Sunitinib Capsules

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

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Further follow-up action as required.	

Sunitinib Capsules

Sunitinib Malate Capsules

Sunitinib Capsules contain Sunitinib Malate equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of sunitinib, $C_{22}H_{27}FN_4O_2$.

Usual strengths. 12.5 mg; 25 mg; 50 mg.

CAUTION- Sunitinib is cytotoxic, extra care required to prevent inhaling particles and exposing the skin to it.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Dissolution (2.5.2).

NOTE- Protect the solutions from light.

Apparatus No. 2 (Paddle),
Medium. 900 ml of *0.1 M hydrochloric acid,*
Speed and time. 50 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Use the filtrate, dilute if necessary, with dissolution medium.

Reference solution. A solution of *sunitinib malate IPRS* containing 0.014 per cent w/v of sunitinib in the dissolution medium. Dilute 1.0 ml of the solution to 10.0 ml with the dissolution medium.

Chromatographic system
- a stainless steel column 15 cm × 4.6 mm, packed with octylsilane bonded to porous silica (5 µm) (Such as Zorbax Eclipse XBD C 8),
- column temperature: 30°,
- sample temperature: 10º,
- mobile phase: a mixture of 70 volumes of a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, add 1.0 ml of *triethylamine*, adjusted to pH 6.5 with *dilute orthophosphoric acid* and 30 volumes *acetonitrile*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2500 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 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{21}H_{46}NO_4P$ in the medium.

Q. Not less than 75 per cent of the stated amount of $C_{22}H_{27}FN_4O_2$.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Protect the solutions from light.

Solvent mixture. 35 volumes of *water* and 65 volumes of *acetonitrile.*

Test solution. Disperse a quantity of the mixed content of the capsules containing 0.1 g of Sunitinib in the solvent mixture, with the aid of magnetic stirrer for 20 minutes and dilute to 100.0 ml with the solvent mixture, filter.

Reference solution (a). A solution of *sunitinib malate IPRS* containing 0.001 per cent w/v of sunitinib in the solvent mixture.

Reference solution (b). A solution of *sunitinib malate IPRS* containing 0.1 per cent w/v of sunitinib and 0.0004 per cent w/v, each of, *trans isomer of sunitinib IPRS*, *desethyl sunitinib IPRS*, *sunitinib-N-oxide impurity IPRS*, *hydroxy impurity of sunitinib IPRS*, *formyl impurity of sunitinib IPRS*, and *desdiethylamino sunitinib IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (2.7 µm) (Such as Poroshell 120 EC-C18),
- sampler temperature: 10°,
- column temperature: 40°,
- mobile phase: A. a buffer solution prepared by dissolving 1.925 g of *ammonium acetate* in 1000 ml of *water*, adjusted to pH 5.85 with *dilute acetic acid*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 235 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	95	5
20	75	25
30	75	25
40	40	60
45	30	70
50	95	5
57	95	5

Name	Relative retention time	Correction factor
Maleic acid	0.05	---
Trans isomer of sunitinib[1*]	0.59	---
Desethyl sunitinib[2*]	0.83	---
Hydroxy impurity of sunitinib[3]	0.86	1.31
Sunitinib-N-oxide impurity[4]	0.90	1.13
Formyl impurity of sunitinib[5]	0.92	0.85
Sunitinib (Retention time: about 35 minutes)	1.0	---
Desdiethyl amino sunitinib[6*]	1.12	---

*Process impurity included for identification only and not included in the calculation of total degradation products.
[1](E)-N-[2-(diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide.
[2](Z)-N-[2-(ethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide.

[3](Z)-N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2-(hydroxymethyl)-4-methyl-1H-pyrrole-3-carboxamide.
[4](Z)-N-[2-(diethyl-N-oxoamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide.
[5](Z)-N-[2-(diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2-formyl-4-methyl-1H-pyrrole-3-carboxamide.
[6](Z)-N-ethyl-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide.

Note – Method is sensitive to decrease and increase of pH in mobile phase to achieve better resolution.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to formyl impurity of sunitinib and sunitinib is not less than 1.5 in the chromatogram obtained with reference solution (b), the column efficiency is not less than 200000 theoretical plates and the tailing factor is not more than 1.5 in the chromatogram obtained with reference solution (a).

NOTE- If peaks are not well separated, adjust the pH of the buffer by ± 0.1 to achieve better separation.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to hydroxy impurity of sunitinib, sunitinib-N-oxide impurity and formyl impurity of sunitinib, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than 3.0 times the area of the principal peak in the chromatogram obtained with reference solution (a) (3.0 per cent). Ignore any peak due to maleic acid.

Uniformity of dosage units (2.5.4). Comply with the tests stated under Capsules.

Other tests. Comply with the tests stated under Capsules.

Assay. Determine by liquid chromatography (2.4.14).

NOTE- Protect the solutions from light.

Solvent mixture. 65 volumes of *0.1 M hydrochloric acid* and 35 volumes of *acetonitrile.*

Test solution. Weigh and mix the content of 20 capsules. Disperse a quantity of the mixed content containing 0.125 g of sunitinib in the solvent mixture, with the aid of ultrasound for 20 minutes with intermittent shaking and dilute to 250.0 ml with the solvent mixture. Dilute 10.0 ml of the solution to 50.0 ml with the solvent mixture, filter.

Reference solution. A solution of *sunitinib malate IPRS* containing 0.01 per cent w/v of sunitinib in the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm × 4.6 mm, packed with octylsilane bonded to porous silica (5 µm) (Such as Zorbax Eclipse XBD C 8),
- column temperature: 30°,
- mobile phase: a mixture of 70 volumes of a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, add 1.0 ml of *triethylamine*, adjusted to pH 6.5 with *dilute orthophosphoric acid* and 30 volumes *acetonitrile*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2500 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{22}H_{27}FN_4O_2$ in the capsules.

1 mg of sunitinib malate $C_{22}H_{27}FN_4O_2$. $C_4H_6O_5$ is equivalent to 0.7482 mg of sunitinib, $C_{22}H_{27}FN_4O_2$.

Labelling. The label states the strength in terms of the equivalent amount of sunitinib.

Storage. Store protected from moisture, at a temperature not exceeding 30°.