Stability Indicating Reverse Phase High-Performance Liquid Chromatography Method for Quantitative Estimation of Impurities in Gadobutrol Solution for Intravenous Administration

**Sanni Babu Najana,[1] Rama Krishna Veni Pokala,[2] Geetha Bhavani K,[3]
Bala Murali Krishna Khandapu[1]* and Hari Babu Bollikolla[1]***

[1]Department of Chemistry, Acharya Nagarjuna University, Nagarjuna nagar, Guntur, Andhra Pradesh, India.

[2]Department of Chemistry, SASI Institute of Technology and Engineering, Andhra Pradesh, India

[3]Department of Chemistry, IIIT-Ongole campus, Prakasam, Andhra Pradesh, India

ABSTRACT

The purpose of this investigation was to establish a HPLC methodology and evaluate Gadobutrol along with impurities A, B and C. The method for Gadobutrol along with impurity-A, B and C analysis was developed on Phenomenex Phenyl-Hexyl C18 column with isocratic elution using mobile phase consisted of formic acid (pH 3.6) and acetonitrile. The method proposed showed a good linearity in the range of 0.8314 – 30.21 ppm (Gadobutrol), 3.2971 – 34.62 ppm (impurity-A), 0.3788 – 34.82 ppm (impurity-B), and 2.9757 – 32.38 ppm for impurity-C. Obtained good method precision (RSD = 2.36% to 3.55%), acceptable accuracy (98.8% to 108.9%), detection limit (0.1250 ppm to 1.0811 ppm) and quantitation limit (0.3788 ppm to 3.2971 ppm) for Gadobutrol and impurity-A, B and C. The method proposed can be utilized to assess the quality of Gadobutrol sample for the presence of impurities A, B and C.

KEY WORDS: GADOBUTROL, RELATED SUBSTANCES, RP-HPLC, STABILITY INDICATING, UV DETECTOR, VALIDATION.

INTRODUCTION

Effective evaluation of process associated impurities is crucial for the development of pharmaceuticals. Process associated impurities are related to the production process and may include precursor substrates, intermediates formed during the procedure of synthesis, solvents used during production or purification (Jinshu et al. 2015; Kung-Tien and Chien-Hsin 2019). As mentioned by the "International Conference on Harmonization" for the qualification of the drug substance, the permissible level for known process associated impurity needs to be <0.15% and the unknown process associated impurity need to be <0.10% (ICH Q3B(R2) 2006; ICH Q3A (R2) 2008). In order to comply with the strict regulatory necessities, it is necessary to identify impurities and carefully monitor their amounts. Gadobutrol is utilised in adult as well as pediatric sufferers, including newborns, with magnetic resonance imaging to diagnose and predict areas with an impaired blood barrier

and/or aberrant central nervous system vascularity (Scott 2018; Glutig et al. 2019; Petronek et al. 2021; Akbas et al. 2022).

The 1, 4, 7, 10-tetraazacyclododecane is used to make the Gadobutrol pharmaceutical substance. Impurities impurity-A, B and C, as well as two other molecules, are produced as by-products during the manufacturing of Gadobutrol. Purification removes the generated two additional compounds, and remaining impurities (A, B, and C) are regulated in the drug material. Impurity-A was designated chemically as 2,2'-[4,10-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetra azacyclododecane-1,7-diyl]diaceticacid (Figure 1). Impurity-B was designated chemically as 2,2',2''-[10-[(1RS, 2SR)-2,3-dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triyl]triacetic acid (Figure 1). Impurity-C was designated chemically as gadolinium 2,2',2''-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl) triacetate (Figure 1) (Akbas et al. 2022).

Also, after so many purification phases, impurities impurity-A, B and C will often occur which can co-purify

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with the Gadobutrol. The existence of impurity-A, B and C impurities in Gadobutrol can potentially influence the efficacy of the final Gadobutrol drug. Therefore, a sensitive, reliable and effective method is required to detect and evaluate impurities A, B and C in Gadobutrol. The specification thresholds for impurities A, B and C impurities were considered as 0.20 % concentration based on new drug substances policy given in ICH Q3A (ICH Q3A (R2) 2008; Al-Sabti and Harbali 2021; Kalauz and Kapui 2022). Detection and evaluation of impurities A, B and C impurities in the Gadobutrol using any analytical approach is not yet documented. Therefore, a sensitive, reliable and effective HPLC dependent method to detect and evaluate impurities A, B and C impurities simultaneously in Gadobutrol was developed and validated herein.

Figure 1: Structures of Gadobutrol and impurities A, B and C
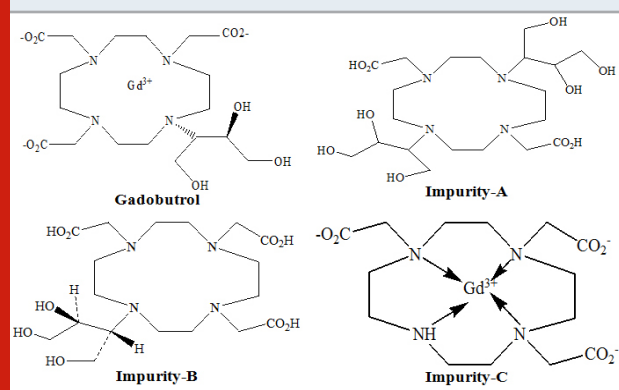
MATERIAL AND METHODS

HPLC grade Merck (Mumbai, India) formic acid, acetonitrile, water- HPLC-grade (Milli Q) were utilized. Impurity-A (85.7% purity), Impurity-B (94.7% purity) and Impurity-C (90.03% purity) were obtained from Aavyan Labs Pvt Ltd. (Hyderabad, India). Jodas Expoim Pvt Ltd. (Hyderabad, India) provided Gadobutrol. Agilent (USA) HPLC 1260 infinity system, Agilent (USA) photodiode array detector, Open lab software, Sartorius MSA6.6S-000-DM microbalance, Bandelin, DT514BH ultra sonicator and Polmon LP-139SA pH meter were used during detection and evaluation of impurity-A, B and C impurities simultaneously in Gadobutrol.

A Phenomenex Luna Phenyl-Hexyl C18, 250 × 4.6 mm, 5 μm column was used at 50 ℃ temperature with isocratic elution at the rate of flow with 1 mL per min. The mobile phase contained of aqueous formic acid (pH 3.6) and acetonitrile in 95.5% volume and 0.5% volume, respectively. Sample quantity of 20 μL, sample injector temperature of 5 oC and wavelength of 195 nm were utilized in the detection besides evaluation of impurities A, B and C impurities in the Gadobutrol. Mixed stock solution (2.0% concentration) for Gadobutrol and impurities A, B and C was prepared in mobile phase. Series of working solutions (LOQ to 150% of Gadobutrol, impurities A, B and C specification value limits) were prepared by diluting appropriate aliquots of

the mixed stock solution (2.0% concentration) with mobile phase. Working solution of Gadobutrol and impurities A, B and C with 20 ppm concentration were also done by diluting appropriate aliquots of stock solution (2.0% concentration) with mobile phase.

This solution with concentration 1 mg/mL was prepared in mobile phase. The Gadobutrol sample was shaken for 5 min after the preparation and filtered using Millipore 0.45 microns. Accurate quantities equal to 0.8314 – 30.21 ppm of Gadobutrol, 3.2971 – 34.62 ppm of impurity-A, 0.3788 – 34.82 ppm of impurity-B, and 2.9757 – 32.38 ppm of impurity-C were prepared. Each quantity solution was infused (20 μL) and recorded the corresponding chromatograms and peak areas for Gadobutrol, impurity-A, B and C by applying suggested HPLC method. The calibration curves for each component (Gadobutrol, impurity-A, B and C) were then generated utilizing its respective peak areas, and corresponding regression linear equations was then created.

The Gadobutrol solution was infused (20 μL) and noted the chromatograms by applying recommended HPLC method. The response areas of impurities A, B and C in Gadobutrol solution were documented. The percentage of impurities A, B and C in Gadobutrol solution was assessed using corresponding regression linear equations. Gadobutrol was subjected to a number of forced degradation tests, involving acid, base, humidity, peroxide, humidity and thermal degradation [ICH Q1A (R2); 2003]. Gadobutrol was subjected to acid made hydrolysis (1.0 N HCl, 60 °C over 1 hr), alkali made hydrolysis (1.0 N NaOH, 60 °C over 1 hr), peroxide made oxidation (bench top 4 hr), thermal made degradation (105 °C, over 24 hr) and humidity made degradation (90% humidity, over 24 hr). The degraded Gadobutrol solutions were infused (20 μL) and noted the chromatograms by applying the suggested HPLC method. The occurrence of impurities A, B and C impurities and percent degradation of Gadobutrol were documented.

RESULTS AND DISCUSSION

Method establishment: Zorbax SB C8, 250 × 4.6 mm, 5 μm column and Phenomenex Luna Phenyl-Hexyl 250 x 4.6 mm, 5 μm columns with isocratic elution with solvents combination of 0.1% aqueous formic acid: acetonitrile with different pH values and different ratio volumes were tried during trail experiments. During trails, sample volume size for analysis, column temperature, sample port temperature and flow rate are kept constant at 20 μl, 50 ℃, 5 ℃ and 1.0 mL/min, respectively. Based on resolution, peak shape and sensitivity values obtained during trails (Figure 2), Phenomenex Luna Phenyl-Hexyl 250 × 4.6 mm, 5 μm column with isocratic elution with 0.1% aqueous formic acid and acetonitrile in 95.5% volume and 0.5% volume, respectively, as mobile phase was opted as optimal conditions to detect and evaluate A, B and C impurities simultaneously in the Gadobutrol sample. The wavelength of choice for the study of A, B and C impurities was 195 nm, where impurities showed more sensitivity.

Validation: The method for A, B and C impurities evaluation in the Gadobutrol was verified in harmony thru ICH strategies (ICH Q2 (R1) 2005).

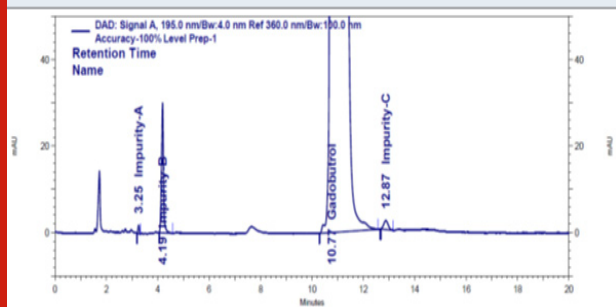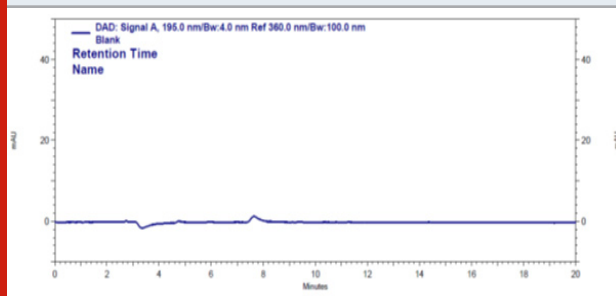**Figure 2: Gadobutrol drug and impurities A, B and C chromatogram**

Figure 3a: Diluent chromatogram

Specificity: The procedure's specificity was tested to ensure that the Gadobutrol and diluent components did

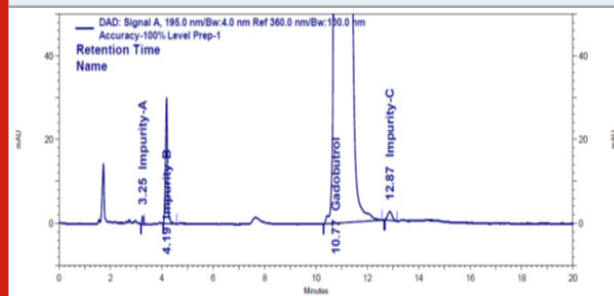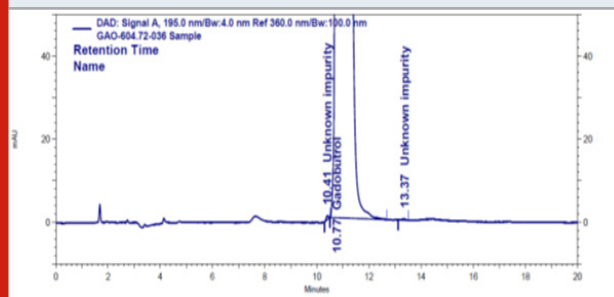**Figure 3c: Impurities A, B and C spiked Gadobutrol sample chromatogram**

Figure 3b: Gadobutrol sample chromatogram

not interfere with the analysis of A, B and C impurities. Gadobutrol sample, Gadobutrol solution spiked with impurities A, B, and C (20 ppm), and diluent blank were made and analysed using the HPLC method described. The typical chromatograms for specificity were displayed in (Figure 3a to 3c).

Table 1. Linear regression details for Gadobutrol and impurity-A, impurity-B and impurity-C

Parameter	Impurity-A	Impurity-B	Impurity-C	Gadobutrol
Linearity (ppm)	3.2971–34.62	0.3788– 34.82	2.9757– 32.38	0.8314– 30.21
Correlation coefficient (r)	0.9988	0.9991	0.9968	0.9991
Intercept value	33855.835	154620.629	-147462.62	454535.662
Slope value	41316.302	479640.138	189669.234	-355480.676
Square of Correlation coefficient (r^2)	0.9976	0.9982	0.9937	0.9982
100% Y-intercept	3.47	1.44	-3.84	-4.11

Quantification and detection limits: Quantification and detection limits were checked for impurities A, B and C at a concentration which gives an S/N fraction ≥ 10 and ≥ 3, respectively. The values of detection limit for Gadobutrol and impurities impurity-A, B and C were 0.2739 ppm, 1.0881 ppm, 0.1250 ppm and 0.9820 ppm, respectively. The quantification limits were 0.8314 ppm (Gadobutrol), 3.2971 ppm (impurity-A), 0.3788 ppm (impurity-B) and 2.9757 ppm (impurity-C). The quantification limit values for Gadobutrol and impurities A, B and C were confirmed by precision results. The determined %RSD of six area responses of Gadobutrol and impurity-A, B and C at their quantification limit level were 5.8% (Gadobutrol), 9.0% (impurity-A), 9.0% (impurity-B) and 11% (impurity-C).

Linearity: The linear quantity range for Gadobutrol and A, B and C impurities was checked in a quantity range from the quantification limit level (0.8314 ppm for Gadobutrol, 3.2971 ppm for impurity-A, 0.3788 ppm for impurity-B and 2.9757 ppm for impurity-C) to 150% of specification quantity limit (30.21 ppm for Gadobutrol, 34.62 ppm for impurity-A, 34.82 ppm for impurity-B and 32.38 ppm for impurity-C). A linear correlation was detected between area responses and concentrations of Gadobutrol and A, B, and C impurities in the range of quantities studied. The linear regression parameters were shown in Table 1.

Method precision: By analysing a Gadobutrol sample spiked with contaminants impurity-A (20 ppm), impurity-B

(20 ppm), and impurity-C (20 ppm), the method precision was confirmed (20 ppm). The method precision was determined by calculating the mean concentration and relative standard deviation of six different Gadobutrol, impurity-A, impurity-B, and impurity-C values (Table 2).

Table 2. Precision study

Sample	Impurity: A (ppm)	Impurity: B (ppm)	Impurity: C (ppm)	Gadobutrol (ppm)
1	21.00	21.50	21.30	
2	21.20	20.70	21.30	
3	21.20	20.20	20.80	9676
4	22.00	20.90	20.10	
5	21.50	21.40	21.30	
6	20.50	21.50	22.40	
Average	21.00	21.00	21.00	NA
Standard deviation	0.01	0.01	0.01	NA
%RSD	2.36	2.51	3.55	NA

Table 3. Accuracy results

S.No.	Theoretical (%)	% Mean Recovery			
		Impu: A	Impu: B	Impu: C	Gadobutrol
1	50	106.7	103.0	106.9	108.7
2	50	103.4	102.0	102.0	105.8
3	50	102.5	104.0	106.9	96.2
Average		104.2	103.0	105.3	103.6
Standard deviation		2.2113	1.00	2.8290	6.5424
RSD		2.1	1.00	2.7	6.3
1	100	108.4	109.6	104.9	93.8
2	100	108.4	107.6	104.9	86.1
3	100	110.0	105.6	102.5	89.9
Average		108.9	107.6	104.1	89.9
Standard deviation		0.9238	2.00	1.3856	3.8501
RSD		0.8	1.9	1.3	4.3
1	150	98.3	112.5	105.6	90.4
2	150	100.3	114.5	98.7	91.1
3	150	97.8	113.5	101.6	90.4
Average		98.8	113.5	102.0	90.6
Standard deviation		1.3229	1.00	3.4646	0.4041
RSD		1.3	0.9	3.4	0.4

Accuracy: Appropriate amounts of impurities A, B and C were spiked with Gadobutrol sample with replicates (n=3) at 50%, 100% and 150% of specification quantity limits. These samples were analysed by way of suggested HPLC method and determined the recovery of impurities A, B and C at each level (Table 3).

Impurity-A, B and C stability in Gadobutrol solution: Impurities-A, B and C spiked to Gadobutrol sample were stored at bench top and analysed by way of suggested HPLC method at 0 hr, 24 hr, 48 hr and 72 hr. Determined the recoveries of Gadobutrol, impurity-A, impurity-B and impurity-C. The recoveries of Gadobutrol, and A, B and C impurities obtained at 24 hr, 48 hr and 72 hr were compared with Gadobutrol and impurities recoveries at 0 hr (Table 4). The same set of experiments was repeated with impurities-A, B and C impurities spiked to Gadobutrol sample stored in refrigerator (Table 4).

Forced degradation: The chromatograms obtained from various stress tests like, involving acid, base, peroxide, humidity and thermal degradation on Gadobutrol are shown in (Figure 4a-4e). (Table 5) summarizes the forced degradation findings. Blank peak, on the other hand, did not overlap impurity A, B, or C peaks (Figure 3a). The retention periods for Gadobutrol (Figure 3b), impurities A, B, and C (Figure 3c) are all different, according to chromatograms. This shows that DFP had no effect on impurity-A, impurity-B, or impurity-C analyses. As a result, it's a very selective method (Marcello et al. 2012; Ravisankar et al. 2015; Ahmad et al. 2022; Lalic et al. 2022). The determined %RSD of 6 area responses of Gadobutrol

and impurities A, B and C at their quantification limit levels confirmed sensitivity and precision at quantification limit concentrations (Marcello et al. 2012; Ravisankar et al. 2015; Leistner and Holzgrabe 2021).

Table 4. Consequences of Impurities-A, B and C stability in Gadobutrol solution

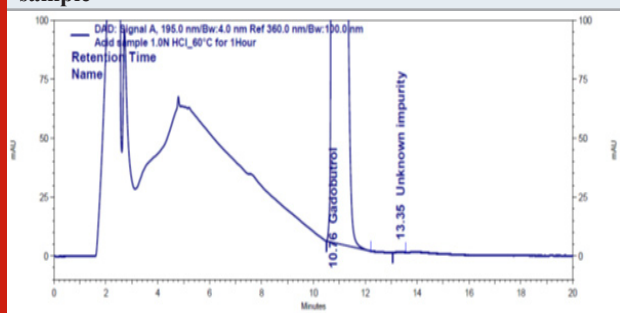| Component	ppm determined		% Difference	ppm determined	% Difference	ppm determined	% Difference
	Initial study	After 24 hr		After 48 hr		After 72 hr	
Stored at bench top							
Impurity-A	26.00	26.60	0.001	25.70	0.003	26.40	0.02
Impurity-B	20.70	20.90	0.02	22.90	0.022	24.60	0.039
Impurity-C	21.30	19.80	0.015	20.30	0.01	21.60	0.003
Gadobutrol	NA	102.5	NA	105.5	3.00	104.2	1.7
Stored in refrigerator							
Impurity-A	26.00	26.70	0.007	25.70	-0.003	25.90	-0.001
Impurity-B	20.70	20.90	0.002	23.00	0.023	24.30	0.036
Impurity-C	21.30	21.30	0.00	21.10	-0.002	20.50	-0.008
Gadobutrol	NA	99.4	NA	95.8	-3.6	102.8	3.4
NA – not available							

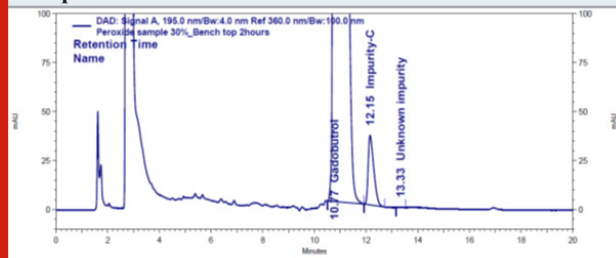**Figure 4a: Chromatogram of acid stressed Gadobutrol sample**

Figure 4b: Chromatogram of base stressed Gadobutrol sample

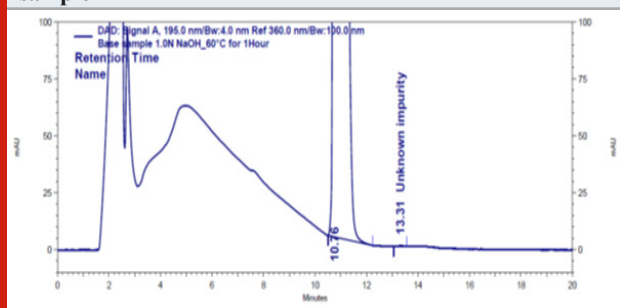**Figure 4c: Chromatogram of oxidative stressed Gadobutrol sample**

Figure 4d: Chromatogram of dry heat stressed Gadobutrol sample
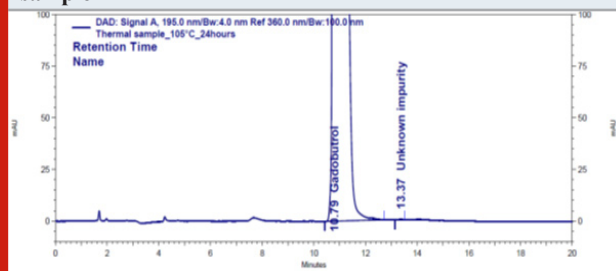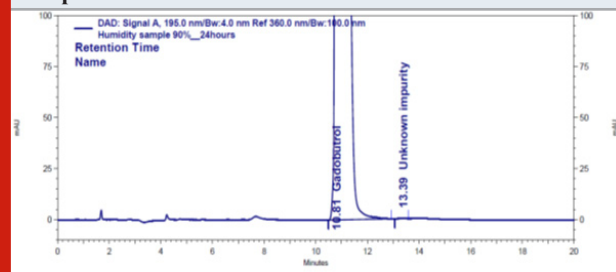

Figure 4e: Chromatogram of humidity stressed Gadobutrol sample

The coefficient of correlation (Table 1) values for Gadobutrol and impurities A, B and C disclose the process was of linear inside the concentration range determined (Soumia et al. 2017; Kowalska et al. 2022). The relative standard deviation (Table 2) determined for impurities-A, B and C was noticed as 2.36% to 3.55% which evidenced that the protocol was precise for evaluation of present impurities (Betz et al. 2011; Musmade et al. 2021). The evaluated values of recoveries (Table 3) for impurities A, B

and C for the suggested method proved that the method was accurate enough for the evaluation of the present impurities in the Gadobutrol sample (Betz et al. 2011; Musmade et al. 2021).

In the chromatograms (Figures 4a-4e) of all Gadobutrol degraded samples, all degradation peaks were resolved well from Gadobutrol peak, and did not display any interfering at the retention times of Gadobutrol and impurities A, B and C. Gadobutrol was realised to be more stable in acid, alkali, thermal and humidity stress conditions but sensitive to peroxide made oxidative condition. These findings for the suggested method proved that method was stability indicating enough for evaluation of the studied impurities in Gadobutrol sample (Ganpisetti et al. 2020; Manchuru et al. 2020; Karaer et al. 2022).

Table 5. Forced degradation results of Gadobutrol sample

Degradation condition	Gadobutrol degraded %	% Occurrence of				
		Impurity: A	Impurity: B	Impurity: C	Unknown impurity	Total Impurities
Control sample	0.02	N.D.	N.D.	N.D.	0.02	0.02
Acid: 1.0 N HCl@60°C/1hr	0.02	N.D.	N.D.	N.D.	0.02	0.02
Base: 1.0 N NaOH@60°C/1hr	0.02	N.D.	N.D.	N.D.	0.02	0.02
Peroxide: 30% H_2O_2@ bench Top/4 hr	2.11	N.D.	N.D.	2.09	0.02	2.11
Thermal: 105°C/24 hr	0.02	N.D.	N.D.	N.D.	0.02	0.02
Humidity: 90% RH/24 hr	0.02	N.D.	N.D.	N.D.	0.02	0.02

N.D. – not detected

CONCLUSION

The findings of the present study shows that HPLC-dependent method is a reliable and effective to detect and evaluate Gadobutrol and impurities A, B and C simultaneously in the Gadobutrol sample was developed and validated. The parameters validated (linear regression, accuracy, robustness, precision, specificity, detection limit, devise suitability, quantification limit) for Gadobutrol and impurities A, B and C were in line with ICH criteria requirement. Our results indicated that Gadobutrol sample quality can be assessed using the method proposed in this study.

ACKNOWLEDGEMENTS

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