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Simple, Direct and Stability-Indicating UV Spectrophotometric Assay of Pioglitazone Hydrochloride in Pharmaceuticals

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Abstract

Pioglitazone hydrochloride (PGH) is an antihyperglycemic agent used in the treatment of type-2 diabetes mellitus. A simple and straight forward UV-spectrophotometric method is presented for the determination of PGH in bulk drug and tablets by measuring the absorbance of drug solution in 0.1M H_2SO_4 at 269 nm. A plot of absorbance versus concentration obeyed Beer's law over 2–36 µg ml^{-1} concentration range (r = 0.9981) with a molar absorptivity of 8.85 × 10^3 l mol^{-1} cm^{-1}. The limits of detection (LOD) and quantification (LOQ) were calculated to be 0.65 and 1.98 µg ml^{-1}, respectively. Intraday accuracy and precision, expressed as %RE and %RSD, were upto 2.0 and upto1.45, respectively; whereas the respective interday values were upto 2.05 and upto 1.36. The method was validated for robustness and ruggedness as well as selectivity. The method, when applied to the determination of the active ingredient in tablets, yielded percent found values of 98.69±1.18 and 101.2±1.25 for two brands of tablets. Accuracy of the method was checked by recovery study via standard addition procedure, and found to be highly satisfactory. To determine the stability-indicating ability of the developed method, the drug was subjected to acid-, alkali-, peroxide-, heat- and light-induced forced degradation, and determined subsequently by the recommended procedure. Results indicated that the drug was vulnerable to alkali-induced stress condition, but remained intact under other stress conditions.

Keywords: *Pioglitazone, determination, UV-spectrophotometry, pharmaceuticals, stability-indicating*

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INTRODUCTION

Pioglitazone hydrochloride (PGH), chemically known as 5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl] -2,4-thiazolidinedione monohydrochloride (Figure 1), is an oral antihyperglycemic agent used to treat type-2 diabetes [1]. It functions by reducing peripheral and hepatic resistance to insulin, resulting in increased insulin dependent glucose disposal and decreased hepatic glucose output [2, 3]. Considering its therapeutic use, several methods have been developed for its determination in pharmaceuticals and body fluids, which have been recently reviewed by Kumar *et al*. [4]. Methods based on diverse techniques such as high-performance liquid chromatography [5–15], high-performance thin layer chromatography [16–21], ultra-performance liquid chromatography [22] and visible spectrophotometry [23, 24], are found in the literature for the determination of PGH in pharmaceuticals.

UV-spectrophotometry has been widely used for the determination of PGH in pharmaceuticals. There are two reports [25, 26] dealing with the direct methods in which the absorbance of the drug solution in 0.1M HCl was measured at 269 nm. Shakya and Singh [27] determined the drug in tablets by measuring the absorbance of the tablet extract in phosphate buffer of pH 7.4 at 238 nm. By measuring the absorbance of PGH in ethanol at 224.4 nm, Ali *et al*. [28] have devised a method for the drug in bulk and dosage forms. A mixture of ethanol–methanol–water was used as the diluent for the assay of the drug in

which the absorbance was measured at 267 nm [23]. Sunitha *et al.* [29] developed a second derivative method in which the absorbance in methanol was measured at 268 nm. The method was applicable for 10–50 µg ml^{-1} PGH. Apart from the above, different variants of UV-spectrophotometry were applied to the determination of PGH when present along with other drugs [30–42] in combined dosage forms.

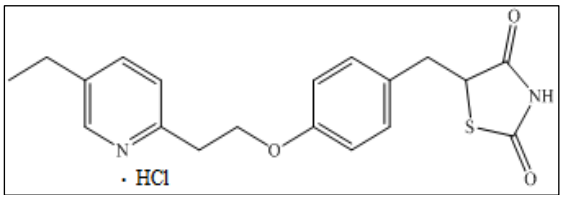


Fig. 1: *Structure of PGH.*

Chemical stability of pharmaceutical molecules is a matter of concern as it affects the safety and efficacy of the drug product. The United States Food and Drugs Administration (USFDA) [43] and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [44] guidance states the requirement of stability testing data to understand how the quality of drug substance and drug product changes with time under the influence of various environmental factors. Knowledge of the stability of the molecule helps in selecting proper formulation and package as well as providing proper storage conditions and shelf life, which is essential for the regulatory documentation.

Despite the availability of abundant literature on the assay of PGH in pharmaceuticals [5–42], none of the reported methods is stability-indicating. Hence, the present paper describes a simple, rapid and sensitive UV-spectrophotometric method, which employs 0.1 M H_2SO_4 as diluent for quantification of PGH. Drug after forced degradation was also assayed following the recommended procedure and the method was found to be stability-indicating, thereby fulfilling the strongly felt need for a stability-indicating assay of PGH. Because of its sensitivity and selectivity, the method was applied to the determination of PGH in spiked urine, with no interference from endogenous substances.

MATERIALS AND METHODS

Apparatus

Shimadzu Pharmaspec 1700 UV/Visible double beam spectrophotometer provided with matched 1-cm quartz cells (Hyderabad, India) was used for all absorbance measurements.

Reagents and Materials

All chemicals and reagents used were of analytical reagent grade. Double distilled water was used throughout the investigation. A 0.1M sulphuric acid was prepared by appropriate dilution of concentrated acid (S.D. Fine Chem., Mumbai, India, sp. gr. 1.82) with water and standardised. Hydrochloric acid (HCl, 0.1M), was prepared by diluting 0.9 ml of concentrated acid (Merck, Mumbai, India) to 100 ml with water. Sodium hydroxide (NaOH, 0.1M), was prepared by dissolving 0.4 g of pellets (Merck, Mumbai, India) in 100 ml of water. Hydrogen peroxide (H_2O_2, 5% v/v), was prepared by diluting 9 ml of the commercially available 30% reagent (Qualigens Ltd., India) to 50 ml with water.

Preparation of Standard PGH Solution

Pure sample of PGH was kindly supplied by Glenmark Pharmaceuticals, Mumbai, India, as gift. A stock standard drug solution equivalent to 400 µg ml^{-1} PGH was prepared by dissolving the required quantity of pure drug in 0.1M H_2SO_4 and diluted to 40 µg ml^{-1} with the same solvent.

PGH containing tablets: Neoglit-30 (30 mg) (Novus Life Sciences Private Limited, Mumbai, India), Oglo-15 (15 mg) (Panacea Biotech., Mumbai, India) were procured from the local market.

Assay Procedures

Procedure for Bulk Drug

Preparation of Calibration Graph

Into a series of 10 ml calibration flasks, aliquots of 40 µg ml^{-1} PGH solution equivalent to 2.0–36.0 µg ml^{-1} PGH were transferred and volume was made up to mark with 0.1M H_2SO_4. After mixing the contents, the absorbance of each solution was measured at 269 nm *versus* 0.1M H_2SO_4.

The calibration curve was constructed by plotting the absorbance *versus* concentration of the drug and unknown concentration was computed from the regression equation derived using Beer's law data.

Procedure for Tablets

Twenty tablets were weighed and pulverized. A quantity of tablet powder containing 40 mg of PGH was transferred into a 100 ml standard flask. The content was shaken well with about 50 ml of 0.1M H_2SO_4 for 20 min. The mixture was diluted to the mark with the same solvent. It was filtered using Whatmann No 42 filter paper. First 10 ml portion of the filtrate was discarded and suitable aliquot (5 ml) was subjected to analysis after dilution to 40 µg ml^{-1} level, following the procedure described earlier.

Procedure for Placebo Blank and Synthetic Mixture

A placebo blank containing starch (10 mg), acacia (15 mg), hydroxyl cellulose (10 mg), sodium citrate (10 mg), talc (20 mg), magnesium stearate (15 mg) and sodium alginate (10 mg) was prepared by homogeneous mixing. About 20 mg of placebo was taken, its solution prepared as described under 'procedure for tablets' and then subjected to analysis. To 20 mg placebo blank, 20 mg of PGH was added and homogenized, and 50 ml of solution prepared as described under 'procedure for tablets'. A convenient aliquot, say 5 ml was then subjected to analysis following the procedure described above, after dilution to 40 µg ml^{-1}.

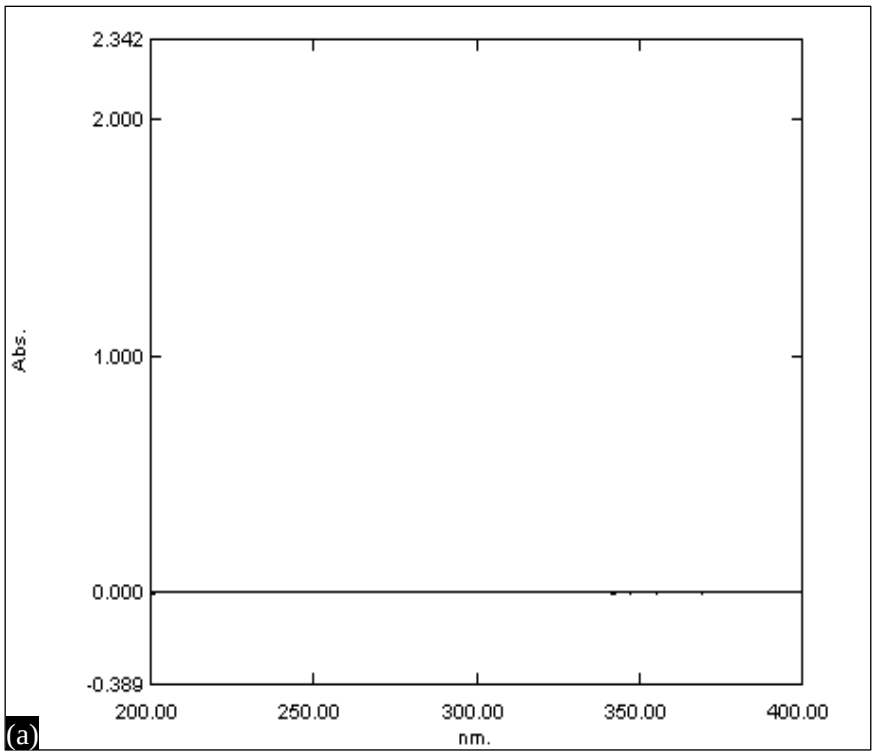
Procedure for Forced Degradation

A 500 µg ml^{-1} PGH solution was prepared in 0.1 M H_2SO_4. About 2 ml of this solution was accurately transferred into three separate 50 ml volumetric flasks; and added 5 ml of 0.1M HCl, 0.1 M NaOH or 5% H_2O_2. The flasks were heated in water bath maintained at 80 °C for 2 h. After cooling to lab temperature acid/base was neutralised with 5 ml of 0.1M NaOH or 0.1M HCl as the case may be, and the mixture was diluted to the mark with 0.1M H_2SO_4 and absorption spectrum of each solution was recorded. For thermal degradation, solid sample was placed in an oven at 80 °C for 3 h, whereas the same was exposed to 1.2 million lux hours in a photo stability chamber for 3 h, for photo degradation. Postexposure to heat or light, solid sample was used to prepare 20 µg ml^{-1} solution in 0.1 M H_2SO_4 for recording the absorption spectrum.

RESULTS AND DISCUSSION

Spectral Characteristics

PGH solution in 0.1M H_2SO_4 exhibited an absorption peak at 269 nm (Figure 2) and the absorbance at this wavelength was found to be linearly dependent upon the concentration of drug. The corresponding blank solution showed negligible absorbance. Therefore this wavelength was used as analytical wavelength throughout the investigation.



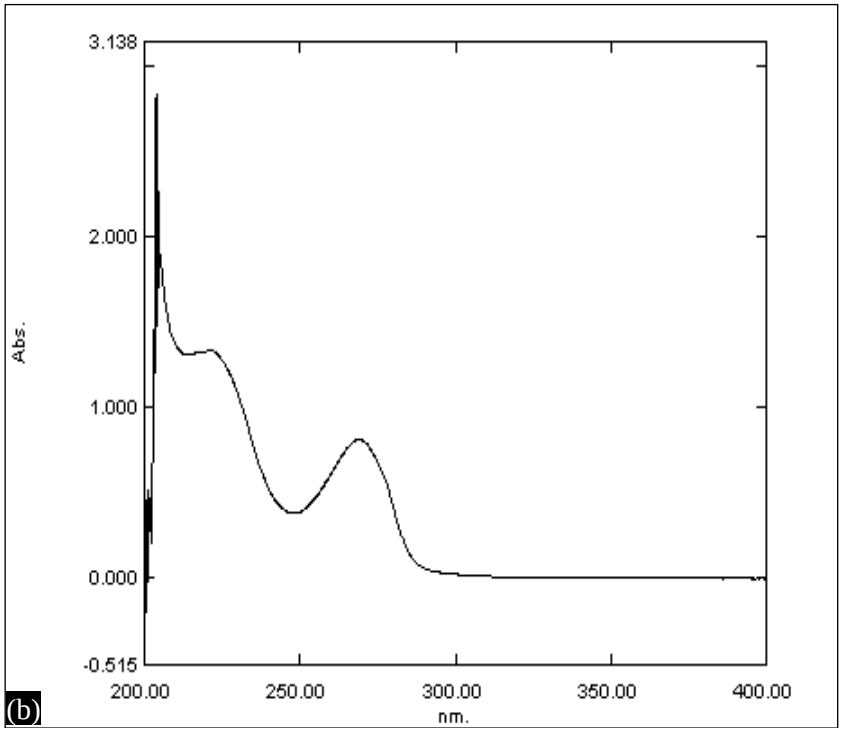


Fig. 2: *Absorption Spectra of: a) 0.1M H_2SO_4 blank; b) PGH in 0.1M H_2SO_4 (20 µg ml^{-1}).*

Method Validation

Linearity and Sensitivity

A linear correlation (Figure 3) was found between absorbance at λ max and concentration of PGH in the range given in Table 1. Regression analysis of the Beer's law data using the method of least squares was made to evaluate the slope (m), intercept (b) and correlation coefficient (r), and the values are presented in Table 1.

Table 1: *Sensitivity and Regression Parameters.*

Parameter	Value
λmax, nm	269
Linear range, µg ml^{-1}	2.0–36.0
Molar absorptivity(ε), L mol^{-1} cm^{-1}	8.85×10^3
Sandell sensitivity*, µg cm^{-2}	0.0403
Limit of detection (LOD), µg ml^{-1}	0.65
Limit of quantification (LOQ), µg ml^{-1}	1.98
Regression equation, y*	
Intercept (b)	0.0412
Slope (m)	0.0279
Standard deviation of b (S_b)	0.0017
Standard deviation of m (S_m)	0.0008
Regression coefficient (r)	0.9981

**y=mx+b, where y is the absorbance, x concentration in µg mL^{-1}, b intercept and m slope.*

The optical characteristics such as Beer's law limits, molar absorptivity and Sandell sensitivity values are also given in Table 1. Limits of detection (LOD) and limits of quantification (LOQ), calculated as per the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, are also given in Table 1.

Accuracy and Precision

Pure drug solution at three levels was analysed seven times during the same day and on five consecutive days to evaluate intraday and interday precision and accuracy of the method. The results of this study presented in Table 2 indicate fairly good precision and accuracy of the method.

Table 2: *Results of Intraday and Interday Accuracy and Precision Study.*

PGH taken, µg ml^{-1}	Intraday accuracy and precision (n=7)			Interday accuracy and precision (n=5)		
	PGH Found, µg ml^{-1}	%RE	%RSD	PGH Found, µg ml^{-1}	%RE	%RSD
10	10.15	1.50	1.05	10.17	1.70	1.36
20	20.40	2.00	1.23	20.41	2.05	1.09
30	29.47	1.76	1.45	30.36	1.20	1.27

%RE-Percent relative error. %RSD-Relative standard deviation.

Robustness and Ruggedness

The robustness of the method was evaluated by measuring the absorbance at three different wavelengths (λmax and λmax±1 nm) whereas the method ruggedness was checked by getting the analysis done by three different analysts and also using three different cuvettes by a single analyst. Intermediate precision values (%RSD) were in the range of 0.98–1.90% indicating acceptable robustness and ruggedness. These results are presented in Table 3.

Table 3: *Results of Robustness and Ruggedness Study.*

PGH taken, µg ml^{-1}	Method robustness* %RSD Wavelength, nm*	Method ruggedness	
		Interanalysts %RSD, (n=3)	Intercuvettes %RSD, (n=3)
10	1.45	1.09	1.90
20	1.57	1.04	0.98
30	0.92	1.79	1.83

*%RSD-Relative standard deviation. *Wavelengths were 269, 270 and 271 nm.*

Selectivity

A systematic study was performed to determine the effect of matrix on the assay by analyzing the placebo blank and synthetic mixture containing PGH. The absorbance of the placebo solution was almost equal to the absorbance of the blank which revealed no interference. The absorbances recorded for synthetic mixture solution containing 10, 20 and 30 µg ml^{-1} PGH were nearly the same as those obtained for pure PGH solution of identical concentrations. This unequivocally demonstrated the noninterference of the inactive ingredients in the assay of PGH. Further, the slope of the calibration plot prepared from the synthetic mixture solution was about the same as that prepared from pure PGH solution. Percent recoveries of PGH ranged from 96.70 to 102.4 with standard deviation values <1.6%, complementing the findings on the placebo blank.

Application to Tablets

The developed method was successfully applied to the determination of PGH in its tablets. The same batch tablets were also assayed by a published HPLC method [4] for comparison and the results obtained by the proposed method agreed well with those of reference method and with the label claim. The results were evaluated statistically by a Student's t-test for accuracy and by a variance ratio F-test for precision with those of the reference method at 95% confidence level as summarized in Table 4. The results showed that the calculated t- and F-values did not exceed the tabulated values inferring that proposed method is as accurate and precise as the reference method.

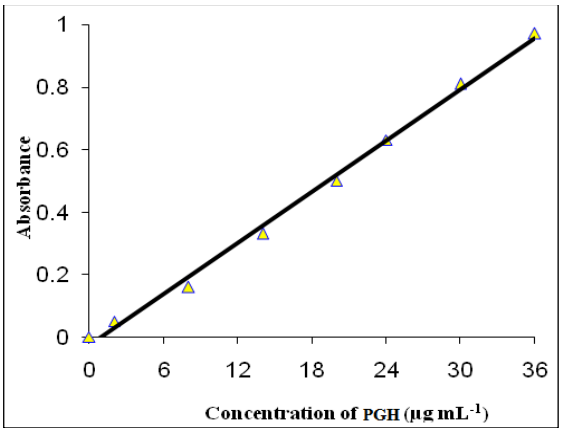


Fig. 3: *Calibration Curve.*

Table 4: *Results of Analysis of Tablets by the Proposed Method and Statistical Comparison of the Results with the Reference Method.*

Tablet brand name	Nominal amount, (mg/tablet)	% Found* (Percent label claim± SD	
		Reference method	Proposed method
Oglo-15	15	97.66±0.86	98.69±1.08 t = 1.58 F = 1.58
Neoglit-30	30	98.99±0.72	101.2±1.25 t = 3.43 F = 3.01

**Average of five determinations*
Tabulated t-value at the 95% confidence level is 2.77.
Tabulated F-value at the 95% confidence level is 6.39.

Accuracy by Recovery Study

The recovery test was done by spiking the preanalyzed tablet powder with pure PGH at three different levels (50%, 100% and 150% of the content present in the tablet powder (taken) and the total was determined by the proposed method. Each test was repeated three times. The recovery percentage values ranged between 97.42% and 103.4% with relative standard deviation in the range 0.89–1.62%. The results of this study shown in Table 5 reveal the accuracy as well as the selectivity of the method.

Table 5: *Results of Recovery Study Using Standard Addition Method.*

Tablet brand name	PGH in tablet, µg ml^{-1}	Pure PGH added, µg ml^{-1}	Total PGH found, µg ml^{-1}	Pure PGH recovered (Percent±SD*)
Oglo-15	9.87	5.0	14.48	97.42±1.50
	9.87	10.0	19.68	99.06±1.06
	9.87	15.0	25.72	103.4±1.62
Neoglit-30	10.12	5.0	15.38	101.7±1.19
	10.12	10.0	20.74	103.1±0.89
	10.12	15.0	24.71	98.38±1.03

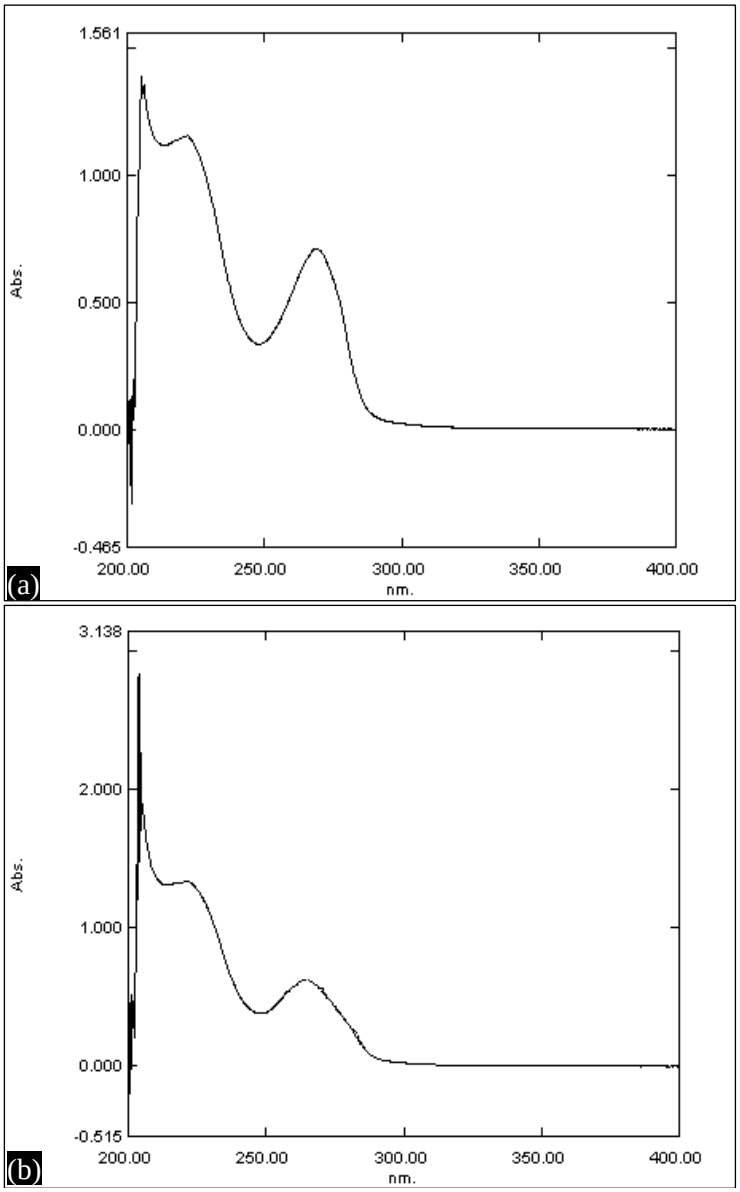
**Mean value of three determinations.*

Results of Forced Degradation Study

The extent of degradation was evaluated based on the comparison of the UV- spectra of "stressed PGH samples" with that of the "pure drug solution". The UV spectra of 20 µg ml^{-1} PGH solution subjecting to acid hydrolysis, oxidation, photolytic and thermal stress conditions showed no significant difference relative to spectrum of pure drug solution, which indicated that PGH does not undergo degradation under these stressed conditions but slight degradation was observed in alkali-induced stressed conditions (Figure 4). The results of this study are compiled in Table 6.

Table 6: *Results of Degradation Study.*

Stress condition	% Degradation*
Acid hydrolysis	No degradation
Base hydrolysis	20.3
Oxidation	No degradation
Thermal (105 °C, 3 h)	No degradation
Photolytic (1.2 million lux h)	No degradation



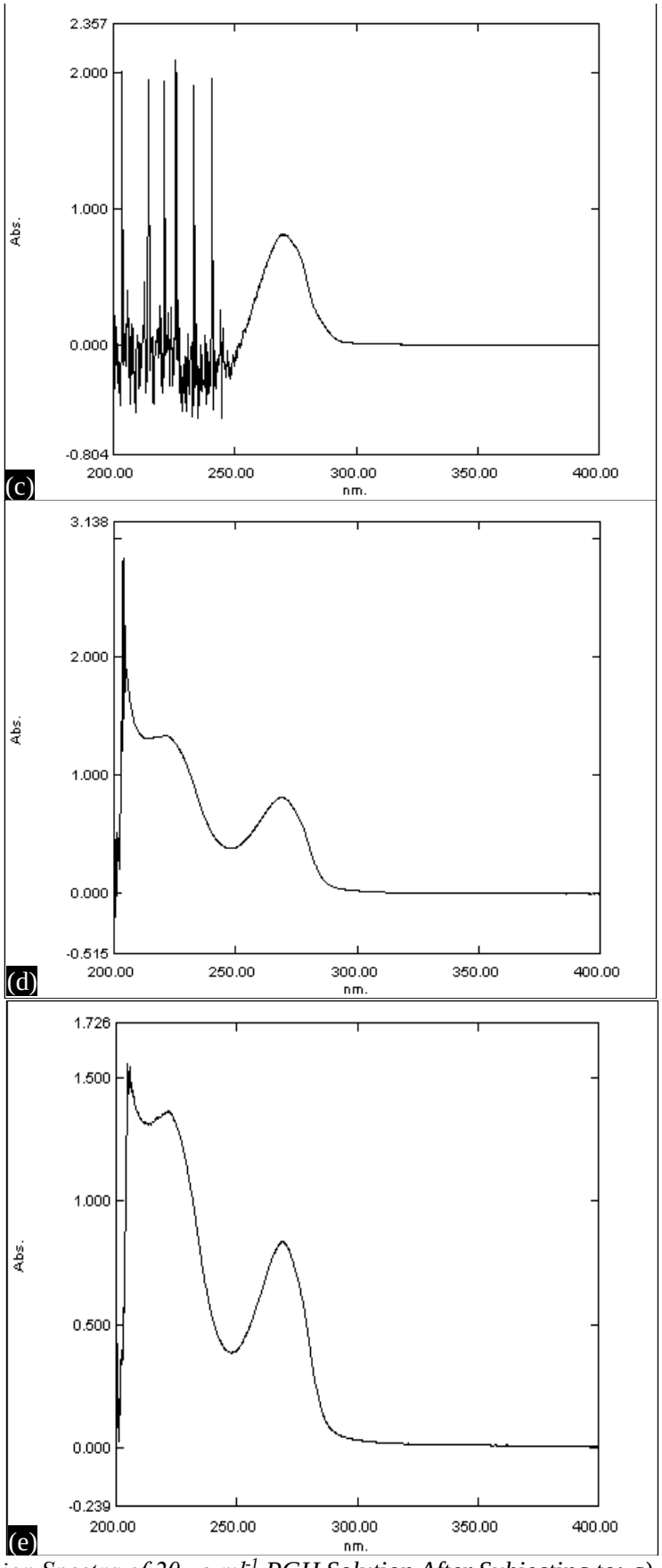


Fig. 4: *UV Absorption Spectra of 20 µg ml^{-1} PGH Solution After Subjecting to: a) Acid Hydrolysis; b) Base Hydrolysis; c) Oxidation; d) Photolytic; and e) Heat.*

Table 7: *Comparison of Performance Characteristics of Proposed Method with Those of Existing UV Spectrophotometric Methods.*

Sl No.	Diluent/s	Methodology	Linear range (µg ml^{-1})	Molar absorptivity, € (L mol^{-1} cm^{-1})	Remarks	Reference
1	Ethanol–methanol–water	Absorbance measured in ethanol– methanol–water at 267 nm	2.5–20.0	NA	Mixed solvents system and narrow linear range	23
2	0.1M HCl	Absorbance measured at 269 nm	5–30	NA	Narrow linear range	25
3	0.1MHCl	Absorbance measured at 269 nm	10–70	9.601×10^4	Narrow linear range	26
4	Phosphate buffer	Absorbance of tablet extract measured at 238 nm in phosphate buffer of pH 7.4	10–50	NA	Less sensitive, narrow linear dynamic range	27
5	Ethanol	Absorbance measured at 224.4 nm	5–25	1.45×10^4	Narrow linear dynamic range, use of organic solvent	28
6	Methanol	Absorbance measured at 268 nm	10–50	NA	Narrow linear range, use of organic solvent	29
7	0.1 M H_2SO_4	Measurement of absorbance of 269	2.0–36.0	8.85×10^3	Sensitive, wide dynamic linear range, uses a single solvent, no organic solvent used; stability-indicating	Present work

CONCLUSIONS

A rapid, straight forward, convenient and sensitive method, which is stability indicating, was developed for the determination of PGH in pharmaceuticals, and validated as per the ICH guidelines. The method enables to determine the drug over a wide linear dynamic range as compared to many previously reported methods as indicated in Table 7. The present method uses a single solvent system in contrast to mixed-solvent or buffer systems employed previously. The method also enables to determine the vulnerability of drug to various stress conditions. The method is cost-effective as compared to most reported methods, which use organic solvents as diluents.

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