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Physico-chemical solid-state characterization of omeprazole sodium: Thermal, spectroscopic and crystallinity studies

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ABSTRACT

The physical characterization of active pharmaceutical substances is crucial to the successful development of the final drug product. The different solid forms and variations in the degree of crystallinity can lead to significantly different physical and chemical properties, including color, morphology, stability, dissolution and bioavailability. In the case of omeprazole sodium (OMS), its chemical structures contain a specific number of water molecules (hydrate). The behavior of pharmaceutical hydrates has become the object of increasing attention over the past decade, primarily due to the potential impact of hydrates on the development process and dosage form performance. The present study was designed to characterize and evaluate the crystallinity of omeprazole sodium, dehydrated omeprazole sodium (DOMS) and omeprazole free base (OM) using a variety of techniques including thermal analysis (thermogravimetry/derivative thermogravimetry (TG/DTG) and differential scanning calorimetry (DSC)), diffuse reflectance infrared Fourier transform (DRIFT) spectroscopy, scanning electron microscopy (SEM) and X-ray powder diffraction (XRPD). Furthermore, an NMR spectroscopy study was also carried out to clarify the conformation and crystal structure.

1. Introduction

Omeprazole, a substituted benzimidazole compound and prototype antisecretory agent, is a potent non-reversible inhibitor of the gastric proton-pump H^+/K^+-ATPase which is responsible for gastric acid secretion. It is an effective drug used in the treatment of acid peptic disorders and has found worldwide popularity over the past decade [1,2].

Omeprazole was launched into the market in Europe in 1988 as Losec® and in the United States in 1990 as Prilosec®. The drug introduced a new approach to the effective inhibition of acid secretion and the treatment of acid-related diseases, proven to be clinically superior to the H_2-receptor antagonists. None of the subsequently developed and produced antisecretory drugs, including those in the proton-pump inhibitor class, have been shown to be significantly superior to omeprazole in clinical practice [3,4].

In relation to improving the solubility and bioavailability of omeprazole, it is important to note that the original drug can exist in the form of salts, known as omeprazole sodium or omeprazole magnesium. Omeprazole sodium ($C_{17}H_{18}N_3NaO_3S{\cdot}H_2O$), 5-methoxy-2-[(RS)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole sodium, is a white hygroscopic powder which is freely soluble in water and in alcohol, very slightly soluble in dichloromethane and soluble in propylene glycol [5–7]. The pH of a 2% solution in water is 10.3–11.3. It is a weak base with pK_{a1} = 7.07 and pK_{a2} = 14.73 [4,8]. Moreover, it is acid labile decomposing rapidly at pH < 5.0 and is sensitive to heat, moisture, organic solvents and to some degree, light. The degradation of omeprazole manifests itself in a loss of drug content and increasing amounts of degradation products [4,9–12].

The drug is a racemate and contains a tricoordinated sulfur atom in the pyramidal structure, which gives two optical active isomers (enantiomers), (S)- and (R)-omeprazole [4,8]. The S isomer (esomeprazole) has higher bioavailability resulting in higher plasma concentrations than those achievable with the R isomer. But these two enantiomers have a similar inhibitory effect on acid formation at the parietal-cell level and are equally effective, and they are transformed to the same active inhibitor within the parietal cell. Esomeprazole was launched as Nexium® in 2000 by AstraZeneca [3,13].

In the case of omeprazole sodium, its chemical structure contains a specific number of water molecules (omeprazole sodium

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hydrate). The behavior of pharmaceutical hydrates has become the object of increasing attention over the past decade, primarily due (directly or indirectly) to the potential impact of hydrates on the development process and dosage form performance [14,15].

The dehydration of a hydrate is one of the most important reactions in the solid state and is of special concern because of potential conversion to metastable or amorphous phases with greatly reduced stability [16]. The removal of water from the crystal lattice leads to more or less distinct internal structural changes that can result in considerably altered physical and chemical properties [17]. Dehydrated forms fall into two categories: those that exhibit significant phase changes upon desolvation (such as a polymorphic transformation or conversion from a crystalline phase to an amorphous phase) and those that do not show such changes [18].

The complex physical properties of hydrates can be better understood from knowledge of their solid-state structure. Characterization of solid-state properties at an early stage, using appropriate analytical methodologies, is an essential pre-requisite in the development of solid dosage forms both from scientific and regulatory points of view [15,19]. For rational drug development, it is therefore essential to evaluate the influence of the polymorphic and salt forms on the physico-chemical properties of substances [20]. Variations in the degree of crystallinity in a pharmaceutical substance may be associated with physico-chemical differences which have an impact at the therapeutic, manufacturing, commercial and legal levels [21].

In 1998, Ruiz et al. [22] published a study on the stability of omeprazole in both granules and powder form by means of differential scanning calorimetry (DSC). They observed the greatest changes in the stability of the basic form of omeprazole when subjected to light, elevated temperature and different pH values. Markovic et al. [13] studied the physical and thermal stability of both enantiomers of omeprazole sodium and indicated that the sodium salts are more stable than neutral forms. Attempting to improve the solubility of omeprazole and consequently increase its bioavailability, Figueiras et al. [23] reported the solid-state characterization and dissolution profiles of the inclusion complexes with modified cyclodextrin. At present omeprazole sodium is formulated in solid dosage and extemporaneous forms, however, little is known about its solid-state properties including the effect of the dehydration process on the physical and chemical stability of this pharmaceutical hydrate.

Thus, this paper deals with the solid-state characterization of the racemate omeprazole sodium salt (OMS), dehydrated omeprazole sodium (DOMS) and omeprazole base (OM) using a variety of techniques including thermal analysis (thermogravimetry/derivative thermogravimetry (TG/DTG) and DSC), diffuse reflectance infrared Fourier transform (DRIFT) spectroscopy, scanning electron microscopy (SEM) and X-ray powder diffraction (XRPD). Also, an NMR spectroscopy study was carried out to clarify the conformational and crystal structure.

2. Materials and methods

2.1. Materials

Bulk omeprazole sodium racemate (100.7%) was kindly donated by Eurofarma SA (São Paulo, Brazil). The omeprazole base reference standard (SQR FB 1030) with stated purity of 100.1% was provided by Brazilian Farmacopeia.

2.2. Dehydration of omeprazole sodium

Dehydrated omeprazole sodium (DOMS) was obtained by subjecting 30 mg of the sample to isothermal thermogravimetric analysis. The conditions were: platinum crucible in synthetic air atmosphere (50 mL min^{-1}) at a heating rate of 2 °C min^{-1} up to a target temperature of 140 °C. The holding time was maintained until constant mass.

2.3. Preparation of omeprazole base form

Omeprazole sodium (400 mg) was dissolved in around 40 mL of distilled water, placed in a separatory funnel and then extracted by addition of 40 mL of methylene chloride twice. The organic phase was evaporated in a rotatory evaporator at a bath temperature of 25 °C and the crystallized solid was obtained (omeprazole base). The identity of the extracted omeprazole base was confirmed by means of DRIFT, DSC, TG and NMR analysis. The results were identical to those obtained for an omeprazole reference standard (SQR FB 1030).

2.4. Karl Fisher titrimetry (KFT)

The total water content of OMS and DOMS was determined by Karl Fisher titrimetry in a Mettler Toledo Volumetric KF titrator model DL38 (Alphaville Barueri, Brazil). The samples were titrated using spectroscopic grade methanol (Darmstadt, Germany). Aliquots of 100 mg of each sample were added to the titrator vessel following instrument equilibration. Each sample was measured in triplicate.

2.5. Thermal analysis

Omeprazole sodium, dehydrated omeprazole sodium and omeprazole base were investigated by thermoanalysis techniques using thermogravimetry/derivative thermogravimetry and differential scanning calorimetry.

2.5.1. Differential scanning calorimetry analysis

The DSC analysis was carried out using a Shimadzu DSC-60 calorimeter, operating at a temperature range of 25–500 °C. Approximately 2 mg of samples were weighed in an aluminum pan and scanned at a heating rate of 10 °C min^{-1}, under synthetic air atmosphere (50 mL min^{-1}). The DSC equipment was preliminarily calibrated with a standard reference of indium.

2.5.2. Thermogravimetric analysis

The TG/DTG curves were obtained with a Shimadzu TGA-50 thermobalance, using platinum crucibles. Approximately 5 mg of samples were measured from 25 to 800 °C at a heating rate of 10 °C min^{-1}, under synthetic air atmosphere (50 mL min^{-1}). The decomposition was monitored as a function of temperature and weight loss. The equipment was preliminarily calibrated with a standard reference of calcium oxalate, stated purity of 99.99%.

2.5.3. Kinetics analysis

The non-isothermal kinetics study was carried out using thermogravimetric analysis. Approximately 5 mg of samples were placed in platinum pans and heated for 5, 10, 15, 20 and 25 °C min^{-1} at the temperature range of 25–800 °C under dynamic synthetic air atmosphere with a flow rate of 50 mL min^{-1}. The kinetics parameters were determined through the Ozawa method using Shimadzu TASYS software [24,25].

2.6. Diffuse reflectance infrared Fourier transform spectroscopy

The DRIFT spectra were obtained with a Shimadzu spectrophotometer, model FTIR Prestige, in a scan range of 400–4000 cm^{-1} with an average of over 32 scans at a spectral resolution of 4 cm^{-1}

in KBr. A background spectrum was obtained for each experimental condition. Each sample (OMS, DOMS, and OM) was prepared by mixing 2% (w/w) of the drug in potassium bromide (KBr).

2.7. X–ray powder diffraction

The crystallinity of each sample was characterized by X-ray powder diffraction obtained with a Siemens diffractometer D5000 model, with a Cu Kα 40 kW tube and current of 40 mA, in the range of 3–65 (2θ) with a pass time of 1 s.

2.8. Scanning electron microscopy

The photomicrographs of OMS, DOMS and OM were taken with a Phillips scanning electron microscope, model XL30. Samples were mounted on metal stubs using double-sided adhesive tape, vacuum-coated with gold (350 Å) in a Polaron E 5000 sputter coating unit and directly analyzed by SEM (400× and 1000×).

2.9. Nuclear magnetic resonance spectroscopy

The ^{1}H NMR spectra were obtained at 22 °C using a Varian AS 400 spectrometer operating at 400.03 MHz. The spectra were obtained in DMSO-d6 solution for OMS and DOMS, and $CDCl_3$ for OM. The complete ^{1}H chemical shifts are given as parts per million (ppm).

3. Results and discussion

3.1. Thermal analysis

The thermal behavior of omeprazole sodium can be observed in the TG/DTG and DSC curves given in Fig. 1. The DSC curve shows three well-defined thermal events, an endothermic followed by exo and endothermic peaks. The endo peak corresponds to the dehydration of OMS (T_{peak} = 128.92 °C; T_{onset} = 123.85 °C; ΔH = −74.71 J/g). The additional exothermic (T_{peak} = 194.36 °C) and endothermic events (T_{peak} = 202.74 °C) correspond to the decomposition process. The first mass loss of the TG/DTG curve refers to the release of crystallization water ($\Delta m \sim 6.6\%$) in a defined way between 120 and 165 °C. The additional mass loss events correspond to the decomposition process at 194–800 °C (Δm = 74.00%). It is clear that between 500 and 600 °C the ignition process occurs (DTG_{peak} = 572.07 °C, $\Delta m \sim 50\%$).

In order to investigate whether the drug has a melting point, a comparative study was performed. After a dehydration process using a TG isothermal procedure, a sufficient amount of the DOMS was submitted to TG and DSC analyses. It was observed that the drug degrades without an endothermic event. The curves obtained for DOMS are shown in Fig. 2.

The DSC curve shows two thermal events, an exothermic at T_{peak} = 192.02 °C followed by an endothermic at T_{peak} = 200.04 °C, both corresponding to the decomposition process. In this case, the first endothermic event between 120 and 165 °C was not observed, and there was no mass loss indicated by the TG/DTG curve, confirming that the crystallization water (bound water) was no longer present. The thermal profile of DOMS is quite similar to that of OMS except that is does not show the dehydration event.

The DSC combined with the TG data showed that the drug dehydration process occurs at the same temperature range as the first endothermic event in the DSC curve, suggesting that omeprazole sodium racemate has no melting event. Generally, for drugs, the first endothermic event refers to the fusion process [26], and this was not observed in the analysis of omeprazole sodium.

On the other hand, in the thermal profile of the omeprazole base a single sharp endothermic peak, typical of the fusion of crystalline substances, was observed. The TG/DTG and DSC curves are given in Fig. 3. The DSC curve of OM was typical of a pure substance, showing an endothermic event at T_{peak} = 154.04 °C; T_{onset} = 152.17 °C; ΔH = −81.32 J/g. This event corresponds to the omeprazole melting point reported in literature [27]. Immediately after the endothermic event, the exothermic event occurs, indicating a decomposition process (T_{peak} = 166.24 °C). The TG curves showed that omeprazole is stable up to 159 °C and that the thermal decomposition process occurs in several stages up to 800 °C (Δm = 97.8%).

Through the DSC investigations it was observed that omeprazole in salt form has a different behavior to the base form. The difference in the thermal profile of the salt form is mainly related to the melting event, suggesting a potential conversion to a metastable or amorphous state. Similar behavior has recently been reported in the literature [28]. Markovic et al. [13] observed that in R- and S-omeprazole sodium the enantiomers did not show melting events. In 1998, Ruiz et al. [22] reported greatest alterations in the melting point of omeprazole base when subjected to different light, temperature and pH conditions.

Using five thermogravimetric curves (not shown), it was verified that the loss of crystallization water of OMS is dependent on the heating rate. Table 1 gives the different heating rates and the

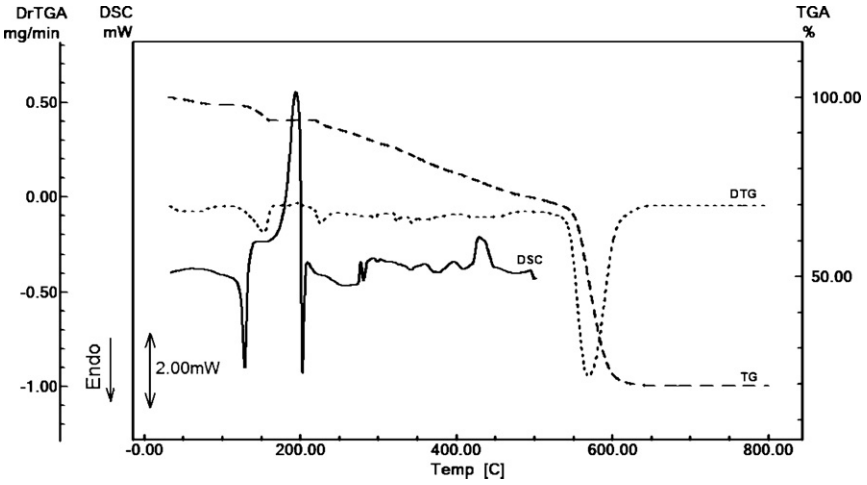


Fig. 1. The DSC and TG/DTG curves of omeprazole sodium obtained under synthetic air atmosphere (50 mL min^{-1}) at a heating rate of 10 °C min^{-1}.

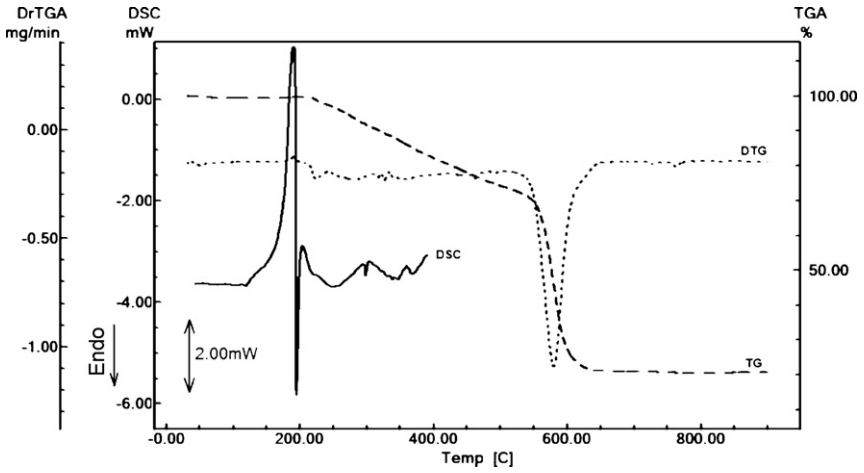


Fig. 2. The DSC and TG/DTG curves of dehydrated omeprazole sodium obtained under synthetic air atmosphere (50 mL min^{-1}) with a heating rate of 10 °C min^{-1}.

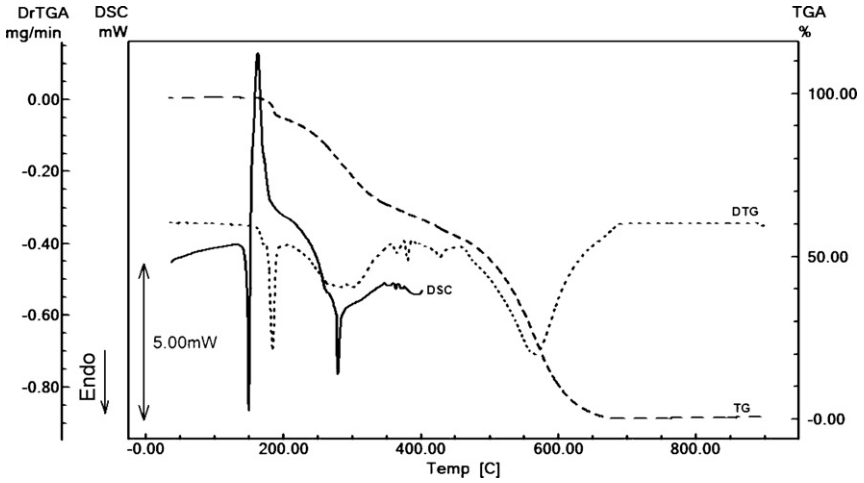


Fig. 3. The DSC and TG/DTG curves of omeprazole base obtained under synthetic air atmosphere (50 mL min^{-1}) at a heating rate of 10 °C min^{-1}.

temperature range where the loss of crystallization water occurs. It was observed that for the TG performed at 1 °C min^{-1} the water content was released at a lower temperature (90–125 °C; DTG_{peak} 117.49 °C). Since the intermolecular force (hydrogen bonding) can lead to very strong water–solid interactions, a slower heating rate facilitates the dehydration process [29].

The water content was also considered by Karl Fisher titrimetry method, which is one of the official techniques of British Pharmacopoeia [7]. The total water content determined for OMS was 6.69 ± 1.97%, which is consistent to 1.4 mol H_2O/mol of OMS. The results were very similar to those obtained by TG analysis. In the case of DOMS, the KFT analysis confirmed that the bound water was released, and only sorbed water was observed (0.663 ± 1.51%).

Table 1
TG measurements at different heating rates. Δm (%) corresponds to loss of crystallization water with respective temperature range and DTG_{peak}.

Heating rate	Δm (%)	Temperature range (°C)	DTG_{peak} (°C)
1 °C min^{-1}	6.40	90–125	117.49
2 °C min^{-1}	6.39	110–140	133.69
5 °C min^{-1}	6.69	115–155	143.26
10 °C min^{-1}	6.34	120–165	149.30
20 °C min^{-1}	6.74	125–175	155.42

3.2. DRIFT analysis

Diffuse reflectance infrared Fourier transform spectroscopy was applied in this study because it is the most suitable technique of the non-destructive spectroscopic methods. DRIFT has become an attractive method in the quantitative analysis of pharmaceutical solids, since the materials are not subject to thermal or mechanical energy during sample preparation, therefore preventing solid-state transformations [30].

The OMS, DMOS and OM were investigated by DRIFT analysis. A comparative spectrum is shown in Fig. 4. The IR spectra of all samples showed characteristic bands of benzomidazole and pyridyl rings below 1700 cm^{-1}. At 1643–1600 cm^{-1} stretching vibrations of C=C–N and S–C=N, along with benzimidazole –O–CH_3 stretching between 1214 and 1191 cm^{-1} accompanied by the resonance band at 1076 cm^{-1} and sulfoxide group vibration (S=O) at 1155 cm^{-1} were observed.

The differences were more pronounced in the region above 3000 cm^{-1}. The OM spectrum showed absorption at 3440–3310 cm^{-1} due to amino (N–H) stretching vibrations characteristic of the drug base form. The OMS spectrum showed a rather intense sharp band at 3441 cm^{-1} as a consequence of O–H stretching, characterizing the crystalline water of the salt form. In the other hand, the dehydration caused a broad band between 3675 and 3070 cm^{-1}.

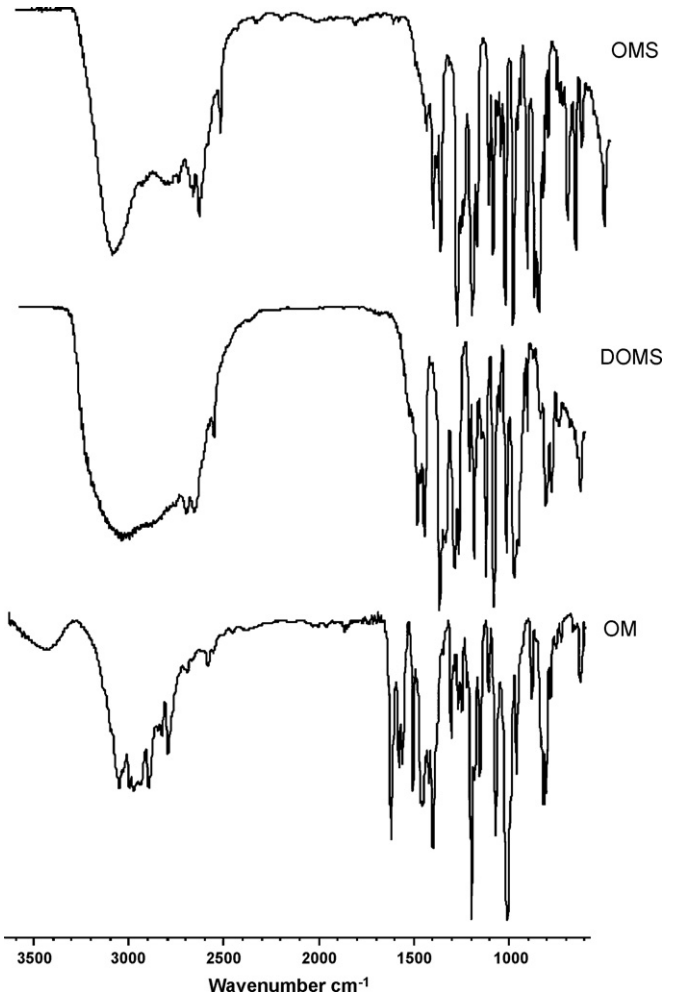


Fig. 4. Comparative DRIFT spectra of OMS, DOSM and OM.

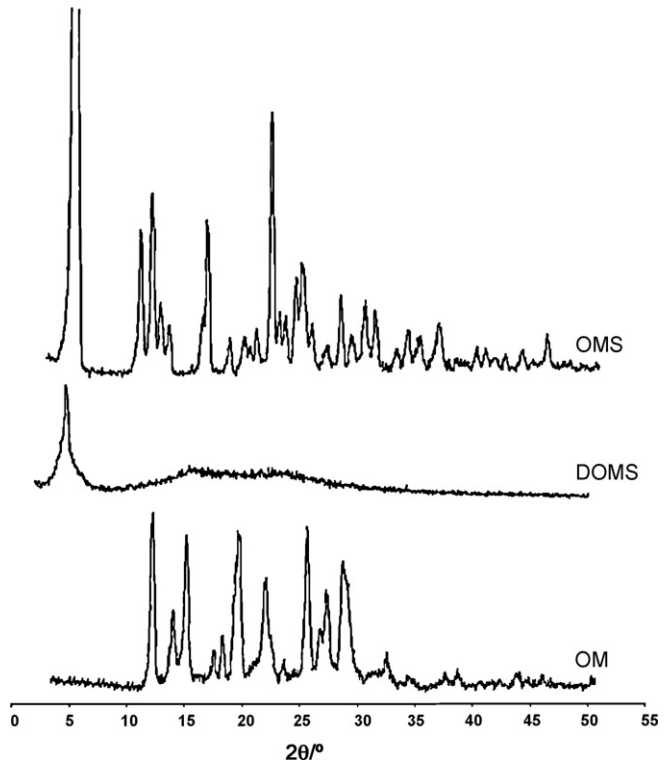


Fig. 5. X-ray powder diffraction patterns of omeprazole sodium (OMS), dehydrated omeprazole sodium (DOMS) and omeprazole base (OM).

3.3. X-ray powder diffraction analysis

X-ray powder diffraction has been used for qualitative and quantitative identification of crystallinity [30,31]. The XRPD patterns of OMS and OM revealed several diffraction peaks which are indicative of its crystalline character, while a hollow pattern was recorded for DOMS which verifies its amorphous state. The diffractograms of OMS, DOMS and OM are shown in Fig. 5, and Table 2 shows the *d*-distances and relative intensities (I/I_o) of the observed peaks in these patterns.

The relative crystallinity (X_c^{rel}) of each sample was calculated based on the Ruland method, in which the area of the crystalline diffraction relative to the total area of the diffractogram is taken as a measure of crystallinity [32]. Although, Ruland is an empirical method, it is widely used to compare diffraction patterns, in which the diffractograms are baseline-corrected, by smoothing the signal/noise ratio [33,34]. Thus, the X_c^{rel} indices calculated were 67.03% for OMS, 4.34% for DOMS and 43.55% for OM.

The crystallinity degree is associated with stability and, therefore, omeprazole sodium appears to be more stable than omeprazole base. Furthermore, through X-ray powder diffraction it was verified that when omeprazole sodium undergoes dehydration, it is unstable, with conversion to an amorphous form. This apparent instability was previously observed in the DSC analysis and confirmed through the TG kinetics parameters.

Table 2
X-ray powder diffraction data for *d*-distances and relative intensities (I/I_o) of OM, OMS and DOMS patterns.

Omeprazole sodium (OMS)			Dehydrated omeprazole sodium (DOMS)			Omeprazole base (OM)		
2θ (degree)	*d* (Å)	I/I_o (%)	2θ (degree)	*d* (Å)	I/I_o (%)	2θ (degree)	*d* (Å)	I/I_o (%)
5.62	15.712	100	5.62	15.574	100	5.62	15.712	1.570
–	–	–	–	–	–	9.18	9.625	100
11.18	7.908	7.794	–	–	–	11.08	7.9788	23.430
12.23	7.231	9.663	–	–	–	12.38	7.144	71.749
16.98	5.217	8.320	–	–	–	14.88	5.949	11.323
22.63	3.926	13.836	–	–	–	15.78	5.611	18.049
25.18	3.534	6.135	–	–	–	17.28	5.127	43.274
						19.78	4.485	29.372
						24.08	3.693	6.278
						24.28	3.562	11.771
						25.63	3.473	19.955
						27.58	3.232	29.484

3.4. Scanning electron microscopy

The SEM photomicrographs of OMS, DOMS and OM are given in Fig. 6. It was observed that OMS and OM are characterized by regular shaped crystals and DOMS is mainly composed of spherical particles with an amorphous character. The shape of the crystals can be visualized by increasing the magnification to 1000× (B, D and F). Orthorhombic crystals were observed in OMS and OM, and DOMS showed homogeneous aggregates of spherical particles confirming its amorphous form.

The results obtained from the DSC, XRPD and SEM analyses revealed that the removal of water from the crystal lattice leads to changes in the internal structural, which produced an amorphous state of omeprazole sodium.

3.5. Kinetics analysis

The stability of OMS, DOMS and OM was investigated using non-isothermal kinetics analysis. The effect of temperature was evaluated in terms of the reaction order and the velocity of the degradation process. One of the main purposes of the kinetics analysis of solid-state decomposition is to determine the reaction mechanisms and activation energy (E_a), which are based on the Arrhenius equation.

The non-isothermal kinetics study was performed by application of the Ozawa method, which is an integral method for determining the activation energies in dynamic heating experiments [24,35]. The kinetics data were calculated by plotting mass loss versus temperature for five TG curves obtained at different heating rates.

Fig. 7 shows the superposition of the thermogravimetric curves which are shifted to higher temperatures when heating rates increase. The inserted figure shows the correlation of the Ozawa plots of the five curves. The activation energy was obtained from a plot of the logarithms of the heating rates as a function of the inverse of the temperature ($1/T$) for a constant $G(x)$, where $G(x)$ is the integrated form of the conversion dependence function, $f(x)$ [25].

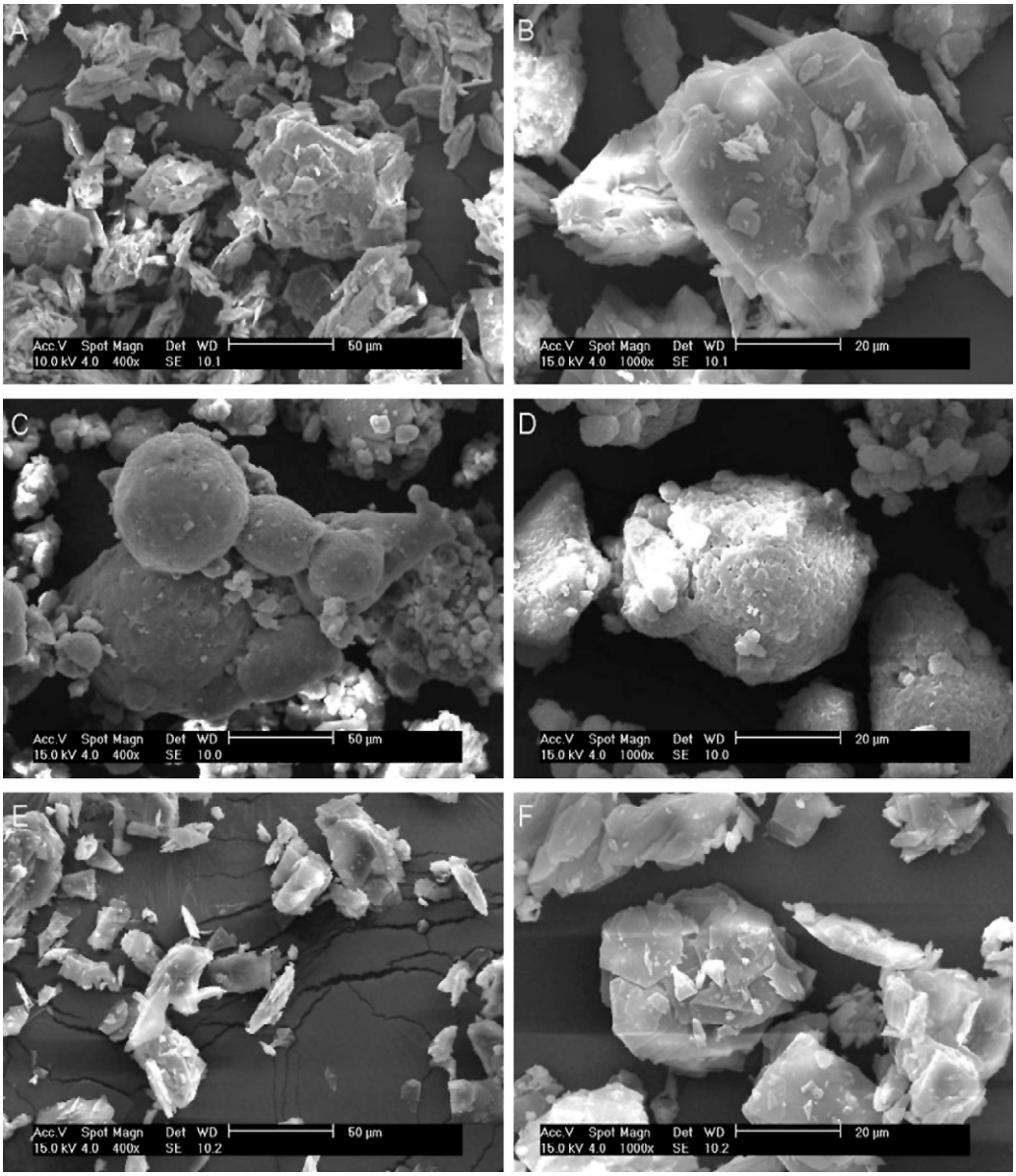


Fig. 6. Scanning electron micrographs of OMS (A and B), DOMS (B and C) and OM (E and F). A, C and E were taken at a magnification of 400× and C, D and F at 1000×.

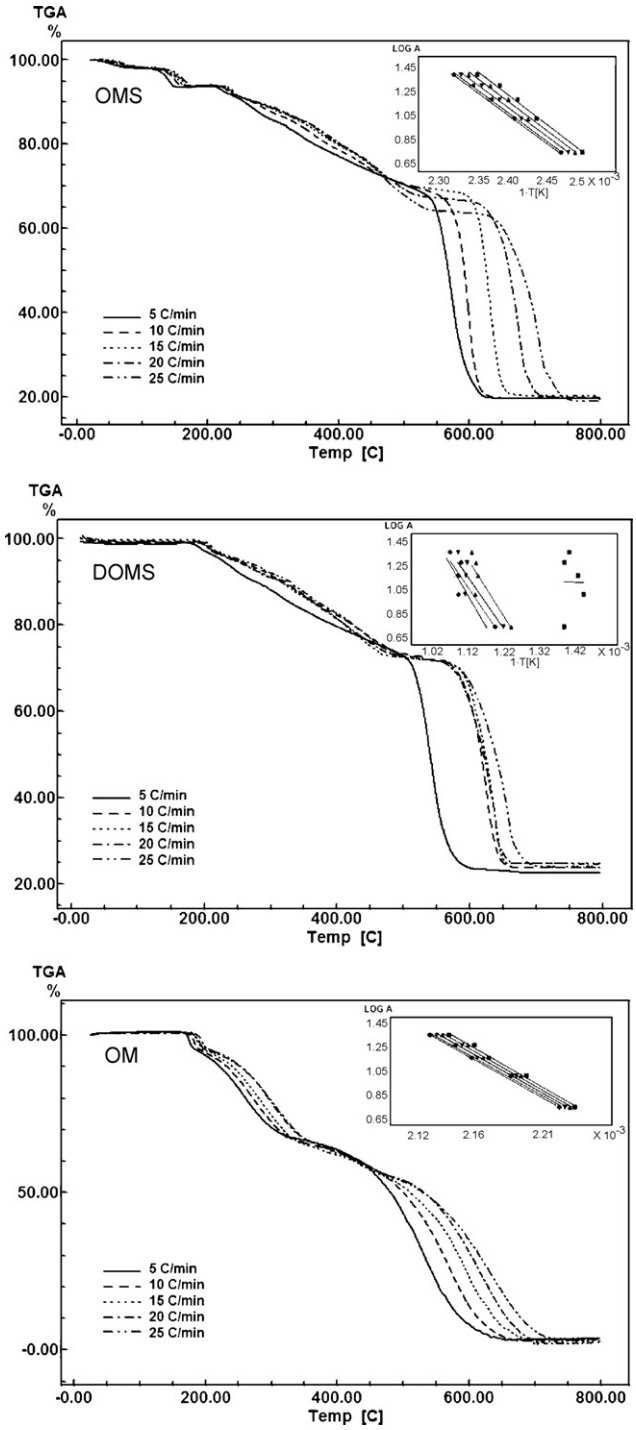


Fig. 7. TG curves of OMS, DOMS and OM obtained at different heating rates under dynamic synthetic air atmosphere. The inserted figure shows the linear tendency and correlation of the Ozawa plots of the five curves.

The kinetics analysis of OMS demonstrated the good linear tendency of the Ozawa plot and the calculated activation energy (E_a) was 250.85 kJ/mol. When omeprazole sodium undergoes dehydration, the molecular structure shifts to the amorphous form and the mechanism of decomposition does not follow a linear correlation. It was not possible to calculate the activation energy for DOMS as a linear tendency of the plot was not achieved. Additionally, the five curves obtained in the kinetics analysis of OM demonstrated a linear tendency and the mechanism of decomposition was shown to

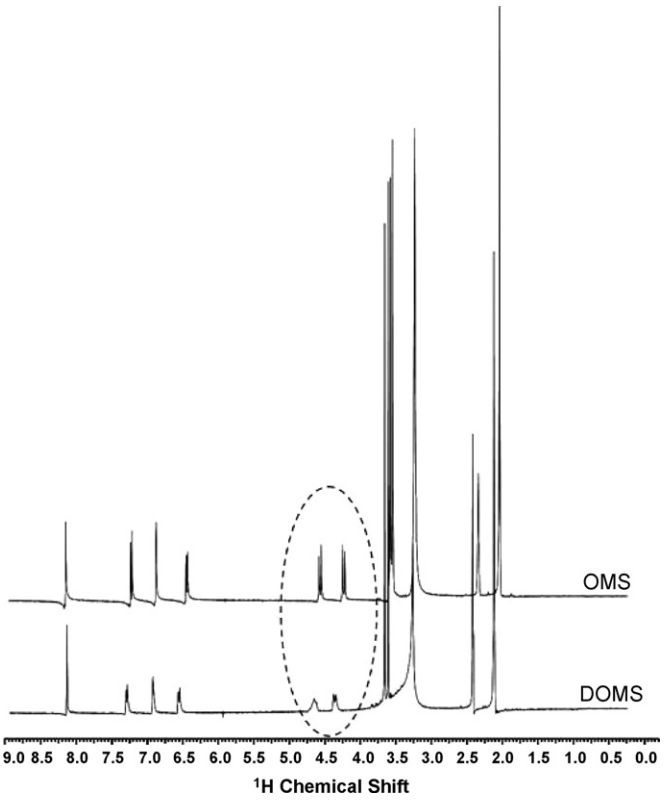


Fig. 8. A comparative ^{1}H NMR spectra of OM and DOMS.

be independent of the concentration of the reactant. The activation energy obtained was 140.47 kJ/mol.

The experimental decomposition kinetics indicates that omeprazole sodium salt is more stable than omeprazole base, and the results are in agreement with the literature. The dehydration of a hydrate is one of the most important reactions in the solid state. The removal of water from the crystal lattice promoted a structural change, which altered the physical and chemical properties; in this case the instability of DOMS was confirmed by the kinetics analysis.

3.6. NMR analysis

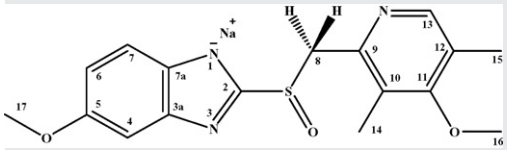
Nuclear magnetic resonance spectroscopy has become an essential tool for the solid-state characterization of pharmaceuticals. The technique can not only differentiate between different forms of materials, but also intimately probe the structural aspects. This technique is especially important for pharmaceuticals in solid forms that cannot be crystallized and studied by single-crystal X-ray techniques [36].

Most hydrates dehydrate to anhydrous solids whose crystal structures are different from that of the original hydrate phase. Some become amorphous when dehydrated, while others retain their three-dimensional packing arrangements after dehydration [17]. In the case of omeprazole sodium, it was previously confirmed that its original crystal structure shifted to an amorphous form.

Attempting to understand the changes in molecular structure, solid-state ^{13}C NMR and ^{1}H NMR spectroscopic analyses were carried out. The data collected from solid-state ^{13}C NMR are not shown because there were no differences in the chemical shifts of the carbon signals of OMS and DOMS, there was only one series of signals.

Nevertheless, through solution-state ^{1}H NMR analysis it was possible to observe differences in the spectrum. The ^{1}H NMR data

Table 3
^{1}H NMR data for omeprazole in DMSO at 400 MHz.



	^{1}H chemical shift, δ (ppm)	
	OMS (multiplicity, J (Hz))	DOMS (multiplicity, J (Hz))
H-13	8.40 (s)	8.40 (s)
H-7	7.30 (d, 8.47)	7.33 (d, 8.58)
H-4	6.95 (d, 2.15)	6.95 (d, 2.17)
H-6	6.55 (dd, 8.47, 2.15)	6.52 (dd, 8.58, 2.17)
H-8a	**4.67 (d, 12.9)**	**4.70**
H-8b	**4.35 (d, 12.9)**	**4.35**
16-OMe	3.72 (s) or 3.69 (s)	3.72 (s) or 3.69 (s)
17-OMe	3.72 (s) or 3.69 (s)	3.72 (s) or 3.69 (s)
14-Me	2.49 (s) or 2.45 (s)	2.49 (s) or 2.45 (s)
15-Me	2.49 (s) or 2.45 (s)	2.49 (s) or 2.45 (s)

The values in bold demonstrate the greatest changes found in the NMR spectrum, showing the difference in the chemical shift and multiplicity.

obtained for OMS and DOMS are given in Fig. 8 and the chemical shifts in Table 3.

The chemical shifts in the ^{1}H NMR spectra of OMS and DOMS were similar. The greatest changes are seen in the DOMS spectrum, more specifically in the shape and intensity at δ 4.7 ppm and δ 4.35, assigned to the hydrogens H-8a and H-8b, respectively. This suggests that the water molecule strongly interacts with these hydrogen atoms.

The water produces a very strong intermolecular force which gives a rigid structure to the crystal lattice. In fact, when the water is removed from the original crystal lattice the internal packing arrangement changes.

Thus, it is suggested that water molecules in the omeprazole sodium monohydrate show hydrogen-bond interactions with one nitrogen of the imidazol ring as well as the sulfoxide group (Fig. 9). In the present study, we are reporting a very likely structure of omeprazole sodium salt (Fig. 10) as shown in the crystal structural model published for omeprazole base form (Fig. 11) in the Cambridge Structural Database with the refcodes VAYXOI [37] and VAYXOI02 [38].

The structure of omeprazole sodium crystallizes with a specific intermolecular water interaction (hydrogen bonding) which stabilizes the salt form. The OMS has a bond donor (nitrogen of the imidazol ring) and one acceptor oxygen from the sulfoxide group. The omeprazol base comprises a dimer with intermolecular N–H···O=S hydrogen bonding, and the dimers are held together by Van der Waals contacts between the neighboring aromatic rings in the crystal structure.

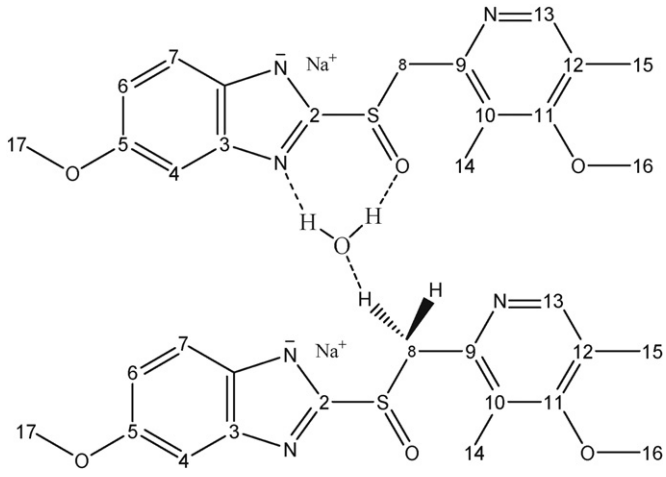


Fig. 9. Molecular scheme showing the hydrogen-bond interactions with one nitrogen of the imidazol ring (C=N···H), sulfoxide group (S=O···H) and hydrogen assigned to C8 (C–H···O).

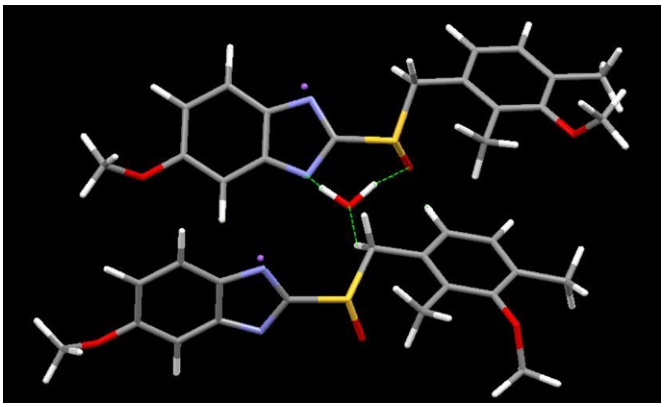


Fig. 10. Molecular packing of omeprazole sodium. The dotted lines represent the hydrogen bonding with the water molecule.

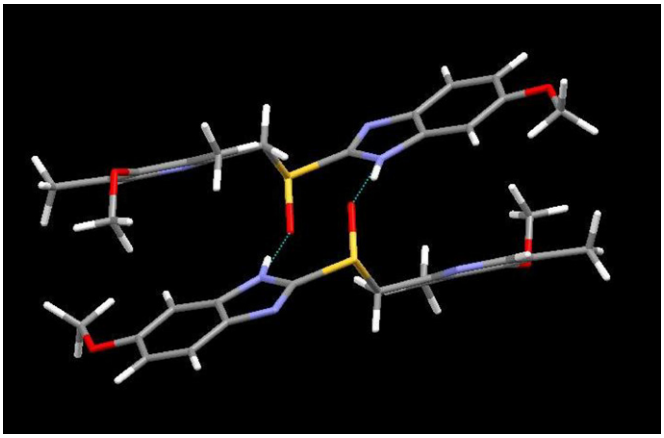


Fig. 11. Molecular packing of omeprazole base. The dotted line represents the intermolecular hydrogen bonds (Ohishi et al. [37] and Deng et al. [38]).

4. Conclusions

Solid-state characterizations of omeprazole sodium, dehydrated omeprazole sodium and omeprazole base were investigated. Using thermal analysis (TG/DTG and DSC) it was observed that omeprazole in salt form has a different behavior to the base form. The difference is observed through the melting event, in which the salt form was characterized by degradation without a fusion process. Omeprazole sodium contains a specific number of water molecules in its crystal structure and the removal of water from the crystal lattice leads to internal structural changes, which produce an amorphous form. This phenomenon was characterized by DSC, TG, XRPD, and SEM. Through TG kinetics investigations it was verified that salt forms of omeprazole are more stable than the base form. Furthermore, using ^{1}H NMR spectroscopic analysis it was elucidated that the crystalline water produces a very strong intermolecular force which gives a rigid structure to the crystal lattice. Therefore, when the water is removed from the original crystal lattice the internal packing arrangement changes to the amorphous state. The water molecule in the omeprazole sodium monohydrate shows hydrogen bonding interactions with one nitrogen of the imidazol ring as well as the sulfoxide group. During a pre-formulation phase, it is essential to consider the influence of the dehydration process on the physical and chemical stability of omeprazole sodium salt.

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