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PAPER

Study of the forced degradation of isoconazole nitrate in bulk drug and cream formulations†

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Bulk drug and cream formulations of isoconazole were subjected to the following ICH-recommended stress conditions: hydrochloric acid (0.1 M), sodium hydroxide (0.1 and 1 M), and hydrogen peroxide (3%). Photostability was monitored for 60 h in a UV chamber. Analysis of drug degradation was performed using an HPLC method that had been validated for linearity, range, precision, accuracy, limits of detection and quantification, and selectivity and robustness in accordance with the criteria established by Resolution 899 of the Brazilian National Health Surveillance Agency (ANVISA). When isoconazole cream was exposed to a light source, the isoconazole content decreased slightly, but no degradation products were formed as indicated by the absence of additional peaks in the HPLC chromatogram. The drug was found to be unstable in both the bulk form and in the cream formulation when subjected to alkaline hydrolysis conditions, exhibiting reductions of *ca.* 43 and 70% of the initial content, respectively. Different sample solutions that had been subjected to alkaline degradation indicated, through subsequent pH adjustments and UV analysis, the presence of an isosbestic point at 275 nm, suggestive of a reversible phenomenon in alkaline media. Reversibility by bringing the pH back to the initial value may be a valuable tool for identifying real degradation processes. In contrast to the drug's instability under alkaline conditions, isoconazole was found to be stable under both acid hydrolysis and oxidative conditions.

Introduction

In pharmaceutical terms, stability refers to the storage time that can elapse before any degradation product(s) reach a level sufficient to present a risk to the patient.[1] One approach to evaluate the stability of a drug is the use of stress tests; stress tests comprise a set of assays aimed at facilitating the development of analytical methodology. The results of these assays provide a better understanding of the active pharmaceutical ingredient and of the drug's stability, as well as information about the degradation pathways and degradation products.[2] There have been reports published on the stability of many drugs, including antihistamines such as fexofenadine,[3] antihypertensive agents such as enalapril maleate,[4] anti-inflammatory agents such as piroxicam,[5] antiparasitic agents such as nitazoxanide,[6] anti-emetic agents such as alizapride[7] and antidepressant drugs such as citalopram,[8] in addition to other classes of drugs. A review of the literature revealed that a large number of methods have been reported for the analysis of the stability of antifungal compounds belonging to the chemical class of azoles, a large group of synthetic compounds that includes imidazoles and triazoles.[9] All azoles operate *via* a common mode of action: they prevent the synthesis of ergosterol, the major sterol component of the fungal plasma membrane, through inhibition of the fungal cytochrome P450-dependent enzyme lanosterol 14-α-demethylase.[10]

To determine the stability of antifungal drugs, stress studies have been performed using a variety of conditions such as hydrolytic, oxidative, photolytic conditions and elevated temperature. One extensively studied factor that affects drug degradation is the susceptibility of the drug to hydrolysis over a pH range corresponding to conditions typical of drugs undergoing degradation. In addition, hydrogen and hydroxyl ions can either accelerate or delay the degradation process.[11] Light also plays a significant role in the degradation of drugs; radiation from light may catalyse the cleavage of bonds and may also cause oxidation, isomerisation, polymerisation and racemisation reactions.[12] The stabilisation of drugs under oxidative conditions involves a number of precautions during both the manufacturing and storage processes.[13]

In general, the stress test conditions were based on those suggested by the International Conference on Harmonisation (ICH).[14] For example, secnidazole[15] samples were incubated under the following hydrolytic conditions: in an acidic medium of 0.1 M HCl at 80 °C for 12 h and in an alkaline medium of 0.1 M NaOH at 80 °C for 8 h. For oxiconazole,[16] the acidic and

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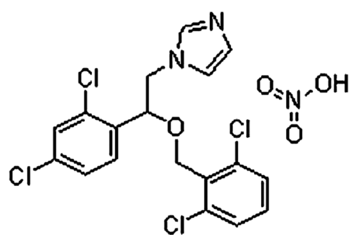

Scheme 1 Structure of isoconazole.

basic solutions were refluxed at 100 °C for 4 h. All imidazole drugs have been shown to be very labile in alkaline solutions (*e.g.*, complete degradation of tinidazole[17] was observed in 0.1 M NaOH). The time of exposure to light of the drug in the photolytic studies ranged from a few hours (tenatoprazole)[18] to several days (tinidazole), and the studies were performed using drugs in either the solid form or in a solution. A 5% potassium permanganate solution was employed to induce oxidation of voriconazole.[19] Chromatographic techniques were utilised during our analysis of drug degradation, as they have been commonly employed for the analysis of drugs under stress conditions.[9,15–17,20]

Isoconazole (1-[(2*RS*)-2-[(2,6-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole, Scheme 1) is a synthetic imidazole derivative with broad-spectrum antifungal activity and is used for the topical treatment of cutaneous fungal infections. Isoconazole blocks the synthesis of ergosterol, an essential component of the fungal cell membrane.

The European Pharmacopoeia has described a method to analyse isoconazole nitrate in bulk form through the use of potentiometric titration. To the best of our knowledge, there have been no reported methods for the analysis of isoconazole in pharmaceutical formulations, and no information regarding the stability of isoconazole has been reported in the literature. Therefore, the main objective of the present study was to carry out a comprehensive stress study on isoconazole by subjecting it to various experimental conditions that promote either acid or alkaline hydrolysis, oxidative decomposition or photo-degradation. There exists an international consensus that analytical measurements should be performed using methods that have been validated to ensure that such methods are credible. Therefore, in the present study, method validation was initially developed to ensure the reliability of the results obtained from the stress studies.

Experimental procedures

Materials

The isoconazole nitrate (IN) reference material (assigned a purity of 100.0 wt%) was obtained from the European Pharmacopoeia. The isoconazole nitrate working standard (Formil Química, São Paulo, Brazil) was characterised and assayed according to the specifications of the European Pharmacopoeia. The isoconazole nitrate bulk material (creams containing 1 wt% of isoconazole nitrate and the base cream employed in that formulation) was obtained from Multilab (São Jerônimo, Brazil). The base cream formulation included the following components: liquid and solid paraffin, cetostearyl alcohol, polysorbate 60, sorbitan monostearate, methylparaben and propylparaben. HPLC-grade methanol, acetonitrile and tetrahydrofuran were purchased from J.T. Baker (USA) and Tedia (Brazil). Hydrochloric acid, sodium hydroxide pellets, orthophosphoric acid and hydrogen peroxide (all of analytical grade) were purchased from Synth (São Paulo, Brazil). Triethylamine (TEA) was obtained from Tedia (Brazil). Milli-Q water was obtained from a Milli-Q purification system (Synergy, Millipore, USA).

Instrumentation

Photodegradation studies were performed in a photostability chamber (424/CF, Nova Ética, São Paulo, Brazil) equipped with a light bank consisting of one fluorescent white cold lamp (similar to ISO 10977-1993) and one UV lamp (spectrum range from 320–400 nm). pH values were measured with a Digimed DM 20 pH meter. Chromatographic separations were performed using a StableBond Phenyl Column, 250 mm × 4.6 mm i.d., 5 µm (Agilent®). A Symmetry C18 (3.9 × 20 mm i.d., 5 µm) guard column was placed before the analytical column. The photodiode array (PDA) analysis was performed using an HPLC system consisting of an LC-20AT pump, an SPD-20A PDA detector, an SIL-20A autoinjector and a DGU-20A5 degasser (Shimadzu, Kyoto, Japan). Data were acquired using LC Solution Software. UV spectra measurements were performed using a Labomed Spectro UV-Vis Auto UV2602 spectrophotometer equipped with Labomed, Inc., Software (Culver City, USA).

Preparation of sample solutions

Typically, an isoconazole cream sample was prepared in the following manner: 500 mg of cream (equivalent to 5 mg of IN) was accurately weighed and transferred to an Erlenmeyer flask containing 50 mL of mobile phase. The mixture was then sonicated in a 40–45 °C water bath until the cream had completely dissolved; the solution was then cooled to room temperature and quantitatively transferred into a 100 mL volumetric flask. The total volume was increased to 100 mL using the mobile phase, and the sample solution was then filtered through a 0.45 µm Teflon filter (Macherey Nagel®, Germany). The working concentration of IN in the prepared sample was determined to be 50 µg mL^{-1} (which is the same concentration as the IN standard).

Forced decomposition study

The drug was subjected to hydrolytic degradation in either 0.1 mol L^{-1} or 1 mol L^{-1} NaOH, or 0.1 mol L^{-1} HCl, at 50 °C for 6 h. Photolytic studies were performed by exposing the solid drug and the sample cream in their original primary packaging to light for 72 h. Drug solutions in the mobile phase (diluent) were exposed to light for 96 h. The total light exposure was greater than 1.2×10^6 lux h^{-1}, and the UV energy was greater than 200 watts h^{-1} m^{-2}. A parallel set of samples, including a solid drug protected by an aluminium foil covering and drug solutions in photoprotective amber glass flasks, were kept in a dark chamber for the same period of time to act as the dark control. The drug concentration of all solutions was determined to be 50 µg mL^{-1}. Oxidative decomposition studies were performed using drug solutions that had been kept at room temperature for 24 h, with a concentration of 50 mg mL^{-1}, in 3% H_2O_2.

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Chromatographic conditions

The solutions of IN cream were optimally resolved on a phenyl-based column (250 mm × 4.6 mm i.d., 5 μm, StableBond®). The sample was eluted at 45 °C at a flow rate of 1 mL min^{-1}, with a mobile phase (pH 2.9) composed of triethylamine 1% (v/v), methanol, acetonitrile and tetrahydrofuran (4 : 3 : 2 : 2 v/v). Prior to being used, the mobile phase was degassed and vacuum filtered through a 0.45 μm, 47 mm regenerated cellulose filter (Sartorius Stedim Biotech, Germany). The injection volume was 10 μL, and the eluent was monitored at 225 nm.

Spectrophotometric conditions

Isoconazole solutions (50 μg mL^{-1}) with different pHs (in the range of 1.0 to 12.0) were monitored by UV-Vis analysis in the range of 200–500 nm. The solvent system used was the same as the mobile phase.

Method validation

The optimised method was validated by evaluating the linearity, range, precision, accuracy, limit of detection (LOD), limit of quantification (LOQ), selectivity, and robustness in accordance with the ICH recommendations. The conditions employed for each parameter are described in detail in the ESI†.

Results and discussion

Method development and method validation

The choice of the method used depends on factors such as the nature of the drug, the complexity of the sample and its intended use. The system suitability parameters were measured to verify system performance. Evaluation of the analyte peak's parameters provided high-quality results, demonstrating that the chromatographic system is both adequate and reliable. The recommended validation characteristics that were analysed included method precision (% RSD), method accuracy (% recovery, % RSD), linear range (correlation coefficient) and method selectivity using a blank (the inactive ingredients in the pharmaceutical formulation). The chromatographic conditions were optimised with the aim of achieving good resolution, symmetrical peak shape and a short elution time for isoconazole.

The *selectivity* of the method was evaluated by injecting the following solutions: mobile phase, a pure standard solution of 50 μg mL^{-1} isoconazole and a cream sample solution. Matrix components (*e.g.* excipients) did not interfere with the elution,

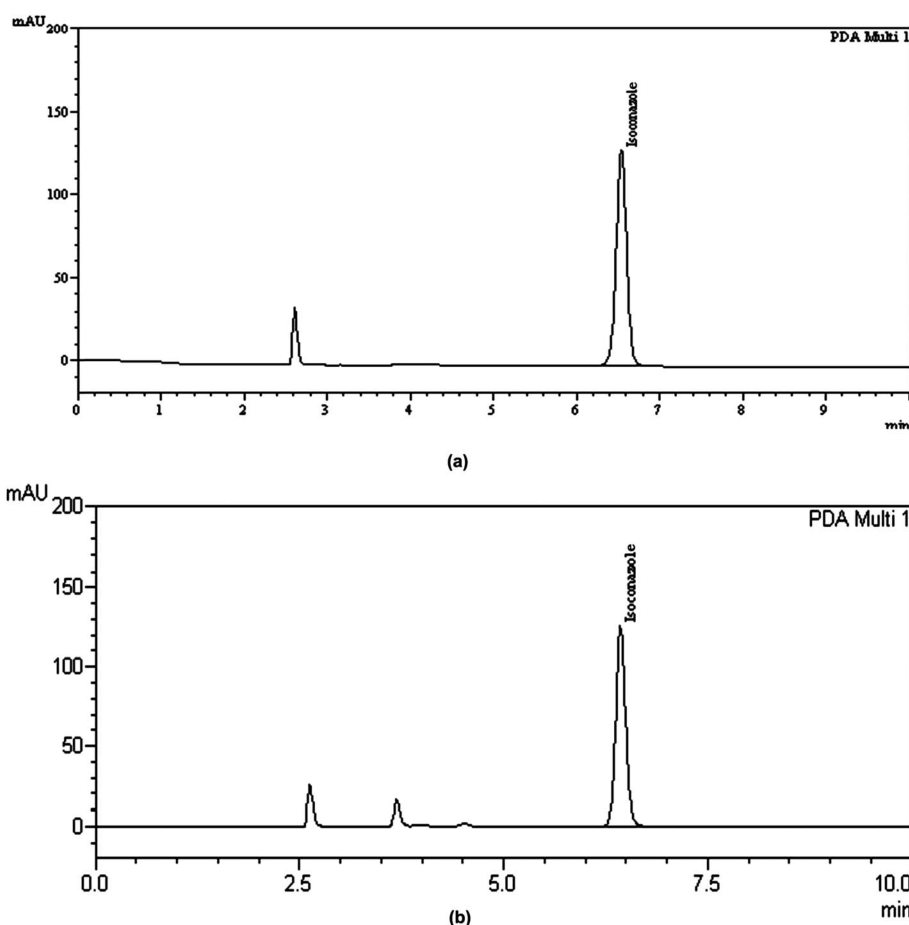

Fig. 1 Typical chromatograms of the (a) isoconazole standard solution (50 μg mL^{-1}) and (b) isoconazole sample cream solution (50 μg mL^{-1}). Mobile phase: TEA 1% pH 2.9, methanol–acetonitrile–THF (8 : 6 : 4 : 4 v/v/v/v), flow rate of 1.0 mL min^{-1}, injection volume of 10 μL. Column: phenyl (5 μm, 250 mm in length, 4.6 mm inner diameter), UV detection at 225 nm.

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and no peaks were observed at t_r values near the isoconazole retention time (6.5 min). Typical chromatograms for the standard and sample solutions are shown in Fig. 1.

To ensure the homogeneity of the peaks in the test solution prepared with the sample of IN cream, the peak purity was examined and satisfactory results were obtained. The peak purity of the analyte was evaluated by recording all spectra in the peak using a diode array detector.

The *linearity* of the method was tested for the IN standard solution (see ESI, Table S1†). The response of the drug was strictly linear in the concentration range of 25.0–75.0 μg mL^{-1}. Linear relationships were observed between the peak area of each compound and its corresponding concentration. The regression curve was calculated using the least squares method; the correlation coefficient was 0.9989 and the representative linear equation was $y = 19\,981x + 1779.1$.

The repeatability (intra-day variation) and the intermediate precision were considered to be measures of the precision of the assay and were calculated as the relative standard deviation values of the assay using isoconazole in the same concentration range (see Table S2†). For the repeatability (intra-day) studies, the mean was 100.92% ± 0.64 with RSD 0.63%. For the intermediate precision (inter-day) studies, the mean was 101.84% ± 1.76, with RSD 1.72%.

Accuracy determination was performed at three concentrations: 80%, 100% and 120% of the concentration claimed on the label of IN cream (see Table S3†). The results were expressed as % recovery; the % recovery was found to be between 98.03 and 104.19%. The mean % recovery was 102.08% ± 1.95, with RSD 1.91%. These results suggest that there is no relevant matrix effect.

In the present study, the LOQ and LOD were based on the data used to construct the calibration curve. The LOQ and LOD were 11.60 μg mL^{-1} and 3.83 μg mL^{-1}, respectively. The results were evaluated using *LC Solution* software (Shimadzu, Japan), which was included with the instrument.

The *robustness* was analysed to confirm that the separations were satisfactory, regardless of conditions external to the method. Good separations were consistently achieved, indicating that the method remained selective for isoconazole under all tested conditions. The results indicated that the sample solutions were stable for up 24 h: the calculated % recovery for the starting solution was 101.60%, and after 24 h the % recovery was 101.20% (*i.e.*, the isoconazole response area for the assay samples did not change significantly over 24 h). Evaluation of the robustness of the method also involved an assessment of the nature of the filters used, as shown in Table 1.

Table 1 Analytical data for robustness in the determination of the IN assay concerning the employment of the filter

Filter	Concentration taken (μg mL^{-1})	Mean peak areas (a.u.)	Recovery (%)
Nylon®	48.4	4 443 536	105.40
Regenerated cellulose	48.4	4 493 858	106.34
Teflon®	48.4	4 430 045	104.82
Polystyrene	48.4	4 414 552	104.45
Polyvinylidene difluoride (PVDF)	48.4	4 459 106	105.51
Polyethersulfone (PES)	48.4	4 384 889	103.74

Table 2 Variations in the chromatographic parameters for robustness evaluation

Filter	Concentration taken (μg mL^{-1})	Mean peak areas (a.u.)	Recovery (%)
No alteration[a]	51.3	1 166 550	105.40
Flow 0.9 mL min^{-1}	51.3	1 233 528	106.34
Flow 1.1 mL min^{-1}	51.3	1 012 714	104.82
Addition of 5% of methanol in the mobile phase	51.3	1 115 615	104.45
Furnace temperature (40 °C)	51.3	1 119 833	105.51
Different column lots[b]	51.3	1 148 177	103.74

[a] Buffer mobile phase : methanol : acetonitrile : tetrahydrofuran (4 : 3 : 2 : 2); flow of 1.0 mL min^{-1}, furnace temperature: 45 °C; wavelength: 225 nm; injection volume: 10 μL and stationary phase SB-Phenyl StableBond column – 4.6 × 250 mm, 5 μm, Agilent. Lot number B08048. [b] SB-Phenyl StableBond column 4.6 × 250 mm, 5 μm, Agilent. Lot number B08084.

As seen in Table 1, all of the % recovery values were considered acceptable. Further robustness tests were carried out by changing some chromatographic parameters, as shown in Table 2.

As shown in Table 2, analyses of the results of this study revealed no significant column-to-column variability. In contrast, changing the mobile phase composition from pH 2.9, TEA 1%, methanol–acetonitrile–THF (8 : 6 : 4 : 4 v/v/v/v) to pH 2.9 TEA 1%, methanol–acetonitrile–THF (7.5 : 6.5 : 4 : 4 v/v/v/v) did affect the results. Varying the chromatographic conditions (*i.e.*, flow rate, column temperature) did not cause any significant differences in the peak areas (less than 2% concentration variation), and little variability in the retention time (<3 min) was observed.

Forced degradation studies

A summary of the results of the forced degradation studies is presented in Table 3.

Fig. 2 shows representative LC chromatograms of sample IN creams subjected to the different stress conditions.

The results of the effect of forced degradation on the drug solution and the drug cream will be further discussed for each condition tested.

Photodegradation studies

Exposure to light may induce chemical degradation in susceptible molecules; the most obvious result of drug photodecomposition is the loss of product potency.[21] The results demonstrated that our sample was stable when exposed to light from one fluorescent white cold lamp and one UV lamp (spectrum range from 320 to 400 nm) for 60 h, a length of time longer than the reported stability time of the sample. After 96 h of exposure, the sample had undergone some degradation, which was confirmed by the decreased peak area of the drug relative to the peak area for the same concentration of non-degraded drug. No additional degradation peaks were observed.

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Table 3 Summary of results from forced degradation studies

Stress conditions	Solution of drug assay			Solution of sample cream assay		
	Taken concentration (μg mL^{-1})	Mean peak area (a.u.)	Recovery (%)	Taken concentration (mg mL^{-1})	Mean peak area (a.u.)	Recovery (%)
Photolysis (96 h)	51.50	1 139 267	94.29	52.45	1 121 091	92.79
Oxidation (3% H_2O_2 (v/v), 24 h)	53.10	1 227 895	101.63	52.20	1 170 506	96.88
Acid hydrolysis (0.1 mol L^{-1} HCl, 6 h)	52.00	1 212 914	100.39	50.65	1 226 567	101.52
Base hydrolysis (0.1 mol L^{-1} NaOH, 6 h)	51.36	514 331	42.57	51.12	8 430 833	69.78

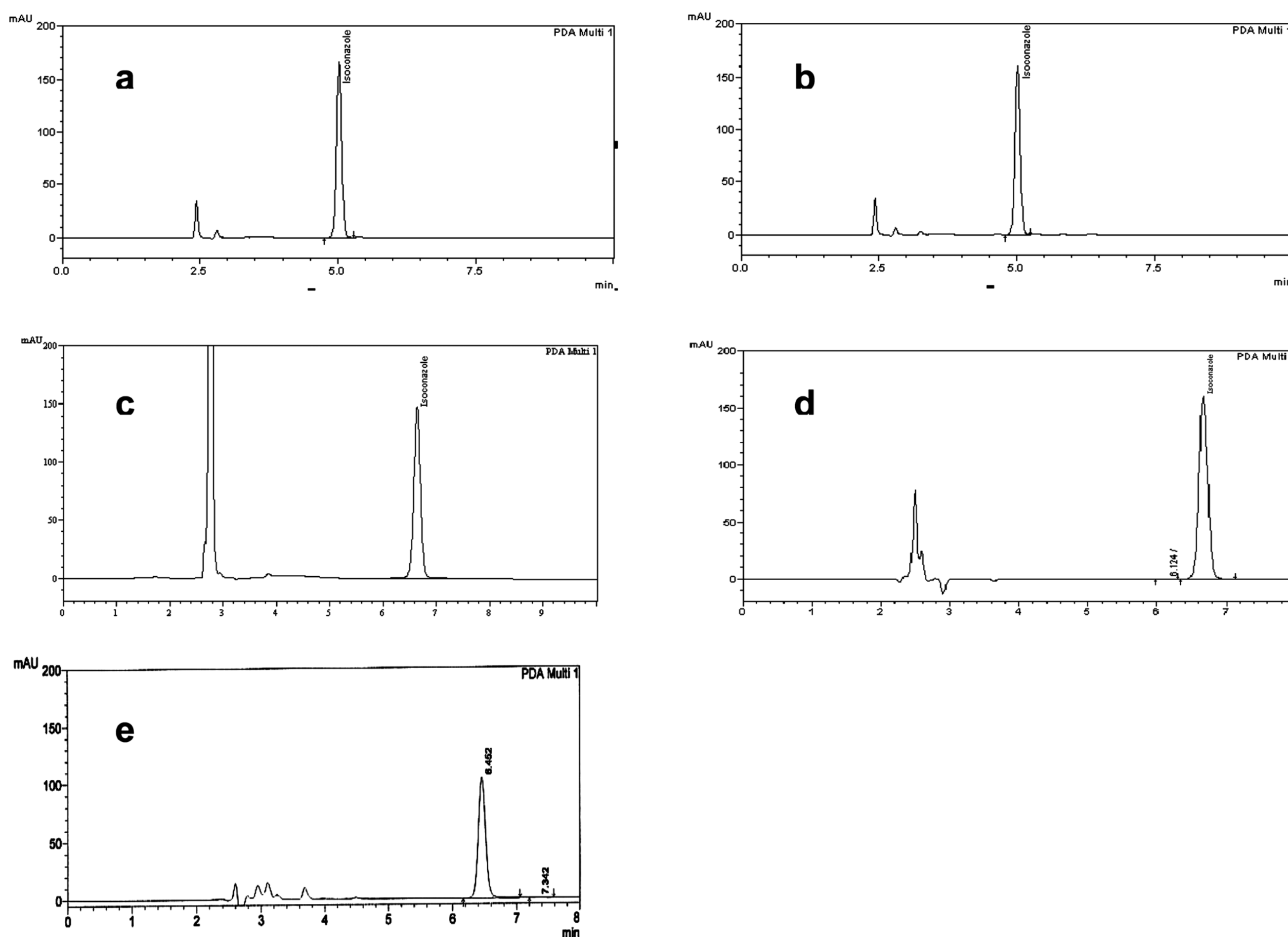

Fig. 2 LC chromatograms of a standard solution of the drug (a) and of the drug subjected to conditions that promote photolysis (b), oxidation (c), acid hydrolysis (d) and alkaline hydrolysis (e).

Chromatographic peak purity results (Fig. 3) were obtained from the spectral analysis report. The peak values were greater than 0.99; this result confirmed that the isoconazole peak was homogeneous and pure in all of the analysed samples.

Oxidative conditions

Table 4 shows the behaviour of the isoconazole raw (bulk) material that had been subjected to the oxidative test conditions.

As shown in Table 4, the drug was found to be stable in 3% H_2O_2 for 24 h at room temperature. It is worth mentioning that the signal observed at 2.5 min in chromatogram c of Fig. 2 is attributed to the preservative used in the H_2O_2 solution.

Hydrolytic studies

Acidic conditions. After incubation at 50 °C in a 0.1 M HCl solution for 6 h, the isoconazole sample did not exhibit any peaks suggestive of degradation. Furthermore, a reduction in drug concentration was not observed. Table 5 shows the percentage of isoconazole remaining in the samples after exposure to acidic conditions for six hours.

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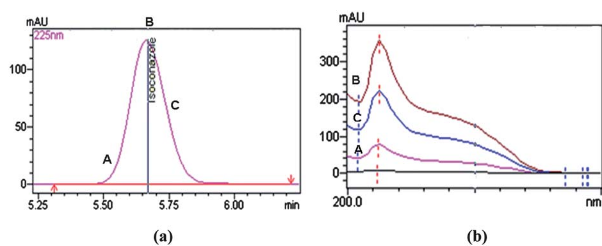

Fig. 3 (a) Chromatogram of the isoconazole sample cream peak after photolysis and (b) corresponding overlaid spectra of isoconazole. Letters A, B and C represent the resolution times in the isoconazole chromatographic peak with the corresponding UV-Vis spectra.

Table 4 Percentages of isoconazole raw material and cream submitted to oxidative hydrolysis

Sample	Taken concentration (μg mL^{-1})	Mean peak area (a.u.)	Assay (%)
Isoconazole raw material	53.10	1 227 895	101.63
Isoconazole cream	52.20	1 170 506	96.88

Table 5 Percentages of isoconazole raw material and cream after hydrolysis acidic conditions

Sample	Taken concentration (μg mL^{-1})	Mean peak area (a.u.)	Assay (%)
Isoconazole raw material	52.00	1 212 914	100.39
Isoconazole cream	50.65	1 226 567	101.52

Alkaline conditions. Isoconazole degradation under alkaline conditions was found to occur more rapidly than isoconazole degradation under acidic conditions; the drug was found to be highly unstable under alkaline conditions. The experiment was carried out using a 0.1 M sodium hydroxide solution at 50 °C, which caused a reduction of *ca.* 60% of the initial concentration of the drug. Consequently, the degradation studies for alkaline conditions were performed using a 1 M sodium hydroxide solution. The height of the drug peak decreased gradually during the investigated period (four hours) without a corresponding increase or the presence of any new peak(s), which suggests that there was no corresponding formation of degradation products (see chromatogram e of Fig. 2). Determination of the peak purity at the retention time of the drug confirmed the absence of impurities that could have co-eluted with isoconazole. The decreasing drug content is presented in Fig. 4.

As shown in Fig. 4, there was a drastic reduction (12.58% of the initial concentration) within the first hour of exposure of isoconazole to the specified alkaline conditions.

Monitoring the UV-Vis spectrum in the range of 200–800 nm by HPLC-DAD did not show any evidence of the formation of degradation products, suggesting the generation of interconvertible species dependent on pH. Thus, multiple isoconazole solutions were prepared at differing pHs (in the range of pH 1.0 to 12.0) and were monitored by UV-Vis analysis in the range of 200–500 nm, as shown in Fig. 5.

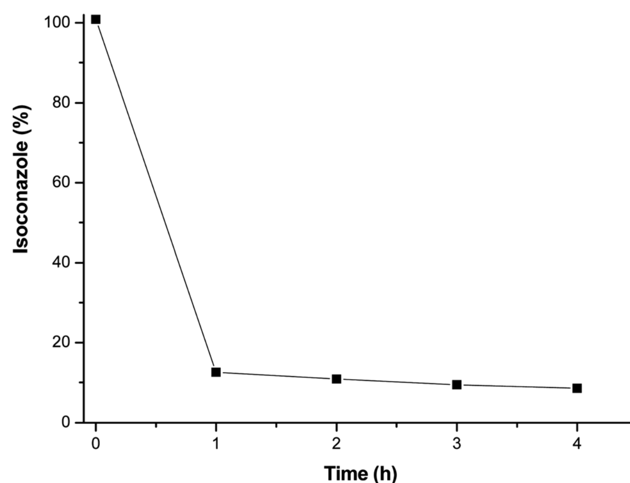

Fig. 4 Percentage of isoconazole remaining after being subjected to alkaline stress conditions.

As shown in Fig. 5, overlaying the UV-Vis spectra recorded at different pHs allowed for identification of an isosbestic point at *ca.* 275 nm, indicating the existence of interconvertible species under hydrolytic conditions.[22] To quantify the degree of degradation, three different solutions of IN cream were prepared (as shown in Table 6), and the pH was adjusted back to the initial pH, which allowed for good recovery of the initial IN content.

Investigation of the reversibility of this degradation process may be accomplished by readjusting the pH back to its initial value. This procedure may be a potential tool for identifying real degradation processes by allowing differentiation between products resulting from degradation processes and those resulting from reversible chemical equilibrium.

Table 7 compares the results of the stress tests for isoconazole nitrate with those for other azoles reported in the literature.

As shown in Table 7, isoconazole nitrate and other azoles were found to be stable in 3% H_2O_2. Furthermore, the majority of the azole drugs exhibited relative stability under oxidative conditions. In some studies, increased levels of degradation were observed when the azole drug(s) were exposed to 30% H_2O_2 (for example, secnidazole). In other cases, exposure to high hydrogen peroxide concentrations did not significantly affect the stability of the azole drug (for example, oxiconazole).

According to the references presented in Table 7, the majority of the azole drugs (such as isoconazole) have been shown to be stable under acidic conditions, with the exception of tenatoprazole,[18] for which the rate of degradation in acidic conditions is faster than the rate of degradation in alkaline conditions. In the majority of the cited works, significant degradation of azole drugs was observed under alkaline conditions; a reduction in the analyte peak area was observed for exposure times in the range of 4 to 8 h.

The majority of the azole drugs investigated in the literature (Table 7) were found to degrade when exposed to light. In contrast, isoconazole was found to be stable when exposed to light. As in the case of isoconazole, no degradation product peaks were detected in any of the secnidazole samples after exposure to light.[15] In most cases, a reduction in the size of the

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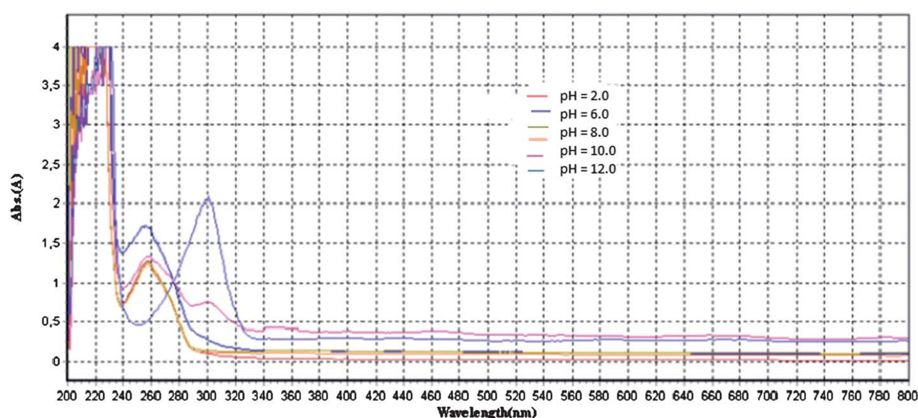

Fig. 5 Overlaid spectra of IN cream samples exposed to different pHs.

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Table 6 Effect of alkaline conditions. Evaluation of the reversibility of the reaction

Sample	IN content (%)
Solution of IN under standard conditions (pH 4.4)	100.86
Solution of the sample submitted to alkaline hydrolysis (1 M (4 h) NaOH solution), then neutralised with 1 M HCl solution, followed by adjustment of the pH back to the initial pH of the sample solution (4.4)	101.40
Solution of the sample submitted to alkaline hydrolysis followed by adjustment of the pH to the initial pH of the sample solution (pH 4.4) with H_3PO_4 (without previous neutralisation with HCl)	101.10

drug peak was not accompanied by a corresponding appearance of degradation product peak(s). Additional peaks were seen in the mass chromatograms of photolysed solutions of secnidazole (UV detector), and the mass of these compounds was equal to that of secnidazole, indicating that these products are the rearrangement products already reported for secnidazole.

Conclusions

These stress degradation studies of isoconazole nitrate provide information regarding the degradation behaviour of this drug when exposed to conditions promoting hydrolysis, oxidation or photolysis. Such data are valuable for the assessment of the safety and potency of a drug product. Isoconazole was found to degrade extensively when exposed to alkaline conditions. A novel finding in this particular study was that the degradation reaction of isoconazole is reversible and that the exact mechanism of degradation may be determined by readjusting the pH back to its initial value. Thus, we have shown that the chemical changes that occur under alkaline conditions with this class of compound are reversible.

The methods used in this study have been thoroughly validated, and the results were determined to be precise, accurate, specific, selective and robust. These methods are proposed for the analysis of isoconazole and its potential degradation products to evaluate the stability of industrial samples.

Table 7 Selected reports of imidazoles with corresponding investigated stress conditions

Drug	Photolysis	Oxidation	Acid hydrolysis	Alkaline hydrolysis	Ref.
Isoconazole nitrate	Stable up to 72 h	Stable at 3% H_2O_2 up to 24 h	Stable at 0.1 M HCl 50 °C up to 6 h	Unstable at 0.1 M NaOH 50 °C up to 6 h	This work
Secnidazole	Unstable up to 96 h	Stable at 3% H_2O_2 up to 6 h	Stable at 0.1 M HCl 80 °C up to 12 h	Unstable at 0.1 M NaOH 80 °C up to 8 h	15
Ornidazole	Relatively unstable up to 720 h	Stable at 3% H_2O_2 up to 8 h, but very unstable at 30% H_2O_2 up to 8 h	Stable at 0.1 M HCl 80 °C up to 72 h and slowly degraded in strongly acidic conditions 5 M HCl 80 °C up to 12 h	Unstable at 0.1 M NaOH 80 °C up to 0 h	23
Oxiconazole	Not evaluated	Stable at 30% H_2O_2 up to 10 h	Relatively stable at 1 M HCl 100 °C up to 1 h	Unstable at 0.1 M NaOH 100 °C up to 1 h	16
Tenatoprazole	Unstable to direct sunlight (1 h)	Unstable at 6% H_2O_2 up to 30 min	Unstable at 0.01 M HCl up to 4 h	Unstable at 1 M NaOH 80 °C up to 4 h	18
Tinidazole	Unstable up to 288 h	Stable at 3% H_2O_2 up to 6 h and unstable at 30% H_2O_2 up to 48 h	Slightly unstable at 0.1 M HCl 80 °C up to 12 h	Unstable at 0.1 M NaOH 80 °C up to 10 min	17
Voriconazole	Unstable up to 336 h	Relatively unstable at 5% $KMnO_4$ up to 3 h	Relatively unstable at 0.1 M HCl 80 °C up to 2 h	Unstable at 0.1 M NaOH up to 0.5 h	19

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