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ORIGINAL PAPER

Validated Stability-Indicating Spectrofluorimetric Method with Enhanced Sensitivity for Determination of Repaglinide in Tablets

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Abstract A simple and highly sensitive spectrofluorimetric method was developed and validated for determination of the antidiabetic agent repaglinide (RG) in tablets. The proposed method is based on measurement of the native fluorescence of RG in 0.1 M H_2SO_4/methanol medium at 360 nm after excitation at 243 nm. The method showed a linear dependence of the relative fluorescence intensity on drug concentration over the range of 0.02–0.50 μg mL^{-1} with lower detection limit of 6.0 ng mL^{-1} and lower quantification limit of 18 ng mL^{-1}. The method was successfully applied for determination of RG in different tablets and the obtained results were in good agreement with those obtained by the official method. The proposed method was extended to investigate the kinetics of oxidative degradation of the drug. A proposal for the degradation pathway was postulated.

Keywords Repaglinide · Spectrofluorimetry · Tablets · Stability-indicating

Introduction

Repaglinide (RG, Fig. 1), (S)-2-ethoxy-4-[2-[[methyl-1-[2-[(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid [1], is a member of the meglitinide family of benzoic acid derivatives, developed from the non-sulfonurea moity of glibenclamide. It is a new antidiabetic agent that's used for the treatment of type 2 diabetes mellitus. RG helps to control blood sugar by increasing the amount of insulin released by the pancreas [2].

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RG is official in the United States Pharmacopoeia (USP) [1] and The European Pharmacopoeia (EP) [3]. The USP [1] recommended HPLC methods for determination of RG in pure form and tablets, where the EP [3] described a non-aqueous titrimetric method for its determination. Reviewing the literature revealed some analytical methods for determination of RG including spectrophotometry [4–9], micellar electrokinetic chromatography [10], high-performance liquid chromatography [11–18], electrochemistry [19] and thin layer chromatography [20, 21].

Spectrofluorimetry is considered a sensitive and simple analytical technique. Only one spectrofluorimetric method has been described for determination of RG based on measuring of its native fluorescence at 282/379 nm ($\lambda_{ex}/\lambda_{em}$) in aqueous phosphate buffer of pH 7.4 [18]. This method has very poor sensitivity (linear within concentration range of 5.0–80.0 μg/mL). On the other hand, RG is formulated in very minute amounts in tablets (0.5, 1 and 2 mg/tablet), so, there is a strong need to develop a sufficiently sensitive, rapid and specific method for its determination in pharmaceutical preparations.

For these reasons, the development of new alternative more sensitive spectrofluorimetric method for the determination of RG was very essential. This encouraged the author to explore a highly sensitive spectrofluorimetric method for determination of RG in drug substance and pharmaceutical preparations.

The main advantages of the proposed method compared with previously reported methods are its simplicity, rapidness and low cost. The detection limit of the proposed method is comparable or better than the detection limits of most of the reported methods. The proposed method is superior to the previously reported spectrofluorimetric method for determination of RG in terms of its higher sensitivity and stability-indication capability. The proposed method was used to investigate the oxidative degradation

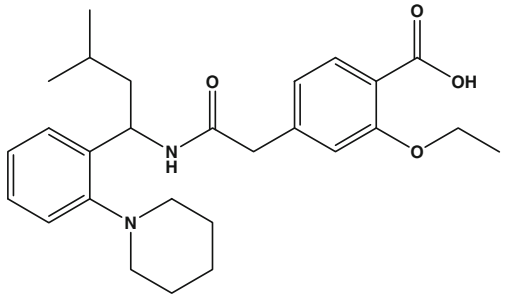


Fig. 1 Chemical structure of repaglinide

behavior of RG according to ICH Guidelines [22]. Since the purpose of stability studies is to monitor possible changes to a product or a material over time at different storage conditions, it is expected that, only those methods that are stability-indicating should be used.

Experimental

Apparatus

- The fluorescence spectra and measurements were recorded using a Perkin-Elmer model LS 45 luminescence Spectrometer (UK), equipped with a 150 W Xenon arc lamp, grating excitation and emission monochromators and a Perkin-Elmer recorder. Slit widths for both monochromators were set at 10 nm. A 1-cm quartz cell was used.
- Hanna pH-Meter (Romania) was used for pH adjustments.

Materials and Reagents

All reagents were of analytical reagent grade, solvents were of spectroscopic grade and distilled water was used throughout the work.

- Repaglinide pure sample was kindly provided by Eipico Co., Cairo, Egypt.
- Sodium dodecyl sulfate (SDS, 95 %) and cetyl trimethyl ammonium bromide (CTAB, 99 %) were purchased from Winlab (UK).
- Acetonitrile, β-cyclodextrin (β-CD) and hydroxy propyl-β-cyclodextrin (HP-β-CD) were obtained from Merck (Germany).
- Methanol and sulfuric acid were obtained from Sigma-Aldrich (Germany).
- n-Propanol was purchased from Riedel-deHäen (Germany).
- Nitric acid was obtained from Panreac (Spain).
- Tween-80, methyl cellulose, glacial acetic acid, sodium acetate trihydrate, boric acid, sodium hydroxide, hydrochloric acid (32 %w/v) and hydrogen peroxide (30 %w/v) were obtained from ADWIC Co., Egypt.
- Acetate buffer (0.2 M, pH 3.7–5.0) and borate buffer (0.2 M, pH 7.5–8.5) solutions were freshly prepared.
- SDS, CTAB, β-CD, methyl cellulose, HP-β-CD and tween-80 were prepared as 0.5 %w/v aqueous solutions.
- 0.1 M Sulfuric acid was prepared.
- 3.0 %w/v hydrogen peroxide, 2.0 M sodium hydroxide and 2.0 M hydrochloric acid were prepared for the forced degradation studies.
- The following tablets were purchased from local pharmacies:
  1- Novonorm® tablets labeled to contain 0.5 mg repaglinide/tablet (batch # 048023658), product of NovoNordisk, Denmark.
  2- Repaglide® tablets labeled to contain 1 mg repaglinide/tablet (batch # MT0740309), product of Multi Apex Pharma, Egypt.

Standard Solution

10.0 mg of RG was accurately weighed and transferred into 100 mL volumetric flask. The volume was completed with methanol and the powder was dissolved with the aid of sonication. This solution was further diluted with the same solvent as appropriate to obtain the working concentration range. The standard solution was stable for ten days when kept in the refrigerator.

General Procedures

Construction of Calibration Graph

Accurate volumes of the standard solution over the concentration range of 0.02–0.50 μg/mL were transferred into a series of 10 mL volumetric flasks. 3.0 mL of 0.1 M sulfuric acid was added to each flask, the volumes were completed with methanol and the contents of the flasks were mixed well. The fluorescence intensities were measured at 360 nm after excitation at 243 nm. The relative fluorescence intensities (RFI) were plotted versus the final concentrations of the drug (μg mL^{-1}) and the corresponding regression equation was derived.

Procedure for Tablets

Twenty tablets were weighed, finely powdered and mixed well. An accurately weighed quantity of the powder equivalent to 5.0 mg RG were transferred into 50 mL volumetric flasks and extracted with 40 mL of methanol by sonication for 30 min. The volume was completed with the same solvent; contents of the flasks were mixed well and filtered. The procedure described under *"Construction of calibration graph*" was followed and the nominal contents of the tablets

were calculated using the calibration graph or the corresponding regression equation.

Procedure for Oxidative Degradation

Aliquots of RG standard solution (equivalent to 100.0 μg) were transferred into a series of small conical flasks; 2 mL of H_2O_2 solution (1.5, 3.0 or 6.0 %w/v solutions) were added and the solutions were heated in a thermostatically controlled water bath at 80 °C for different time intervals (20–80 min). At the specified time, the contents of each flask were cooled; the solutions were quantitatively transferred into 25 mL volumetric flasks and completed to volume with methanol. 1.0 mL of the resulting solutions was transferred into 10 mL volumetric flasks and the procedure described under *"Construction of calibration graph"* was followed.

Results and Discussion

Fluorescence properties and spectral characteristics of RG were carefully investigated under different conditions. The effect of different buffers, acids, solvents and organized media on the fluorescence behavior of RG was studied in order to establish the optimum conditions for a sensitive spectrofluorimetric assay for its determination. It was found to exhibit an intense native fluorescence at 360 nm after excitation at 243 nm. Figure 2 shows the fluorescence excitation and emission spectra of RG in 0.1 M sulfuric acid/methanol medium. As can be seen, RG exhibits three excitation wavelengths at 208, 243 and 297 nm. This is justified in theory by the light absorption promoting electron from the ground electronic state to three excited states [23]. A wavelength of 243 was selected as the optimum excitation wavelength as it gave the highest emission band with best reproducibility. The fluorescence emission spectrum of RG gives a band with a characteristic wavelength of 360 nm corresponding to the transition from the first excited singlet state to the ground state.

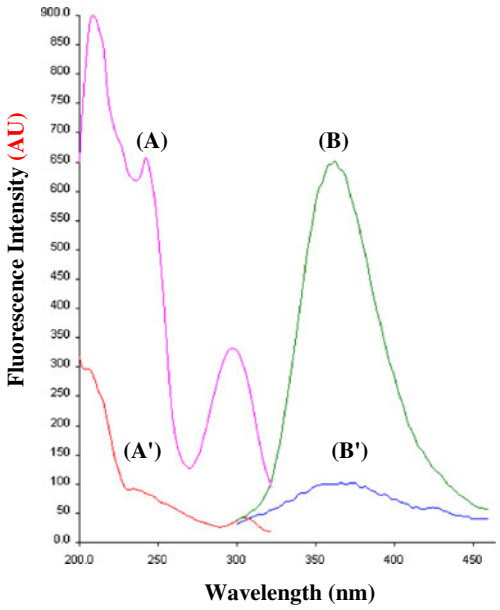


Fig. 2 Fluorescence spectra of: (A, B): RG (0.5 μg mL^{-1}) in 0.1 M H_2SO_4: methanol system. (A′, B′): Blank Where: (A, A′): Excitation spectra. (B, B′): Emission spectra.

Optimization of Experimental Conditions

Investigation of Fluorescence Spectral Characteristics of RG in Different Media

The fluorescence spectral behavior of RG was investigated in presence of acetate buffer of pH values ranged from pH 3.7–5.0, borate buffer over the pH range of 7.5–9.5 and different acids including; hydrochloric, nitric; acetic and sulfuric acids (0.1 M solution of each acid). The results showed that maximum RFI was achieved with 0.1 M sulfuric acid (Table 1).

RG has pK_a values of 6.20 and 3.96 assigning to aromatic amino and carboxylic groups, respectively [24]. According to the study of Mandic and Gabelica [24], the molar absorption spectra of RG undergo hypsochromic and hypochromic shifts upon deprotonation of aromatic acid proton around pH 4.0, since the electrons of carboxylate anion are less capable to conjugate with the aromatic ring than electrons of undissociated carboxyl group. This means that under the optimum conditions (in presence of 0.1 M H_2SO_4) the carboxylic group presents in the undissociated from resulting in increase of intensity of the band centered on 243 nm [24], and consequently, the fluorescence intensity increased.

Effect of Diluting Solvent

The effect of different diluting solvents on the RFI of RG was investigated using water, methanol, acetone, acetonitrile and n-propanol. It was found that methanol was the best solvent for dilution as it gave the highest RFI and the lowest

Table 1 Effect of different buffers and acids on RFI of RG (0.4 μg mL^{-1})

Medium	RFI
Acetate buffer pH 3.7	30
Acetate buffer pH 5.0	50
Borate buffer pH 7.5	46
Borate buffer pH 8.5	27
0.1 M HNO_3	36
0.1 M acetic acid	103
0.1 M HCl	299
0.1 M H_2SO_4	435

blank reading. The RFI decreased greatly upon using water, n-propanol or acetonitrile for dilution, on the other hand, the RFI completely quenched upon using acetone as diluting solvent (Fig. 3).

Effect of the Ratio of 0.1 M H_2SO_4: Methanol

The effect of the ratio of 0.1 M H_2SO_4: methanol (v/v) was carefully studied in order to achieve the maximum RFI. It was found that maximum RFI was obtained when the ratio was 3:7 (0.1 M H_2SO_4: methanol, v/v) as shown in Table 2.

Table 2 Effect of the ratio of 0.1 M H_2SO_4: methanol on RFI of RG (0.4 μg mL^{-1})

Ratio of 0.1 M H_2SO_4: methanol (v/v)	RFI
1:9	414
2:8	429
3:7	435
4:6	413
5:5	380
6:4	346
7:3	291
8:2	265
9:1	216

Effect of Organized Media

The effect of different organized media on the RFI of RG was studied in order to see if a significant increase in fluorescence intensity could be achieved. Different surfactants such as SDS, CTAB, and tween-80 and different macromolecules including β-CD, HP-β-CD and methyl cellulose were tested by addition of 1 mL of 0.5 % aqueous solution to the drug. It was obvious that no significant increase in the RFI of RG was achieved using any of the studied organized media. So, the present work was carried out in absence of organized media.

Effect of Time

The effect of time on the RFI of RG was also studied. It was found that the fluorescence intensity was immediately developed and remained stable for more than two hours.

Effect of Temperature

Another factor that affects the fluorescence intensity is temperature. The effect of temperature was studied in the range of 40–100 °C in thermostatically controlled water bath. It was found that increasing the temperature resulted in decrease in the RFI of RG. This effect can be explained by higher external conversion as the temperature increases, facilitating non-radiative deactivation of excited singlet state [25]. Therefore, all the measurements were carried out at room temperature.

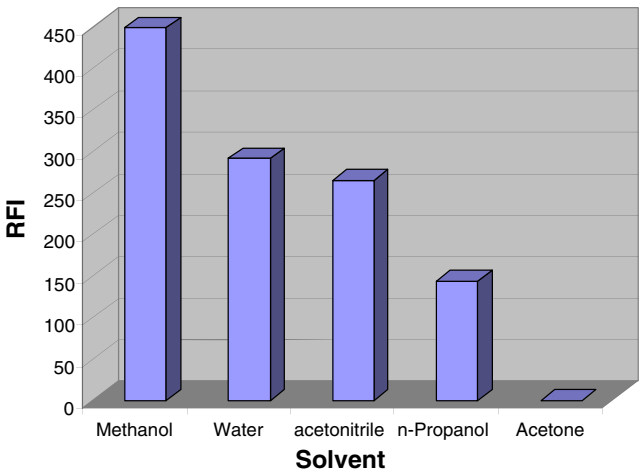


Fig. 3 Effect of different diluting solvents on RFI of RG (0.4 μg mL^{-1})

Validation of the Method

The proposed method was validated according to ICH guidelines [26] by testing linearity, range, accuracy, limit of quantification (LOQ), limit of detection (LOD), specificity, precision and robustness.

Linearity and Range

The regression plot showed a linear dependence of RFI on drug concentration over the range of 0.02–0.5 μg/mL. Statistical evaluation [27] of the regression line for RG regarding standard deviation of the residuals ($S_{y/x}$), standard deviation of the intercept (S_a) and standard deviation of the slope (S_b) is given in Table 3. The small values of the figures points out to low scattering of the points around the calibration graph and thus indicating the high accuracy and high precision of the method.

Accuracy

The accuracy of an analytical method is defined as the similarity of the results obtained by this method to the true values [26]. To test the accuracy of the proposed method it was applied to the determination of pure samples of RG over the concentration range of 0.02–0.50 μg mL^{-1}. The results obtained were in good agreement with those obtained using the official HPLC method [1]. Using student *t*-test and variance ratio *F*-test revealed no significant difference between the performance of the two methods regarding accuracy and precision, respectively (Table 4).

Table 3 Performance data for the proposed spectrofluorimetric method

Parameter	Results
Concentration range (μg mL^{-1})	0.02–0.50
Limit of detection (LOD) (ng mL^{-1})	6.0
Limit of quantification (LOQ) (ng mL^{-1})	18.0
Correlation coefficient (r)	0.9999
Slope	1077.53
Intercept	7.28
Standard deviation of the residuals ($S_{y/x}$)	2.62
Standard deviation of the intercept (S_a)	1.97
Standard deviation of the slope (S_b)	6.50
% RSD	0.82
% Error (% RSD/√n)	0.37

Limit of Quantification (LOQ) and Limit of Detection (LOD)

LOQ was determined according to ICH Q2 (R1) recommendation [26] by establishing the lowest amount of analyte which can be quantitatively determined with suitable precision and accuracy. LOD was also determined by evaluating the lowest amount of analyte which can be detected but not necessarily quantitated as exact values. The results are summarized in Table 3.

LOD and LOQ were calculated according to the following equations [26]:

$$LOQ = 10S_a/b$$

$$LOD = 3.3S_a/b$$

Where, S_a is the standard deviation of the intercept of regression line and b is the slope of the regression line.

Precision

Repeatability Repeatability was evaluated through replicate analysis of different concentrations of the drug. Each sample was analyzed three successive times. The repeatability, expressed by SD, % RSD and % Error values, was fairly acceptable (Table 5).

Table 5 Precision data for the proposed method of determination of RG in pure form

Conc. (μg mL^{-1})	% Found	% RSD	% Error
Repeatability			
0.10	97.60±1.52	1.56	0.90
0.20	98.71±1.39	1.41	0.81
0.40	99.98±1.04	1.04	0.60
Intermediate precision			
0.10	101.2±1.25	1.24	0.71
0.20	101.22±1.33	1.31	0.76
0.40	98.16±1.43	1.45	0.84

Intermediate Precision Intermediate precision was evaluated through replicate analysis of three samples of the drug on three successive days. The results indicated the high precision of the proposed method (Table 5).

Robustness

The robustness of the proposed method is demonstrated by the constancy of RFI of RG with the deliberate minor change in the volume of 0.1 M H_2SO_4 (3.0±0.2). This minor change that may take place during the experimental operation did not greatly affect the RFI of RG.

Specificity

The specificity of the proposed procedure was proven by its ability to determine RG in its tablets confirming that there was no interference by tablet excipients and additives; such as microcrystalline cellulose, calcium hydrogen phosphate, anhydrous maize starch, amberlite, povidone, glycerol, magnesium stearate, meglumine, poloxamer, iron oxide

Table 4 Application of the proposed and comparison methods to the determination of RG in pure form

Parameter	Proposed method			Reference method [1]	
	Conc. taken (μg mL^{-1})	Conc. found (μg mL^{-1})	Found %	Conc. taken (μg mL^{-1})	% Found
Pure form	0.02	0.020	100.00	5.00	99.98
	0.10	0.099	99.00	8.00	100.56
	0.20	0.202	101.00	10.00	100.01
	0.40	0.397	99.25		
	0.50	0.502	100.40		
$\bar{x} \pm SD$		99.93±0.82		100.18±0.33	
t		0.498 (2.447)*			
F		6.325(19.247)*			

*Values between parentheses are the tabulated t and F values at p=0.05 [27]

Table 6 Application of the proposed and reference methods to the determination of RG in tablets

Pharmaceutical preparation	Proposed method		Reference method [1]	
	Conc. taken (μg mL^{-1})	% Found	Conc. taken (μg mL^{-1})	% Found
Novonorm® tablets (0.5 mg RG/tablet)	0.10	97.77	5.00	98.70
	0.20	97.50	8.00	97.88
	0.40	99.14	10.00	98.21
$\bar{x} \pm$ SD		98.14±0.88		98.26±0.41
Nominal Content (mg RG/tab.)		0.491		
t		0.226 (2.776)*		
F		4.542 (19.00)*		
Repaglid® tablets (1 mg RG/tablet)	0.10	98.99	5.00	100.55
	0.20	101.26	8.00	98.70
	0.40	101.08	10.00	100.02
$\bar{x} \pm$ SD		100.44±1.26		99.76±0.95
Nominal Content (mg RG/tab.)		1.004		
t		0.752 (2.776)*		
F		1.754 (19.00)*		

*Values between parentheses are the tabulated t and F values at p=0.05 [27]

and yellow (E172) (for 1 mg Repaglide® tablet) [28]. These matrix components did not interfere with the proposed method (Table 6).

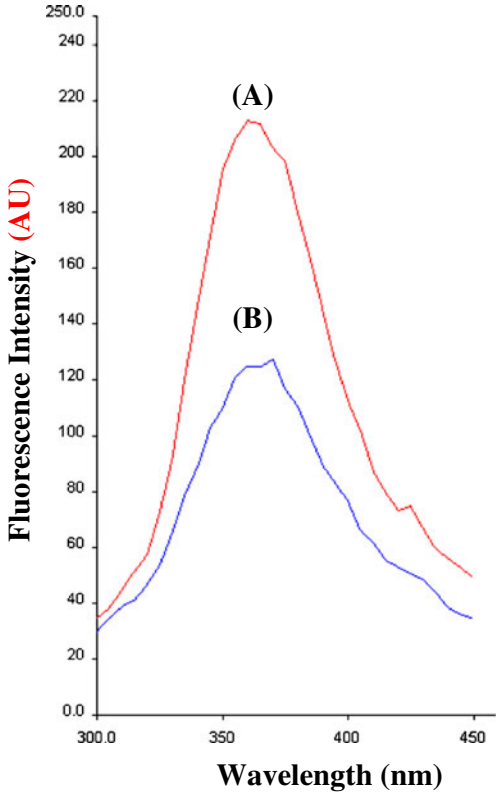


Fig. 4 Emission spectra of: (**A**): RG (0.1 μg mL^{-1}) in 0.1 M H_2SO_4: methanol system. (**B**): Laboratory-prepared mixture containing RG (0.1 μg mL^{-1})/metformin (50 μg mL^{-1}) in 0.1 M H_2SO_4: methanol system

Applications

Pharmaceutical Application

The proposed method was applied to the determination of RG in commercially available tablets (Table 6). The average percentages found of different concentrations were based on the average of three replicate determinations. The results shown in Table 6 are in good agreement with those obtained with the official HPLC method [1].

RG is also co-formulated with metformin in Prandimet® tablets in the ratios of 1:500 and 2:500 (RG: metformin, respectively). A trial was performed to determine RG in laboratory-prepared mixture with metformin, in the same ratio as in the tablets, as a preliminary step to extend the method for

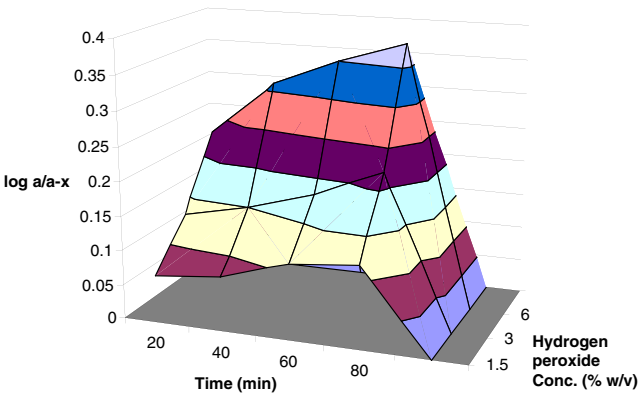


Fig. 5 Three-dimensional plot showing the effect of heating times with different concentrations of hydrogen peroxide at 80 °C on RG (0.4 μg mL^{-1})

Table 7 Results of the oxidative degradation study of RG

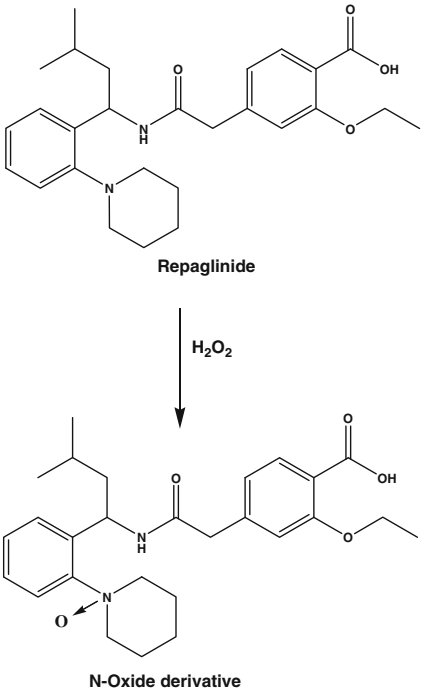
Conc. of H_2O_2 (%w/v)	Reaction rate constant (K, min^{-1})	Half life time ($t_{½}$, min)
1.5	2.0×10^{-3}	346
3.0	3.5×10^{-3}	198
6.0	5.7×10^{-3}	121

determination of RG in co-formulated tablets. It was observed that the fluorescence of RG was greatly quenched in presence of metformin in such high concentration (500 or 250 folds) (Fig. 4). This may be due to deactivation of the lowest excited singlet state of RG by interaction with metformin in solution. The mechanisms of quenching may entail internal conversion, electron transfer or photodissociation as modes of deactivation of the excited analyte [23].

Application of the Proposed Method to Study the Oxidative Degradation of RG

Significant degradation of RG was observed under oxidative conditions. The oxidative treatment of RG with H_2O_2 solution was accompanied by a gradual decrease in the RFI. Upon heating in a thermostatically controlled water bath at 80 °C for 80 min, 60 % degradation of the drug was observed. The degradation was found to be temperature dependent (Fig. 5). The rate of degradation of the drug upon addition of hydrogen peroxide was determined kinetically. The apparent first order degradation rate constants and half-life times were calculated (Table 7).

Scheme 1 represents a proposal for the expected oxidative degradation pathway of RG. By analogy to previous reports [29, 30], it is proposed that the main pathway of oxidative degradation of RG is via the formation of N-oxide derivative.



Scheme 1 Proposal for the oxidative degradation pathway of RG

Limitation

The proposed method was found to be unable to detect alkaline or acidic degradation of RG. Although it is expected that RG probably undergoes hydrolysis of its amide linkage when subjected to acidic or alkaline treatments. This may be explained on the basis that the degradation products are fluorescents since the cleavage of the amide linkage did not affect the moieties that contribute to fluorescence.

Conclusion

The developed spectrofluorimetric method represents a rapid and highly sensitive method for stability-indicating assay of RG in different tablet formulations. Based on problems encountered from post publications, the present study has served to develop a simple, satisfactory, rapid, highly sensitive and fully validated assay method of RG in pharmaceutical preparations.

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