Prasugrel and Aspirin Gastro-resistant Capsules

Prasugrel Hydrochloride and Aspirin Gastro-resistant Capsules

Prasugrel and Aspirin Gastro-resistant Capsules contain prasugrel hydrochloride equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of prasugrel, $C_{20}H_{20}FNO_3S$ and aspirin, $C_9H_8O_4$.

Usual strength. Prasugrel 10 mg and Aspirin 75 mg.

Identification

In the Assay of prasugrel, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution and in the Assay of aspirin, 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).

For Prasugrel –

Apparatus No. 2 (Paddle),
Medium. 900 ml of *0.01M hydrochloric acid,*
Speed and time. 100 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14)

Test solution. Dilute the filtrate with *acetonitrile* to obtain a solution having a known concentration similar to the expected concentration of the reference solution.

Reference solution. A 0.024 per cent w/v solution of *prasugrel hydrochloride IPRS* in *acetonitrile*. Dilute 5.0 ml of the solution to 100.0 ml with the dissolution medium. Further dilute 5.0 ml of the solution to 50.0 ml with *acetonitrile*.

Chromatographic system
- a stainless steel column 10 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm), (Such as Oyster ODS 3),
- sample temperature: 15°,
- mobile phase. a mixture of 60 volumes of *0.01M potassium dihydrogen orthophosphate,* adjusted to pH 2.7 with *dilute orthophosphoric acid* and 40 volumes of *acetonitrile*,
  flow rate: 1 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 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 $C_{20}H_{20}FNO_3S$ in the medium.

Q. Not less than 75 per cent of the stated amount of $C_{20}H_{20}FNO_3S$.

For Aspirin –

A. Apparatus No. 1 (Basket),
Medium. 1000 ml of *0.1 M hydrochloric acid,*
Speed and time. 100 rpm and 120 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14)

Test solution. Use the filtrate, if necessary, dilute suitably with the dissolution medium to obtain a solution with a known concentration similar to the expected concentration of the reference solution.

Reference solution. Weight and transfer 30 mg of *aspirin IPRS* to 200- ml volumetric flak add 5 ml of *acetonitrile* and dissolve with the aid of ultrasound and dilute to volume with the dissolution medium. Dilute 5.0 ml of the solution to 100.0 ml with the dissolution medium.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as
  Inertsil ODS 2),
- sample temperature: 5°,
- mobile phase A. a buffer solution prepared by dissolving 1.78 gm of *potassium dihydrogen ortophosphate* in 1000 ml of *water,* adjusted to pH 2.3 with *dilute orthophosphoric acid*,
  B. a mixture of 70 volumes *acetonitrile* and 20 volumes *methanol.*
- a gradient programme using the conditions given below,
  flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 10 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	55	45
10	55	45
11	20	80
15	20	80
16	55	45
20	55	45

Inject the reference solution. The test is not valid unless the column efficiency is not less than 3000 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 $C_9H_8O_4$ in the medium.

Complies with the acceptance criteria given under Acid stage.

B. Apparatus No. 1 (Basket),
Medium. 1000 ml of a buffer solution prepared by mixing of 75 volumes of *0.1 M hydrochloric acid* and 25 volumes of *0.2 M trisodium phosphate dodecahydrate,* adjusted to pH 6.8 with *2 M hydrochloric acid* or *2 M sodium hydroxide*,
Speed and time. 100 rpm and 90 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14)

Test solution. Dilute the filtrate, if necessary, with the dissolution medium.

Reference solution. Weight and transfer 30 mg of *aspirin IPRS* to 200-ml volumetric flak add 5 ml of *acetonitrile,* dissolve with the aid of ultrasound and dilute to volume with the dissolution medium. Dilute 5.0 ml of the solution to 10.0 ml with the dissolution medium.

Use chromatographic system as described under acid stage.

Inject the reference solution and the test solution.

Calculate the content of $C_9H_8O_4$ in the medium.

Q. Not less than 75 per cent of the stated amount of $C_9H_8O_4$.

Related substances. Determine by liquid chromatography (2.4.14).
For Prasugrel –

Solvent mixture. 90 volumes of *acetonitrile* and 10 volumes of *water.*

Test solution. Disperse a quantity of the mixed powdered content of the capsules containing 100 mg of Prasugrel in 20 ml of *water,* with the aid of ultrasound. Add 140 ml *acetonitrile,* further sonicate for 30 minutes with intermittent shaking and dilute to 200.0 ml with *acetonitrile.*

Reference solution. A 0.0055 per cent w/v solution of *prasugrel hydrochloride IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the the solvent mixture.

Note- Method is sensitive for buffer pH and column temperature.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm), (Such as Inertsil ODS 3V),
- column temperature: 30°,
- sample temperature: 15°,
- mobile phase: A. *0.01M potassium dihydrogen orthophosphate,* adjusted to pH 3.1 with *dilute orthophosphoric acid*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
  flow rate: 1.5 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 20 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	70	30
40	50	50
50	25	75
60	25	75
62	70	30
70	70	30

Name	Relative Retention time	Correction factor
Prasugrel impurity HYTP [1]	0.9	0.83
Prasugrel	1.0	-
Prasugrel impurity -A_1 [2]	1.4	0.76
Prasugrel impurity -A_2 [2]	1.5	0.76

[1] (5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-7a-hydroxy-5,6,7, 7a-tetrahydrothieno [3, 2-c]pyridine-2(4 H)-one)
[2] (5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7,tetra hydrothieno [3,2-c] pyridine-2(3H)-one)

Inject the reference solution. The test is not valid unless 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 5.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to prasugrel impurity A (Sum of the areas of prasugrel impurity A_1 and A_2) is not more than 30 times the area of the principal peak in the chromatogram obtained with the reference solution (3.0 per cent) and the area any peak corresponding to prasugrel impurity HYTP is not more than 7 times the area of the principal peak in the chromatogram obtained with the reference solution (0.7 per cent), the area of any other secondary peak is not more than 7 times the area of the principal peak in the chromatogram obtained with the reference solution (0.7 per cent) and the sum of the areas of all the secondary peaks, other than prasugrel impurity A_1 and A_2, is not more than 30 times the area of the principal peak in the chromatogram obtained with the reference solution (3.0 per cent). Ignore the peaks due to aspirin, salicylic acid and any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

For Aspirin –
Solvent mixture. 90 volumes of *acetonitrile* and 10 volumes of *water.*

Test solution. Disperse a quantity of the mixed powdered content of the capsules containing 375 mg of Aspirin in 40 ml of the solvent mixture, with the aid of ultrasound for 45 minutes with intermediate shaking and dilute to 50.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture and filter.

Reference solution. A 0.0075 per cent w/v solution of *aspirin IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Inertsil ODS 3V),
- sample temperature: 15°,
- mobile phase: A. *0.01M potassium dihydrogen orthophosphate,* adjusted to pH to 2.5 with *dilute orthophosphoric acid*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
  flow rate: 1 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 10 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	60	40
15	60	40
25	20	80
26	60	40
35	60	40

Name	Relative retention time	Correction factor
Aspirin	1.0	-
Salicylic Acid	1.48	0.86

Inject the reference solution. The test is not valid unless the column efficiency is not less than 3000 theoretical plates, the tailing factor not more than 2.0 and the relative standard deviation for replicate injections is not more than 5.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to salicylic acid is not more than 30 times the area of the principal peak in the chromatogram obtained with the reference solution (3.0 per cent), the area of any other secondary peak is not more than 5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.5 per cent) and the sum of the areas of all the secondary peaks, other than salicylic acid is not more than 20 times the area of the principal peak in the chromatogram obtained with the reference solution (2.0 per cent). Ignore the peak due to prasugrel.

Uniformity of content. Complies with the test stated under Capsules.

Determine by liquid chromatography (2.4.14), as described under Assay of prasugrel with the following modification.

Test solution. Disperse one intact capsule in 20 ml *water*, with the aid of ultrasound. Add 140 ml *acetonitrile*, sonicate for 30 minutes with intermediate shaking and dilute to 200.0 ml with *acetonitrile*, filter,

Inject the reference solution and the test solution.

Calculate the content of $C_{20}H_{20}FNO_3S$ in the capsule.

Other tests. Comply with the tests stated under Capsules.

Assay. Determine by liquid chromatography (2.4.14).

For Prasugrel –

Solvent mixture. 90 volumes of *acetonitrile* and 10 volumes of *water.*

Test solution. Disperse a quantity of the mixed powdered content of 20 capsules containing 100 mg of Prasugrel in 20 ml *water* and 140 ml *acetonitrile* with the aid of ultrasound for 30 minutes with intermediate shaking and dilute to 200.0 ml with the *acetonitrile*. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture and filter.

Reference solution. A 0.0055 per cent w/v solution of *prasugrel hydrochloride IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as
  Inertsil ODS 3V),
- sample temperature: 15°,
- mobile phase. a mixture of 60 volumes of a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen phosphate* in 1000 ml of *water,* adjusted to pH 2.7 with *diluted orthophosphoric acid* and 40 volumes of *acetonitrile,*
  flow rate: 1 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 3000 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 $C_{20}H_{20}FNO_3S$ in the capsules.

For Aspirin –

Solvent mixture. 90 volumes of acetonitrile and 10 volumes of water.

Test solution. Disperse a quantity of the mixed powdered content of 20 capsules containing 375 mg of Aspirin in the solvent mixture, with the aid of ultrasound for 45 minutes with intermittent shaking and dilute to 50.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture and filter.

Reference solution. A 0.075 per cent w/v solution of *aspirin IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as
  Inertsil ODS 3V),
- sample temperature: 15°,
- mobile phase. a mixture of 60 volumes *0.01M potassium dihydrogen phosphate,* adjusted to pH 2.5 with *dilute orthophosphoric acid* and 40 volumes of *acetonitrile,*
  flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 3000 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 $C_9H_8O_4$ in the capsules.

Storage. Store protected from moisture, at a temperature not exceeding 25°.

Labelling. The label states the strength in terms of the equivalent amount of prasugrel and aspirin.