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Development and validation of novel stability indicating RP-HPLC method for the determination of assay of voriconazole in pharmaceutical products

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***Abstract*---**For the determination of the assay of voriconazole in bulk and in pharmaceutical dosage forms, a novel stability indicating RP-HPLC method was designed and validated, exhibiting a very low run time. The stability-indicating nature of the approach is supported by the fact that it is unique, quick, precise, accurate, and capable of isolating the voriconazole peak from any contaminating or degrading components. Isocratic elution on a 100 mm x 4.6 mm, 3µm agilent C18 column at 45°C and a UV detection wavelength of 256 nm constitutes the analytical procedure at at a flow rate of 1.0 mL/min. After injecting 20µL of voriconazole sample, the elution peak occurred at 3.5 minutes, and the entire run time was 15 minutes. Between 98% and 102% was a reasonable range for the percentage of recovery. It was determined that the method's RSD for precision and accuracy was less than 2%. The method has been verified for routine analysis of voriconazole in bulk materials and its formulations according to the standards established by the International Conference on Harmonization (ICH).

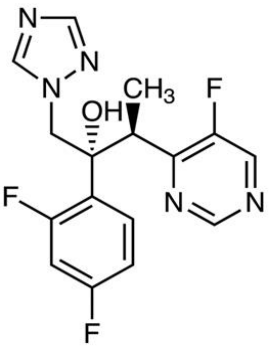
***Keywords*---**RP-HPLC, isocratic, stability-indicating assay, voriconazole.

Introduction

Chemically, voriconazole (2R,3S) -2-(2,4-difluorophenyl) -3-(5-fluoro-4-pyrimidinyl)-1-(1H-1,2,4triazol-1-yl) -2-butanol. VCZ is used to treat aspergillosis (lung fungal infection), candidemia (blood fungal infection), candidiasis (candida esophagitis), and other fungal infections (infections in the skin, stomach, kidney, bladder or wounds). It inhibits CYP-dependent 14-alpha-sterol demethylase, damaging the cell membrane and stopping fungal growth [1VCZ has been demonstrated to be effective in vitro against a wide range of yeasts, as well as mould and dermatophyte isolates. It has a wide tissue distribution, including transport into the central nervous system, and is metabolised in the liver, making it suitable for oral or parenteral administration [2].

VCZ is official in the United States Pharmacopeia [3]. When it comes to analysing a large number of commercial batches simultaneously, the USP method of VCZ analysis has a serious flaw: it takes an extremely lengthy time to run. Furthermore, the reported procedures are not very exact and reliable in extracting the known contaminants and degradants from the VCZ peak in a timely manner. Few analytical methods have been published for the determination of VCZ in pure medication, pharmaceutical dosage forms, and biological materials utilising liquid Chromatography [4-16] either separately or in any combination. This study focuses on the creation and verification of an innovative, easy-to-use, quick, and trustworthy isocratic RP-HPLC technique with UV detection for the analysis of VCZ in bulk solution and in medicinal dosages. The new methodology was validated for its applicability in accordance with ICH recommendations [17] for the determination of VCZ in bulk solution and in pharmaceutical dosage forms.

The method development was initiated with different C18 columns like Inertsil ODS-3V (250 x 4.6mm, 5µm), Zodiac (250 x 4.6mm, 5µm), Devolosil (100 x 4.6mm, 3µm) and acetic acid and diortho phosphoric acid buffer with methanol as organic modifier in different ratios. The method development was conducted with different column temperature like 25°C, 30°C, 45°C and 50°C, and with different injection volume like 5µL, 10µL and 20µL. The structure of VCZ is represented in Fig.



Materials and Methods

Merck Company's Analytical Grade acetic acid, Diortho Phosphoric Acid, and HPLC Grade methanol (Mumbai, India) were utilised for study alongwith Milli-Q system-made water (Merck Millipore, Mumbai, India). The Typical Performance of Voriconazole (Ajanta Pharmaceutical Ltd. Mumbai, India). At Loba Chemie Pvt. Ltd. in Mumbai, India, we were able to acquire hydrochloric acid (AR), sodium hydroxide (AR), and hydrogen peroxide (AR). In order to treat the infection, voriconazole tablets were purchased at a drugstore. The study used a Systronic HPLC system SYS LC 138, which included a liquid pump, an Agilent Gradient System with a UV VIS Spectrophotometric detector, and a Rheodyne 7725i injector with a 20µl capacity loop. Agilent C18 (1004.6 mm) column was used for separation and quantification.

Chromatographic conditions

The mobile phase was prepared by mixing methanol and water in a ratio of 80:20 v/v. The mobile phase was filtered using 0.45 µm filter and degassed by ultrasonic vibrations prior to use. The flow rate was 1 ml/min. All determinations were performed at ambient temperature. An accurately weighed sample (10 mg) of voriconazole was transferred to a 10 ml volumetric flask and dissolved in methanol to obtain a solution of strength 1000 µg/ml. One millilitre of this solution was then transferred in 10 ml volumetric flask and made up the volume was made up to the mark with mobile phase. This gave the standard stock solution of 1000 µg/ml.

From the standard solution of voriconazole (1000 µg/ml), appropriate dilutions were prepared in mobile phase to get final concentrations in the range of 5-25 µg/ml. These standard solutions were analyzed in five replicates. The peak areas were plotted against concentration and the data was subjected to linear regression. The standard chromatogram of voriconazole is shown in fig. 1

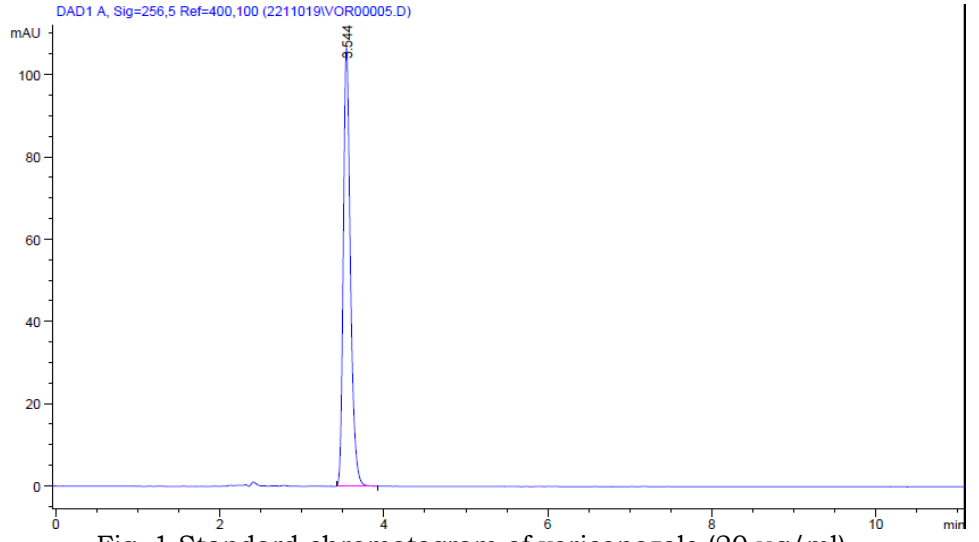


Fig. 1 Standard chromatogram of voriconazole (20 µg/ml)

RP-HPLC Assay procedure

Twenty 200-mg voriconazole tablets were weighed and powdered. After weighing out enough powder to make up 10 mg, it was transferred to an ultrasonic bath for 15 minutes in 5 ml of methanol in a 10 ml volumetric flask, and the volume was brought up to 10 ml with more methanol. No. 41 Whatmann filter paper was used to filter the solution. Concentrations between 5 and 25µg/ml were obtained by diluting the filtrate with the mobile phase. As a result of injecting the tablet sample solution, a chromatogram was obtained. An estimate of the voriconazole peak area was made. The amount of voriconazole in the sample was determined using the regression equations and peak regions. This led to the determination of the voriconazole dosage per tablet.

Method Validation

By injecting five different concentrations of the drug synthesised in the mobile phase between 5 and 25 µg/ml into the HPLC system and measuring the peak regions, we were able to determine the linearity of the approach. Inter- and intra-day variance analyses confirmed the reliability of the approach. The three medication concentrations were analysed three times a day in intraday experiments. Three separate medication concentrations were analysed over the course of three days in the inter day fluctuation investigations. Recovery trials confirmed the method's accuracy. Percentage recovery was determined after trials were conducted at 100%, 100%, and 120% of the original loss.

Individual analytical procedures each have a detection limit, which is the smallest amount of analyte in a sample that can be detected, but not necessarily quantified to an exact number. The quantitation limit of a given analytical method is defined as the smallest sample concentration of analyte that can be measured quantitatively with acceptable levels of accuracy and precision. Standard deviation of response and slope of calibration curve were used in the formula to derive these values.

The method's robustness was determined by performing the analysis while changing the mobile phase composition (methanol concentration was varied by ±1%) and the flow rate (flow rate was varied by ±0.05 ml/min), and observing the impact on the region of peak of interest and retention durations. Chromatographic analysis was performed on commonly used tablet excipients to look for any interfering peaks during the voriconazole retention time. The peak purity values provided by the UV VIS Spectrophotometric detector further proved the detector's specificity. Interference from the matrix's elements is not present if the value is greater than 900.

Forced degradation studies

1. For acidic conditions: To 7.5 ml of voriconazole stock solution Using a volumetric flask with a 25 ml capacity, we introduced 2.5 ml of 3 N HCl and then filled the rest of the way with mobile phase. For 150 minutes, the volumetric flask was maintained at room temperature. A total of 10 ml of solution was withdrawn from the flask every 30 minutes, neutralised, and

diluted with mobile phase. It was in a stable chromatographic environment that this solution was injected. For the blank, mix together in a 10 ml volumetric flask 0.5 ml of a 3 N HCl solution and 0.5 ml of a 0.1N NaOH solution with mobile phase.

2. For alkaline conditions: To 7.5 ml of voriconazole stock solution In a volumetric flask with a 25 ml capacity, 2.5 ml of 0.1N NaOH was introduced, and the rest of the volume was brought up with mobile phase. For 150 minutes, the volumetric flask was maintained at room temperature. The volume of this flask was brought up to 10 ml by removing 5 ml with a pipette after every 30 minutes, then neutralising it and diluting it with mobile phase. The chromatographic conditions were maintained during injection of this solution. For the blank, mix together in a 10 ml volumetric flask 0.5 ml of a 3 N HCl solution and 0.5 ml of a 0.1N NaOH solution with mobile phase.
3. For neutral conditions: The 5 ml of voriconazole stock solution was combined with 45 ml of water in a 100 ml round bottom flask and refluxed for 1 hour in a boiling water bath. Once the solution had finished refluxing, it was cooled to room temperature, topped off to 50 ml, and injected under stable chromatographic conditions.
4. For dry heat-induced degradation: The voriconazole sample was collected in a petri dish and then baked at 70 degrees for 48 hours. The aforementioned sample (10 ml) was prepared by dissolving 10 ml of it in methanol and diluting it to 10 ml with water. From here, the mobile phase was used to dilute the solution to the right concentration, and it was injected under stable chromatographic conditions.
5. For Oxidative degradation: In a 10 ml volumetric flask, 1.5 ml of voriconazole stock solution was mixed with 1 ml of 30% w/v H2O2 and the remaining space was filled with mobile phase. Temperature-controlled volumetric flask left at room temperature for 15 minutes. Overnight, 1 ml of 30% w/v H_2O_2 was stored at room temperature in a 10 ml volumetric flask to serve as the blank. The surplus of hydrogen peroxide was driven off by heating both solutions in a boiling water bath. After bringing the total volume to 10 ml with the mobile phase, we stabilised the chromatographic conditions before injecting.
6. For Photolytic degradation: Voriconazole samples were irradiated with a combined 1.2 million lux of light from a cool white fluorescent and near ultraviolet lamp in a photostability chamber. A ten milligramme sample was diluted with methanol to a level of 10 millilitres. From here, the mobile phase was used to dilute the solution to the right concentration, and it was injected under stable chromatographic conditions.

Accelerated stability study of tablets

Accelerated stability study were conducted for the pharmaceutical dose form under ICH recommendations at 40±2°/75±5% RH. In the current investigation, an accelerated stability analysis was performed on a sample of voriconazole tablets. The pills were kept in a stability chamber at 40 degrees Celsius and 75% relative humidity for 30 days. At the end of the first, second, third, and fourth weeks, ten tablets were taken away. After withdrawal, the tablets were crushed to yield a powder with a weight corresponding to 10 mg of voriconazole. This powder was

then added to 6 ml of methanol in a 10 ml volumetric flask, ultrasonically mixed for 15 minutes, and the remaining volume was filled with methanol to make up 10 ml. No. 41 Whatmann filter paper was used to filter the solution. The filtrate was diluted to a concentration of 15 µg/ml in the mobile phase. It was determined by injecting sample solutions of tablets into a chromatograph. The drug concentration peaks were measured.

Results and Discussion

The assay was calculated from the equation of regression line. The percentage of drug found in formulation was 99.81±0.21%. The results of analysis show that the amount of drug was in good agreement with the label claim of the formulation. The data obtained in the calibration experiments when subjected to linear-regression analysis showed a linear relationship between peak areas and concentrations in the range of 5-20 µg/ml for voriconazole. The equation of the regression line is y = 24537×+27363 (r^2 = 0.9923).

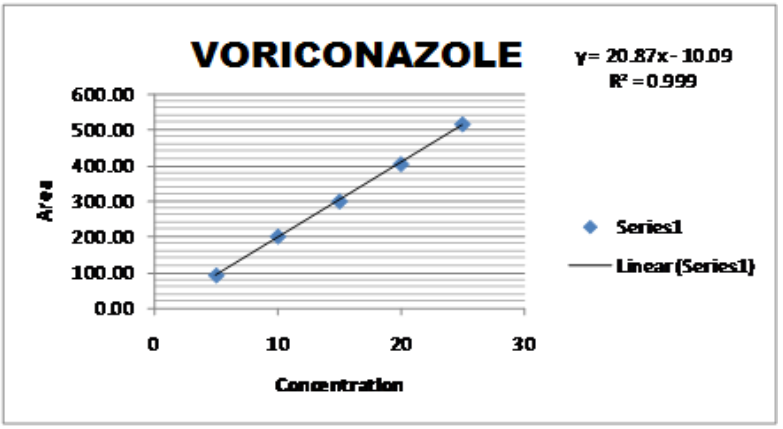


Fig. 2 Calibration curve of Voriconazole

The % RSD figures for intra-day and inter-day precision studies showed that the devised approach was accurate to within 2%. There were good recoveries (99.74%–100.39%) of the medication at each concentration of addition, demonstrating the reliability of the approach. The chromatographic study of commonly used tablet excipients revealed that voriconazole retained its original retention time without interference from any other peaks. The separation of the voriconazole peak from the peaks for degradation product was also indicative of the test's specificity. Using a UV VIS Spectrophotometric Detector, we were able to confirm the peak purity profile, demonstrating the detector's sensitivity. The sensitivity of the approach was demonstrated by the finding that both the LOD and LOQ for voriconazole were in the submicrogram range. In a robustness analysis, it was observed that the drug's peak regions varied by ±0.0093% and that its retention time varied by 8.231 to 8.268 min. Because the monitored parameters, such as the regions of peaks of interest and retention duration, were not significantly impacted by checking the parameters by adjusting the parameters such mobile phase composition and flow rate, it was determined that

the method was robust. Table 1 shows a summary of the validation parameters for the suggested HPLC procedure.

Table 1: Summary of Validation

Parameter	Result
Linearity indicated by coefficient of correlation (r^2)	0.9923
Precision indicated by % RSD	< 2%
Accuracy indicated by % Recovery	99.74-100.39
Limit of Detection	0.1841 µg/ml
Limit of Quantification	0.5581 µg/ml
Range	5-25 µg/ml
Linear regression equation	y = 24537× + 27363

It was shown that the medicine voriconazole deteriorated in an acidic environment. The typical chromatogram obtained after 60 minutes of treating voriconazole with 3 N HCl is shown in fig. 2a, and the results provided in Table 2 can be seen below. In alkaline conditions, the degradation process was stronger and occurred more rapidly. The typical chromatogram obtained after 30 minutes of treating voriconazole with 0.1 N NaOH is shown in fig. 2b, and the results provided in Table 2 can be seen below. Peak area for voriconazole in the degradation sample was found to be reduced by 56.92% compared to the comparable peak area for zero time samples, suggesting that voriconazole was hydrolyzed following refluxing with water on boiling water bath. In figure 2c, we see the chromatogram of a voriconazole sample destroyed by hydrolysis in neutral pH. Peak area for voriconazole in the degradation sample was found to be 0.24 percent lower than the same peak area for zero time samples after voriconazole was heated. Not any more peaks of deterioration were found. The chromatogram of a voriconazole sample that was heated in an oven at a low, dry temperature is displayed in Figure 3a. The amount of voriconazole in the sample decreased slightly after being exposed to light in accordance with ICH recommendations, but no new peaks appeared. The chromatograms of voriconazole samples destroyed by photolysis are displayed in Fig. 3b. Although no new peaks were observed after treating voriconazole with 1 ml of 30% w/v H2O2 at normal condition for 15 minutes and 5 ml of 30% w/v H2O2 at normal condition for 24 hours, the peak area for voriconazole was found to be less in both cases (by 1.17% and 5.40%, respectively, compared to the corresponding peak area for zero-time samples). Voriconazole samples damaged by oxidative conditions are displayed as chromatograms in Figs.4a and 4b.

Table 2 Result of Forced Degradation Studies of Voriconazole

Condition	Time (Min.)	% Degradation	Retention time of degradation Products (min.)
0.1 N NaOH	30	55.58	4.45
	60	78.75	4.44
	90	100	4.44
3 N HCl	30	11.60	4.41
	60	16.92	4.41

	90	25.11	4.42
	120	29.99	4.45
	150	35.06	4.44
30% H_2O_2(1 ml)	15	1.17	None Detected
30% H_2O_2(5 ml)	20 h	5.40	None Detected
Dry Heat 70°	48 h	0.24	None Detected
Photolytic	-	4.68	None Detected
Neutral (Reflux)	1 h	56.92	4.3

Chromatogram of voriconazole subjected to hydrolytic conditions

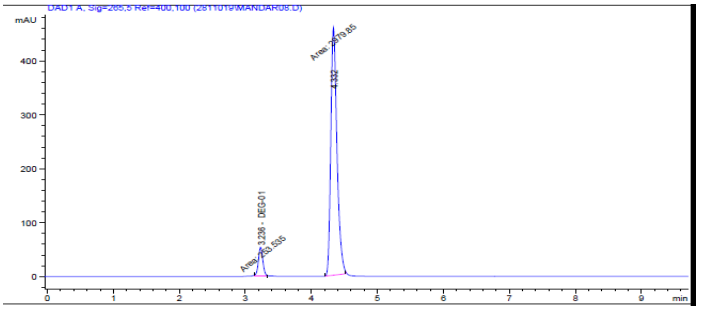


Fig 2A: acid hydrolysis under acidic condition

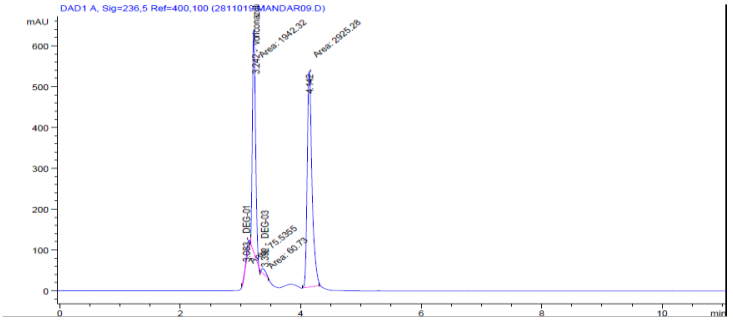


Fig 2B: hydrolysis under basic condition

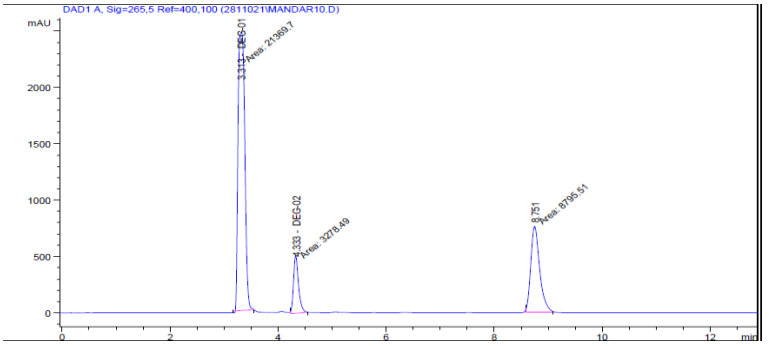


Fig 2C: hydrolysis under neutral condition

Chromatogram of voriconazole subjected to heat and light

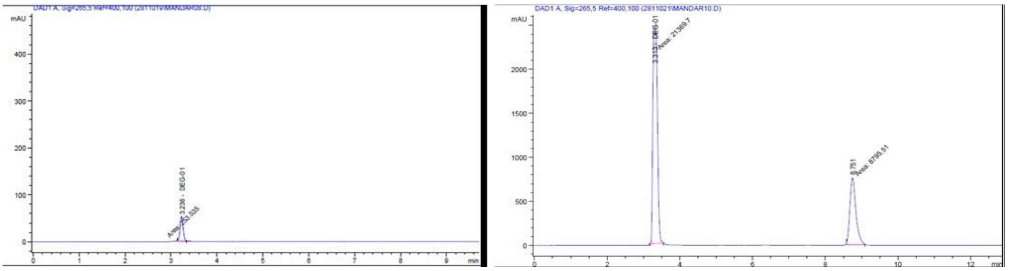


Fig 3A: upon exposure to heat and 3B: upon exposure to light.

Chromatogram of voriconazole subjected to oxidative conditions

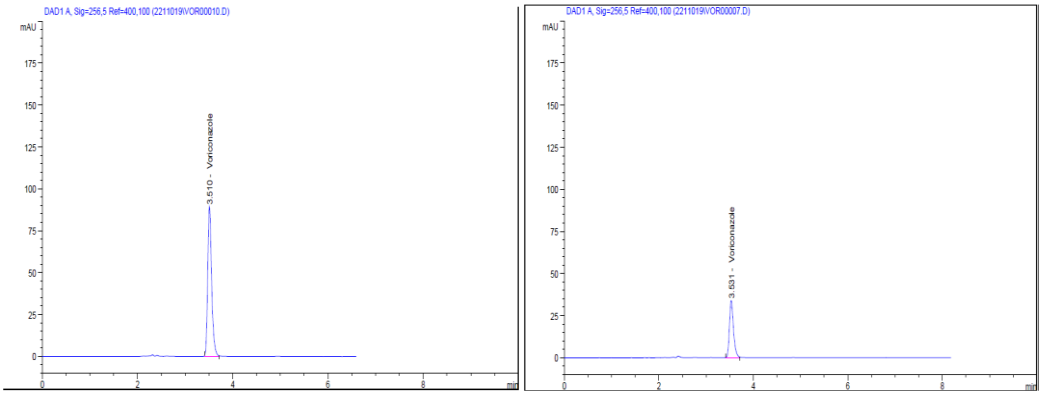


Fig 4A: 30% H_2O_2 (15 min) degradation, 4B: 30% H_2O_2 (20 h) degradation

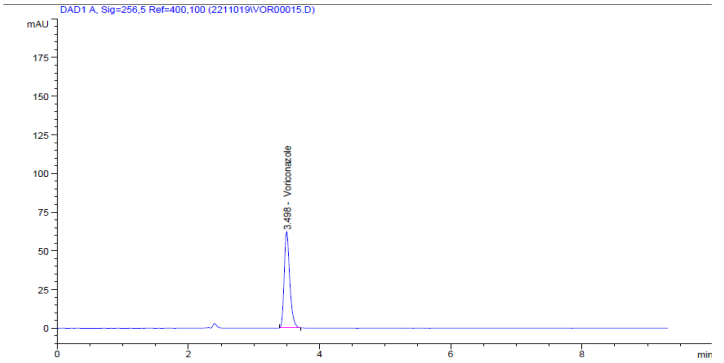


Fig. 5 shows the initial chromatogram of voriconazole tablets

During an accelerated stability testing at 40 degrees Celsius and 75% relative humidity, the percentage of degradation discovered in tablets marketed without primary packaging was 18.21%, 26.03%, 36.66%, and 37.19% after the first, second, third, and fourth weeks, respectively. The degradation product didn't show any sort of peak. This highlights the need for moisture-resistant main packaging. [17-19]. Thus, the research demonstrates that voriconazole degrades in hydrolytic circumstances that are acidic, alkaline, or neutral, whereas it is generally stable when subjected to dry heat, oxidation, or photolysis. All the

degradation products created under different settings have been resolved using a newly developed stability indicating approach [20]. The UV spectrum of the degraded product reveals that the products generated under acid, alkaline, and neutral hydrolysis conditions are identical. The procedure was found to be straightforward, reliable, precise, targeted, and selective. That's why it could be useful for assaying the product in stability tests.

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