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Ultrasound-compacted and spray-congealed indomethacin/polyethyleneglycol systems

A. Fini [a,*], L. Rodriguez [b], C. Cavallari [b], B. Albertini [b], N. Passerini [b]

[a] *Istituto di Scienze Chimiche, Università di Bologna, Via San Donato 15, Bologna 40127, Italy*
[b] *Dipartimento di Scienze Farmaceutiche, Università di Bologna, Via San Donato 19, Bologna 40127, Italy*

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Abstract

The product obtained by ultrasound (US)-assisted compaction was compared with a solid dispersion for systems containing polyethyleneglycols (PEGs) of different molecular weights and indomethacin (IMC), at the weight ratio 9:1, obtained by traditional melting and followed by a new US-assisted spray-congealing technique. US-discharge during compaction affects crystallinity of both IMC and PEG: pure IMC changes to an amorphous form and, when in mixture with PEG, partially dissolves in the excipient: this causes an increase of the dissolution rate of the drug. Differential scanning calorimetry (DSC) thermograms do not reveal any endothermic peak associated with the melting of the drug, while X-ray diffractograms show a loss of crystallinity of both IMC and PEG in the US-compacted granules. The extent of a back-crystallisation, which reduces the dissolution rate, as a function of the ageing of the material, depends on the type of the selected PEG. When a molten IMC/PEG mixture was transformed into microspheres by an US-assisted spray-congealing technique, the behaviour at dissolution almost recalls that of US-compacted granulates and some differences are briefly discussed.

Keywords: Indomethacin; Pegs; Ultrasound; Compaction; Spray congealing; Dissolution

1. Introduction

Improvement of the release of a poorly soluble drug is a problem common to many researchers. Together with micronisation, other methods have been proposed to increase the dissolution rate such as formation of soluble salts or complexes, use of surfactants and the preparation of solid dispersions or solutions. In these products, the drug is at a high thermodynamic activity level having particles with a large surface area or in an amorphous form (Alonso et al., 1988; Gupta et al., 1991). For this purpose, polyethyleneglycols (PEGs) have been widely employed for their low cost and high solubility (Draguet-Brughmans et al., 1984; Ginés et al., 1990; Singla and Vijan, 1990; Bonora and Veronese, 1998). They are characterised by a low melting point and the high viscosity of the molten phase. Many papers (Chiou and Riegelman, 1971; Ford, 1984; Ford et al., 1986; Craig, 1990; Craig and Newton, 1991a,b; Rabasco et al., 1991; Ginés

* Corresponding author. Tel.: +39-051-244540; fax: +39-051-249770
E-mail address: fini@biocfarm.unibo.it (A. Fini).

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et al., 1996; Khan and Jiabi, 1998; Damian et al., 2000; Forster et al., 2001; Naima et al., 2001) have shown the efficacy of solid dispersion with PEG in improving dissolution rate, absorption amount and therapeutic action of insoluble drugs, as compared with traditional pharmaceutical forms, such as dry granulates. However, recently together with promising breakthroughs of this technique (Serajuddin, 1999), Craig (2002) reviewed the current consensus with regard to the solid-state structure and dissolution properties of solid dispersions.

Ultrasound (US) was introduced into traditional processes of pharmaceutical technology a few years ago. Our group has studied US-assisted compaction and US-spray-congealing of a variety of systems including indomethacin (IMC)/β-cyclodextrin (β-CD) (Fini et al., 1997), theophylline/Eudragit® RL (Rodriguez et al., 1998), ketoprofen/Eudragit® S100 (Sancin et al., 1998) and theophylline with different waxes (Rodriguez et al., 1999), where physical modifications of the structure of the drug and/or the excipient improved the release of the drug from different pharmaceutical forms thus prepared.

US uses acoustical waves with a frequency above 18,000 Hz, which is the threshold of the human ear. US can modify many materials, causing plastic deformation, moulding and welding (Levina and Rubinstein, 2000). Since many materials of pharmaceutical interest are thermoplastic, US can also affect technological processes where these materials are involved. US has been used to direct compaction, obtaining tablets of increasing hardness and glassy appearance, but also to prepare a new generation of granulates by milling of US-compacted matrices. These powders show a modified release of the active drug, different to that of granulates obtained under a dry traditional compaction (Khan and Jiabi, 1998).

Besides these effects on solids, US also acts on liquids or melt mixtures, causing cavitation and an extreme molecular motion, that divide a drop of liquid material into a number of microdrops of sizes in a very narrow range. This physical principle was therefore employed in pharmaceutical technology to design an US-apparatus suitable for the spray-congealing process in order to prepare multiparticulate delivery systems (Rodriguez et al., 1999). It was thus interesting to examine the effects obtained on the same system by the application of US, delivered by these two different techniques.

In a previous paper (Fini et al., 1997), we described US-compaction and tested the influence of US-discharge on granulates of IMC, as a model drug, and β-CD, as an excipient, concerning morphological and structural changes of both components and the behaviour to release. In this paper, we used solid PEGs of different molecular weights and IMC as a model drug. IMC is a poorly soluble drug (O'Brien et al., 1984; Lheritier et al., 1995), while PEG is a low-melting solid that behaves suitably for spray-congealing and whose semicrystalline nature can be modified under US. The aim of this study was to compare the release of IMC from formulations prepared from granulates, obtained by US-compaction, and microspheres obtained with US-spray-congealing process, recently proposed (Rodriguez et al., 1999). Moreover, possible interactions between the drug and the excipient, and the nature of IMC in the final systems were examined by means of differential scanning calorimetry (DSC), IR spectroscopy and X-ray diffraction. Finally, we studied the influence of different molecular weight PEGs and ageing of the final materials on the dissolution of the drug.

2. Materials and methods

2.1. Materials

IMC (γ or I form) (O'Brien et al., 1984) was a commercial sample (Sigma Chemical Co., St Louis, MO), and PEG 4000, 5500 and 6000 are white solids with a melting point in the range 55–62 °C and were purchased from Polichimica, Bologna, Italy.

2.2. Preparation of the samples

2.2.1. Physical mixing

The mixture contained IMC 10%, PEG (4000–6000) 88%, magnesium stearate 1%, talc 1% (w/w) and was stirred for 15 min in a Turbula.

2.2.2. Traditional compaction

The mixture thus obtained was compacted into tablets using a single-punch tabletting machine (Korsch, mod EKO, Berlin, Germany) at a compression pressure of 50 kN cm^{-2}. The tablets were then milled and sieved in order to obtain the dry granules and then the 75–150 μm fraction was selected for dissolution tests. This material was identified as *dry granules*.

2.2.3. US-compaction

The physical mixture was compacted with an US-assisted tabletting machine operating at 25,000 Hz, using different US-energy to form a wafer (weight 1 g; diameter 25 mm), characterised by a yellow colour. The wafers were milled and sieved, selecting powders with the size range 75–150 μm, used for further examinations: this material was identified as *US-granules*.

2.2.4. US-spray-congealing

Ten grams of IMC/PEG (4000–6000) (10:90, w/w) physical mixture heated up to 60 °C to melt PEG: in these conditions, IMC dissolves in the melt and the mass turns yellow.

The solidified material thus obtained was identified as *solid dispersion*, since, even if the drug dissolves in the molten PEG, in most cases it separates as amorphous and/or crystalline phases, when the carrier solidifies.

The molten mixture was used to fill the container feeding the US-spray-congealing machine. The temperature of the container was kept 10 °C above the melting point of PEG and the mass was stirred to prevent sedimentation or solidification. The fluid escaped by gravity from the container at a rate of 300 ml min^{-1} on the plate sonotrode (3 cm in diameter). On the contact with the vibrating surface, the fluid is divided by US-energy that supplies the surface energy necessary to form the microdroplets, without significantly increasing their kinetic energy. Microspheres thus formed took less than 2 s to solidify and to reach the bottom of the container where they were collected and sieved. The size range 75–150 μm was selected. This material was identified as *US-microspheres* throughout the paper.

2.3. US compacting machine

Similarly to a traditional machine, there is an upper and a lower punch and a die; new elements are a piezoelectric transducer, an amplifying booster and a sonotrode acting on the upper punch. The transducer generates US-waves, whose amplitude is increased by the booster and are transmitted through the sonotrode to the punch that vibrates at US-frequency and compacts the material present in the volume between the two punches. A microprocessor interfaced to the system enables perfect co-ordination of the different operations. The transducer, the booster and the sonotrode form a column across which US are transmitted in such a way that a wave maximum is displayed on the lower face of sonotrode. Time, energy and amplitude of the US-waves are carefully controlled in order that the final compaction force can be modulated. Materials under compaction experience a pressure at a US-frequency (25 kHz), higher than the elastic relaxation time of the powder to be compacted, that undergoes plastic deformation, when the material is thermoplastic. In this case, compaction occurs through synterisation and compaction force has little effect on the final material. In the case of non-thermoplastic materials, a mechanism of packing and reciprocal accommodation of the particles, degassing the mixture, has a greater effect.

2.4. US-spray-congealing machine

The US generator unit is the same as that described above. While in the previous machine this unit was kept vertical in order to facilitate the operations of filling the die and recovering the compacted material, this machine is almost horizontal in order to facilitate the pouring of the melt. The terminal position of this apparatus is again a sonotrode that in this case has the form of

a spoon, vibrating at an US-frequency that divides the feeding drop into microdroplets.

The vibrating plate is heated by induction to prevent the solidification of the falling drop on contact. The material sprayed out in the form of microspheres is collected in an air-cooled box 2 m high, where on falling to the bottom they have enough time to solidify. Positioned vertically above the sonotrode plate is a container, thermostated 10 °C higher than the melting point of PEG, continuously supplying the material to be sprayed, by means of a screw pump.

While US is able to physically modify a compacted material, in the case of the spray-congealing process US provides additional surface energy to form microspheres of reduced size. However, experimental results showed the unexpected US effects on microspheres with respect to an untreated solid dispersion.

2.5. Characterisation of the samples

2.5.1. Scanning electron microscopy (SEM)

The morphology of IMC, PEG 4000, physical mixture, solid dispersion and US-granules was examined with an SEM (Philips, XL30). The samples were previously sputter-coated with gold.

2.5.2. Differential scanning calorimetry

These tests were performed using a Perkin Elmer DSC 6 and using nitrogen as purge gas (20 ml/min). The instrument was calibrated for temperature using indium and lead, and for enthalpy using indium. The experiments were performed in non-hermetically sealed aluminium pans; the weight of each sample was 8 ± 1 mg and the heating rate was 10 °C/min.

2.5.3. X-ray diffractometry

A PW A10 BASED diffractometer was employed, using Cu as anticathode ($K\alpha = 1.5406$ Å) in the range $(5–70)/2\theta$ at a scanning rate of 0.02°/s.

2.5.4. Evaluation of the drug content

The evaluation of the drug content in the US-microspheres was calculated by dissolving a determined amount of the selected fraction in deionised water; the solution was then analysed using a UV spectrophotometer at a selected wavelength (221 nm). This analysis was repeated for three times.

2.6. Dissolution tests

Dissolution studies were performed using a USP XXIII basket apparatus, connected by a peristaltic pump (Gilson Minipuls 3) to a flow-through spectrometer (Unicam UV/Vis spectrophotometer, mod. UV2) and the absorbance at 221 nm was automatically recorded. The pump operated at a rate of 12.5 ml min^{-1} and the dissolution medium was deionised water. The determinations were performed at a rotational speed of 50 rpm and at a constant temperature of 37 °C.

3. Results and discussion

In the previous papers, we analysed the effects of US-assisted compaction on a variety of active agents (IMC, theophylline, ketoprofen) coupled to a series of excipients such as β-CD, Eudragit® RL and S100, respectively (Fini et al., 1997; Rodriguez et al., 1998; Sancin et al., 1998): in the first case examined, the drug had a lower melting point than that of the excipient, while Eudragit® showed only a glass transition, being an amorphous substance. The thermal effects associated with US-discharge affected the melting of the drugs, which deposited as an amorphous film on the excipient particles. The hydrophilicity of β-CD and the partial amorphisation of the drug led to a great increase of the dissolution rate of the drug with respect both to the pure drug and to the physical mixture.

In this paper, we used PEG as an excipient, which differentiate from previous ones for having a lower melting point than the drug and displaying the ability to form solid solutions or dispersions with many drugs (Leuner and Dressman, 2000). We mixed PEG and IMC at the weight ratio 9:1 using different PEGs (4000, 5500 and 6000); the mixtures were compacted using different US energy levels (300, 450 and 600 J). US thermal effects modify the physical state of PEG and IMC: both compounds soften under US and we hy-

pothesised that they mutually mix forming a solid dispersion, directly under US compaction, without preliminary heating. These hypotheses are supported by the following experimental tests.

Fig. 1 shows the SEM micrographs of pure IMC (a), PEG 4000 (b), their physical mixture (c), traditional compaction (d), solid dispersion (f and h) and US-compacted granules (e and g), at different magnifications. IMC exists in irregularly shaped crystals, as well as PEG 4000. In the physical mixture and traditionally compacted material, both IMC and PEG 4000 maintain their original shape. On the contrary, the solid dispersion (f and h) appears in the form of irregular particles in which the crystals of the drug and the excipient cannot be identified: the sample appears stratified and very small particles are present on a quite smooth surface.

IR spectra (not reported) do not reveal dramatic changes of peak frequency suggesting the absence of chemical interactions between the drug and the excipient, as also reported by Ford et al. (1986). X-ray diffractograms of US-granules (Fig. 2b) show a higher and irregular baseline with respect to the physical mixture (Fig. 2a), suggesting a loss of crystallinity of both drug and excipient inside the granules. In fact, peaks within 10° and 15° are not so well separated as in the physical mixture (Wulff and Alden, 1999; Owusu-Ababio et al., 1998; Dordunoo et al., 1996). The peak characteristics, particularly intensity, demonstrated that crystallinity of both components of the system had been considerably diminished, under US treatment: the same was observed in the case of the formation of a solid dispersion between ibuprofen and PEG (Khan and Jiabi, 1998) and between lactose and PEG 4000 (Chidavaenzi et al., 2001).

In these cases, thermal analysis offers limited information; in fact no endothermic peak related to the melting of IMC could be detected, even in the physical mixture, as shown in Fig. 3. The peak temperature is shifted to lower values for US-treated materials and solid dispersion (Fig. 3e and f), with respect to pure PEG. IMC can dissolve in the molten PEG, as can be detected by hot stage microscopy; this occurs also at about 55–60 °C during the scan of the thermograms and the drug remains dissolved up to 200 °C (Khan and Jiabi, 1998; Fini et al., 1997; Lloyd et al., 1997). This fact explains the absence of the melting peak of IMC in the thermograms and the lower peak temperature of that associated with the melting of PEG. In the case of a different solubility (e.g. ibuprofen/PEG or PEG/lactose), thermograms should contain endothermic peaks of all the components (Khan and Jiabi, 1998; Chidavaenzi et al., 2001). However, thermal analysis represents an important technique to assess the crystallinity of the final material (Briggner et al., 1994; Craig, 1995; Chidavaenzi et al., 2001) and to evidence the presence of the different polymorphic forms of PEG.

The absence of any endotherm, however, cannot exclude that the drug (and the excipient; Ford et al. 1986) is in an (at least partially) amorphous form inside the granules: this suspicion was also supported by the final yellow colour of the granules. In fact, also after the dissolution of IMC in molten PEG or after US-discharge on pure IMC, the resulting mass turns yellow. In this last case, experimental data suggested the presence of amorphous IMC: IMC crystals transformed into a yellow and a viscose paste, that slowly solidified into a vitreous mass, recovering crystallinity only at a slow rate. These processes were followed by DSC. It was also reported that IMC and PEG 6000 form a eutectic containing 13% of the drug (Ford and Rubinstein, 1998); this percentage is very close to that used in our experiments.

Fig. 4 shows the dissolution profiles of IMC from all the formulations described. Two groups of profiles can be seen in the graph. The fastest release of the drug was observed with the solid dispersion (Craig, 2002), which reaches 85% of the drug dissolved in less than 5 min, and for US-compacted samples. Dry granules, obtained by traditional compaction, physical mixture or pure IMC display a comparable behaviour to the

Fig. 1. SEM micrographs of: (a) IMC, 500 × ; (b) PEG 4000, 500 × ; (c) physical mixture, 250 × ; (d) solid dispersion, 1500 × ; (e) solid dispersion, 250 × ; (f) US-compacted granules, 250 × ; (g) dry compacted granules; (h) US-compacted granules, 2000 × .

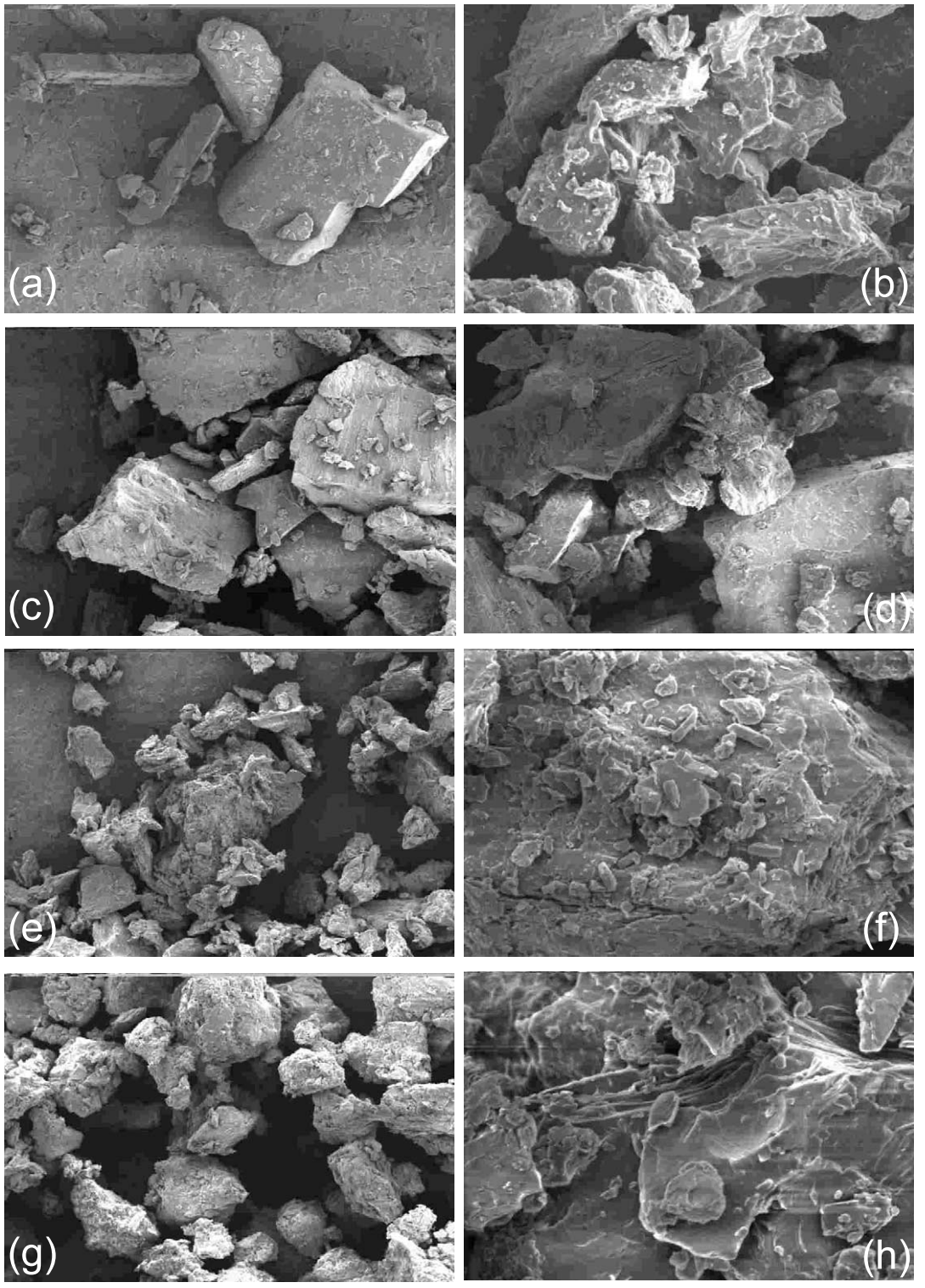

Fig. 1

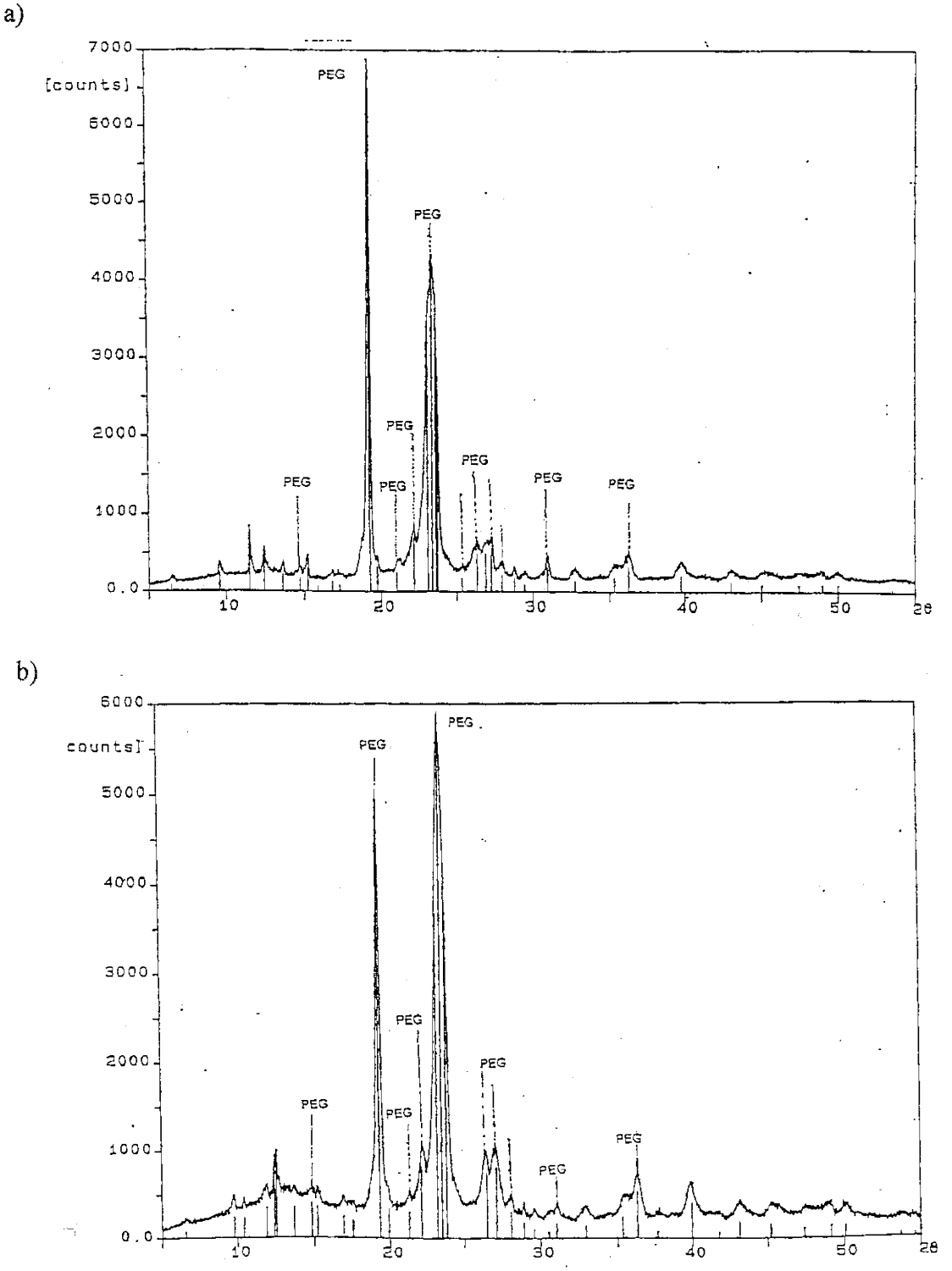

Fig. 2. X-ray diffractograms of (a) physical mixture and (b) US-granules (600 J).

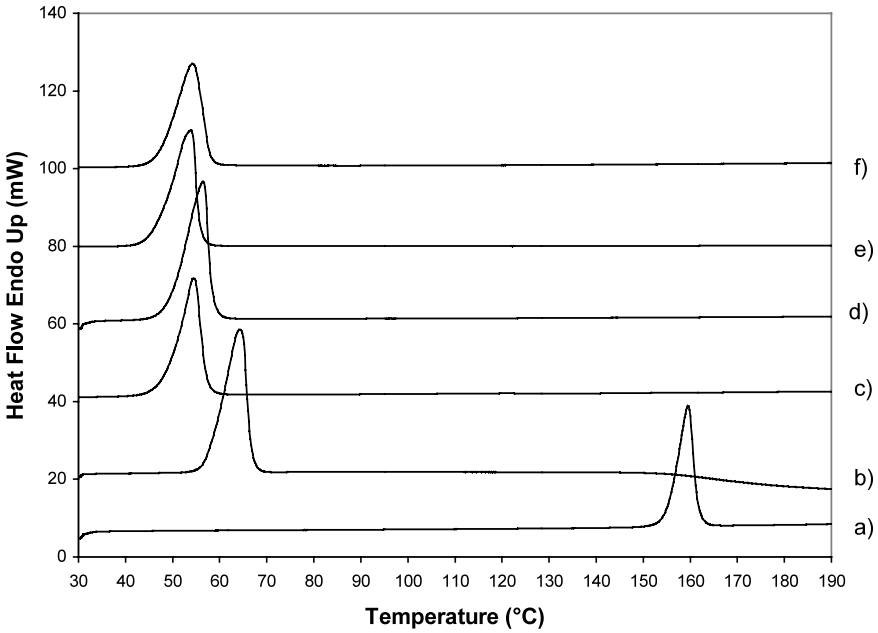

Fig. 3. DSC thermograms of (a) IMC, (b) PEG 4000, (c) physical mixture, (d) dry granules, (e) solid dispersion, and (f) US-granules (600 J).

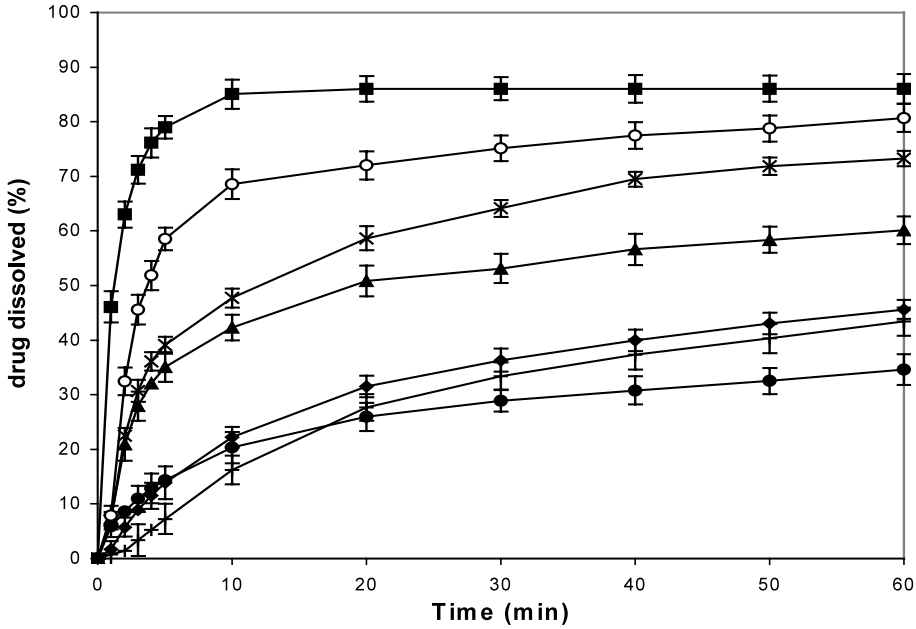

Fig. 4. Dissolution profiles of IMC and IMC/PEG compounds (75/150 μm fraction) differently treated in deionised water: (●) dry granules; (+) IMC; (◆) physical mixture; (▲) US-granules (300 J); (×) US-granules (450 J); (○) US-granules (600 J); (■) solid dispersion.

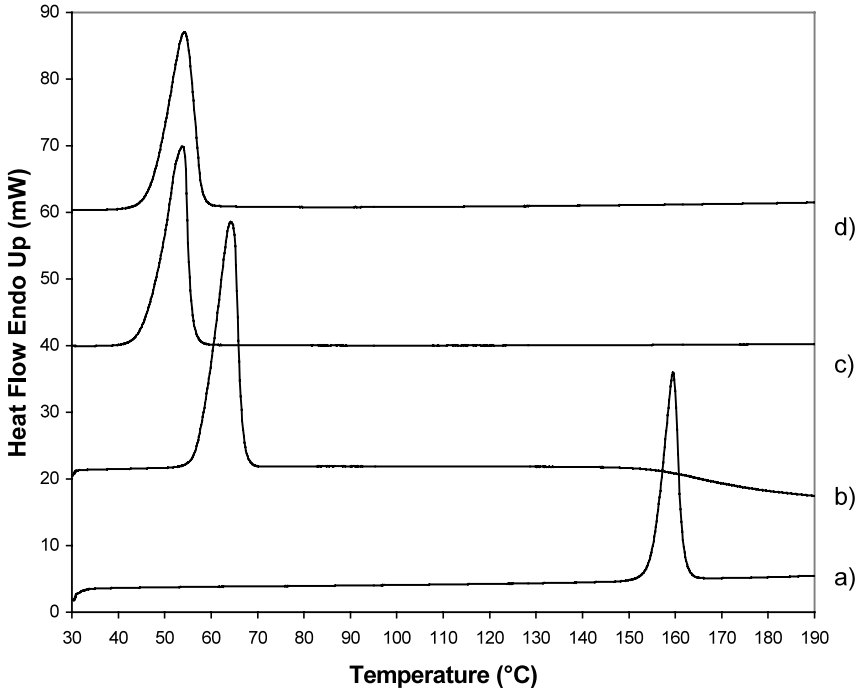

Fig. 5. DSC thermograms of (a) pure IMC and (b) IMC/PEG 4000 dry granules compared to (c) US-microspheres and (d) solid dispersion.

release, but clearly different from that of the first group. There is also the possibility that the semicrystalline nature of PEG changes under the mentioned processes, modifying the release of the drug: this aspect, though important, was not investigated here. Moreover, the presence of IMC can hinder chain diffusion and packaging inside PEG, also resulting in, at least, partially amorphous material. As a result, crystallinity of both components can be reduced. As expected, the greatest effects on dissolution are observed when IMC undergoes a physical change under the reported technological processes. The most dramatic change is that related to the preparation of the solid dispersion with the melting method, when IMC is dissolved in the molten PEG. It appears that in compacted systems US produces effects more and more similar to those of a solid dispersion, as US-energy increases. US-energy provides the necessary softening of PEG to drive a dispersion of IMC into the excipient. In these cases, however, the viscosity of PEG remained high enough to prevent a complete dissolution of IMC in the whole mass of PEG granules, as happens during real melting, when the drug is homogeneously and molecularly dispersed in the case of a solid dispersion.

The dissolution profiles of US-granules containing PEGs with different molecular weights support

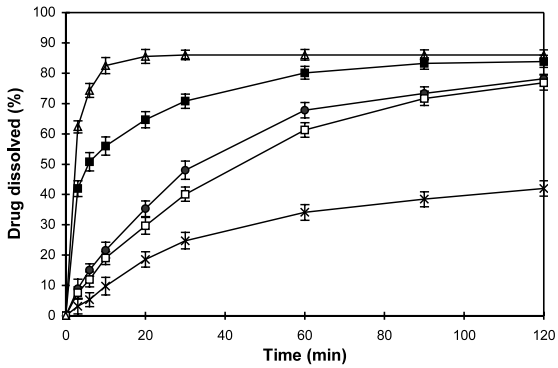

Fig. 6. Dissolution profiles of US-microspheres containing different PEGs: (■) PEG 4000; (●) PEG 5500; (□) PEG 6000 compared to the solid dispersion (▲, PEG 4000) and pure IMC (×).

this idea. US-granules with PEG 4000 show a higher release than US-granules containing PEG 6000. This result agrees with previous findings (Ford, 1984; Corrigan et al., 1979; Ford et al., 1986; Leuner and Dressman, 2000) that dissolution rates of the drug from PEG dispersions decrease as the molecular weight of the glycol decreases. Evidently, the extent of the IMC transformation into an amorphous form is higher with the PEG having the lowest molecular weight and melting point. However, the lower viscosity of PEG 4000 allows a certain grade of recrystallisation of the system that reduces the release of IMC after 2 years' storage. While using PEG 6000, this phenomenon is practically absent. This also agrees with a previous report that IMC/PEG solid dispersions tend to increase the degree of amorphousness within the type of polymer, and that the crystallinity of PEG controls the IMC release from the solid dispersion (Ford, 1986).

Very interesting results were found when molten IMC/PEG mass was dropped onto the surface of a sonotrode, vibrating at US-frequency. After the contact with the vibrating plate, the molten mass was shattered into droplets, which fall by gravity and solidify in less than 2 s, under a cooled air stream.

The thermal analysis of the US-microspheres (Fig. 5) produces thermograms where the peak of IMC is practically absent. No difference was observed between the solid dispersion and the US-microspheres: these samples have the PEG melting peak at a lower temperature than that of the pure PEG: this can be attributed to a partial amorphisation and/or to PEG partially present in the once folded chain form (Corrigan et al., 2002), even though no conclusion can be drawn from the form of the melting endotherm (Chidavaenzi et al., 2001). The dissolution profiles of US-microspheres, obtained with different types of PEGs, are reported in Fig. 6. In this case not only do the microparticles with different PEGs behave differently to each other, as regards the release of the active principle, but also the extent of the release is lower with respect to the starting solid dispersion prepared with PEG 4000, in the absence of US.

It can be hypothesised that US-vibrations tend to accelerate a partial phase separation inside the mass of the final microspheres, or to catalyse the nucleation of IMC microcrystals, or to reorganise the droplets into a solid mass with lower density (US produce cavitation), where diffusion to produce recrystallisation is facilitated. These ideas are also supported by the fact that ageing of US-microspheres produce a more dramatic change in decreasing IMC release than in the case of US-granules (where on the contrary the density of the final material tends to increase). From these results, it appears that US produces better technological effects when used for compaction: the increase of IMC release from formulations was obtained without any time-consuming techniques and the effect is almost the same as obtained with a solid dispersion, prepared by fusion, while when applied to the spray-congealing apparatus, US effects are of limited importance. This fact is particularly interesting because solid dispersions, prepared from soluble carriers, such as PEGs, usually have the disadvantage of difficult handling (Chiou and Riegelman, 1971): according to our technique, it should be possible to prepare a formulation behaving as a solid dispersion by means of a single compaction.

Whatever the mechanism, US produces positive effects on dissolution, when applied to the compaction of a solid physical mixture of IMC/PEG (with respect to traditional compression): dissolution of US-compacted samples, at the highest energy level, recalls the behaviour of solid dispersion, while traditionally compacted material behaves like the physical mixture (Fig. 5). US has a different effect when applied to the molten mass to form US-microspheres, with respect to the untreated solid dispersion, obtained by solidification of the same molten mass. This aspect requires further investigations but outlines, however, that US application to pharmaceutical technology provides very interesting results, when properly interpreted.

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