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Stability indicating thin-layer chromatographic method for estimation of antidiabetic drug Remogliflozin etabonate

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Abstract

Background: A sensitive, precise, and stability-indicating high-performance thin-layer chromatographic (HPTLC) method has been developed for the analysis of Remogliflozin etabonate in tablet formulation. HPTLC plates precoated with silica gel 60 F_{254} were used as the stationary phase; methanol: ethyl acetate: toluene: NH_3 (2:4:4:0.1, v/v/v) was used as mobile phase, and densitometry was used for the quantitative estimation of the drug. The proposed method was validated with respect to linearity, accuracy, precision, and robustness and applied for the estimation of drug in tablet dosage form.

Results: The R_f value of Remogliflozin etabonate was observed to be 0.61. The densitometric estimation was performed in reflectance mode at 229 nm. The method was found to be linear in the range of 500–8000 ng/band for Remogliflozin etabonate. The possible degradation pathway was estimated by performing forced degradation studies. The degradant peaks were well resolved from the drug peak with acceptable resolution in their R_f value.

Conclusion: An accurate and precise high-performance thin-layer chromatographic method has been developed for the quantification of Remogliflozin etabonate in tablets. Forced degradation studies were performed, and drug was found to be highly susceptible to acid, base hydrolysis, and oxidative stress degradation and gets converted into active drug Remogliflozin. Both Remogliflozin etabonate and Remogliflozin bands were well resolved. The method was applied for the analysis of drug in tablet formulation, and it can be used for routine quality control analysis, as well as for the analysis of stability samples.

Keywords: Remogliflozin etabonate, HPTLC, Validation, Forced degradation studies

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Background

Remogliflozin etabonate (REM) is chemically Ethyl[(2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-[5-methyl-1-propan-2-yl-4-[(4-propan-2-yloxyphenyl)methyl]pyrazol-3-yl]oxyoxan-2-yl]methyl carbonate (Fig. 1). REM is an inactive prodrug which upon the administration and absorption is converted to its active form remogliflozin which acts particularly on the sodium-glucose co-transporter subtype 2 (SGLT2) and used for the treatment of Diabetes Mellitus Type-2 [1–5].

Extensive literature review for the quantitative analysis revealed that various analytical methods have been reported for the estimation of REM. Analysis of REM in human plasma and blood has been reported by liquid chromatography coupled with mass spectrometric method [6, 7]. UV spectroscopy and high-performance thin-layer chromatography (HPTLC) method for the estimation of REM in bulk and tablet dosage form has been reported [8]. REM is not official in any pharmacopoeia.

The HPTLC method provides accurate and precise results which are comparable to that of liquid chromatographic method. Reduced sample preparation methods, less analysis time, and small quantity of mobile phase required are some of its advantages over liquid chromatography. Densitometric scanning used in HPTLC for quantitative analysis offers advantage of accuracy, precision, and specificity over conventional methods used in TLC. Stability and degradation samples can also be analyzed using a densitometer. HPTLC has become part of many pharmacopoeial monographs for the estimation of the drug and impurities. The method submitted to FDA must have a stability-indicating nature which helps to identify the possible stability issues related to the drug and the degradation pathway. So, the present
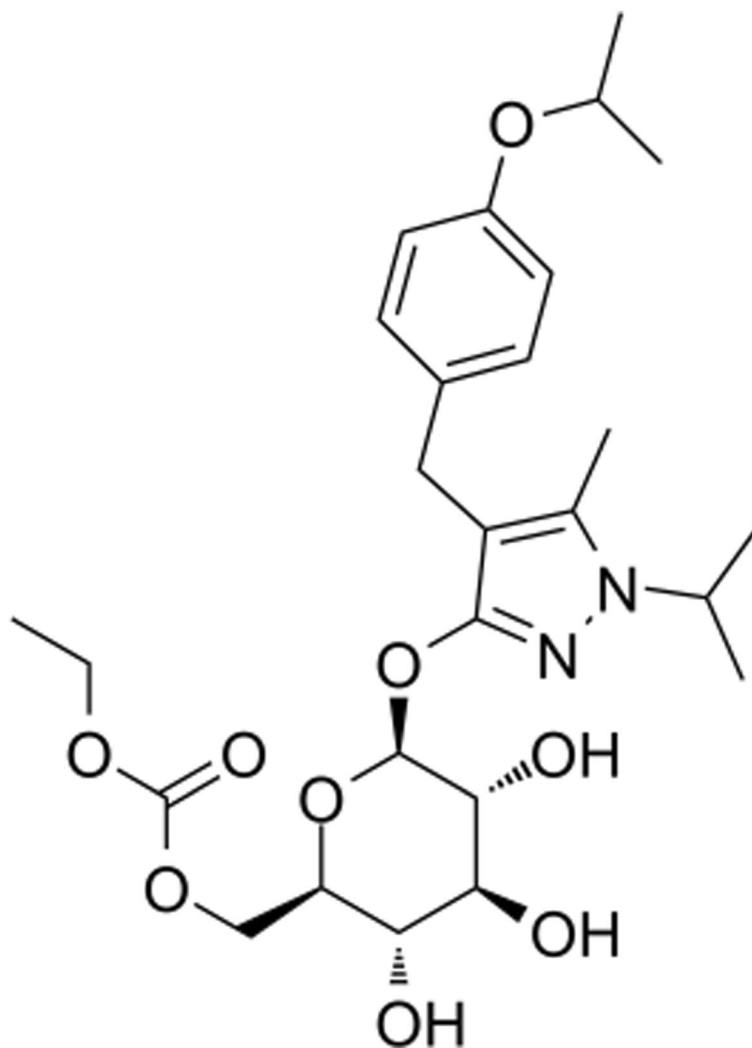

Fig. 1 Chemical structure of Remogliflozin etabonate

study involves development and validation of the stability-indicating high-performance thin-layer chromatographic method for the estimation of REM in tablet formulation.

Methods

HPTLC instruments

CAMAG (Muttenz, Switzerland) HPTLC instrument containing Linomat V sample applicator was used for the study (Hamilton, Bonadauz, Switzerland). Aluminum HPTLC plates (10 cm × 10 cm), precoated with silica gel F_{254} were used as stationary phase (E. Merck, Darmstadt, Germany; supplied by Anchrom Technologists, Mumbai, India). Densitometric scanning of developed densitograms were performed using Camag TLC scanner. Shimadzu electronic balance was used for weighing drugs and chemicals (AX 200, Shimadzu Corp., Japan).

Chemicals and reagents

Analytically pure REM (99.23% w/w as per the certificate of analysis provided by company) was obtained as gift sample from Reputed Pharmaceutical company. Methanol (HPLC grade) was procured from Avantor Performance Materials India Ltd.; Ethyl acetate (AR grade) and toluene (HPLC grade) were procured from Loba Chemie Pvt. Ltd., and Ammonia solution (25%) was purchased from Aatur Instru Chem. Pvt. Ltd., India. Marketed formulation with a brand name Remo-Zen (each film-coated tablet contains Remogliflozin etabonate 100 mg by Glenmark Pharmaceuticals Ltd., Mumbai, India) was procured from the local pharmacist.

Chromatographic system

Sample application

Standard and formulation samples of REM were applied on stationary phase (precoated plates containing silica gel F_{254}) in the form of narrow band (6 mm) with the help of sample applicator and distance of 9 mm was kept between two bands. The bands were applied using continuous drying stream of nitrogen gas.

Mobile phase and development

Linear ascending chromatographic development was performed using mobile phase methanol: ethyl acetate: toluene: NH_3 (2:4:4:0.1, v/v/v). The development was carried out in twin-trough glass chamber previously equilibrated with the mobile phase for 30 min. The mobile phase was allowed to migrate a distance of 80 mm, and after development, plates were removed and dried.

Densitometric analysis

The developed TLC plates were scanned in the reflectance mode using winCATS software. The light source used was deuterium lamp, and bands were scanned at 229 nm. The dimension of the slit was 5 mm in length and 0.45 mm in width. Peak area and peak height data were obtained for each developed band, and regression equation was developed by plotting peak areas versus concentration.

Preparation of standard stock solution

REM (10 mg) was weighed accurately and transferred to 10-mL volumetric flasks and dissolved in a few milliliter of methanol and sonicated for 5 min. Solution was diluted up to the mark with methanol which gave a concentration of 1000 μg/mL. The above solution was further diluted in another volumetric flask to obtain a working standard of 500 μg/mL REM.

Validation

International Conference on Harmonization (ICH) published a guideline Q2 (R1) for the validation of analytical method [9]. The developed method was validated with respect to linearity, accuracy, precision, specificity, and robustness.

Linearity of calibration curves

Linearity of the method was studied by plotting calibration curves over a range of 500–8000 ng/band. Peak area versus concentration data were used to plot calibration curve ($n = 6$).

Accuracy

The accuracy is the closeness of test result to the true value. To perform accuracy, recovery studies were carried out. Known amount of REM was spiked at three concentration levels (50, 100, and 150%) to a pre quantified formulation. The solutions were diluted and analyzed by developing densitograms using optimized chromatographic conditions. The peak area was noted, and the amount of REM was estimated with the help of regression equation.

Intermediate precision

Intermediate precision study was performed using intraday and interday precisions. Intraday precision was carried out by estimating drug solutions of REM (500, 4000, 8000 ng/band) at three levels covering low, medium, and high concentrations of the calibration curve. The study was performed three times on the same day. Inter-day precision was determined by estimating drug solutions of REM (500, 4000, 8000 ng/band) at three levels covering low, medium, and high concentrations, and the study was conducted for 3 days. Developed densitograms were analyzed, peak area was obtained, and variability of data was calculated in terms of percentage of relative standard deviation (%RSD).
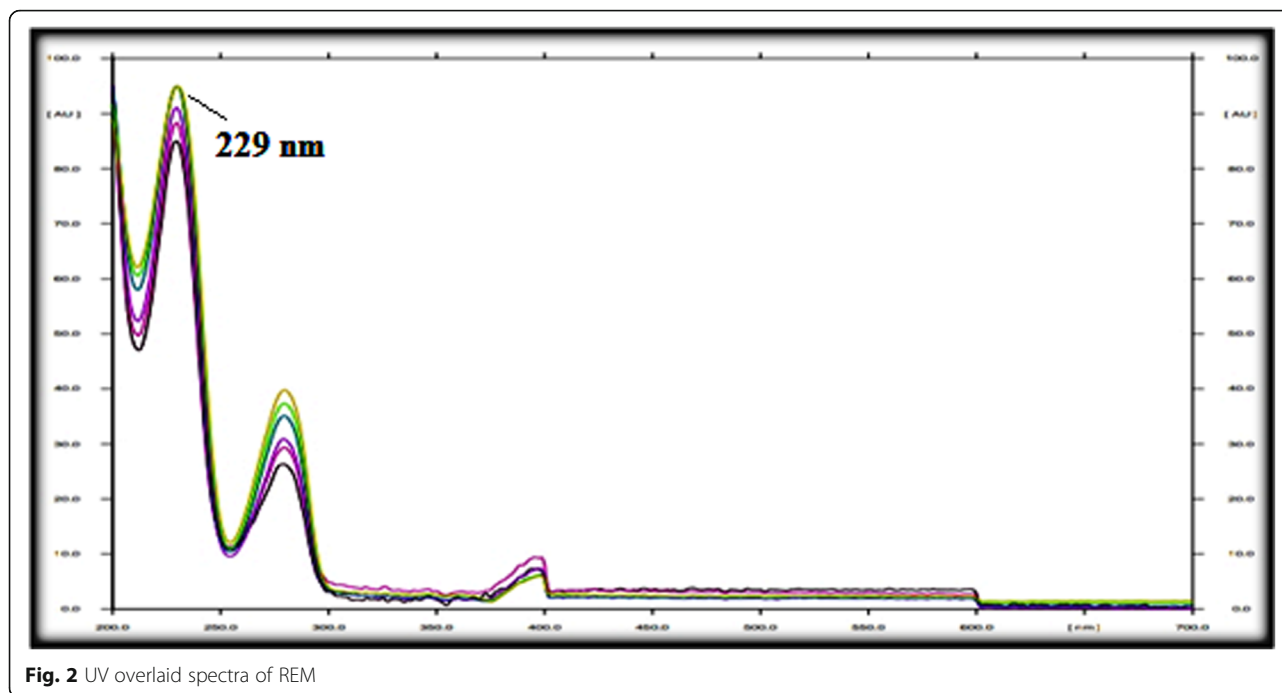
Fig. 2 UV overlaid spectra of REM

Repeatability

Repeatability of the method was assessed by applying band of REM (4000 ng/band) six times on an HPTLC plate. The plates were developed, and peak areas were determined. To study the scanner repeatability, the same spot was scanned six times, peak area was determined, and variability in the result was analyzed.

Specificity

To check the interference of impurities, degradants, and matrix in the estimation of drug, specificity study was performed by preparing synthetic mixture. Synthetic mixture was prepared using formula REM (30%), Talc 10%, microcrystalline cellulose 20%, Starch 20%, and Lactose 20% [10–12]. Synthetic mixture was analyzed for the drug using the optimized chromatographic method, and interference due to exipients were noted.

Sensitivity

The lowest amount of analyte that can be detected in a method is called limit of detection (LOD), and the lowest amount of anlayte that can be quantified is called limit of quantification (LOQ). LOD and LOQ were calculated using the following equation as per ICH guidelines.

$$LOD = 3.3 \times \sigma/S$$

$$LOQ = 10 \times \sigma/S$$

where σ is the standard deviation of y-intercepts of regression lines, and S is the slope of the calibration curve.

Robustness

Small deliberate changes were introduced in the method to assess the robustness of the method. Changes in mobile phase ratio and chamber saturation time were introduced, and the effects on densitogram were analyzed. The study was performed triplicate and %RSD was calculated.
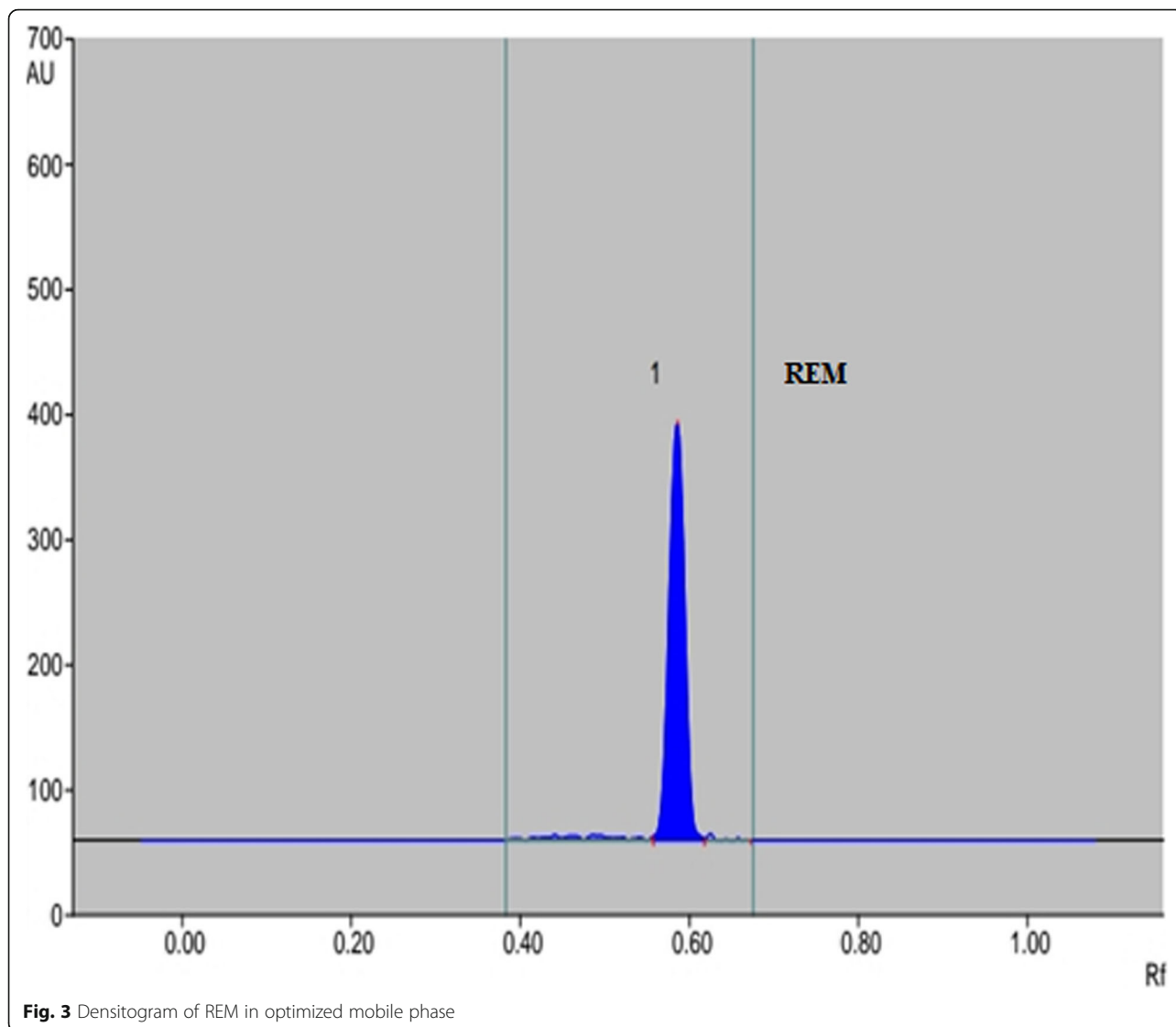
Forced degradation study

To find out the intrinsic stability of the drug molecule and possible degradation pathway, forced degradation studies were performed as per ICH guideline Q1A (R2) and Q1B using different stress conditions [13, 14]. Stress studies were performed using acid and base hydrolysis, oxidative hydrolysis, thermal degradation, and UV light exposure conditions.

Alkali hydrolysis

To perform base hydrolysis, 2 mL stock solution (500 µg/mL) of REM was taken in 10 mL volumetric flasks, and 2.5 mL of 0.1N NaOH was added to it. Solution was kept at room temperature for 30 min, neutralized and diluted with methanol up to the mark. The solution was analyzed and developed; densitogram showed complete degradation of REM. Hence, the same study was repeated by keeping solution for 5 min. The solution was neutralized and diluted up to the mark with methanol.

Acid hydrolysis

To perform acid hydrolysis, 2 mL of stock solution of REM (500 µg/mL) was taken in 10-mL volumetric flasks, and 2.5

Fig. 3 Densitogram of REM in optimized mobile phase

mL of 0.1N HCl was added. Then the mixture was heated in a water bath at 70 °C for 30 min and allowed to cool to room temperature. The solution was neutralized with 0.1 N NaOH, and it was diluted up to the mark with methanol.

Oxidative stress degradation

To perform oxidative stress degradation, 2 mL stock solution (500 μg/mL) of REM was taken in 10-mL volumetric flasks, and 2.5 mL of 3% hydrogen peroxide was added. Then the mixture was heated in a water bath at 70 °C for 30 min and allowed to cool to room temperature and diluted up to the mark with methanol.

Thermal degradation

To perform dry heat degradation study, pure drug samples of REM was exposed in the oven at 70 °C for 2 h. It was cooled, and drug was weighed (10 mg) and

transferred to 10-mL volumetric flask. It was dissolved and diluted up to the mark using methanol.

Photo degradation

Analytically pure samples of REM were exposed to UV light for 24 h. A 10 mg of drug was weighed and transferred to a 10-mL volumetric flask. It was dissolved and diluted up to the mark using methanol.

All the reaction solutions were applied using applicator microliter syringe on TLC plates. Plates were developed using optimized chromatographic conditions, and densitograms were recorded.

Solution stability

The stock solutions of REM was stored at room temperature for 24 h and analyzed at 0, 4-, 8-, and 24-h intervals.

Table 1 Regression analysis of calibration curve

Parameters	Results
Linearity (ng/band)	500–8000
Correlation coefficient (r^2)	0.9979
Slope of regression equation	1760.4
Standard deviation of slope	10.08
Intercept of regression	100.08
S.D of y-intercept	56.71

Analysis of marketed formulation

Twenty tablets were weighed and powdered. The powder equivalent to the 25 mg of REM was weighed and transferred to the 50-mL volumetric flask. A small amount of (10 mL) methanol was added to the above volumetric flask and sonicated for 10 min. The solution was filtered using Whatman filter paper No. 45, and the volume was made up to the mark with methanol (500 μg/mL).

Using a sample applicator, 8 μl of sample was applied on the stationary phase which gave 4000 ng/band concentration of REM. The stationary phase plates were developed as per optimized chromatographic conditions and scanned. The areas were
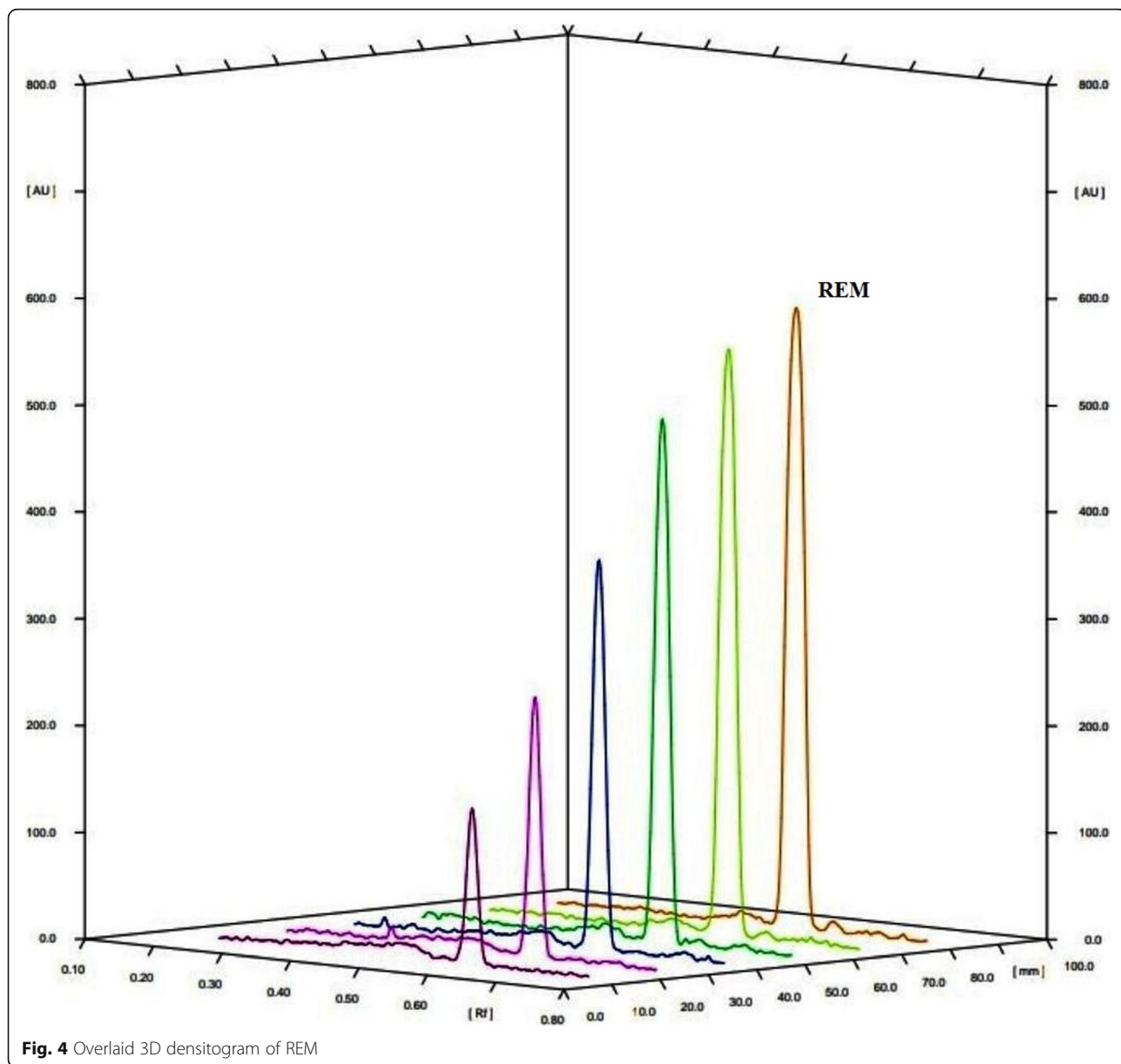

Fig. 4 Overlaid 3D densitogram of REM

Table 2 Summary of robustness studies

Method/parameter condition	Normal conditions	Normal R_f value	Deliberate changes	R_f ± S.D. ($n = 3$)	Effect on drug spot
Mobile phase ratio (Methanol: ethyl acetate: toluene: ammonia, v/v/v)	2:4:4:0.1	0.61	2:**4.5**:3.5:0.1	0.64 ± 0.01	Compact band
			2:3.5:**4.5**:0.1	0.59 ± 0.03	Compact band
Chamber saturation time (min)	30		25	0.62 ± 0.01	Compact band
			35	0.63 ± 0.02	Compact band
Migration distance (mm)	80		85	0.61 ± 0.01	Compact band
			75	0.62 ± 0.02	Compact band

determined, and quantification was carried out by keeping this value in regression equation.

Results

The thin-layer chromatographic method was developed and validated for the analysis of REM. The stationary phase used was silica gel F_{254} precoated aluminum plates, and optimized mobile phase selected for the analysis was a mixture of methanol: ethyl acetate: toluene: NH_3 (2:4:4:0.1v/v/v, pH 8 ± 0.2). To select the detection wavelength, developed plate was subjected to densitometric measurements in scanning mode in the UV region of 400–200 nm, and the overlaid spectrum was recorded using CAMAG TLC Scanner. The overlaid spectra showed that drug was absorbed appreciably at 229 nm. So, it was selected as detection wavelength (Fig. 2). The optimized conditions gave the compact band of REM with retardation factor (R_f) value of 0.61 (Fig. 3). The mobile phase chamber was saturated with the mobile phase for 30 min, and solvent was allowed to migrate to a distance of 80 mm. The calibration curve of the drug was found to be linear in the range of 500–8000 µg/band with a linear correlation coefficient (r^2) 0.9979. The regression data are shown in Table 1, and overlaid 3D densitogram was shown in Fig. 4.

In the accuracy study, recovery of REM was found in the range of 97.73–99.19 %w/w. Intermediate precision was performed by intraday and interday precision studies. Intraday precision was checked by measuring the response of three concentrations of REM covering the entire range for three times a day. Percentage RSD for REM was found to be 0.49–1.84. Similarly, interday precision was carried out by measuring response for 3 consecutive days, and %RSD was found to be 1.13–1.99%. Repeatability study was performed by scanner repeatability study and injection repeatability study. Drug solution (4000 ng/band) was applied, analyzed six times and percentage RSD value of the response was found to be less than 1%. The LOD for the REM was found to be 100 ng/band, and LOQ of REM was found to be 300 ng/band. Validation parameters are summarized in Table 2.

To perform the robustness study, small but deliberate changes were introduced in the method parameters like mobile phase ratio, solvent migration distance, and chamber saturation time. The mobile phase composition methanol: ethyl acetate: toluene: NH_3 (2:4:4:0.1, v/v/v) was changed to methanol: ethyl acetate: toluene: NH_3 (2:4.5:3.5:0.1, v/v/v) and methanol: ethyl acetate: toluene: NH_3 (2:3.5:4.5:0.1, v/v/v). The optimized chamber saturation time was 30 min which was changed to 25 and 35 min. The migration distance of 80 mm was changed to ± 5 mm. None of these changes affected the performance of the developed HPTLC method (Table 3).

Forced degradation study

Forced degradation was performed by acid–base hydrolysis, photo degradation, dry heat degradation, and oxidative stress degradation. The degraded samples were analyzed by the developed method.

Base hydrolysis (0.1 N NaOH) performed for 30 min at room temperature (25 ± 2 °C), which showed complete degradation of REM with degradation product peak at R_f value 0.46 (Fig. 4). So, the same study was repeated for 5 min. After neutralization using acid (0.1 N

Table 3 Summary of validation parameters

Parameters	Results
Linearity (ng/band)	500–8000 ng/band
Limit of detection (ng/band)	100
Limit of quantitation (ng/band)	300
Accuracy (%)	97.73–99.19%
Intermediate precision (%RSD)[a]	
Intraday ($n = 3$)	0.49–1.84
Interday ($n = 3$)	1.13–1.99
Instrument precision (%RSD)	
Scanner ($n = 6$)	0.93
Injection ($n = 6$)	0.87
Robustness (%RSD)	0.33–0.52

[a]RSD is relative standard deviation, and "*n*" is the number of determinations

HCl), the solution was made up to the mark with methanol. The sample was spotted and analyzed. The densitogram showed the resolved peak of drug and degradation product at R_f values 0.61 and 0.46, respectively (Fig. 5).

Acid hydrolysis study was performed by heating the sample for 30 min at 70 °C. The degraded sample showed degradation product spot at R_f 0.39 for REM. The degradation product peaks were well resolved with the drug peak (Fig. 6). Oxidative stress degradation study was performed using hydrogen peroxide, and it showed that REM was susceptible to oxidative stress and gave degradation product spot at R_f 0.43 (Fig. 6), whereas

REM was found to be stable to dry heat and photo degradation. The summary of forced degradation study results are given in Table 4.

The degradation study thereby indicated that REM was highly susceptible to acid and base hydrolysis and oxidative stress degradation.

Analysis of tablet dosage form

Tablet formulation containing 100 mg of REM was analyzed by the developed method which gave percentage recovery of 99.95 ± 1.26 %w/w (Table 5).
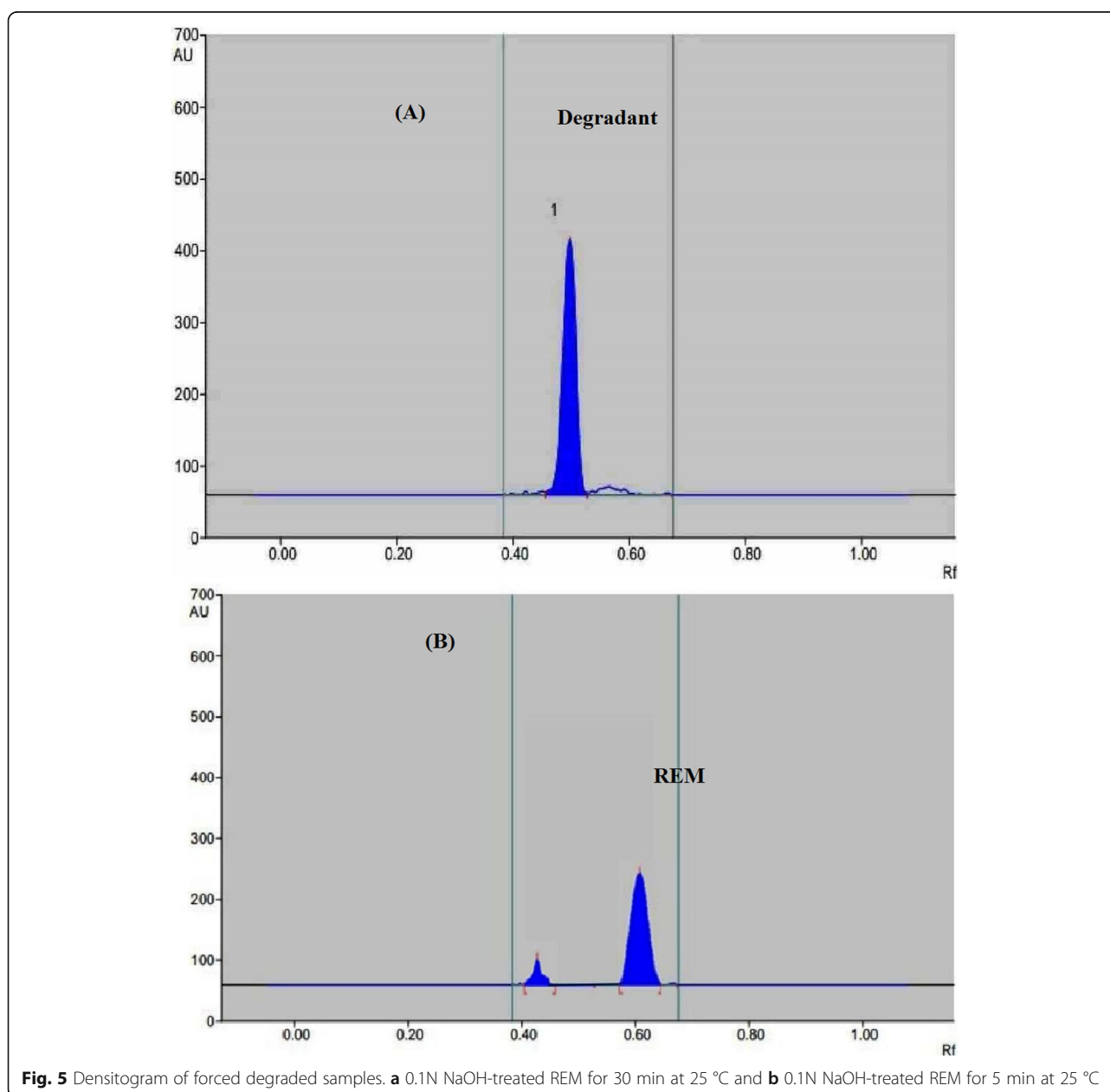

Fig. 5 Densitogram of forced degraded samples. **a** 0.1N NaOH-treated REM for 30 min at 25 °C and **b** 0.1N NaOH-treated REM for 5 min at 25 °C
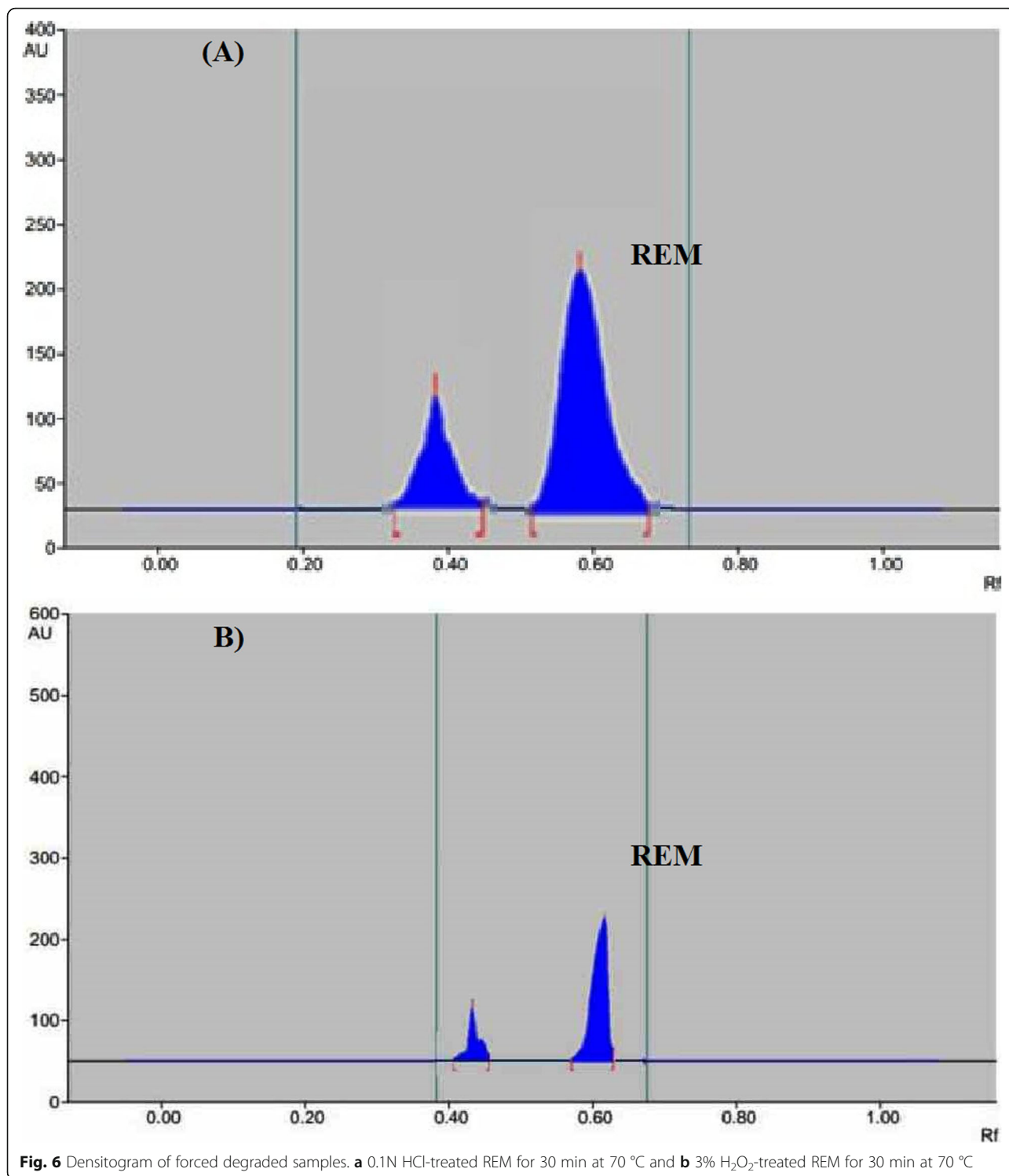
Fig. 6 Densitogram of forced degraded samples. **a** 0.1N HCl-treated REM for 30 min at 70 °C and **b** 3% H_2O_2-treated REM for 30 min at 70 °C

Discussion

For the development of the HPTLC method, mobile phase selection was performed based on the polarity of the solvent. Compact and well resolved band were the minimum requirement for this method. Different solvents like methanol, butanol, ethyl acetate, and toluene alone and in combination with other solvents were tried in different fractions so that REM and degradation

Table 4 Forced degradation studies

Type of degradation	Stress condition	Time	Percentage amount of drug (%)	R_f values of degradation product
Base degradation	0.1 N NaOH, 25 °C	30 min	0	0.46
Base degradation	0.1 N NaOH, 25 °C	5 min	75.45	0.46
Acid degradation	0.1 N HCl, 70 °C	30 min	64.84	0.39
Oxidative stress degradation	3% H_2O_2, 70 °C	30 min	81.08	0.43
Dry heat degradation	70 °C	2 h	98.62	-
Photolytic degradation	UV light	24 h	99.03	-

products can be well resolved. Mobile phases like methanol, isopropyl alcohol, toluene, hexane, methanol: ethyl acetate, methanol: toluene, and methanol: toluene: ethyl acetate in different proportions were tried which gave a tailed spot. A mixture of methanol: ethyl acetate: toluene: NH_3 (2:4:4:0.1 v/v/v, pH 8 ± 0.2) was selected and optimized as mobile phase which gave a compact band of REM with an R_f value of 0.61.

The method showed linearity in the range of 500–8000 µg/band, and the regression data shows good linear relationship over the concentration range studied, demonstrating the suitability of the method for analysis. The results of the accuracy studies were near to the true value (100%) which indicates that the method is accurate. The method was found to be precise as the % RSD for the intermediate precision was found to be less than 2%, and for repeatability, it was found to be less than 1%. The low LOQ value indicates the sensitivity of method, and nanogram quantity of drug can be estimated accurately and precisely. The method was found to be robust and none of the deliberate changes affected the method's performance.

Forced degradation studies were carried out to find out a likely degradation pathway. The degradation study indicated that REM was highly susceptible to acid and base hydrolysis and oxidative stress degradation. Remogliflozin etabonate undergoes extensive ester hydrolysis in the presence of acid, base, and hydrogen peroxide and gets converted into an active drug Remogliflozin with R_f value of 0.45. HPTLC is not an adequate method to confirm the structure of degradants. Other methods like mass spectroscopy and NMR should be used to prove that the degradation product is remogliflozin. The

degradation pathway is depicted in Fig. 7. Dry heat and photo degradation was performed using the powder form of the drug instead of stock solution which is a limitation of this method. The drug was stable to dry heat and photolytic degradation conditions used in the method. Degradation products did not affect the quantification of the drug.
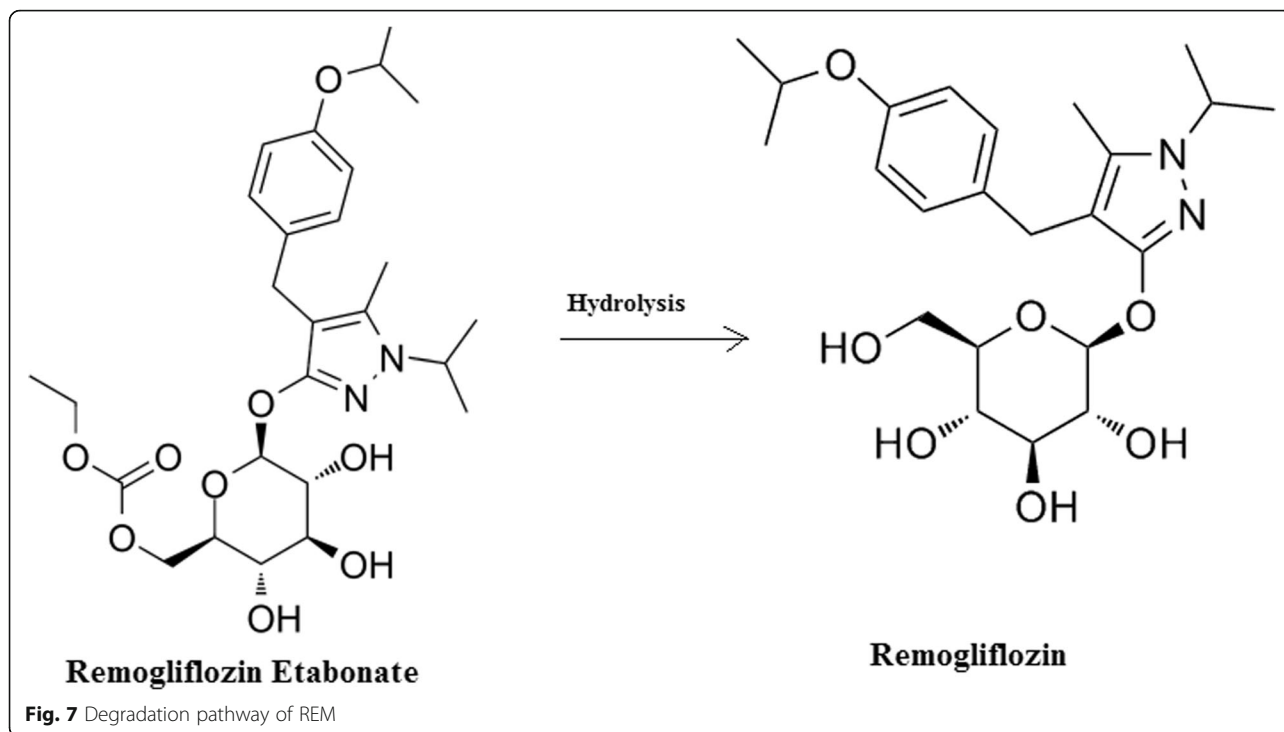
Conclusion

Accurate and precise thin-layer chromatographic method has been developed and validated for the estimation of REM. The method was developed using mobile phase methanol: ethyl acetate: toluene: NH_3 (2:4:4:0.1, v/v/v). The R_f value of the drug was 0.61, and the method was linear in the range of 500–8000 ng/band. The method was validated in accordance with ICH guidelines Q2 (R1). Forced degradation studies were carried out, and the drug was found to be highly susceptible to acid–base hydrolysis and oxidative stress degradation and gets converted into the active drug Remogliflozin. Both REM and Remogliflozin spots were well resolved. Compared with the reported HPTLC method [8], the developed method is more sensitive and has a stability-indicating nature. The range for the developed method starts from 500 ng/band, while for reported method, range starts from 1500 ng/band. The assay results of both the methods were statistically compared using F test. No statistically significant difference was observed at 95% confidence interval. The method can be used for routine quality control evaluation of bulk drug and formulation, as well as for the analysis of stability samples.

Table 5 Analysis of tablet dosage form

Amount of drug applied (ng/band)[a]	Amount of drug found (ng/band)	% Amount of drug ± S.D. ($n = 3$)
4000	3998.12	99.95 ± 1.26

[a] Each film-coated tablet contains Remogliflozin etabonate 100 mg

Fig. 7 Degradation pathway of REM

Authors' contributions
We assure that "all authors have read and approved the manuscript". All the authors have equal contribution and participation in this research work. DS, IG, and UC have worked on HPTLC. VP and AM has performed literature review and formulation analysis. DN has done statistical comparison and manuscript preparation. The authors read and approved final manuscript.

Availability of data and materials
All data and materials are available upon request.

Declarations

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
No competing interests to declare.

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References
1. Fujimori Y, Katsuno Y, Nakashima I (2008) Remogliflozin etabonate, in a novel category of selective low affinity sodium glucose cotransporter inhibitors, exhibit antidiabetic efficacy in rodent models. J Pharmacol Exp Ther 327(1):268–276. https://doi.org/10.1124/jpet.108.140210
2. PubChem, "Remogliflozin etabonate", https://pubchem.ncbi.nlm.nih.gov. Accessed 18 Sept 2019.
3. ChEMBL, "Remogliflozin etabonate", https://www.ebi.ac.uk/chembl/compound_report_card/CHEMBL2028665/. Accessed 18 Sept 2019.
4. Product information of remogliflozin A by Cayman Chemicals, Accessed 18 Sept 2019.
5. "Safety data sheet" of remogliflozin etabonate Published by Axon Medchem BV, Netherland, accessed on 05 Apr 2019.
6. Polli JW, Humphreys JE, Harmon KA, Webster LO, Reese MJ, MacLauchlin CC (2012) Assessment of remogliflozin etabonate, a sodium-dependent glucose co-transporter-2 inhibitor, as a perpetrator of clinical drug interactions: a study on drug transporters and metabolic enzymes. J Diabetes Metab. 3:1–8
7. Sigafoos JF, Bowers GD (2012) Assessment of the drug interaction risk for remogliflozin etabonate, a sodium-dependent glucose cotransporter-2 inhibitor: evidence from in vitro, human mass balance, and ketoconazole interaction studies. Drug Metab Dispos 40(11):2090–2101. https://doi.org/10.1124/dmd.112.047258
8. Tayade AB, Patil AS, Shirkhedkar AA (2019) Development and validation of zero order UV-spectrophotometric method by area under curve technique and high performance thin layer chromatography for the estimation of remogliflozin etabonate in bulk and in house tablets. Inventi Rapid: Pharm Anal Qual Assurance 3:1–5
9. ICH Guideline Q2A (R1), Validation of analytical procedure, text and methodology Q2 (R1) (2005).
10. Ulhas D, Deshmukh N, Sadaphal K (2018) Oral pharmaceutical formulations of remogliflozin. WIPO PCT/IB2018/054091
11. Abebe A, Martin K, Patel JM, Desai D, Timmins P (2010) Bilayer tablet formulation. WIPO 13/509, 210
12. Ulhas D, Deshmukh N, Sadaphal K (2019) Pharmaceutical composition comprising remogliflozin and antidiabetic agents. WIPO PCT/IB2019/051116

13. ICH Guideline Q1A (R2), Stability testing of new drug substances and products Q1A (R2) (2003).
14. ICH Guideline Q1B, Stability testing: photostability testing of new drug substances and products Q1B (1996).

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