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Improving furosemide polymorphs properties through supramolecular complexes of β-cyclodextrin

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ABSTRACT

In this work, complexes of β-cyclodextrin and the two solid forms of furosemide were prepared and characterized for their potential pharmaceutical applications, with the interactions between the two compounds being studied in the solution and solid states. The solubility studies revealed different behaviors of the polymorphs. In particular, it was observed that the binary complex significantly increased the solubility of furosemide form I in the gastric simulated fluid, which resulted in a rise in the bioavailability of this formulation after oral administration. In addition, results using ssNMR, FT-IR, DSC, TGA, SEM and XRPD provided evidence of the formation of complexes after utilizing kneading and freeze-drying methods. A comparison with previous developed complexes that used maltodextrin as the ligand was performed. Our results suggest that these novel supramolecular complexes showed promise to be used in drug delivery systems with an application in pharmaceutical formulations.

1. Introduction

It is well known that pharmaceutical solids can exist in various solid-state forms which have different physicochemical properties that affect their performance. In particular, polymorphic changes in the active pharmaceutical ingredient (API), may lead to significant effects on the bioavailability of the final product after oral administration [1].

Pharmaceutical complexes in solid state are usually developed in order to improve the profile of a single organic molecule, in terms of solubility, stability, bioavailability and organoleptic properties [2–4]. For example, supramolecular complexation is a commonly used technique to increase the solubility of poorly water-soluble drugs. Among the macromolecules utilized to solubilize drugs, the cyclodextrins (CDs) are the most widely used as they are an effective alternative. CDs are able to form inclusion complexes with many different types of appropriately sized and preferential non-polar molecules, both in solution and solid state [5–7].

Furosemide (FUR, Fig. 1) is widely applied as a strong loop diuretic in the treatment of edematous states associated with cardiac, renal, and hepatic failure, and also in the treatment of hypertension [8]. It is known to exist in seven polymorphic forms: four true polymorphs (I, II, III, IV), two solvates (IV – DMS and V – dioxane) and one amorphous form [9–11]. Since FUR has a low water solubility and low permeability, it belongs to Class IV in the Biopharmaceutics Classification System [12]. The relatively poor and variable oral absorption of FUR (60–70% [8]), which occurs site-specifically in the stomach and upper small intestine [13], has been ascribed to the poor dissolution of FUR at low pH as well as to the involvement of intestinal efflux proteins [14].

In previous reports, several approaches, including CDs, have been developed to increase the solubility and/or the dissolution rate of FUR [15–17]. However, to date, the effect of excipients on the performance of different solid-state forms has not been widely studied. A recent investigation of ours focused on supramolecular complexes of different polymorphs of FUR and maltodextrin [18], which certainly showed better solubility properties than their precursors.

Based on these above considerations, the aim of the present investigation was to prepare and characterize new supramolecular systems of FUR polymorphs I and II with β-cyclodextrin (βCD, Fig. 1). The objective of producing these complexes was to enhance the low solubility of FUR, which represents a limiting factor that is responsible for its poor and highly variable human bioavailability, and also to compare these complexes with the supramolecular ones with maltodextrin. Complexation was studied using solubility analysis, solid-state Nuclear Magnetic

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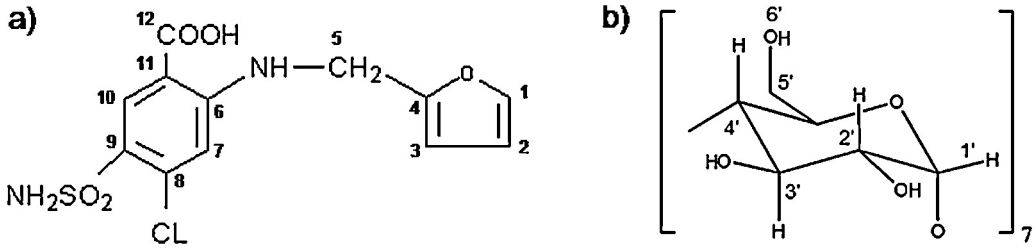

Fig. 1. Chemical structure of (a) FUR and (b) βCD, showing the carbon and proton numbering used in the NMR spectra.

Resonance (ssNMR), Fourier-transform Infrared Spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), Scanning Electron Microscopy (SEM), and X-ray Powder Diffraction (XRPD). The ^{1}H spin lattice relaxation time measurements were also carried out in solid state.

2. Materials and methods

2.1. Chemicals and reagents

Furosemide was provided by Parafarm (Argentina) and β-cyclodextrin (MW = 1135) was kindly supplied by the Ferromet agent of Roquette (France). All other chemicals were of analytical grade. A Millipore Milli Q Water Purification System (Millipore, Bedford, MA, USA) generated the water used in these studies.

2.2. Obtaining the polymorphic forms of furosemide

The two solid forms of FUR, I and II, were prepared as in our previous report [18]. Form I was recrystallised from a methanol solution and Form II was obtained from an acetone solution.

2.3. Solid sample preparations

The solid-state systems of FUR polymorphs I and II at an equimolar ratio with βCD were prepared as follows.

2.3.1. Kneading method (KN)

The FUR I:βCD (KN [kneading method] I) and FUR II:βCD (KN II) systems were prepared by accurately weighing appropriate amounts of βCD and then transferring these to a mortar. An ethanol–water (50:50, v/v) mixture was added to the βCD powder, and the resultant slurry was kneaded for about 10 min. For each system, the corresponding solid form of FUR was added at small amounts with the simultaneous addition of solvent in order to maintain a suitable consistency. This slurry was kneaded thoroughly for about 30 min, and the resultant paste was dried in a vacuum at 40 °C for 48 h and protected from light.

2.3.2. Freeze-drying method (FD)

To prepare the FUR I:βCD (FD [freeze-drying] I) and FUR II:βCD (FD II) systems, appropriate amounts of FUR (forms I or II) and βCD were suspended in water and sonicated at 25.0 ± 0.1 °C (constant water temperature) until the drug was completely dissolved. Solutions were then frozen at −40 °C for 24 h to ensure a complete solidification before the freeze-drying was started (Freeze Dry 4.5 Labconco Corp., Kansas City, MI).

2.3.3. Physical mixture (PM)

Physical binary mixtures of FUR I:βCD (PM I) and FUR II:βCD (PM II) were prepared by simply blending uniformly the corresponding components with a mortar and pestle.

2.4. Solubility studies

The effects of βCD on the solubility of solid forms of FUR were studied at 25.0 ± 0.1 °C in aqueous and buffered aqueous solutions of pH 2.0 and 6.5, with the solubility measurements being obtained according to the method of Higuchi and Connors [19]. An excess of the FUR forms I or II were added to solutions containing increasing concentrations of βCD ranging from 2.6 to 15 mM. FUR, in the absence of βCD, was used to determine the intrinsic solubility. The suspensions were sonicated for 15 min (ULTRASONIC LC 30 H Elma), before being placed for 72 h in a constant temperature water bath [Haake DC10 thermostat (Haake, Paramus, NJ, USA)]. These suspensions were then sonicated at several time intervals, and after the equilibrium was reached, the remaining solid FUR was removed by filtration through a 0.45 μm membrane filter (Millipore, USA). The clear solutions were suitably diluted and analyzed by UV–vis spectrophotometry (SHIMADZU UV-160A spectrophotometer) at λ = 277 nm.

2.5. Solid state NMR (ssNMR)

High resolution solid state ^{13}C spectra of FUR I and II, βCD and the PM I and II, KN I and II, FD I and II systems were recorded with the ramp cross polarization/magic angle spinning (CP-MAS) sequence, with proton decoupling during acquisition [20]. All ssNMR experiments were performed at room temperature in a Bruker Avance II spectrometer operating at 300.13 MHz for protons which was equipped with a 4 mm MAS probe. The operating frequency for carbons was 75.46 MHz. Glycine was used as an external reference for the ^{13}C spectra and for setting the Hartmann–Hahn matching condition in the cross-polarization experiments. Spectra were recorded with 2000 scans, with the contact time during CP being 2 ms and the recycling times being 5 s in all cases. The spinning rate for all the samples was 10 kHz.

^{1}H spin-lattice relaxation times in the laboratory frame (^{1}H T_1) were measured in static conditions with saturation recovery pulse sequence. In this experiment, the initial ^{1}H magnetization was saturated by a train of 40 pulses π/2 during a period of 160 μs and then allowed to recover along the *z*-axis during a time between 10 μs and 300 s. The recycling delay in these experiments was 5 s.

2.6. FT-IR spectroscopy

The FT-IR spectra were recorded on a Nicolet 5 SXC FT-IR Spectrophotometer (Madison, WI, USA), with the potassium bromide disks being prepared by compressing the powder.

2.7. Thermal analysis (DSC and TGA)

The DSC curves of the samples were obtained with a DSC TA 2920, and the TGA curves were recorded on a TG TA 2920. The samples were placed in aluminum hermetic pans, and the experiments were carried out under a nitrogen gas flow, at a heating rate of 10 °C/min, and over a temperature range of 25–350 °C.

2.8. SEM

Microscopic morphological structures of the raw materials and the solid-state systems were investigated and photographed using a scanning electron microscope of type LEO Model EVO-40 XVP. The samples were fixed on a brass stub using a double-sided aluminum tape, and to improve the conductivity, samples were gold-coated under vacuum by employing a PELCO Model 3 sputter coater.

2.9. XRPD

X-ray powder diffraction patterns of the samples were recorded using a Philips PW1710 diffractometer with Ni filtered Cu–Kα radiation. Measurements were taken from 2° to 40° (2θ) at steps of 0.05°, a voltage of 45 kW and a current of 30 mA for the generator.

3. Results and discussion

3.1. Phase solubility analysis

FUR is a weak acid (pK_a = 3.8) of low water solubility. In this study, the effect of βCD on the solubilities of FUR I and II was investigated at 25.0 ± 0.1 °C in aqueous and buffered solutions of pH 2.0 and 6.5, thus simulating the biologic fluids in which the drug molecule was unionized and ionized, respectively. Fig. 2 displays the phase solubility diagrams, which were obtained by plotting the changes in FUR solubility as a function of βCD concentration.

The interactions of the FUR I:βCD and FUR II:βCD systems in both aqueous and buffer solutions of pH 2.0 displayed typical A_L type solubility curves [21], indicating the formation of soluble binary complexes of a presumably 1:1 stoichiometry. In turn, in buffer solutions of pH 6.5, the solubility isotherm of the FUR I:βCD system displayed a typical A_L type isotherm whereas the profile of FUR II:βCD could be classified as an A_N type, indicating a different complexation behavior for each polymorph. The A_N curve may be originated from an alteration in the effective nature of the solvent in the presence of large concentrations of βCD or from a self-association of βCD at higher concentrations [21].

The apparent stability constant (K_C) values, shown in Table 1, were estimated from the slope of the initial linear portion of the diagrams and the intrinsic solubility of each polymorph (S_0) according to the following equation:

$$K_C = \frac{\text{slope}}{S_0(1 - \text{slope})} \quad (1)$$

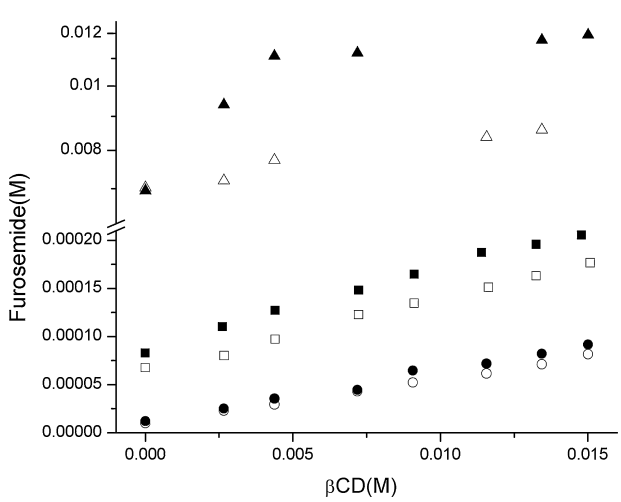

Fig. 2. Effect of βCD on the solubility of FUR I in aqueous solutions (□), buffer pH 2.0 (○) and buffer pH 6.5 (△), and on the solubility of FUR II in aqueous solutions (■), buffer pH 2.0 (●) and buffer pH 6.5 (▲).

From the K_C values and analyzing the effects of pH, it can be observed that the ionization affected the interaction of the each FUR polymorph with βCD. These results showed that unionized FUR (at pH 2.0), a more lipophilic form, exhibited a greater affinity for the host than the ionized species. In particular, we observed that βCD at pH 2.0 significantly increased the solubility of both polymorphs.

Additionally, these studies revealed the different solubility behaviors of the polymorphs. Whereas form I had the highest intrinsic solubility in water, FUR II had a greater solubility in buffer solutions of pH 2.0, and 6.5. Also, it can be noted that the apparent solubility of each FUR polymorph was significantly increased upon complexation with βCD in buffer solutions of pH 2.0, as shown in Table 1. However, the FUR I:βCD system showed the highest solubility value in the buffer solution of pH 6.5. Moreover, we observed that βCD at pH 2.0 produced a greater increase in the solubility, in comparison with MD [18].

3.2. Solid state characterization

3.2.1. ssNMR

Solid state NMR (ssNMR) provided a direct way to probe drug–CD interactions in solid complexes and additionally, it has been applied to identify and analyze the polymorphic forms of drugs [22]. The carbon numbering of the FUR and βCD molecules is displayed in Fig. 1 while Fig. 3 shows the ^{13}C CP-MAS spectra of βCD, FUR I and II, the corresponding physical mixtures (PM I and II) and the complexes (KN I and II). The carbon assignments of FUR I and II can be observed in our previous report [18]. It is interesting to remark that polymorphs I and II had very different ^{13}C CP-MAS spectra, and in both cases the signals were inside the region between 100 and 180 ppm, and at 42 ppm. The ^{13}C CP-MAS spectrum of βCD, with multiple and sharp resonances for each type of carbon (in the region 50–110 ppm), typical of crystalline systems, has been previously correlated with distinct values of dihedral angles of the glycosidic alfa (1 → 4) bond for carbons 1 and 4, and with torsion angles describing the orientation of the hydroxyl groups [23–25].

For the binary systems, the insets display the region between 113 and 180 ppm in order to visualize better the signals belonging to FUR. Signals of FUR have low signal to noise ratio relative to the CD ones probably due to the long T_1 of the FUR polymorphs that is by far longer than the applied repetition delay used in the experiments (5 s). Testing longer recycling delays for these experiments (around 20 s) did not give an important improvement in the intensity of FUR with the disadvantage of making the time of the whole extremely long.

It is interesting that the PM I and PM II spectra do not exactly correspond to the addition of the separate FUR and βCD spectra. First, only carbon signals belonging to FUR I can be distinguished, and in addition, the resonances appear in the region corresponding to βCD become wider with some remaining sharp peaks. There is also evidence of some interactions taking place between the βCD and FUR molecules during the preparation of this solid, and finally, the PM I and PM II spectra look quite similar.

The KN I and KN II spectra showed that the signals belonging to βCD (C1′–C6′) broadened and formed groups of wide signals in the range 50–110 ppm, then displaying less degree of crystallinity than the corresponding PMs. This fact is indicative that a solid-phase transformation has occurred, and the complexes are new solid forms. Moreover, the presence of sharp FUR signals with the same chemical shifts as in the free drug spectrum, suggests that a certain amount of pure FUR remained, without interaction with βCD (see insets in Fig. 3). Indeed, both complexes presented only signals of FUR I. Therefore a phase conversion from FUR II to form I occurred in the mixing process of preparation of KN II. Although on comparing KN I with KN II, the spectra appear to be

Table 1
Summary of solubility studies at 25.0 ± 0.1 °C.

Solvent	FUR I:βCD system			FUR II:βCD system		
	S_0 (μg/ml)	S_{max} (μg/ml)	K_C (M^{-1})	S_0 (μg/ml)	S_{max} (μg/ml)	K_C (M^{-1})
Water	35.6	58.5	114	27.4	54.5	96
Buffer pH 2.0	4.4	27	467	6.1	31.1	437
Buffer pH 6.5	2325	4290	19	2480	3950	–

very similar, there are in fact some fine differences in the wide signals at 73 ppm and 60 ppm that can be distinguished between both spectra.

In our previous study of binary systems of FUR using MD as ligand, we also observed an interconversion of polymorphs during complexation, showing only FUR I signals in the ^{13}C CP-MAS of the complexes [18].

The ^{13}C CP-MAS spectra of the FD complexes (not shown) displayed wide signals, but only in the region corresponding to βCD, without the presence of FUR signals. This was probably due to the liophilization process that induced an amorphization of the compounds.

To obtain additional information on the interaction between FUR polymorphs and βCD, we carried out ^1H T_1 relaxation time experiments.

To determine the ^1H T_1 values from the saturation-recovery experiments in each compound, the broad ^1H spectrum was first integrated. Then, the behavior of ^1H magnetization as a function of the recovery time was fitted using one or two relaxation times. The resulting values of T_1 for all the compounds are shown in Table 2, together with the proportion of the sample corresponding to each relaxation time. Note that the high crystallinity of FUR I and FUR II led to very long values for T_1 (45.8 s and 35.2 s) with a different order of magnitude to those of βCD (1.0 s). Moreover, the T_1 values in the PMs led to two relaxation times close to those belonging to each pure component, with one value being close to βCD ^1H T_1, and the higher value being related to the FUR relaxation times.

It is interesting to note that KN I and KN II had the greater proportion of samples with the shorter T_1 values (1.1 s and 1.3 s), which were different to the short relaxation values in the corresponding PMs (0.7 s and 0.8 s). This fact provides evidence of the presence of a new solid form originated by the molecular interaction between FUR and βCD. Also, in the case of FD I and FD II, a new solid form was observed with relaxation times of 1.2 s and 0.9 s, respectively. It should be noted that there was a certain amount of sample with a long T_1 value in all the cases, with this long T_1 being related to the amount of free FUR which was not interacting with βCD.

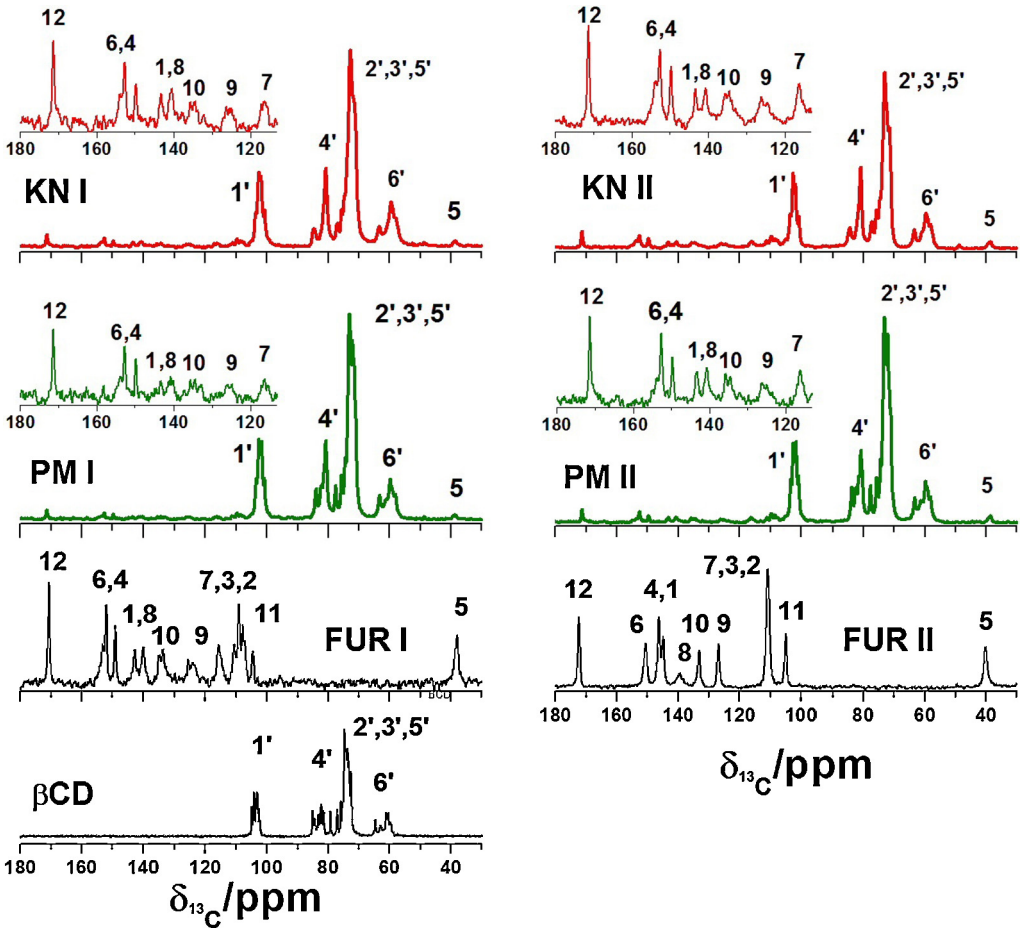

Fig. 3. ^{13}C CP-MAS spectra of: βCD, FUR I and II, PM I and II, KN I and II. For the binary systems, the insets display the region between 113 and 180 ppm in order to visualize better the signals belonging to FUR.

Table 2
^{1}H-T_1 values obtained by fitting the experimental data of ^{1}H magnetization vs. recovery time with one or two parameters for the relaxation times. Errors are within 7%. The percentage in parenthesis corresponds to the proportion of sample for the corresponding relaxation time.

	T_1 (s)	
βCD	1.0	
FUR I	45.8	
FUR II	35.2	10
PM I	28.2 (10%)	0.7 (90%)
KN I	17.9 (10%)	1.3 (90%)
FD I	21.8 (1%)	1.2 (99%)
PM II	16.3 (10%)	0.8 (90%)
KN II	12.4 (10%)	1.1 (90%)
FD II	20.7 (2%)	0.9 (98%)

3.2.2. FT-IR

Segments of the FT-IR spectra of the raw materials and the binary systems are shown in Fig. 4. The identification of the individual forms FUR I and II, where the main differences between the polymorphs occurred in the 3400–3200 cm^{-1} and 1350–1100 cm^{-1} regions, can be seen in our previous report [18].

For KN I, the bands corresponding to the C=O (1671 cm^{-1}) and S=O stretch (1322 cm^{-1}) vibrations were shifted to higher frequencies. In the case of the FD I spectrum, the characteristic C=O band disappeared, with the S=O stretch band being shifted to higher frequencies. In addition, the PM I spectrum corresponded simply to the superposition of the FT-IR spectra of the components. Bearing in mind these spectral changes, there is undoubtedly clear evidence of interactions having occurred between FUR I and βCD,

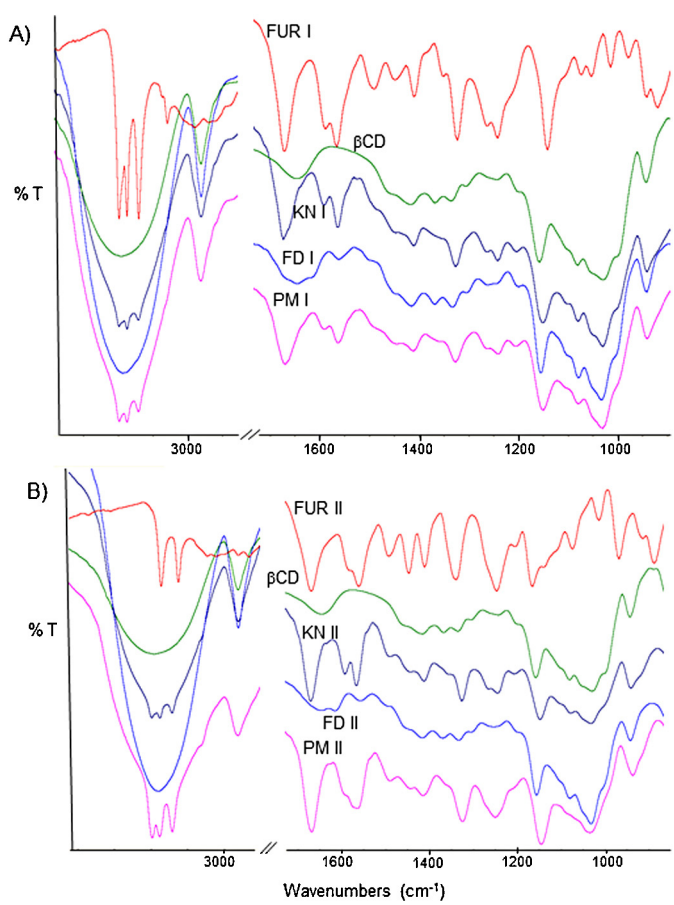

Fig. 4. FT-IR spectra of: (a) FUR I:βCD systems and (b) FUR II:βCD systems.

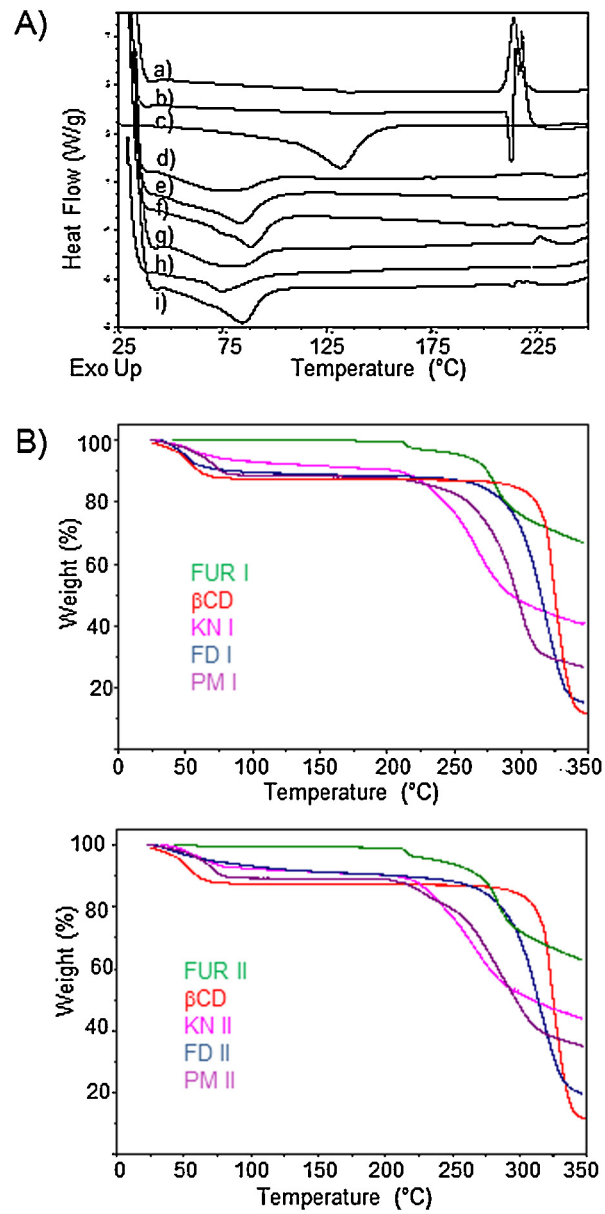

Fig. 5. (A) DSC curves of: (a) FUR I, (b) FUR II, (c) βCD, (d) KN I, (e) FD I, (f) KN II, (g) PM I, (h) FD II, (i) PM II. (B) TGA curves.

suggesting that the formation of complexes in the solid state, when prepared by KN and FD methods, involved the interaction of the sulphonamide group and the aromatic ring of FUR.

In the case of the KN II, FD II and PM II spectra a superposition of the spectra of FUR I and βCD can be observed, indicating that a polymorphic transformation may have occurred during sample preparation. These results are in agreement with those reported previously using MD as the ligand [18], which suggests that a polymorphic transformation might have occurred by mechanical grinding during sample preparation.

3.2.3. DSC and TGA

The DSC and TGA profiles of raw materials and the binary systems are shown in Fig. 5(A) and (B), respectively, and the characterization of the individual forms FUR I and II can be seen in our previous report [18].

Comparison of the DSC curves of the systems prepared by KN and FD with those obtained by PM confirmed an interaction between the components in the former ones. In fact, the complete

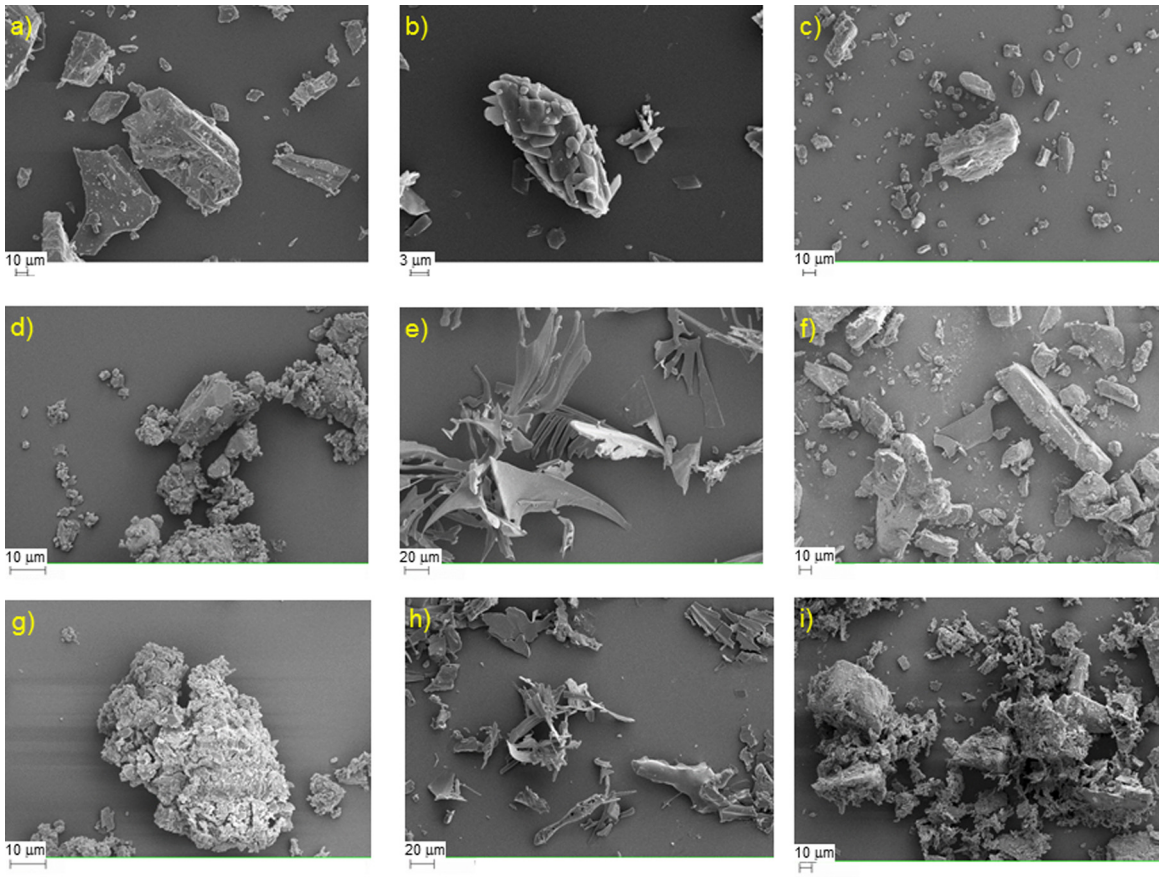

Fig. 6. Scanning electron microphotographs of: (a) FUR I, (b) FUR II, (c) βCD, (d) KN I, (e) FD I, (f) PM I, (g) KN II, (h) FD II, (i) PM II.

disappearance of the FUR thermal events in the curves of the KN and FD systems indicated the complexation of the drug into the βCD cavity. Interestingly, in the PMs, characteristic events were observed for the individual components.

The TGA curves for FD I, KN I, FD II and KN II revealed the dehydration process, with mass losses of 10.2%, 7.7%, 8.2% and 8.1%, respectively, compared with 12.5% in βCD. This behavior suggests that most of the water molecules in the βCD cavity were replaced during the inclusion process. Interestingly, the TGA curves showed that the FD systems had a higher thermal stability than the KN systems.

3.2.4. SEM

Supporting evidence for the complexation of FUR polymorphs I and II with βCD was obtained using SEM, with Fig. 6 showing the distinct morphological differences between the samples. The individual forms FUR I and II have been described in our previous report [18]. The βCD particles had an irregular shape with cracks on their surfaces and, there were adherences of smaller particles to the surface of large particles.

A drastic change in the morphology and shape of particles was observed in the FD and KN products. Microphotographs showed the presence of particles of irregular size and shape, in which the original morphology of both components disappeared, thus suggesting interaction of the drug with βCD in the solid state and may also indicate the presence of new solid phases. The images of FD I and FD II showed laminated structures of irregular size and shape with smooth surfaces and a fragile aspect, while KN I and KN II revealed a less ordered structure with compact and irregular arrangements formed by the adherence of particles of different sizes. In contrast, both PMs showed the characteristic crystals of FUR mixed with particles of βCD, demonstrating the absence of interactions in these solid systems.

These results are consistent with our previous study, in which we found that the solid-state systems of FUR polymorphs with the MD prepared by kneading had less ordered structures and that the original morphology of the raw materials disappeared [18]. However, it should be appreciated that the kneading systems were different, because βCD has a lamellar structure while those of MD are compact structures.

3.2.5. XPRD

The XPRD patterns of the raw materials and the binary systems are shown in Fig. 7, with the samples of FUR form I and II having been characterized previously [18]. The pattern of βCD exhibited characteristic peaks that were consistent with its crystalline nature.

In the XRPD patterns for the KN and PM systems, it was possible to observe the characteristic peaks of FUR and βCD, but the intensities of these crystalline peaks were lower than those of the intact materials due to dilution. This result indicated that the crystalline nature of the drug was maintained in both KN and PM. Additionally, the PXRD patterns for KN I, KN II, PM I and PM II were distinguishable, revealing that these solids were not the same. In contrast, in the kneading systems or PMs prepared with MD [18], it was not possible to differentiate between I and II, thus making it difficult to confirm spectroscopically of the complex formation. The systems obtained by FD showed undefined, broad, diffuse peaks of low intensities, indicating a decrease in the degree of crystallinity, although some characteristic βCD peaks were still detectable. This feature indicates the formation of a significant amount of amorphous material. Moreover, the diffractogram was not identical to

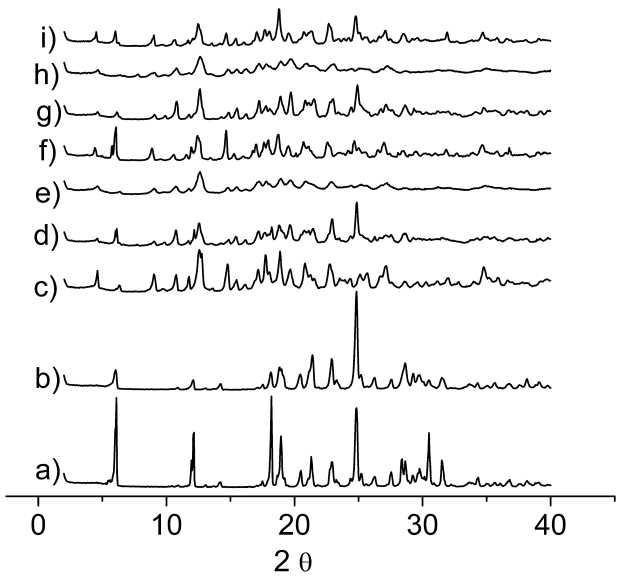

Fig. 7. Powder X-ray diffraction patterns of: (a) FUR I, (b) FUR II, (c) βCD, (d) KN I, (e) FD I, (f) PM I, (g) KN II, (h) FD II, (i) PM II.

that of pure βCD, indicating that new supramolecular systems had been formed. These results correlate well with those evidenced by thermal analysis and SEM studies.

4. Conclusions

In this study, the interaction of the ligand βCD with the guest FUR forms I and II resulted in the formation of different supramolecular complexes, which were then characterized. These distinct modes of complexation were confirmed with our results, therefore we can postulate that these complexes are new solid forms.

The solubility of FUR is one of the critical factors responsible for its poor and highly variable human bioavailability, which we were able to improve by the use of βCD. Furthermore, it was shown that the βCD solubilization of both FUR polymorphs could be enhanced through pH adjustments. Consequently, the FUR:βCD supramolecular complexes might result in a more effective drug delivery system for oral administration.

The solubility experiments performed using βCD in this work and MD in a previous contribution indicated that both complexes were useful in terms of improving the drug solubility, but with the βCD complexes showing the highest solubility enhancement. These results clearly indicate that complex formation is a useful tool for improving the absorption of FUR, due to the increase of the drug solubility in physiological simulated fluids.

In conclusion, although previous experiments performed on the MD and βCD systems provided evidence that the MD complexes could not be characterized spectroscopically due to the amorphous character of MD, in the present study we found spectroscopic evidence of complex formation. It is important to point out that in all the systems (PMs and KNs) with both MD and βCD ligands, only form I was expressed, implying that a polymorphic transformation had occurred during the preparation (kneading or mixing) of the systems.

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