Levodopa and Carbidopa Tablets

Published on: 07 February, 2024 **Last date for comments:** 22 March, 2024

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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.

Document History and Schedule for the Adoption Process

Description	Details
Document version	1.0
First draft published on IPC website for public comments	February 7, 2024
Last date for comments	**March 22, 2024**
Monograph revisions proposed for inclusion in	**IP 2026**
Tentative effective date of monograph revisions	**July, 2026**
Draft revision published on IPC website for public comments	--
Further follow-up action as required.	

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Change **to**: **Levodopa and Carbidopa Tablets**

Co-careldopa Tablets

Levodopa and Carbidopa Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of carbidopa, $C_{10}H_{14}N_2O_4$ and levodopa, $C_9H_{11}NO_4$.

Usual strengths. Levodopa, 100 mg and Carbidopa, 10 mg; Levodopa, 100 mg and Carbidopa, 25 mg; Levodopa, 250 mg and Carbidopa, 25 mg

Identification

In the Assay, the principal peaks in the chromatogram obtained with test solution (a) and test solution (b) correspond to the peaks in the chromatogram obtained with reference solution (a).

Tests

Dissolution (2.5.2)

Apparatus No. 1 (Basket),
Medium. 750 ml of *0.1 M hydrochloric acid,*
Speed and time. 50 rpm and 30 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 the dissolution medium.

Reference solution (a). A 0.0133 per cent w/v solution of *carbidopa IPRS* in the dissolution medium.

Reference solution (b). A 0.133 per cent w/v solution of *levodopa IPRS* in the dissolution medium.

Reference solution (c). Dilute a suitable volume of reference solution (a) and reference solution (b) with the dissolution medium to obtain a solution having a known concentration similar to the test solution.

Chromatographic system
- a stainless steel column 30 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (10 µm) (Such as Micro Bondapak C18),
- mobile phase: a buffer solution prepared by dissolving 11 g of *sodium dihydrogen orthophosphate anhydrous* in 950 ml of *water,* add 1.3 ml of 0.024 per cent w/v solution of *sodium 1-decanesulphonate* in *water,* adjusted to pH 2.8 with *orthophosphoric acid* and dilute to 1000 ml with *water*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

The relative retention time with reference to carbidopa, for levodopa is about 0.4.

Inject reference solution (c). The test is not valid unless resolution between the peaks due to levodopa and carbidopa is not less than 6 and the relative standard deviation for replicate injections is not more than 2.0 per cent for both the peaks.

Inject reference solution (c) and the test solution.

Calculate the contents of $C_{10}H_{14}N_2O_4$ and $C_9H_{11}NO_4$ in the medium.

Q. Not less than 80 per cent of the stated amounts of $C_{10}H_{14}N_2O_4$ and $C_9H_{11}NO_4$.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE— Protect the solutions from light and maintain them at 2° to 8° until they are injected. Use within 12 hours.

Test solution. Disperse a quantity of the powdered tablets containing 125 mg of Carbidopa in 80 ml the mobile phase, with the aid of ultrasound for 15 minutes with intermittent shaking and dilute to 100.0 with the mobile phase. Centrifuge a portion of the solution at 3000 rpm for 5 minutes. Dilute 5.0 ml of the supernatant to 50.0 ml with the mobile phase.

Reference solution (a). A solution containing 0.05 per cent w/v of *levodopa IPRS* and 0.0125 per cent w/v of *carbidopa IPRS* in the mobile phase. Dilute 1.0 ml of the solution to 100.0 ml with the mobile phase.

Reference solution (b). A solution containing 0.125 per cent w/v of *carbidopa IPRS*, 0.00025 per cent of *dihydroxybenzaldehyde*, 0.00125 per cent of *dihydroxyphenylacetone* and 0.0025 per cent w/v of *levodopa impurity B IPRS* in the mobile phase. Dilute 1.0 ml of the solution to 10.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as YMC-Pack ODS-A),
- sample temperature: 5°,
- mobile phase: a mixture of 95 volumes of a buffer solution prepared by dissolving 6 g of *sodium dihydrogen orthophosphate anhydrous* in 1000 ml of *water*, adjusted to pH 2.2 with *orthophosphoric acid* and 5 volumes of *ethanol*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Name	Relative retention time	Correction factor
Levodopa impurity A[1]*	0.8	---
Levodopa	1.0	---
Methyldopa[2]	1.8	---
Levodopa impurity B[3]*	2.0	---
Carbidopa	2.3	---
Dihydroxybenzaldehyde[4]*	5.6	---
Dihydroxyphenylacetone[5]	6.2	0.71
Carbidopa impurity A (3-O-Methylcarbidopa)[6]*	6.6	---

*Process-related impurities, included for identification only; not to be included in total impurities.

[1]3-(3,4,6-trihydroxyphenyl)alanin, impurity based on label claim of levodopa,

[2]impurity based on label claim of carbidopa,

[3]3-methoxy-*L*-tyrosine, impurity based on label claim of levodopa,

[4]3,4-dihydroxybenzaldehyde, impurity based on label claim of carbidopa,

[5]3,4-dihydroxyphenylacetone, impurity based on label claim of carbidopa,

[6](s)-2-hydrazinyl-3-(4-hydroxy-3-methoxyphenyl)-2-methyl-propanoic acid.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to carbidopa and levodopa impurity B is not less than 1.5 and dihydroxybenzaldehyde and dihydroxyphenyl acetone is not less than 1.5 and signal-to-noise ratio is not less than 10 for dihydroxybenzaldehyde and dihydroxyphenyl acetone peaks in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 3.0 per cent for both the peaks in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. Run the chromatogram 5 times the retention time of carbidopa. The area of any peak corresponding to methyldopa is not more than 0.7 times the area of the carbidopa peak in the chromatogram obtained with reference solution (a) (0.7 per cent), the area of any peak corresponding to dihydroxyphenyl acetone is not more than the area of the carbidopa peak in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any other secondary peak is not more than 0.05 times the area of the levodopa peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than the area of the levodopa peak in the chromatogram obtained with reference solution (a) (4.0 per cent). Ignore any peak related to carbidopa with an area less than 0.1 times the area of carbidopa peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and any peak related to levodopa with an area less than 0.0125 times the area of levodopa peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

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

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

Test solution. Disperse one intact tablet in 40 ml the mobile phase, with the aid of ultrasound for 15 minutes with intermittent shaking and dilute to 50.0 with the mobile phase. Centrifuge a portion of the solution at 3000 rpm for 5 minutes. Dilute a suitable volume of the supernatant with the mobile phase to obtain a solution containing of 0.01 per cent w/v of Carbidopa.

Reference solution. A 0.01 per cent w/v solution of *carbidopa IPRS* in the mobile phase.

Inject the reference solution and the test solution.

Calculate the content of $C_{10}H_{14}N_2O_4$ in the tablet.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Test solution (a). Weigh and powder 20 or more tablets. Disperse a quantity of the powder containing 250 mg of Carbidopa in 80 ml of the mobile phase, with the aid of ultrasound for 15 minutes with intermittent shaking and dilute to100.0 with the mobile phase. Centrifuge a portion of the solution at 3000 rpm for 5 minutes. Dilute 5.0 ml of the supernatant to 100.0 ml with the mobile phase.

Test solution (b). Dilute a suitable volume of test solution (a) with the mobile phase to obtain a solution containing 0.0125 per cent w/v of Levodopa.

Reference solution (a). A solution containing 0.0125 per cent w/v, each of, *levodopa IPRS* and *carbidopa IPRS* in the mobile phase.

Reference solution (b). A 0.00025 per cent w/v solution of *levodopa impurity B IPRS* in reference solution (a).

Run the chromatogram 5 times the retention time of carbidopa.

Inject reference solution (a) and (b). The test is not valid unless resolution between the peaks due to levodopa impurity B and carbidopa is not less than 1.5 in the chromatogram obtained with reference solution (b), 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 for both the peaks in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and test solution (a) for carbidopa and test solution (b) for levodopa.

Calculate the content of $C_{10}H_{14}N_2O_4$ and $C_9H_{11}NO_4$ in the tablets.

Storage. Store protected from light and moisture, at temperature not exceeding 30º.