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Original Article

Development and Validation of a Stability Indicating HPTLC Method for Simultaneous Estimation of Telmisartan and Gallic Acid as per ICH Q1A (R2)

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ABSTRACT

Background: A simple, selective and sensitive HPTLC method was developed for simultaneous estimation of Telmisartan (TEL) and Gallic acid (GA). Oxidative stress produces hypertension, GA having antioxidative property that reduces ROS. TEL is safer angiotensin-1 receptor blocker. **Objectives:** Literatures suggest antioxidant with cardiovascular drug produce synergistic effect. **Materials and Methods:** The stationary-phase used was aluminium-backed silica gel $60F_{254}$ HPTLC plates (20 cm×10 cm, thickness-0.2 mm). The mobile-phase consisted of ethyl acetate: methanol: chloroform: acetic acid in the ratio of 4:2:2:0.2(v/v). Drugs were exposed to different stress conditions (Acid, Alkali, Oxidative, Thermal and Photolytic) for 8 hr, analysed at intervals of 2 hr. Detection and quantification were performed densitometrically (200-400 nm). **Results:** Calibration plots showed good linear relation, with better correlation coefficient (R^2). AUC of the drugs were between the concentration ranges of 200-1200 ng/spot. For GA, R_f value was 0.60, LOD-5.494 ng/spot, and LOQ-16.65 ng/spot. For TEL, R_f value was 0.67, LOD-19.877 ng/spot, and LOQ-60.235 ng/spot. In alkaline solution, TEL degraded up to 12.5%, and GA degraded completely. Whereas, in oxidative environment 30% and 30.55% degradation of TEL and GA were noted. **Conclusion:** Developed method was validated as per ICH guidelines, the performed forced degradation study will help for drug stability and formulation development.

Keywords: Method development and validation, Telmisartan, HPTLC, Gallic acid, Forced degradation study.

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INTRODUCTION

Cardiovascular diseases are cardiac conditions that include structural problems, diseased vessels, and blood clots. Some most common types of cardiovascular diseases are coronary heart disease, heart failure, cardiac arrest, high blood pressure, Arrhythmias, Coronary artery disease, Congenital heart disease, Stroke[1,2] etc. As an effect of drastic modification in lifestyle and dietary habits, cardiovascular diseases have become pretty prevalent in the young generation. There has been an increment of hypertensive cases falling under the age group 25-60 by 24.8% and 60-69 by 14.3% in recent decades.[3,4] The stressful environment has become a regular part of day-to-day life, causing exaggerated production of Reactive Oxygen Species (ROS), which is directly associated with CVDs. As a result, it leads to multiple other human ailments and increases the death rate in the age group mentioned earlier. Globally, "cardiovascular disease accounts for an estimated 31% of the worldwide mortality and disease burden from all non-communicable diseases."[5]

Further, rates of cardiovascular diseases are increasing in developed countries. "In the Heart Outcomes Prevention Evaluation (HOPE) study, investigators predict a 29% increase in ischemic heart disease mortality and a 28% increase in mortality rates from cerebrovascular disease in developed countries from 1990 to 2022."[6,7] Among different antihypertensive drugs, Angiotensin II receptor blockers are long-acting and well-tolerated. TEL a subclass of Angiotensin II (AT-II) receptor blockers (Figure 1) is used to treat essential arterial hypertension. It is a brand-new benzimidazole derivative chemically, possesses outstanding efficacy, is quite safe, and has few adverse effects.[8,9] The actions of free radicals and other reactive oxidative species involved in atherogenesis can be reduced by antioxidants.[10,11] Hence it is considered a natural defence system for human health. GA (Figure 2) has a polyphenolic structure that makes the drug a potential anti-oxidant,[12-14] also been reported to prevent cardiological issues.[15,16] Gallic acid is predominantly present in fruits of individual plants *Terminalia bellerica* (Family-Combretaceae), *Emblica Officinalis* (Family-Euphorbiaceae), and *Terminalia chebula* (Family-Combretaceae),[17] which combinedly forms

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a very popular ayurvedic formulation called "Triphala," that has reported to be used as rejuvenator also effective in the prevention of hypertension.[18] This polyphenolic drug has a wide range of therapeutic windows and is considered safe at a higher concentration of 1000 mg/kg without any adverse or long-term side effects and non-toxic up to 5000 mg/kg.[19] As per literature study, AT1 receptor blocker, i.e., TEL, and anti-oxidant, i.e., GA, both have a common intersection area of cardiovascular disease curing potential. Hence, it is expected to have a synergistic effect in a combined dosage form (Figure 3). Pre-formulation data is an integral part for the preparation of fixed-dose formulation. A forced degradation study is an important pre-formulation study usually performed to identify the degradation pathways, determine the stability of drugs in the dosage forms, identify the chemical properties of the molecules, solve associated problems related to the stability of the drug molecule, to generate a degradation profile of the drug. The ICH Q1A-assessment of stability for novel medicinal compounds and their products-recommendations are relevant to forced degradation investigations. The common technical document for the registration of pharmaceuticals for human use is called ICH M4Q (R1): Module 3: Quality.[20] In this study, different stressed conditions like acid (0.1M HCl), alkaline (0.1N NaOH), oxidation (hydrogen peroxide solution (3.0%, v/v), UV light (at 254 nm), and Thermal (hot air oven at 60ºC) were applied to the drug substance for a time period of 8 hr., so as to determine the stability of drug molecules under accelerated situations. The validation of the stability procedures, degradative pathways, and percentage degradation of the molecule are studied using the forced degradation technique, as per the ICH guidelines. An advanced scientific analytical technique HPTLC has been used for the sample analysis.

As per literature review, many published data were found regarding forced degradation of TEL alone by UV,[21] HPLC[22,23] and simultaneous estimation of TEL along with other class of antihypertensive drugs,[24,25] diuretics.[26] Very few numbers of papers are available, that utilizes HPTLC method for the estimation of TEL.[27] But, the simultaneous estimation of GA and TEL as well as forced degradation is a novel approach to the formulation development sector that combine an appropriate cardiovascular medicine with an antioxidant. As a result, there were no published data for a sensitive, stability-indicating HPTLC approach for the simultaneous determination of GA and TEL. Nevertheless, the primary goal of this work was to develop and test a stability-indicating approach that could simultaneously measure GA and TEL along with its formed degradation products.

MATERIALS AND METHODS

Materials and Chemicals

TEL was received as a gift sample from Glenmark Pharmaceuticals Ltd., Sikkim, while GA (99.5% pure) was acquired from Loba Chemie Pvt. Ltd., We bought glacial acetic acid from Rankem. The experiment only utilised analytical-grade substances.

Instrumentation

The study was conducted using a Camag HPTLC system from Muttens, Switzerland, which included a Camag Linomate V automatic sample applicator, Hamilton syringe (100 µL), Camag HPTLC scanner-3, Camang Vision CATS software, Camag twin trough chamber (20 cm x 10 cm) and ultrasonicator, Equitron-Hot air oven, and UV cabinet. Precoated silica gel aluminium plate 60 F 254 (20 cm × 10 cm with 0.2 mm thickness) was the type of HPTLC plate that was employed (E. Merck, Mumbai, India).

Preparation of Standard Stock Solutions

By precisely measuring 10 mg of each drug in a separate 10 mL volumetric flask, dissolving the mixture, and adjusting the volume to the proper concentration with methanol, standard stock solutions of GA and TEL were prepared. For the simultaneous

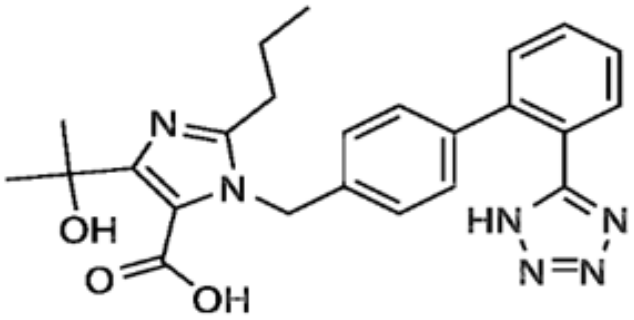


Figure 1: IUPAC Name- 2-(4-{[4-Methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid.

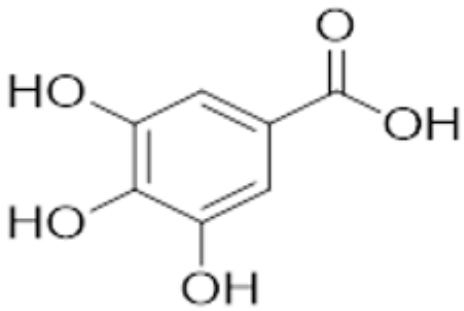


Figure 2: IUPAC name: 3,4,5-trihydroxy benzoic acid.

quantitative study of both drugs, appropriate aliquots from the aforementioned stock solutions were transferred, and a standard mixture solution (100 µg/mL) was produced. Afterward, a series of standard solutions containing both drugs were prepared for the final concentration range of 200-1200 ng/spot by appropriately dilution of the mixture to produce a linear calibration curve. Standard working concentrations of both medications were prepared from respective standard stock solutions in order to conduct quantitative investigations and evaluate different validation parameters.

Chromatographic condition

The precoated silica gel on aluminium plate 60 F 254 (20 cm x 10 cm, pre-washed with methanol and activated by heating for 5 min at 60°C prior to chromatography) was used as the stationary phase for this experiment. To develop an appropriate mobile phase, a different combination of solvents was tested at various ratios. We came to the conclusion that ethyl acetate, methanol, chloroform, and acetic acid in the ratio of 4:2:2:0.2, (v/v/v/v), produced isolated peaks with superior resolution. Other crucial factors that were considered for chromatography includes, the amount of mobile phase used: 20 mL, sample application rate: 150 nL/sec, sample volume: 10 µL, For better result TLC chamber was kept close for solvent saturation, saturation time was 20 min at room temperature (25±2)°C and RH (60±5)%, sample application band width 6 mm, 7 mm between bands, 5 mm x 0.45 mm slit size, 10 mm/s scanning speed, and densitometric UV detector used at 280 nm and 296 nm for GA and TEL, respectively, in the reflectance-absorption mode.

HPTLC Method development

In order to get the optimum separation and resolution between GA and TEL for HPTLC analysis, a variety of mobile and stationary phases were initially tried. To obtain a good separation and produce two well-resolved peaks for GA and TEL, the mobile phase (4:2:2:0.2, v/v) of ethyl acetate, methanol, chloroform, and acetic acid was established. The wavelengths at which both drugs exhibit substantial absorbance, 280 nm and 296 nm respectively, for the simultaneous assessment of GA and TEL, the detected R_f values were 0.60 and 0.67, respectively.

Forced degradation and sample preparation of GA and TEL

The drug molecules were subjected to stress conditions for a shorter duration of time so as to identify the degradant products and the degradation mechanisms. The frequently used degradation conditions are as follows (Figure 4).

Photolytic and UV degradation

For photolytic degradation, the powdered drugs were subjected to UV light (at 254 nm) for 8 hr and for thermal degradation kept at 60°C for 8 hr individually. The average peak area was calculated after triplicate analyses of 1 mL of the (1000 µg/mL) solution (10 µL; corresponding to 1000 ng each band) were performed by HPTLC as previously mentioned at regular intervals of 2 hr. Chromatographic plates were developed.

Acid, base, and oxidative degradation

10 mg of each drug was dissolved in small quantity of methanol, and the final volume was then achieved up to 10 mL with hydrogen peroxide solution (3.0%, v/v), 1 M HCl, and 1 M NaOH in separate volumetric flasks. To eliminate out any potential degradation caused by light, the solution was left at ambient temperature for 8 hr while remaining completely dark. 1 mL of the solution was neutralised to pH-7.0, diluted to 10 mL with methanol, and then examined in triplicate (10 µL; equivalent to 1000 ng each band) by HPTLC at regular intervals of 2 hr. As previously indicated, the average peak area was calculated from the developed chromatographic plate.

Method validation

Linearity

A series of combined dilutions and standard curves were plotted in HPTLC with a concentration range of both TEL and GA between 200-1200 ng/band. Least-squares linear regression analysis was used to examine the data on peak area versus concentration. The study mentioned above identified crucial variables like slope, intercept, and correlation coefficient.

Precision

Replicate (n=3) analyses of standards and samples were conducted in order to assess the intra- and inter-day precisions of the procedures. This process was repeated three times in same day and on three different days respectively. The relative standard deviation [%RSD] for repeated observations was used to calculate precision.

Accuracy

In order to demonstrate the correctness of the suggested procedures, recovery studies using the usual addition approach were carried out. TEL and GA-containing samples that had already been examined were spiked with standard TEL and GA, and the resulting mixes were examined in triplicate (n=3) using the suggested procedures. Accuracy was represented as a percentage of recovery.

Robustness

The mobile phase composition, saturation time and temperature were changed for HPTLC. The samples were examined in triplicate for every change in circumstance. The remaining parameters were kept fixed at their ideal values while the impact of changing one set of conditions was examined.

Sensitivity

Regarding LOD and LOQ, the sensitivity of the approaches was established. Regression equations for TEL and GA were used to calculate the LOD and LOQ parameters.

$$LOD = 3.3 * \frac{Standard\ deviation\ (\sigma)}{slope\ (m)}$$

$$LOQ = 10 * \frac{Standard\ deviation\ (\sigma)}{slope\ (m)}$$

RESULTS

Unconventional studies were conducted to optimise factors impacting simultaneous drug estimation using HPTLC and detected at 297 nm and 280 nm for TEL and GA respectively (Figure 5). The mobile phase was determined to have the optimum sensitivity, efficiency, peak shape, and stable baseline when composed of ethyl acetate: methanol: chloroform: acetic acid in a ratio of 4:2:2:0.2 (v/v). Additionally, we have discovered no chemical or physical interactions between the medications, demonstrating the drugs' compatibility. We can infer that the method is particular to these components from the separately developed peaks of pure drugs TEL and GA respectively (Figures 6 and 7). The retention factors for TEL and GA that were obtained under ideal circumstances were 0.67±0.02 and 0.60±0.01, respectively. In the concentration range of 200-1200 ng/band, both medicines' calibration plots were linear, with (n=3, R^2=0.9909) for TEL and (n=3, R^2=0.9930) for GA, respectively. The limit of detection and quantification for GA were determined to be the LOD-5.494 ng/spot, LOQ-16.65 ng/spot respectively, and for TEL the LOD-19.877 ng/spot, LOQ-60.235 ng/spot respectively. These results show enough sensitivity of the method. Table 1 shows the linearity parameters of the calibration curve. By adding 80, 100, and 120% of the drug to the pre-analysed sample, the recovery research was carried out in triplicate at three different concentrations; the mean recovery was, as shown in Table 2, 100.132±0.40 for GA and 99.82±0.78 for TEL, respectively. Table 3 shows the findings of the robustness analysis, which took into account three different development factors. Results obtained from measurements of intra-day and inter-day variation in the determination of 200-1200 ng/spot of TEL and GA in triplicate. The table shows that the results of the analysis of variance for each amount were within the allowed range, or (±2%). The intra- and inter-day precisions of TEL were 0.7016 and 0.5616, respectively, and the intra- and inter-day precisions of GA were 0.1008 and 0.0979. The results are listed in Table 4 and are expressed as (%RSD).

TEL and GA were simultaneously determined in forcefully degraded samples using the validated HPTLC method. TEL and GA exhibit further degradation peaks at R_f values of 0.02 and 0.82 for acid, 0.02 and 0.84 for oxidation, and 0.02, 0.06, and 0.23 for alkali. While thermal degradation exhibits negligible degradation for TEL and GA, photolytic stress conditions exhibit further degradation peaks at Rf values at the sample application point and 0.84. The peak purity profile analyses supported the finding that the peak of the degradation product did not obstruct the drug response (Table 5). This technique demonstrates that degradation products and drugs may indeed be separated (Figure 8).

After 8 hr of stressed study, samples of TEL and GA were obtained and applied to chromatographic plate in order to obtain a chromatogram. Degradation study shows significant degradation in acid 13.75% and 18.2%, respectively. A nearly similar amount of degradation was seen in the oxidative stress study, i.e., 30% and 30.55% for TEL and GA. For TEL 22.5% and 30.95% drug loss was observed for GA in the thermal degradation study. In photolytic degradation at 254nm, TEL degraded up to 12.5% and GA up to 11.65%. In the case of alkali hydrolysis, 12.5% of

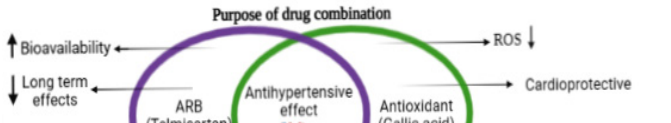


Figure 3: Combined effect of AT1 Receptor blocker along with anti-oxidants.

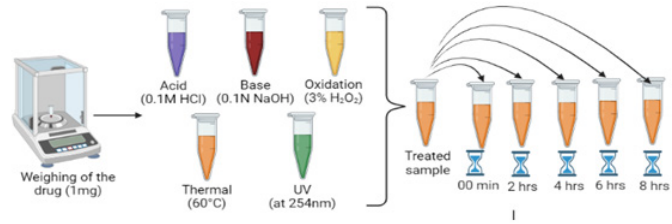


Figure 4: Different forced degradation conditions and sample collection for analysis.

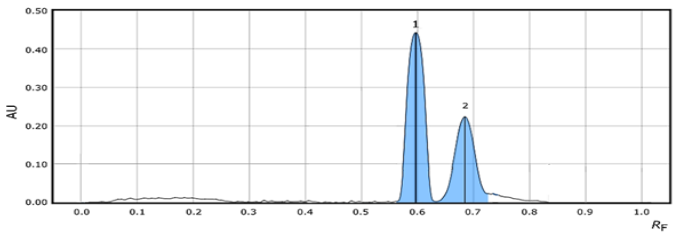


Figure 5: Distinctly separated peaks of (1) Gallic acid (Rf - 0.60) and (2) Telmisartan (Rf-0.67).

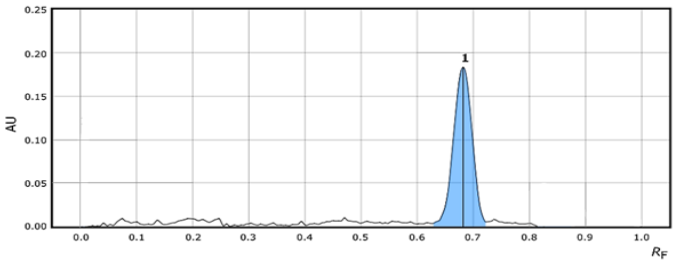


Figure 6: Isolated peak of Telmisartan (Rf- 0.67).

Table 1: Linear regression data for calibration plots.

Parameters	Gallic acid	Telmisartan
Linear range (ng/spot)	200-1200	200-1200
Correlation coefficient ($R^{2)}$	0.9909	0.9930
Slope ±SD	2.00 x 10^{-5}	8.00 x 10^{-6}
Intercept ±SD	0.0142	0.0023

Table 2: Accuracy study of Gallic acid and Telmisartan.

Level of accuracy (%)	Conc. (ng/band)			GA			TEL		
	Conc. taken	Conc. added	Total conc. known	AUC (Theoretical)	% Recovery	% RSD	AUC (Theoretical)	% Recovery	% RSD
0	400	0	400	0.0222	101.783	0.8371	0.0054	106.3580	0.2659
80		320	720	0.0286	99.650	0.3508	0.00796	99.16247	0.4449
100		400	800	0.0302	100.039	0.0334	0.0086	96.12403	1.8478
120		480	880	0.0318	99.056	0.3174	0.00924	96.64502	0.2239
Mean % RSD						0.384675	Mean % RSD		0.695625

Table 3: Robustness study data for Telmisartan and Gallic acid.

Changes in parameters		Conc. (ng/band)	TEL			GA		
			Mean AUC (n= 3)	SD	% RSD	Mean AUC (n= 3)	SD	% RSD
Saturation time in (min.)	22	1000	0.01069	3.84 x10^{-5}	0.3596	0.03462	0.00002	0.0580
	20							
	18							
Mobile phase ratio (EA:MeOH:$CHCl_3$: Acetic acid)	4:2:2:0.2		0.00841	1.18 x10^{-4}	1.4069	0.02991	0.00003	0.1074
	3.8:2.1:2.1:0.2							
	4.2:1.9:1.9:0.2							
Temp (in °C)	23		0.00723	6.61 x10^{-5}	0.9145	0.02686	0.00002	0.0559
	25							
	27							
Mean % RSD					0.893667	Mean % RSD		0.073767

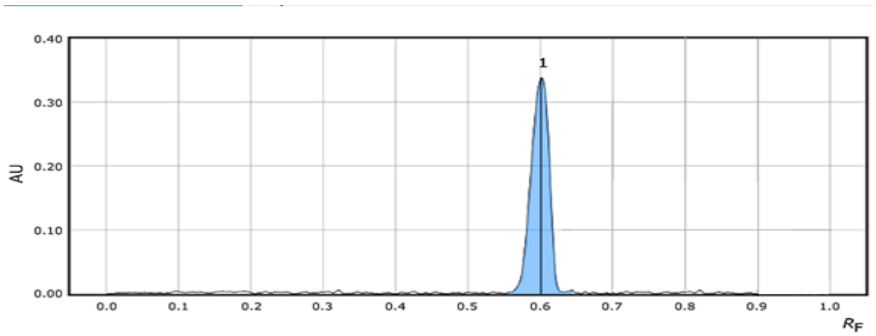
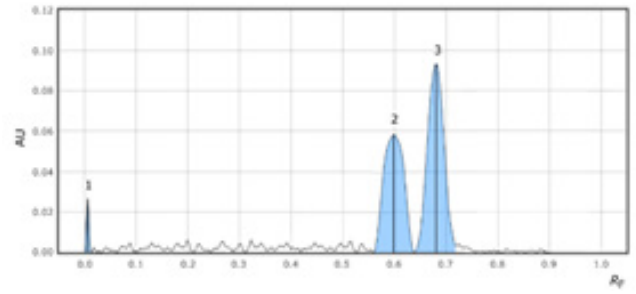
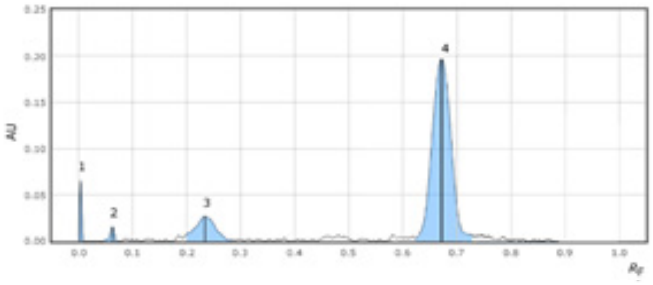


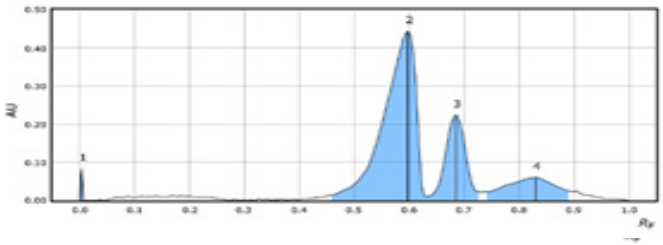
Figure 7: Isolated peak of Gallic acid (Rf - 0.60).



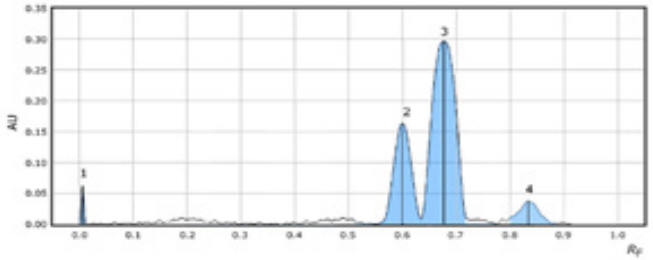
a. Thermal degradation (at 60°C) peaks



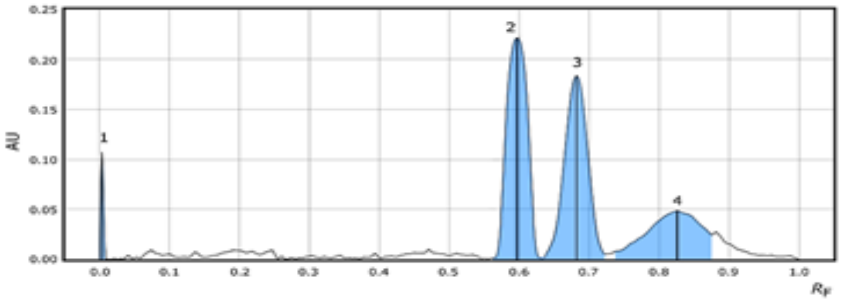
b. Alkaline (0.1N NaOH) degradation peaks



c. Photolytic degradation under UV radiation-254nm peaks



d. Acid (0.1M HCl) degradation peaks



e. oxidative (3% H_2O_2) degradation peak

Figure 8 (a-e): Developed chromatographic plates of different forced degradation condition

Table 4: Summary of validated data.

Parameters		Gallic acid	Telmisartan
R_f value		0.6	0.67
Linearity	(in ng/spot)	200-1200	200-1200
LOD		5.494	19.877
LOQ		16.65	60.235
Correlation coefficient (R^2)		0.9909	0.9930
Precision (%RSD)	Repeatability	0.04976	0.28229
	Intra-day	0.1008	0.7016
	Inter-day	0.0979	0.5616
Accuracy (%RSD)	80%	0.3508	0.4449
	100%	0.0334	1.8478
	120%	0.3174	0.2239
	Mean	0.384675	0.695625
Robustness (%RSD)		0.0738	0.8937
Specificity		Specific	Specific

Table 5: Qualitative estimation of produced degradants based on R_f values.

Degradation condition	No. of degradation products	R_f of degradation
Acid	1	0.82
Base	3	0.02, 0.06, 0.23
Oxidative	2	0.02, 0.84
Thermal	-	-
Photolytic	1	0.84

Table 6: Overall simultaneous forced degradation study data of Gallic acid and Telmisartan.

Drug name	Time (in hr.)	Different conditions with % degradation				
		Acid (0.1 M HCl)	Alkali (0.1 M NaOH)	Oxidative (3% H_2O_2)	Thermal	UV
Gallic acid	0	0	100	0	0	0
	2	3.8	100	6.1	13.2	4.5
	4	8.15	100	12.2	21.95	6.3
	6	13.25	100	21.8	26	8.65
	8	18.2	100	30.55	30.95	11.65
Telmisartan	0	0	0	0	0	0
	2	1.25	5	11.25	3.75	1.25
	4	3.75	6.25	18.75	11.25	2.5
	6	7.5	8.75	25	18.75	5
	8	13.75	12.5	30	22.5	12.5

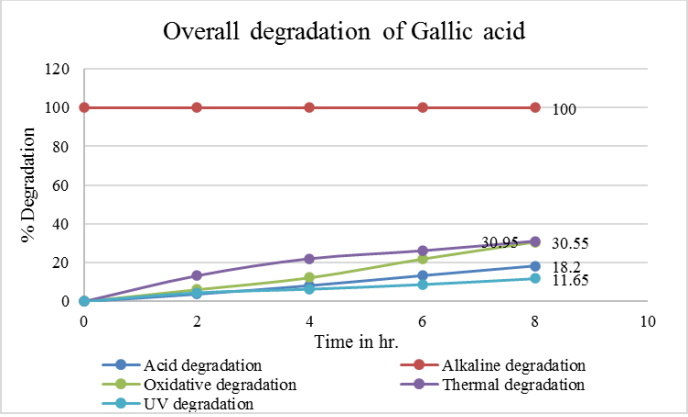


Figure 9: Overall degradation graph of Gallic acid.

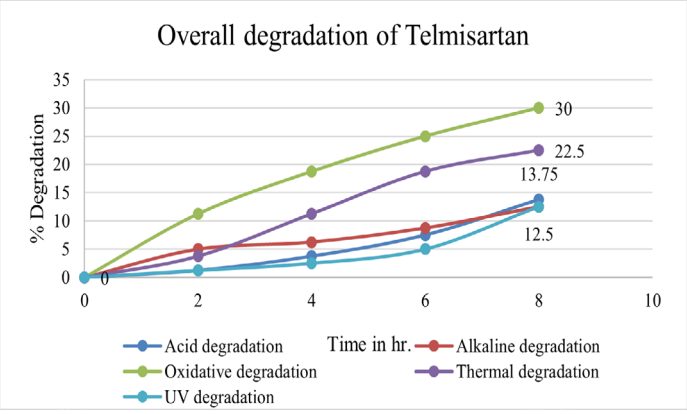


Figure 10: Overall degradation graph of Telmisartan.

degradation was estimated for TEL, and complete degradation of GA was observed at the beginning of the experiment (at 0 hr) (Table 2).

DISCUSSION

After selection of a suitable mobile phase, method development and validation for simultaneous determination of both TEL and GA were done. The mean percent RSD value was within the acceptable range (±2%). Assay (percent) and retention factor (R_f) were not considerably impacted. %RSD value in all robustness parameters was found to be within ±2%. The low RSD value (±2%) confirmed the suitability of the method for analytical as well as the bio-analytical study of TEL and GA. Data from validation experiments are summarized in (Table 4). As per ICH Q1A (R2) samples were prepared from forced degraded studies and analysed for determination of degradants. The overall percentage degradation of both the drugs is presented in (Figures 9 and 10, Table 6) Hence, we can conclude that during formulation

development, we cannot use any alkaline substance at any point of operation as, GA is highly unstable in an alkaline medium.

CONCLUSION

The suggested method can be employed for the routine simultaneous analysis of the TEL and GA in pharmaceutical preparations because it is very reproducible and consistent. The proposed HPTLC approach allows for the simple, precise, and reliable quantitative simultaneous determination of TEL and GA in pharmaceutical dosage forms and bulk without any influence from degradants produced by their thermal, acidic, alkaline, oxidative, and photolytic degradation. The approach was simpler than previously reported methods for determining TEL and original in the sense that the proposed medication combination is theoretically novel. As a result, no reported data for simultaneous estimate of TEL and GA is provided. The method was validated as per the proposed ICH guideline and is suitable from a quality-control point of view, where economy and speed are essential. By identifying related impurities, the approach can be used to assess the drug's purity from various sources. It might be extended to look into drug degradation kinetics and estimate them in plasma and other biological fluids. Because it isolates the medicine from its degradation products, it can be used to assess stability.

FUTURE SCOPE

The performed forced degradation study gives complete idea regarding potential degradation pattern of APIs in different stressed conditions that will be helpful during formulation development. By using this developed and validated method, a fixed dose formulation of GA and TEL can be determined simultaneously, as well as other formulation containing above stated drugs can also be assayed.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This investigation aimed to enhance the simultaneous drug estimation using High-Performance Thin-Layer Chromatography (HPTLC) for TEL and GA. Detection occurred at 297 nm and 280 nm for TEL and GA, respectively. The optimal mobile phase comprised ethyl acetate: methanol: chloroform: acetic acid in a 4:2:2:0.2 (v/v) ratios, demonstrating sensitivity, efficiency, peak shape, and a stable baseline. No observable chemical or physical interactions between the drugs were noted, indicating their compatibility.

Distinct peaks for pure TEL and GA confirmed the method's specificity, with retention factors of 0.67±0.02 for TEL and 0.60±0.01 for GA under ideal conditions. Linear calibration plots within the 200-1200 ng/band concentration range were established, and limits of detection and quantification were determined for both drugs. Recovery studies yielded satisfactory results, with mean recoveries of 100.132±0.40 for GA and 99.82±0.78 for TEL. Robustness analysis and precision measurements exhibited reliable and reproducible outcomes.

The validated HPTLC method successfully determined TEL and GA in forcefully degraded samples, unveiling substantial degradation under diverse stress conditions. Peak purity profile analyses confirmed the effective separation of degradation products from the drugs, offering a comprehensive characterization of the HPTLC method for simultaneous drug estimation and degradation studies of TEL and GA.

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