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Note

Microencapsulation of semisolid ketoprofen/polymer microspheres

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Abstract

Ketoprofen controlled release microspheres were prepared, by emulsion/solvent evaporation, at 15 °C, in order to avoid the formation of semisolid particles. An identical procedure was carried out at 60 °C to speed up the solvent evaporation and the formed semisolid microspheres were directly microencapsulated by complex coacervation and spray-dried in order to recover them as free flowing powder. Microspheres and microcapsules were characterized by scanning electron microscopy, differential scanning calorimetry, X-ray diffractometry, in vitro dissolution studies, and then used for the preparation of tablets. During this step, the compressibility of the prepared powders was measured. Microspheres and microcapsules showed compaction abilities by far better than those of the corresponding physical mixtures. In fact, it was impossible to obtain tablets by direct compressing drug and polymer physical mixtures, but microspheres and microcapsules were easily transformed into tablets. Finally, in vitro dissolution studies were performed and the release control of the tablets was pointed out. Microspheres were able to control ketoprofen release only after their transformation into tablets. Tablets containing eudragit RS were the most effective in slowing down drug release.

Keywords: Ketoprofen; Microspheres; Microcapsules; Tablets

Ketoprofen is a NSAID readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 0.5–2 h after a dose, but it causes a certain irritation in the gastrointestinal mucous membrane and possesses a bitter taste and aftertaste. The half-life in plasma is about 2–3 h (Martindale, 1996). The short half-life and the low single administration dose make ketoprofen a very good candidate for the formulation of controlled release dosage forms and considerable efforts have been performed in this direction (Conte, 1992; Habib and Mesue, 1995; Khan et al., 1996; Rodriguez et al., 1996; Parejo et al., 1998). At the same time, great attention has been devoted on the possibility to prepare ketoprofen microspheres or microcapsules in order to formulate oral controlled release systems, to protect the gastric mucous membrane from drug irritation or to mask its unpleasant taste (Kawashima et al., 1993; Giunchedi et al., 1994; Orienti et al., 1995;

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El Gibaly et al., 1996; Palmieri et al., 1996). Previously the authors studied the possibility to prepare ketoprofen microspheres by the spray-drying technique. The preparation was possible only under certain experimental conditions and using an excess of polymer because of the very long ketoprofen recrystallization time (Palmieri et al., 2000).

The aim of this study was to verify the possibility to obtain ketoprofen solid microspheres by emulsion/solvent evaporation, containing the drug and one water insoluble polymer, such as an acrylic or cellulosic polymer, for the final formulation of oral controlled release dosage forms.

Ketoprofen (ACEF, Fiorenzuola d'Arda, Italy) and ethylcellulose NF 50 (Aqualon, Dusseldorf, Germany) or cellulose acetate (Eastman, Kingsport, TN) or eudragit RS (Röhm, Darmstadt, Germany) were first dissolved in CH_2Cl_2 using w/w drug/polymer ratios of 2:1 and 1:1. The resulting solutions were then emulsified in a previously prepared 0.4% gelatine type A (ACEF, Fiorenzuola d'Arda) solution. The recovery of the free flowing microspheres was possible only if the emulsions were stirred at a temperature of 15 °C or lower. In this way, 8 h were necessary to evaporate all the CH_2Cl_2. If a temperature higher than 18–20 °C was used, the microspheres could not be recovered as they were semisolid and stuck each other when filtered under vacuum or centrifuged. In order to speed up the preparation time, the authors decided to repeat the process at 60 °C for 1 h and then to cool the system using an ice bath. In this way, the microspheres were normally filtered but after having allowed them to dry at room temperature under vacuum, they newly became sticky and formed a sponge-like unique block. For this reason the authors decided to immediately microencapsulate the semisolid microspheres as soon as they were formed at 60 °C. Ketoprofen and ethylcellulose or cellulose acetate or eudragit RS were first dissolved in CH_2Cl_2 using w/w drug/polymer ratios of 2:1 and 1:1. The resulting solutions were then emulsified in a previously prepared 1.4% gelatine solution. These emulsions were then stirred at 60 °C for 1 h to be sure that the internal organic phase was completely evaporated. The temperature was then lowered to 40 °C and a certain volume (equivalent to the previous used volume of gelatine solution) of a 1.4% acacia (ACEF, Fiorenzuola d'Arda) solution was added to the systems containing the already formed semisolid microspheres. The addition of acetic acid until pH 4–4.5 gave rise to the coacervation process. After 30 min the systems were cooled to 5 °C, left for 30 min and then spray-dried (Büchi Mini Spray Dryer B-191, Switzerland) to recover the free flowing microcapsules. Microspheres and microcapsules were analyzed by UV (Cary 100, Varian, Leinì, Italy), optical microscope (Italian Zeiss, Arese, Italy), SEM (Cambridge Instruments Limited, Cambridge, UK), DSC (Pyris 1, Perkin-Elmer, Bologna, Italy) and X-ray diffractometry (PW 1730, Philips, Milan, Italy). Then all batches of microspheres and microcapsules were compressed by an instrumented 10 stations rotary press (Ronchi, Cinisello Balsamo, Italy). The authors also tried to obtain tablets from the drug/polymer physical mixtures, by direct compression, but tablets did not form even using elevated compression forces. Finally, in vitro dissolution studies (Erweka DT6, Heusenstamm, Germany) were performed on all the different batches of microspheres, microcapsules and tablets.

SEM images of the microspheres show that they possess a grossly spheroidal form, even if sharp corners are very well visible. The microencapsulated microspheres are bigger. This suggests the formation of microcapsules having more than one internal semisolid core. The surface of microcapsules is not smooth and the small spheres of the coacervate material are visible. DSC curves show that a partial ketoprofen recrystallization occurs if the microspheres are prepared below 18 °C, but it is impossible to verify if the rest of the ketoprofen is engaged in the formation of solid solutions or if it is simply still in an amorphous form. X-ray powder diffractometry confirms the presence of ketoprofen crystals inside the microspheres structure. Both microspheres and microcapsules showed good compressibility, particularly if compared with that of the corresponding physical mixtures which were unable to give tablets. The ketoprofen/eudragit RS microspheres and the corresponding microcapsules show a bet-

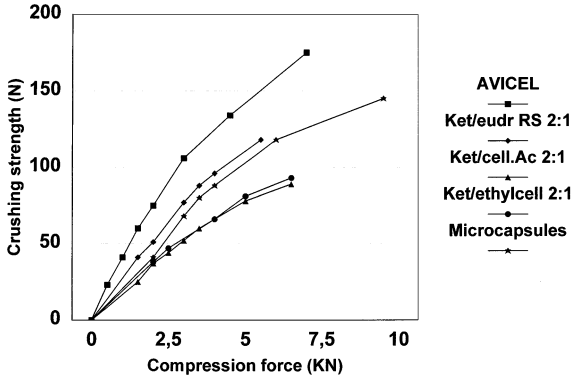

Fig. 1. Crushing strength/compression force curves of the microspheres composed by ketoprofen and eudragit RS or ethylcellulose or cellulose acetate in the 2:1 w/w ratio, compared with the curve given by the Avicel PH 102.

ter compaction ability in comparison with that of the ketoprofen/cellulosic derivatives (Fig. 1). Dissolution studies show that both microspheres and microcapsules, independently from the type of polymer present in them, are able to slow down the drug release only in HCl 0.1 N even if those containing eudragit RS are more effective. No release control is shown in phosphate buffer (Fig. 2). All batches of tablets (Fig. 3) show a very strong drug release control in the acidic medium. In phosphate buffer, the release kinetics always accelerates but, whereas tablets obtained from the compression of the microspheres are still able to slow down the drug release, those derived from the compression of the microcapsules are unable to control the ketoprofen release.

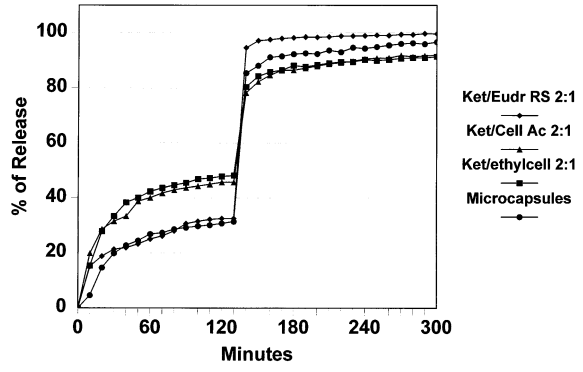

Fig. 2. In vitro ketoprofen release kinetics of the microspheres and microcapsules.

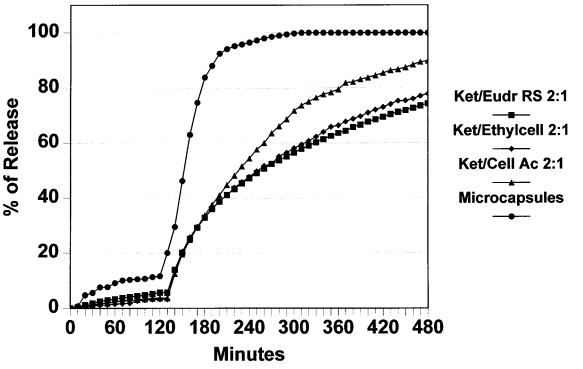

Fig. 3. In vitro ketoprofen release kinetics of the tablets obtained from the microspheres and microcapsules.

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