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Research paper

Solid-state characterization and dissolution profiles of the inclusion complexes of omeprazole with native and chemically modified β-cyclodextrin

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Abstract

The aim of this work was to investigate the formation of the inclusion complex between omeprazole (OME), a benzimidazolic derivative and a methylated cyclodextrin, methyl-β-cyclodextrin (MβCD), with an average degree of substitution of 0.5. Inclusion complex between OME and β-cyclodextrin (βCD), a natural cyclodextrin, was used as reference. In aqueous media, apparent stability constants (K_s), which describe the extent of formation of the complexes, have been determined by UV spectroscopy and ^{1}H NMR experiments. The stoichiometry of the complexes was found to be 1:1 mol:mol OME:cyclodextrin (CD) and the value of K_s was higher for OME:MβCD than for OME:βCD inclusion complexes. Solid binary systems of OME and CDs were prepared by different techniques, namely kneading, spray-drying and freeze-drying. The formation and physicochemical characterization of solid inclusion complexes were investigated by differential scanning calorimetry (DSC), Fourier transform-infrared (FTIR), X-ray diffractometry (XRD) and scanning electron microscopy (SEM). The results show that freeze-drying method produces true inclusion complexes between OME and both CDs. In contrast, crystalline drug was detectable in kneaded and spray-drying products. The dissolution of OME from the binary systems was studied to select the most appropriate system for the development of a buccal drug delivery formulation. It was concluded that the preparation technique played an important role in the dissolution behaviour of the drug and the inclusion complex between OME and MβCD obtained by spray-drying and freeze-drying allowed better performances.

Keywords: Omeprazole; β-Cyclodextrin; Methyl-β-cyclodextrin; Physicochemical characterization; Dissolution profile; Inclusion complex

1. Introduction

Omeprazole is a proton pump inhibitor with a molecular structure composed by a substituted pyridine ring linked to a benzimidazole by a sulfoxide chain, as illustrated in Fig. 1 [1]. Omeprazole is very slightly soluble in water. In solution omeprazole degrades rapidly at low pH values [2] and this compound is photo and heat sensitive [3]. This drug has been widely used in the treatment of peptic ulcer, reflux oesophagitis and Zollinger–Ellison syndrome [4]. Preformulation studies have shown that moisture, heat, solvents, and acidic substances have deleterious effects on the stability of omeprazole. Other investigators have observed a degradation of omeprazole under exposure to UV light, various salts, and some metal ions. The degradation of the proton pump inhibitor manifests itself in a loss of drug content and increasing amounts of degradation products [5].

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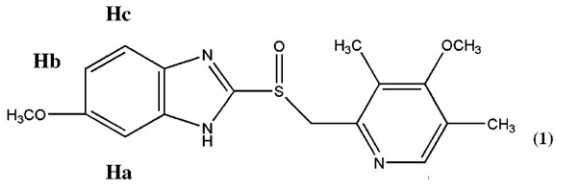

Fig. 1. Omeprazole chemical structure.

The most important property of cyclodextrins is their ability to form complexes with a great variety of organic substances in solution and in the solid state. The physicochemical properties of the included substances are altered upon complexation and cyclodextrins are widely used for enhancement of aqueous solubility, stability and bioavailability of apolar drugs [6]. Chemically, they are cyclic oligosaccharides containing at least 6 D-(+) glucopyranose units, attached by α-(1,4) glucosidic bonds. The four natural cyclodextrins, α-, β-, γ- and δ-cyclodextrins, with 6, 7, 8 or 9 glucose units, respectively, differ in their ring size and solubility [7]. Cyclodextrins with fewer than six units cannot be formed due to steric hindrances while the higher homologs more than nine glucose units are very difficult to purify. The cavity size of α-cyclodextrin is insufficient for many drugs and γ-cyclodextrin is expensive. In general, δ-cyclodextrin has weaker complex forming ability than conventional cyclodextrins [8]. With drugs like digitoxin and spiranolactone, δ-cyclodextrin showed greater solubilizing effect than α-cyclodextrin but the effect of δ-cyclodextrin was less than those of β- and γ-cyclodextrins. β-Cyclodextrin has been widely used in the early stages of pharmaceutical applications because of its ready availability and cavity size suitable for the widest range of drugs [9]. However, its anomalous low aqueous solubility is a serious barrier in its wider utilization [10]. Since native cyclodextrins have low solubility in aqueous solvents, derivatives have been made by chemical modifications of the hydroxyl groups which greatly improve their solubility and their ability to dissolve hydrophobic compounds, as well as reducing their toxicity [11].

The purpose of this study is to improve the solubility and dissolution rate of omeprazole in artificial saliva in order to develop a promising buccal system drug delivery and thereby improve its bioavailability. This was achieved through the formation of an inclusion complex with a chemically modified β-cyclodextrin, methyl-β-cyclodextrin. Such complex formation was compared with the inclusion complex formed with β-cyclodextrin and both complexes were confirmed by a variety of techniques, including solubility determination, ^{1}H NMR spectroscopy, infrared spectrophotometry (FTIR), differential scanning calorimetry (DSC), X-ray diffraction (XRD) and scanning electron microscopy (SEM). The work also included the determination of the dissolution profile of the drug itself, the physical mixtures and the inclusion complexes formed with both cyclodextrins.

2. Materials and methods

2.1. Materials

β-Cyclodextrin (βCD; Kleptose®, $M_w = 1135$) and methyl-β-cyclodextrin (MβCD; CRYSMEB®, $M_w = 1190$ and DS = 0.5) were kindly donated by Roquette (Lestrem, France) and Omeprazole (OME) ($M_w = 345.42$) was kindly donated by Belmac Laboratory, S.A. (Barcelona, Spain). Deuterium oxide (D_2O; 99.97%) and NaOD were purchased from Euriso-top (Peypin, France) and Sigma Aldrich (Madrid, Spain), respectively. All other reagents (chemicals and solvents) were of analytical reagent grade.

2.2. Determination of apparent stability constants (K_s)

The detection of the formation of inclusion complexes between OME and cyclodextrins (βCD and MβCD) was performed by ^{1}H NMR spectroscopy and confirmed by phase solubility studies, according to the method of Higuchi and Connors [12].

Spectra were recorded at 25 °C on a Varian 500 MHz spectrometer using a 5 mm NMR probe and a simple pulse-acquired sequence with solvent presaturation. Acquisition parameters consisted of 24 k points covering a sweep width of 8 kHz, a pulse width of 18 μs and a total repetition time of 15 s. Digital zero filling to 64 k and a 0.5 Hz exponential was applied before Fourier transformation. A nonlinear least squares procedure resorting to the Levenberg–Maquardt algorithm on the differences observed in the chemical shifts due the presence of cyclodextrins was used in order to estimate the apparent stability constant (K_s) values. [13]. Samples were prepared maintaining the OME concentration constant (2 mM) and changing cyclodextrin concentration in a molar ratio relatively to drug concentration since 1:0.1 until 1:7 (OME:cyclodextrin). The K_s values of the inclusion complexes formed calculated for both methods are reported in Table 1.

2.3. Preparation of inclusion complexes in solid state

Solid systems were prepared with equimolar ratio of OME and MβCD, according to the previous phase solubility studies, using three distinct methods: kneading, spray-drying and freeze-drying. Physical mixtures were prepared as a reference and inclusion complexes between OME and βCD were also prepared for the purpose of comparison.

2.3.1. Physical binary mixtures (PMs)

OME:βCD and OME:MβCD PMs were prepared by simply blending OME and βCD or MβCD, previously sieved (63–160 μm sieve granulometric fraction), with 1:1 molar ratio uniformly in a mortar.

2.3.2. Kneaded binary systems (KN)

βCD and MβCD were wetted in a ceramic mortar with basic aqueous solution (pH = 10 ± 0.5) until a paste was

Table 1
K_s values of the inclusion complexes calculated by different methods

Inclusion complexes	Type of diagram	St/(10^{-3} M)[a]	SE[b]	K_s (M^{-1})[c]	K_s (ppm)[d]
OME:βCD	A_L	5.8 ± 0.001	1.7	56.9 ± 2.3	60
OME:MβCD	A_L	11.3 ± 0.012	3.4	77.4 ± 1.4	90

[a] OME solubility in CD solutions (13.2×10^{-3} M βCD and 42×10^{-3} M MβCD).
[b] Efficiency of solubilization (coefficient between OME solubility in the presence and in the absence of cyclodextrin).
[c] Determination of apparent stability constants by phase solubility studies.
[d] Determination of apparent stability constants by ^{1}H NMR spectroscopy.

obtained (about 30% of the total weight of cyclodextrin and OME). The required amount of OME was then slowly added and the slurry was kneaded for about 45 min. During this process an appropriate quantity of basic aqueous solution was added in order to maintain a suitable consistency and to minimize instability of OME. The final product was then allowed to equilibrate during 48 h at room temperature and humidity, protected from light.

2.3.3. Spray-dried binary systems (SD)

Equimolar quantities of βCD or MβCD and OME were dissolved in hydro-alcoholic solution (2:1 v/v) at $pH = 10 \pm 0.5$, respectively. The resulting solution was stirred for 24–48 h. After dissolution was completed, the solution was spray dried in a LabPlant SD-05, under the following conditions: inlet temperature 102 °C, outlet temperature 60–65 °C, flow rate of the solution 400 mL/h, airflow rate 40–50 m^3/h and atomizing air pressure 1.0–1.1 bar [14].

2.3.4. Lyophilized binary systems (LPh)

βCD or MβCD was added to basic aqueous solution ($pH = 10 \pm 0.5$). OME was then added to this solution under stirring, according to the stoichiometry 1:1. The solution stirring was maintained for 24–48 h. Furthermore, the resultant clear solution was frozen by immersion in an ethanol bath at −50 °C (Shell Freezer, Labconco, Freezone® model 79490) and then the frozen solution was lyophilized in a freeze-dryer (Lyph-lock 6 apparatus, Labconco) for 72 h.

In all binary systems prepared the pH of the solutions (10 ± 0.5) was controlled in order to avoid OME degradation. The obtained powders were sieved (63–160 μm) and their drug content was determined by UV assay at 305.5 nm.

2.4. Thermal analysis

Differential scanning calorimetry (DSC) measurements of the pure materials and binary systems were carried out using a Shimadzu DSC-50 System (Shimadzu, Kyoto, Japan) with a DSC equipped with a computerized data station TA-50WS/PC. The thermal behaviour was studied by heating the samples (2 mg) in a sealed aluminium pan from 25–250 °C, at a rate of 10 °C/min and under a nitrogen flow of 20 cm^3/min, using an empty pan sealed as reference.

Indium (99.98%, mp 156.65 °C, Aldrich®, Milwaukee, USA) was used as standard for calibrating the temperature.

2.5. X-ray diffraction (XRD)

X-ray powder diffraction patterns of OME, βCD, MβCD and binary systems were obtained at room temperature with a Philips X'Pert, model PW 3040/00 diffractometer system equipped with cobalt (Co) as anode material and a graphite monochromator using a voltage of 40 kV and a current of 35 mA. The diffractograms were recorded in the 2θ angle range between 5–50° and the process parameters were set at: scan step size of 0.025 (2θ); scan step time of 1.25 s; and acquisition time of 1 h.

Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the binary systems with a reference. The relation used for the calculation of the crystallinity was the relative degree of crystallinity $(RDC) = I_{SA}/I_{REF}$, where I_{SA} is the peak height of the sample under investigation and I_{REF} is the peak height of the same angle for the reference, with the highest intensity. OME was used as a reference sample for calculating RDC values of binary systems [15,16].

2.6. Fourier transform-infrared spectroscopy (FTIR)

Spectra were recorded using a Jasco FT/IR-420 spectrometer associated with an ATR horizontal reflexion (Miracle™, PIKE Technologies). Spectra acquisitions were performed directly in powder samples with the application of 16 scans at a resolution of 4 cm^{-1} over the range 4000–400 cm^{-1}.

2.7. Scanning electron microscopy (SEM)

The surface morphology of raw materials (OME, βCD and MβCD) and binary systems was examined by means of a scanning electron microscope (Jeol, JSM 5310, Tokyo, Japan). The samples were fixed on a brass stub using double-sided tape and then made electrically conductive by coating in a vacuum with thin layer of copper. The photographs were taken with a Pentax (model MZ-10) camera at an excitation voltage of 10 kV and magnification factors of 200 and 3500.

2.8. Dissolution studies

The dissolution profiles of the inclusion complexes previously obtained were collected using a Vankel

VK7000 apparatus. The assay was performed according to the USP rotating paddle method. The dissolution media consisted of 1000 mL of enzyme-free artificial saliva (pH = 7.0), [17]. The media were previously filtered, degassed and maintained at 37 ± 0.5 °C according to USP XXVIII [18]. The stirring speed was set at 75 ± 2 rpm and the temperature was maintained at 37 ± 0.5 °C. Aliquots from samples containing 20 mg of OME or its equivalent in physical mixture or inclusion complex form, prepared by KN, SD and LPh techniques, were withdrawn each 5 min for a period of 60 min and analyzed by UV–vis spectroscopy (UV-1603, Shimadzu, Kyoto, Japan) at 301 nm. Six replicates have been made for each experience. Dissolution profiles were evaluated by the dissolution efficiency parameter at 60 min (DE_{60min}), calculated from the area under the dissolution curve, according to the method of Khan, [19] and by the percent of drug dissolved at 6 min (DP_{6min}).

3. Results and discussion

3.1. Determination of K_s values

Numerous methods have been used for the determination of association constants in host–guest chemistry including NMR, calorimetry, spectroscopy, chromatography, capillary electrophoresis, solubility isotherms and potentiometry [20]. NMR spectroscopy has shown the potential to provide almost complete information on guest–host interactions, namely, stoichiometry, binding constants, energy of the complexation process and structure of the complexes in solution and in solid state [21]. This information may be obtained mainly using ^{1}H NMR experiments based on the chemical shift changes that occur for the protons of the drug and the cyclodextrin when the inclusion occurs. Changes in the chemical shifts values of the protons in OME molecule were observed when the drug was complexed with βCD and MβCD. The upfield shifts observed in OME Ha, Hb and Hc protons suggested the occurrence of inclusion of the benzimidazole moiety in the cyclodextrin cavity. These results were confirmed by 1D ^{1}H and 2D rotating frame nuclear Overhauser effect NMR spectroscopy (ROESY) and Molecular Dynamics [22].

In this work, we use a method for the determination of K_s of the inclusion complexes formed between OME and both cyclodextrins based on NMR measurements and phase solubility studies, being used this last method for comparison purpose.

A non-linear least squares procedure resorting to the Levenberg–Maquardt algorithm on the differences observed in the chemical shifts due the presence of cyclodextrin was used [13]. These values were calculated using the protons of the drug (OME) that bring about largest chemical shift variations (see Fig. 2) in the presence of increased concentrations of cyclodextrin (βCD and MβCD).

Table 1 shows the type of diagram obtained in the phase solubility studies for both cyclodextrins. It was observed that OME solubility increased linearly with cyclodextrin concentration indicating an A_L type diagram with the formation of complexes with 1:1 stoichiometry. The St value represents the maxima OME solubility observed in the presence of the maxima cyclodextrin concentration used in this study. The efficiency of solubility (ES) and the apparent stability constants (K_s) calculated indicated that MβCD forms an inclusion complex with OME more stably than the natural cyclodextrin (βCD). The agreement of the calculated K_s values indicates that these methods are useful in order to characterize the interaction between the host and the guest during inclusion complex formation.

3.2. Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) is frequently the pharmaceutical thermal analysis technique of choice because of its ability to provide detailed information about both the physical and energetic properties of a substance [23]. The DSC profiles of pure components and binary systems in the melting region of the drug and dehydration of the carrier are shown in Fig. 3. The thermal curve of OME was typical of a crystalline anhydrous substance with a sharp fusion endothermic at 159.8 °C, corresponding to the melting point of the drug, followed by an exothermal effect at 173.9 °C, attributable to its thermal decomposition [24]. The DSC curves of both cyclodextrins (βCD and MβCD) show a broad endothermic effect around 60 and 100 °C associated with crystal water losses [25]. In the PM systems is clearly distinguishable the drug endothermic peak (melting point). This indicates that in such systems the drug has basically maintained its original crystallinity [26]. Thermograms of PMs also show the broad endothermic effect due to the cyclodextrins' dehydration process.

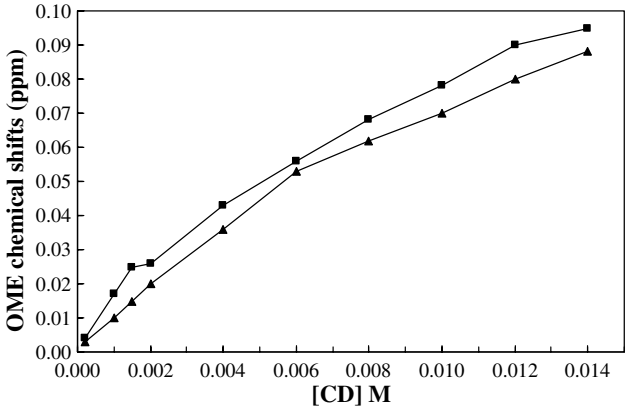

Fig. 2. ^{1}H NMR chemical shifts increments of OME (CH_3 1group) versus CDs [βCD (▲) and MβCD (■)] molar concentration.

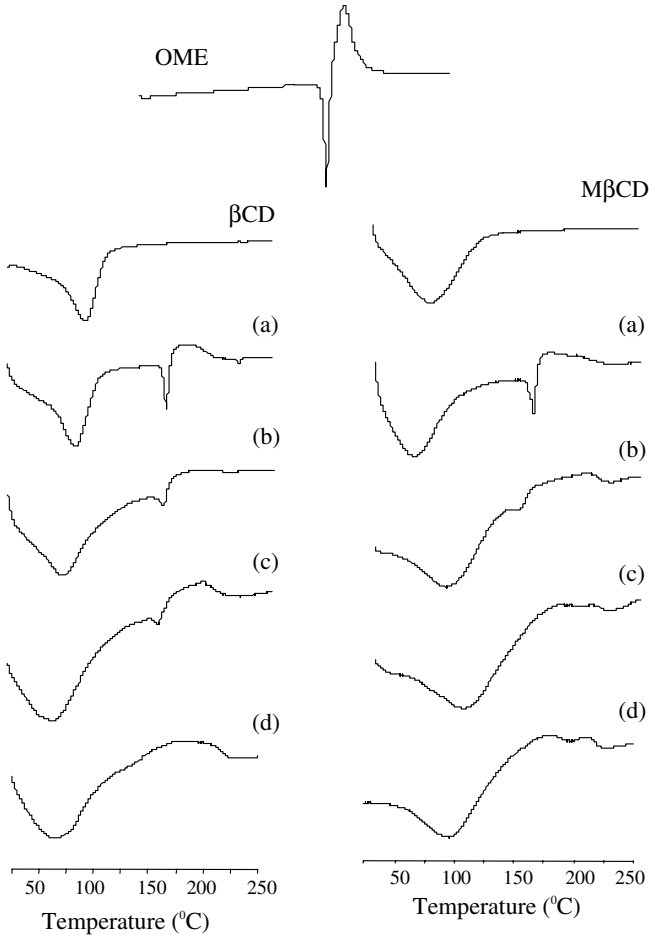

Fig. 3. DSC thermograms of the binary inclusion complexes. Omeprazole (OME), β-cyclodextrin (βCD), methyl-β-cyclodextrin (MβCD), (a) physical mixtures, (b) kneaded, (c) spray dried and (d) lyophilized systems.

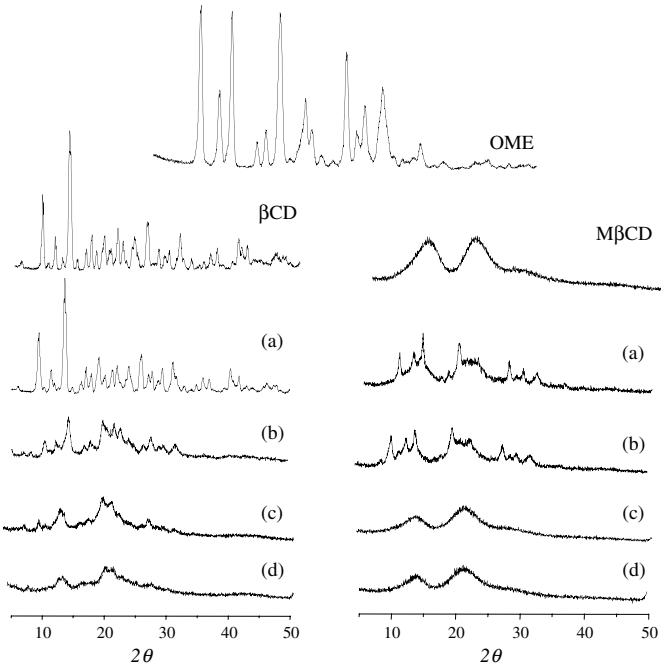

Fig. 4. X-ray diffractograms of binary systems. Omeprazole (OME), β-cyclodextrin (βCD), methyl-β-cyclodextrin (MβCD), (a) physical mixtures, (b) kneaded, (c) spray dried and (d) lyophilized systems.

Considering KN systems, there is a substantial size reduction, a broadening and a shift to lower temperatures of the drug melting point (149.5 °C). Comparing with that of PM systems it could be ascribed to some drug–cyclodextrin interaction [27]. This fact was also observed in OME:βCD SD system. In these systems we can assume the occurrence of a reduction of drug crystallinity or probably to have occurred a partial dispersion at a molecular level in the solid product [14], but did not seem to be indicative of a true inclusion complex formation.

The disappearance of the OME melting point in LPh products with both cyclodextrins and in SD product with MβCD suggests the formation of a true inclusion complex [28]. On the other hand, the absence of the OME melting point in SD and LPh systems when MβCD is used indicates a more stable and strong interaction with this cyclodextrin.

3.3. X-ray diffraction (XRD)

The XRD diffractograms of the pure components (OME, βCD and MβCD), physical mixtures and inclusion complexes are shown in Fig. 4 and RDC values of these systems are presented in Table 2. In the X-ray diffractogram of OME powder, sharp peaks at a diffraction angle (2θ) of 10.6, 12.8, 14.3, 19.9, 27.7 and 32.0 are present, suggesting that the drug is present as a crystalline material. The XRD patterns of βCD revealed several diffraction peaks which are indicative of their crystalline character [29], while a hollow pattern was recorded for MβCD which comprove its amorphous state. It was possible to observe that diffractograms of PMs result from the combination of those of the components analyzed separately and no inclusion complex was obtained by physical mixture. In the PM with MβCD was observed a decrease in peak intensity, probably due to the amorphous character of this cyclodextrin.

The KN products presented diffraction patterns quite similar to those of respective PMs but with lower crystallinity. Such a fact can be explained by the presence of reciprocal interactions in the solid state between host and guest [15]. Also, in the OME:βCD SD system it was possible to observe a decrease in the crystallinity degree, although some characteristic OME peaks were still detectable, thus confirming that in these systems there is no formation of a true inclusion complex.

A total drug amorphization was instead induced by freeze-drying for both cyclodextrins and by spray-drying for MβCD. X-ray diffraction patterns of OME:βCD and OME:MβCD systems were characterized only by large diffraction peaks in which it is no longer possible to distinguish characteristic peaks of OME. These results confirm that OME is no longer present as a crystalline material and its solid complexes exist in the amorphous state. This fact was observed with other lipophilic drugs [30].

Table 2
Peak intensities and RDC values ($2\theta = 27.713$) for OME:βCD and OME:MβCD systems

2θ	OME	OME:βCD				OME:MβCD			
		PM	KN	SD	LPh	PM	KN	SD	LPh
27.713	2573	983	526	450	281	553	538	339	266
		OME:βCD				OME:MβCD			
		PM	KN	SD	LPh	PM	KN	SD	LPh
	Ref.	0.382	0.204	0.175	0.109	0.215	0.209	0.132	0.103

Omeprazole (OME), physical mixture (PM), kneaded (KN), spray dried (SD) and lyophilized (LPh) systems.

The OME peak at 27.7 was used as reference in order to obtain RDC values for OME:βCD and OME:MβCD systems (see Table 2). RDC values for solid systems decreased in the following order: PM > KN > SD > LPh. These observations are in agreement with powder diffractograms and comprove the amorphous state of lyophilized products for both cyclodextrins.

The results of DSC and powder X-ray diffraction analyses revealed the production of an amorphous state of the drug in the lyophilized product, as a consequence of drug–carrier solid-state interactions indicative of possible formation of an inclusion complex.

3.4. Scanning electron microscopy (SEM)

SEM microphotographs of raw material (OME, βCD and MβCD) and binary solid systems are reported in Figs. 5A and B. OME is characterized by regular shaped crystals, βCD particles presented a parallelogram shape [31] and MβCD is composed of spherical particles with

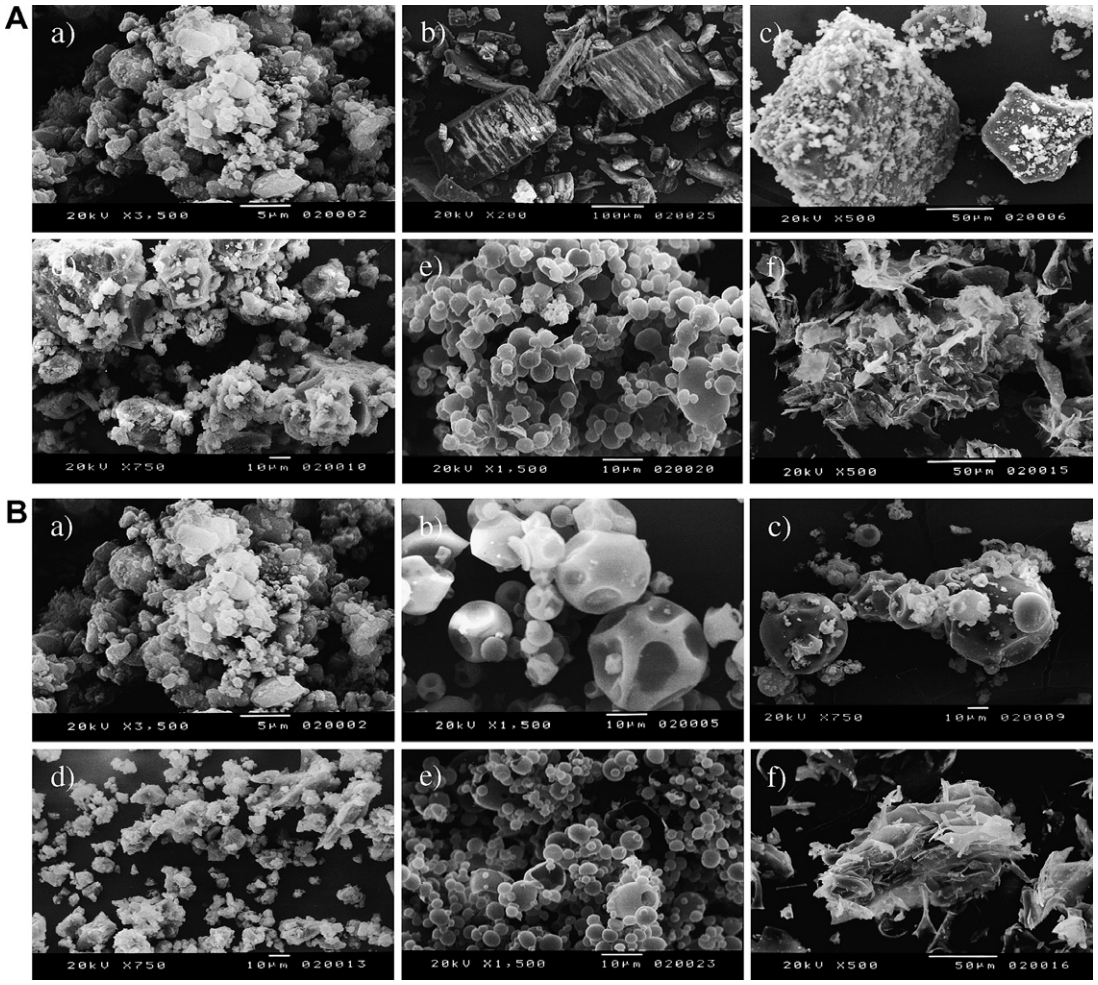

Fig. 5. (A) Scanning electron microphotographs of omeprazole (a), β-cyclodextrin (b), physical mixture (c), kneaded (d), spray dried (e) and lyophilized (f) systems. (B) Scanning electron microphotographs of omeprazole (a), methyl-β-cyclodextrin (b), physical mixture (c), kneaded (d), spray dried (e) and lyophilized (f) systems.

amorphous character. In OME:CD PMs, the characteristic OME crystals, which were mixed with excipient particles or adhered to their surface, were clearly detectable, thus confirming the presence of crystalline drug. This fact was observed in physical mixtures between βCD and other poorly water soluble drugs [32]. In the KN products it was possible to distinguish OME crystals agglomerated on the surface of CD particles that had lost their original shapes and in this case crystal sizes were smaller. In SD products the original morphology of raw material disappeared, and it was not possible to differentiate the two components (drug and cyclodextrin). The SD systems showed amorphous and homogeneous aggregates of spherical particles, a particular aspect characteristic of this type of systems [33]. Finally, LPh products appeared to be of a lesser crystalline structure with a soft and fluffy appearance and again, crystals of the single components were still not distinguishable [3]. We can conclude based on additional information that the modification of the KN products' appearance when compared with PMs was due to the effect of the kneading process [34]. On the other hand, the drastic change of the particle shape and aspect in SD and LPh products, indicative of the presence of a new solid phase, could be simply a consequence of a crystalline habitus change in those systems or it may support the evidence of the presence of a new solid phase [31]. Nevertheless, the SEM technique is inadequate to conclude in genuine complex formation, the obtained microphotographs support the idea of the consecution of a new single component [35].

3.5. Fourier transform-infrared spectroscopy (FTIR)

More evidences of complex formation were obtained from a FTIR study, which investigated the functional groups of OME involved in the complexation. The infrared spectra of different samples are presented in Fig. 6.

In OME spectra, C═C─N and S─C═N stretching link vibrations (1626.7 cm^{-1}) and Ar─C─O─CH_3 vibration (1203.4 cm^{-1}) accompanied by the resonance band at 1075 cm^{-1} were used to assess the interaction between cyclodextrins and guest molecule (OME) in the solid state [14].

Spectra of all binary systems did not show new peaks indicating that no chemical bonds were created in the formed compounds. However, we can observe that the intensity of both bands is decreased in all binary solid systems. In SD and LPh products, it can be observed that these bands practically disappear, probably owing to a restriction of the vibration related to the complexation process. The band situated at 1203.4 cm^{-1} is related to bending vibrations of the methoxy groups of OME and such behaviour could be interpreted in terms of a restriction due to the inclusion of this group within the CD cavity. These results are in agreement with ^1H NMR experiments previously reported [22].

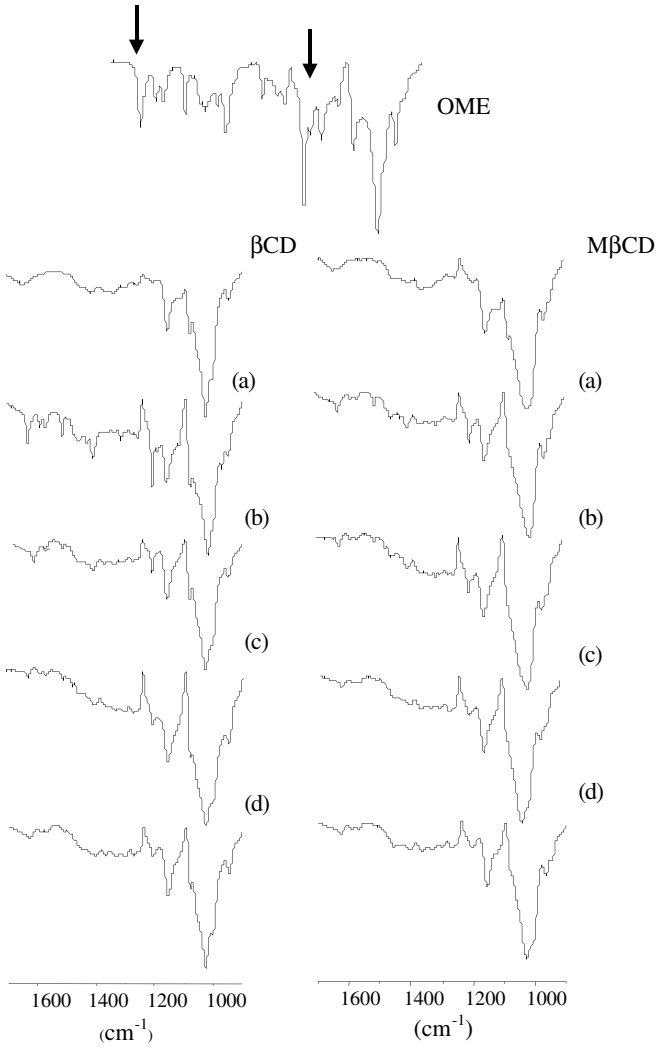

Fig. 6. FTIR spectra of binary systems. Omeprazole (OME), β-cyclodextrin (βCD), methyl-β-cyclodextrin (MβCD), (a) physical mixtures, (b) kneaded, (c) spray dried and (d) freeze dried systems.

3.6. Dissolution studies

The dissolution profiles for the systems under study are presented in Fig. 7. The reported values are arithmetic means of six measurements. For their evaluation, two parameters, dissolution efficiency calculated after 60 min and percentage of dissolved drug calculated after 6 min (DE_{60} and DP_6), were measured for all products studied (Table 3).

In artificial saliva media, significant differences were observed between the dissolved drug amounts in pure, physically mixed and complexed forms ($P < 0.001$) as well as in the dissolution rate. After 6 min, the percentage of dissolved pure drug is nearly 12% and above 90% when complexed with βCD and MβCD.

Relatively to both PMs, DE_{60} brought about a significance difference in comparison with pure OME ($P < 0.05$). This fact appears as a consequence of the mechanical treatment, which increases the contact between the drug and the carrier. On the other hand, DP_6 for both

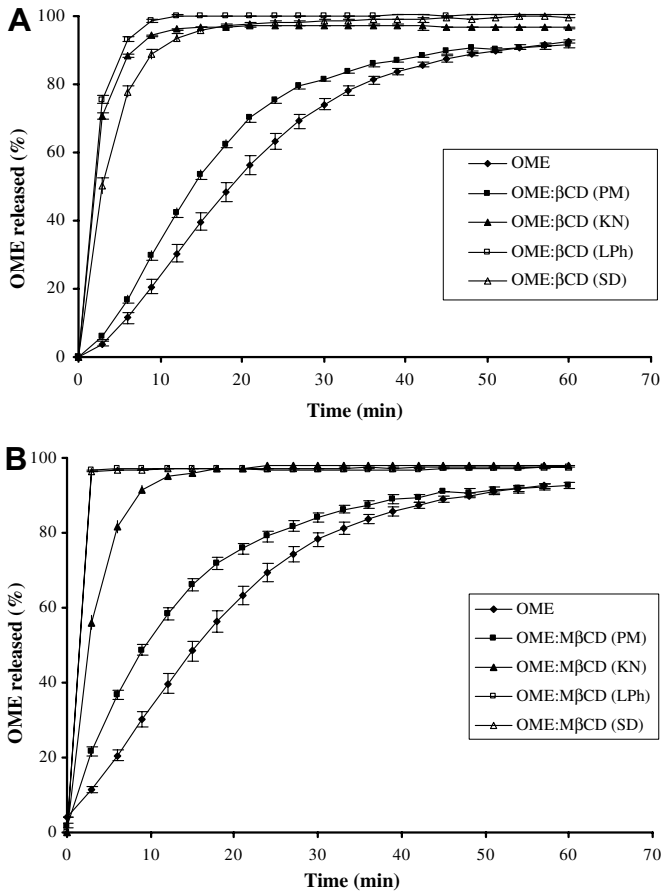

Fig. 7. Dissolution profiles of OME in artificial saliva (pH = 7.0) in binary systems: (A) βCD systems and (B) MβCD systems.

PMs had a significance difference ($P < 0.001$), probably due to the greater solubilizing and amorphizing power of MβCD toward OME than the parent βCD. Finally, PMs also had shown an enhancement of OME dissolution rate with respect to OME alone. This fact can be attributed to the improved wettability of PMs due to the presence of cyclodextrins [14], as well as, in early stages of the dissolution process, CD molecules will operate locally on the hydrodynamic layer surrounding the particles of OME, this action resulting in an in situ inclusion process, producing a rapid increase in the amount of dissolved drug [36]. Finally, PMs also have shown an enhancement of OME dissolution rate with respect to OME alone. This fact can be attributed to the improved wettability of PMs due to the presence of cyclodextrins [14]. Also possible, in early stages of the dissolution process, is that CD molecules will operate locally on the hydrodynamic layer surrounding the particles of OME, resulting in such action in an in situ inclusion process which leads to a rapid increase in the amount of dissolved drug [36]. Finally, it was possible to observe that in KN products the DE_{60} and DP_6 values were lower than for the other complexes (SD and LPh), indicating that spray-drying and freeze-drying are the selected methods to prepare inclusion complexes between OME and cyclodextrins, in order to obtain a buccal delivery formulation. On the other hand, SD and LPh systems prepared with MβCD presented advanced DE_{60} and DP_6 values relatively to the same systems prepared with βCD, suggesting that MβCD forms a more stable and soluble complex with OME.

4. Conclusion

Equilibrium constants for the inclusion complexes were evaluated by ^{1}H NMR spectroscopy and confirmed by phase solubility studies. MβCD proved to have better solubilizing and complexing properties for OME than the parent βCD, as stated by the higher K_s values obtained.

The results obtained by SEM, DSC, FTIR and XRD show that a stable OME:MβCD inclusion complex could be prepared at a 1:1 molar ratio by spray-drying and freeze-drying methods with a good performance of dissolution profile in artificial saliva media.

Taking into account these results, we believe that the complexation effectively enhanced the solubility of OME, which consequently can increase its bioavailability and might improve its pharmaceutical potential.

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Table 3
Dissolution parameters for OME in pure, physically mixed and complexed form in simulated saliva dissolution media

	OME	OME:βCD				OME:MβCD			
		PM	KN	SD	LPh	PM	KN	SD	LPh
DE_{60min} (%)	63.7 ± 3.7	74.2 ± 2.3	92.7 ± 0.7	96.0 ± 2.2	96.3 ± 0.8	77.4 ± 1.6	92.4 ± 1.5	97.2 ± 0.6	97.3 ± 0.9
DP_{6min} (%)	11.5 ± 1.5	16.9 ± 1.1	88.4 ± 0.6	77.9 ± 1.7	93.2 ± 0.8	36.8 ± 1.2	81.3 ± 1.6	97.0 ± 0.1	97.5 ± 0.1

All results are presented as mean values ± SD.

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