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TP 301

Quantitation of Acetaldehyde, Ethylene Oxide, 2-Chloroethanol, Ethylene Glycol, 1,4-Dioxane & Diethylene Glycol in PEG 3350 by using dynamic headspace GC-MS/MS

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1. Overview

Polyethylene glycol 3350 (PEG 3350) is used to treat occasional constipation and it is in a class of medications called osmotic laxatives. PEG 3350 is an addition polymer of ethylene oxide and water with formula H(OCH2CH2)n OH, in which **n** represents the average number of oxyethylene groups. The average molecular weight of PEG 3350 is 3015–3685 g/mol (Da).

Acetaldehyde, Ethylene Oxide (EtO), 2-Chloroethanol (2-CE), Ethylene Glycol (EG), 1,4-Dioxane and Diethylene Glycol (DEG) are the probable impurities of PEG 3350. All these above impurities are highly toxic & hazardous substances.

As per the USP monograph, different chromatography techniques and sample preparation methods are used to quantify above mentioned impurities. This study reports a single sensitive and reliable analytical method for quantitation of all above impurities by using dynamic headspace (Trap) coupled with GC-MS/MS system. Limit of impurities and detail method of analysis are shown in table 1

Table 1 Limit of impurities & detail method of sample analysis

No.	Impurity	Limits (As per USP)	Techniques used (As per USP)	LOQ (Achieved)	Technique used (As per Shimadzu)
1	Acetaldehyde	30 ug/g	LC-UV	2 ug/g	Dynamic Headspace with GC-MS/MS – MRM/SIM Mode **(Single Method)**
2	EtO	1 ug/g	GC-FID	1 ug/g	
3	1,4-Dioxane	10 ug/g	GC-FID	2 ug/g	
4	EG	620 ug/g	LC-DRI	200 ug/g	
5	DEG	1380 - 2000 ug/g	LC-DRI	200 ug/g	
6	2-CE	NA	NA	1 ug/g	

❑ LOQ = Limit Of Quantification

2. Introduction

This study reports highly sensitive single method for the simultaneous quantification of multiple probable impurities of PEG 3350 by using dynamic headspace (Trap) coupled with triple quadrupole gas chromatography (GC-MS/MS) system.

3. Materials and methods

For this study, individual impurity reference standards were procured from Sigma Aldrich, whereas PEG 3350 powder sample was procured from local medical store.
10% of PEG 3350 powder sample solution (as such sample solution) and respective levels of matrix-matched calibration standard solutions were prepared in acetonitrile. Standard addition method was used to quantify impurities in the PEG 3350 sample. This method was part validated with respect to (w.r.t) precision, linearity/accuracy and sample analysis.
GCMS-TQ8050 NX equipped with headspace sampler HS-20 NX (Trap) (Figure 1), manufactured by Shimadzu Corporation Japan, was used to quantify impurities in the PEG 3350 sample.

Figure 1. Shimadzu GCMS-TQ8050 NX with HS-20 NX (Trap)

3-1. Method development

Instrumental method was developed w.r.t chromatography and mass spectrometry parameters. Individual Certified Reference Standard (CRS) were used to prepare standard stock solution. Further, from this stock, a standard solution mixture was prepared and then analyzed in the scan mode for identification. Steps such as precursor ion selection and MRM optimization at different Collision Energies (CE) were performed. SIM/MRM method with segmented MRM and optimum CE energies was generated.
Acetaldehyde, EtO and 2-CE were quantified by using MRM ion transitions. Whereas EG,1,4-Dioxane and DEG were quantified by using SIM ion transitions. Instrument parameters are given in Table 3 and optimized MRM/SIM transitions are given in Table 4.

3-2. Sample and standard solution preparations

• Preparation of sample solution (Matrix blank)
10% PEG 3350 sample solution was prepared in acetonitrile & then analyzed (100 uL in HS vial).

• Preparation of matrix matched calibration level solutions
5 levels of 10% matrix match calibration sample solutions of PEG 3350 were prepared from below five levels of solvent standard. Calibration levels of solvent standard are given in Table 2.

Table 2 Calibration levels of solvent standard (actual conc. in ppm)

No.	Name	Level 1	Level 2	Level 3	Level 4	Level 5
1	Acetaldehyde	0.2 ppm	0.5 ppm	1 ppm	1.5 ppm	2 ppm
2	EtO	0.1 ppm	0.25 ppm	0.5 ppm	0.75 ppm	1 ppm
3	2-CE	0.1 ppm	0.25 ppm	0.5 ppm	0.75 ppm	1 ppm
4	1,4-Dioxane	0.2 ppm	0.5 ppm	1 ppm	1.5 ppm	2 ppm
5	EG	20 ppm	50 ppm	100 ppm	150 ppm	200 ppm
6	DEG	20 ppm	50 ppm	100 ppm	150 ppm	200 ppm

3-3. Analytical Conditions

Table 3 Instrument configuration and analytical conditions - HSGC-MS/MS

GCMS System : GCMS-TQ8050 NX with HS-20 NX (Trap)

Chromatography Parameters
Column : SH-I--624 Sil MS 60.00 m, 0.25 mm I.D., 1.4 µm df (S/N:1649778)
Injection Mode : Split (30:1)
Flow Control Mode : Column Flow
Carrier Gas : Helium
Column Flow : 1.4 mL/min

Temp. Program	Ramp Rate (ºC/min)	Temp. (ºC)	Hold Time (min)
	-	35	1.0
	30	235	12.33

GC Run Time : 20 minutes
Ionization Mode : Electron Ionization (EI)
Interface Temp. : 250 ºC
Ion Source Temp. : 240 ºC

Headspace parameters
Oven Temp. : 110 ºC
Sample Line Temp. : 130 ºC
Transfer Line Temp. : 150 ºC
Trap Cooling Temp. : -10 ºC
Trap Desorption Temp. : 280 ºC
Shaking Level : 5
Equilibrating Time : 30 minutes
Mult Inj. Count (MIC) : MIC-1
Pressurizing Gas Pressure : 192 kPa
GC Cycle Time : 40 minutes

Table 4 MRM & SIM Ion transitions

Peak ID	Compound	Quantifier	CE-1	Qualifier	CE-2	Qualifier	CE-3
1	Acetaldehyde	44>29	6	44>28	6	44>14	18
2	EtO	44>29	6	44>28	6	44>14	18
3	2-CE	80>31	6	80>44	5	82>31	6
4	1,4-Dioxane	88	-	58	-	-	-
5	EG	62	-	43	-	-	-
6	DEG	75	-	76	-	-	-

4. Results

Calibration curve for all six impurities are reported in Figure 2

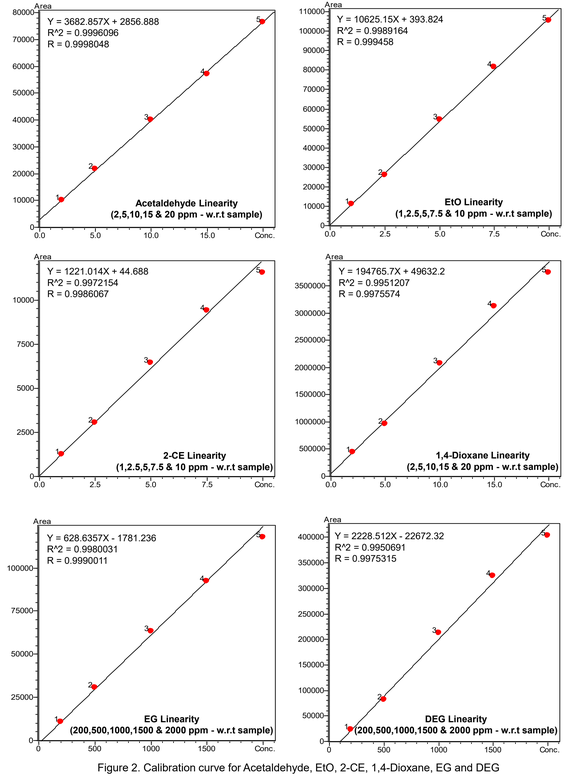

Figure 2. Calibration curve for Acetaldehyde, EtO, 2-CE, 1,4-Dioxane, EG and DEG

Summary Of Results

Validation parameters like LOQ precision, matrix match linearity / recovery and impurity content in sample were studied. Standard addition method was used to quantify impurities in the PEG 3350 sample. The summary of the results are shown in Table 5.

Table 5 Summary of the results

No.	Validation Parameter	Acetaldehyde	EtO	2-CE	1,4-Dioxane	EG	DEG
1	LOQ precision (% RSD)	2.1	4.8	9.9	3.3	5.3	8.3
	Conc. (w.r.t sample)	2ppm	1ppm	1ppm	2 ppm	200ppm	200ppm
2	Linearity (r2)	0.99961	0.99892	0.99722	0.99512	0.99800	0.99507
3	Sample analysis (ppm)	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

❑ BLQ = Below Limit Of Quantification

Merits of headspace injection method

- Dynamic headspace has an edge over liquid injection technique in terms of sample preparation, less matrix interference and trace level quantitation.
- All impurities can be measured easily in single run with very low LOQ conc. by using dynamic headspace mode of analysis.
- No clean up reagents or extraction salts are used and hence no additional sample preparation which minimizes errors.

5. Conclusion

- Trace level quantification of Acetaldehyde, EtO, 2-CE, 1,4-Dioxane, EG and DEG in PEG 3350 sample was successfully performed by using Shimadzu GCMS-TQ8050 NX with HS-20 NX (Trap) dynamic headspace sampler.
- Dynamic headspace mode outperforms the current regulatory limits, delivering multifold times more sensitivity compared to other injection techniques.
- Shimadzu GCMS-TQ8050 NX features a new highly efficient detector and superior noise reduction technology that enhance sensitivity and enables quantitation of impurities even at trace levels.

6. References

[1] EURL-SRM – Analytical Observation Report, Version 1.1 (December 2020)

[2] The Polyethylene Glycol 3350 Revision Bulletin (December 2020)

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