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Microwave generated solid dispersions containing Ibuprofen

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ABSTRACT

The purpose of this study was to apply the attractive technique of the microwaves irradiation (MW) for the preparation of solvent-free solid dispersions (SD). In particular, the microwave technology has been considered in order to prepare an enhanced release dosage form for the poorly soluble drug Ibuprofen (IBU), employing PVP/VA 60/40 (PVP/VA 64) and hydroxypropyl-β-cyclodextrin (HP-β-CD) as hydrophilic carriers. Their physico-chemical characteristics and dissolution properties were compared to the corresponding physical mixtures and the drug alone. The results of physico-chemical characterization attested a correspondence of the solid state of the drug before and after irradiation treatment and that an amorphous form of the drug was obtained. This result, together with the presence of the hydrophilic polymers determined a remarkable enhancement of the in vitro dissolution rate of the drug suggesting that the microwave technique could be considered as a new and interesting method to prepare drug–polymer systems.

1. Introduction

According to Biopharmaceutical Classification System (BCS) drugs can be divided into four classes, depending on their solubility and permeability. Drugs which belong to class II are characterized by low solubility and high permeability (Amidon et al., 1995). The low dissolution profile of relative insoluble drugs is the rate-limiting step in the absorption of a drug from a solid dosage form (Kerč et al., 1998). Various techniques can be useful to achieve an improvement of dissolution rate. The most popular approaches are the incorporation of the drugs into inert lipidic vehicles such as oils, surfactants dispersions, self-emulsifying formulations and the preparation of solid dispersions (SD) based on cyclodextrin inclusion complexes, polyvinylpyrrolidone and polyethylene glycols 4000 and 6000 (Chiou and Riegelman, 1971; Ford, 1986; Yüksel et al., 2003). Recently a novel approach based on the use of microwave irradiation has been proposed for the preparation of SD.

Microwaves irradiation (MW) is a well-known method for heating and drying materials (Wiesbrock et al., 2004). Microwaves, with their ability to penetrate any substance, allow the production of heat in any point of the sample at the same time. This is due to the presence in it of molecules characterized by a dipolar moment able to absorb microwave energy and convert it into heat (Kappe, 2004). This phenomenon occurs when the microwave frequency is close to the resonance frequency of the polar molecules. The efficient heating of materials by microwaves depends on the capacity of a specific material to absorb microwave energy. In the recent years, the use of microwaves has become very attractive in organic chemistry (Kappe, 2004). Infact with respect to conventional heating, i.e. conduction, convention or radiation with infrared light, microwaves irradiation offers several advantages such as: rapid volumetric heating, no overheating at the surface, addressable heating, energy-saving and low operating cost (Zhou et al., 2003). In addition the main advantage of not using organic solvents is the absence of any risk originating from residual solvents (Passerini et al., 2002).

Microwave energy has been employed to change the crystalline state of a drug, instead of conventional heating. Kerč et al. (1998), using felodipine as a model drug and a porous silicon dioxide, reported that microwave energy can influence the crystalline status of the drug and the time of exposure plays an important role in achieving the amorphous state of the drug, improving consequently its dissolution rate. Microwave irradiation was also successfully used to obtain an inclusion complex of carvedilol and β-cyclodextrin as reported by Xianhong et al. (2004). In order to improve solubility of class II drugs, Bergese et al. (2003) employed β-cyclodextrin and PVP CL M as carriers, attesting a reduction in residual cristallinity. β-cyclodextrin was used because it instantaneously reaches a resonant state with the MW field, while in the case of PVP CLM electrothermal coupling probably occurs via the

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adsorbed water, that has a high mobility similar to that of bulk pure water.

In this study drug-carrier systems were prepared by MW irradiation using Ibuprofen as a model drug (Class II) in the presence of hydroxypropyl-β-cyclodextrin (HP-β-CD) or PVP/VA 60/40 as carrier. As known, HP-β-CD is a cyclodextrin modified by the incorporation of hydroxypropyl groups, which has applications similar to β-CD but it is characterized by higher water solubility and less nephrotoxic properties (Nash, 1994).

PVP/VA, also known as copovidone, is a water-soluble copolymer of vinylpyrrolidone and vinyl acetate, used in technological processes as a binder, film-forming agent or protective layer for oral solid dosage forms, or a matrix in certain rapid-dissolution dosage forms (Zingone et al., 1992; Moneghini et al., 1998; Bühler, 2005; Wang et al., 2005).

2. Materials and methods

2.1. Materials

Ibuprofen was purchased from Comifar (Padova, Italy); PVP-VA 60/40 was provided from BASF (Ludwigshafen, Germany) and HP-β-cyclodextrin by Wacker (Burghausen, Germany). All the chemicals were of reagent grade, and all materials were used as received.

2.2. Preparation of binary systems

MW activated systems (SD) in different ratios of Ibuprofen to PVP/VA or HP-β-CD (SD IBU:PVP/VA and SD IBU:HP-β-CD) were prepared by MW. For Ibuprofen and PVP-VA a ratio 1:1 (w/w) was chosen, while for Ibuprofen and HP-β-CD 1:1 and 1:2 molar ratios were used. Initially, drug and polymer were gently mixed for 3 min. A fixed amount of this mixture (i.e. 1 g) was subjected to MW for different times at the chosen power of 600 W in a domestic microwave oven (mod. CE297DN – Samsung). Only one beaker at a time was placed inside the microwave oven in a precise place, determined using a luminous antenna, which is lit up when irradiated by MW. Temperatures of the treated samples were recorder at the end of the cycle using a thermometer (immersion type). The samples were so pulverized using an analytical mill (model A10 Janke & Kunkel IKA Labortechnik – Germany) for few seconds, and 80–250 μm particle size fractions were selected by sieving. As a comparison in the same manner and ratios of SD, physical mixtures of the untreated components and physical mixtures of the separately treated components at 600 W were prepared. These samples were named PM IBU:PVP/VA and PM IBU:HP-β-CD for the untreated components, while TPM IBU:PVP/VA and TPM IBU:HP-β-CD for the treated ones.

2.3. Assay of the total drug content

Known amounts of the drug–polymer binary systems (SD, PM and TPM) were dissolved in anhydrous ethanol and then the drug content was evaluated spectrophotometrically at 220 nm (Mod. 552, Perkin–Elmer, Norwalk USA), value at which the absorbance of the polymers is negligible. Calibration curve was obtained by plotting the absorbance of the standard drug solutions against the concentration. The percent drug content was compared to the calculated value. The experimental value was the average of three replicates.

2.4. Hot stage microscopy (HSM)

Microscopic observations of morphological features and changes during heating in the samples were monitored performing hot stage microscopy studies. A hot plate (FP 52 Mettler, Greifensee, Swiss), connected to a temperature controller (FP 5 Mettler) was used. A little amount of each sample was placed on a glass slide and heated at 10 °C/min the temperature range of 30–100 °C.The behaviour of the samples was observed via an optical microscope (Reichert Biovar, Wien, Austria) (magnification 10×).

2.5. Differential scanning calorimetry (DSC)

Calorimetric analysis was performed with a DSC mod. TA 4000 (Mettler, Greifensee, Switzerland), equipped with a measuring cell DSC 20. Samples, containing a fixed amount of Ibuprofen, were placed in pierced aluminium pans and heated at a scanning rate of 10 °C per min from 30 to 130 °C under air atmosphere.

2.6. Powder X-ray diffraction studies (PXRD)

Samples were studied by means of XRD technique using a STOE D500 (Siemens, Monaco, Germany) diffractometer with Cu Kα radiation (l = 1.5418 Å), monochromatised by a secondary flat graphite crystal. The scanning angle ranged from 3° to 40° of 2θ, steps were of 0.05° of $2\underline{\theta}$, and the counting time was of 1 s/step. The current used was 20 mA and the voltage 40 kV.

2.7. Scanning electron microscopy (SEM)

The shape and surface characteristics of pure components and binary systems were observed by SEM. Samples were sputter-coated with Au/Pd using a vacuum evaporator (Edwards, Milano, Italy) and examined using a scanning electron microscope (model 500, Philips, Eindhoven, The Netherlands) at 10 kV accelerating voltage using the secondary electron technique.

2.8. Determination of drug dissolution

Ibuprofen release profiles were obtained according to the USP 27 paddle method: 100 rpm, 900 ml of water as dissolution medium (Passerini et al., 2002; Mallick et al., 2008), $T = 37 \pm 0.1$ °C, sink conditions ($C < 0.2C_s$). The aqueous solution was filtered and continuously pumped to a flow cell in a spectrophotometer and absorbances were recorded at 220 nm. Polymers did not interfere with the UV analysis. Experimental points were the average of at least three replicates, and standard deviations did not exceed 5% of mean value. Dissolution profiles of IBU from MW activated systems were compared to that of the pure drug, PM and TPM at the same experimental conditions.

3. Results and discussion

3.1. Analysis of drug content

The analysis of drug content confirmed the theoretical value of the formulations, with values ranging from 97% to 101%.

3.2. Hot stage microscopy (HSM)

This analysis was used to observe changes in the crystalline status of Ibuprofen before and after MW treatment. Changes in the PM samples morphology were noted as a function of temperature, infact crystalline IBU began to melt at 65 °C and completely changed to liquid at 76 °C. After melting, an aggregation with each considered polymer particles occurred.

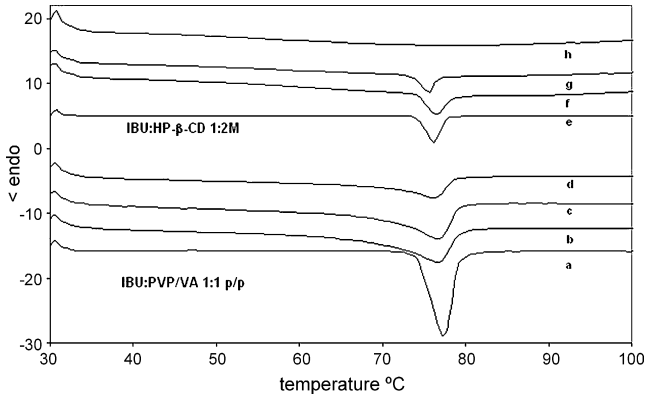

Fig. 1. DSC thermograms of IBU:PVP/VA systems: Ibu (a), PM (b), SD 600 W 3 min (c), SD 600 W 6 min (d); IBU:HP-β-CD systems: Ibu (e), PM (f), SD 600 W 10 min (g), SD 600 W 15 min (h).

3.3. Differential scanning calorimetry (DSC)

Drug–polymer interaction was detected by DSC analysis. Samples treated at 600 W for different times were analysed in order to evaluate the time at which amorphisation of the drug occurred. For SD IBU PVP/VA 1:1 (w/w) after 6 min of treatment a strong reduction in cristallinity was found (Fig. 1d). A prolonged treatment till 10 min lead to a complete amorphisation of Ibuprofen but the obtained sample was a sticky powder difficult to handle. In the case of IBU:HP-β-CD complex, a molar ratio 1:1 of IBU:HP-β-CD did not lead to any amorphisation of the drug even when a power of 600 W was applied for 15 min. In this particular case the powder did not show good processing features. For this reason a molar ratio 1:2 of IBU:HP-β-CD was chosen since after 15 min a complete amorphisation of the drug was obtained together with good handling properties (Fig. 1h). Therefore IBU:PVP/VA treated at 600 W for 6 min and IBU:HP-β-CD 1:2 M treated at 600 W for 15 min were used for further characterizations.

As reported in Table 1, starting IBU was characterized by a melting peak of 76.5 °C; after MW treatment at 600 W for 6 and 15 min only a slight shift of the melting point was evident. Usually this may be caused by a variation of the different crystal habit or to a reduction in particle size. As assumed by Rasenack and Müller (2002), Ibuprofen can be present either in a needle-shaped or a plate-shape habit characterized respectively by a melting point of 75.2 and 75.1 °C and according to Potthast et al. (2005) Ibuprofen does not exhibit genuine polymorphism. In addition, the enthalpy related to the endothermal event was 125.8 J/g in the native IBU and slightly diminished in IBU treated for 6 and 15 min. This variation could be ascribed to an initial reduction in cristallinity, directly linked to the irradiation time. DSC profiles of the polymers treated and untreated showed that no modification occurred following MW irradiation.

As known, the amorphous polymers did not show any fusion peak or phase transition in the experimental range adopted, apart from a broad endotherm due to the dehydratation of PVP/VA and HP-β-CD, which lies between 40–80 °C and 60–100 °C respectively.

Table 1
Melting temperature and enthalpy of fusion of starting Ibuprofen and Ibuprofen MW treated at 600 W for 6 and 15 min

	Melting temperature (°C)	Enthalpy of fusion
Ibuprofen	76.5	125.8
Ibuprofen 600 W 6 min	76.4	118.7
Ibuprofen 600 W 15 min	75.8	112.0

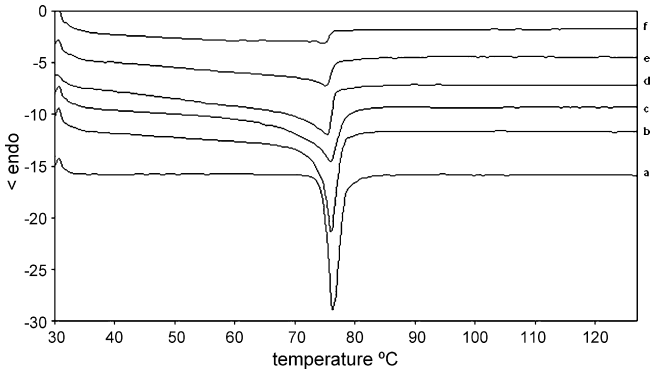

Fig. 2. DSC thermograms of IBU:PVP/VA systems: Ibu (a), PM pan (b), PM (c), TPM (d), SD water bath 6 min (e), SD 600 W 6 min (f).

In the thermal profile of PM and TPM with PVP/VA an endothermal peak corresponding to the melting of IBU was still recognized due to the presence of the drug in a crystalline form. Only a little shift of the melting point was observed attesting a decrease of drug cristallinity and the initial formation of interactions in accordance with the literature (Fig. 2) (Cirri et al., 2004; Novoa et al., 2005; Rawlinson et al., 2006). In order to confirm this assumption, the two starting materials were directly weighed in an aluminium DSC pan, avoiding therefore any mixing operation. The corresponding thermogram attested that this interaction occurred only after mixing the two components (Fig. 2b). From the DSC analysis of the MW activated systems, the positive influence of the hydrophilic polymer on the solid state of the drug was attested. In order to assess the validity of the technology adopted in respect of a traditional method, we analysed an SD sample prepared by melt agglomeration. A physical mixture of IBU:PVP/VA 1:1 (w/w) was heated in a water bath. When the temperature was about 76 °C (measured with an immersion type thermometer) the sample was left inside the bath for 6 min. After cooling down, DSC profile revealed the presence of Ibuprofen still in a crystalline status confirming the validity and rapidity of the employed technology (Fig. 2e).

Thermograms of HP-β-CD MW activated systems confirmed the amorphous state of Ibuprofen while the corresponding physical mixtures, treated and untreated, still displayed characteristic peaks of drug without interactions (Fig. 3).

3.4. Powder X-ray diffraction (PXRD)

The diffractograms of the polymers before and after treatment attested that no modifications occurred after MW treatment. The

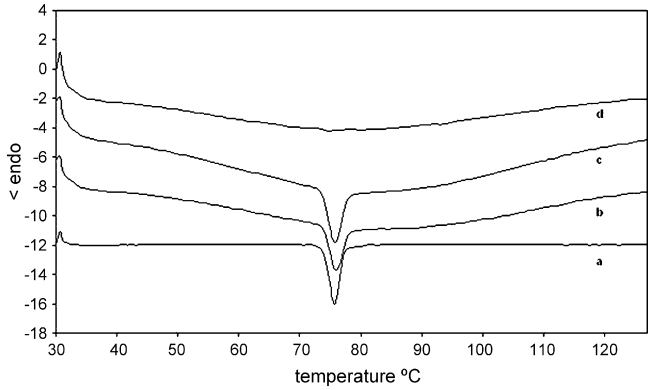

Fig. 3. DSC thermograms of IBU:HP-β-CD systems: Ibu (a), PM (b), TPM (c), SD 600 W 15 min (d).

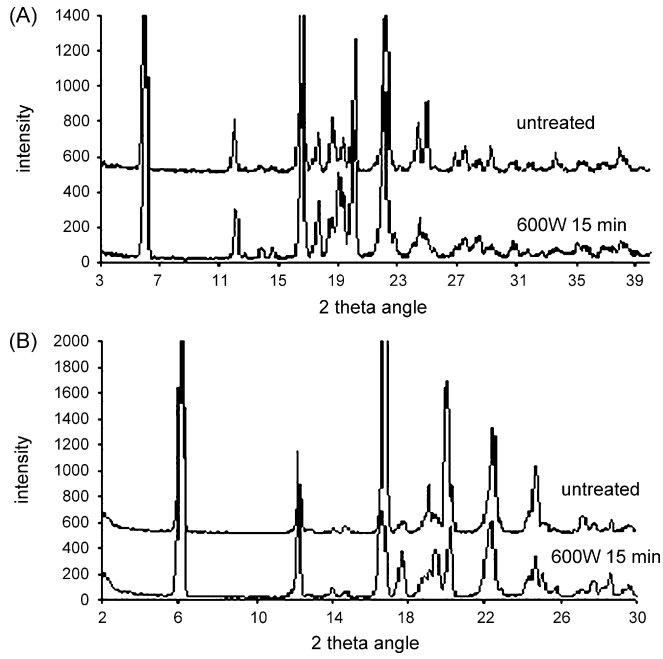

Fig. 4. PXRD of untreated and treated Ibu at 2θ angle of 3°–40° (A), at 2θ angle of 2°–30° (B).

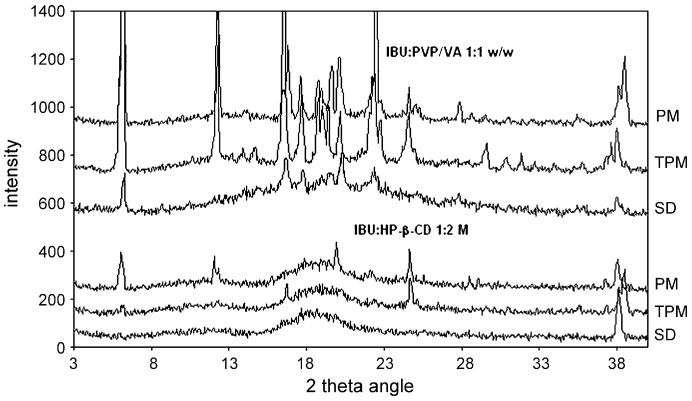

Fig. 5. PXRD of IBU:PVP/VA 1:1 (w/w) and IBU:HP-β-CD 1:2 M.

patterns of treated and untreated IBU were characterized by a substantial superimposition in the range 3°–40° of 2θ angle and only little variations in the intensity of the signals were noticed (Fig. 4A). To confirm that this behaviour can be ascribed to a different crystalline habitus and a reduction in particle size as seen in DSC, a deepened analysis was performed employing new experimental conditions (scanning angle ranged from 2° to 30° of 2θ, steps were of 0.05° of 2θ, and the counting time was of 4 s/step). Generally, when the patterns of two crystal forms are identical in terms of peak positions, they have the same internal crystal structure, whereas if

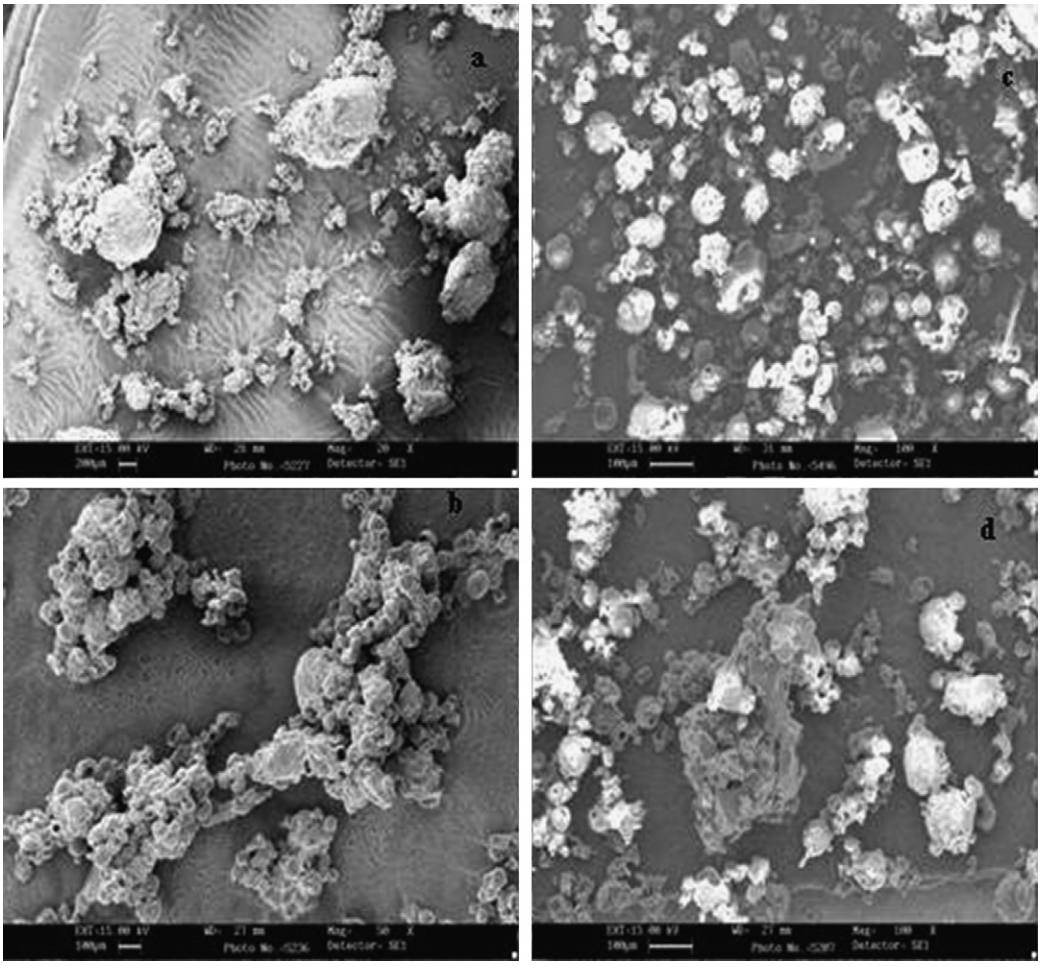

Fig. 6. SEM analysis of IBU:PVP/VA PM (a) and SD 600 W 6 min (b); IBU:HP-β-CD PM (c) and SD 600 W 15 min (d).

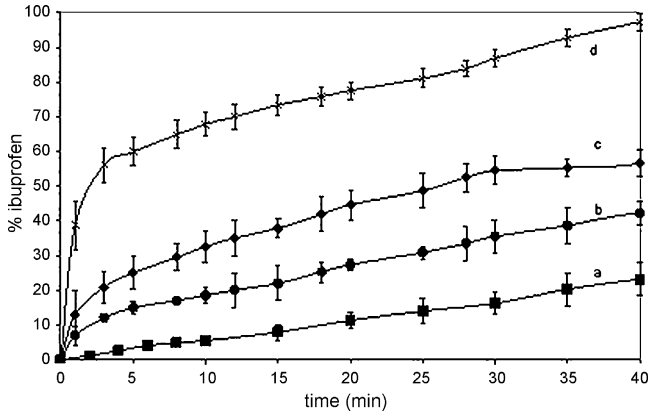

Fig. 7. Dissolution profile of Ibu (a), IBU:PVP/VA PM (b), IBU:PVP/VA TPM (c), IBU:PVP/VA SD 600 W 6 min(d).

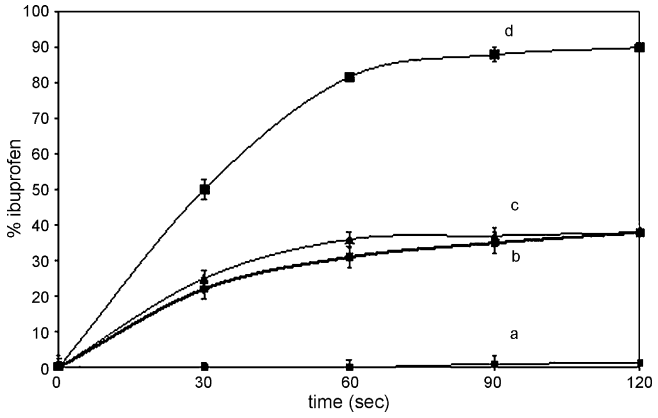

Fig. 8. Dissolution profile of Ibu (a), IBU:HP-β-CD TPM (b), IBU:HP-β-CD PM (c), IBU:HP-β-CD SD 600 W 6 min(d).

the patterns are different the crystals have different internal structure and are recognized as polymorphs (Garekani et al., 2001). The difference in the relative intensity of the peaks is due to either the variation of the crystal habit, because the relative abundance of the planes exposed to X-ray source is altered, or to differences of the size of the crystals (Garekani et al., 2001). As shown in Fig. 4B, the adopted different experimental conditions confirmed the previous assumption: no polymorphic modification but only crystal habit variation occurred together with a reduction in particle size.

The PXRD patterns of IBU activated systems confirmed DSC data: the drug was in an amorphous form in the CD system while a strong reduction in cristallinity was observed in the PVP/VA system. In both PM and TPM systems the drug was still in a crystalline state and the XRD signals corresponded to that of the starting drug (Fig. 5).

3.5. Scanning electron microscopy

SEM observation of treated IBU revealed that the drug was originally in a needle-like form, while after MW treatment it assumed a rough surface. Starting and treated PVP/VA and HP-β-CD appeared quite similar. In the IBU:PVP/VA physical mixture, beyond the presence of the single components, the initial formation of agglomerates was detected indicating that some interactions occurred as previously noted in DSC analysis (Fig. 6a). The complete drug–polymer interaction was observed in the SD system where only the presence of agglomerates was evident (Fig. 6b). In the IBU-HP-β-CD binary systems, SEM analysis of physical mixtures revealed that the two components maintain their original structure while a strong aggregation in the activated system occurred (Fig. 6c,d).

3.6. Dissolution test

From the dissolution profile of the MW systems with both polymers employed, it was evident a remarkable improvement of the dissolution rate of Ibuprofen compared to that of the pure drug. Infact, as reported in Fig. 7, from SD IBU:PVP/VA treated at 600 W for 6 min, 90% of the drug was released, while at the same time only 55% of the drug was released from the PMT IBU:PVP/VA and 38% from the PM IBU:PVP/VA. The corresponding percentage for the pure drug was 20%. The better dissolution profile of the drug in the TPM with respect to PM can be ascribed to the reduction in crystal size of Ibuprofen, although this performance was considerably lower than those of the solid dispersion.

Ibuprofen-HP-β-cyclodextrin MW system (SD IBU:HP-β-CD) was able to produce 90% of the drug in solution within 5 min, while at the same time only 48% and 41% of the drug was released from respectively treated and untreated physical mixture. The corresponding percentage of the pure drug was only 4% (Fig. 8).

The amorphisation grade of the drug due to the chosen polymers and the employed technique, was responsible of the improved dissolution profiles of all MW systems.

4. Conclusions

In this study, the microwaves technique was applied to the preparation of SD. In particular, it was proved that this technique is a viable and alternative mean to prepare solvent-free binary systems. These activated systems, prepared with PVP/VA 60/40 and HP-β-cyclodextrin as carriers, were able to remarkably increase the dissolution profile of the poorly soluble Ibuprofen. The physical characterization of the MW activated systems attested a complete amorphisation of the drug and no formation of polymorphic forms was found.

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