

Original Article

SOLID-STATE STABILITY AND SOLUBILITY DETERMINATION OF CRYSTALLINE FORMS OF MOXIFLOXACIN HYDROCHLORIDE

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ABSTRACT

Objective: This study aims to evaluate possible crystalline changes that can occur with MOX under the influence of temperature and relative humidity (RH) as well as to determine the relative solubility of the observed crystalline forms.

Methods: Thermoanalytical methods with the support of non-thermal analysis such as X-ray powder diffraction and infrared spectroscopy were used for testing structural changes of Moxifloxacin hydrochloride (MOX) stored under four different conditions. Additionally, relative solubilities of the observed crystalline forms were determined by the shake-flask method.

Results: After storage for 1 mo at 0 % relative humidity (RH) and 40 % RH, MOX remained with crystal structure unchanged and shown to have a good physical stability at these conditions. However, when the drug was stocked for 1 mo at 90 % RH and 75 %, a hydrated crystalline form was identified in both conditions. In the solubility assay, it was observed that the hydrated form is less soluble than initial MOX.

Conclusion: Pharmacotechnical wet processes are not recommended for the pharmaceutical production of this drug because solvent granulation and drying conditions from processing provides a favorable environment for the transition of crystalline forms. According to DSC, TG, PXRD, HPLC and FT-IR results, they showed good correlation with each other and ensure reliable interpretation of solid form stability studies. Moreover, these findings suggest that stability studies of a polymorphism associated with the evaluation of relative solubility are essential for a stable formulation development and to choose between dry or wet granulation processes.

Keywords: Moxifloxacin hydrochloride, Crystal form, Thermal Analysis, Non-thermal methods, Shake-Flask.

INTRODUCTION

The global pharmaceutical market has shown continued growth over the past 10 y, mainly due to the emergence of new drugs. Regulatory agencies, such as Food and Drug Administration (FDA) [1] and Brazil's National Health Surveillance Agency (ANVISA) [2], concerned with the therapeutic performance of these new formulations, developed regulatory procedures to submit the drug under the influence of a variety of environmental factors such as temperature and humidity. The studies of a drug kept under different conditions provide additional information on its stability and structural changes [3-5]. The reasons for determining the stability of a drug are based on public health concern, since the loss of stability can lead to the formation of degradation products that may cause toxicity to the patient [6] or even cause a polymorphic transition of the drug.

The existence of several solid forms of active pharmaceutical ingredients (APIs) is a very important topic in the pharmaceutical solids, in which crystalline compounds have the capability to exist in multiple crystalline architectures and it is associated with distinct crystal arrangements of the molecules in the three-dimensional space [7]. Crystalline forms include hydrates/solvates, salts, co-crystals and polymorphs, and different crystalline forms can be observed in processes involving solvents, attrition during the drug formulation, wet granulation or phase transition induced by stress conditions [8-10]. Different solid forms often exhibit distinct chemical and physical properties such as melting point, stability, photosensitivity, solubility and dissolution rate, which can influence in its pharmacological activity [11-13]. Among all solid-state properties of a drug, solubility is directly related to its bioavailability.

Therefore, solubility studies showed great emphasis in recent years, and its importance can be seen by the publication of ANVISA resolution RDC number 31 declaring obligatory these studies by pharmaceutical companies [14].

Accordingly, it is essential to conduct screening, characterization and control of solid forms in APIs as early as possible during the development of the new drug, since about 80 percent (%) of pharmaceutical formulations are found in solid forms. In this context, typical structure-sensitive analytical techniques are important tools in the study of crystalline forms of drugs.

Powder X-ray diffraction (PXRD) is a widely applied technique in these studies because changes in the diffraction pattern can be indicative of crystalline changes since the technique is able to detect the properties of the crystalline drug lattice. Infrared spectroscopy (IR) is helpful for solid-state information of drugs since this technique can provide information on the structure and molecular conformation of the solid and detection of hydration/dehydration processes [7, 15]. Thermoanalytical methods have been used more recently for the evaluation of polymorphic systems, which allow obtaining information such as purity, melting/transition point and enthalpy [16-19]. In addition, the main advantage of these methods is a short time of analysis in comparison with other techniques.

Moxifloxacin hydrochloride (MOX) is a fourth generation synthetic fluoroquinolone antibacterial agent. This medication generally is prescribed to the patient in high doses (about 400 mg daily). Several crystalline forms of MOX are described, which were designated as "Form I" (anhydrous) [20], "Form II" (monohydrate) [20], "Form III" (anhydrous) [21], "Form IV" [22], "Form A" [23], "Form B" [23], "Form C" [24], "Form X" [25], and "Form Y" [25]. Besides these forms, there is a stable monohydrate form, which did not name [26, 27]. Therefore, it is important to monitor and to investigate the transition of crystalline forms of MOX, which can affect the bioavailability and effective clinical use of solid formulations. Thus, the aims of the present study are to evaluate possible crystalline changes that can occur with MOX under the influence of temperature and relative humidity (RH) as well as to determine the relative solubility of the observed crystalline forms.

MATERIALS AND METHODS

MOX was acquired from Dr. Reddys™, India. Silica gel, sodium dichromate (Synth™, Diadema, São Paulo, Brazil), sodium oxalate (Vetec™, Rio de Janeiro, Rio de Janeiro, Brazil) and sodium chloride (Vetec™, Rio de Janeiro, Rio de Janeiro, Brazil) were used to conduct the stability study. Methanol high performance liquid chromatography (HPLC) grade (Vetec™, Duque de Caxias, Rio de Janeiro, Brazil), tetrabutylammonium hydrogen sulphate (Sigma-Aldrich™, Saint Louis, Missouri, USA), phosphoric acid (Vetec™, Duque de Caxias, Rio de Janeiro, Brazil), anhydrous sodium sulphite (Vetec™, Duque de Caxias, Rio de Janeiro, Brazil), potassium dihydrogen phosphate (Jand Química™, São Paulo, São Paulo, Brazil), Polytetrafluoroethylene (PTFE) hydrophilic filters 13 mm diameter and 0.50 µm porosity (Advantec MSF™, Dublin, California, USA) and deionized water obtained by using a Millipore™ Direct-Q 5™ water purification system (Millipore™, Billerica, Massachusetts, USA) were used to prepare mobile phase for HPLC analysis. Other reagents employed were of analytical grade and used without further purification.

Stability study

The measurements were performed on initial sample of MOX and on following samples: stored at 0 % RH (silica gel/20 °C), 40 % RH (saturated solution of Na₂Cr₂O₇.2H₂O/20 °C), 90 % RH (saturated solution of Na₂C₂O₄/20 °C) and 75 % RH (saturated solution of NaCl/40 °C).

Thermogravimetry (TG)

A TG curve was obtained employing a SII Nanotechnology Inc™. (Tokyo, Japan) model EXSTAR TG/DTA7300™ thermo-balance in the temperature range of 30 to 600 °C, using opened aluminum crucibles and weighing approximately 4 mg of sample, under a dynamic dry N₂ atmosphere (50 ml/min) and at a heating rate of 10 °C/min. The TG instrument was first calibrated using indium (156.6±0.3 °C and heat of fusion of 28.58±0.3 J/g) and standard weights under the same conditions as the samples.

Differential scanning calorimetry (DSC)

DSC experiments were conducted using a high-sensitivity DSC calorimeter (model EXSTAR DSC7020™, SII Nanotechnology Inc.™, Tokyo, Japan). Samples (approximately 4 mg) were encapsulated in hermetically sealed aluminum pans. All experiments were performed under a nitrogen purge gas of 50 ml/min and at a heating rate of 10 °C/min, in a temperature range from 30 to 300 °C. An Indium standard with purity more than 99.99 % was used for calibrating the temperature.

PXRD analysis

Diffractograms were obtained in a Powder X-ray diffractometer (model Ultima IV™, Rigaku™, Japan), using a CuKα tube (1.5418 Å), the voltage of 40 kV and current of 30 mA, in the range of 5 to 55 (°2θ).

IR analysis

IR spectra were recorded on a Fourier Transform (FT) IR Spectrophotometer Shimadzu™ (Tokyo, Japan), model IR Affinity-1™, equipped with MIRacle™ attenuated total reflectance (ATR) (Pike Technologies, USA). After recording a background spectrum, the samples were placed on the zinc selenide (ZnSe) crystal. In each sample, 32 scans were recorded with resolution of 2 cm⁻¹.

HPLC method

The quantification of MOX in each stored condition was performed using an HPLC method according to its monograph at European Pharmacopeia [28]. Sample solutions (0.05 mg/ml of MOX) were prepared by dilution of 5 mg of MOX in solution A composed of 0.5 g/l of tetrabutylammonium hydrogen sulphate, 1.0 g/l of potassium dihydrogen phosphate, 0.2 % v/v of phosphoric acid and 0.5 g/l of anhydrous sodium sulphite. The solutions were then sonicated for 10 min and filtered through 0.5 µm filters before the HPLC analysis. Chromatographic separations were carried out using an HPLC system (Shimadzu™, Kyoto, Japan) series LC-10A, consisting of LC-10ADVP pump, DGU-14A degasser, 7725i manual injector with a

20 µl loop (Rheodyne™, Rohnert Park, California, USA), CTO-10AVP column oven, SPD-10AVP integrated UV detector, SCL-10 AVP controller and CLASS-VP 5.02 integration system software. Briefly, the pharmacopeial method involves an isocratic elution with the column Eclipse XDB™ (Agilent™, USA) (Phenyl, 5 µm, 4.6 mm x 250 mm) at 45 °C and the mobile phase of 28 volumes of methanol and 72 volumes of a solution containing 0.5 g/l of tetrabutylammonium hydrogen sulphate, 1.0 g/l of potassium dihydrogen phosphate and 3.4 g/l of phosphoric acid. The injection volume was 20 µl, the flow rate was 1.3 ml/min and spectrophotometric detection at 293 nm.

Relative solubility determinations by Shake-flask method

Samples of initial MOX and samples under 90 % RH at 20±0.5 °C were added in excess (approximately 30 mg) to 2 ml Eppendorf tubes containing 500 µl of Milli-Q water. The tubes (triplicate samples) were placed on a shaker table (Solab, SL 180 DT™, Piracicaba, São Paulo, Brazil) and were shaken at 150 rpm for 24 h at room temperature. After the shaking period, the suspensions were filtered through a 0.50 µm PTFE hydrophilic filter and the filtrate was adequately diluted and quantified by the HPLC method previously described.

RESULTS AND DISCUSSION

DSC curves of initial MOX, as well as samples stored for 1 mo at 0 % RH and 40 % RH on 20 °C, are illustrated in fig. 1. The thermal profile of the initial MOX displays one sharp endothermic peak at 256.7 °C (T_{onset} = 255.13 °C and ΔH_{fus} = 139 J/g) coming from the drug melting followed by its decomposition. This profile is characteristic of a MOX crystalline substance described by Rao *et al.* [24]. The samples of stored MOX at 20 °C in 0 % RH and 40 % RH showed the peak profiles and the thermal parameters such as heat of fusion and melting point (onset) similar for the initial sample, showing that they do not change significantly during the storage. DSC curves of the samples stocked for 1 mo at 90 % RH in 20 °C and 75 % RH at 40 °C are also represented in fig. 1. Only observing the curve profile of MOX exposed at 90 % RH in 20 °C is evident the appearance of a new endothermic peak, which was possibly caused by the humidity of the environment where it was packaged. In addition, occurred the displacement of the second endothermic event and the enlargement of the peak. The curve profile of MOX stored in the condition of 75 % RH and 40 °C showed an alteration in the second endothermic peak with displacement and peak broadening, as observed with the MOX stored at 90 % RH and 20 °C.

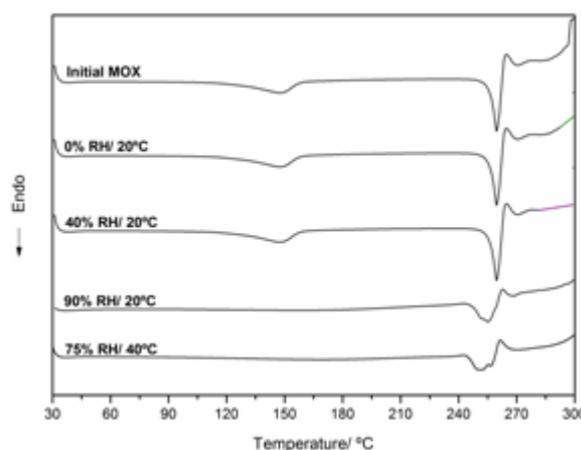


Fig. 1: DSC curve of MOX at initial time and MOX stored for 1 mo at 0 % RH/20 °C, 40 % RH/20 °C, 90 % RH/20 °C and 75 % RH/40 °C

Table 1 presents the changes in thermal parameters of the samples stocked in the conditions mentioned above in comparison with the initial MOX. By employing the analysis of variance (Scot-Knott), it is possible to establish that there was an alteration with the enthalpies of the drug.

Table 1: Initial thermal parameters and HPLC results as well as after 1 mo of storage at 20 °C in 90 % RH and 40 °C at 75 % RH for MOX

Sample	HPLC Content average ±standard deviation (%)	DSC		TG Mass loss (%)
		ΔH average ±standard deviation (J/g)	Onset average ±standard deviation (°C)	
Initial MOX	100.0	139.0±1.0	255.0±2.0	3.2
MOX stored at 90 % RH/20 °C	57.1*±0.6	66.5±0.3	251.0±3.0	41.3
MOX stored at 75 % RH/40 °C	94.1*±0.8	86.0±1.0	247.0±3.0	4.2

* These values were obtained by comparison of samples peak areas with initial MOX

The TG curves of MOX showed one principal mass loss event in the range of 228.3 °C to 360.9 °C with the loss of 36.3 % resulting to the decomposition of the API (fig. 2). The TG analysis of the samples storage for 1 mo at 20 °C in 0 % RH and 40 % RH revealed no changes in the thermal parameters of the analyzed compound. Hence, the thermal analysis proved the stability of MOX after 1 mo of storage in these conditions. For samples after 1 mo of storage in 90 % RH at 20 °C and in 75 % RH at 40 °C, TG curves exhibited changes in the profile in comparison with the initial MOX (fig. 2) and it is possible to visualize the appearance of an initial mass loss of the drug, probably related to the loss of water molecules that were incorporated into the structure of MOX due to its exposure to the humid environment. In both samples (90 % RH and 75 % RH), the second mass loss did not change.

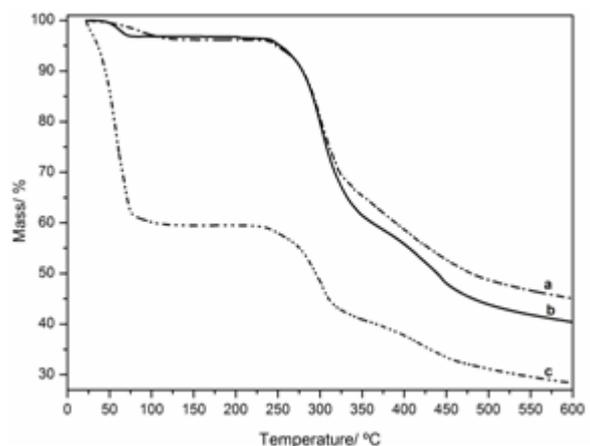


Fig. 2: TG curve of MOX stored for 1 mo at 75 % RH/40 °C (a), the initial sample of MOX (b) and the stored sample for 1 mo at 90 % RH/20 °C (c)

The fig. 3 illustrated the PXRD patterns of the initial MOX and samples stored for 1 mo at 20 °C in 0 % RH and 40 % RH. As can be observed in fig. 3, the PXRD profile of MOX exhibits a typical crystalline diffraction pattern, with a sharp main peak at 8.5° 2θ and secondary peaks at 7.1, 10.2, 17.7, and 21.5° 2θ. The PXRD analysis of the initial MOX reveals that the observed peaks of this sample match to the experimental ones of the anhydrous substance described as "form C" by Rao *et al.* [24]. The PXRD patterns of the stored MOX samples under 0 % RH and 40 % RH at 20 °C are also compared in fig. 3. There were not any visible changes between powder diffractograms of the initial MOX and the sample stored at these different conditions, confirming the thermal results. The fig. 4 illustrated the PXRD patterns of MOX storage at 20 °C in 90 % RH and at 40 °C in 75 % RH. In both stocked MOX occurred the same alterations compared from the initial sample of the drug. First distinguishable diffraction peaks appeared at 11.2, 20.4 and 23.6° 2θ. Additionally, there was lack of the peak at 7.1° 2θ and the unique peak which remains unchanged in the stored samples was at 5.8° 2θ in comparison with the initial sample. The most representative diffraction peaks at 8.5 and 10.2° 2θ of initial MOX were displaced in diffractograms of samples stored under these conditions.

A significant increase in the intensity of peaks at 14.5 and 27.5° 2θ was also observed. The experimental PXRD patterns of MOX at 20 °C in 90 % RH and 75 % RH at 40 °C are matched to the hydrated "form

II", which was described in a patent by Greenberg *et al.* [20]The results are shown in table 2.

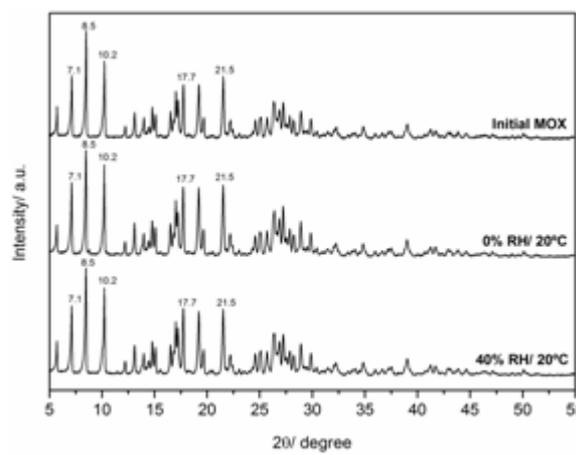


Fig. 3: PXRD patterns of the initial MOX and samples stored for 1 mo at 20 °C in 0 % RH and 40 % RH

Therefore, these results demonstrate that the storage conditions under high humidity have substantial influence on the MOX stability, contributing to the occurrence of the crystalline form transition of anhydrous MOX to the hydrate form. As already reported in the literature, the humidity causes significant effects on drugs if there are reactive species in the formulation being decisive in the physical or chemical modification (such as hydrolysis or hydrate formation) [29]. In order to predict the hydrate stability through the induction of the loss of water incorporated, we performed a heating using the TG by raising the temperature to 200 °C. Thus, the diffractogram provided the same major peaks (5.8, 8.4, 10.0, 11.2, 14.5, 20.4, 23.6, 27.5 degrees 2θ) of hydrated form before heating, occurring only the decrease in the intensity of the peaks. Thus, it was concluded that the hydrate form is stable and even with the heat is unable to return in its original form.

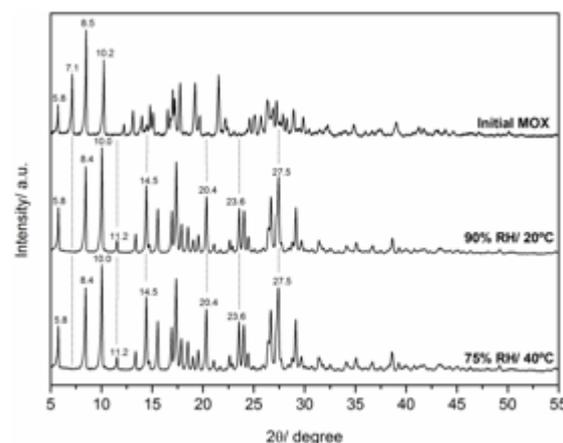


Fig. 4: PXRD patterns of the initial MOX and samples stored for 1 mo at 20 °C in 90 % RH and 40 °C in 75 % RH

Table 2: PXRD peaks (Positions in 2 θ) from hydrate "form II" reported in the literature [20] and from MOX hydrate obtained after storage for 1 mo at 90 % RH/20 °C and at 75 %/40 °C

Hydrate "form II" described in the literature [20](2 Theta)	Hydrate obtained after MOX storage (2 Theta)
5.8	5.8
8.5	8.4
10.1	10.0
11.6	11.6
13.4	13.4
14.5	14.5
14.8	14.8
15.6	15.6
17.0	17.0
17.2	-
17.4	17.4
17.5	-
17.9	17.9
18.6	18.6
19.1	19.1
19.6	19.6
20.4	20.4
21.1	21.1
21.8	21.7
22.7	22.7
23.0	23.0
23.6	23.6
24.1	24.1
24.5	24.6
26.5	26.4
26.7	26.6
27.0	-
27.3	27.2
27.5	27.5
27.8	27.8
28.5	28.4
28.9	28.9
29.2	29.1

The IR spectra corroborated with the results obtained by the other techniques. There were not any visible changes in IR spectra of the initial sample and the sample stored at the temperature 20 °C in 0 % RH and 40 % RH. The most important changes occurred for the samples stored at 90 % RH and 75 % RH, as illustrated in fig. 5. One of the detected changes occurred in the region of O-H stretching vibrations involved in the hydrogen bonds region from approximately 3600-3150 cm^{-1} . The other alteration occurred in the 1705 cm^{-1} , region of C=O stretching vibrations. These spectral variations can be attributed to the hydration of MOX due to its exposure at high humidity, as observed in the previously demonstrated results.

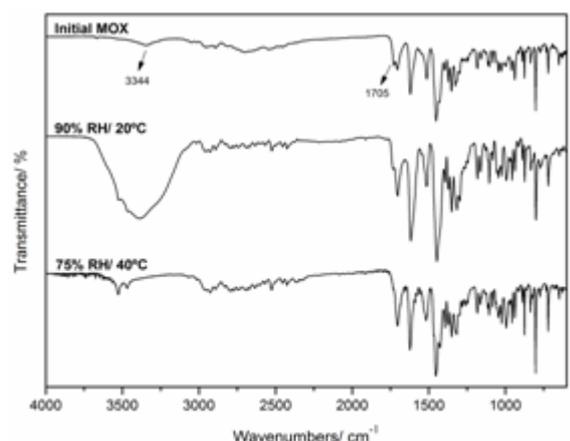


Fig. 5: IR spectra of the initial MOX and these stored for 1 mo at 90% RH/20 °C and 75 % RH/40 °C

As a final evaluation of this stability study, the samples that have displayed differences in its crystal lattice (exposed for one month at 20 °C in 90 % RH and at 40 °C in 75 % RH) were analyzed (triplicate samples) by the HPLC method for MOX assay [28]. This HPLC method for the quantification of MOX is important because it is possible to conclude if occurred the drug degradation, or if really happened the appearance of another crystalline form. The representative chromatograms obtained from the initial MOX and the samples stored under stress conditions are illustrated in fig. 6. The initial MOX showed retention time of 12.24 min approximately, and the area obtained from this analysis was considered as 100 % in order to compare the content with the stored samples. In this analysis, no alteration in the chromatographic profile and in the time retention of both samples were observed and there were no peaks from degradation products, evidencing that is the same substance, but in another crystalline form. As can be seen in table 1 the API's storage under the stress conditions showed a reduction in its concentration, which is justified by the presence of water in the structure of the hydrates as observed in thermogravimetric analysis.

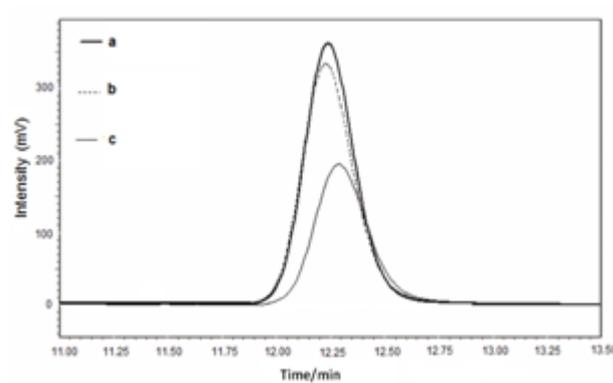


Fig. 6: Representative HPLC chromatograms of: initial sample of MOX (a), MOX after 1 mo at 75 % RH/40 °C (b) and 90 % RH/20 °C (c)

As previously mentioned in the literature, the improper solubility of a drug can cause damage in its bioavailability or give rise to large fluctuations in the fraction absorbed in the body fluids [30-32]. Therefore, it is extremely important to carry out solubility studies in drugs that exhibit more than one crystalline form as the case of MOX. The shake-flask method was employed to determine the relative solubility of the solid forms of MOX. Since both storages for 1 mo (90 % RH at 20 °C and 75 % RH at 40 °C) provided compounds with the same diffractograms, IR spectra, thermal parameters, and retention time as shown in the chromatogram, subtypes that were obtained identical hydrates. Therefore, only the sample stored in 90 % RH at 20 °C was selected to perform the shake-flask assay.

The theoretical solubility value of the MOX is 19.6 mg ml^{-1} as describe in the literature [33]. Then, the initial MOX and the sample storage under the condition mentioned above were added in excess (three times more) in the water to measurement its solubility employing the HPLC method for MOX assay [28]. The initial MOX showed 23.5 (± 0.8) mg/ml of solubility in water. The value was slightly higher than expected. On the other hand, the hydrate presented as the solubility in water the value of 20.6 (± 0.7) mg/ml , which was below than the value obtained for the initial form of the drug. This difference in solubility was expected, since it is known that the solubility of a drug can vary with any change in its physical properties, as the crystal form. Moreover, it was observed that the hydrate form is less soluble in aqueous media that the corresponding anhydrous form (initial MOX), which is also observed in most cases of drugs that exhibit anhydrate/hydrate forms [34]. Since solubility is related to the drug absorption, the occurrence of this crystalline transition can harm the drug therapy. Moreover, these data suggest the importance of conducting an investigation of these parameters in the early stages of the development of a new drug.

CONCLUSION

Even though the storage were varied, only the conditions 90 % RH/20 °C and 75 % RH/40 °C have a substantial influence on the MOX stability, contributing to the occurrence of the drug crystalline form transition, but just one hydrate form of MOX was detected. This paper also reported the occurrence of decreased solubility of the drug when it transits from initial solid form to the hydrated form. Therefore, pharmacotechnical wet processes are not be recommended for the pharmaceutical production of this drug because solvent granulation and drying conditions from processing provides a favorable environment for the transition of crystalline forms.

Different techniques were tested for the evaluation of the solid-state stability of MOX, and according to DSC, TG, PXRD, HPLC and FT-IR results, they showed good correlation with each other. Among these techniques, the thermal analysis proved to be enabled to identify and characterize hydrate forms. Furthermore, these methods are a powerful tool for a quick screening of structural changes occurring during the crystalline form transition and required a minimal sample amount and a short time of analysis in comparison with other techniques. Moreover, the associations of thermal analysis with non-thermal methods (PXRD and IR) ensure reliable interpretation of solid form stability studies.

These findings also suggest that stability studies of polymorphism associated with the evaluation of relative solubility are essential for a stable formulation development and to choose between dry or wet granulation processes.

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CONFLICT OF INTERESTS

Declared None

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