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RESEARCH PAPER

Characterization of the Mechanism of Interaction in Ibuprofen-Eudragit RL100® Coevaporates

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ABSTRACT

The present study is a preliminary exploration of the affinity between a carboxylic model drug, the nonsteroidal antiinflammatory agent ibuprofen (IBU) and Eudragit RL100 (RL) polymer. Due to the presence of a variable amount of quaternary ammonium groups in this matrix, physical and chemical interaction with the carboxylic drug can occur, which reinforces its scant mechanical dispersion in the polymer network and can ultimately affect its release profile in vitro and in vivo. To study these aspects, IBU was mixed at increasing weight ratios and in different chemical forms (free acid, sodium salt, and n-butyl ester), to investigate further the role of the carboxylic group in the interaction with the RL polymer. Therefore, IBU-RL solid dispersions (coevaporates) were obtained and fully characterized in the solid state through spectroscopic, calorimetric, and x-ray diffractometric analyses. The in vitro release pattern of the drug, in the different chemical states, was studied for the coevaporates, compared with drug-RL physical mixtures, along with drug adsorption profiles from aqueous solutions on the surface of the polymer granules.

Key Words: Ibuprofen; Eudragit; Bioavailability; Coevaporates; Solid dispersion.

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INTRODUCTION

Solid dispersions are physical systems in which small solid particles of a drug are dispersed or encapsulated within a matrix, usually a polymer network. They are investigated in the modern pharmaceutical technology to enhance the dissolution rate and absorption of drugs with a low systemic bioavailability.[1] Melting and solvent evaporation procedures have been usually followed to obtain such systems. Solid dispersions prepared by removing a volatile organic solvent, in which both the drug and the polymeric material have been previously dissolved, can be more appropriately called coevaporates.[2–5]

In the field of modified drug delivery, interesting potentialities are offered by acrylic polymers, such as Eudragit® Retard, extensively used for film coating of solid dosage forms, as well as in the preparation of inert matrices or micromatrices for controlling the drug delivery via oral or other routes.[6–14]

Eudragit RS (RS) and RL (RL) are copolymers of poly(ethyl-acrylate-*co*-methyl-methacrylate-*co*-trimethylamino-ethyl-methacrylate chloride) [poly(EA-MMA-TAMCl)]. The introduction of the hydrophilic ammonium groups (TAMCl) is aimed at modifying the permeability of the acrylic polymer. The main difference in RS and RL consists in the amount of ammonium groups: their composition is in fact EA:MMA:TAMCl=1:2:0.2 (RL) and 1:2:0.1 (RS). These polymers are insoluble in aqueous media, but are able to swell and become permeable to solutes, thanks to the presence of the ionized TAMCl groups, but in a pH-independent manner (Eudragit Technical Sheets, Rohm, Germany).

Interactions between these polymer matrices and drugs can be characterized by a physical adsorption, e.g., electrostatic interactions and/or hydrogen bonding with the quaternary ammonium groups present in the polymer. The resulting interactions, added to the scant mechanical dispersion of the drug within the polymer network, can of course strongly influence the drug loading and its following release into an external dissolution medium.

The present study is intended as a preliminary exploration of the affinity between a carboxylic drug and any polymer selected to prepare a potential multiple-unit drug delivery dosage form. Description of microparticulate controlled release formulations in the literature, in fact, often lack a preliminary evaluation of the (chemical and physical) interactions that can occur between the components but also dramatically affect the homogeneity of the system, the drug loading and the following release profile, as well as the reliability of the properties of the system upon storage.

Ibuprofen (IBU) was chosen as a model carboxylic drug in this study. A nonsteroidal, antiinflammatory drug (NSAID) IBU is widely used in both conventional as well as in controlled-release oral formulations, mainly because of its short plasmatic half-life.[2,9,15–24] With the aim at investigating deeper the role of the carboxyl group in interactions with Eudragit polymers, we carried out experiments on IBU-RL interaction, using the drug in the acid-free form (IBU/A), as sodium salt (IBU/S), and as its n-butyl ester (IBU/B), e.g., with a permanently masked carboxyl function. The RL polymer was preferred to RS one because of its higher number of binding sites for the drug, i.e., ammonium groups on the polymer backbone.

Ibuprofen RL solid systems were prepared by coevaporation of common solutions in ethanol at different drug–polymer weight ratios. The resulting coevaporates were characterized in the solid state using Fourier-transform infrared (FT-IR) spectroscopy powder x-ray diffractometry (PXRD), and differential scanning calorimetry (DSC). The strength of drug interaction with the polymer network was further assessed by in vitro release experiments and adsorption–desorption tests.

MATERIALS AND METHODS

Eudragit® RL100 was kindly gifted by Rofarma Italia S.r.l. (Gaggiano, Milan, Italy) and was used as received. Ibuprofen sodium salt (IBU/S) was purchased from Sigma (Aldrich-Sigma Chimica S.r.l., Milan, Italy). All other reactants and solvents were of analytical grade or higher.

Preparation of IBU Acid and n-Butyl Ester

The acid-free form of the drug (IBU/A) was obtained from an IBU/S aqueous solution. The acid was precipitated by adding cold diluted acetic acid. The white solid was filtered off, washed with water, dried, and recrystallized from methanol. Melting point (M.p.), IR and elemental analysis confirmed the structure assigned to the drug.

The n-butyl ester (IBU/B) was prepared by refluxing for 24 h 1 gram of IBU/S and 400 μL of thionyl chloride in 20 mL of n-butanol. The reaction mixture was then filtered and evaporated off under vacuum at 70° C. The oily residue was further purified

by washing with a 2% cold aqueous sodium bicarbonate solution and extraction with ethyl acetate.

Preparation of Coevaporates

The total amount of drug and RL was kept constant (1 gram) for all batches. Thus, a weighed amount of the selected drug (IBU/A or IBU/S) was dissolved in 50 mL of absolute ethanol. The corresponding amount of RL polymer was added to obtain the desired drug–polymer weight ratio (5%, 10%, 20%, or 33%), and the mixture was left at room temperature under stirring for several hours, to complete the polymer dissolution and to permit a thorough mixing of the two components. The ethanol was then removed off in vacuum, at a maximal internal temperature of 40° C.

In the case of IBU/B coevaporates, the drug ester and RL were dissolved in n-butanol (50 mL) and the final evaporation of the solvent was carried out at 70°C under high vacuum.

The solid residue obtained was pulverized in a mortar and further dried at 30°C for 24 h under vacuum (Buchi TO-51; Buchi, Switzerland). At the end, the material was sieved (420 μm, 40 mesh) and stored in tightly closed amber glass containers at room temperature, away from direct light and heat.

In the case of batches prepared with higher polymer ratios, the sticky material obtained after the solvent evaporation was triturated with light petroleum ether to obtain a solid.

Preparation of Physical Mixtures

Drug and RL mixtures were triturated for about 30 min in a porcelain mortar to obtain the same weight ratios as the coevaporates. The mixture was then sieved and stored as indicated above.

Spectroscopic Characterization of Drug-RL Systems

Differential Scanning Calorimetry (DSC)

Drug solubility in the polymer matrix was analyzed by a Mettler DSC12E calorimeter, connected to a Haake D8-G thermocryostat and a detector system consisting of a Mettler Pt100 sensor, with a calorimetric sensitivity of about 3 μV/mW and a background noise less than 60 nV (<1 mW).

Calibration was performed by using an indium sample. The DSC analysis was carried out on weighed amounts (10–15 mg) of pure drugs, pure RL, and all the prepared coevaporates and physical mixtures (PhMs). The samples were sealed in holed 40 μL aluminum pans (Mettler Me-26763), while an empty pan was used as reference. Each sample was subjected to a heating scan in a temperature range chosen on the basis of the drug melting point (30–180° C), at a scan rate of 5° C min^{-1}.

FT-IR Spectroscopy

Samples and pure ingredients were examined as KBr discs containing about 20 mg of drug. Spectra were recorded with a Perkin-Elmer 1600 instrument.

Powder X-Ray Diffractometry

X-ray diffraction spectra were recorded using a Philips PW 1050/25 powder diffractometer using a 40 kV generator and a 20 mA stream, with a copper anodic tube. The diffractograms of coevaporates and PhMs were compared to those of pure drugs and polymer.

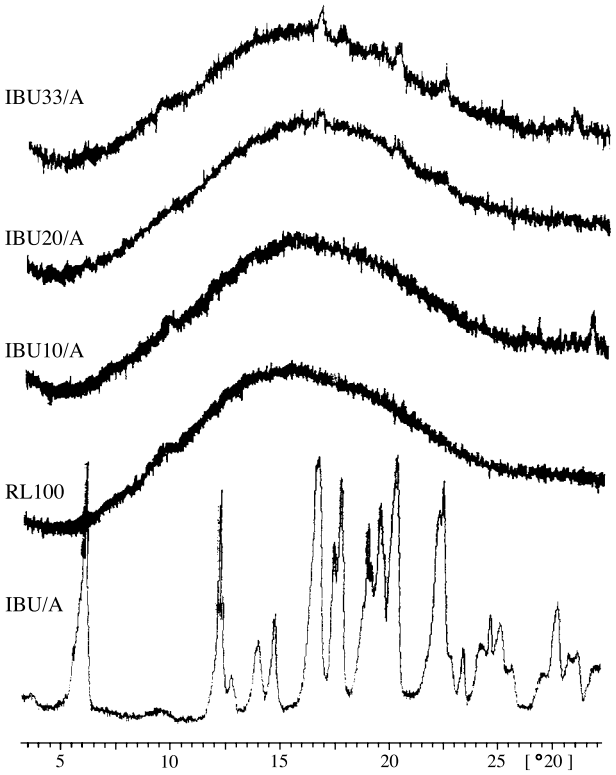

Figure 1. Powder x-ray diffractometric curves of IBU/A and its coevaporates with RL.

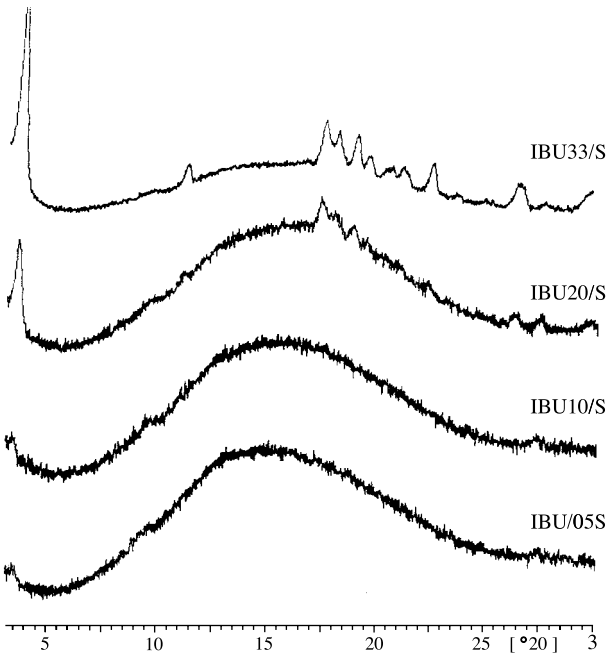

Figure 2. Powder x-ray diffractometric curves of IBU/S and its coevaporates with RL.

Drug Dissolution Studies

The drug release from the polymer matrixes was evaluated at room temperature during 24 h. Fifty mg of each batch were dispersed into 100 mL of phosphate buffer solutions at different pH (4.5, 7.4, 9.0) (Italian Pharmacopoeia, FUI X Ed.) and stirred at 100 rpm. At different time intervals, 1-mL aliquots of solution were withdrawn and replaced with the same volume of fresh buffer. The samples were filtered [0.45 μm polytetrafluorothylene (PTFE) membrane filters] and the amount of dissolved drug was measured by UV spectrophotometry at 265 nm, with respect to calibration curves obtained for the various drugs at the respective pH.

Drug Adsorption Tests

Assays were carried out to evaluate the eventual spontaneous adsorption of the drugs onto the polymer particles at physiological pH. Drug solutions were prepared with 50 mL of pH 7.4 phosphate buffer and a 10 times weight of powdered polymer, with respect to the drug, was added. The dispersions were continuously stirred at room temperature for 20 days, with periodic withdrawal of 1-mL aliquots to evaluate by ultraviolet analysis (Imax = 265 nm) the eventual reduction of drug concentration in the buffer solution. The results were expressed as the amount of adsorbed drug onto the polymer.

The effect of pH and ionic strength on the adsorption was studied by carrying out the same tests using saline and a pH 4.5 phosphate buffer solution for the three drug forms. Further experiments were performed in an alkaline medium (pH 9.0 phosphate buffer) and at different drug/polymer weight ratios.

In separate experiments, the drug stability under the conditions used for the above assays was verified.

RESULTS AND DISCUSSION

The physical state of the drugs in the RL coevaporates and in the corresponding PhMs was determined by usual spectroscopic techniques (FT-IR, PXRD, and DSC). The x-ray diffractometry profile of RL polymer indicated the presence of a completely amorphous material; pure IBU/A and IBU/S crystals instead showed

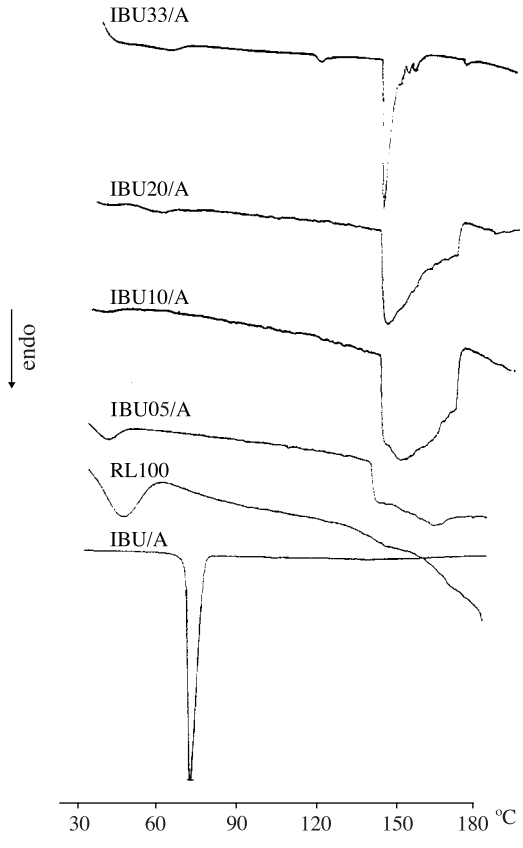

Figure 3. DSC thermograms of pure RL, IBU/A, and corresponding coevaporates.

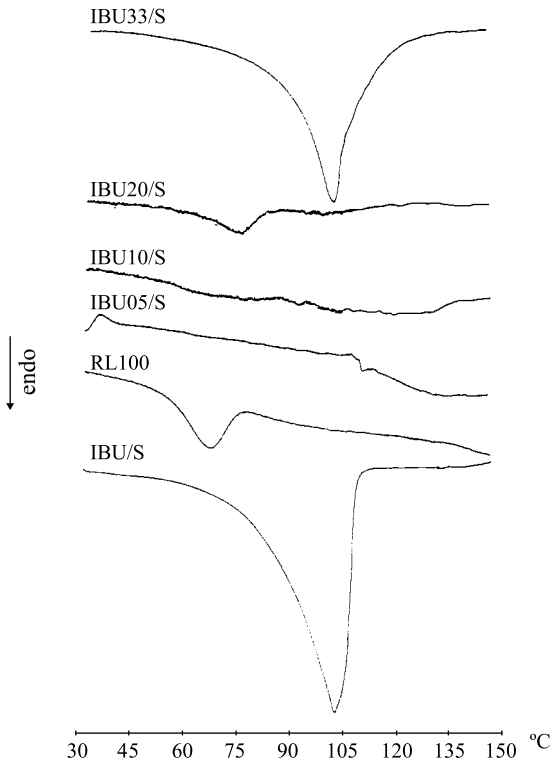

Figure 4. DSC thermograms of pure RL, IBU/S, and corresponding coevaporates.

the classical diffractograms of crystalline products (Figures 1 and 2). The diffraction pattern of coevaporates containing up to 20% of the acid form (IBU05/A, IBU10/A, and IBU20/A) did not show any interference due to drug crystals. Conversely, the IBU33/A system, obtained with a lower polymer amount, showed some signals owing to drug crystals (Figure 1). Therefore, in the acid form, IBU seemed able to crystallize within the polymer network under the experimental conditions of coevaporation when its concentration exceeded the solubility in the polymer itself. At the lower weight ratios, the drug existed in an amorphous or microcrystalline state, however thoroughly dispersed in the polymer matrix.

When the corresponding coevaporates containing the sodium salt were tested (Figure 2), signals related to the drug crystals were already visible at a 20% drug concentration, suggesting a lower solubility of the drug in the salified form within the polymer network. Also, a computation of the PXRD data indicated that, at the same drug concentration (33%, w/w), IBU/S still showed about a three-fold higher residual crystallinity in the coevaporates than the acid form of the drug. Of course, no sign of crystalline material was seen in the coevaporates obtained from the drug butyl ester (data not shown).

The DSC curves of the pure ingredients and their mixed systems are reported in Figures 3–6. The pure drugs (acid and sodium salt) showed a clear endothermic peak associated to crystal melting (76.9° C for IBU/A and 100.5° C for IBU/S) (Figures 3 and 4). No melting signal was obviously observed for the butyl ester, due to its oily state. As known, the amorphous polymer did not show any fusion peak or phase transition, apart from a broad signal around 55–60° C, due to a partial loss of residual humidity (Figure 3).

The thermal behavior of the solid dispersions and mixtures suggested that the polymer inhibited the melting of drug crystals. A large endothermic peak is only visible above 140° C, probably due to a beginning polymer degradation. The systems containing higher drug ratios (IBU33/A and IBU33/S) showed a melting peak at 146° C and 97.5° C, respectively. As already discussed for the PXRD analysis, these findings confirmed that, over a certain concentration, the excess of drug was not able to form a homogeneous solid solution with the polymer.

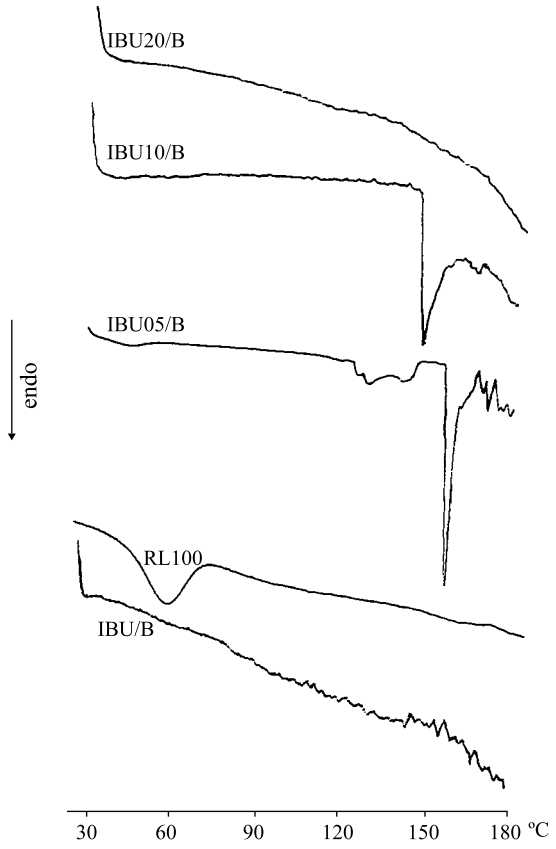

Figure 5. DSC thermograms of pure RL, IBU/B, and corresponding coevaporates.

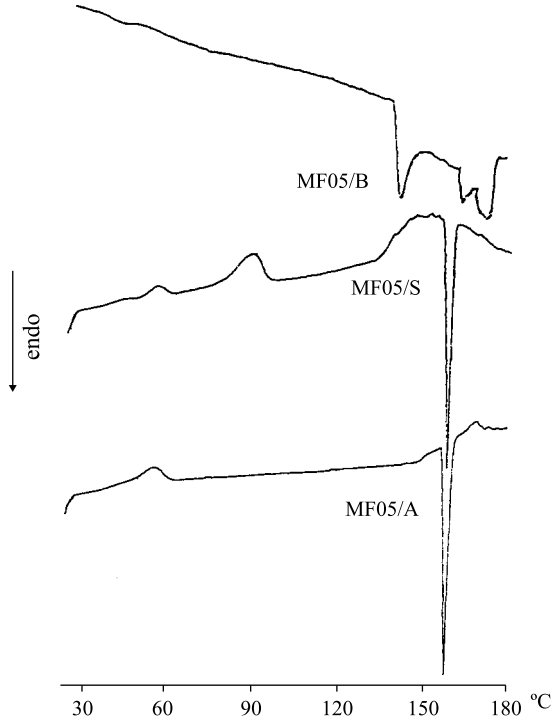

Figure 6. DSC thermograms of the PhMs between RL and the different drugs, at a 5% (w/w) drug concentration.

The corresponding PhMs displayed a peculiar behavior. In fact, both the mixtures obtained with the acid drug or its sodium salt, at two drug concentrations (5% and 20%), showed a strong endothermic peak centered around 160° C, preceded by a weaker exothermic signal around 100° C. This should indicate that, instead of melting, drug crystals underwent a crystalline modification, followed by the formation of a salt or a complex with the polymer that, conversely, showed a neat melting point. An exemplary DSC pattern is depicted in Figure 6 for the drug/RL PhMs at a 5% drug concentration.

The fact that such a phenomenon was visible when the mixture was prepared in the dry state, and not from the ethanol solution (as in the coevaporates), suggested that it is the consequence of an electrostatic interaction between the drug and RL, for instance, for the formation of a zwitterionic adduct. The polar solvent hindered such interactions, and the drug preferably ''dissolved'' within the polymer network.

The calorimetric curve of the corresponding solid systems between RL and drug butyl ester are shown in Figures 5 and 6. Although at the higher tested drug concentration (20%) no endothermic signal was visible, when the ester drug was evaluated at lower percentages (5% and 10%), a clearly visible endothermic peak appeared around 145° C and 155° C; moreover, its intensity reduced with increasing IBU/B percentage (e.g., IBU10/B vs. IBU05/B, Figure 5). Similarly, in the 5% IBU/B-RL PhM a weak but net endothermic peak was seen around 145° C (Figure 6). These findings suggest that, at low drug concentrations, the butyl ester form of IBU is able to disperse homogeneously in the polymer, forming little crystalline aggregates; conversely, over a certain percentage an intermolecular combination was prevalent, which disrupts its crystalline state.

Further suggestions about the nature of the interaction between the drug and RL were drawn from the infrared spectroscopy. For brevity, we reported only the comparison between IBU acid and its coevaporates (Figure 7). In particular, in the region of carbonyl group stretching, while for the free IBU acid a strong peak at 1720 cm^{-1} was observed, for its coevaporates a broader and weaker signal was visible, falling around 1725 cm^{-1},

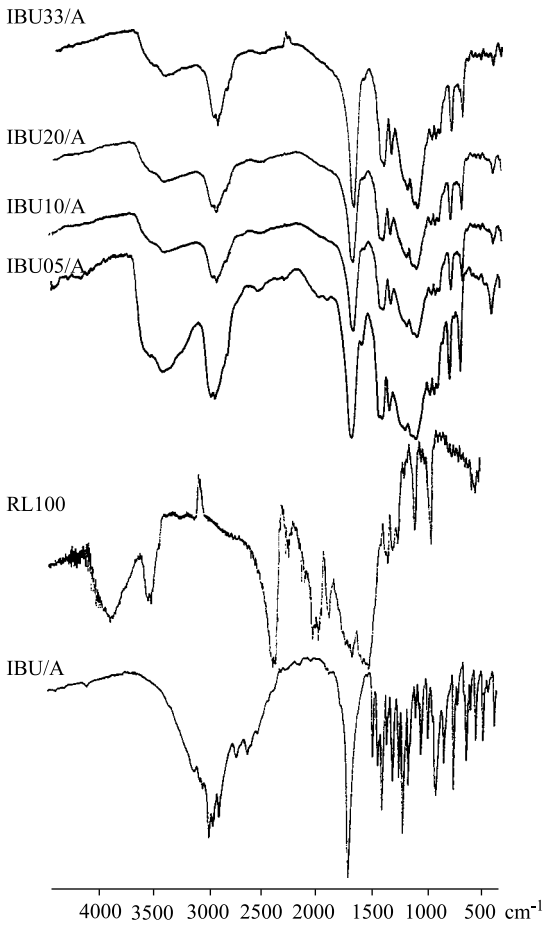

Figure 7. Comparison of the IR spectra of RL, IBU/A, and corresponding coevaporates.

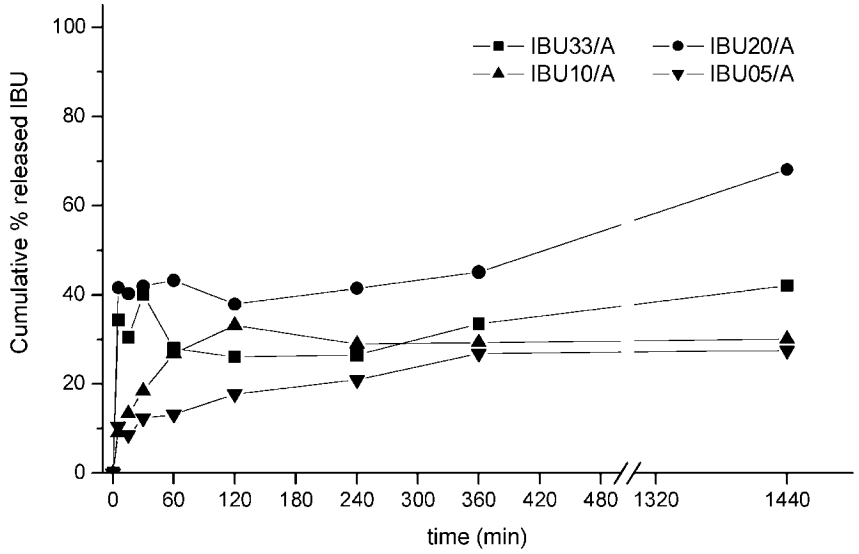

Figure 8. In vitro drug dissolution curves at pH 4.5 from IBU/A-RL coevaporates.

which associates both the stretching of the drug carboxyl and the ester C═O group of the polymer (at 1736 cm^{-1} for pure RL). The corresponding PhM obtained with a low IBU/A percentage (MF05/A) only showed the polymer ester signal whereas, at higher drug concentrations (MF20/A), the IBU carboxyl group stretching peak is prevalent. For the sodium salt of the drug, instead, while in all the coevaporates, as well as in the 5% PhM only the RL ester carbonyl group has been detected (1735 cm^{-1}), in the 20% IBU/S PhM a new, relatively weak set of signals appeared between 1720–1700 cm^{-1}, which could be associated with the new ''chemical entity'' already observed in the DSC experiments (see above).

In the IR spectra of coevaporates from the IBU butyl ester no chemical interaction between the two components has been observed, as expected: at all the tested weight ratios (5%, 10%, and 20%), in fact, the only strong peak is the one around 1737 cm^{-1} due to the ester function introduced in the IBU molecule.

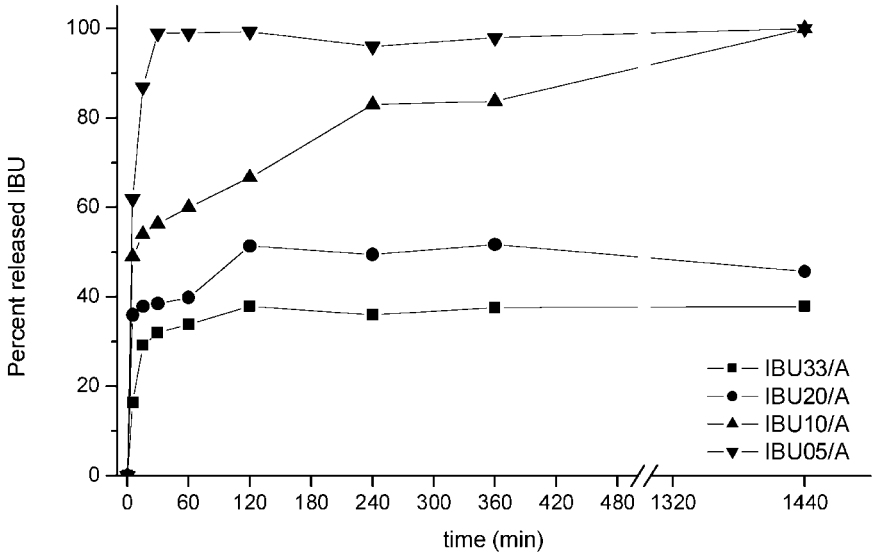

Figure 9. In vitro drug dissolution curves at pH 7.4 from IBU/A-RL coevaporates.

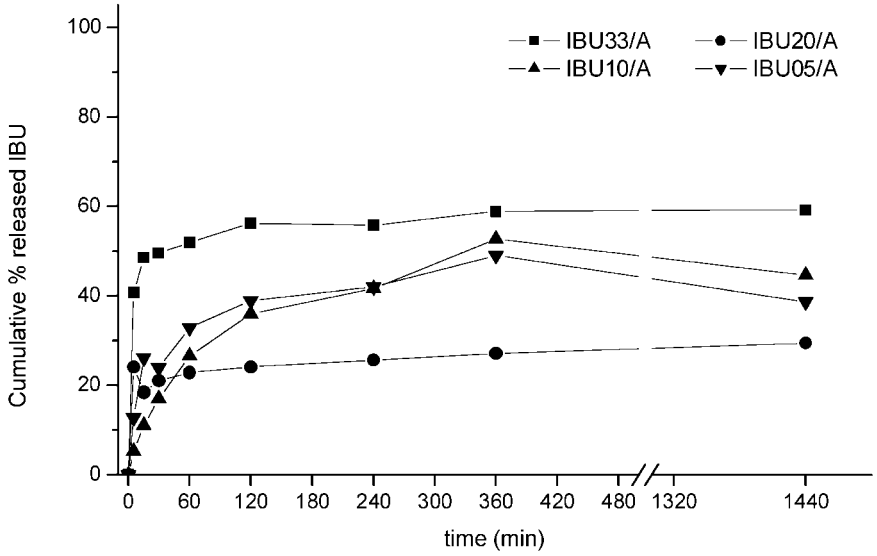

Figure 10. In vitro drug dissolution curves at pH 9.0 from IBU/A-RL coevaporates.

The dissolution profiles of the drugs from coevaporates and PhMs have been evaluated at room temperature and different pH values (Figures 8–12). As expected, the pH of the dissolution medium strongly affected the release rate of the drug in the acid form (Figures 8–10), while the drug concentration in the coevaporates exerted a less linear effect. In every case, all the systems showed a rapid drug leakage in the first 30 min, suggesting that the interaction forces with the polymer matrix are weaker than the dissolution capacity in the external medium. Moreover, while at pH 4.5 and 9.0 not more than 50–60% of the loaded drug was released from the polymer dispersions, at pH 7.4 the release of the drug was almost quantitative. In this kind of experiment, the net drug release profile depends on an equilibrium between the drug dissolution rate in the external aqueous medium and the following readsorption of the dissolved drug molecules

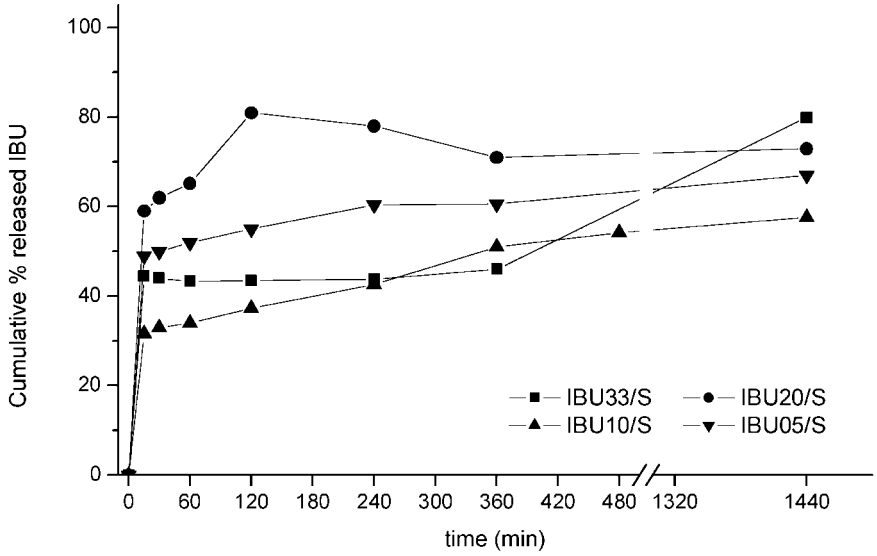

Figure 11. In vitro drug dissolution curves at pH 4.5 from IBU/S-RL coevaporates.

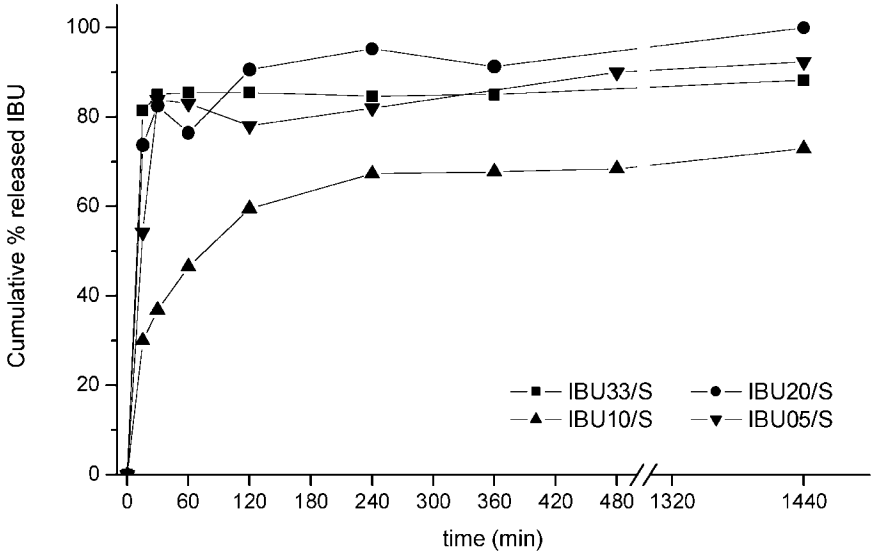

Figure 12. In vitro drug dissolution curves at pH 7.4 from IBU/S-RL coevaporates.

back onto the polymer particle surface.[11,12] Therefore, it would seem that at outer pH values the latter step predominated upon the dissociation and dissolution phases of the drug (in the acid form). Noteworthy, at pH 4.5 the dissociation of IBU is minimal (IBU has a pk_a value of 4.45), thus the observed release curve is basically linked to its physical diffusion through the polymer network.

In the test carried out at pH 7.4 a higher linearity between IBU release and its weight ratio with the polymer was observed in the different coevaporates. In particular, the release rate of the active was slowed by increasing its concentration in the solid system (e.g., IBU33/A vs. IBU05/A, Figure 9). It would suggest that the micro-dispersion of the drug in the polymer, easily achieved when the concentration of the former was lower,

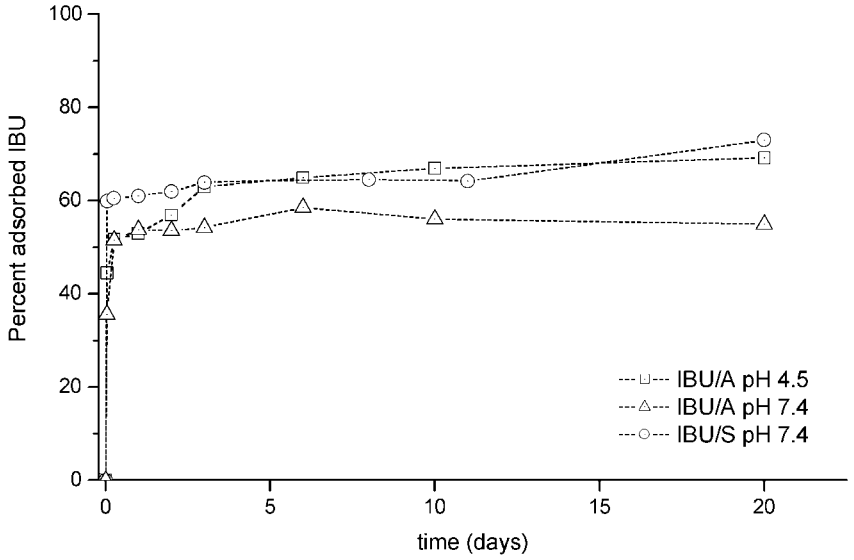

Figure 13. Adsorption test profiles of IBU/A and IBU/S onto RL particle surface from different pH buffer solutions.

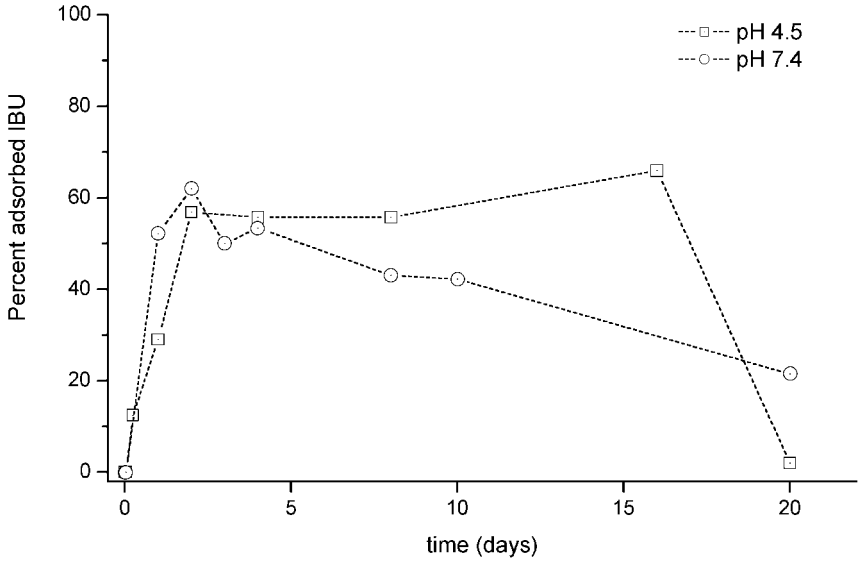

Figure 14. Adsorption test profiles of IBU/B onto RL particle surface from different pH buffer solutions.

facilitated its dissociation from the polymer network itself, upon contact with the dissolving buffer solution.

With the drug sodium salt (Figures 11 and 12), a marked burst effect was observed, with a rapid release of the drug (up to 70%) in the first minutes of the test. In this case the drug, already existing in a dissociate form, rapidly desorbed from the polymer particles surface to dissolve in the dispersing aqueous medium. After 1–2 h, a plateau was reached until the end of the test (24 h). At pH 7.4, such a drug concentration corresponded to 60–90% of the initially loaded drug, while, at a lower pH, a reduced amount of active was released. In this case too, however, no significant correlation was obtained between IBU/S release profile and the drug/RL weight ratio in the different coevaporates tested. This latter consideration would suggest the lack of a complete physical homogeneity in the solid systems, and therefore the experimentally registered release curves derived from the contemporary development of diffusional and dissolutive phenomena, that hinder the interpretation of the kinetics of drug release.

Only the coevaporate obtained with a 10% IBU/S weight ratio (IBU10/S) showed a slower and more gradual drug release, definitively more suitable for a pharmaceutical controlled delivery system.

Figure 13 displays the adsorption of IBU/A and IBU/S onto RL particles from neutral (pH 7.4) or weakly acid (pH 4.5) solutions. Such an adsorption is the result of the electrostatic interaction between the (anionic) drug and the quaternary ammonium groups in the polymer matrix.[25,26] The adsorption profile shown by IBU with respect to RL displayed an initial rapid association of the drug to the polymer surface (50–60% of the drug present in solution), after which an equilibrium was attained (adsorbed/dissolved drug), which remained unchanged for the following 20 days of the test. In these experiments, the chemical state of the active (acid or salt) and the pH of the dissolving medium did not seem to strongly affect the process. Such a behavior suggests that this drug is able to rapidly interact with and saturate the binding ''sites'' on the RL, and remarkably, is a slightly different result from that observed in previous studies with other NSAIDs (e.g., flurbiprofen or diflunisal).[27] The phenomenon deserves a deeper exploration, for instance, in relation to the different variables used in this study.

In particular, masking the free carboxylic group in the IBU butyl ester (Figure 14) led to an initial adsorption onto polymer particles, due to a mechanical interaction rather than to a chemical bond; however, while the acid and the salified drug forms remained associated to the polymer, in the case of IBU/B after 4–5 days of incubation a slow leak of the drug back to the dissolution medium started, leading, after 20 days, to an almost complete discharge of the ester from the polymer granules surface.

In summary, the comparison between the adsorption profile of the three different chemical forms of this drug (Figures 13 and 14) suggested that the uptake initially observed onto the RL particle surface was due to a physical interaction and that the binding between the drug and the polymer ''active sites'' occurred as a

further step and would account for linking the drug to the polymer itself.

CONCLUSIONS

The development of solid systems, in which a drug is dispersed in a polymer matrix, is one of the most explored fields in pharmaceutical technology. Scientists are searching for novel ways to improve and optimize the biopharmaceutical properties, and thus the therapeutic efficacy of new and old active compounds. In this paper, the interaction between IBU, a model drug with relevant clinical applications, and an inert polymer matrix consisting of Eudragit RL100®, was analyzed.

The evaluation of solid dispersions obtained by the coevaporation of ethanol solutions of the polymer and IBU in various chemical forms (acid-free, sodium salt, or butyl ester) and at different weight ratios allowed the tracing of an interaction profile, which confirmed that between this kind of polymer, whose backbone contains positively charged quaternary ammonium groups, and (anionic) carboxyl drug molecules, chemical bonds can be formed that reinforce or modify the usual mechanical interaction between a generic pair of drug and polymer. These interactions can ultimately affect the release profile of the drug in the biological media.

This kind of study represents an important preliminary and/or preformulative phase, often undervalued, for the optimization of polymer-based drug delivery systems, such as microparticles. The overall biological behavior of the system can in fact also depend on the nature and strength of the possible interactions among its components.

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