

Guidance Document

Testing of Diethylene Glycol and Ethylene Glycol in Liquid Orals by Gas Chromatography

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Disclaimer

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Introduction

In order to support the revision of the IP General Monograph on 'Oral Liquids' through Amendment List 09 to Indian Pharmacopoeia (IP) 2022 dated October 10, 2025, IPC is publishing methods that may be applied for testing of Diethylene Glycol (DEG) and Ethylene Glycol (EG) in oral liquids. The methods published herein are for guidance purpose and shall not be considered as official requirements of the IP. Users are encouraged to adopt these methods for testing DEG and EG in their products. Alternately, users may also develop their *in-house* method(s) and apply the same for testing of their products with the approval of the competent authority. However, it shall be responsibility of the users to establish the suitability of the methods for intended purpose after due validation.

Accordingly, following methods are published by the IPC for guidance:

Method-1

Ethylene glycol and diethylene glycol. Determine by gas chromatography (2.4.13).

Internal standard solution. A 0.25 per cent w/v solution of 2,2,2- trichloroethanol in methanol.

Test solution. Mix 5 g of the liquid preparation for oral use with 15 ml of methanol, add 1.0 ml of the internal standard solution and dilute to 25.0 ml with methanol. Allow to stand for 5 to 10 minutes and filter. [NOTE- If necessary, centrifuge a portion of the solution for 2 to 3 minutes and filter the supernatant liquid].

Reference solution (a). A 5.0 per cent w/v solution of propylene glycol IPRS in methanol.

Reference solution (b). A 0.125 per cent w/v solution of ethylene glycol IPRS in methanol.

Reference solution (c). A 0.125 per cent w/v solution of diethylene glycol IPRS in methanol.

Reference solution (d). Dilute 1.0 ml, each of, reference solution (a), reference solution (b) reference solution (c) and the internal standard solution to 25.0 ml with methanol.

Chromatographic system

- a fused silica column 30 m × 0.53 mm, packed with 6 per cent cyanopropylphenyl and 94 per cent dimethyl polysiloxane (3.0 µm) (such as DB-624),
- temperature:
 - column. 100° hold for 4 minutes, 100° to 120° @ 50° per minute, and hold 10 minutes, 120° to 220° @ 50° per minute and hold for 6 minutes,
- inlet port. 220° and detector at 250°,
- split ratio: 10:1,
- flame ionization detector,
- flow rate: 4.5 ml per minute, using nitrogen as the carrier gas,
- injection volume: 1 µl.

| Name | Relative retention time |
|-------------------------|-------------------------|
| Ethylene glycol | 0.8 |
| Propylene glycol | 1.0 |
| 2,2,2- Trichloroethanol | 1.7 |
| Diethylene glycol | 2.4 |

Inject reference solution (d). The test is not valid unless the resolution between the peaks due to ethylene glycol and propylene glycol is not less than 3.0 and the relative standard deviation of the ratio of the area of each, ethylene glycol and diethylene glycol peaks to that of the internal standard peak for replicate injections is not more than 8.0 per cent.

Inject reference solution (d) and the test solution. In the chromatogram obtained with the test solution, the ratio of the area of the peak corresponding to ethylene glycol and diethylene glycol to that of the internal standard, each of, is not more than 4 times the ratio of area of the corresponding peaks to that of the internal standard in the chromatogram obtained with reference solution (d) (0.1 per cent).

Method-2

Ethylene glycol and diethylene glycol. Determine by gas chromatography (2.4.13).

Internal standard solution. A 0.006 per cent w/v solution of *pentadecane* in *acetone*.

Test solution. Weigh and transfer 0.2 g of the liquid preparation for oral use to a 10-ml volumetric flask, add 1.0 ml of the internal standard solution, vortex the solution for 3 minutes and dilute to volume with *acetone*.

Reference solution (a). A solution containing 0.02 per cent w/v, each of, *ethylene glycol IPRS* and *diethylene glycol IPRS* in *acetone*.

Reference solution (b). Weigh and transfer 0.2 g of the liquid preparation for oral use to a 10-ml volumetric flask, add 1.0 ml of the internal standard solution and 1.0 ml of reference solution (a), vortex the solution for 3 minutes and dilute to volume with *acetone*.

Reference solution (c). Weigh and transfer 0.2 g of the liquid preparation for oral use to a 10-ml volumetric flask, add 1.0 ml of the internal standard solution and 0.5 ml of reference solution (a), vortex the solution for 3 minutes and dilute to volume with *acetone*.

Blank solution. Dilute 1.0 ml of the internal standard solution to 10.0 ml with *acetone*.

[NOTE—1. *Sample will not completely dissolve in acetone. Therefore, undissolved residue/precipitate will be observed in Test solution, Reference solution (b) and Reference solution (c).*

2. *After injecting reference solution (b) and (c), Inject 2 injections of blank solution to prevent the carryover.]*

Chromatographic system

– a fused silica column 30 m × 0.32 mm, packed with 100 per cent polyethylene glycol (1.0 μm) (such as Elite-WAX column),

– temperature:

column. 100° for 2 minutes, 100° to 180° @ 8° per minute, and hold at 180° for 8 minutes, 180° to 220° @ 15° per minutes and hold at 220° for 10 minutes,

– inlet port. 220° and detector at 270°,

– split ratio: 3:1,

– flame ionization detector,

– flow rate: 3 ml per minute, using nitrogen as the carrier gas,

– injection volume: 1 μl.

| Name | Relative retention time |
|---|-------------------------|
| Acetone | 0.18 |
| Pentadecane (Retention time: about 7.0 minutes) | 1.0 |
| Ethylene glycol | 1.32 |
| Diethylene glycol | 2.09 |

Inject reference solution (b) and (c). The test is not valid unless the relative standard deviation of the ratio of peak area of each analyte to that of the internal standard, for replicate injections is not more than 15.0 per cent in the chromatogram obtained with reference solution (b) and the signal-to-noise ratio for ethylene glycol peak is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the ratio of the peak area of any peak corresponding to ethylene glycol and diethylene glycol to that of the internal standard, each of, is not more than ratio of the peak the area of the corresponding peaks to that of internal standard in the chromatogram obtained with reference solution (b) (0.10 per cent).