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Influence of the preparation method on the physical–chemical properties of ketoprofen–cyclodextrin–phosphatidylcholine ternary systems

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ABSTRACT

The aim of this work was to assess the effectiveness and actual advantages of the microwave (MW) technology for preparing ternary complexes of ketoprofen (Keto) with β-cyclodextrin (β-Cd) or methylated-β-cyclodextrin (Meβ-Cd) and phosphatidylcholine (EPC3) with respect to conventional preparation methods, such as co-grinding and sealed-heating. The products obtained with the different techniques were characterized by differential scanning calorimetry (DSC), X-ray powder diffractometry, FT-IR spectroscopy and dissolution studies. For each method, the influence of different experimental conditions on the physical–chemical properties of the final products has been also investigated. DSC analysis was used to monitor physical stability of ternary complexes during 2 years storage under ambient conditions. MW irradiation resulted to be a rapid and very convenient preparation technique. In fact, it was more effective than the considered conventional methods, enabling obtainment in shorter times of products with better performance. In particular, the Keto–Meβ-Cd–EPC3 product prepared by MW treatment at 750 W for 10 min allowed achievement of about 80% of drug dissolution after 60 min, in comparison with the 50% and 63% values obtained for the corresponding products prepared by 30-min co-grinding or 60-min sealed-heating. Moreover, such ternary products were more effective in improving drug dissolution than the corresponding Keto–Meβ-Cd systems. Furthermore, the MW treatment at such irradiation energy enabled obtainment of totally dehydrated samples, which maintained unchanged solid-state characteristics and showed no susceptibility to ambient humidity after 2 years storage at ambient temperature. Therefore, MW-treated Keto–Meβ-Cd–EPC3 systems can be successfully used for formulation of tablets with enhanced drug dissolution behaviour.

1. Introduction

Ketoprofen is a potent non-steroidal anti-inflammatory drug belonging to Class II of Biopharmaceutics Classification System (BCS), whose poor water-solubility can cause formulation problems and limit its therapeutic applications and bioavailability. Cyclodextrin complexation has been successfully employed in improving the solubility and dissolution properties of ketoprofen [1] and a clear influence of the complex preparation methods on the drug dissolution behaviour has been demonstrated [2]. Moreover, previous studies pointed out that the presence of suitable auxiliary substances such as phospholipids had a synergistic effect in improving the cyclodextrin solubilizing power towards ketoprofen [3]. On the other hand, it has been demonstrated that the improved drug dissolution rate obtained by cyclodextrin complexation gives rise to a corresponding enhancement of its bioavailability [4].

Microwave (MW) technology has recently received an increasing interest in the pharmaceutical field even though its applications are still rather limited [5,6]. It has been shown that the polarizing aspect of MW heating gives rise to enhanced mass transport, and it can be exploited as an effective tool for generating drug solid dispersions at molecular or nano-scale level in a suitable stabilizing medium [7]. In particular, MW irradiation has been recently experimented as a new method for preparing interaction products of drugs with different kinds of cyclodextrins [8–13]. We recently used a new MW-based method for the preparation of ternary interaction products of ketoprofen with cyclodextrins and phospholipids which showed improved dissolution performance with respect to the corresponding binary drug–cyclodextrin or drug–phospholipid systems [3].

Therefore, in the present work, it seemed of interest to continue our studies and to investigate more in depth the actual effectiveness and advantages of such a new technology. With this aim we prepared selected ketoprofen:cyclodextrin:phosphatidylcholine ternary complexes by MW irradiation [3] and we characterized and compared their physical–chemical properties with those of the corresponding products obtained by conventional preparation

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methods, such as co-grinding and sealed-heating. For each considered technique, the influence of different experimental conditions was also evaluated, in order to individuate the most suitable ones for improving drug–carrier interactions and enhancing ketoprofen dissolution performances. The solid-state characterization of the ternary systems obtained by the different preparation methods was mainly performed by DSC analysis, supported by X-ray powder diffractometry and FT-IR spectroscopy, whereas their dissolution behaviour was assessed according to the dispersed amount method [1]. DSC analysis was also used to monitor the effect of ageing on the physical stability of selected ternary complexes. In fact, since the amorphous forms are in general thermodynamically unstable and more reactive than their crystalline forms, it is important to evaluate their stability and the influence of ageing conditions on drug recrystallization [14]. Moreover, the adsorption of environmental humidity may substantially affect the physicochemical, mechanical, and biological properties of the drug [15].

2. Materials and methods

2.1. Materials

Ketoprofen (Keto) was a gift from Menarini (Firenze, Italy). Egg phosphatidylcholine (EPC3) was kindly supplied from Lipoid GmbH (Germany), β-cyclodextrin (β-Cd) from Roquette (France) and methyl-β-cyclodextrin (Meβ-Cd) with an average substitution degree per anhydroglucose unit DS 1.8 from Wacker-Chemie GmbH, Germany. All other chemicals and solvents used in this study were of analytical reagent grade.

2.2. Preparation of ternary solid systems

Four different methods were employed to prepare ternary systems of Keto with each cyclodextrin and EPC3.

Physical mixtures (P.M.) were prepared by 15 min tumble mixing the previously sieved (75–150 μm) drug:Cd:phospholipid powders at the 20:76:4 w/w ratio, corresponding to the 1:1 mol/mol drug:Cd and 5:1 w/w drug:phospholipid ratios, previously selected as the best interaction ratios [3].

MW-irradiated products were obtained by subjecting physical mixtures at a 500 or 750 W energy for 5 or 10 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.

Co-ground products (GR) were prepared by grinding physical mixtures in a high-energy vibrational micromill at a vibrational frequency of 24 Hz for 15 or 30 min (Mixer Mill Type MM 200, Retsch, GmbH, Düsseldorf, Germany).

Sealed-heated products (SH) were obtained by placing known amounts of physical mixtures in glass vials in the presence of about 10 μL of bidistilled water. The vials were sealed and kept at 90 °C for 10, 30 or 60 min.

2.3. Differential scanning calorimetry (DSC)

DSC analyses were performed with a Mettler TA 4000 (Star^e Software) apparatus (Mettler Toledo, Switzerland) equipped with a DSC 25 cell. Weighed samples (5–10 mg, Mettler M3 microbalance) were scanned in pierced aluminium pans under static air at a scan rate of 10 °C min^{-1} over a 30–200 °C temperature range. The instrument was calibrated for temperature and heat flow using Indium as a standard (99.98% purity; T_{fus} 156.61 °C; ΔH_{fus} 28.71 J g^{-1}). The relative degree of crystallinity of Keto in mixtures with phospholipids and Cds, expressed as a percentage of the drug mass fraction in the starting sample (Keto$_{RDC\%}$), was calculated by [16]:

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

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

2.4. X-ray powder diffractometry

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

2.5. Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra (PerkinElmer Mod. 1600) of individual components and the selected ternary systems were obtained as Nujol dispersion in the 4000–600 cm^{-1} region.

2.6. Dissolution tests

Dissolution studies of Keto alone and from the ternary systems obtained with the different techniques and experimental conditions were performed according to the dispersed amount method [1,2]. Samples containing 200 mg of drug or its equivalent as ternary system with EPC3 and Cd 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 were withdrawn with a syringe-filter (pore size 0.45 μm), replaced with an equal volume of fresh medium and spectrometrically assayed 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 [17].

2.7. Storage stability studies

Samples of ternary systems obtained with the different techniques were stored in glass jars with lids for 2 years in an air-conditioned room, controlled for temperature (23–25 °C) and relative humidity (R.H. 50%). At defined time intervals, aliquots were withdrawn and subjected to DSC analysis.

3. Results and discussion

The DSC curves of individual components and the respective drug–carriers ternary systems prepared by MW irradiation, co-grinding and sealed-heating techniques at different treatment times are shown in Fig. 1. The thermal curve of Keto was characterized by a flat profile followed by a sharp endothermic peak at 96.5 °C (ΔH_{fus} = 102.2 J/g) indicative of its crystalline anhydrous state. β-Cd showed an intense, broad endothermal band, in the 80–140 °C range, associated with water loss (14.5% as mass fraction), whereas EPC3 exhibited an endothermal effect peaked at about 85 °C, attributable to the fusion of its crystalline portion. The typical drug-melting endotherm was well detectable in the thermal curves of all MW-treated KETO–β-Cd–EPC3 ternary systems, even if shifted to lower temperature, broadened and reduced in intensity as a consequence of interactions between the components. This effect became more evident with increasing the treatment time, but no complete drug amorphization was achieved. The same

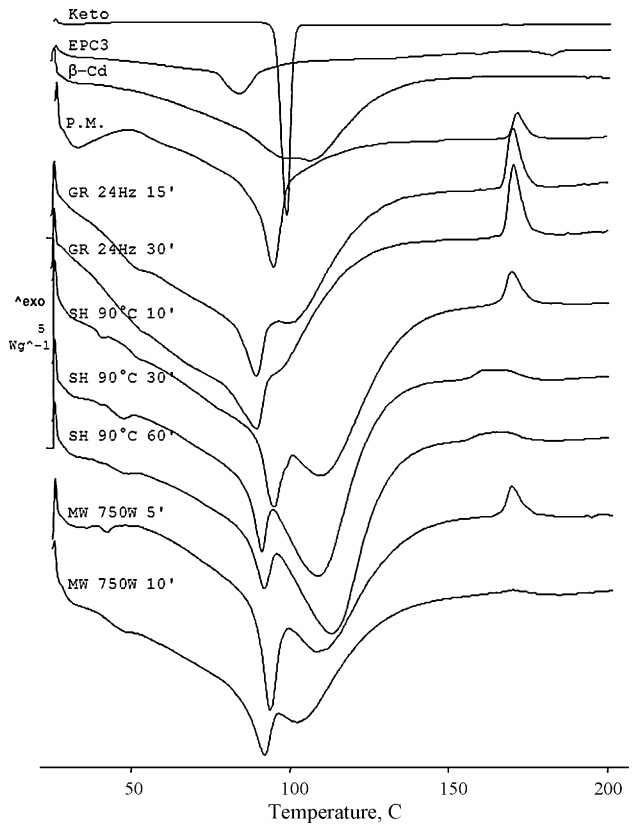

Fig. 1. DSC curves of pure ketoprofen (Keto), β-cyclodextrin (β-Cd) and phosphatidylcholine (EPC3) prepared by physical mixture (P.M.), microwave (MW) irradiation, co-grinding (GR) and sealed-heating (SH) techniques at different treatment times.

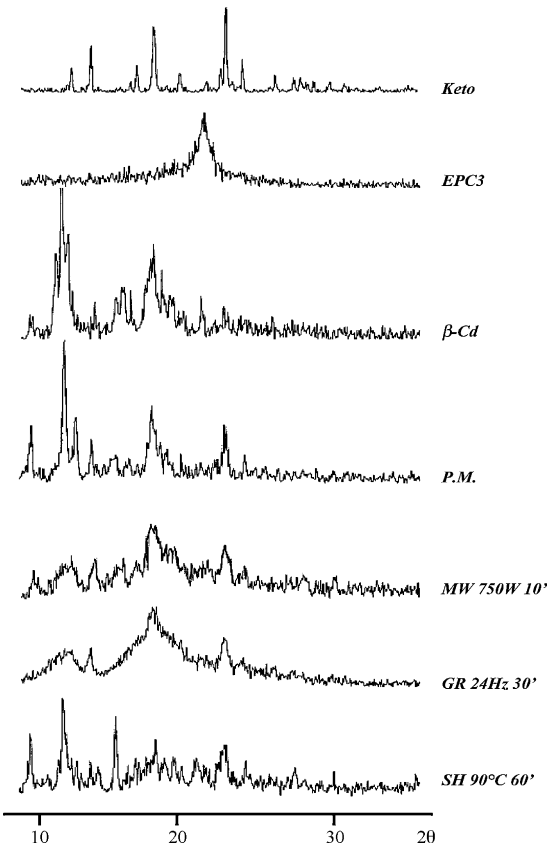

Fig. 2. X-ray powder diffraction patterns of ketoprofen (Keto), β-cyclodextrin (β-Cd) and phosphatidylcholine (EPC3) and their ternary physical mixtures (P.M.) and the products obtained by microwave (MW) irradiation, co-grinding (GR) and sealed-heating (SH) under different experimental conditions.

behaviour was observed for the co-ground and sealed-heated products. In fact, also in this case only a partial loss of drug crystallinity can be detected with increasing the treatment time, demonstrated by the progressive shift and broadening of the drug-melting peak. However, MW irradiation allowed a substantial reduction of the treatment time needed to induce drug amorphization compared to the other considered methods. In fact the relative degree of drug crystallinity ($Keto_{RDC\%}$) in the sample MW-irradiated for only 10 min at 750 W was 35%, while 30-min co-grinding or 1-h sealed-heating were necessary for achieving a similar result.

Fig. 2 shows the X-ray powder diffraction patterns of the individual components and of the most representative ternary systems obtained with each preparation technique. Such analysis substantially confirmed the DSC results, revealing the presence of residual drug diffraction peaks in all treated ternary systems, even though reduced in intensity in comparison with the simple physical mixture.

The results of dissolution experiments of Keto–β-Cd–EPC3 ternary systems obtained with the different techniques and experimental conditions are presented in Fig. 3 in terms of drug dissolved percent (D.P.) at 10, 30 and 60 min. Independent of the preparation method used, all the ternary systems exhibited better dissolution properties than drug alone. The improvement of the drug dissolution rate obtained with physical mixtures can be attributed both to improved drug particle wettability and formation of readily soluble complexes in the dissolution medium. The sample treatment allowed a further enhancement of the drug dissolution properties with respect to the physical mixtures, and it depended by both the type and the conditions of the treatment. The best results were given by the product MW-treated for 10 min at 750 W, which reached about 70% of dissolved drug at the end of the test. Moreover, the MW-treatment at 500 W for 10 min gave rise to an increase of drug dissolution rate comparable to that of the product obtained after 1-h sealed-heating and better than that of the product obtained after 30-min co-grinding. The better performance of the MW-treated system could be attributed to the high efficiency shown by MW irradiation in obtaining a drug molecular dispersion into the carrier [6]. This effect is directly related to its greater ability to reduce the residual drug crystallinity, as emerged by previous DSC studies. MW radiations, in virtue of their marked penetration power, generate in the materials fast and selective heating and other non-thermal effects, including diffusion activation energies [18,19]. It has been shown that such MW-induced diffusion effects can be exploited to efficiently disperse hydrophobic drugs into hydrophilic matrices, thus improving their dissolution properties [7].

In order to evaluate the role of the amorphous or crystalline status of Cd in the performance of the final product, the most effective experimental conditions found for each preparation method were then applied for obtaining ternary systems of Keto with EPC3 and Meβ-Cd, the amorphous derivative of β-Cd.

The thermal curves of Keto–Meβ-Cd–EPC3 ternary systems are illustrated in Fig. 4. The DSC curve of Meβ-Cd was characterized by a broad endotherm effect between 60 and 120 °C, associated with water loss (7.5% as mass fraction), indicative of its amorphous hydrate state. In the case of the physical mixture, the broad endothermic band associated to the Meβ-Cd dehydration process partially masked the melting peak of Keto, making it difficult to separately evaluate the two effects. All the treated systems showed instead only the broad dehydration band of Meβ-Cd and the disappearance of the Keto melting peak, thus indicating complete drug amorphization and/or its inclusion complexation, as a consequence

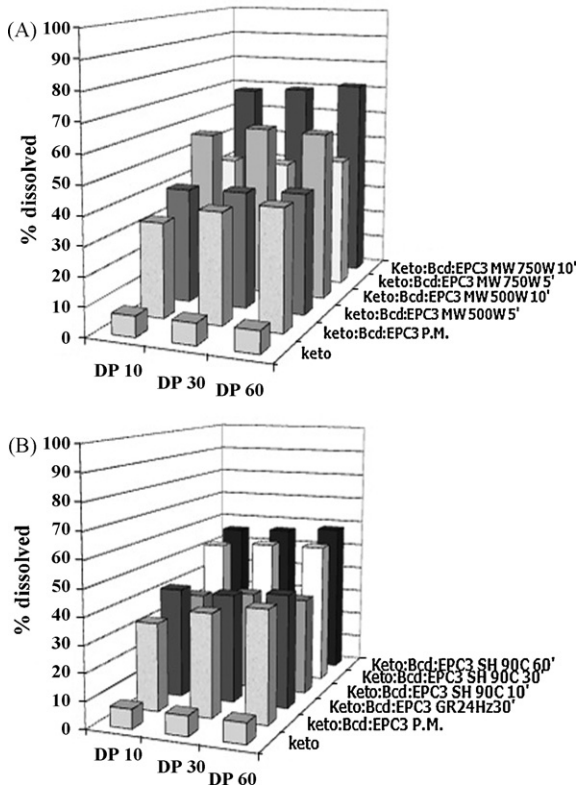

Fig. 3. Dissolution data of the various ternary systems in terms of drug dissolved percent at different times (D.P. 10′, 30′ and 60′) prepared (A) by microwave (MW) irradiation at different irradiation power and time and (B) by co-grinding (GR) and sealed-heating (SH) at different treatment times with respect to their physical mixtures (P.M.).

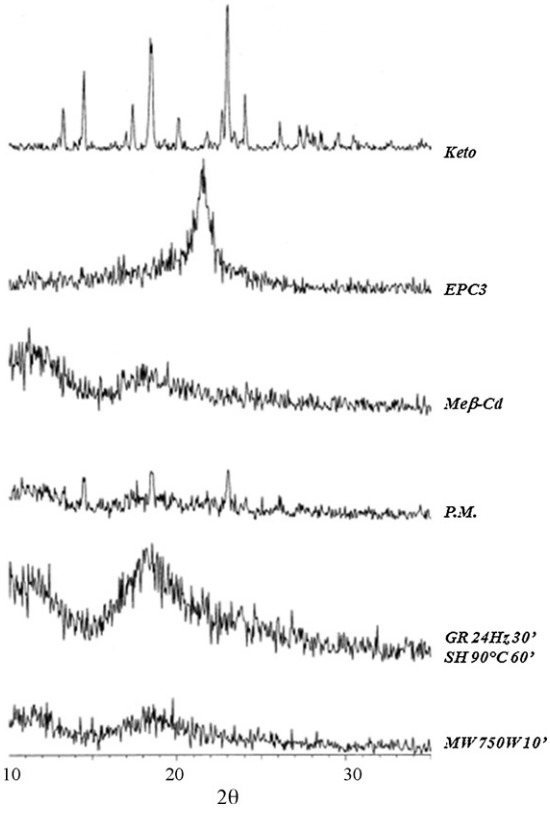

Fig. 5. X-ray powder diffraction patterns pure ketoprofen (Keto), methyl-β-cyclodextrin (Meβ-Cd) and phosphatidylcholine (EPC3) and their ternary physical mixtures before (P.M.) and the products obtained by microwave (MW) irradiation, co-grinding (GR) and sealed-heating (SH) under different experimental conditions.

of the more marked amorphizing ability shown by such an amorphous carrier. It is important to point out that this result could not be taken for granted. In fact, sometimes, the effect of the sample treatment on the drug amorphization can be more marked for its combinations with crystalline than with amorphous cyclodextrins

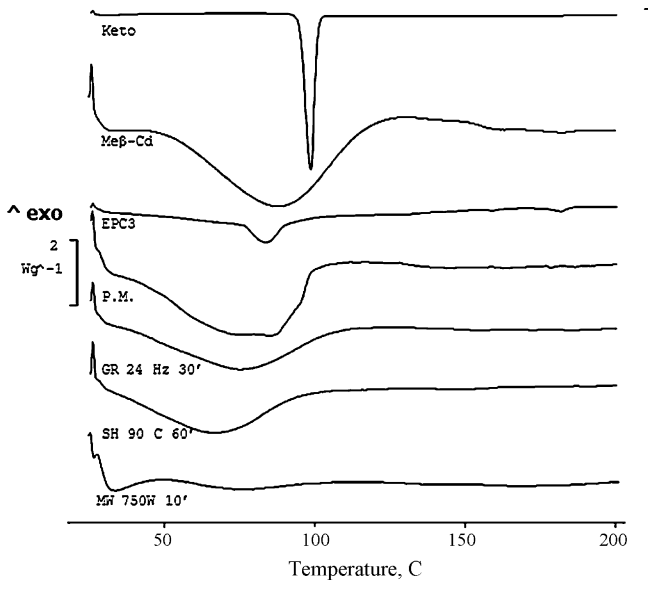

Fig. 4. DSC curves of pure ketoprofen (Keto), methyl-β-Cyclodextrin (Meβ-Cd) and phosphatidylcholine (EPC3) and their ternary physical mixtures before (P.M. and the products obtained by microwave irradiation (MW), co-grinding (GR) and sealed-heating (SH) under different experimental conditions.

[20]. Moreover, the MW treatment allowed obtainment of totally dehydrated samples. This effect should give rise to both higher water affinity and better dissolution properties [21] and better stability in the time of these products.

X-ray analyses were in good agreement with the DSC findings (Fig. 5). In fact, residual crystallinity peaks of Keto can be easily individuated in the diffractogram of the ternary physical mixture. On the contrary, totally flat profiles were detected in all treated ternary systems and in particular for the MW system, thus confirming the complete drug amorphization and/or inclusion complexation.

Infrared absorption frequencies of the most characteristic bands of Keto alone and in the various ternary systems with Meβ-Cd and EPC3 are collected in Table 1. IR spectrum of Keto is characterized by the presence of two typical carbonyl absorption bands at 1697 and 1655 cm^{-1}, attributed to the carboxyl carbonyl and ketonic carbonyl stretching, respectively [22]. The acid carbonyl band appeared unchanged in the physical mixtures, whereas it was shifted to higher frequency in the case of products obtained by the different techniques, and this effect was particularly evident for the MW products. A similar effect has been observed also for binary

Table 1
Carbonyl stretching bands (cm^{-1}) of ketoprofen (Keto) as simple physical mixture (P.M.) and after microwave (MW), co-grinding (GR) and sealed-heating (SH) treatment with methyl-β-cyclodextrin (Meβ-Cd) and phosphatidylcholine (EPC3).

Sample	C=O ketone	C=O acid
Keto	1655	1697
Keto:Meβ-Cd:EPC3 P.M.	1654	1696
Keto:Meβ-Cd:EPC3 MW 750 W 10′	1654	1735
Keto:Meβ-Cd:EPC3 GR 24 Hz 30′	1654	1733
Keto:Meβ-Cd:EPC3 SH 90 °C 60′	1656	1730

Table 2
Percent dissolved (D.P.) and dissolution efficiency (D.E.) at 30 and 60 min of ketoprofen (Keto) alone and from its ternary systems with phosphatidylcholine (EPC3) and methyl-β-cyclodextrin (Meβ-Cd) as physical mixture before (P.M.) and after the microwave (MW), co-grinding (GR) and sealed-heating (SH) treatments.

Samples	Technique	D.P.30	D.P.60	D.E.30	D.E.60
Keto		7.49	7.69	6.90	7.24
Keto:Meβ-Cd:EPC3	P.M.	49.54	50.55	45.59	47.82
Keto:Meβ-Cd:EPC3	MW 750 W 10′	79.14	79.57	75.07	77.71
Keto:Meβ-Cd:EPC3	GR 24 Hz 30′	51.59	52.32	48.20	50.08
Keto:Meβ-Cd:EPC3	SH 90 °C 60′	65.82	67.21	60.16	63.34

products of Keto with Meβ-Cd obtained by various methods, such as kneading, sealed-heating and freeze-drying [2], and it has been attributed to the breakdown of the intermolecular hydrogen bonds between drug molecules [23] and the formation of hydrogen bonds of monomeric drug with the carrier [24].

The results of dissolution tests expressed in terms of drug D.P. and D.E. at different times (30 and 60 min) are summarized in Table 2. Also in this case all the ternary systems showed better dissolution properties than Keto alone. The improvement of dissolution rate shown by the simple physical mixture was due to the combination of the wetting properties of Meβ-Cd and phospholipid towards the drug. On the other hand, MW irradiation resulted the most effective preparation method also in the case of ternary products with Meβ-Cd, followed in order by sealed-heating and co-grinding. Probably, the highly dehydrated samples obtained by MW irradiation gave rise not only to a higher wettability and greater affinity towards water, but also to a marked improvement of its surface area, thus favouring the interaction among the components and the drug dissolution in the medium [21,25]. Unexpectedly, the co-ground products, despite their totally amorphous state, showed the worse dissolution parameters. This was probably due to possible particle aggregation phenomena, sometimes associated with grinding of solids [26].

Finally, DSC analysis was used to monitor physical stability of ternary complexes stored 2 years in closed glass vials under ambient conditions. The thermal data of ternary systems of Keto with Cds and EPC3 in physical mixtures, MW-treated, co-ground and sealed-heated products freshly prepared and after 2 years storage at room temperature are collected in Table 3. The MW treatment at 750 W for 10 min of Keto–Cd–EPC3 systems allowed obtainment of stable anhydrous and non-hygroscopic forms with both types of Cds, as demonstrated by the maintenance of the dehydration enthalpy at a low constant value during the storage. On the contrary, all other systems showed a marked increase of the dehydration band with ageing.

Table 3
Thermal parameters of ternary systems of ketoprofen (Keto) with Cd and phosphatidylcholine (EPC3) as physical mixture (P.M.), microwave (MW)-irradiated, co-ground (GR) and sealed-heated (SH) products freshly prepared and after 2 years storage.

	T peak (°C)	Δ*H* fus (J/g)	Δ*H* dehydr. (J/g)
Keto:β-Cd:EPC3			
P.M.	94.1	89.02	144.5
P.M. stored	91.2	48.60	306.9
MW 750 W 10′	90.6	40.59	20.8
MW 750 W 10′ stored	90.0	42.64	23.7
GR 24 Hz 30′	84.9	52.80	146.6
GR 24 Hz 30′stored	82.0	9.47	197.8
SH 90 °C 60′	87.2	23.00	181.1
SH 90 °C 60′stored	88.1	27.32	339.5
Keto:Meβ-Cd:EPC3			
MW 750 W 10′	–	–	10.0
MW 750 W 10′ stored	–	–	12.8

4. Conclusions

It has been shown that the physical–chemical properties of Keto–Cd–EPC3 ternary systems are clearly influenced by both the type of preparation technique and experimental conditions, as well by the type of Cd (β-Cd or Meβ-Cd) present in the product. In particular, the amorphous Cd-derivative exhibited a better performance than the corresponding native one from the point of view of both amorphizing and solubilizing efficacy towards the drug. On the other hand, among the preparation methods considered, the MW irradiation resulted to be a convenient, rapid and easy preparation technique, more effective than conventional methods such as co-grinding and sealed-heating in improving the drug dissolution properties. The high speed of performance of such a technology, taking advantage of the high penetration power of MW radiations, allowed shorter reaction times and cost savings, greatly reducing the time to obtain anhydrous and amorphous samples, compared with the longer operating time required by the other conventional methods.

Moreover, the products obtained by MW irradiation were found to be the most stable, showing practically unchanged solid-state characteristics and no susceptibility to ambient humidity after 2 years storage under ambient conditions.

Therefore, MW-treated Keto–Meβ-Cd–EPC3 systems, being in addition more effective than the corresponding binary ones without EPC3 [3], can be rightly selected for formulation of tablets with enhanced drug dissolution behaviour. It can be reasonably expected that the improved Keto dissolution rate obtained by ternary complexation with Meβ-Cd and EPC3 will result in an increase of drug bioavailability [4], thus suggesting the possibility of a reduction of drug dosage and hence of the appearance of undesired side effects.

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