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DEVELOPMENT AND VALIDATION OF A STABILITY INDICATING RP-HPLC METHOD FOR SIMULTANEOUS ESTIMATION OF TENELIGLIPTIN AND REMOGLIFLOZIN ETABONATE IN BULK AND TABLET DOSAGE FORM

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ABSTRACT

For the simultaneous quantitation of Remogliflozin Etabonate (REM) and Teneligliptin (TEN) in bulk and dosage form, a unique, accurate, reliable, and selective stability demonstrating RP-HPLC method was designed and validated. To verify the approach's stability demonstrating characteristics, the drugs were treated to a range of environments (alkaline, thermal, photolytic, acid and oxidative). To accomplish an isocratic separation of proposed drugs, a PDA detection system at 235 nm and a Thermo BDS Hypersil C18 column (150 × 4.6 mm, 5 µm) were used. Acetonitrile : Water (50:50 v/v) was employed as eluent and forced at 1 mL/min. The approach had used 20 µL injection volume and column temperature was kept at 25°C. The retention time for drugs (REM and TEN) were 3.7 min and 7.0 min correspondingly. The approach showed linearity from 80-240 µg/mL having R^2 = 0.9999 for REM and 8-24 µg/mL having R^2 = 0.9999 for TEN. The % RSD was discovered to be less than 2 %. The percent recovery was discovered to be between 98% and 102%. REM was more susceptible to degrade in acidic, thermal and photolytic environments. TEN also showed degradation in alkaline, acidic and photolytic

environment. The proposed methodology was regarded as being robust, linear, reliable, precise and accurate and able to analyse the drugs in tablet.

Keywords: RP–HPLC, Validation, Teneligliptin, Forced degradation, Remogliflozin Etabonate, Simultaneous Estimation

INTRODUCTION

The term "diabetes" describes a collection of metabolic diseases characterized by elevated blood sugar levels brought on by either insufficient insulin synthesis, improper insulin cellular response, or both. According to the International Diabetes Foundation's (IDF) most recent 2021 data, an estimated 537 million adults worldwide have diabetes mellitus. Diabetes currently affects over 62 million Indians, or 7.1% of the total adult population. Type 2 diabetes affects the vast majority of people (> 90%) **[1-3]**.

As stated by International Conference on Harmonisation (ICH), a drug is subjected to stress trials in order to determine its basic stability attributes and is done under more adverse circumstances than accelerated conditions. This study give details on the inherent stability of drugs **[4, 5]**. Stress investigations are conducted on a drug to identify its intrinsic stability qualities, like the degradation channels, resulting to the detection of products of degradation and thus confirming the appropriateness of the suggested approach, according to the ICH guideline Q1A (R2) **[6-8]**.

The oral selective sodium-glucose co-transporter type II (SGLT2) inhibitors like Dapagliflozin, Canagliflozin, Empagliflozin, Remogliflozin Etabonate play vital role in the kidney's ability to reabsorb glucose. Blood glucose is removed via the urine when this transporter is inhibited. In addition to treating non-alcoholic steatohepatitis, REM (**Figure 1A**) is used to treat Type II diabetes **[9, 10]**.

Dipeptidyl peptidase-4 inhibitors (DPP-4) inhibitors such as Sitagliptin, Vildagliptin, Linagliptin, Saxagliptin, Teneligliptin Hydrobromide Hydrate (**Figure 1B**) work by raising incretion levels (GLP-1 and GIP), which block the release of glucagon. Thus, the synthesis of the hormone insulin is increased, stomach emptying is slowed down, and blood glucose levels are decreased **[8, 9]**. Additionally, because of their complimentary modes of action, SGLT-2 and DPP-4 inhibitors work well together to treat type 2 diabetes, and there have been no occurrences of hypoglycemia recorded in individuals who have received this novel treatment regimen **[13, 14]**.

The quantitation of REM and TEN in combination were outlined in the literature. Various chromatographic **[15–17]** and Spectrophotometric **[18, 19]** approaches were reported. The reported method shows

the separation of the proposed drugs in combination by HPLC. However, no approach is yet cited for the separation of degradants and analyte (REM and TEN) when used in combination using a stability-indicating liquid chromatographic technique. Therefore, it is worthwhile to develop a liquid chromatographic method in which the drugs were subjected to different environments **[20-24]** and representing the separation of degradants from analyte peak and former among themselves. The proposed approach aimed to develop and validate stability indicating assay method and validated as ICH Q2 (R1) **[25]**.

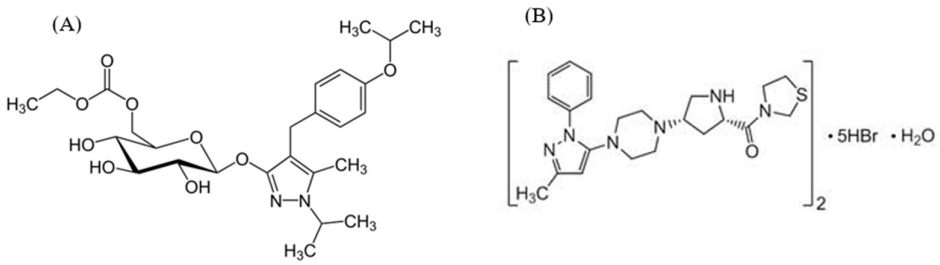

Figure 1: Structure of (A) REM and (B) TEN

MATERIALS AND METHODS

Materials and Chemicals

Glenmark Life Sciences Limited (Pune, India) provided REM (99.78 %) and TEN (99.64 %) pure samples as a gift. Acetonitrile (ACN) and HPLC grade water from Merck Life Science Limited, Mumbai, India, Methanol from Finar in Ahmedabad, India and Ortho phosphoric acid (OPA) from SD Fine Chem Limited Mumbai, India were purchased. REM 100 mg and TEN, which is equivalent to Teneligliptin 10 mg was purchased in pharmaceutical tablet dosage form (Zeta plus-R) from the local pharmacy.

Instrumentation and Chromatographic conditions

Agilent Technologies 1200 Infinity series HPLC and PDA Detector and autosampler were used as the system for the proposed technique. EZChrom programme assessed the chromatographic results. Thermo BDS Hypersil C_{18} (150 x 4.6 mm, 5 µm) column was employed in the suggested approach. The ratio of ACN to Water (pH adjusted to 4.8 with OPA) in the mobile phase was 50: 50 v/v. 1 mL/min flow rate was held constant while the temperature of column was sustained at 25 °C. Methanol was used as the diluent. The injection volume for each measurement was 20 µL and the estimation of analytes were done at 235 nm. Isocratic mode was employed for the separation.

Solutions

The stock (standard) solution of REM and TEN was prepared at 2000 µg/mL REM and 200 µg/mL TEN. The tablet powder equivalent to 100 mg of REM and 10 mg of

TEN was weighed to get the resultant solution (test) comprising 160 µg/mL REM and 16 µg/mL TEN. Methanol was utilised as diluent.

Validation of the Proposed Approach

The system suitability parameter was estimated by injecting six replicates of REM (160 µg/mL) and TEN (16 µg/mL). Various outcomes like Tailing factor (T_f), Resolution (R_s), Retention time (R_t), Theoretical Plates (N) were examined and % RSD were computed for each outcomes. The chromatograms of sample solution and standard solution of REM and TEN were compared to confirm the method's specificity. To establish the method's specificity, the solutions were additionally exposed to various stimuli (acid, base, peroxide, etc.). Peak purity testing, which confirmed that the chromatographic peak of the analyte was result of individual constituent, was used to further analyse the selectivity. Five concentration levels were prepared to assess the linearity, from 80 – 240 µg/mL REM and 8 – 24 µg/mL TEN. The graph was plotted and the values of the equation of the curve were computed. The system precision was assessed by repeatedly introducing the six replicates of mixtures comprising 160 µg/mL REM and 16 µg/mL TEN and % RSD was calculated. Method Precision involves intra-day and inter-day investigation, which was determined by administering three replicates of a standard solution of REM (120, 160, 200 µg/mL) and TEN (12, 16, 20 µg/mL) on similar day and on three subsequent days, individually. The recovery study of the proposed approach was evaluated at three levels (50, 100, and 150% level) utilising the preanalysed sample spiked with standard solution of REM and TEN at 3 levels. The LOD and LOQ was calculated by substituting the data (SD of y – intercept) in the equations provided by ICH guidelines **[25]**. The robustness of the proposed method was evaluated by doing various modifications in parameters like Column temperature (± 2 °C), wavelength (± 2 nm), Flow rate (± 0.2 mL/min), pH (± 0.2) and Mobile phase ratio (± 4 %). The outcomes were reported in % RSD. The stability of the REM and TEN solutions was tested by keeping the sample solution in a volumetric flask with a tight lid at 25 °C for 24 h.

Forced Degradation Studies

The proposed drugs were exposed to different environments: Acid (1 mL of stock solution, 1 mL 0.1 N HCl, 40°C for 1 h), Alkaline (1 mL of stock solution, 1 mL 0.1 N NaOH, 40°C for 1 h), Oxidative (1 mL of stock solution, 1 mL 3 % H_2O_2, room temperature (RT) for 2 h), Photolytic (sunlight, 2 h) and Thermal (80°C, 2 h). For photolytic and thermal degradation, solid sample containing 100 mg REM and 10 mg TEN was used. The solutions were neutralised after acidic and alkaline

hydrolysis with alkali and acid correspondingly. The oxidative degradation solution was neutralised with diluent. Appropriate dilutions were done after photolytic and thermal degradation to get the solution comprising 200 µg/mL REM and 20 µg/mL TEN. Methanol was utilised as diluent.

RESULTS AND DISCUSSION

Method Development and Optimisation

A stability demonstrating RP-HPLC approach for the simultaneous quantitation of REM and TEN in API and dosage form was the goal of the current investigation. To accomplish the goal, the drugs were exposed to different environments as per ICH Q1A (R2) recommendations. The approach was designed, optimised and validated to distinguish the degradants and analyte response. The solubility of REM and TEN was tested in several solvents such as methanol, water, acetonitrile but they are finally soluble in methanol, therefore it was chosen as a diluent. Chromatographic parameters including mobile phase content, velocity of flow, quantitation wavelength, pH of mobile phase, analytical column, and column temperature were optimised during the method development process. Various analytical columns such as ODS C_{18} (250 × 4.6 mm, 5µm) and Thermo BDS Hypersil C_{18} (150 × 4.6 mm, 5µm) were tested during method development. Thermo BDS Hypersil C_{18} (150 × 4.6 mm, 5µm) was finalized as it will gives well resolved peaks and reduces peak tailing. The system suitability parameters like R_t, N, T_f, R_s were also taken into consideration. Taking pK_a of the drugs into the consideration, various mobile phases, including water, methanol, OPA and acetonitrile were tried in an isocratic manner. With the combined use of methanol and water in different ratio, only one peak was observed. Acetonitrile and Methanol both were employed as organic modifiers, but ACN provides the satisfactory results (good peak resolution and fast elution). The Combination of ACN: water; pH adjusted to 4.8 with OPA (50:50 % v/v) was optimised at rate of 1 mL/min. Acidic pH was chosen on the basis of pKa of REM (6.8) and TEN (8.7) to enhance analyte ionisation and OPA was used for pH adjustment. Peak broadening was seen at lower temperatures (> 25°C), so the column temperature for the approach was kept at 25°C. The measurement was done at 235 nm (**Figure 2**). The iso absorptive point was observed at 235 nm for REM and TEN, hence the quantitation was done at this wavelength for the proposed drugs.

Method Validation

A novel stability demonstrating HPLC method was established and validated for the concurrent quantitation of REM and TEN. The validation of the approach starts from the system suitability. Various Parameters (R_s, T_f, N, R_t) were assessed and they

fulfilled the USP criteria ($T_f \leq 1.5$, $T_f \geq 2000$, $R_s \geq 2$). **Table 1** represents the outcomes of various above said parameters. Therefore, the system was considered suitable for use. Since no excipients co-elute with the analyte peak, the peak purity value (REM: 0.9992 and TEN: 0.9995) proved the method's selectivity. The chromatogram of drugs served as a confirmation of the method's specificity because it showed no interference from placebo or a blank substance at the R_t of the proposed drugs. **Figure 3** represents the chromatogram of blank, placebo, test and standard solution of proposed drugs. The linearity was confirmed by using five concentration levels of 80 - 240 µg/mL of REM and 8 - 24 µg/mL TEN. The graph between the response and the concentration of the drug was plotted to produce the equation. The correlation coefficient was found 0.9999 for both drugs, demonstrating the good linearity of the proposed approach. The parameter was carried out three times. **Table 2** represents the outcomes.

The repeatability of REM (160 µg/mL) and TEN (16 µg/mL) were found to have % RSD values of 0.825 and 1.780, respectively. The proposed approach can be considered to be repeatable since the % RSD value is less than 2. **Table 3** depicts the outcomes of intraday and interday precision. The % RSD in all investigations were found below 2 %, therefore the approach can be considered as precise. The recovery study was conducted using pre-analyzed test solution spiked with standards at 3 levels (50 %, 100 %, and 150 %). The recoveries covering the range from 99.92 – 100.09 % for REM and 99.93 – 100.51 % for TEN (**Table 3**) were found. The LOD values for REM and TEN were 1.76 µg/mL and 0.23 µg/mL individually. The LOQ values for REM and TEN were 5.35 µg/mL and 0.71 µg/mL individually. The robustness was evaluated by altering certain methodology parameters. The parameters included variations in the wavelength (± 2 nm), pH of eluent (± 0.2), column temperature (± 2°C), flow rate (± 0.2 mL/min) and mobile phase ratio (± 4%). The outcomes were compared and confirmed that the modifications to the parameters had not caused any appreciable changes in the responses (peak area, Rt, or N). **Table 4** represents the outcomes. At time intervals (0, 6, 12, 18, 24 h), the stability of the test solution of REM (160 µg/mL) and TEN (16 µg/mL) were conducted. Investigation was done into how the assay results changed after 24 h of storage. There was no noteworthy alteration in the drug concentration, and the difference between the assay results was calculated to be less than 2%. Standard and sample solutions can be utilised up to 24 h after preparation, according to the information in **Table 5**. The mean % purity of REM and TEN in tablet

was found to be 99.53 % ± 0.49 and 99.45 % ± 0.19 correspondingly. The % RSD for REM and TEN in assay was found to be 0.49 and 0.19 % correspondingly. According to the label claim, the percentage assay was deemed to be acceptable.

Forced Degradation Studies

The solutions of drugs (REM and TEN) were exposed to different stimuli like 3 % H_2O_2, 0.1 N NaOH, thermal, 0.1 N HCl, and light environments to justify the capability of suggested approach to distinguish degradant peak from the analyte peak. The samples were subjected to different degradation conditions were analysed by proposed approach. From the study, it was showed that REM was more susceptible to acid hydrolysis. During the hydrolysis, Remogliflozin Etabonate gets transformed into Remogliflozin (active drug). TEN was more prone to acidic hydrolysis may be due to the presence of carbonyl and heterocyclic moiety present in the structure. Both the drugs showed > 10 % degradation towards alkaline condition. Oxidative Stress study was performed in 3 % Hydrogen peroxide at room temperature and both drugs found stable towards peroxide and least degradation was observed. In case of solid state study, the drugs were exposed to sunlight and it was examined that both drugs were more liable to the photo degradation. TEN showed > 10 % degradation when exposed to heat at 80°C. In all the degradation study, the peak of degradant was well resolved from the analyte peak demonstrating that the approach is specific and selective. The chromatogram of mixture in different stressed condition was represented in **Figure 4 and Figure 5**. **Table 6** represents the percent degradation of the proposed drugs in various degradation environments as well as peak purity value. The peak purity outcomes proved that the peak of analyte was homogenous and spectrally pure in all the stress conditions.

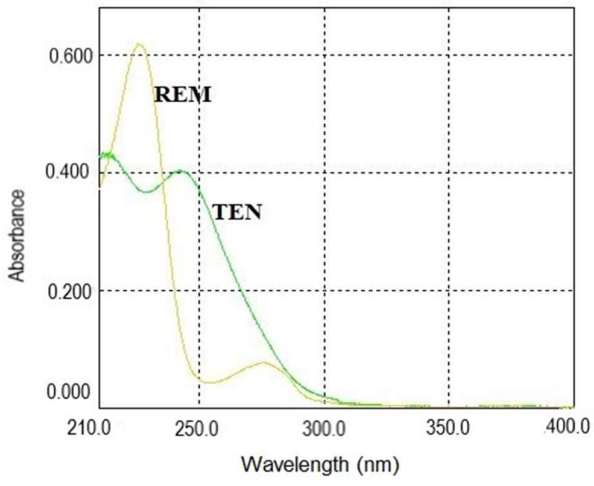

Figure 2: Overlay UV Spectra of REM and TEN

Table 1: System Suitability Parameters

Parameter (n = 6)	REM (Mean ± SD), % CV	TEN (Mean ± SD), % CV
Retention Time	**3.740 ± 0.02, 0.55**	**7.03 ± 0.01, 0.18**
Theoretical Plate	**2551 ± 11.06, 0.43**	**4025 ± 38.01, 1.17**
Tailing Factor	**0.97 ± 0.01, 1.03**	**0.99 ± 0.01, 1.01**
Resolution	**--**	**12.35 ± 0.09, 0.70**

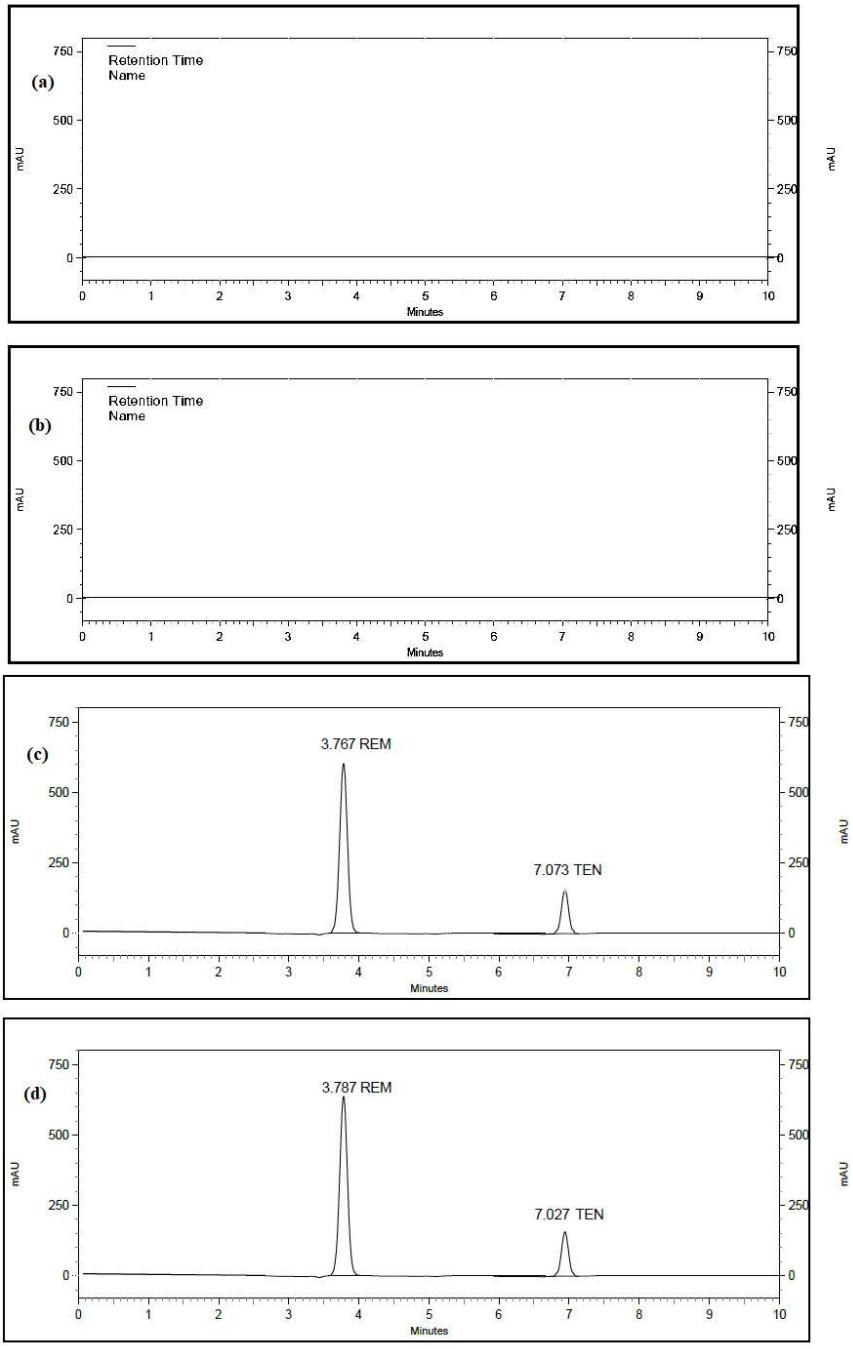

Figure 3: HPLC Chromatogram of (a) Blank, (b) Placebo, (c) Standard Solution of REM (160 µg/mL), and TEN (16 µg/mL), (d) Sample Solution of REM (160 µg/mL) and TEN (16 µg/mL)

Table 2: Linearity Data

REM			TEN		
Conc. (µg/ml)	Peak Area (n = 3) Mean ± SD	% CV	Conc. (µg/ml)	Peak Area (n = 3) Mean ± SD	% CV
80	808070 ± 946.533	0.11	8	145032 ± 410.819	0.28
120	1618410 ± 5094.498	0.31	12	218753 ± 3631.083	0.35
160	2426893 ± 4080.224	0.16	16	295036 ± 581.447	0.19
200	3239334 ± 3937.098	0.12	20	368959 ± 678.779	0.18
240	4078521 ± 5130.121	0.19	24	440793 ± 7541.052	0.68
Slope	20405		18543		
Intercept	83048		2976		
Correlation Coefficient	0.9999		0.9999		

Table 3: Precision and Accuracy Data

DRUG	Precision			Accuracy	
	Conc. (µg/ml)	Intraday (% CV n = 3)	Interday (% CV, n = 3)	Level (%)	% Recovery (Mean ± SD)
REM	120	0.68	0.70	50	99.98 ± 0.319
	160	1.04	1.33	100	100.09 ± 0.370
	200	1.10	0.79	150	99.92 ± 0.159
TEN	12	0.62	1.48	50	100.60 ± 0.171
	16	0.77	1.92	100	99.93 ± 0.119
	20	1.32	1.18	150	100.51 ± 0.472

Table 4: Robustness Data

Chromatographic Factors	Level	REM (Mean Peak Area ± SD), % CV	TEN (Mean Peak Area ± SD), % CV
Change in wavelength (± 2 nm)	233	2432552 ±14352.05, 0.59	296419 ±711.40, 0.24
	235	2449232 ± 27431.39, 1.12	295752 ± 1212.58, 0.41
	237	2459787 ± 24105.91, 0.98	295555± 1891.55, 0.64
Change in Flow Rate (± 1 ml/min)	0.9	2417983 ± 10639.12, 0.44	291715 ± 2887.97, 0.99
	1.0	2426893 ± 3883.02, 0.16	295036 ± 560.56, 0.19
	1.1	2449962 ± 22049.65, 0.90	293591 ±2877.19, 0.98
Change in Column Temperature (± 2 ºC)	23	2435401 ± 16804.26, 0.69	291601 ± 1691.28, 0.58
	25	2456021 ± 10560.89, 0.43	292301 ± 1169.20, 0.40
	27	2432552 ± 15568.33, 0.64	296419 ± 711.40, 0.24
pH of eluent (± 0.2)	4.6	2419204 ± 25125.17, 1.03	291248 ± 1425.85, 0.41
	4.8	2442145 ± 26524.21, 1.12	295236 ± 1224.59, 0.41
	5.0	2427347 ± 23418.41, 1.12	294756 ± 1146.24, 0.41
Change in Mobile Phase Ratio (± 4%)	48:52	2449219 ± 23147.18, 1.12	297298 ± 1536.78, 0.41
	50:50	2448249 ± 21428.21, 1.12	297075 ± 1426.75, 0.41
	52:48	2444758 ± 24866.48, 1.12	296763 ± 1478.48, 0.50

Table 5: Solution Stability Data

REM (160 µg/ml)			TEN (16 µg/ml)	
Time (h)	Peak Area	% Stability	Peak Area	% Stability
0	2426893	100	295036	100
6	2419556	99.69	294035	99.66
12	2410895	99.34	293058	99.32
18	2403895	99.07	292584	99.16
24	2395896	98.72	289865	98.24

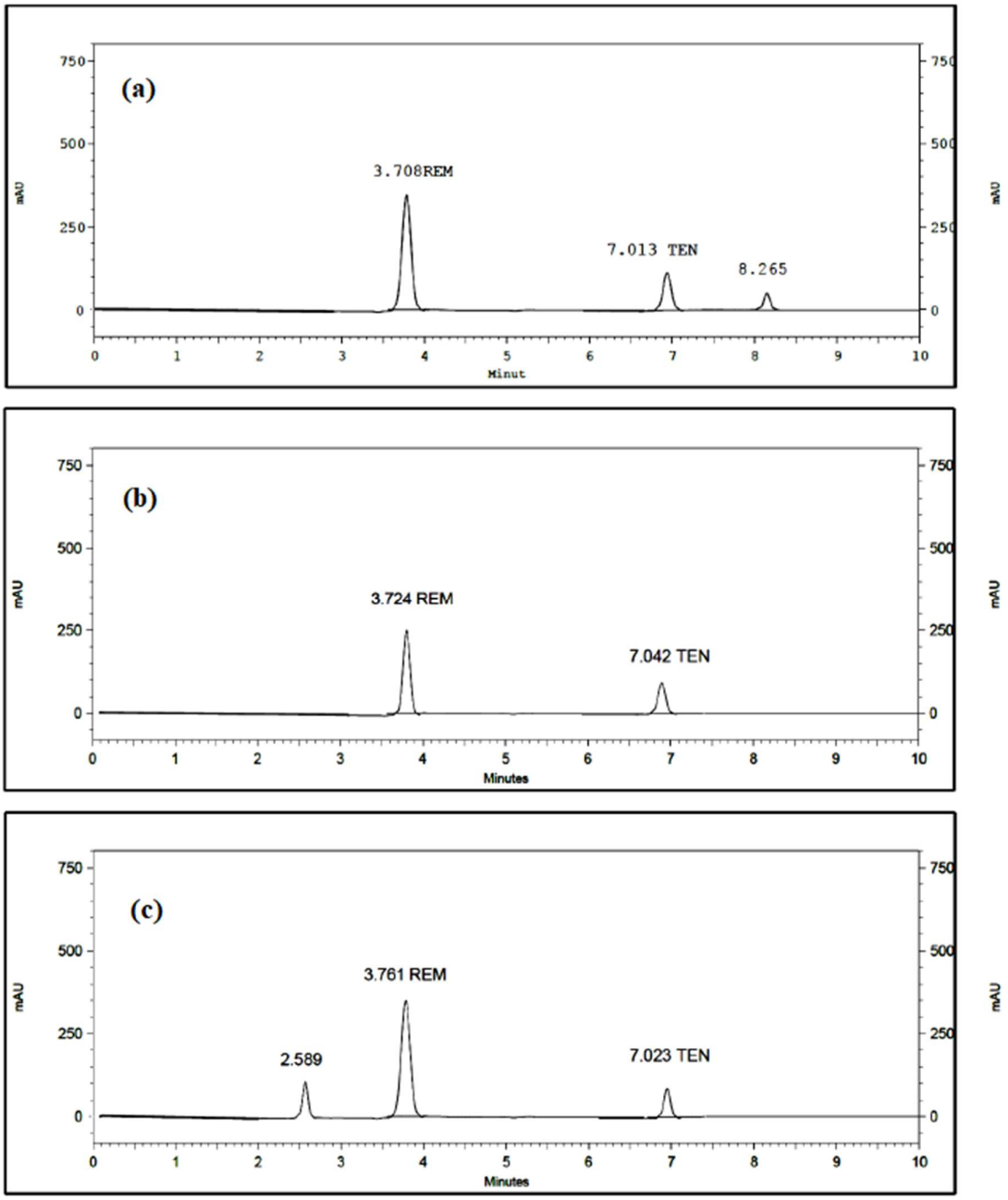

Figure 4: HPLC Chromatogram of (a) Acidic degradation of binary mixture, (b) Alkaline degradation of binary mixture (c) Oxidative degradation of binary mixture

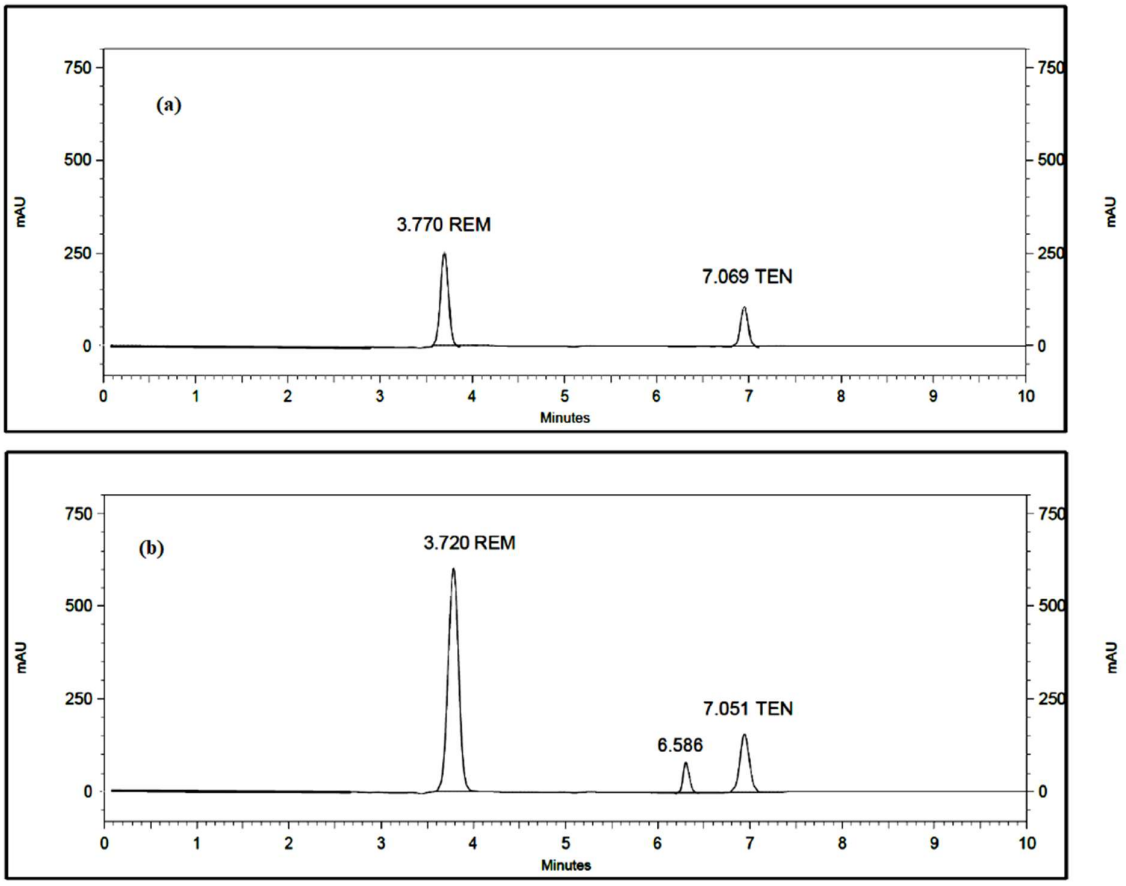

Figure 5: HPLC Chromatogram of (a) Photolytic degradation of binary mixture, (b) Thermal degradation of binary mixture

Table 6: Forced Degradation Study Data

Degradation Condition	Drug	R_t of observed Peak	% of degradation	Peak Purity	Resolution
Acidic (0.1 N HCl, 40 °C, 1 h)	REM	3.708	13.90	0.9994	-
	TEN	7.013 8.265 (I)	12.23	0.9996	12.443
Alkaline (0.1 N NaOH, 40 °C, 1 h)	REM	3.724	6.72	0.9994	-
	TEN	7.042	9.50	0.9996	12.462
Oxidative (3% H_2O_2, RT, 2 h)	REM	3.761 2.589 (I)	8.11	0.9994	-
	TEN	7.023	5.58	0.9996	12.489
Thermal (80°C, 2 h)	REM	3.720	11.05	0.9994	-
	TEN	7.051 6.586 (I)	5.58	0.9996	12.454
Photolytic (UV light exposure, 365 nm for 24 h)	REM	3.770	11.01	0.9994	-
	TEN	7.069	12.92	0.9991	12.428

CONCLUSION

A novel, simple, precise, selective, accurate and specific stability representing RP-HPLC approach was designed and validated for concurrent quantitation of REM and TEN in API and formulation. The drugs (REM and TEN) were subjected to different stimuli as per ICH Q1A (R2) to evaluate the inherent

stability. The outcomes showed the susceptibility of REM towards acidic, thermal and photo degradation. TEN was more prone to degrade in photolytic, alkaline and acidic conditions. So, both the drugs should be kept away from light to improve its expiry. The suggested approach was validated for the parameters outlined in ICH Q2 (R1). The established approach has proven effective in distinguishing the drug from its product of decomposition and quantify the drug concentrations in bulk and the dosage form.

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CONFLICT OF INTEREST

The researchers have no reported conflicts of interest.

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