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New stability indicating RP-HPLC-PDA method for determination of mifepristone in bulk and tablet formulation

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Abstract

Background: Mifepristone is progestational and glucocorticoid hormone antagonist. The objective of this study is to develop simple and economical stability indicating RP-HPLC method for the determination of mifepristone in bulk and tablet formulation.

Result: The chromatographic separation was achieved on Qualisil BDS C8 column with mobile phase containing of mixture of Buffer (Potassium dihydrogen *ortho* phosphate, pH to 3.0 with *ortho* phosphoric acid) and Organic Solvent (Acetonitrile) 60:40 *v/v* pumped at flow rate 0.6 mL min^{-1}. The detection of elute was performed using PDA detector at 305 nm. Mifepristone was eluted at 8.67 min. According to international conference on harmonization Q2(R1) guideline, method was validated and shows satisfactory results for accuracy, precision, linearity, ruggedness, robustness, detection limit, quantitation limit. The method indicated to be linear in the series of concentration 3–18 µg mL^{-1}, and correlation coefficient was 0.9997. In acidic, basic, oxidative, thermal, photolytic forced degradation conditions, the peak of degradation product was clearly and well separated from drug peak without any interference in quantitative analysis. This represents stability indicating nature of established method.

Conclusion: The established RP-HPLC method is simple, accurate, specific, precise, robust, rugged, sensitive, and economical in nature which can be utilized for routine analysis of mifepristone in bulk and pharmaceutical formulation.

Keywords: Mifepristone, Stability indicating RP-HPLC method, Forced degradation studies

Background

Mifepristone is also known as RU-486 and chemically 17β-Hydroxy-11β-(4-dimethylamino) phenyl-17-(1-propynyl)-4, 9-estradien-3-one (Fig. 1). It is progestational and glucocorticoid hormone antagonist. As a glucocorticoid receptor antagonist, the drug has been used to treat hypercortisolism in patients with nonpituitary Cushing syndrome. The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species, the compound inhibits the activity of endogenous or exogenous progesterone which results in the termination of pregnancy [1–4]. Detailed literature survey revealed that HPLC [5] simultaneous determination of mifepristone with misoprostol, LC–MS [6–12], and HPTLC [13] methods has been reported for determination of mifepristone in bulk and biological fluids. UV spectrophotometric methods [14, 15] have been reported. As far as up to our knowledge till date, no stability indicating simple, reliable RP-HPLC method has been established for determination of mifepristone in bulk and pharmaceutical formulation. So, the goal of research work is to

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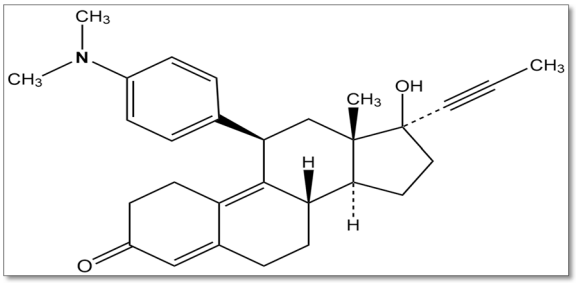

Fig. 1 Chemical structure of mifepristone

establish simple, accurate, rapid, specific, reproducible, and economical stability indicating RP-HPLC method for determination of mifepristone in bulk and pharmaceutical formulation. The established method was further validated according to ICH guidelines Q2 (R1) [16, 17].

Method

Pure sample

Mifepristone purity of 99.9% was received from Teva pharmaceutical, Mumbai, India, as a gift sample.

Formulation

200 mg tablet formulation of mifepristone manufactured by Zee laboratories LTD under the brand name RELEZED was used.

Chemicals and reagents

HPLC grade solvents Methanol (Rankem, avantor performance materials India Ltd. Thane, India), Acetonitrile (Merck specialities Pvt. Ltd. Worli, Mumbai, India), *ortho*phosphoric acid (Lobachemie Pvt. Ltd. Mumbai, India), Potassium dihydrogen *ortho*phosphate (Lobachemie Pvt. Ltd. Mumbai, India), sodium hydroxide (Lobachemie Pvt. Ltd. Mumbai, India), hydrochloric acid (RFCL Ltd. New Delhi, India), and Hydrogen peroxide (Merck life science Pvt. Ltd. Worli, Mumbai, India) were purchased for experimental work. Double distilled water was obtained from distillation process. The marketed formulation (RELEZED 200 mg) was purchased from local market for scientific study purpose.

RP-HPLC instrumentation and chromatographic condition

Analysis of mifepristone was done on chromatographic system high-performance liquid chromatography UFLC-LC 20 AD (Shimadzu Corporation, Japan) consisting of LC-20 AD binary solvent delivery system (pump), SPD-M20A diode array detector and CTO 10 AS vp; column oven, a Rheodyne injector with 20 µL loops and a Hamilton syringe (100 µL). The chromatographic separations were achieved on a Qualisil BDS C8 column (250 mm × 4.6 mmi.d. 5 µm) using mobile phase consisting of *acetonitrile: 10 mM potassium dihydrogen orthophosphate 40:60 v/v* ratio, pH was adjusted to 3.0 with *ortho*phosphoric acid. Before analysis, mobile phase was filtered through 0.2 µm membrane filter and degassing was performed by ultrasonicator (ENERTECH Electronics Pvt. Ltd., India). Whole experiment was carried out at 32 °C, and flow rate was kept at 0.6 mL min^{-1}. The sample solution of 20 µL was manually injected into column using Hamilton syringe. The eluted analyte was detected at 305 nm. Data gathering and study were carried out by LC-Solution data processor software (Shimadzu Corporation, Japan). For reflux propose, Radleys Carousel 6 plus reaction station (England) apparatus was used.

Methodology

Selection of wavelength

From standard stock solution, 1 mL of solution was withdrawn and transferred into volumetric flask having capacity 10 mL and volume was make up by methanol up to the mark and scanned in UV region from 200 and 400 nm using UV–visible double beam spectrophotometer (Model-2450, SHIMADZU, Japan) with data processing software UV probe v2.21 and from the acquired UV spectra a wavelength of 305 nm was selected as ideal wavelength used as PDA detector wavelength in RP-HPLC analysis.

Preparation of mobile phase

Acetonitrile and 10 mM potassium dihydrogen orthophosphate in the ratio of 40:60 v/v were used as a mobile phase. pH of mobile phase was adjusted to 3.0 by orthophosphoric acid. Before analysis, mobile phase was filtered through 0.2 µm membrane filter and degassing was performed by ultrasonicator.

Preparation of standard solution

Standard stock solution was prepared by dissolving accurately weighed 10 mg mifepristone in 100 mL volumetric flask containing methanol to obtain concentration of 100 µg mL^{-1}.

Method validation

The established chromatographic methods were absolutely validated followed by ICH guidelines Q2 (R1) and Q1A (R2) for the validation of analytical methods and Stability testing of new substance and product, respectively [16, 17].

Linearity

From standard stock solution, six sets of series of concentration ranging from 03 to 18 µg mL^{-1} were obtained by diluted 0.3–1.8 mL concentration from 100 µg mL^{-1} with

methanol in 10 mL volumetric flask and analyzed it. Linear curve equation was made by plotting the peak area *versus* drug concentration.

Precision

Precision studies were carried out by using drug standard solution in concentration taken in the calibration range. The precision of the developed method by means of intra-day variation (% RSD) was observed by analyzing standard drug solution in three sets of concentration of Mifepristone, i.e., 6 μg mL^{-1}, 9 μg mL^{-1}, and 12 μg mL^{-1} on same day. Inter-day precision (% RSD) was studied by analyzing the drug solution in same concentration used for intraday three times on three days in one week period.

Repeatability studies were performed by analyzing six replicates of same concentrations (9 μg mL^{-1}) on same day.

Accuracy

Accuracy study of established method was determined by percent recovery studies. To the pre-tested sample, standards drug concentrations were added at three different points (80%, 100%, and 120%). At each level of the amount, three estimations were evaluated and the percentage recovery and percentage mean recovery were calculated.

Ruggedness

Ruggedness study of established method was estimated by analysis of same aliquots 9 μg $mL^{-1}$of pure mifepristone at same operational and environmental conditions by two different analysts.

Detection and quantitation limit

Detection limit and quantification limit were determined by analysis of lower concentration of the linear range of the linear curve equation which were calculated using formulae "L.O.D = 3.3 × ASD/M" and "L.O.Q = 10 × ASD/M," where "ASD" is average standard deviation of the peak areas of the mifepristone ($n = 3$), taken as a measure of noise, and "M" is the slope related to linear curve equation.

Analysis of tablet formulation

Twenty tablets of mifepristone (RELEZED having label claim 200 mg) were accurately weighed, average weight determined then transferred to a clean waterless mortar and crushed into fine powder by pestle. Above fine powder equivalent to 10 mg mifepristone was transferred to volumetric flask having capacity 100 mL containing 70 mL of methanol; this mixture subjected to sonication for 10 min after that volume was made by methanol up to the mark and filtered through 0.45 μm Whatman filter paper its give 100 μg mL^{-1} concentration. From this stock solution, sets of same concentration (i.e., 1.5 mL) separately transferred to volumetric flask having capacity 10 mL and volume was made by methanol up to the mark to get final concentration of 15 μg mL^{-1} and this solution was injected into column with Hamilton syringe. The peak area recorded and drug concentration in sample were estimated from linear curve equation.

System suitability

System suitability study was done to confirm that the HPLC system is working correctly and can provide accurate and precise results. It was evaluated by injecting 10 μg mL^{-1} solution of mifepristone six times. Solution of concentration of 10 μg $mL^{-1}$of mifepristone was prepared by pipette out 1.0 mL solution from the standard stock solution into volumetric flask having capacity up to 10 mL and diluted with methanol up to the mark. The following parameters of system suitability like theoretical plates, tailing factor, retention time and capacity factor were evaluated.

Robustness

Robustness study was performed for established RP-HPLC method by change in the chromatographic conditions, To study the impact of flow rate on the resolution, the flow rate was changed by 0.2 units, i.e., 0.4 and 0.8 mL min^{-1} from the actual flow rate 0.6 mL min^{-1}. The impact of temperature of column on resolution was studied at 30 °C and 34 °C instead of 32 °C. The impact of change in the composition of mobile phase was observed by changing the % of acetonitrile in gradient by 2%. The impact of pH was studied by changing pH by 0.2 units from the actual value 3.0 keeping remaining method conditions were kept constant.

Forced degradation studies

Forced degradation studies were carried out on mifepristone under several conditions as per ICH guidelines Q1A (R2) and Q1 B.

Acidic condition

For acid degradation study, 10 mg of pure mifepristone transferred in 10 mL volumetric flask and dissolved in 10 mL 0.1 N methanolic HCl and refluxed at 70 °C for 3 h. 0.1 mL solution was taken out, and methanol is used for the dilution of resulting solution.

Basic condition

Base degradation study was carried out by taking 10 mg of pure mifepristone transferred in 10 mL volumetric flask and dissolved in 10 mL 0.1 N methanolic NaOH and

refluxed at 70 °C for 3 h. 0.1 mL solution was taken, and methanol is used for the dilution of resulting solution.

Oxidative condition

10 mg of pure mifepristone was dissolved in 10 mL 12% methanolic hydrogen peroxide solution, up to the mark. This solution is kept for 24 h in dark place to avoid the degradation effect of light. Methanol is used for the dilution of resulting solution.

Dry heat condition

Dry heat degradation study was performed by taking 10 mg of pure mifepristone in a clean and dry petri dish and kept in hot air oven at 80 °C for 8 h. After completion of stipulated time, resulting dilution was made by using methanol.

Wet heat condition

The 10 mg mifepristone was taken into a 10 mL volumetric flask, and volume make-up was done by methanol kept in a hot air oven at 80 °C for 8 h. After an 8-h, volumetric flask was removed from the hot air oven, 0.1 mL of concentration was withdrawn and transferred to a volumetric flask having a capacity of 10 mL. Volume was made by methanol up to the mark.

Photolytic condition

Photolytic degradation study was performed exposing sample for 7 days to sun light. The previously exposed sample was correctly weighed and diluted with methanol to get desired resulting solution.

Results

HPLC method development

The proposed RP-HPLC method was optimized with a vision to establish a suitable, easy, and economical stability indicating HPLC method. Optimization of mobile phase was attempted by using mixture of different solvent (buffers and organic solvent like ammonium acetate, potassium dihydrogen *ortho* phosphate, methanol, and acetonitrile) with different pH conditions. The different mobile phase and their proportion were tried for mobile phase optimization. The best chromatogram obtained *with acetonitrile: potassium dihydrogen ortho-phosphate (40:60 v/v)* pH adjusted to 3.0 with *ortho* phosphoric acid. The established solvent system was found to have very good symmetry with retention time (8.67 ± 0.02) and sharp well-defined peak. The detection was performed by PDA detector at 305 nm. The total run time of system was 15 min, and a typical chromatograph of mifepristone standard and sample is shown in Fig. 2.

Method validation

Linearity

The linearity parameter was performed by established RP-HPLC method in the range of concentration 03–18 μg mL^{-1}. Linear regression data obtained from linear curve are shown in Table 1.

Precision

Intra-day, inter-day precision, and repeatability were studied under precision parameter. The data obtained for all precision parameter are depicted in Table 1.

Accuracy

Accuracy of proposed method was determined by recovery studies. Standard drug solution was added in pre-tested sample at three different points 80%, 100%, 120%. The results obtained are depicted in Table 1.

Ruggedness

Ruggedness study for established method was determined by six replicates of two sets obtained from homogeneous solution of pure mifepristone analyzed under same operational and environmental conditions by two different analysts. The results obtained in acceptable range in terms of % RSD less than 2 are depicted in Table 1. The results demonstrate no statistical variances between different analyst using same operational and environmental condition, suggesting that the established RP-HPLC methods are rugged.

Detection limit and quantitation limit

DL and QL of pure mifepristone were found to be 0.15 μg mL^{-1} and 0.50 μg mL^{-1}, respectively. The values of DL and QL indicate the sensitivity of established method.

Analysis of tablet formulation

The established RP-HPLC method has been effectively applied for the assay of mifepristone in bulk sample and tablet formulation. The result of assay of mifepristone was found to be in the range of 98–100% which is depicted in Table 2.

Robustness

Robustness parameter was studied by making small alterations in mobile phase proportion, flow rate, temperature, and pH condition (±02%), and the effect of changes on results was examined. The standard deviation and % RSD of peak area of drug was calculated for each parameter. The results are shown in Table 1. The %

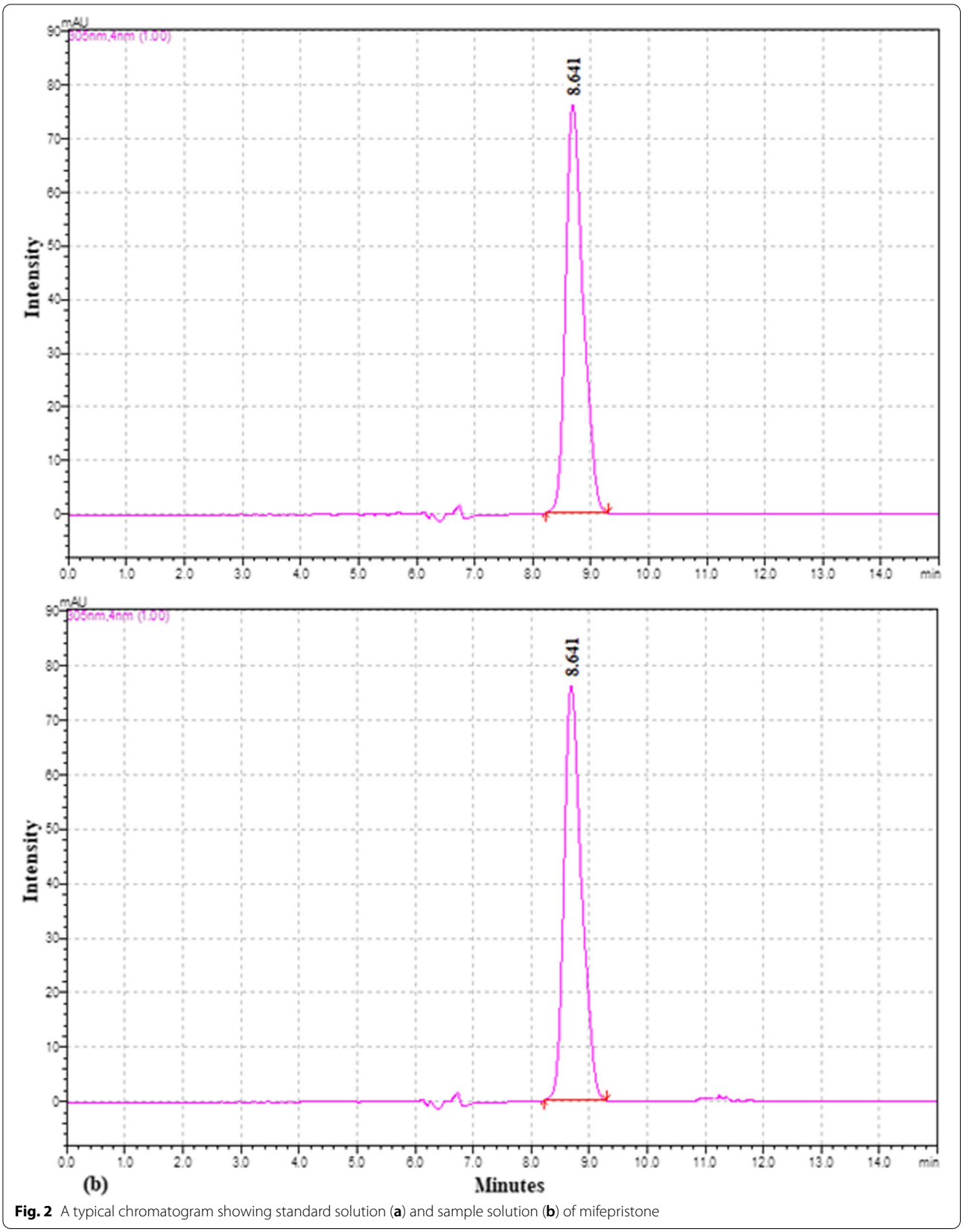

Fig. 2 A typical chromatogram showing standard solution (**a**) and sample solution (**b**) of mifepristone

Table 1 Results of validation parameter

Concentration of MFP (μg mL^{-1})	Peak area Mean ± SD ($n = 6$)	Amount found (μg mL^{-1}) ($n = 3$)	% amount found (μg mL^{-1}) ($n = 3$)	% RSD
Linearity studies of mifepristone				
3	348,508 ± 579.06	–	–	0.17
6	637,116 ± 7790.85	–	–	1.22
9	950,741 ± 3787.78	–	–	0.40
12	1,246,160 ± 14,321.09	–	–	1.15
15	1,571,188 ± 9559.71	–	–	0.61
18	1,885,411 ± 12,610.39	–	–	0.67
Precision studies of mifepristone				
Intra-day precision				
6	–	6.00	99.98	0.11
9	–	9.00	100.00	0.06
12	–	11.94	99.48	0.90
Inter-day precision				
6	–	6.02	100.36	0.40
9	–	9.02	100.24	0.11
12	–	11.94	99.54	0.57
Precision studies [repeatability]of mifepristone				
9		8.97	99.63	
9		9.02	100.19	
9		9.01	100.09	
9		9.00	100.05	
9		9.01	100.15	
9		9.00	100.03	
Mean ± SD		9.00 ± 0.02	100.02 ± 0.20	
% RSD		0.20	0.20	
Ruggedness studies				
9 (Analyst I)			99.82 ± 0.41	
9 Analyst II)			99.91 ± 0.27	
Parameters	**Tailing factor**	**Theoretical plates**	**% RSD**	
Robustness studies of mifepristone				
Change in pH of buffer				
2.8	1.43	4046.3	0.60	
3.0 (Optimized condition)	1.13	4097.1	0.26	
3.2	1.21	4033.5	0.17	
Change in mobile phase composition				
Acetonitrile/buffer (45:55)	1.35	4076.5	0.67	
Acetonitrile/buffer (40:60; optimized condition)	1.13	4097.1	0.29	
Acetonitrile/buffer (35: 65)	1.15	4087.6	0.24	
Change in flow rate				
0.4 mL	1.41	4010.4	0.75	
0.6 mL (Optimized condition)	1.13	4097.1	0.38	
0.8 mL	1.26	4088.9	0.56	
Change in temperature				
30 °C	1.39	4038.4	0.63	
32 °C (Optimized condition)	1.13	4097.1	0.44	
34 °C	1.18	4054.7	0.53	

Table 1 (continued)

Initial amount (μg mL^{-1})	Excess drug added to the analyte (%)	Total amount found ± SD (μg mL^{-1})	Recovery (%) ($n = 3$)	%RSD ($n = 3$)
Accuracy studies of mifepristone				
6	80	10.77 ± 1.09	99.45	1.09
6	100	12.02 ± 0.02	100.28	0.29
6	120	13.23 ± 0.10	100.35	1.35

Table 2 Analysis of tablet formulation

Drug	Amount taken (μg mL^{-1})	Amount found (μg mL^{-1})	% amount found
MFP	9	8.95	99.41
	9	8.90	98.87
	9	9.00	99.96
	9	8.99	99.92
	9	8.97	99.62
	9	9.00	100.04
	Mean ± SD	8.97 ± 0.04	99.64 ± 0.44
	% RSD	0.44	0.44

Table 3 System suitability

Parameters	Standards	Results
Retention time (R_t)	–	8.641
Theoretical plates	More than 2000	4097
Tailing factor	Less than 2	1.1
Capacity factor	More than 2	2.4

RSD lower than 2 indicates robust nature of developed method.

System suitability

System suitability parameter was determined by injecting 10 μg mL^{-1} solution of mifepristone six times into column. The studies of system suitability included theoretical plate, tailing factor, capacity factor, and resolution. The data are given in Table 3.

Forced degradation studies

Forced degradation studies were performed by established RP-HPLC method on pure mifepristone to determine the stability and specificity of method. The pure mifepristone was subjected to various stress condition like acidic, basic, oxidative, dry heat, wet heat, and photolytic, but the degradation product of mifepristone was observed in all stress condition except in thermal and photolytic conditions. Mifepristone was well separated from all degradation products shown in Fig. 3. The data found after forced degradation studies are depicted in Table 4.

Discussion

A new simple stability indicating method developed for determination of mifepristone in bulk and pharmaceutical formulation was found to be economical, precise, linear, and accurate. The analytical conditions were optimized for time saving analysis using acetonitrile: 10 mM potassium dihydrogen ortho-phosphate 40:60 v/v ratio as a mobile phase. The established solvent system was found to have very good symmetry with retention time (8.67 ± 0.02) and sharp well defined peak. The pure drug mifepristone was stable in the mixture of mobile phase for a period of 48 h at laboratory temperature and under refrigerator condition. The calculated % RSD for precision was lower than 2 signify that the proposed RP-HPLC method was highly precise in nature. The % recovery value in the range of 99–100% indicated that accuracy of the established RP-HPLC method was more satisfactory. The results of recovery studies were very close to 100% which accordance with ICH guidelines. Developed HPLC method was found to robust while small changing in pH, flow rate, mobile phase, and temperature. The developed method with less retention time and good separation and can be applied for routine analysis of mifepristone in bulk and formulation. The result of ruggedness and robustness parameters shows results in accordance with ICH guidelines. From analyzed tablet formulation, the % amount found and it shows that there is no interference of excipients present in tablet formulation. In stability study, it was found that drug degraded in acidic, basic and oxidative condition only and no degradant found in dry heat, wet heat and photolytic condition. The peak purity and peak of mifepristone obtained under all stress condition during forced degradation studies was pure, and homogeneous and mifepristone were well separated from all degradation products. It indicated that the developed method has stability indicating power and specific for the determination of mifepristone in bulk and pharmaceutical formulation.

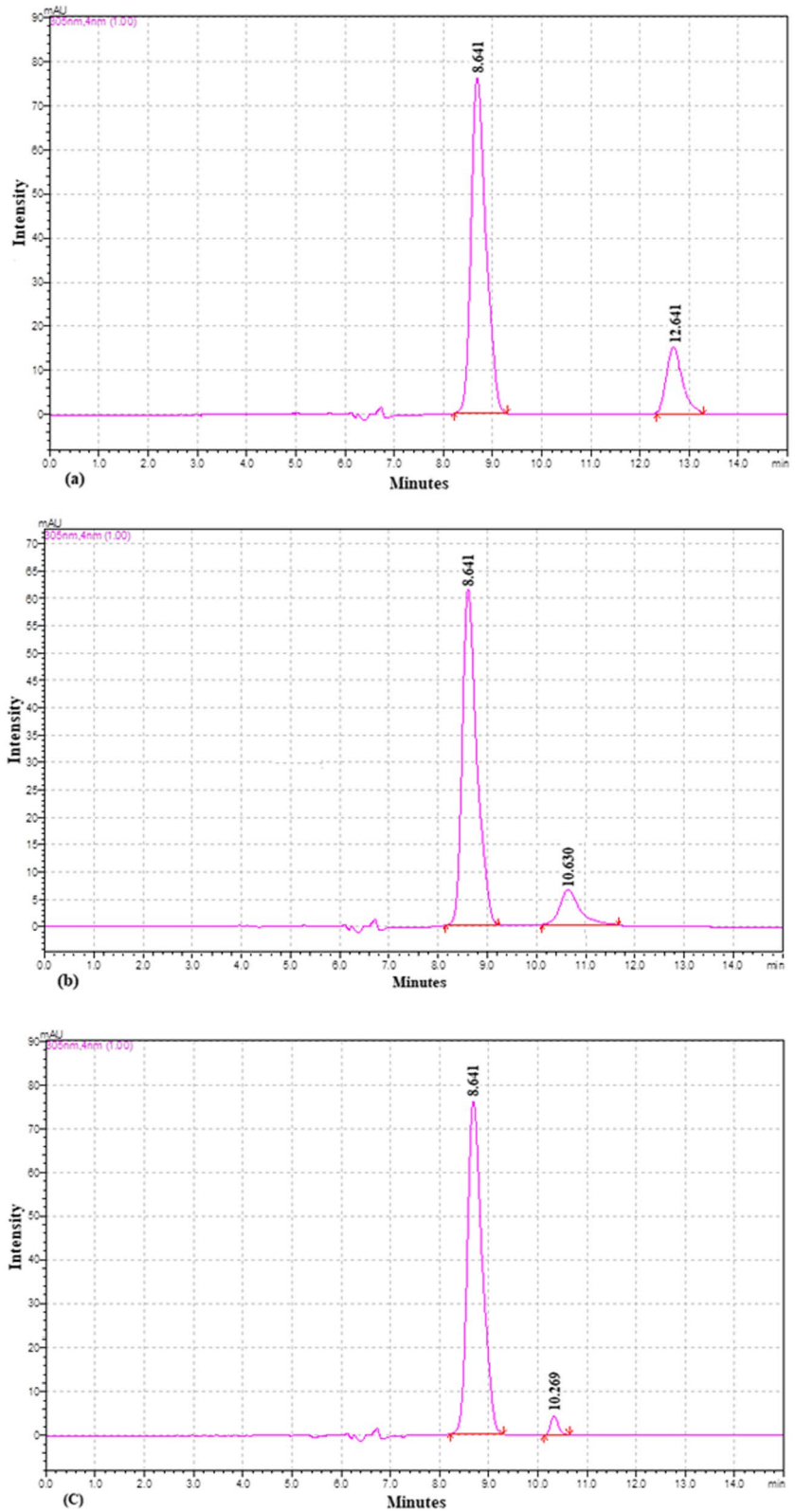

Fig. 3 Showing chromatogram of standard solution of mifepristone after forced degradation studies, **a** acidic hydrolysis (0.1 N methanolic HCl reflux at 70 °C for 3 h), **b** alkali hydrolysis (0.5 N methanolic NaOH reflux at 70 °C for 5 h), **c** oxidative degradation with 6% H_2O_2 at room temperature for 8 h

Table 4 Results of forced degradation studies

Degradation condition	Procedure	Observation	% degradant found
Acid hydrolysis	0.1 N Methanolic HCl reflux at 70 °C for 3 h	Degradant observed	24.12
Base hydrolysis	0.5 N Methanolic NaOH reflux at 70 °C for 5 h	Degradant observed	9.75
Oxidative	12% H_2O_2 at room temperature for 8 h	Degradant observed	5.21
Thermal (dry heat and wet heat)	Solution kept in hot air oven at 80 °C for 8 h	No degradant observed	–
Photolytic	Drug exposed to direct sunlight for 7 days	No degradant observed	–

Conclusion

The RP-HPLC method was established and validated for the determination of mifepristone in bulk and tablet formulation. This method is simple, accurate, specific, precise, robust, rugged, sensitive and economical. Pure mifepristone peak was well separated from its degradation product; hence, it proves sensitivity of the method. The retention time for mifepristone is 8.67 min only, and total run time is 15 min; hence, so many samples also be analyzed in short period of time. As per ICH guidelines, method was validated and showing satisfactory results for all the method validation parameters tested. Therefore, these established RP-HPLC method can be utilized for routine analysis of mifepristone in bulk and pharmaceutical formulation.

Abbreviations

HPLC: High-performance liquid chromatography; RP: Reverse phase; SD: Standard deviation; PDA: Photodiode array detector; DL: Detection limit; QL: Quantitation limit.

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Authors' contributions

MMGK, MF and AT completed the laboratory work, collected and analyzed the data and drafted the manuscript. SD, MGK and AS supervised the work and assisted in the data analysis. All authors read and approved the final manuscript.

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Availability of data and materials

Data and materials are available upon request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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