Drug Development and Industrial Pharmacy, 26(3), 253–259 (2000)

RESEARCH PAPER

Study of Omeprazole–γ-Cyclodextrin Complexation in the Solid State

M. J. Arias,[1,*] J. R. Moyano,[1] P. Muñoz,[1] J. M. Ginés,[1] A. Justo,[2] and F. Giordano[3]

[1]*Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Seville, 41012-Seville (Spain)*
[2]*Institute for Materials Science, CSIC-University of Seville, 41092-Seville (Spain)*
[3]*Pharmaceutical Department, Faculty of Pharmacy, University of Parma, 43100-Parma (Italy)*

ABSTRACT

The possibility of obtaining inclusion complexes between omeprazole (OME) and γ-cyclodextrin (γ-CD) by kneading, spray-drying, coprecipitation, and freeze-drying was evaluated. All these methods lead to the isolation of a true inclusion compound, as evidenced by differential scanning calorimetry (DSC), infrared spectroscopy, and X-ray diffractometry on powder (PXRD). Moreover, PXRD and scanning electron microscopy (SEM) afforded data concerning crystallinity and surface characteristics of the solid phases obtained. In all cases, a significant increase of the release rate with respect to the drug alone was found, and it was attributed to the formation of an inclusion compound. Among the solid phases obtained, the coprecipitated product presented the highest dissolution rate.
Key Words: *γ-CD; Dissolution rate; DSC; Inclusion complex; Omeprazole; PXRD.*

INTRODUCTION

Omeprazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-1*H*-benzimidazole (OME) is a well-known antiulcerative drug that acts by inhibiting the acid gastric secretion by blocking the H^+/K^+-ATPase pump. The main pharmaceutical drawbacks are substantially related to the physicochemical instability to heat, light, and acidic media, even with coated formulations (1). Moreover, the low aqueous solubility of OME (ap-

* To whom correspondence should be addressed. María José Arias-Blanco, C/Duero, 51, Valencina de la Concepción, 41907 Sevilla, Spain. Telephone: +34 95 455 66 18. Fax: +34 95 455 67 26. E-mail: mjarias@fafar.us.es

proximately 0.4% at 25°C) is responsible for low dissolution rates and hence low bioavailability (2).

The complexation with cyclodextrins (CDs) is an established procedure to improve the biopharmaceutical properties of drugs with poor water solubility (3–5).

β-Cyclodextrin (β-CD) and some of its derivatives have hitherto attracted—mainly for economic reasons (low price)—most of the experimental works, leading to several industrial applications. It is recognized that γ-CD, the homologue containing 8 glucopyranose units, shows more favorable toxicological properties (5,6), higher water solubility, larger cavity dimensions, and the ability to accommodate a wider variety of molecules than β-CD.

In this paper, we report on the possibility of obtaining inclusion compounds of OME with γ-CD with the aim of developing, from the technological and biopharmaceutical standpoints, more efficient formulations of OME.

Different preparation techniques, such as kneading, spray-drying, coprecipitation, and freeze-drying, were tested. The solid phases obtained were characterized by differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), X-ray diffraction on powder (PXRD), and scanning electron microscopy (SEM). The dissolution rate of each preparation was also assessed by the USP 23 rotating basket method.

EXPERIMENTAL

Materials

Micronized OME was supplied by Andrómaco S.A. (E-Madrid). γ-CD was purchased from Cyclolab (H-Budapest). Both were used as received with no further purification. All other products were analytical reagent grade.

Methods

Physical Mixture

A 1:2, mol:mol, OME:γ-CD physical mixture was prepared by gentle mixing of components in a Turbula apparatus for 15 min.

Kneading

For the kneading method, 1.786 g of γ-CD were wetted with pH 9.23 boric/borate buffer (1 ml) and kneaded for 10 min with a pestle in a china mortar. When a homogeneous paste was formed, the stoichiometric amount of OME for a 1:2 mol:mol OME:γ-CD ratio (0.214 g) was added in small portions. The kneading process continued for 20 min with the further addition of approximately 2 ml of the buffer solution. The buffer was used to minimize instability of OME (7). The final product was then allowed to equilibrate at room temperature and humidity for 48 hr protected from light.

Spray-Drying

The γ-CD (3.572 g) was dissolved in 200 ml of a solution previously alkalinized with 25% aqueous ammonia (final pH 9.5). OME (0.428 g) was dissolved in 100 ml of 96% ethyl alcohol. Both solutions were mixed and sonicated; the final solution was spray-dried (Büchi 190 M [CM-FLAWID], flow rate 800 $ml \cdot hr^{-1}$; inlet temperature 102°C; outlet temperature 60°C; airflow rate 400 $NL \cdot hr^{-1}$).

Coprecipitation

For coprecipitation, 0.829 g of OME were added to 30 ml of a 0.16 M γ-CD solution in boric/borate buffer (pH 9.23). The suspension was stirred for 5 days at room temperature. The precipitate was separated by filtration under vacuum and washed with a few milliliters of ice-cold methanol to remove the noncomplexed drug.

Freeze-Drying

For freeze-drying, 2.000 g of the 1:2 mol:mol OME:γ-CD physical mixture, wetted with a small amount (5 ml) of boric/borate buffer, were kneaded, forming a homogeneous suspension, which was then freeze-dried (Telstar model Cryodos, Terrassa, Barcelona, Spain).

The final products (with the exception of spray-dried preparations) were pulverized and sieved between 50-μm and 200-μm mesh.

Differential Scanning Calorimetry

The DSC measurements were carried out using a Mettler DSC 821® module controlled by Mettler Star® software (CM-Schwerzenbach). The thermal traces were obtained by heating from 40°C to 250°C ($10\ K \cdot min^{-1}$) under inert N_2 dynamic atmosphere ($100\ ml \cdot min^{-1}$) in open aluminum crucibles. All measurements were performed in triplicate.

Fourier Transform Infrared Spectroscopy

A Jasco FT-300-IE apparatus (Tokyo, Japan) was used for the FTIR spectroscopy. Each sample was analyzed as a KBr disk in the 400–4000 cm^{-1} wavenumber range (resolution 4 cm^{-1}). The number of scans was adjusted automatically as a function of sample concentration in the disk.

Powder X-Ray Diffraction

Powder X-ray diffractograms were recorded using Siemens Kristallofex D-5000 equipment (Munich, Germany) with nickel-filtered CuK_α radiation at a scan rate of $1°\cdot min^{-1}$, 2θ range from 2° to 30°.

Scanning Electron Microscopy

The photomicrographs of the systems were obtained through a Philips XL30 electron microscope (Eindoven, The Netherlands). Samples were previously coated with graphite.

Dissolution Rate

The dissolution behavior was investigated according to the USP 23 rotating basket method (Turu Grau model D-6) (Terrassa). The dissolution medium was 1 L of pH 9.23 boric/borate buffer. The rotation speed was 50 rpm, and the temperature was adjusted at 37°C ± 0.5°C. Hard gelatin capsules containing the preparations under examination (equivalent to 25 mg OME) were placed in the baskets and tested for dissolution rate. At fixed time intervals, 3-ml aliquots were withdrawn and analyzed (Hitachi U-2000, ultraviolet [UV] spectrophotometer, λ_{max} = 303.5 nm) for OME contents. All assays were performed in triplicate.

RESULTS AND DISCUSSION

Differential Scanning Calorimetry

DSC runs are reported in Fig. 1. In the case of OME (Fig. 1a), a single sharp endothermic effect corresponding to the melting of the drug was observed (T_{onset} = 158.8°C, T_{peak} = 160.2°C, and $\Delta H_f = -76.9$ J/g). This effect was immediately followed by an exotherm related to the decomposition of the drug (T_{onset} = 162.8°C, T_{peak} = 172.3°C, and $\Delta H_f = -219.5$ J/g).

The thermal trace shown by γ-CD (Fig. 1b) is characterized by a broad endothermic effect at about 69°C, which presents a shoulder around 83°C; this behavior can be attributed to the partial dehydration process of commercial γ-CD (8).

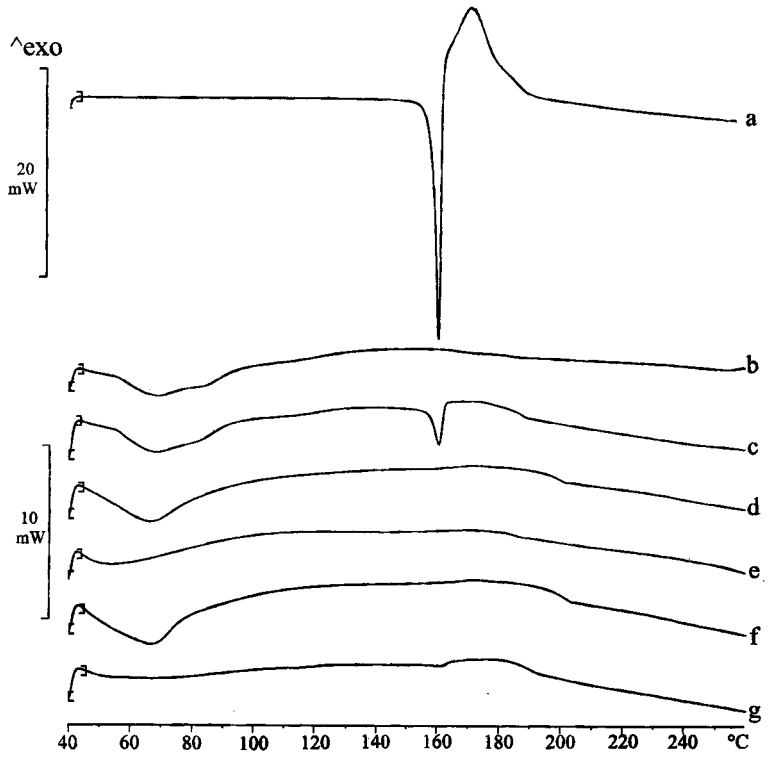


Figure 1. DSC curves of (a) OME and (b) γ-CD and 1:2 mol:mol OME:γ-CD systems obtained by (c) physical mixing, (d) kneading, (e) spray-drying, (f) coprecipitation, and (g) freeze-drying.

The DSC record of the physical mixture (Fig. 1c) corresponds to the simple superposition of the curves of OME and γ-CD. Thus, dehydration of the CD (about 68°C), melting (160.8°C and $\Delta H_f = -10.0$ J/g), and decomposition of OME (188.2°C) are present. This clearly indicates that the preparation of the physical mixture, as well as the heating, causes no interaction between the components.

In the DSC runs of all other preparations under study, that is, kneaded (Fig. 1d), spray-dried (Fig. 1e), and coprecipitated (Fig. 1f) systems, the melting endotherm of OME is absent, probably as a consequence of the inclusion compound formation. The freeze-dried sample (Fig. 1g), however, shows a residual endothermic effect (T_{onset} = 156.9°C, T_{peak} = 161.1°C, and $\Delta H_f = -0.35$ J/g), indicating that a small fraction corresponding to approximately 3.5% of crystalline free OME [calculated by the ratio of fusion enthalpies (9)] is still present. It can be observed that only products obtained by kneading and coprecipitation show the dehydration endotherm of the CD (at 66.7°C and 65.9°C, respectively), while for spray-dried and freeze-dried systems, this endotherm is absent. This is obviously a consequence of different preparation methods, with the freeze-drying involving thorough dehydration of the solid phase. Moreover, the degradation exotherms shown by all samples in DSC curves indicate that neither the CD in the physical mixture nor the possible inclusion of OME can prevent the thermal decomposition of the drug. Analogous behaviors have been reported for systems prepared by grinding (10).

Fourier Transform Infrared Studies

The infrared spectra of the different samples are presented in Fig. 2. Two bands, characteristic of OME infrared spectra, at 1625.7 cm^{-1}, [C═C—N and S—C═N stretching link vibrations (11)] and at 1204 cm^{-1} (Ar—C—O—CH_3 vibration accompanied by the resonance band at 1077 cm^{-1}) have been used for diagnostic purposes in the analysis of the solid-state interactions between components.

In particular, it can be observed that, for the physical mixture (Fig. 2c), these two bands are practically unchanged for position and intensity with respect to the IR spectrum of OME alone. This indicates that no interaction between CD and drug involving the functional groups responsible for the relevant IR absorption has been produced by simple mixing.

In the IR spectra of all other binary systems, the absorption band at 1625 cm^{-1} disappears, probably owing to a restriction of the vibration related to the complexation process. The intensity of the band at 1204 cm^{-1} is also significantly decreased when comparing spectra recorded on the interacted systems (Fig. 2, curves d–g) with those of the physical mixture (Fig. 2c). Since this band is related to bending vibrations of the methoxyl groups of OME, this behavior could be interpreted in terms of a restriction due to the inclusion within the cavity of the CD.

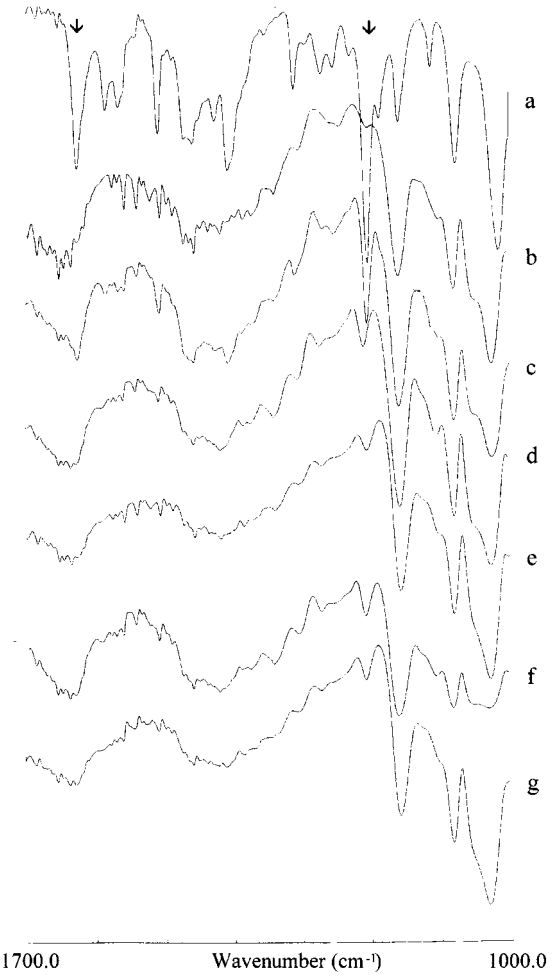


Figure 2. FTIR spectra of (a) OME and (b) γ-CD and 1:2 mol:mol OME:γ-CD systems obtained by (c) physical mixing, (d) kneading, (e) spray-drying, (f) coprecipitation, and (g) freeze-drying.

Powder X-Ray Diffraction

The PXRD patterns of the systems under study are presented in Fig. 3. As expected, the physical mixture

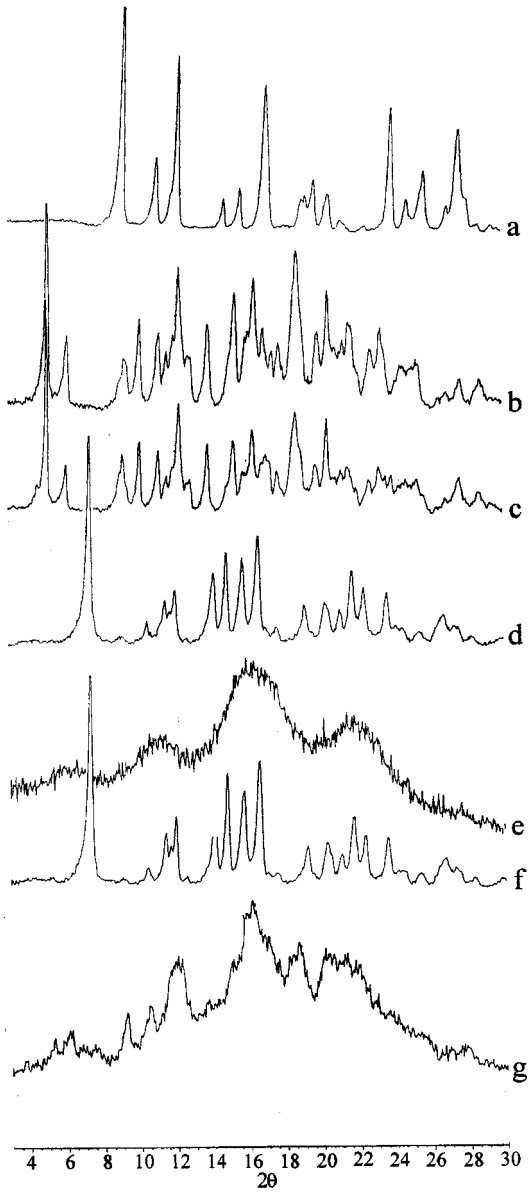


Figure 3. X-ray diffraction patterns on powder of (a) OME and (b) γ-CD and 1:2 mol:mol OME:γ-CD systems obtained by (c) physical mixing, (d) kneading, (e) spray-drying, (f) coprecipitation, and (g) freeze-drying.

(Fig. 3c) corresponds to the simple superposition of those corresponding to pure components.

The diffractograms of products prepared by kneading and coprecipitation (Fig. 3, traces d and f, respectively) are both characterized by a similar and original pattern. New peaks at 7.363°, 10.471°, 11.447°, 16.627°, 22.387°, and 23.634° (2θ), as well as the absence of the peaks situated at 5.082° (CD), 6.156° (CD), 9.244° (OME), 9.347° (CD), 11.109° (OME), 13.883° (CD), 18.723° (CD), 23.924° (OME), 25.724° (OME), and 27.649° (OME) (2θ), indicate the formation of a new crystalline phase by kneading and coprecipitation.

Solid phases obtained by spray-drying and freeze-drying (Fig. 3, curves e and g, respectively) showed a remarkable decrease of crystallinity, particularly for the spray-dried sample. These results can be interpreted on the basis of the formation of amorphous phases, possibly an amorphous inclusion compound. It should be noted that this interpretation is further confirmed by IR spectra.

It is interesting to underline that, since the amorphous state implies the disorder of molecules in the lattice at a more or less long range, various amorphous phases of the same compound can be obtained by different methods (e.g., quenching of the melt, neutralization, grinding, etc.), each showing slightly different spectral and thermal properties. In our case, however, the PXRD patterns for spray-dried and freeze-dried amorphous products indicate a higher crystallinity degree for the latter, related to the proportion between amorphous and crystalline product, as confirmed also by DSC traces. The presence of a small fraction of noninteracted OME in the freeze-dried sample is probably due to the preparation procedure (lyophilization of a suspension), whereas for spray-drying, a solution (i.e., a completely dispersed system) was used.

Scanning Electron Microscopy

The SEM photomicrographs of samples under study are shown in Fig. 4. Although this technique, of course, is not conclusive for assessing the existence of a true inclusion compound in the solid state, it can be of some utility to prove the homogeneity of the solid phases. While micronized OME (Fig. 4a) is characterized by the presence of crystalline particles of regular size, γ-CD appears as crystalline particles without a definite shape. The kneaded system (Fig. 4b) showed crystalline particles of a single component, and no drug crystals could be distinguished. A similar morphology was presented by samples prepared by coprecipitation (Fig. 4c), although in this case the crystal size was smaller. The freeze-dried product (Fig. 4d) appears as a less crystalline substance with a soft and fluffy appearance, while as in the former cases, the crystals of single components are undistinguishable.

Finally, the spray-dried sample shows the typical morphology of preparations generally obtained by this method, that is, very small size spherical particles with a high tendency to aggregation (12).

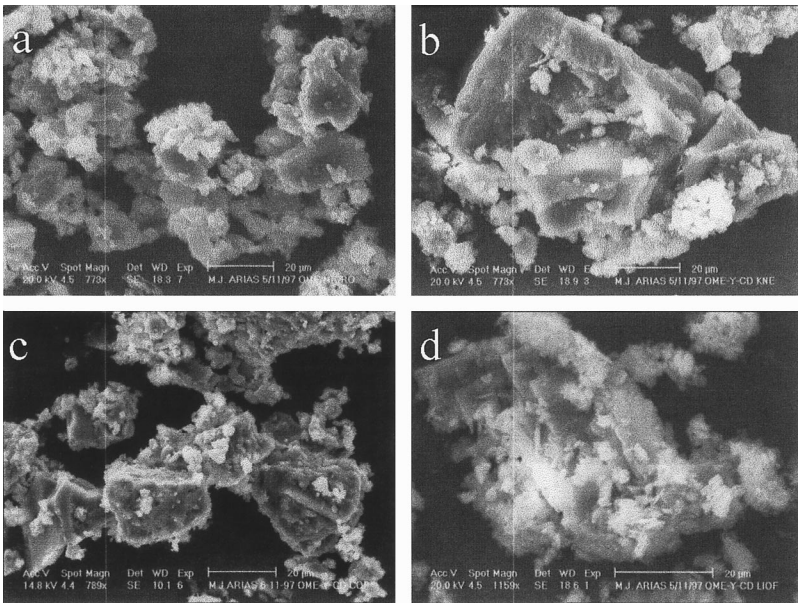
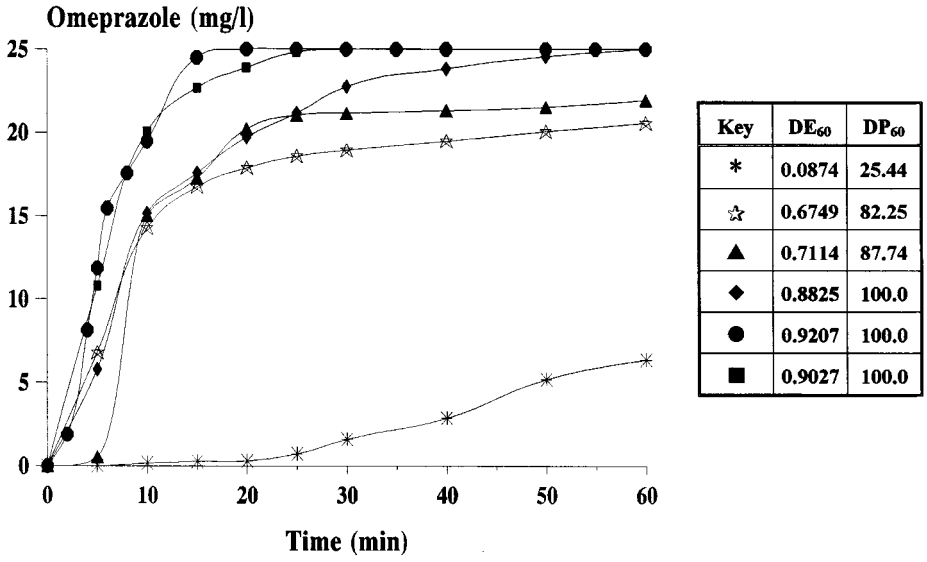


Figure 4. SEM photomicrographs of (a) micronized OME and 1:2 mol:mol OME:γ-CD systems obtained by (b) kneading, (c) coprecipitation, and (d) freeze-drying.

Dissolution Rate Studies

The dissolution profiles for the systems under study are displayed in Fig. 5. For their evaluation, two parameters, dissolution efficiency (13) and percentage of dissolved drug, calculated after 60 min (DE_{60} and DP_{60}, respectively), were measured. The results (see the inset of Fig. 5) indicate that complete dissolution of OME from samples prepared by coprecipitation and freeze-drying was achieved within approximately 20 min, while the



Key	DE_{60}	DP_{60}
*	0.0874	25.44
☆	0.6749	82.25
▲	0.7114	87.74
◆	0.8825	100.0
●	0.9207	100.0
■	0.9027	100.0

Figure 5. Dissolution curves and dissolution parameters of micronized OME and 1:2 mol:mol OME:γ-CD systems (*, OME; ☆, physical mixture; ▲, kneaded; ◆, spray-dried; ●, coprecipitated; and ■, freeze-dried).

product of spray-drying had a lower dissolution rate. This can be ascribed to the high tendency to agglomeration of the spherical particles, probably as a consequence of the presence of electrostatic forces.

On the other hand, the behavior of the kneaded product, which shows DE_{60} and DP_{60} values lower than those of the coprecipitated preparation, is probably due to self-aggregation of particles (see Fig. 4b), thus affording a lower surface area available for dissolution.

Finally, it must be stressed that the physical mixture also shows a significant enhancement of OME dissolution rate with respect to OME alone. This can be attributed to two concomitant effects, the improved wettability of the physical mixture due to the presence of a highly hydrophilic component, γ-CD, as well as the possible in situ formation of the relevant inclusion compound. Both effects lead to the improvement of OME dissolution rate; this would also explain the similarity of the dissolution behavior of the physical mixture with that of the solid complexes obtained by the aforementioned methods.

CONCLUSIONS

The reported results demonstrate that all tested techniques (freeze-drying, spray-drying, coprecipitation, and kneading) can form an inclusion compound between OME and γ-CD with characteristic properties in terms of DSC traces, IR spectra, and PXRD patterns. The kneading technique is of particular interest for industrial-scale preparations due to its low cost.

The dissolution behavior shown by the OME-γ-CD 1:2 mol:mol physical mixture suggests that this preparation can be used as an alternative to solid complexes: The relevant release profiles are very similar in terms of both dissolution efficiency and percentage of drug dissolved.

ACKNOWLEDGMENTS

J. R. M. thanks the University of Parma for a postdoctoral grant.

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