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Research Paper

Enhanced Release of Indomethacin from PVP/Stearic Acid Microcapsules Prepared Coupling Co-freeze-drying and Ultrasound Assisted Spray-congealing Process

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Purpose. Fast releasing indomethacin microparticles were prepared encapsulating co-freeze-dried indomethacin/poly(vinylpyrrolidone) particles (IMC/PVP) into molten stearic acid (SA), by means of a ultrasonic spray-congealing technique.
Materials and Methods. IMC particles were suspended in a PVP aqueous solution and the system was then freeze-dried. A suspension was prepared from the co-freeze dried IMC/PVP powder into molten SA that was then atomized into small droplets using ultrasound. Solidification in air produced microparticles having regular macroscopic morphology and coated by a SA thin external film. At each step the material was examined by electron microscopy (SEM and EDAX), thermal analysis and dissolution tests.
Results. SEM examination did not reveal a smooth surface, differently from what was observed in the case of pure SA microparticles, obtained by the same method. The external film was found to uniformly protect the internal core of the capsules: EDAX spectra demonstrated the absence of the IMC identifying Cl peak on the surface, when the spectra were carried out at low energy of the electron beam. HPLC analysis verified that the drug was uniformly distributed inside the final microparticles at all the size fractions considered. Thermal microscopy confirmed the presence of IMC crystals, after the fusion of the external SA coat.
Conclusions. The behavior of microparticles to dissolution at pH 7.4 was superior to that of pure drug, reaching 70% of the drug released, after 20 min. Finally the system examined is stable towards aging: no difference in the dissolution behavior could be detected for the final microparticles after 8 months at 25°C.

KEY WORDS: co-freeze-drying; fast release; gastro-protected microcapsules; indomethacin/PVP/stearic acid; stability; ultrasound spray congealing.

INTRODUCTION

Conventional pharmaceutical forms do not always allow a proper control of the release of the drug, which, at the same time, must be protected from the gastric medium and subsequently also promoted to guarantee a rapid dissolution and availability. These aspects appear not ready to be solved by a unique or rapid technological process, since many parameters are involved in the preparation of formulations, fulfilling all the requirements. For poorly soluble drugs the rate of oral absorption is often controlled by the dissolution rate in physiological fluids: therefore together with permeability, solubility and dissolution behavior of a drug are key determinants of its oral bioavailability. There have been numerous efforts to improve drug dissolution rate. These include, (a) reducing particle size to increase surface area; (b) solubilization in surfactant systems; (c) formation of water-soluble complexes; (d) use of pro-drug and drug derivatization; and (e) manipulation of solid state of drug substance to improve drug dissolution, i.e., by decreasing crystallinity of drug substance through formation of solid solutions or by close association with hydrophilic polymers.

The association to hydrophilic polymer to improve dissolution rate is widely reported for indomethacin (IMC), a poorly soluble drug. Poly(vinylpyrrolidone) (PVP), a water-soluble polymer, was used as a carrier of solid dispersions to increase the dissolution rate while suppressing re-crystallization (1,2); in systems where PVP is associated with SiO_2 also the apparent equilibrium solubility of IMC was increased (3). Supercritical carbon dioxide was used to prepare IMC co-precipitates with the aim to improve the dissolution rate of the drug; studies have been carried out also with starch (4) and cyclodextrins (5).

In this paper we start to consider a different approach to dissolution improvement with the application of multistep processes in series to each other to prepare a suitable pharmaceutical form of the drug, in order to obtain, first, a

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satisfactory final result and then make the process itself easy and commercially applicable. The main aim of this paper was to obtain a readily dissolving anti-inflammatory drug, suitably gastro-protected. The problem was studied through the association between a poorly soluble drug (IMC) and a hydrophilic excipient (PVP), by means of a freeze-drying step; followed by a spray congealing process, using stearic acid (SA) to coat the co-freeze-dried IMC/PVP particles for gastro-protection. This last process was carried out using an improved version of a modern atomizer, previously described, supplying ultrasound (US) energy rather than centrifugal, pressure or kinetic energy, as traditional devices (6–8).

In particular the purpose of this work was to produce enteric IMC microparticles using stearic acid as external coating. Crystalline IMC was chosen as a model drug, because it is not temperature sensitive and it is very poorly soluble in water (0.40 mg/100 ml). Then IMC was coupled to a hydrophilic material, such as PVP, which, for its good solubility in water, outstanding chemical stability and complexing ability towards both hydrophobic and hydrophilic substances, is widely used in the pharmaceutical industry (9). Finally particles produced in the freeze-drying step were coated with molten SA by a spray congealing technique assisted by US. All these steps should guarantee a prompt release of IMC, such as that needed for a pain relief drug, as well as protection of the gastric district towards this gastrolesive drug (10).

MATERIALS AND METHODS

Materials

Indomethacin (IMC) was a commercial sample of pharmaceutical grade (Sigma Chemical Company, St. Louis, MO) with a melting point of 161°C (γ form); IMC was sieved and only the ≤200 μm fraction was used. PVP K30 was kindly supplied by BASF (Ludwigshafen, Germany) and used as received. Stearic acid (SA) of pharmaceutical grade (69–71°C) was purchased from Fluka (Buchs, Switzerland). Other solvents were commercial sample of reagent grade.

METHODS

Preparation of Microparticles

Freeze-Drying Step

Two grams PVP K30 was mildly heated in 400 ml water up to complete dissolution: the solution was added to 2 g IMC (mean size ≤200 μm). The system thus obtained (1:1 w/w) was poured into suitable containers and rapidly frozen at −80°C (CL HETOFRIG, Birkeröd, Denmark) and subsequently freeze-dried (Christ Freeze Dryer ALPHA 1-2, Milan, Italy). The final material was milled in a mortar at room temperature and sieved, collecting the size fraction ≤200 μm.

Spray-Congealing Step

SA (5.6 g), at 80°C (10° above the melting point) and co-freeze-dried particles (1.4 g) or pure IMC (0.7 g) were mixed under constant stirring; then the suspension was poured in a thermostated reservoir (preset at 80 ± 1°C) surrounding the sonotrode. The reservoir was not stirred, because the US cavitation effect prevented the settling of the suspended material. Once in contact with the sonotrode, the molten mass was atomized by US energy into small droplets, which, freely falling solidified by cooling at room temperature. The microparticles, collected in a cylindrical chamber, were stored in a vacuum dessiccator over silica gel at room temperature. Each formulation was produced in duplicated experiments. The instrument used in this study was developed in our laboratory using a sonotrode type UIP 250 (Hielscher, Berlin, Germany), as the active part; the frequency was 25 kHz and the power output was 2.2 kW (11)

Characterization of the Samples

Drug Content

Freeze-Dried Product. Sample of freeze-dried product corresponding to the amount of 1 mg of drug was accurately weighed and added to 500 ml pH 7.4 phosphate buffer. The sample was shaken for 10 min at room temperature until complete dissolution. Finally, the drug content was assayed spectrophotometrically (UV-Vis spectrophotometer model UV2; Unicam, Cambridge, UK) at 266 nm. To verify the homogeneity of the drug loading, the determination was performed in 100–200, 200–400, 400–800 μm size fractions.

Microparticles. Chromatographic analysis were performed using a Jasco PU 1580 liquid chromatograph connected to a UV-Vis detector (Model Jasco MD 910, Tokyo, Japan) and to a computerized integration system. Separations were obtained by means of HPLC, using C18 Phenomenex Luna (4 μm, 150 × 4.60 mm i.d.) (Chemtek Analitica, Bologna, Italy) column at room temperature, using acetonitrile at a flow rate of 1 ml/min (detector UV) (12).

Particle Size Analysis

The size distribution of the drug, freeze-dried materials and microparticles were evaluated by sieve analysis, using a vibrating shaker (Octagon Digital, Endecotts, London, UK) and a set of five sieves (Scientific Instruments, Milan, Italy) ranging from 75 to 500 μm.

Scanning Electron Microscopy (SEM) and EDAX Analysis

The shape and surface characteristics of the microparticles were observed by SEM. Microparticles were sputter-coated with Au/Pd using an Edwards Auto 306 (Milan, Italy) electron-beam evaporator and examined using a scanning electron microscope (Philips 500, Eindhoven, NH) at 10 kV accelerating voltage. A very thin coat of Au/Pd was applied to each sample using a vacuum evaporator, then the material was examined at different magnification.

EDAX analysis was performed during the SEM examination of the particles. An electron beam of modulated energy (max. 3.84 keV), incident on the sample and interacting with the sample causes the emission of X-rays (secondary fluorescence), that are characteristic of the elements present

in the sample, allowing a qualitative analysis of its chemical composition.

Differential Scanning Calorimetry (DSC) Analysis

DSC measurements were performed using a Perkin-Elmer DSC 6 (Perkin-Elmer, Beaconsfield, UK). The calibration of the instrument was performed with indium and lead. Experiments were performed in non-sealed aluminum pans. Samples, weighing 5–10 mg, were placed into the DSC under a nitrogen flux (20 ml/min) and heated from 25 to 200°C at a scanning rate of 10°C/min. All of the microparticles were analyzed 24 h after the preparation to avoid possible differences because of the aging of the samples. Each analysis was performed in duplicated experiments.

Hot Stage Microscopy (HSM)

Physical changes in the samples during heating were monitored by HSM. A hot plate (FP 52 Mettler, Greifensee, CH) connected to a temperature controller (FP 5 Mettler) was used. A small amount of the samples was placed on a glass slide with cover glass and heated at 10°C/min from 30 to 200°C. Changes in the samples were registered by an optical microscope (Reichert Biovar, Wien, Austria), equipped by a 10× magnification.

Micro-FT-IR Spectroscopy

ATR, near-normal reflection–absorption spectra were recorded by a Nicolet FT-IR Nexus 470 connected to a Nicolet Continuum microscope. Experimental details: source globar (SiC candle); beam splitter m-IR: KBr; detector: MCT (CdTe, doped by Hg) (Hg/Cd); spectral window: 4,000–650 cm^{-1}; side resolution: 7–80 μm; spectral resolution: 4 cm^{-1}.

X-Ray Powder Diffraction Analysis (XRPD)

Single components, freeze-dried materials and the microparticles were studied by X-ray powder diffraction technique using Philips PW 3719 diffractometer controlled by a computer. Experimental conditions: Cu Kα radiation ($\lambda = 1.78896$ A); 40 kV and 30 mA. Scanning interval: 5–50° 2θ; Time per step: 1 s; Graphite monochromator on the diffracted beam.

Drug Release Studies

In vitro dissolution tests were carried out using the USP 24 paddle method (Pharmatest, Steinhein, Germany) rotating at 100 rpm. Buffered solutions (pH 2 and pH 7.4) were employed as dissolution media. The buffer solution was filtered and continuously pumped (12.5 ml/min) to a flow cell in a spectrophotometer (UV2 spectrometer, Unicam, Cambridge, UK). The amount of drug dissolved in buffer pH 2 was analyzed at 230 nm and at 266 nm in buffer pH 7.4.

The dissolution tests were performed at least in triplicate and SD values were then calculated.

Solid State Stability Studies

Dissolution tests, DSC and XRPD analysis were carried out on the freeze dried powders and microparticles after 4 and 8 months in storage at room temperature at 0% RH using the methods described in the previous section (13,14).

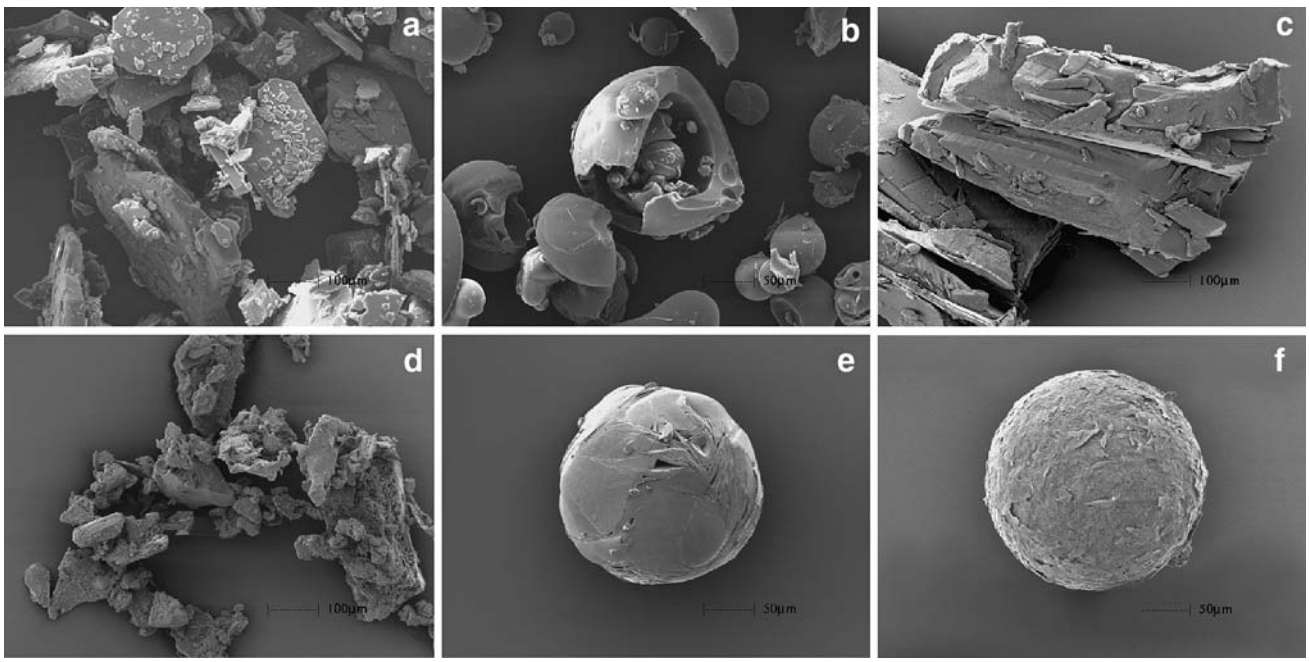

Fig. 1. SEM micrographs: (a) pure IMC; (b) PVP; (c) SA; (d) IMC/PVP freeze-dried powder; (e) IMC/SA microparticles; (f) IMC/PVP freeze-dried microparticles coated by SA.

RESULTS AND DISCUSSION

The Co-Freeze-Dried System

IMC is very poorly soluble in water and this fact prevented the preparation of an initial aqueous solution together with PVP. It was therefore chosen to prepare an aqueous dispersion of the unionized drug, where the drug had a size ≤200 μm. During the freeze-drying process the polymer deposited on the drug particles: this was particularly evident on the SEM micrographs taken on the final microparticles (Fig. 1). In fact IMC has a plated morphology, which is present even at the lowest sizes (Fig. 1a), this aspect is readily visible even on the co-freeze-dried particles (Fig. 1d), while the typical irregularly rounded structure of PVP particles (Fig. 1b) is completely lost. The polymer coating smooths and rounds the IMC plate morphology and, after encapsulation into molten SA (Fig. 1c), the final product shows spherical microparticle form (Fig. 1e and f). In this case the system is reversed with respect to that encountered when a physical mixture IMC/PVP was compacted under US (15). Here in fact examination at electronic microscope suggested that IMC was covering with a thin film the PVP particles, as a consequence of the physical effects originated by US discharge. In both cases association between IMC and PVP appears particularly efficient in promoting dissolution (15,16), even though this close association concerns only the interfaces and not the bulk of the particles, since both processes maintain unaltered in one case the PVP particles (US compaction) and in the second one the IMC plates (freeze-drying). However this can represent a useful help, at least in the first moments of dissolution (16–20).

Further analysis of the co-freeze-dried material confirms these views.

Figure 2 shows EDAX spectra for the different materials employed throughout this paper. EDAX is a microanalysis technique, which furnishes qualitative analysis of the sample composition, through the emission of X photons, when a solid sample is irradiated by an electron flux, finely focused. As an answer to this irradiation, there is an electromagnetic emission from the element present inside the sample: each element present in the molecules of drug and excipients (with an atomic number at least >10) can be thus evidenced by a typical emission peak. Graph of Fig. 2 are shown in terms of intensity (ordinate) *vs.* energy (abscissa) of the answer. The intensity of the answer can be modulated by the intensity of the irradiation, which can come in contact only with the external surface of the particle or penetrate inside the sample, offering information on the spatial distribution of each component or homogeneity of the sample. Of course each component of a mixture must possess an identification element: this is the case of IMC, which is (among the components employed) the one (of the co-freeze-dried or spray-congealed) intermediates containing a Cl atom. Lower atomic number elements (H, C...) cannot be distinguished and their answer is shown by an unresolved complex peak.

The Cl peak is clearly evident in the spectrum of IMC (Fig. 2a) and is absent in PVP (Fig. 2b) and SA (Fig. 2c), but visible in the co-freeze-dried particles (Fig. 2d), when high intensity beam was used; an incident beam of low intensity was used with microparticles, which could penetrate only for a few microns under the surface, that is the answer signal concerned mainly PVP and SA and did not reach embedded IMC particles, as it occurred in IMC/PVP particle with low intensity beam (Fig. 2e and f). This clearly demonstrated the organization of each co-freeze-dried particle, containing an IMC core coated by PVP; and of the final microparticles (see below, the spray congealing system), where the coating of both PVP and SA prevent the electron beam to reach the IMC core.

Figure 3 shows the thermograms of the three pure substances IMC (Fig. 3a), SA (Fig. 3b) and PVP (Fig. 3d); for comparison we prepared by the same way also microparticles

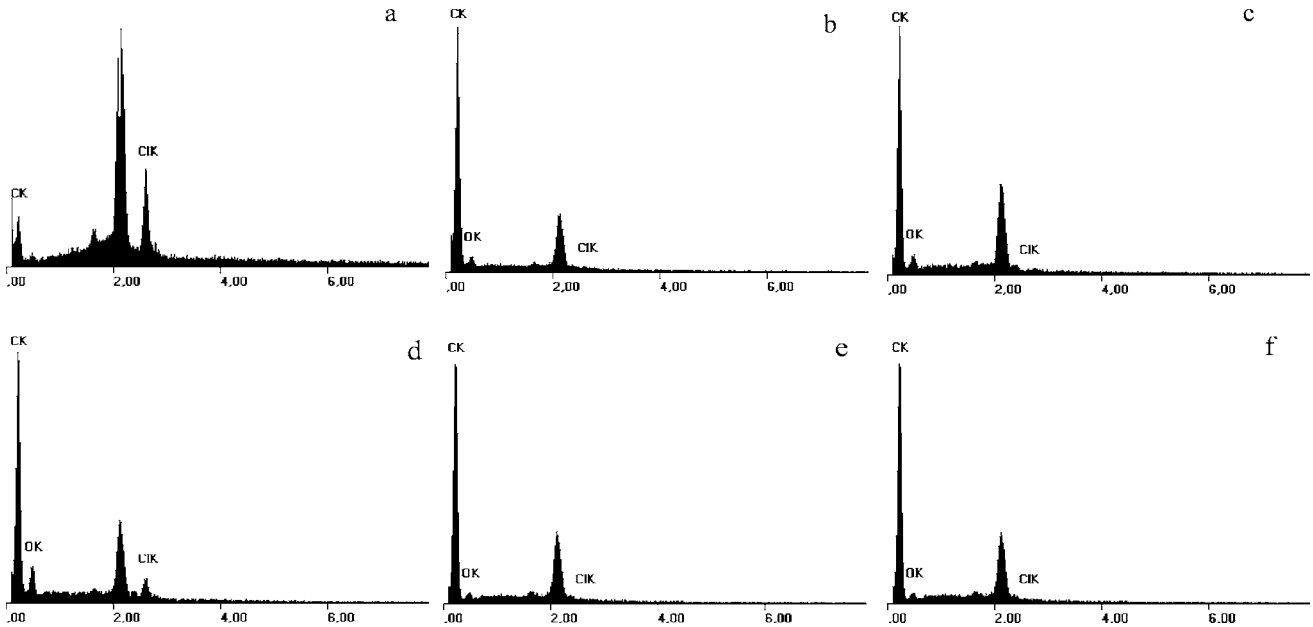

Fig. 2. EDAX spectra (intensity *vs* energy of the signal): (a) IMC; (b) PVP; (c) SA; (d) IMC/PVP freeze-dried particles; (e) final microparticles (*sample 1*); (f) final microparticles (*sample 2*).

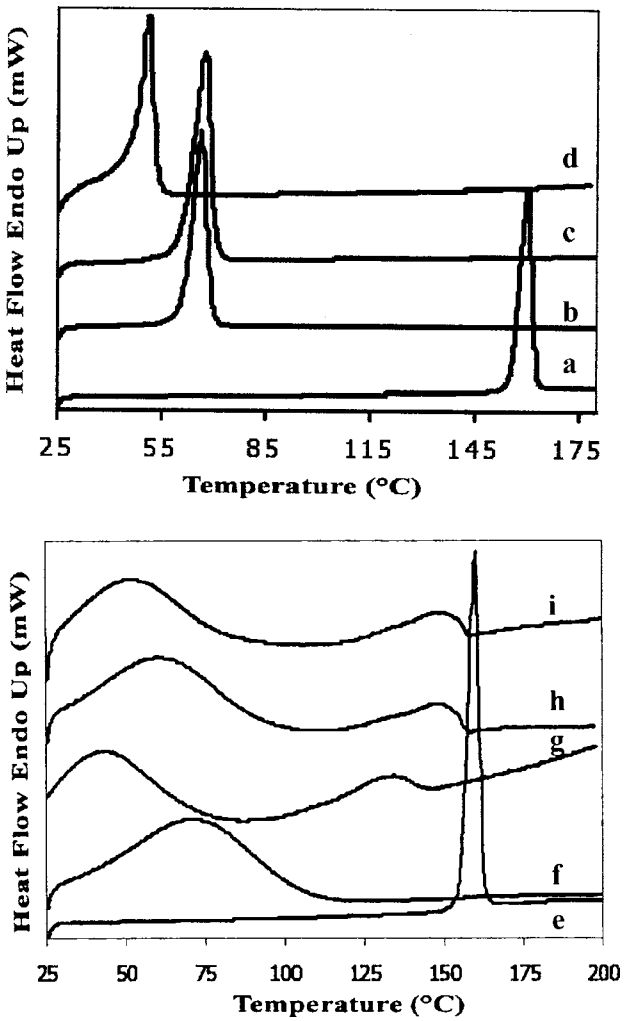

Fig. 3. Thermograms (*above*): (a) IMC; (b) SA; (c) IMC/SA microparticles; (d) PVP. (*below*): (e) IMC; (f) PVP; (g) IMC/PVP powder: after 1 month; (h) IMC/PVP powder: after 4 months; (i) IMC/PVP powder: after 8 months.

containing only IMC and SA, without PVP. It can be appreciated in Fig. 3c that no IMC melting peak is evident, since IMC dissolves into molten SA, during the temperature scanning.

In the second part of Fig. 3 three different situations are described for the intermediate IMC/PVP freeze-dried powders. The thermogram profiles (Fig. 3g, h and i) show two rounded endotherms at $T < 50°C$ and at $125 < T < 150°C$. This second endotherm shifts towards higher temperatures with aging after 4 and 8 months. The first endotherm is present also in pure PVP (Fig. 3f) and is related to dehydration of the polymer with temperature: in pure PVP it can approximately be estimated at about 75°C; while in the freeze-dried sample (Fig. 3g), after 1 month of its preparation, the maximum appears shifted below 50°C; after aging, the peak is found at higher temperature, without reaching the original value (Fig. 3h and i). This was attributed both to the presence of IMC and to different organization of the polymer chains after freeze-drying, which allows a different bonding of the adsorbed water. It is interesting to outline that, despite the severe experimental conditions, which should have ensured a complete dehydration, the sample still contained humidity, as a consequence of the well-known hydrophilicity of PVP.

The second endotherm is found in the temperature range of IMC melting: even in this case the endotherm is not well defined, as if IMC could not be free to melt as usual or as if a side phenomenon could occur.

HSM photos (Fig. 4) confirm a reaction occurring between IMC and PVP, at least at high temperatures. The optical microscope examination of the co-freeze-dried material at room temperature indicated a notable inhomogeneity of the particles (see for comparison Fig. 1a). Plate-shaped particles are visible starting from 135°C; PVP, which coats IMC particles appears to react with IMC particle surface, forming a low melting system well visible around the border of the IMC plates in the temperature range 135–154°C. It is possible that IMC dissolves into amorphous PVP, which is in a rubbery state and glass transition PVP temperature could be reached during thermal analysis. This could explain also the endothermic event observed at increasing temperature and reported on the thermogram: it could concern a real thermal transition, more complex than a simple melting. In fact at 155°C in the microscope plate a large number of molten drops are visible, suggesting that the events described interested an increasing number of particles, starting from the smallest ones. FT-IR analysis does not reveal any interaction occurring in the co-freezed system (spectra not reported). This was expected, since it was prepared at low temperature and in heterogeneous phase. Possible interaction IMC/PVP could be detected when preparation of the system is carried out in homogeneous phase or at high temperature, such as in the case of solid dispersions (21).

These results allow a few partial conclusions. The preliminary treatment, to prepare the core for spray-congealed microparticles, leaves IMC crystalline and coated by the hydrophilic and soluble PVP polymer. Thus IMC particles are both protected by a polymer film and coupled with a hydrophilic agent.

The Spray-Congealed System

Using an ultrasound assisted atomizer it was possible to obtain microparticles starting from a SA/co-freeze-dried IMC/PVP suspension at 8:2 weight ratio. The content of IMC inside the microparticles, as determined by HPLC after complete dissolution in suitable solvents, agrees with the theoretical value, irrespective of the size fractions considered. This is an important feature of the whole process, where unforeseen and preferential concentrations of the drug are avoided.

Examination carried out on final microparticles confirmed previous results and hypothesis.

Color of the Particles

Pure IMC is known to dissolve into molten SA, turning yellow the final solution (15); adding the co-freeze-dried particles only a pale yellow suspension could be obtained, since PVP that covers IMC particles is not soluble into molten SA and prevents dissolution of the IMC coated particles.

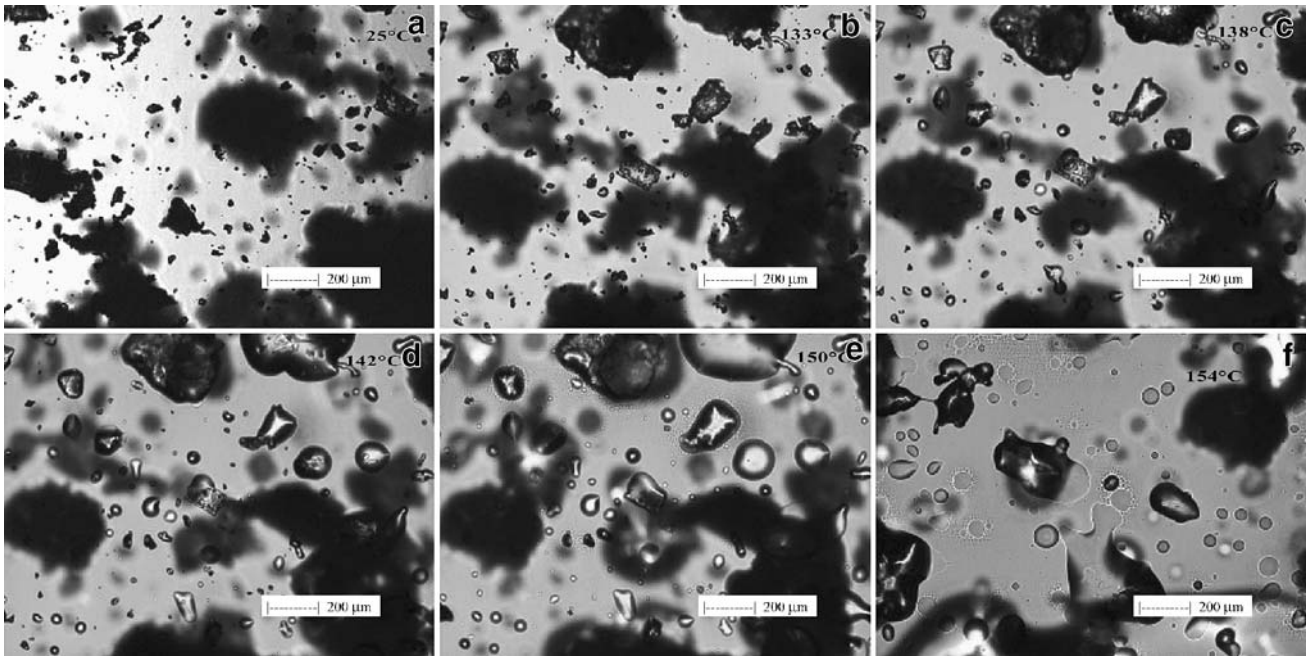

Fig. 4. HSM micrographs of IMC/PVP co-freeze-dried particles (1 month) at different temperatures.

Size of the Particles

The coating by PVP increased the size of the co-freeze-dried particles with respect to the starting IMC particle size: thus it is not surprising the distribution of the microparticles size (Fig. 5). In fact starting from a powder ≤200 µm, we obtained about 40% of final microparticles having a diameter >200 µm. When on the contrary we used pure IMC (in the absence of any PVP coating), the drug could dissolve into the molten SA and about 60% of the microparticle had a particle size fraction 100–200 µm. The size fraction 200–400 µm was chosen for dissolution tests.

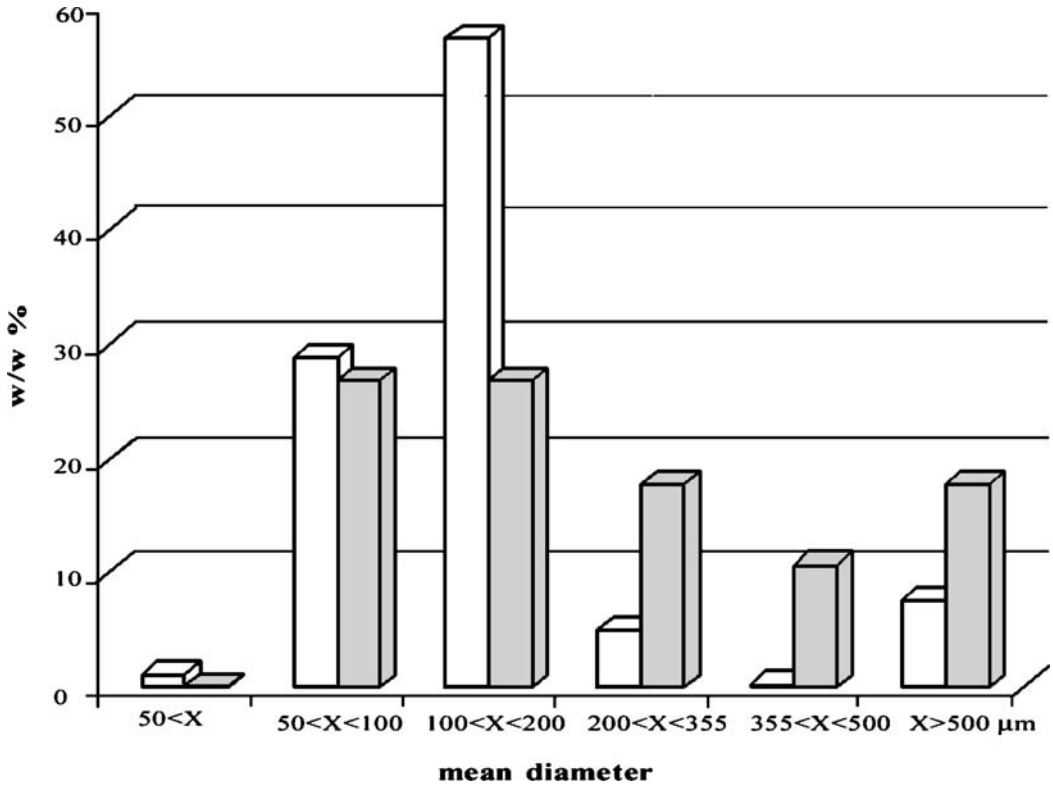

Fig. 5. Size distribution of IMC/PVP/SA (*right*) and IMC/SA (*left*) microparticles.

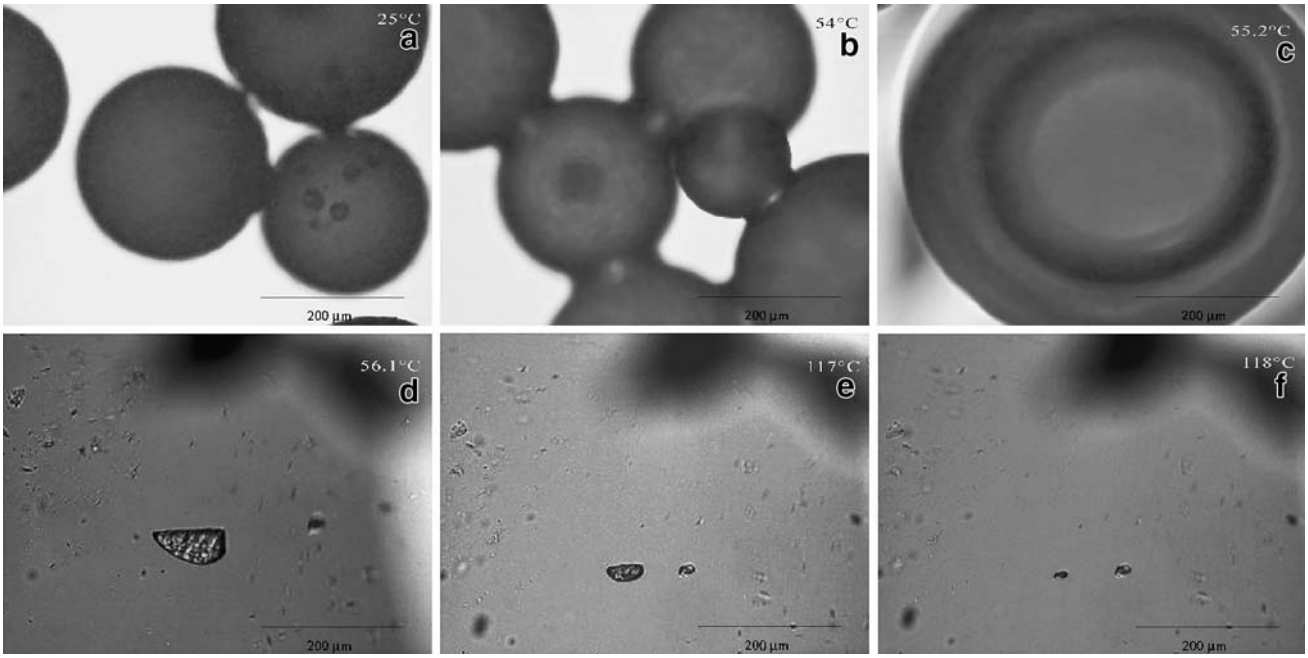

Fig. 6. HSM micrographs of IMC/PVP/SA microparticles at different temperatures.

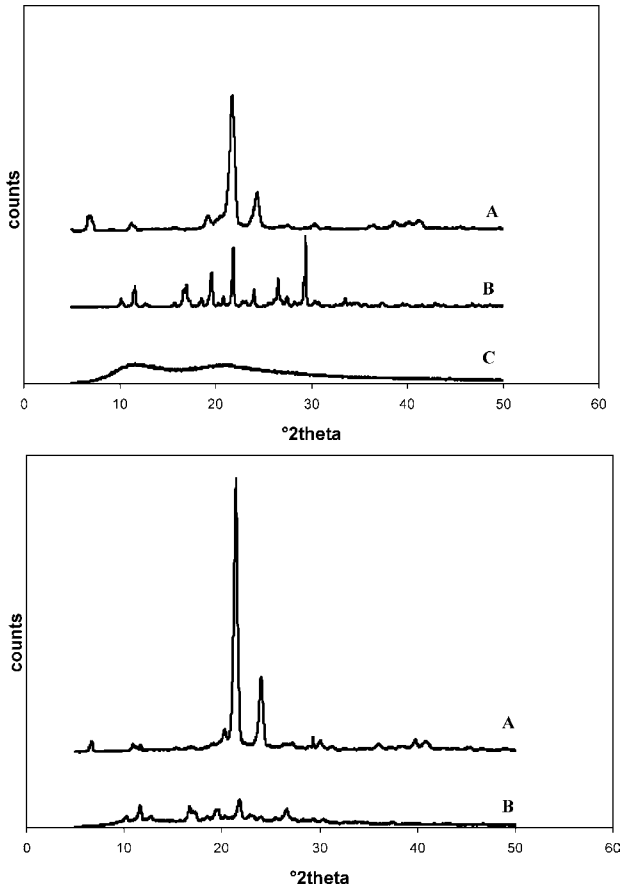

Fig. 7. XRPD profiles: (*above*) (A) pure SA; (B) pure IMC; (C) pure PVP. (*below*) (A) IMC/PVP/SA microparticles; (B) IMC/PVP co-freeze-dried powder.

Shape of the Particles

The shape and morphology of final particles were examined at SEM (Fig. 1e and f): they have a quite regular spherical shape with a surface appreciably smooth, despite the apparently fibrous nature of the SA particles used to obtain the cover. Actually microparticles formed only by SA show a surface more regular than when they contain a second component, pure IMC or co-freeze-dried IMC/PVP particles. The drug loading of microparticles was found higher than 90% of the theoretical one, independently of the particle size.

DSC, HSM, XRPD of the Particles

DSC offers further information on the structure of microparticles: the endotherm peak for the melting of SA appears shifted down to lower temperature and this thermal event is fused together with that of the dehydration of the polymer; no signal for the presence of peak attributed to IMC. HSM (Fig. 6) on the contrary confirms that crystals of IMC coated by PVP are protected toward dissolution into molten SA, since, while a thermogram of microparticles containing pure IMC shows only the peak of SA melting at about 64°C, HSM reveals that, in this temperature range, IMC crystals are clearly visible and disappear above 120°C in present system formed by final microparticles.

X-ray diffractogram (Fig. 7) of the pure IMC is characterized by a high number of peaks, narrow and symmetric, suggesting the crystallinity of the compound; SA diffractogram shows few peaks of high intensity in the range 20–30° 2θ; peaks are broader and less numerous than those of the drug. Diffractogram of the microparticles containing SA and 10% IMC recalls that of pure fatty acid, since IMC peaks (if any) are of very low intensity, suggesting that the drug is both present as dissolved into the fatty matrix or as amorphous, as

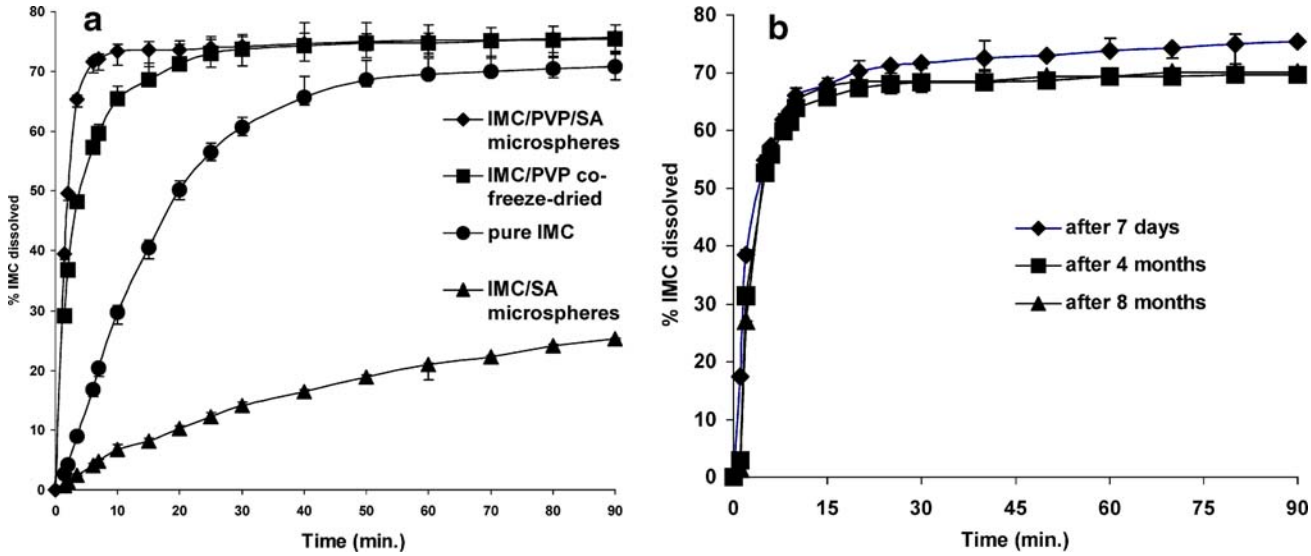

Fig. 8. Dissolution profiles: (*above*) pure IMC/SA microparticles; pure IMC; IMC/PVP co-freeze-dried powder; IMC/PVP/SA microparticles. (*below*) IMC/PVP/SA microparticles, as a function of time.

documented by HSM observation. PVP demonstrates to be an amorphous material: and also microparticles containing the IMC/PVP lyophilized material present a diffractogram having peaks of low intensity and with an irregular baseline; for this, typical peaks of IMC diffractogram are present, but the profile is not so sharp as for the pure drug. It emerges that freeze-drying maintains, at least partially, the crystallinity of the drug and that in these conditions the drug cannot dissolve into the molten carrier, as it occurred in the absence of the co-freeze-dried polymer. Diffractograms registered after 4 and 8 months (not reported) from the preparation of microparticles did not change the profile suggesting s notable stability of the system.

These results confirm that microparticles are formed by a practically pure SA coat on a core constituted by IMC crystals surrounded by an irregular PVP film. Due to experimental conditions, which did not allow too high interactions among the components during these treatments, each layer could separately operate to the release of the drug: SA acts as a protective layer, ensuring a delayed release; PVP provides an accelerated release at favorable pH, that is after dissolution of SA at pH 7.4.

Dissolution Studies

The final systems in the form of microparticles were studied for the release profile of the active agent. Dissolution of IMC, which is a weak carboxylic acid, is without problems in buffer at pH 7.4 (that is $pH > pK_a + 2$); however in the presence of hydrophilic co-freeze-dried particles appear to represent a further improvement; while in the case of microparticles, where the particles are coated only by a SA film, the improvement allows 75% IMC dissolved after 3–4 min. Possibly beside the hydrophilicity of the polymer, IMC solubilization into anionic surfactant micelles formed by stearate anions represents a synergistic driving force to dissolution, as it was previously observed with other type of surfactants (22).

Results suggest the important role of PVP: microparticles containing IMC dissolved into a SA matrix release, at the best, only 20% of the original IMC content after a few hours; while in microparticles containing co-freeze-dried IMC together with PVP release was higher than 70% after a few minutes. Hydrophobic SA not only prevents IMC dissolution from IMC/PVP/SA microparticles at acidic pH (data not shown), but it controls IMC release also at high pH from IMC/SA system, unless it is coupled with the strongly hydrophilic PVP in microparticles.

Figure 8 reveals also an interesting feature of microparticles that is the release is almost complete after 10 min. This aspect is rather important for a pain relief drug, which necessitates a rapid onset of its activity. The same rapid dissolution can be observed in Fig. 8 after 4 and 8 months suggesting a notable stability of the system, which allows the practical applicability of the method.

Finally we observed (data not reported) that the extent and the rate of the release are inversely related to the particle size, as expected: as a consequence the selection of a suitable microparticle size can represent a further control or promotion of the release.

CONCLUSIONS

The described technique offers a mild, safe and efficient formulation to improve IMC dissolution rate without any use of organic solvents, and potential problems of toxic residues are thus avoided; moreover the use stearic or other fatty acids presents the advantage of low toxicity compared to other polymeric excipients.

Microparticles prepared by the ultrasonic spray congealing technique showed IMC improved release and enteric behavior suitable for oral use in capsules, suspensions or to produce controlled release tablets.

Moreover the same technique is currently under study in our lab to encapsulate co-evaporates for controlling release, for taste masking, to improve drug loading in nanoparticles, testing a variety of encapsulating materials and active agents.

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