Fluvoxamine Maleate Tablets

» Fluvoxamine Maleate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fluvoxamine maleate ($C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$).

Packaging and storage—Preserve in tight containers. Store at room temperature.

Labeling—If a test for *Related compounds* other than *Test 1* is used, then the labeling states with which *Related compounds* test the article complies.

USP Reference standards ⟨11⟩**—***USP Fluvoxamine Maleate RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩**—**

Medium: water; 900 mL, degassed.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure—Determine the amount of $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 246 nm on portions of the solution passed through a suitable 0.45-µm filter, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Fluvoxamine Maleate RS in the same *Medium*. When there are known interferences due to excipients, excipient interference corrections may be applied, as necessary.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Change to read:

Related compounds—[NOTE—If *(E)*-5-methoxy-4′-difluoromethylvalerophenone-*O*-2-aminoethyloxime is a known impurity, *Test 2* is recommended.]

TEST 1—

Buffer solution, Mobile phase, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Identification solution—Dissolve a quantity of maleic acid in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a concentration of about 0.35 mg per mL.

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay stock preparation,* prepared as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution,* the *Test solution,* and the *Identification solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of impurities in the portion of Tablets taken by the formula:

$$100(C/D)F(r_i / r_S)$$

in which C is the concentration, in mg per mL, of USP Fluvoxamine Maleate RS in the *Standard solution; D* is the expected concentration, in mg per mL, of fluvoxamine maleate taking into account the labeled amount and the amount of sample taken to prepare the *Test solution; F* is the response factor of each impurity as given in *Table 1;* r_i is the individual peak area of each impurity in the *Test solution;* and r_S is the peak area of fluvoxamine maleate in the *Standard solution.* The limits of impurities are specified in *Table 1.* [NOTE—Disregard any peak due to maleic acid or to the reagent blank.]

TEST 2—

Diluent—Prepare a mixture of methanol and water (60 : 40).

Acetate buffer—Dissolve about 13.6 g of sodium acetate trihydrate in 1000 mL of water.

Mobile phase—Prepare a filtered and degassed mixture of *Acetate buffer,* acetonitrile, and methanol (550 : 300 : 150). Add 2 mL of triethylamine. Adjust with glacial acetic acid to a pH of 4.5. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Quantitatively dilute the *Standard preparation,* prepared as directed in the *Assay,* with *Diluent* to obtain a final

Table 1

Compound Name	Relative Retention Time	Response Factor	Limit %
Maleic acid	about 0.19	—	—
5-Methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-(*E*)-*O*-[2-[(2-succinyl)amino]ethyl]oxime	about 0.50	1.0	0.8
5-Methoxy-4′-(trifluoromethyl)valerophenone(*E*)-*O*-(2-aminoethyl)aminoethyl oxime maleate	about 0.67	1.4	0.2
Z-isomer	about 0.79	1.0	0.5
Fluvoxamine	1.0	—	—
4′-(Trifluoromethyl)valerophenone(*E*)-*O*-2-(2-aminoethyl)aminoethyl oxime maleate	about 1.18	1.0	0.2
(*E*)-*O*-2-(2-Aminoethyl)-4-(trifluoromethyl)-α-phenyl-acetophenone oxime maleate	about 1.74	1.0	0.2
4′-(Trifluoromethyl)valerophenone(*E*)-*O*-(2-aminoethyl)oxime maleate	about 2.00	1.0	0.2
5-Methoxy-4′-(trifluoromethyl)valerophenone oxime	about 3.45	0.6	0.2
5-Methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-(*E*)-*O*-(2-aminoethyl] oxime maleic acid monoamide	about 4.3	1.0	0.2
5-Methoxy-4′-(trifluoromethyl)valerophenone ketone	about 4.2	0.3	0.2
Unknown impurities	—	1.0	0.1
Total	—	—	1.8

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solution having a known concentration of about 0.001 mg per mL of fluvoxamaine maleate.

Test solution—Transfer 5 mL of the *Assay stock preparation* (the supernatant after centrifugation), prepared as directed in the *Assay,* to a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 2.0 mL per minute. The column temperature is maintained at 40°. Chromatograph 20 µL of the *Resolution solution,* and record the peak responses as directed for *Procedure.* Identify the peaks using the relative retention times given in *Table 2*; the resolution, *R,* between the *Z*-isomer and fluvoxamine maleate is not less than 1.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the impurities and fluvoxamine maleate. Calculate the percentage of impurities in the portion of Tablets taken by the formula:

$$100(C/D)(1/F)(r_i / r_S)$$

in which C is the concentration, in mg per mL, of USP Fluvoxamine Maleate RS in the *Standard solution; D* is the expected concentration, in mg per mL, of fluvoxamine maleate taking into account the labeled amount and the amount of sample taken to prepare the *Test solution; F* is the response factor of each impurity as given in *Table 2;* r_i is the individual peak area of each impurity in the *Test solution;* and r_S is the peak area of fluvoxamine maleate in the *Standard solution.* The limits of impurities are specified in *Table 2.*

Assay—

Buffer solution—Dissolve approximately 5 g of 1-pentanesulfonic acid sodium salt and 0.7 g of monobasic potassium phosphate in 620 mL of water. Adjust with phosphoric acid to a pH of 3.00 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (62 : 38). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Transfer approximately 6 mg of fluvoxamine maleate to a 50-mL volumetric flask. Heat the sample at 120° for 10 minutes. Cool to room temperature, and add 3.0 mL of 0.1 N hydrochloric acid. Heat the solution in a water bath for 10 minutes. Cool to room temperature, add 50 mg of fluvoxamine maleate, and dissolve in 25 mL of *Mobile phase.* Dilute with *Mobile phase* to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Fluvoxamine Maleate RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Assay stock preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg of fluvoxamine maleate, to a 500-mL volumetric flask, add about 250 mL of *Mobile phase,* sonicate for about 15 minutes, shake by mechanical means for about 15 minutes, dilute with *Mobile phase* to volume, and mix. Centrifuge a portion of this solution for 10 minutes.

Assay preparation—Transfer 5.0 mL of the supernatant from the *Assay stock preparation* to a 100-mL volumetric flask and dilute to volume with *Mobile phase*. Pass a portion of this solution through a filter having a 45-µm or finer porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 234-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1.7 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.19 for maleic acid, 0.5 for 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-(*E*)-*O*-[2-[(2-succinyl)amino]ethyl]oxime, 0.79 for the *Z*-isomer, and 1.0 for fluvoxamine maleate; and the resolution, *R,* between the *Z*-isomer and fluvoxamine maleate is not less than 2.0 and not less than 5.0 between 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-(*E*)-*O*-[2-[(2-succinyl)amino]ethyl]oxime and the *Z*-isomer. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the fluvoxamine maleate peaks. Calculate the quantity, in mg, of fluvoxamine maleate ($C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$) in the portion of Tablets taken by the formula:

$$10{,}000C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Fluvoxamine Maleate RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Table 2

Compound Name	Approx. Relative Retention Time	Response Factor	Limit %
(E)-5-methoxy-4′-difluoromethylvalerophenone-*O*-2-aminoethyloxime	0.58	1.0	0.2
(E)-*N*-[2[[[α-(4-methoxybutyl)-4-(trifluoromethyl)benzylidene] amino]oxy]ethyl]aspartic acid	0.70	1.0	•1.2•(RB 1-Jul-2009)
(E)-5-methoxy-4′-trifluoromethylvalerophenone-*O*-[2-*N*-(aminoethyl)aminoethyl]oxime	0.75	1.0	0.2
Z-isomer	0.85	0.5	0.5
Fluvoxamine	1.0	—	—
(E)-4′-trifluoromethyl-valerophenone-*O*-2-aminoethyloxime	1.86	1.0	0.2
5-Methoxy-4′-trifluoromethylvalerophenone oxime	about 1.99	1.0	0.2
5-Methoxy-4-trifluoromethylvalerophenone	about 2.17	1.0	0.2
Unknown impurities	—	1.0	0.2
Total	—	—	1.5

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