Journal of Pharmaceutical and Biomedical Analysis 50 (2009) 683–689

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Physical–chemical characterization of binary and ternary systems of ketoprofen with cyclodextrins and phospholipids

Marzia Cirri, Francesca Maestrelli, Natascia Mennini, Paola Mura*

Department of Pharmaceutical Sciences, University of Florence, via Schiff 6 Sesto Fiorentino, 50019 Florence, Italy

ARTICLE INFO

Article history:
Received 30 July 2008
Received in revised form 28 October 2008
Accepted 5 November 2008
Available online 13 November 2008

Keywords:
Cyclodextrin
Phospholipids
Ketoprofen
DSC
X-ray powder diffractometry

ABSTRACT

Binary and ternary interaction products of ketoprofen (an anti-inflammatory drug very poorly water soluble) with phospholipids (phosphatidylcholine (EPC3) and phosphatidylglycerol (EPG)) and cyclodextrins (β-cyclodextrin and its methylated derivative (MeβCd)), were prepared to evaluate their ability in improving drug dissolution properties. The different binary and ternary drug–carrier(s) systems were obtained by microwave irradiation, in order to investigate the effectiveness of such a newly proposed preparation technology in bringing about effective solid-state interactions among the components. The effect of different experimental conditions such as microwave irradiation power (500 and 750 W) and treatment time (5, 10 and 15 min) on the physicochemical properties of the products has been also assessed. All solid systems were characterized by differential scanning calorimetry (DSC) analysis, supported by X-ray powder diffractometry, and examined for dissolution properties. The study pointed out the better performance of ternary systems than the binary ones and allowed selection of the best drug–phospholipid–Cd combination and of the most effective preparation conditions. In particular drug–EPC3–MeβCd ternary systems obtained by using the greatest microwave irradiation energy and the longest treatment time exhibited complete drug amorphization and allowed achievement after 60 min of almost 80% dissolved drug, with an increase in dissolution efficiency of 10.7 and 1.4 times in comparison with drug alone and the corresponding drug–Cd binary system, respectively. The synergistic effect between cyclodextrin and phospholipid in enhancing the drug dissolution properties has been attributed to the combination of the surfactant properties of phospholipids and the wetting and solubilizing power of cyclodextrins and/or the possible formation of a "multicomponent" complex.

1. Introduction

Natural cyclodextrins and their derivatives are known to form inclusion complexes with a variety of poorly soluble drugs [1]. Cyclodextrin complexation generally give rise to favourable changes of the characteristics of the guest molecule, such as increased solubility, enhanced dissolution properties, improved stability, reduced side effects, etc. [2–4]. Moreover, some works have demonstrated that the presence of a suitable third component can significantly improve cyclodextrin complexation and solubilizing efficiency [5–7]. The use of natural and synthetic phospholipids as pharmaceutical excipients appears of particular interest, due to their demonstrated ability in improving the dissolution behaviour, and, consequently, the bioavailability of poorly soluble drugs [8–10]. However, at present, their use as possible ternary components to improve the cyclodextrin solubilizing and/or complexing effectiveness has not yet been considered.

On the other hand, different methods have been proposed for obtaining cyclodextrin inclusion complexes, including coprecipitation, freeze-drying, kneading and cogrinding and the most effective must be selected from time to time based on a series of factors such as low cost, swiftness, simplicity, ease of scaling up and performance of the obtained product.

Applications of microwave technology in chemical and pharmaceutical fields are attracting a growing interest, particularly in virtue of their speed of performance and cost savings [11]. Microwaves are electromagnetic waves with a frequency between 300 MHz and 300 GHz. The operating frequencies for industrial, scientific and domestic purposes range from 915 to 2450 MHz. Heating in a microwave oven is the result of the interaction of an electromagnetic field with the chemical components, giving rise to vibrations and molecular frictions within the materials [12]. However, the intensity of the resulting vibrations partly depends also on the structure of the molecules, their shape and size, the viscosity of the materials, the temperature and the intermolecular bonds. To date, only a few studies are reported in literature about the application of microwave technology in the pharmaceutical field, concerning the preparation of solid dispersions [13], the drug release from

* Corresponding author. Tel.: +39 055 4573672 fax: +39 055 4573673.
E-mail address: paola.mura@unifi.it (P. Mura).

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doi:10.1016/j.jpba.2008.11.003

controlled-release solid dosage forms [14,15] the dehydration of cyclodextrin [16], or the inclusion complexation with cyclodextrins [17–21].

Previous studies demonstrated the improved solubility and dissolution properties of ketoprofen (a poorly soluble non-steroidal anti-inflammatory drug) by cyclodextrin complexation [22] and pointed out a clear influence of the complex preparation method on the drug dissolution behaviour [23].

Based on all these premises, in this work it was considered worthy of interest to extend our previous studies and to investigate the possible synergistic effect of the combined use of phospholipids (phosphatidylcholine and phosphatidylglycerol) and cyclodextrins on the dissolution properties of ketoprofen. Microwave irradiation was investigated as a preparation technique of such drug–cyclodextrin–phospholipid systems. Differential scanning calorimetry (DSC) and X-ray powder diffractometry were used to characterize the various solid systems, in order to identify the best experimental conditions (i.e. intensity of the irradiation power and length of the exposure time) for obtaining the most effective solid-state interactions and then the best drug dissolution properties.

2. Materials and methods

2.1. Materials

Ketoprofen (Keto) was a gift from Menarini (Firenze, Italy). Egg phosphatidylcholine (phosphatidylcholine 99.9% and lysophosphatidylcholine 0.1%) (EPC3) and phosphatidylglycerol (phosphatidylglycerol-Na 99.45%, lysophosphatidyl glycerol 0.1%, phosphatidylcholine 0.05%, phosphatidic acid 0.4%) (EPG) were kindly supplied from Lipoid GmbH (Germany). β-Cyclodextrin (βCd) was a gift from Roquette (France) and methyl-β-cyclodextrin (MeβCd) with an average substitution degree per anhydroglucose unit DS 1.8 was kindly donated by Waker-Chemie GmbH, Germany. All other chemicals and solvents used in this study were of analytical reagent grade.

2.2. Preparation of binary and ternary systems

Physical mixtures (P.M.) of binary and ternary systems of Keto with each phospholipid and/or cyclodextrin were obtained by 15 min tumble mixing of the individual components previously sieved (75–150 μm). Different drug:phospholipid (w/w) ratios were used, i.e. 20:1, 10:1 and 5:1, whereas equimolar drug:cyclodextrin binary systems were prepared. Ternary drug:phospholipid:cyclodextrin systems were prepared in the 20:76:4 (w/w) ratio to maintain, as far as possible, the drug:phospholipid and drug:cyclodextrin ratios used in the respective binary systems. The various physical mixtures were subjected to a microwave (MW) treatment at various combinations of irradiation power (500 and 750 W) and time (5, 10 and 15 min) in a microwave oven (Whirlpool MT 20, Whirlpool Corp., USA) equipped with a single magnetron emitter operating at 2.45 GHz. The irradiation energy supplied was calculated as the product of power and time. The instrument was equipped with a Pyrex turntable on which the samples were placed and rotated to achieve uniform irradiation. The irradiated samples (MW) were dried under vacuum at room temperature.

2.3. Solid-state studies

2.3.1. Differential scanning calorimetry

DSC analysis was carried out with a Mettler TA4000 Star^e system (Mettler Toledo, Switzerland) equipped with a DSC 25 cell. Samples of about 5–10 mg were accurately weighed (Mettler MX5 microbalance) in pierced aluminium pans and scanned at 10 °C min^{-1} in the 25–250 °C temperature range, under static air. The instrument was calibrated using Indium as a standard (99.98% purity; melting point 156.61 °C; fusion enthalpy 28.71 J g^{-1}). The relative degree of crystallinity of Keto in mixtures with phospholipids and Cds, expressed as a percentage of the Keto mass fraction in the starting sample, $\text{Keto}_{\text{RDC\%}}$, was calculated by Eq. (1) [24]:

$$\text{Keto}_{\text{RDC\%}} = \frac{\Delta H_{\text{mix}}}{\Delta H_{\text{st}}} \times 100 \quad (1)$$

where ΔH_{mix} and ΔH_{st} are the heats of fusion of Keto measured in the mixtures and in the starting pure Keto sample, respectively.

2.3.2. X-ray powder diffractometry

X-ray powder diffraction patterns were recorded at ambient temperature with a Bruker D8 (θ/θ geometry) diffractometer using a Cu Kα radiation and a graphite monochromator. The samples were analyzed over the 10–38° 2θ range at a scan rate of 0.03 s^{-1}.

2.4. Dissolution studies

In vitro dissolution studies of Keto alone and from the different binary and ternary drug–carrier systems were performed according to the dispersed amount method [22]. Samples containing 200 mg of drug or its equivalent as binary or ternary system with phospholipid and/or cyclodextrin were added to 75 mL of water and stirred at 100 rpm at 37 ± 0.5 °C in a 150 mL beaker up to 60 min. A glass three-blade propeller (19 mm diameter) was centrally immersed in the beaker, at 25 mm from the bottom. At fixed time intervals, samples withdrawn with a syringe-filter (pore size 0.45 μm) and replaced with an equal volume of fresh medium were spectrometrically determined at 260 nm (UV–vis 1600 Shimadzu spectrophotometer, Japan). Each test was repeated three times (coefficient of variation <2%). Dissolution efficiency (D.E.) was calculated from the area under the dissolution curve at time t and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [25].

3. Results and discussion

Two different phospholipids, i.e. egg phosphatidylcholine (EPC3) and phosphatidylglycerol (EPG), were initially examined as possible carriers for improving Keto dissolution properties. Drug:phospholipid physical mixtures were prepared at different (w/w) ratios (i.e. 20:1, 10:1 and 5:1) and tested for dissolution behaviour in order to select the most successful phospholipid type and the best drug-to-carrier ratio. EPC3 was more effective than EPG in improving drug dissolution, and the greater was the phospholipid content, the greater was the increase in the drug dissolution rate (Fig. 1). The system Keto:EPC3 at 5:1 (w/w) ratio showed the best performance, giving rise to a constant 1.6-fold increase of the drug dissolved amount in comparison with pure drug. On the contrary, the slight drug dissolution increase observed in the presence of EPG was practically not affected by the different Keto:EPG ratios. The observed favourable effect on drug dissolution behaviour in the presence of phospholipids could be ascribed to their surfactant properties, due to the simultaneous presence in their molecule of a polar head, given by the phosphate group, and a hydrophobic tail, given by the aliphatic chain. On the other hand, the different performance of the selected phospholipids could be attributable to their different nature. In fact the best dissolution profile obtained in the case of EPC3 may result from the formation of electrostatic drug–carrier interactions between the positively charged polar head of EPC3 and the carboxylic group of Keto. A similar effect has been reported for carbamazepine–phospholipid systems [26].

DSC analysis was then performed, in order to gain more insight about possible drug–carrier solid-state interactions and shed light

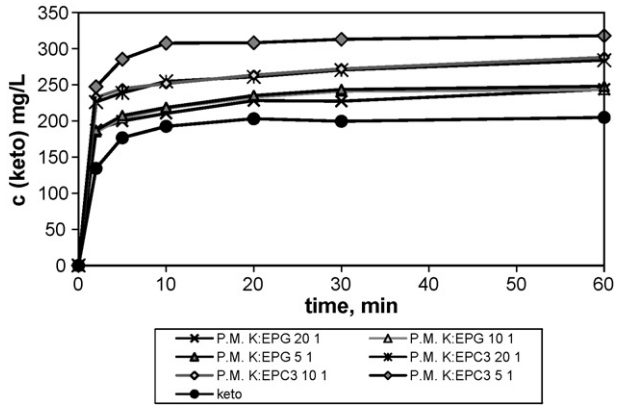

Fig. 1. Dissolution curves of ketoprofen (Keto) alone and from its physical mixtures (P.M.) with phosphatidylcholine (EPC3) and phosphatidylglycerol (EPG) at different w/w ratios.

on the different dissolution behaviour shown by the examined systems. The DSC curves of pure Keto and phospholipids, and their physical mixtures at different drug:excipient ratios are shown in Fig. 2A and B and the main characterizing thermal parameters together with the residual degree of drug crystallinity are summarized in Table 1.

The thermal curve of Keto indicated the anhydrous and crystalline nature of the drug, exhibiting a sharp endothermic peak at 96.5 °C (ΔH_f = 102.2 J/g) due to the melting process. Physical mixtures with EPC3 showed a progressive lowering in the onset temperature and a concomitant reduction in enthalpy of the drug melting peak with increasing the phospholipid content, indicative of an advancing loss of drug crystallinity. In particular, the residual crystallinity of Keto decreased from 82% for the 20:1 (w/w) system to 58.6% for the 5:1 (w/w) one. This finding suggested possible solid-state interactions between the drug and the examined phospholipid. On the contrary, in the presence of EPG, the reduction in the melting peak intensity of Keto was much less evident and practically not affected by variations of the drug:excipient ratio, thus indicating scarce interactions between drug and EPG, according to the findings of dissolution studies.

On the basis of these results, the binary 5:1 (w/w) Keto:EPC3 combination was thus chosen as the best one for further studies. As a following step, we studied and compared the effect of microwave irradiation on the physical–chemical properties of different binary mixtures, i.e. the selected Keto–EPC3 combination and the Keto:βCd and Keto–MeβCd systems, both at 1:1 mol:mol ratio, according to the stoichiometry indicated by phase-solubility studies [22].

The samples were subjected to the microwave treatment for different times (5, 10 and 15 min) at two irradiation powers (500 and 750 W). Independent of the power intensity used, in all cases the 15-min microwave treatment gave rise to products of soft and sticky consistency, which were difficult to manipulate. These time conditions were thus discarded.

The thermal curves of pure components and of some representative binary products of Keto with EPC3, βCd and MeβCd obtained by microwave treatment at different combinations of irradiation power and exposure time are presented in Fig. 3A, B and C, respectively, and their main thermal parameters are summarized in Table 2. It was previously verified that the microwave treatment of pure components did not cause any perceptible modification of their thermal behaviour. The endothermic peak of Keto was still well detectable in all the treated drug:EPC3 binary systems and no appreciable reductions in the drug fusion enthalpy value were registered with respect to the simple physical mixture, thus indicating the poor efficacy of the microwave treatment in bringing about solid-state interactions between the components leading to drug amorphization. In fact at the highest irradiation power used,

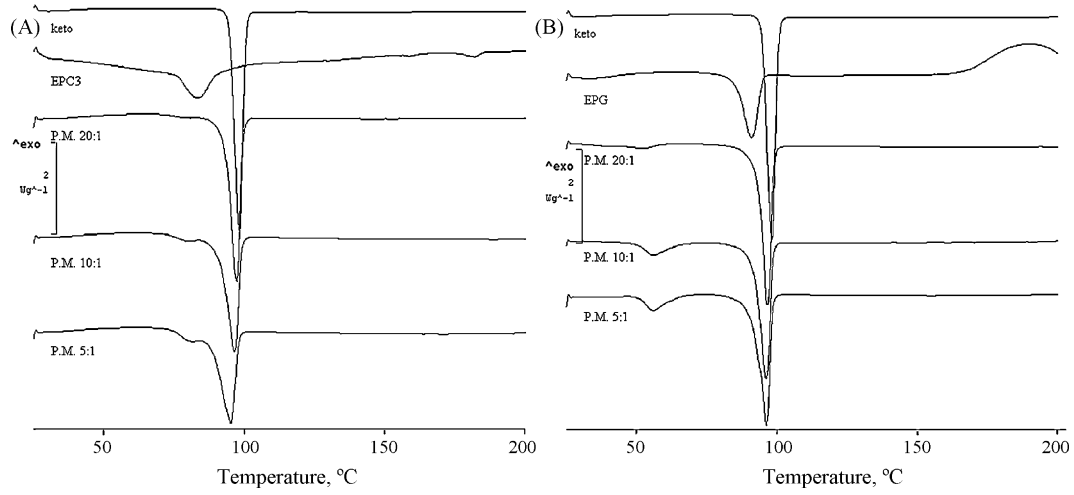

Fig. 2. DSC curves of pure ketoprofen (Keto), phosphatidylcholine (EPC3) and phosphatidylglycerol (EPG), and of their P.M. at different w/w ratios.

Table 1
Thermal parameters of ketoprofen (Keto) alone or in binary physical mixtures with phosphatidylcholine (EPC3) or phosphatidylglycerol (EPG) at different w/w ratios.

Sample	T_{onset} (°C)	T_{peak} (°C)	T_{endset} (°C)	ΔH_{fus} (J/g)	Residual degree of crystallinity (%RDC)
Keto	94.6	96.5	99.4	102.2	100.0%
Keto:EPC3 20:1	92.9	96.3	99.5	83.8	82.0%
Keto:EPC3 10:1	91.1	95.8	99.0	65.7	64.3%
Keto:EPC3 5:1	88.6	94.6	97.9	62.7	61.3%
Keto:EPG 20:1	92.9	95.5	98.8	79.9	78.2%
Keto:EPG 10:1	91.7	95.4	98.5	78.8	77.1%
Keto:EPG 5:1	92.0	95.6	98.4	77.9	76.2%

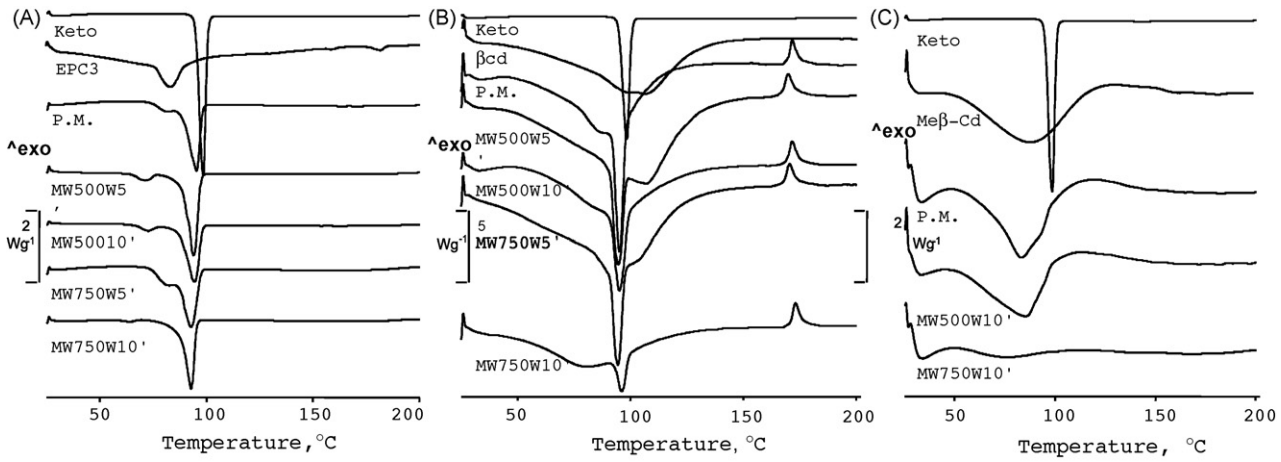

Fig. 3. DSC curves of pure ketoprofen (Keto), phosphatidylcholine (EPC3), β-cyclodextrin (βCd) and methyl-β-cyclodextrin (MeβCd) and their binary P.M. and microwave (MW) irradiated products.

the residual drug crystallinity reached about 50% of the original value, in comparison with the residual 61.3% present in the starting physical mixture.

As for the products with βCd (Fig. 3B), the microwave treatment at the lowest irradiation power scarcely affected the crystalline nature of the drug. On the contrary, the combination of the highest irradiation power and duration gave rise to a marked amorphizing effect toward Keto, making it possible to reach about 26% of residual crystallinity with respect to the 97% of the untreated physical mixture. The greater the irradiation energy supplied, the more intense the Cd dehydration process, and thus the less intense the residual endothermic dehydration band [16]. Almost complete loss of water was achieved only in particular conditions of the microwave treatment, i.e. 500 and 750 W for 10 min, corresponding, respectively, to a 300 and 450 kJ energy. The obtained Cd dehydration leads not only to an improvement of its wettability and affinity towards water, but also to a strong increase in its surface area [27], thus further favouring the interaction with the drug.

The thermal curves of the combinations of Keto with MeβCd (Fig. 3C) before and after the microwave treatment at the lower irradiation power showed rather similar profiles. In both cases, the wide Cd dehydration band almost completely covered and masked the endothermic peak of Keto, making exact determination of the residual drug crystallinity difficult. By contrast, the irradiation at 750 W for 10 min gave rise to almost complete Cd dehydration and total disappearance of the drug melting peak, thus suggesting its full amorphization, and/or possible inclusion complexation. These results confirmed that only specific microwave conditions allowed efficacious Cd drying, thus facilitating its interaction with the drug.

The dissolution profiles of the most representative binary systems with EPC3 and both the examined Cds subjected to the microwave irradiation are illustrated in Fig. 4A and B, respectively. The dissolution behaviour of pure drug was substantially unaffected by the microwave treatment, according to the unchanged DSC profile. The simple physical mixture (5:1, w/w) of Keto with EPC3 showed quite the same dissolution profile as those of the irradiated systems, thus indicating that the microwave treatment did not induce additional drug–carrier interactions able to enhance the drug dissolution rate. Also these results were perfectly in line with DSC findings. On the contrary, a clear effect of microwave irradiation was observed in the presence of βCd, and it was even more evident in the case of MeβCd, where the combination of the highest irradiation power and the longest exposure time gave rise to a 1.7-fold increase in the first step of the dissolution followed by a constant 1.4-fold increase up to the end of the process, compared to the corresponding physical mixture. This result indicated that suitable conditions of microwave treatment gave rise to effective drug–Cd solid-state interactions and/or induced possible complex formation, thus leading to a significant improvement of the drug dissolution behaviour. By comparing the dissolution profile of the irradiated sample with that of pure drug, an increase of 12.9-fold was observed after only 2 min; the difference became only slightly less evident from 10 min up to the end of the test, where a constant 9-fold increase in the dissolution rate was registered.

Moreover, the microwave technique, using the combination of the highest microwave irradiation power and the longest treatment

Table 2
Thermal parameters of ketoprofen (Keto) alone and as physical mixture with phosphatidylcholine (EPC3) or cyclodextrin (Cd) (P.M.) or after the microwave (MW) treatment at different power intensity and time conditions.

Sample	T_{onset} (°C)	T_{peak} (°C)	ΔH_{fus} (J/g)	Residual degree of crystallinity (RDC%)
Keto	94.6	96.5	102.2	100%
Keto:EPC3 P.M.	88.6	94.6	62.7	61.3%
Keto:EPC3 MW 500 W 5 min	89.2	92.8	61.2	59.9%
Keto:EPC3 MW 500 W 10 min	87.5	93.5	60.8	59.5%
Keto:EPC3 MW 750 W 5 min	87.4	96.3	54.9	53.7%
Keto:EPC3 MW 750 W 10 min	87.7	92.1	51.4	50.3%
Keto:β-Cd P.M.	91.9	94.7	99.2	97.0%
Keto:β-Cd MW 500 W 5 min	90.9	94.0	83.1	81.3%
Keto:β-Cd MW 500 W 10 min	91.3	94.6	76.0	74.4%
Keto:β-Cd MW 750 W 5 min	90.9	93.8	81.5	79.7%
Keto:β-Cd MW 750 W 10 min	92.9	96.0	26.7	26.1%
Keto:Meβ-Cd P.M.	64.9	82.8	n.d.	–
Keto:Meβ-Cd MW 500 W 10 min	54.6	85.4	n.d.	–
Keto:Meβ-Cd MW 750 W 10 min	57.2	75.9	–	–

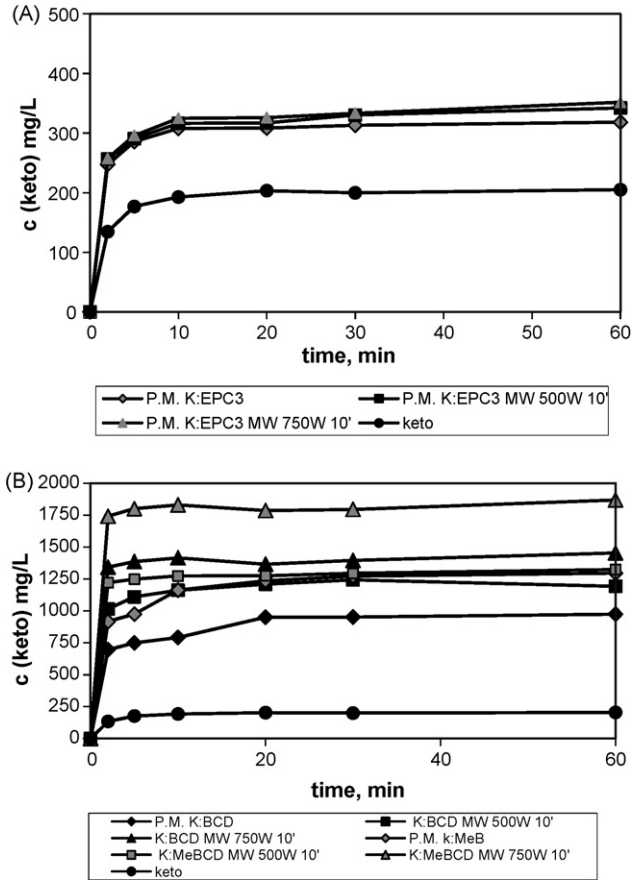

Fig. 4. Dissolution curves of ketoprofen (Keto) from MW irradiated binary products with (A) phosphatidylcholine (EPC3) and (B) β-cyclodextrin (βCd) and methyl-β-cyclodextrin (MeβCd).

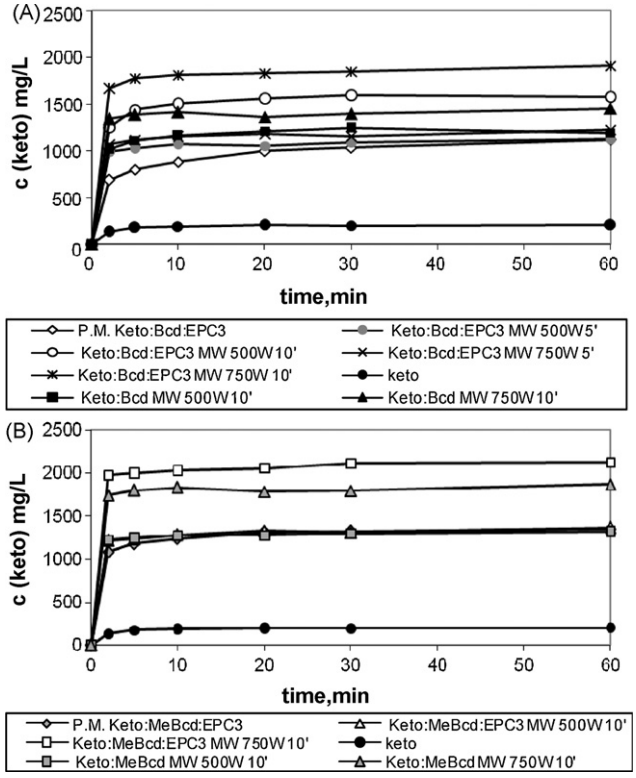

Fig. 5. Dissolution curves of ketoprofen (Keto) from MW irradiated ternary systems with phosphatidylcholine (EPC3) and (A) βCd or (B) MeβCd.

time, resulted more efficacious than some conventional methods previously used for preparing Keto:Cd complexes. In fact, comparing the dissolution efficiency (D.E.) at 10 min of the different samples, the value obtained for the Keto:βCd system irradiated 10 min at 750 W resulted about 1.2-fold higher than those obtained for the corresponding systems prepared by kneading (40 min), grinding (60 min) or sealed-heating (180 min) [23]. On the other hand, the Keto:MeβCd binary system irradiated 10 min at 750 W showed a D.E. value at 10 min which was 1.2-fold higher with respect to that of the corresponding 60-min co-ground system [23]. These findings indicated that microwave irradiation, under suitable experimental conditions, can be an effective alternative technique for preparing Keto:Cd solid systems endowed with good dissolution properties, resulting, at the same time, in a simple and fast method.

Continuing our investigation, we then examined the possible synergistic effect towards the drug dissolution properties due to the simultaneous use of the two carrier types. The influence of the different microwave treatment conditions was therefore evaluated on ternary systems of Keto with EPC3 and both the examined Cds. The dissolution profiles of the different Keto:Cd:EPC3 ternary systems treated by microwave irradiation are shown in Fig. 5A and B, together with those of the corresponding binary systems, for comparison purposes. The results of the dissolution test in terms of percent drug dissolved and D.E. at 30 and 60 min are summarized in Table 3. In the case of ternary systems with βCd, irrespective of the intensity of the applied irradiation power, the 5-min treatment yielded only a slight improvement in the initial step of the dissolution process compared to the corresponding untreated ternary physical mixture. On the contrary, the difference became more evident in the 10-min treated systems. In fact the Keto:βCd:EPC3 sample irradiated 10 min at 500 W showed an 8-fold increase in the drug dissolution rate for the entire duration of the test compared to the pure drug. Moreover, the same sample irradiated 10 min at 750 W gave the best performance, exhibiting an almost constant 9.3-fold increase in drug dissolution rate than Keto alone during all the test and allowing achievement of about 70% drug dissolved at the end of the test. In the case of systems with MeβCd, the microwave treatment at the highest irradiation power and time made it possible to obtain almost 80% drug dissolved after 60 min with a corresponding D.E. value about 11-fold greater than the pure drug.

A synergistic effect of Cd and EPC3 in improving the dissolution properties of the drug was revealed. In particu-

Table 3
Percent dissolved (D.P.) and dissolution efficiency (D.E.) at 30 and 60 min of ketoprofen (Keto) alone and from its binary and ternary systems with phosphatidylcholine (EPC3) and cyclodextrin (Cd) as simple P.M. and after the MW treatment under different power intensity and time conditions.

Sample	D.P.30	D.P.60	D.E.30	D.E.60
Keto	7.49	7.69	6.90	7.24
BIN Keto:βCd P.M.	35.69	36.54	31.17	33.64
TERKeto:βCd:EPC3 P.M.	38.76	42.08	33.37	36.89
BIN Keto:βCd MW 500 W 10 min	46.61	44.72	42.49	44.08
BIN Keto:βCd MW 750 W 10 min	51.31	53.52	50.19	51.80
TER Keto:βCd:EPC3 MW 500 W 5 min	40.93	42.18	38.29	39.93
TER Keto:βCd:EPC3 MW 500 W 10 min	59.91	59.27	54.74	57.16
TERKeto:βCd:EPC3 MW 750 W 5 min	43.30	45.89	41.74	43.17
TER Keto:βCd:EPC3 MW 750 W 10 min	65.16	69.53	61.43	64.89
BIN Keto:MeβCd P.M.	47.70	48.59	42.03	45.09
TER Keto:MeβCd:EPC3 P.M.	49.54	50.55	45.59	47.82
BIN Keto:MeβCd MW 500 W 10 min	48.55	49.66	46.03	47.57
BIN Keto:MeβCd MW 750 W 10 min	56.28	58.08	54.14	56.51
TER Keto:MeβCd:EPC3 MW 500 W 10 min	65.00	69.27	64.79	66.46
TER Keto:MeβCd:EPC3 MW 750 W 10 min	79.14	79.57	75.07	77.71

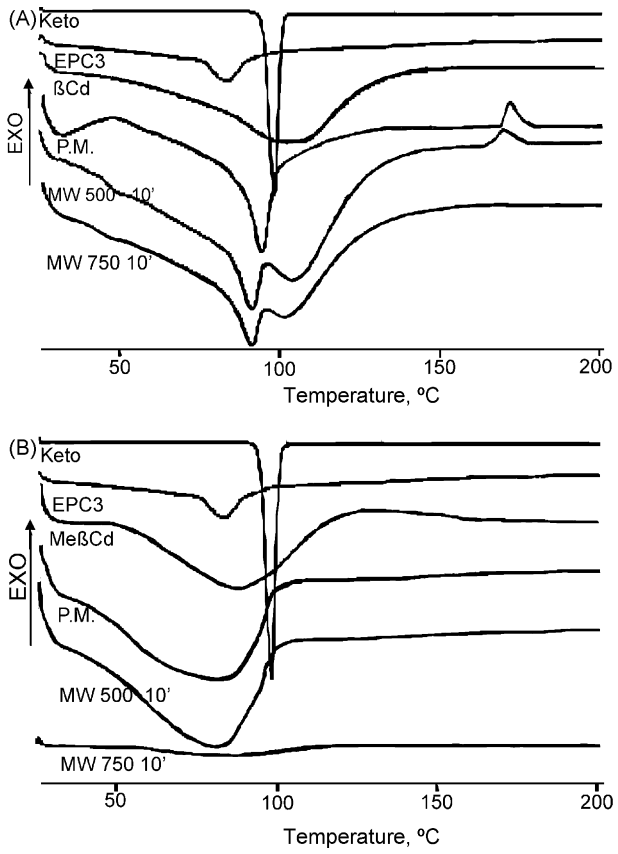

Fig. 6. DSC curves of pure components (ketoprofen (Keto), phosphatidylcholine (EPC3), β-cyclodextrin (βCd) and methyl-β-cyclodextrin (MeβCd)) and (A) Keto:βCd:EPC3 or (B) Keto:MeβCd:EPC3 ternary P.M. and MW irradiated products.

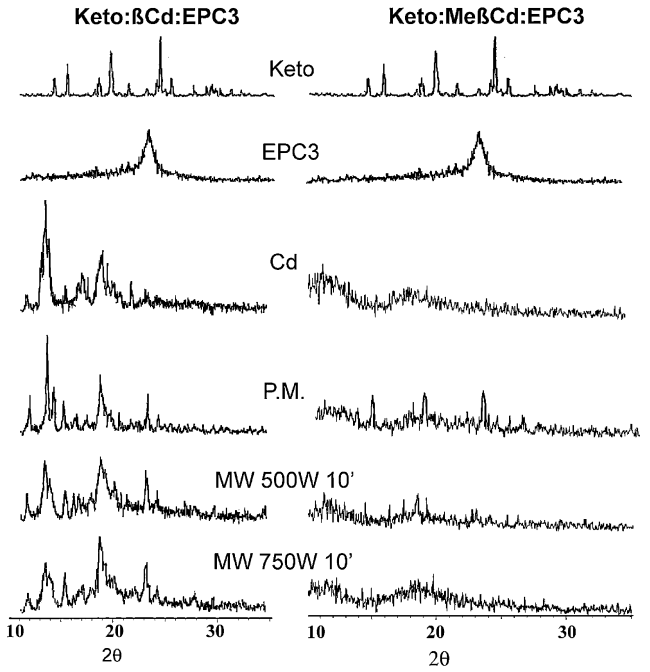

Fig. 7. X-ray powder diffraction patterns of single components and (A) Keto:βCd:EPC3 and (B) Keto:MeβCd:EPC3 ternary P.M. and MW irradiated products.

lar, the Keto:βCd:EPC3 and Keto–MeβCd:EPC3 ternary systems microwave-treated for 10 min at both the irradiation powers used (500 or 750 W) yielded an about 1.5-fold increase in the dissolution rate with respect to the corresponding Keto:βCd and Keto–MeβCd binary systems subjected to the same microwave treatment. Such an effect, which was greater than the simple sum of the effects due to the individual components, could be ascribed to the combination of the surfactant properties of the phospholipid and the wetting and solubilizing power of Cd and/or to the possible formation of a "multicomponent" complex [7,28–30]. On the other hand, the obtained result demonstrated the absence of a possible competition between drug and phospholipid for the interaction with the cyclodextrin, which could be hypothesized due to the known complexation ability of Cds toward this kind of molecules [31–33].

Fig. 6A and B shows the thermal curves of the most representative ternary systems. In the presence of native βCd (Fig. 6A) the endothermic peak of Keto is still detectable in all cases, independent of the microwave treatment applied, even if shifted to lower temperature and markedly broadened and reduced in intensity with respect to the ternary untreated mixture. However, in no case did microwave irradiation allow the obtainment of totally amorphous products, even though the amorphizing effect was more marked than in the corresponding binary systems. In fact, the microwave treatment at 500 W for 10 min of the ternary Keto:βCd:EPC3 system allowed achievement of 40.7% of residual drug crystallinity compared with the 74.4% obtained with the corresponding Keto:βCd binary system. The ternary product irradiated 10 min at 750 W displayed a residual crystallinity of 20.7%, with respect to the 26.1% found for the corresponding binary system (see Table 2). DSC curves of ternary systems containing MeβCd (Fig. 6B) exposed to the combination of the 750 W irradiation power with the longest exposure time exhibited a flat profile, indicative of the almost total loss of water in the system, which promoted complete drug amorphization and/or inclusion complexation.

X-ray diffraction analysis (Fig. 7) substantially confirmed the DSC findings. A decrease in the intensity of the diffraction peaks of Keto was observed in the microwave-treated ternary system Keto:βCd:EPC3 with respect to the starting physical mixture. In fact, the partial amorphizing effect registered in the untreated Keto:MeβCd:EPC3 physical mixture (attributed to the mixing with the amorphous Cd derivative), became clearly more evident after microwave treatment. In particular, a totally amorphous pattern was registered for the ternary system subjected for 10 min to 750 W, thus demonstrating the effectiveness of the microwave treatment in inducing complete drug amorphization and/or inclusion complexation.

4. Conclusions

The microwave technique demonstrated to be an interesting alternative to the more traditional methods used for preparing powerful drug–Cd solid systems in the presence or not of a third component such as the phosphatidylcholine. In fact microwave irradiation under suitable time and power intensity conditions was able to bring about effective solid-state interactions between the components and promoting drug amorphization. Moreover, the simultaneous use of Cd and phosphatidylcholine revealed a favourable synergistic effect in improving the drug dissolution properties. This result was probably due to the combination of the surfactant properties of phospholipids and the wetting and solubilizing power of cyclodextrins and/or the possible formation of a "multicomponent" complex [7,28–30]. In particular, for all ternary systems, the combination of the highest microwave irradiation power and the longest treatment time gave the best performance, allowing achievement of about 70% drug dissolved after 60 min for products containing βCd and almost 80% drug dissolved for those with MeβCd.

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