules, leading to loss of surface active properties and yielding poorly soluble degradation products (e.g., fatty acids). The extent of degradation will likely depend on the capability of the drug substance purification process to remove residual enzymes. Also, some surfactants, e.g., polysorbates, can generate reactive oxygen species, which can in turn react with methionine and tryptophan residues in proteins, leading to oxidation and, potentially, biophysical destabilization (i.e. aggregate and/or particulate formation). Therefore, the levels of peroxides in such surfactants should be monitored and controlled and the handling of solutions should be carefully controlled.

Functional Mechanism

In protein therapeutics, the hydrophilic moiety will strongly interact with the aqueous media, whereas the hydrophobic portion may interact with either air at the air-water interface, or with hydrophobic regions in the protein structure, or with hydrophobic surfaces (e.g., on the primary container).

Dosage Forms

Surfactants are commonly used to stabilize protein therapeutics. Proteins are most commonly delivered by intravenous, subcutaneous, or intramuscular injections. Surfactants are added to both ready-to-use solutions and to lyophilized drug products. For lyophilized powders, surfactants can mitigate protein degradation also during reconstitution prior to administration. When protein therapeutics are developed to be delivered with prefilled syringes (PFS), surfactants play a critical stabilizing role as the internal barrels of PFS are commonly lubricated with silicone oil. Interacting with hydrophobic patches in protein structures, the presence of silicone can trigger protein destabilization (aggregation and/or particulate formation). Surfactants also protect protein therapeutics during manufacturing operations (e.g., mixing and filling) and during administration (e.g., after dilution in an intravenous bag).

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include attributes related to identity and impurities (i.e. elemental impurities, peroxides, etc.). In particular, the level of endotoxin may be relevant for parenteral dosage forms.

General Chapters

The following general chapters may be useful in ensuring consistency in selected surfactant functions: [\(1\)](#), [\(85\)](#), [\(232\)](#), [Subvisible Particulate Matter in Therapeutic Protein Injections \(787\)](#), [\(788\)](#), [Visible Particulates in Injections \(790\)](#), [Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections \(1787\)](#), [Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions \(1788\)](#), and [Visual Inspection of Injections \(1790\)](#).

SUSPENDING AND/OR VISCOSITY-INCREASING AGENT

Description

Viscosity-increasing and suspending agents are used in pharmaceutical formulations to stabilize dispersed systems (e.g., to inhibit sedimentation of the dispersed phase of suspensions or emulsions), to reduce the rate of solute or particulate transport, or to decrease the fluidity of liquid formulations.

Physical Properties

Each of the mechanisms—increased viscosity, gel formation, or steric stabilization—is a manifestation of the rheological character of the excipient. Because of the molecular weights and sizes of these excipients, the rheological profiles of their dispersions are non-Newtonian. Dispersions of these excipients display viscoelastic properties. The molecular weight distribution and polydispersity of the macromolecular excipients in this category are important criteria for their characterization.

Chemical Properties

The majority of the suspending and viscosity-increasing agents are:

- Hydrophilic carbohydrate macromolecules (acacia, agar, alginic acid, carboxymethylcellulose, carrageenans, dextrin, gellan gum, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, maltodextrin, methylcellulose, pectin, propylene glycol alginate, sodium alginate, starch, tragacanth, and xanthan gum)
- Noncarbohydrate hydrophilic macromolecules, including gelatin, povidone carbomers, polyethylene oxide, and polyvinyl alcohol
- Minerals (e.g., attapulgite, bentonite, magnesium aluminum silicate, and silicon dioxide) comprise the second largest group of suspending and viscosity-increasing agents
- Aluminum monostearate is the one nonmacromolecular, nonmineral excipient in this functional category. It consists chiefly of variable proportions of aluminum monostearate and aluminum monopalmitate

Functional Mechanism

A number of mechanisms contribute to the dispersion stabilization or viscosity-increasing effect of these agents. The most common is the increase in viscosity due to the entrapment of solvent by macromolecular or insoluble particle networks that disrupt laminar flow. Other mechanisms include gel formation via a three-dimensional network of excipient molecules or particles throughout the solvent continuum and steric stabilization wherein the macromolecular or mineral component in the dispersion medium adsorbs to the surfaces of particles or droplets of the dispersed phase. The latter two mechanisms increase formulation stability by immobilizing the dispersed phase.

Dosage Forms

Viscosity-increasing or suspending agents are typically used in creams, emulsions, gels, lotions, ointments, pastes, shampoos, and suspensions as noted above. They may also be employed in solid dosage forms to retard drug release at the site of administration.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include molecular weight, molecular weight distribution, polydispersity, particle size, and zeta potential.

General Chapters

The following general chapters may be useful in ensuring consistency in selected viscosity-increasing functions: [\(429\)](#), [\(776\)](#), [\(786\)](#), [\(846\)](#), [\(911\)](#), [\(912\)](#), [\(913\)](#), [\(914\)](#), and [\(1911\)](#).

SWEETENING AGENT

Description

Sweetening agents are compounds or blends of compounds of natural or synthetic origin that have the ability to elicit a sweet taste to the drug product formulation. They are normally used to mask undesirable

tastes and to promote patient compliance. A related functional category is *Flavor and Fragrance*.

Physical Properties

Sweeteners can be broadly grouped into nutritive and non-nutritive. Nutritive sweeteners deliver calories. The primary physical properties relevant to sweeteners relate to their compatibility with the other ingredients in the formulation (e.g., acidic ingredients), processing conditions (e.g., heating), particle size and distribution, moisture content, isomerism, sweetness, and taste-masking capability. These properties may be formulation-dependent.

Chemical Properties

Sweeteners can be divided into three main groups: sugars (which have a ring structure), sugar alcohols (sugars that do not have a ring structure), and artificial sweeteners. All sweeteners are water-soluble. The stability of many sweeteners is affected by pH and other ingredients in the formulation. Some sweeteners may catalyze the degradation of some active ingredients, especially in liquids and in cases in which the manufacturing processes involve heating.

Functional Mechanism

Sweetening agents bind to specific G-protein coupled receptors located on the taste cell membrane on the tongue that are responsible for the sensation of sweetness. The better the fitting of a chemical structure of the sweetener is to a corresponding receptor, the longer the sweetener molecule remains attached to the receptor and the sweeter the substance is perceived to be. The standard for sweetness is sucrose.

Dosage Forms

Sweeteners are used to sweeten oral (solid and liquid) dosage forms to mask unpleasant taste or make the pharmaceutical product more palatable. Typical dosage forms that use sweeteners include tablets, lozenges, liquids, and pastes.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include particle size, particle distribution, moisture content, sweetness, and solubility.

General Chapters

The following general chapters may be useful in ensuring consistency in selected sweetening functions: [\(429\)](#), [\(731\)](#), [\(781\)](#), and [\(921\)](#).

Additional Information

Products that contain aspartame must include a warning on the label stating that the product contains phenylalanine. Sugar alcohols have a glycemic index well below that of glucose. However, sorbitol is slowly metabolized to fructose and glucose, which raises blood sugar levels. Sugar alcohols in quantities generally greater than 20 g/day act as an osmotic laxative, especially when they are contained in a liquid formulation. Preservative systems should be carefully chosen to avoid incompatibility with the sweetener, and some sweeteners are incompatible with certain preservatives.

TONICITY AGENT

Description

The tonicity agents are solutes such as salts, sugars, and amino acids that contribute to solution osmolality. The tonicity agents are included in formulations to avoid crenation or hemolysis of red blood cells and/or to mitigate pain and discomfort if solutions are injected or introduced into the eyes and nose. This requires that the tonicity of solutions for injection must be approximately the same as that of blood. When drug products are prepared for administration to membranes, such as eyes, nasal or vaginal tissues, solutions should be made isotonic with respect to these tissues.

Physical Properties

All solutes do not contribute equally to tonicity, which in general depends only on the number of solute particles present in a solution, not the kinds of solute particles. For example, mole for mole, sodium chloride solutions display a higher tonicity than glucose solutions of the same molar concentration. This is because when glucose dissolves, it remains one particle, but when sodium chloride dissolves, it becomes two particles: Na^+ and Cl^- .

Chemical Properties

Tonicity agents can be ionic or nonionic in nature. Examples of ionic tonicity agents are alkali metal or earth metal halides such as sodium chloride (NaCl), sodium sulfate (Na_2SO_4), or boric acid. Nonionic tonicity agents include glycerol, sorbitol, mannitol, propylene glycol, or dextrose. Sodium chloride and dextrose are commonly added to adjust tonicity.

Functional Mechanism

Tonicity is a medical term that relates to the osmotic pressure difference between the internal and external sides of a cell membrane. In many cases, tonicity and osmolality are not the same because some solutes are able to rapidly pass through the cell membrane. Tonicity applies to the impermeant solutes within a solvent, in contrast to osmolality, which takes into account both permeant and impermeant solutes. For example, urea is a permeant solute, meaning that it can pass through the erythrocyte membrane freely and does not contribute to tonicity of a solution with respect to blood. In contrast, sodium chloride is impermeant and cannot pass through the erythrocyte membrane without the help of a concentration gradient and, therefore, contributes to a solution's tonicity. Different biological membranes may show different permeability to a given solute.

Dosage Forms

Tonicity agents may be used in liquid and semisolid dosage forms, including injections, creams, lotions, solutions, and sprays, intended for parenteral, topical, mucosal, ophthalmic, and inhalation use. The tonicity should be assessed with respect to the biological membrane relevant to the dosage form (e.g., erythrocyte for parenteral formulations and conjunctiva for ophthalmic solutions). Solutions of sodium chloride, dextrose, and Lactated Ringer's are common examples of pharmaceutical preparations that contain tonicity agents.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include attributes related to impurities.

General Chapters

The following general chapters may be useful in ensuring consistency in selected tonicity agent functions: [\(1\)](#), [\(4\)](#), [\(5\)](#), [\(771\)](#), [\(785\)](#), [Excipient Biological Safety Evaluation Guidelines \(1074\)](#), [\(1160\)](#), and [Vaccines for Human Use—Polysaccharide and Glycoconjugate Vaccines \(1234\)](#).

TRANSFER LIGAND

Description

Transfer ligands, also known as auxiliary ligands, auxiliary chelating ligands, and exchange ligands, are used as a step in the preparation of some radiopharmaceuticals whereby a radiometal (e.g., stannous-reduced technetium Tc 99m) is first chelated by a relatively weak chelating ligand (transfer ligand) and is subsequently transferred to the principal chelating ligand or complexing moiety to form the final radiopharmaceutical.

Physical Properties

Transfer ligands must be readily soluble in aqueous solution.

Chemical Properties

Transfer ligands must have rapid complexation kinetics and must form relatively weak chelates compared to complexation with the principal ligand. Examples of such transfer ligands include citrate, gluconate, and tartrate.

Functional Mechanism

Transfer ligands typically undergo rapid reactions to form weak chelates. This procedure is especially useful when the kinetics of complexation with the principal ligand is slow or when a heating step is necessary to expose chelating groups on the principal ligand.

Dosage Forms

Transfer ligands are used primarily in liquid radiopharmaceutical dosage forms intended for injection.

Performance-Related Properties

Performance-related properties for transfer ligands are: solubility, rapid complexation kinetics with the desired radiometal, and relatively weak chelation of the radiometal compared with the principal ligand.

General Chapters

The following general chapters may be useful in ensuring consistency in selected transfer ligand functions: [\(621\)](#) and [\(821\)](#).

VEHICLE

Description

Vehicles have typically been considered as carriers or inert media used as a diluent in which the active ingredient is formulated or administered. Vehicles are often liquid solvents but the term may be applied to solid carriers and diluents. Vehicles may be considered to be drug carriers that are compatible with the drug or formulation and facilitate the formulation and administration of the drug. Vehicles may be used to directly manufacture liquid dose forms or be copresented with powder or tablets for reconstitution by the pharmacist or patient.

Physical Properties

Liquid vehicles may be aqueous (e.g., sodium chloride injection, bacteriostatic), nonaqueous (e.g., oils), with appropriate viscosity, solubilizing, or suspending properties or solid (e.g., sugar spheres).

Chemical Properties

Vehicle components should be compatible with the active ingredient and may include buffers, preservatives, tonicity agents, and flavor. Vehicle composition is dependent on formulation objectives.

Functional Mechanism

Functional mechanism is dependent on composition and formulation objectives. Examples include solvency, suspension, stability, or taste-masking.

Dosage Forms

Liquid vehicles enable manufacture of liquids and suspensions dosage forms or may be a component of the dose form when copresented for reconstitution in injections dosage forms. Hard fats are the common carrier for suppository dosage forms, and sugar spheres may be a vehicle for solid dosage form preparation. Related functional categories are: *Wetting and/or Solubilizing Agent, Solvent, Diluent, and Pharmaceutical Water*.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include viscosity, tonicity, pH, or particle size.

General Chapters

The following general chapters may be useful in ensuring consistency in vehicle functionality: [\(51\)](#), [\(71\)](#), [\(616\)](#), [\(699\)](#), [\(731\)](#), [\(1174\)](#), [\(1227\)](#), and [\(786\)](#).

Additional Information

Vehicles may facilitate the formation of a stable drug suspension and cover a wide range of excipients including but not limited to inert powders (e.g., talc); polymers; liquid solvents; suspending agents; sugars; oils; and semisolid or solid pegylated lipids. Glycerides including oils are often suitable vehicles for delivery of liposoluble compounds. Liquid to solid surfactants help the formation of a stable suspension in aqueous media. Cosolvents such as ethanol, glycerol, or propylene glycol may be included to solubilize the active ingredient.

VISCOSITY-LOWERING AGENT

Description

Proteins such as monoclonal antibodies can display high viscosities in highly concentrated solutions. This buildup of viscosity can pose issues in the successful development of high concentration monoclonal antibody formulations, especially for subcutaneous administration. Viscosity-lowering agents are used to reduce the viscosity of high concentration protein formulations. A number of agents including amino acids, salts, polar solvents, etc. may be used to reduce the viscosity of monoclonal antibody formulations.

Physical Properties

The viscosity-lowering agents such as amino acids, salts, and other excipients are dissolved in aqueous solution for preparation of formulation. Hence, the physical form and particle properties of the viscosity-lowering agent are generally not relevant to the final properties of the solution or lyophilized protein formulation. However, bioburden and endotoxin levels need to be controlled as for any excipient to be used in the formulation of an injectable drug product.

Chemical Properties

The control of the chemical purity of viscosity-lowering agents is critical for protein formulations as with any other excipient as presence of reactive impurities can potentially lead to protein aggregation or inactivation of the protein. Because these agents can be included at significant levels in the formulation, they should be also be monitored for impurities such as trace metals that can cause oxidation and/or aggregation of proteins.

Functional Mechanism

The build-up of viscosity at high protein concentrations (e.g. ,>100 mg/mL) is related to increased protein-protein interactions in solution. The intermolecular interactions between protein molecules can be due to both electrostatic and hydrophobic interactions that can result in increased noncovalent protein association at high concentrations resulting in buildup of viscosity.

Amino acids such as arginine, histidine, proline, and lysine have been used to reduce the viscosity of monoclonal antibody solutions. These amino acids reduce viscosity by a combination of mechanisms including screening of electrostatic charge and/or binding to specific residues on the protein molecule to reduce interaction between protein molecules. As an example, the amino acid arginine, which is commonly used to reduce viscosity, is known to interact with the aromatic residues on the protein leading to reduced protein-protein interaction and lowering of viscosity. Inorganic salts such as sodium chloride can screen charges on the protein surface, modulating electrostatic attractive or repulsive forces leading to an impact on viscosity. It has been shown that depending on the nature of the protein-protein interaction, salts can either reduce or increase viscosity for a given molecule and need to be evaluated for viscosity reduction. In addition to amino acids and salts, organic cosolvents can also reduce viscosity but their use needs to be carefully evaluated from a biocompatibility perspective.

The viscosity of a monoclonal antibody can be dependent on the solution pH. A change in solution pH can alter the charge on the protein surface and the interaction between protein molecules, resulting in viscosity

changes. The use of formulation pH can be a viable approach to reduce viscosity but needs to be carefully balanced with any impact of pH changes on stability and other formulation properties. A number of novel excipients have also been evaluated for viscosity lowering of monoclonal antibody formulations, but the suitability of their use for parenteral administration needs to be established.

Dosage Forms

The viscosity-lowering agents are generally used as excipients in injections especially formulations to be used for administration by the subcutaneous route. Because the injection volume that can be administered by subcutaneous route is small, the delivery of higher protein doses requires development of higher concentration formulations that can exhibit high viscosities. The selection of the viscosity decreasing agent should be carefully studied during formulation development to ensure that its inclusion does not impact protein stability, loss in potency, or other issues with delivery systems to be used for administration.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include purity of the viscosity-lowering agents and control of any impurities that can impact protein stability.

General Chapters

The following general chapters may be useful in ensuring consistency in selecting bulking agent functions: [\(1\)](#), [\(695\)](#), [\(696\)](#), [\(891\)](#), [\(1151\)](#), [\(1911\)](#), and [\(1241\)](#).

WATER-REPELLING AGENT

Description

A water-repelling agent is a hydrophobic excipient that is resistant to but not impervious to penetration by water.

Physical Properties

A water repellent surface can be characterized by the nonspreading of water droplets. Topical water-repelling agent coatings are resistant to wash off when immersed in water.

Chemical Properties

The majority of water-repelling agents are silicone polymers with a high degree of backbone flexibility and hydrophobic surface characteristics. They have the typical chemical properties of silicones.

Functional Mechanism

Water-repelling agents repel water due to the presence of hydrophobic functional groups on the silicone molecule. Another important property is their ability to spread easily and cover the skin. An advantage of silicones is their chemical and thermal stability and their resistance to photodegradation, especially ultraviolet radiation.

Dosage Forms

Water-repelling agents are used in topical skin care products such as creams, lotions, ointments, and sunscreens.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include hydrophobicity as measured by water contact angle.

General Chapters

The following general chapters may be useful in ensuring consistency in selected gelation functions: [\(3\)](#), [\(731\)](#), [\(911\)](#), and [\(912\)](#).

WET BINDER

Description

Wet binders are incorporated into formulations to agglomerate powder to form granules using a granulating fluid such as water, hydroalcoholic mixtures, or other solvents. Wet binders include natural materials such as sugars and starch and semisynthetic and synthetic polymers such as modified cellulose and povidone. The typical use level of wet binder is between 2% and 20%, depending on wet binder physicochemical properties, formulation components, and composition. The wet binder may be incorporated either dissolved in the granulating fluid or dry blended with the other powders to be wet granulated.

Physical Properties

Important physical properties include solubility in the granulating fluid, spreadability on the powder substrate, the ability to cause the powders to adhere and agglomerate, and the ability to provide plasticity to the granules. Homogeneous incorporation of a binder into a dry blend also depends on particle size distribution and morphology. High viscosity may reduce spreadability. Viscosity is dependent on polymer structure and molecular weight. Excessive levels of binder, especially high viscosity grades, may form gels and retard drug dissolution.

Chemical Properties

Wet binders are a diverse range of materials usually polymeric. The chemical nature of polymers, including monomer sequence, functional groups, degree of substitution, and branching, can influence the complex interactions during granulation.

Functional Mechanism

The adhesive properties of binder solutions facilitate agglomeration of powders into granules. The binder may modify interfacial properties of poorly water-soluble drug substances, improving wettability, and facilitating subsequent dissolution from the tablet. During drying, binders produce solid bridges between the powder particles, yielding granules with improved properties such as flow, handling, mechanical strength, resistance to segregation, reduced dustiness, and compatibility.

Dosage Forms

Wet binders are used to manufacture solid oral dosage forms including tablets, capsules, granules, pills, and pellets.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include viscosity. Particle size distribution may be important when incorporating the binder by dry blending.

General Chapters

The following general chapters may be useful in ensuring consistency in binder functions: [\(786\)](#), [\(911\)](#), [\(912\)](#), [Viscosity—Rolling Ball Methods \(913\)](#), and [\(1911\)](#).

WETTING AND/OR SOLUBILIZING AGENT

Description

Solubilizers can be used to dissolve otherwise insoluble molecules. They function by facilitating spontaneous phase transfer to yield a thermodynamically stable solution. Solubilizers may be classified into four main groups: hydroalcoholic solvents such as alcohol and propylene glycol; lipophilic or oily solvents such as glycerides; surfactants, also referred to as wetting agents; and polymeric solvents (e.g., polyethylene glycols). Related functional categories are *Surfactant*, *Complexing Agent*, and *Solvent*.

Physical Properties

The physical properties of solubilizers vary with their chemical structures. Hydroalcoholic solvents classically are low viscosity liquids with good miscibility or solubility in aqueous media. They typically are low molecular weight molecules (<300 Da) appropriate for highly aqueous delivery systems. Oils and their derivatives are slightly more viscous, immiscible with aqueous media, and serve as solubilizers for lipophilic drug actives (e.g., emulsions). Polyethylene glycol (polymeric) solubilizers vary in molecular size and solid

state properties (liquid to solid). Another category is surfactants that are amphiphilic in nature due to their dual molecular structure (i.e. presence of both a lipophilic and a hydrophilic moiety in their molecular construct). The solubilization capacity and the melt characteristics of the surfactant are dictated by the type and size of the molecular moieties.

Chemical Properties

The key chemical properties of solubilizers relate to their HLB value and miscibility with the intended solvent. HLB may be measured experimentally (practical HLB) or mathematically (theoretical HLB). The HLB value is a useful tool in relative ranking of the solubilizer for its function against other excipients. On a scale of 1–20, oily solvents are identified with an HLB of 1–3; water insoluble surfactants/cosurfactants fall in the HLB range of 3–6; water-dispersible surfactants have HLB values of 6–11; and water-soluble surfactants are known to possess HLB of 12 or higher. Another surfactant characteristic is the CMC, which is the lowest concentration at which the surfactant molecules begin to aggregate, forming a micellar solution. Solubilizers come in a wide range of chemical structures affecting their physical and surface-active properties.

Functional Mechanism

The functional mechanism depends upon the nature of the solubilizing agent. Surfactants typically reduce surface tension and form micelles within the solvent system for the solute to dissolve or disperse. The mechanism of solubilization with surfactants often is associated with a favorable interaction of the insoluble agent and the interior core of the solubilizer assembly (e.g., micelles). Hydroalcoholic solvents such as propylene glycol enable solubilization based on changes in the dielectric constant of the medium. In other cases, unique hydrophobic sites that are capable of forming inclusion complexes are present. Other types of solubilizers use a range of polymeric chains that interact with hydrophobic molecules to increase solubility by dissolving the insoluble agent into the polymeric chains. Surface active agents facilitate solubilization, micellization, or wetting of the solute by enhancing the spreading and penetrating properties of a liquid by lowering its surface tension.

Dosage Forms

Wetting and/or solubilizing agents are mainly used in injections and oral dosage forms (including liquids, suspensions, solutions, tablets, and capsules) to improve the solubility and/or wettability of otherwise insoluble, hydrophobic molecules.

Performance-Related Properties

Properties that may be important for excipient performance in a dosage form include fluidity (viscosity), molecular weight distribution, visual appearance (clarity and color), purity, presence of peroxides, and CMC.

General Chapters

The following general chapters may be useful in ensuring consistency in selected solubilizing agent functions: [\(401\)](#), [\(429\)](#), [\(791\)](#), [\(841\)](#), [\(846\)](#), [\(854\)](#) and [\(857\)](#), [\(891\)](#), [\(911\)](#), [\(912\)](#), and [\(913\)](#).

Additional Information

The physical and chemical properties of the solute (active drug) and the route of administration dictate the type and combination of solubilizers that are appropriate. Because of the complex nature of solute–solvent–solubilizer interactions, careful consideration, identification, and control of the CMAs of solubilizers is required. To achieve the desired drug concentration in the formulation, it may be necessary to use two or more types of solubilizers. Combinations of solvents and surfactants can create a variety of systems including: aqueous or oily solutions; micellar solutions; self-emulsifying drug delivery systems; micro/nanoemulsions; and colloidal dispersions. Whereas solutions are dispersions of the solute at the molecular level, micellar solutions consist of a surfactant forming an aggregate that envelopes the solute in the solvent system. Nanomicroemulsions typically are much larger or complex aggregates and may consist of at least four types of solubilizers: hydroalcoholic solvent (water, alcohol, etc.), oil (e.g., glycerides), and

primary and secondary surfactant (e.g., cosurfactant). Generally, these molecular aggregates can solubilize the solute by incorporating the drug into the hydrophobic regions of the formulation.▲ (USP 1-May-2021)

¹ ~~This general information chapter provides nonmandatory information that does not create compendial requirements. For additional information about nonmandatory general chapters and alternative methods and procedures, see *General Notices, 6.30 Alternative and Harmonized Methods and Procedures.*~~

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