Asian Journal of Chemistry; Vol. 33, No. 7 (2021), 1645-1650

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2021.23256

GC-FID Technique for the Quantitative Evaluation of Multiple Residual Organic Solvent Impurities in Fosaprepitant Dimeglumine Drug

H. RAMAKRISHNA REDDY[1,2,*], S.R. PRATAP[3,4], N. CHANDRASEKHAR[1,2] and S.Z.M. SHAMSHUDDIN[1,3]

[1]Research and Development Centre, Bharathiar University, Coimbatore-641046, India
[2]Research and Development Centre, Department of Chemistry, Shridevi Institute of Engineering and Technology, Tumkuru-572106, India
[3]Chemistry Research Laboratory, HMS Institute of Technology, Tumkuru-572104, India
[4]Channabasaveshwara Institute of Technology, Gubbi-572216, India

*Corresponding author: E-mail: rkreddy_h@yahoo.co.in

Received: 21 April 2021; *Accepted*: 25 May 2021; *Published online*: 26 June 2021; AJC-20408

A proficient and distinct methodology is established for the quantification of multiple residual organic solvent impurities in fosaprepitant dimeglumine drug substance by gas chromatography with headspace sampler (HS-GC) and flame ionization detector (FID). Chromatographic separation was executed on a fused silica dimethylpolysiloxane capillary column (HP-1; USP G2 phase having dimensions, 60 m length × 0.53 mm dia & 5 µm film thickness). The validation of optimized method was carried out in accordance with relevant validation principles. The authenticated procedure was noticed to be specific, precise, linear, accurate, robust and rugged with concentration ranging from lowest quantification level (LQL) to 200% specification level for each residual organic solvent impurities (methanol, ethanol, acetone, isopropyl alcohol, dichloromethane, methyl *tert*-butyl ether, ethyl acetate, tetrahydrofuran, cyclohexane and toluene). The established technique was productively useful to determine the residual solvent impurities in fosaprepitant dimeglumine.

Keywords: Fosaprepitant dimeglumine, Residual solvent impurities, Gas chromatography.

INTRODUCTION

Fosaprepitant dimeglumine (Fig. 1) is an antiemetic drug for intravenous operations. It is distributed as a sterile, lyophilized powder in a sealed vial under the brand name 'EMEND' for injection by Merck and Co., Inc. When fosaprepitant for injection is administered intravenously this quickly converted to aprepitantin the human body. Aprepitant is antagonist (selective) of mankind substance P/neurokinin-1 (NK_1) receptors. Fosaprepitant for injection, blended with various antiemetic agents, is identified in adults for the control of acute plus delayed nausea as well as vomiting concerned with initial/repetitive courses of high emetogenic cancer chemotherapy (HEC) associated with high-dose cisplatin and for avoiding delayed nausea plus vomiting related with initial and repeat courses of moderate emetogenic cancerous chemotherapy (MEC) [1,2].

In the synthesis, aprepitant is used as the initial raw material, which reacts with tetrabenzyl pyrophosphate in anhydrous tetrahydrofuran with sodium hexamethyldisilazide as a base to obtain dibenzyl ester intermediate. A benzyl group of dibenzyl ester is removed in anhydrous methanol to generate a single-benzyl ester intermediate, which is hydrogenated to remove a remaining benzyl group and salified with meglumine to obtain fosaprepitant dimeglumine. Fosaprepitant dimeglumine is highly hygroscopic and strenuous for purification. Hence, multiple organic solvents belong to ICH Class II and Class III (methanol, ethanol, acetone, isopropyl alcohol, dichloromethane, methyl *tert*-butyl ether, ethyl acetate, tetrahydrofuran, cyclohexane and toluene) have been used in the purification process of the drug substance [3,4].

These processes related to organic solvents which cannot be removed and controlled completely during the synthesis. Thus, monitoring of these residual organic solvent impurities in the drug substance is mandatory according to regulatory requirements to ensure human safety [5-7]. From the literature survey, it reveals thus far, there is no specific methodology reported to determine these residual organic solvent impurities in fosaprepitant dimeglumine drug substance. Generally, in

This is an open access journal, and articles are distributed under the terms of the Attribution 4.0 International (CC BY 4.0) License. This license lets others distribute, remix, tweak, and build upon your work, even commercially, as long as they credit the author for the original creation. You must give appropriate credit, provide a link to the license, and indicate if changes were made.

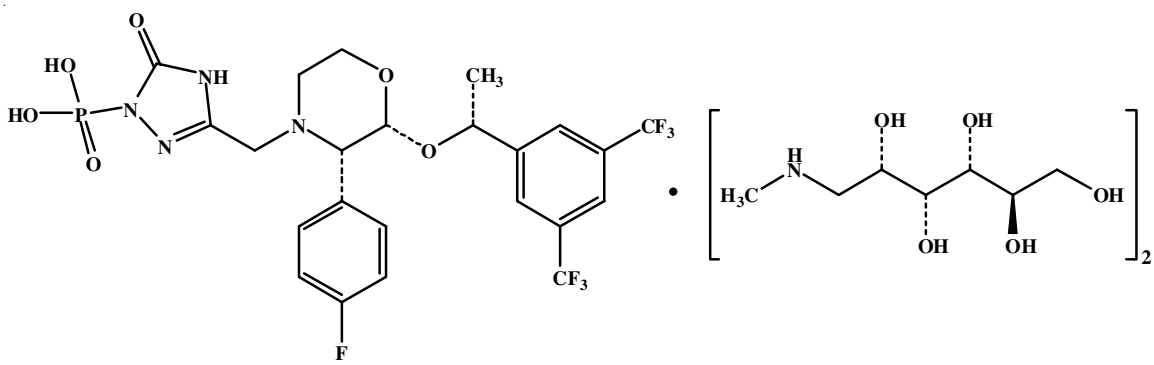

Fig. 1. Structure of fosaprepitant dimeglumine

the pharmacopoeia monographs, specific methods for residual solvents will not be available for active pharmaceutical ingredients. However, some of the HS-GC methods for mixture of residual solvents have been reported. The reported methods have some limitations due to poor separation of closely eluting solvents, sample solvent compatibility and all the desired solvent impurities were not separated [8-11]. Hence, there is a need to develop and establish specific and suitable methods to monitor the residual solvent impurities during process optimization and final stage of drug molecule. In this context, this paper describes a distinct and reliable method with HS-GC technique for the quantitative estimation of residual organic solvent impurities in fosaprepitant dimeglumine drug material. Projected procedure is sensitive at lower concentrations for all listed residual solvent impurities of fosaprepitant dimeglumine drug substance.

EXPERIMENTAL

Methanol, ethanol, acetone, isopropyl alcohol, dichloromethane, methyl *tert*-butyl ether, ethyl acetate, tetrahydrofuran, cyclohexane, toluene and benzyl alcohol (all were of GC grade solvents with purity 99% and procured from Merck).

Instrumentation and chromatographic conditions: Gas chromatography equipped with head space sampler and flame ionization detector (7890A, Agilent Technologies) was utilized for the execution of analysis. Samples were introduced in a Splitless/Split injection port and detection by a flame ionization detector (FID). For the separation of analytes of sample, a capillary column (HP-1; 60 m length, 0.53 mm inner dia & 5 µm film thickness) was employed.

GC conditions: Column oven temperature: Initial temperature (50 ºC) for 9 min; increased to 130 ºC @ 8 ºC/min, hold for 6 min; then increased to 220 ºC @ 30 ºC/min, hold for 12 min; Injector and detector temperature: 140 ºC and 260 ºC, respectively; Carrier gas: helium employed as a carrier gas with an invariable pressure of 6 psi. Make-up gas for FID: helium gas with 40 mL/min flow rate was used; Fuel gases: Used hydrogen gas and zero air with flow rate of 40 and 400 mL/min. correspondingly. Split ratio: 10:1. Total run time of chromatography: 40 min.

Head space conditions: Oven temperature: 80 ºC; Transfer line temperature: 180 ºC; Loop temperature: 180 ºC; Vial equilibration duration: 20 min; Vial pressurization duration: 0.2 min; Loop equilibration time: 0.05 duration; Loop fill time: 0.2 min; Inject duration: 0.5 min; Vial pressure: 11.6 psi; Injection volume: 1 mL.

Preparation of standard and sample solution: The residual solvents standard solution was prepared by using benzyl alcohol as sample solvent to attain a concentration of about 0.15 mg/mL of ethanol, acetone, isopropyl alcohol, methyl *tert*-butyl ether and ethyl acetate; 0.09 mg/mL of methanol; 0.018 mg/mL of dichloromethane; 0.021 mg/mL of tetrahydrofuran; 0.117 mg/mL of cyclohexane and 0.0266 mg/mL of toluene. [This standard solution concentration is equal to about 5000 ppm of C_2H_5OH, 3000 ppm of CH_3OH, 5000 ppm of acetone, 5000 ppm of isopropyl alcohol, 600 ppm of dichloromethane, 5000 ppm of methyl *tert*-butyl ether, 5000 ppm of ethyl acetate, 720 ppm of tetrahydrofuran, 3880 ppm of cyclohexane, 890 ppm of toluene for 30 mg/mL of test concentration as per the ICH specification limits].The test sample solution was prepared with benzyl alcohol to attain a concentration of 30 mg/mL.

Validation of the method: The test procedure validation was executed as stated by the ICH (Q2R1), USP<1225> and other relevant regulatory guidelines [12-20]. As part of test method validation, the characteristics such as accuracy, specificity, precision, ruggedness, linearity, the lower limits of both quantification and detection, solution stability, robustness, range of the test method and system suitability were evaluated.

RESULTS AND DISCUSSION

Method development: The selected drug substance contains a complex sample matrix with multiple solvent impurities that have different volatile nature and thus chosen a head space sampling technique with FID detection. In this technique, the sample will be directly transferred into a head space glass vial, followed by the addition of a known volume of suitable diluent and sealing the vial with septa. Separation of solvent impurities takes place from the diffusion of volatile components into the gaseous phase based on their partition coefficients. During method optimization, different chromatographic feasibilities were evaluated. The variable experimental trials include selection of suitable sample solvent (solvents with a high boiling point than the analytes of interest like *N*-methyl pyrrolidone; *N,N*-dimethylacetamide; *N,N*-dimethylformamide, benzyl alcohol), capillary silica columns with diverse stationary phase and dimensions (mid-polar phase; AT-624 and non-polar phase; HP-5, HP-1) and varied GC chromatographic conditions (detector, injector and oven temperature; split ratio, column flow). The final methodology was enhanced with benzyl alcohol as a sample solvent due to its miscibility nature, high boiling point

and good recovery of all solvent impurities from the sample matrix. Wide separation of multiple solvent impurity components was achieved with a short run time by using a non-polar phase (100% dimethylpolysiloxane with 60 m length HP-1) capillary column with modified chromatographic parameters.

Specificity: The specificity of the method was evaluated by examining benzyl alcohol (blank), standard, test sample solution, test sample spiked with standard and each individual solvent impurities. The chromatograms acquired for sample solution, standard solution and spiked sample solution (with residual solvent standards) illustrate no intervention of analyte peaks with each other and thus the method is specific (Fig. 2).

Precision: Repeatability was evaluated from the area response in addition to the retention time of each solvent impurity peak acquired from six repeatable standard determinations. The RSD (%) for retention time and peak area response for each solvent impurity were less than 1% and 5%, respectively, which illustrate the repeatability of the procedure.

Reproducibility was evaluated from six reproducible outcomes of quantification obtained from the homogeneous test sample matrix. The RSD (%) for the quantified outcomes of every solvent impurity from samples were less than 5%, which illustrate the reproducibility of the procedure.

Ruggedness: The ruggedness of the procedure was assessed from spiked sample analysis through a diverse instrument, column, analyst with different day. The RSD (%) for the quantified outcomes of every solvent impurity from six verifications (inter precision) along with the cumulative RSD (%) for twelve verifications (both intra and inter precision) were less than 5%, which illustrate the ruggedness of the procedure.

Linearity: The test method linearity was established from eight levels of concentration over the range LQL to 200% of ICH limit for each residual solvent impurity. A linear correlation and regression were determined among the concentrations and peak area responses of each residual solvent. The correlation coefficient (r) and regression coefficient (R^2) values for all ten residual solvent impurities found to be higher than 0.995. The statistical characteristics like slope, *y*-intercept and % *y*-intercept were interpreted and found within the acceptable limit for all solvent impurities. The data tabulated in Table-1 demonstrate the linearity of procedure.

Lowest detection limit (LDL) and lowest quantitation limit (LQL): Lowest detection and quantitation limits have been derived from the slope and residual standard deviation obtained trough linearity. The resultant LDL and LQL values for each solvent impurity are shown in Table-2.

TABLE-1
LINEARITY FOR METHANOL, ETHANOL, ACETONE, ISOPROPANOL, DICHLOROMETHANE, METHYL *tertiary* BUTYL ETHER, ETHYL ACETATE, TETRAHYDROFURAN, CYCLOHEXANE AND TOLUENE

Level (%)	Methanol		Ethanol		Acetone		Isopropanol		Dichloromethane	
	Conc. (µg/mL)	Area response	Conc. (µg/mL)	Area response	Conc. (µg/mL)	Area response	Conc. (µg/mL)	Area response	Conc. (µg/mL)	Area response
QL	24.0	7419	40.0	11846	40.0	13924	64.0	18462	24.0	7419
25	749.9	236084	1251.0	381445	1249.6	478531	1249.6	365482	749.9	236084
50	1499.7	480226	2502.0	759543	2499.3	967398	2499.3	738821	1499.7	480226
80	2399.5	759679	4003.2	1203326	3998.8	1527824	3998.8	1175625	2399.5	759679
100	2999.4	952085	5004.0	1521655	4998.5	1986475	4998.5	1476322	2999.4	952085
120	3599.3	1106195	6004.8	1816113	5998.2	2297610	5998.2	1768449	3599.3	1106195
150	4499.1	1417982	7506.0	2271378	7497.8	2895787	7497.8	2205864	4499.1	1417982
200	5998.8	1845276	10008.0	3024994	9997.0	3916742	9997.0	2820032	5998.8	1845276
Correlation (r)	1.000		1.000		1.000		0.999		1.000	
Regression (R^2)	0.999		1.000		1.000		0.999		0.999	
Slope	308.589		302.267		390.503		285.657		308.589	
y-intercept	10883.124		1531.987		-10351.988		24853.056		10883.124	
% y-intercept	1.1		0.1		-0.5		1.7		1.1	
Level (%)	Methyl *tertiary* butyl ether		Ethyl acetate		Tetrahydrofuran		Cyclohexane		Toluene	
	Conc. (µg/mL)	Area response	Conc. (µg/mL)	Area response	Conc. (µg/mL)	Area response	Conc. (µg/mL)	Area response	Conc. (µg/mL)	Area response
QL	40.0	11846	40.0	13924	64.0	18462	10.0	21884	32.1	21876
25	1251.0	381445	1249.6	478531	1249.6	365482	972.5	1982763	223.1	139253
50	2502.0	759543	2499.3	967398	2499.3	738821	1945.0	3862297	446.2	291335
80	4003.2	1203326	3998.8	1527824	3998.8	1175625	3112.0	6327198	713.9	442831
100	5004.0	1521655	4998.5	1986475	4998.5	1476322	3890.0	7584283	892.4	538632
120	6004.8	1816113	5998.2	2297610	5998.2	1768449	4668.0	9210225	1070.9	651249
150	7506.0	2271378	7497.8	2895787	7497.8	2205864	5835.0	11696449	1338.6	832410
200	10008.0	3024994	9997.0	3916742	9997.0	2820032	7780.0	15721664	1784.8	1076368
Correlation (r)	1.000		1.000		0.999		1.000		1.000	
Regression (R^2)	1.000		1.000		0.999		1.000		0.999	
Slope	302.267		390.503		285.657		2009.310		603.300	
y-intercept	1531.987		-10351.988		24853.056		-35116.710		8913.256	
% y-intercept	0.1		-0.5		1.7		-0.5		1.7	

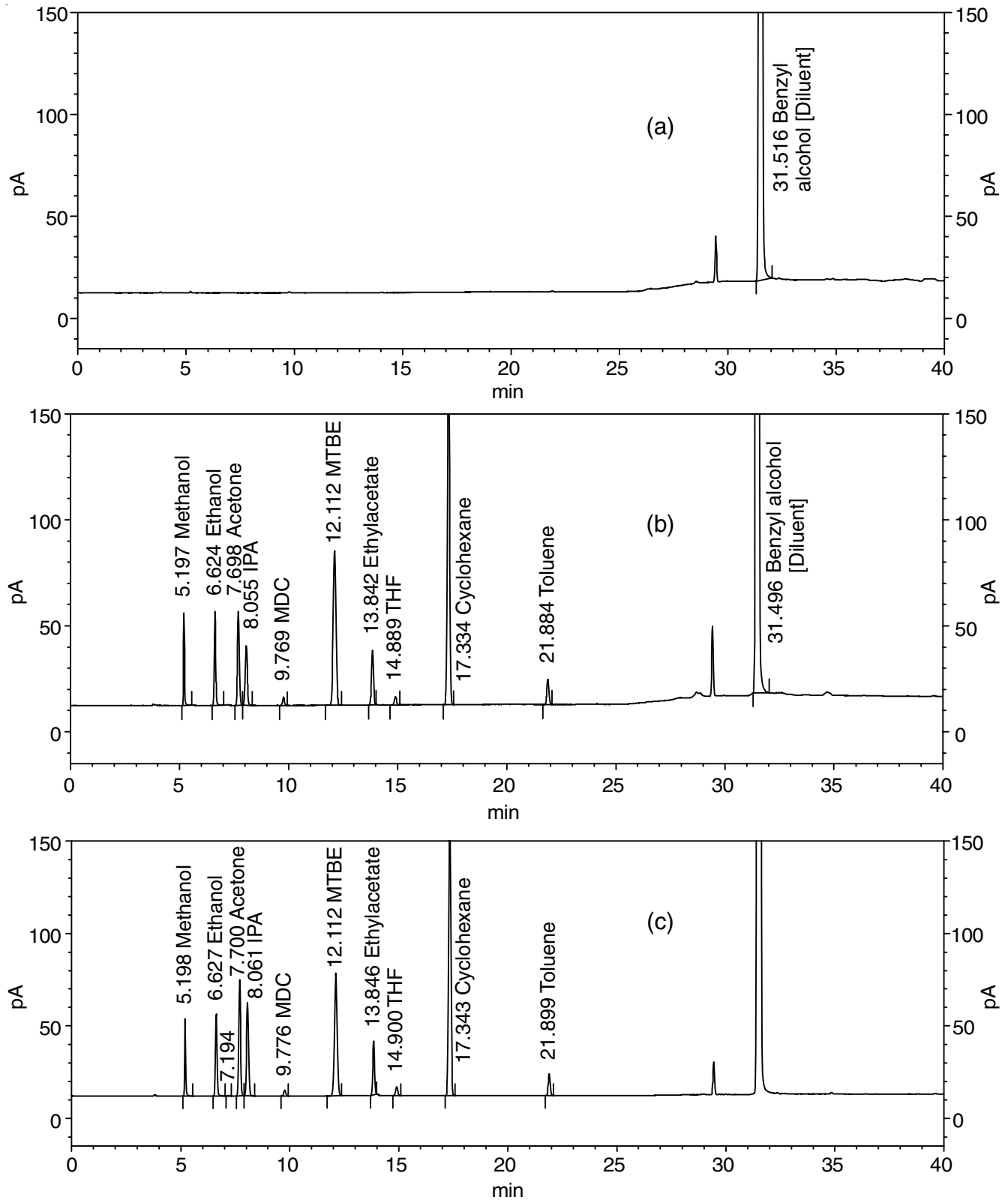

Fig. 2. Chromatogram of (a) blank, (b) standard and (c) sample spiked with solvent impurities

Distinct visible peaks were examined at LDL concentration and precision at LQL level was confirmed from the % recovery of spiked sample determinations at LQL level. Thus, the method is sensitive.

Accuracy and range: The test method accuracy was verified by spiking all residual solvent impurities at five different levels (LQL, 50%, 100%, 150% and 200%) of nominal concentration for each solvent as per ICH limits. At lower level (50%) and higher level (200%), performed six determinations and triplicate analysis for the remaining levels. The recovery (%) was determined from the quantity of solvent standard added and recovered

TABLE-2
LOWEST DETECTION LIMIT AND
LOWEST QUANTITATION LIMIT

Solvent impurity	LDL (ppm)	LQL (ppm)
Methanol	7.3	24
Ethanol	12.1	40
Acetone	12.1	40
Isopropanol	19.4	64
Dichloromethane	16.4	54
Methyl *tertiary* butyl ether	6.9	23
Ethyl acetate	19.7	65
Tetrahydrofuran	16.1	53
Cyclohexane	3.0	10
Toluene	9.7	32.1

from the test sample matrix. The recovery for all ten solvents at each level found to be within the acceptable range of 80-120%, which confirms the accuracy of the method. The range of the test procedure was obtained based on the linearity, recovery and precision acquired from the accuracy parameter (Table-3).

Robustness: Robustness of test procedure was assessed for minor variations in the chromatographic parameters. The varied parameters; initial carrier gas flow rate (5.8 psi, 6 psi and 6.2 psi), initial column oven temperature (45 ºC/min, 50 ºC/min and 55 ºC/min), injector temperature (265 ºC, 270 ºC and 275 ºC) and detector temperature (255 ºC, 260 ºC and 265 ºC). The consequence of dissimilarities in method was assessed for peak area response, resolution and recovery and no significant change observed (Table-4).

System suitability: The system suitability was assessed for a standard solution in every factor of validation study. The specified system suitability factors; RSD for peak area response of all solvent impurities and resolution between closely eluting solvent peaks (acetone and IPA) were evaluated from the standard solution. The % RSD criteria of < 10.0% and resolution factor > 1.5 demonstrate the correctness of the analytical system.

Conclusion

Gas chromatography with an FID technique for the specified multiple solvent impurities in fosaprepitant dimeglumine drug substance was established and validated in accordance to analytical regulatory guidelines. The technique established was specific, robust, accurate, sensitive and linear in the range LOQ to 200% specification limit as per ICH. The test method was successfully adopted to analyze the residual organic solvent impurities (methanol, ethanol, acetone, isopropyl alcohol, dichloromethane, methyl *tert*-butyl ether, ethyl acetate, tetrahydrofuran, cyclohexane and toluene) in the samples of fosaprepitant dimeglumine drug substance. Consequently, this method can be endorsed by quality control laboratories in the regular monitoring and control of these solvent impurities during the in-process and final stages. Further, this method can be successfully applied to other drug molecules having any of these residual solvent impurities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

TABLE-3
ACCURACY AND RANGE

Accuracy level	Sample	Accuracy (%)									
		Methanol	Ethanol	Acetone	IPA	DCM	MTBE	Ethyl acetate	THF	Cyclo-hexane	Toluene
LOQ	1	96.7	98.8	97.3	97.5	91.9	99.1	98.8	94.0	96.0	103.4
	2	98.8	96.5	97.8	96.7	95.2	93.9	96.0	94.7	94.0	100.9
	3	100.4	97.3	95.5	99.2	94.3	99.6	99.5	92.8	95.0	101.9
	4	98.3	95.5	96.0	101.3	91.7	100.9	98.6	95.7	93.0	105.6
	5	97.5	98.3	96.8	98.1	90.6	98.7	98.2	94.5	96.0	96.9
	6	99.2	96.0	98.3	101.7	91.1	95.7	97.2	94.2	94.0	102.8
50%	1	99.2	97.9	99.5	100.1	99.0	96.4	100.6	97.5	96.9	96.3
	2	99.8	98.5	96.4	99.6	95.3	96.1	99.6	96.3	97.8	98.1
	3	100.8	97.4	95.5	99.2	96.9	96.6	96.8	97.1	97.3	97.3
100%	1	101.1	99.6	98.0	99.7	98.2	100.4	99.7	97.0	96.6	98.4
	2	100.9	97.7	98.3	100.3	98.4	98.0	97.4	98.7	95.7	99.0
	3	100.7	98.0	99.5	99.6	100.5	96.2	97.8	97.8	96.6	98.2
150%	1	101.9	100.1	99.8	98.7	101.2	98.1	99.9	96.2	97.9	97.2
	2	100.3	99.1	99.2	99.6	100.8	99.2	100.2	100.4	97.6	97.5
	3	99.8	99.9	100.1	100.2	101.8	100.5	99.0	101.2	99.8	103.0
200%	1	101.7	99.8	101.9	98.5	99.0	100.8	103.7	98.5	96.4	98.5
	2	100.1	98.7	100.9	99.2	99.1	99.5	101.4	97.2	96.8	100.8
	3	99.7	100.2	102.1	99.1	100.7	98.9	102.4	96.3	96.0	100.4
	4	102.0	101.2	99.7	99.7	103.5	102.2	99.9	99.4	97.6	97.0
	5	100.5	99.7	99.9	98.5	100.6	100.1	99.5	98.3	95.0	98.5
	6	99.8	98.4	101.1	100.2	99.8	100.6	101.3	99.8	96.6	99.4
Overall mean % recovery		99.9	98.5	98.7	99.4	97.6	98.6	99.4	97.0	96.3	99.6
Overall mean % RSD		1.4	1.5	2.0	1.2	4.0	2.2	1.9	2.3	1.6	2.6

IPA = Isopropanol, DCM = Dichloromethane, MTBE = Methyl *tertiary* butyl ether, THF = Tetrahydrofuran

TABLE-4
ROBUSTNESS

Chromatographic conditions		Methanol	Ethanol	Acetone	IPA	DCM	MTBE	Ethyl acetate	THF	Cyclo-hexane	Toluene
% RSD for area response											
As such conditions		2.8	2.3	2.1	2.5	6.3	3.1	2.8	2.4	3.6	2.7
Flow	5.8 psi	2.5	3.3	2.6	2.8	5.7	2.9	2.6	2.3	4.1	3.2
	6.2 psi	2.6	2.7	2.5	2.2	4.5	2.8	2.3	2.7	4.9	3.5
Column temperature	45 °C/min	2.8	3.1	2.2	2.9	6.8	3.9	3.2	2.2	6.4	4.2
	55 °C/min	2.2	2.8	2.7	4.0	5.7	2.7	2.6	2.8	4.7	2.9
Injector temperature	265 °C	4.1	2.5	3.6	2.7	4.9	4.1	3.9	3.6	3.8	3.8
	275 °C	3.6	3.0	1.9	3.4	7.3	3.6	2.7	2.5	4.1	5.1
Detector temperature	255 °C	2.7	2.6	2.4	2.8	6.3	5.2	2.9	3.7	5.4	4.6
	265 °C	3.2	2.9	2.2	3.2	5.9	4.3	3.3	5.1	4.2	3.7
% Recovery											
As such conditions		101.1	99.6	98.0	99.7	98.2	100.4	99.7	97.0	96.6	98.4
Flow	5.8 psi	97.4	96.7	96.2	100.1	95.7	98.4	98.9	96.2	95.9	98.1
	6.2 psi	95.8	98.5	98.4	97.7	98.4	99.1	97.4	97.3	96.3	97.3
Column temperature	45 °C/min	98.1	99.3	95.2	98.4	95.3	97.5	96.8	95.8	95.1	97.8
	55 °C/min	96.6	95.4	95.7	99.2	97.1	98.2	98.1	96.1	95.7	96.6
Injector temperature	265 °C	99.1	97.3	97.4	97.1	95.2	96.2	98.9	95.5	95.1	95.2
	275 °C	95.9	98.0	95.1	98.3	96.0	97.8	99.3	96.8	96.4	97.8
Detector temperature	255 °C	97.3	97.5	96.4	96.9	95.9	96.9	97.9	96.0	96.2	96.0
	265 °C	96.2	95.9	95.3	98.5	97.3	98.8	98.3	96.7	95.4	96.9

REFERENCES

1. N. Candelario and M. Lu, *Cancer Manag. Res*., **8**, 77 (2016); https://doi.org/10.2147/CMAR.S93620
2. M. Xu and J. Chu, Chinese Patent CN105974016A (2016).
3. D.R. Joshi and N. Adhikari, *J. Pharm. Res. Int.*, **28**, 1 (2019); https://doi.org/10.9734/jpri/2019/v28i330203
4. K. Grodowska and A. Parczewski, *Acta Pol. Pharm*., **67**, 13 (2010).
5. K. Pilaniya, H.K. Chandrawanshi, U. Pilaniya, P. Manchandani, P. Jain and N. Singh, *J. Adv. Pharm. Technol. Res*., **1**, 302 (2010); https://doi.org/10.4103/0110-5558.72422
6. K.R. Dhangar, R.B. Jagtap, S.J. Surana and A.A. Shirkhedkar, *J. Chil. Chem. Soc*., **62**, 3543 (2017); https://doi.org/10.4067/S0717-97072017000200024
7. S.B. Puranik, P.N.S. Pai and G.K. Rao, *Indian J. Pharm. Sci*., **69**, 352 (2007); https://doi.org/10.4103/0250-474X.34542
8. A. Latif, H.S. Makhdoom, M. Imran, M. Mazhar, E. Anwar, M. Sarwar and M. Ashraf Tahir, *Pharm. Anal. Acta*, **8**, 8 (2017); https://doi.org/10.4172/2153-2435.1000553
9. S. Adepu and R.V. Valli Kumari, *Int. J. Pharm. Sci. Rev. Res.*, **31**, 63 (2015).
10. P.R. Battu and M.S. Reddy, *Int. J. PharmTech. Res.*, **1**, 230 (2009).
11. S.B. Puranik and S. Sharath, *Int. J. Pharm. Chem. Res.*, **1**, 22 (2012).
12. H. Bridwell, V. Dhingra, D. Peckman, J. Roark and T. Lehman, *Qual. Assur. J*., **13**, 72 (2010); https://doi.org/10.1002/qaj.473
13. B. Magnusson and U. Ornemark, Eurachem Guide: The Fitness for Purpose of Analytical Methods-A Laboratory Guide to Method Validation and Related Topics, Eds.: 2 (2014).
14. International Conference on Harmonization (ICH), Q2 (R1) (2005).
15. USP <1225>; Validation of Compendial Methods (2014).
16. National Association of Testing Authorities, Australia; Guidelines for the Validation and Verification of Quantitative and Qualitative Test Methods (2012).
17. World Health Organization WHO Technical Report Series 937, Validation Annex 4 (2006).
18. Guidance for Industry Analytical Procedures and Methods Validation Chemistry, Manufacturing and Controls Documentation U.S. Department of Health and Human Services Food and Drug Administration (2000).
19. M. Thompson, S.L.R. Ellison and R. Wood, *Pure Appl. Chem.*, **74**, 835 (2002); https://doi.org/10.1351/pac200274050835
20. Center for Drug Evaluation and Research (CDER), Reviewer Guidance Validation of Chromatographic Methods (1994).