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Preparation of Solid Dispersions of Nonsteroidal Anti-inflammatory Drugs With Acrylic Polymers and Studies on Mechanisms of Drug-Polymer Interactions

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ABSTRACT This work studied the mechanisms of interaction between Eudragit RS100 (RS) and RL100 (RL) polymers with 3 nonsteroidal anti-inflammatory drugs: diflunisal (DIF), flurbiprofen (FLU), and piroxicam (PIR). Solid dispersions of polymers and drugs at different weight ratios were prepared by coevaporation of their ethanol solutions. The resulting coevaporates were characterized in the solid state (Fourier-transformed infrared spectroscopy (FT-IR) IR, differential scanning calorimetry, powder-x-ray diffractometry) as well as by studying the in vitro drug release in a gastroenteric environment. Absorption tests from drug solutions to the solid polymers were also performed to better explain the mechanism of interactions between them. The preparative conditions did not induce changes in the crystalline state of the drugs (amorphization or polymorphic change). Drugs strongly interacted with the ammonium groups present in polymers, giving an electrostatic interaction that reinforced the mere physical dispersion of drug molecules within polymer networks. Such interactions are related to the chemical structure of the drugs and to their dissociated or undissociated state. The dispersion of drugs in the polymer matrices strongly influenced their dissolution rate, which appeared slower and more gradual than those of the pure drugs, when polymer ratios were increased. RL coevaporates usually displayed higher dissolution rates. The kinetic evaluation of the dissolution profile, however, suggested that both the drug solubility in the external medium and its diffusion capacity within the polymer network are involved. In the sorption experiments, RL showed a greater adsorptive capacity than RS, in relation to the greater number of quaternary ammonium functions, which behave as activity sites for the electrostatic interactions. In the presence of Tris-HCl buffer (pH 7.4), drug adsorption was reduced, as a consequence of the competition of the chloride ions with drug anions for the polymer binding sites. In general, DIF and FLU displayed a similar interaction with RS and RL active sites; PIR's was different. The different molecular structures of these agents can justify such findings. The presence of a carboxyl group (instead of another dissociable acidic moiety, like the hydroxy-enolic one in the PIR molecule) could help explain the strong interaction with RS and RL polymers' quaternary ammonium centers. Preliminary studies like ours are important in helping develop better forecasting and increasing the understanding of the incorporation/release behavior of drugs from particulate delivery systems that can be made from these polymers.

Key Words: Eudragit RS100, Eudragit RL100, diflunisal, flurbiprofen, piroxicam, solid dispersions, coevaporates.

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INTRODUCTION

Eudragit RS100 (RS) and RL100 (RL) are copolymers of acrylic and methacrylic acid esters that con-

tain a low level of quaternary ammonium groups. RS has a lower content of charged groups, thus displaying less water permeability and swellability in comparison with RL (Eudragit technical sheets). Eudragit acrylic resins exhibit a broad spectrum of physicochemical properties and are used in a variety of pharmaceutical applications, such as film coating of oral formulations and preparation of controlled-release drug systems (eg, micro- and nanoparticulate systems) [1-3]. Flurbiprofen-RS and -RL systems have been proposed, for instance, as films for transdermal delivery [4] and as nanosuspensions for ophthalmic application [5, 6].

In developing new drug delivery systems, many studies have been carried out to investigate the influence of Eudragit acrylic resins on the release of drugs from matrices [7-10]. The nature of drugs and polymers, and their reciprocal interactions, significantly influence the drug release pattern [11, 12]. In particular, the incorporation and release of nonsteroidal anti-inflammatory drugs (NSAIDs) from RS and RL polymers was shown to be strongly dependent on the acidic nature of these drugs, which allows chemical interactions, physical interactions, or both to occur (zwitterionic adducts, ion pairs, ion-exchange resin behavior) with the ammonium group on the RS and RL backbone [11, 13-15].

Solid dispersions between diflunisal (DIF) and RS or RL polymers have been previously described and evaluated for the ability of the polymer network to reduce DIF phototoxicity [16]. The present work was aimed at studying the mechanisms of interaction between RS and RL polymers with DIF or 2 other NSAIDs: flurbiprofen (FLU) and piroxicam (PIR). Solid dispersions of drugs and polymers at different weight ratios were obtained by evaporation of their ethanol cosolutions. The coevaporates were characterized in the solid state; the solubility of the drugs in the polymers and their crystallinity were examined by Fourier-transformed infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and powder x-ray diffractometry (PXRD).

To investigate the strength of the interactions occurring between these drugs and RS or RL polymers, specific sorption assays from drug solutions onto polymer particles were carried out. Dissolution studies were performed to evaluate the influence of such interactions on the drug release pattern from coevaporates.

MATERIALS AND METHODS

Materials

RS and RL polymers were kindly donated by Röfarma (Gaggiano, Italy). Drugs and Avicel PH-101 were purchased from Sigma-Aldrich Chimica Srl (Milan, Italy). Lactose and magnesium stearate (Ph Eur grade) were purchased from Carlo Erba (Milan, Italy). Solvents and buffers were of analytical grade.

Preparation of drug/Eudragit solid dispersions (coevaporates)

Drug-polymer coevaporates were prepared by the solvent method. The chosen drug and polymer (RS or RL) were weighed and dissolved in 50 mL absolute ethanol at different drug-to-polymer ratios (1:1, 1:2, and 1:5) (Tables 1 and 2). The clear solution was stirred at room temperature for 4 to 6 hours, and the solvent was removed under reduced pressure in a rotary evaporator at an external maximum temperature of 40°C. The solid residue was dried under vacuum at 30°C for 24 hours (Büchi TO-51 oven, Flawil, Switzerland), pulverized in a mortar, and sieved. The powder below 420 μm was stored in closed glass containers away from light and humidity. The solid dispersions containing higher polymer ratios, which were generally rubbery and scarcely manageable, were preliminarily triturated with light petroleum ether before exsiccation.

Determination of drug content

Drug amount in coevaporates was determined by dissolving hundreds of micrograms of each sample in 5 mL of UV-grade methanol. The drug concentration was determined spectrophotometrically (UV-1601, Shimadzu , Duisburg, Germany) at 254, 252, and 253 nm for DIF, FLU, and PIR, respectively, versus a calibration curve in methanol. The mean of

Table 1. Properties of Eudragit RS100 (RS) Coevaporates

System	Drug/RS Ratio (wt/wt)	Loading Efficiency (mg)		Percent Incorporation	Production Yield (%)
		Theoretical Drug Content	Actual Drug Content		
DS11	1:1	50	43	86.0	90
DS12	1:2	33	27	81.8	93
DS15	1:5	16	14	87.5	88
FS12	1:2	33	25	75.7	64
FS15	1:5	16	13	81.2	76
PS12	1:2	33	25	75.7	58
PS15	1:5	16	16	100.0	73

Table 2. Properties of Eudragit RL100 (RL) Coevaporates

System	Drug/RL Ratio (wt/wt)	Loading Efficiency (mg)		Percent Incorporation	Production Yield (%)
		Theoretical Drug Content	Actual Drug Content		
DL12	1:2	33	28	84.8	86
DL15	1:5	16	14	87.5	66
FL12	1:2	33	29	87.9	93
FL15	1:5	16	16	100.0	70
PL12	1:2	33	27	81.8	72
PL15	1:5	16	13	81.2	67

at least 3 determinations was calculated. The polymers did not show interference (< 3%) with the absorbance of the drugs at these wavelengths.

Results are expressed both as the drug content (mg incorporated drug) and percent incorporation (actual amount of drug in coevaporates vs the initially added amount) (Tables 1 and 2).

Preparation of the physical mixtures

For the sake of comparison, physical mixtures having the same composition of the solid dispersions were prepared by simply triturating the drugs and the polymers in a porcelain mortar. The mixtures were then sieved (420 μm) and stored in amber-glass capped containers.

FT-IR spectroscopy

IR spectra of pure drugs and polymers, and of coevaporates and physical mixtures, were obtained with a Perkin-Elmer 1600 spectrophotometer (Monza, Italy), using KBr disks (about 10-mg sample for 100 mg dry KBr). The scanning range used was 4000 to 500 cm^{-1} at a scan period of 1 minute.

DSC

Thermal analysis was performed on the drugs, coevaporates, physical mixtures, and Eudragit polymers using a Mettler DSC12E differential scanning calorimeter (Mettler- Toledo AG, Greifensee, Switzerland) equipped with a Haake D8-G thermocriostat, a detection system (Mettler Pt 100 sensor), and a computer.

The instrument was calibrated with an indium standard. Samples (10-15 mg) were weighed and sealed into 40-μL aluminum pans. DSC runs were conducted over a temperature range of 25 to 240°C, 25 to 130°C, and 25 to 230°C for DIF, FLU, and PIR, respectively, at a rate of 5°C/min. The accuracy of scanning was ± 0.4°C, and the reproducibility was 0.1°C.

X-ray powder diffractometry

Diffraction patterns of DIF/RS and FLU/RS systems were recorded with a Philips diffractometer PW 1050/25 for powders. A voltage of 40 kV and a current of 30 mA for the generator were used, with Cu as the tube anode material. The solids were exposed to Cu-K_α radiation (α_1 = 1.54060 Å and α_2 = 1.54439 Å, with an α_1/α_2 ratio of 0.5), over a range of 2Θ angles from 3° to 30°, at an angular speed of 1° (2Θ) per minute, using divergence and receiving slits of 0.5° or 1° and 0.2°, respectively.

Drug-to-polymer adsorption experiments

A weighed amount of each drug was dissolved in 50 mL pH 7.4 phosphate buffer (0.11M), to obtain a UV absorbance of about 1.0 at 252, 247, and 352 nm for DIF, FLU, and PIR, respectively. A 10-fold weight of grounded RS or RL (420 μm-sieve fraction) was added to the solution, and the mixture was magnetically stirred at room temperature for about 20 days. Solution samples were periodically drawn, filtered over paper, and assayed spectrophotometrically at the respective λ_{max} of the drug. The amount of drug adsorbed onto the polymer particles was

then calculated with respect to the initial absorbance.

The effect of ionic strength on drug adsorption to the polymers was also studied by using a 50-mM Tris-HCl buffer solution, at pH 7.4. The absence of drug degradation in both the above experimental conditions but without the polymers was preliminarily assessed.

In vitro drug dissolution studies in gastroenteric environment

The drug dissolution experiments were carried out by the rotating paddle method (FUI x Edition), using 300-mg tablets containing about 25 to 30 mg of drug. Tablets were obtained with the following composition (in weight):

- Coevaporate: 30% to 50%
- Lactose (diluent): 20% to 35%
- Avicel PH 101 (disgregant): 30% to 34%
- Mg stearate (lubricant): 1%

All ingredients were triturated in a mortar for 15 minutes. The mixture was then compressed with an IR press (1.3-cm punch, pressure: 2-3 ton). Tablets disaggregated within 5 to 10 minutes (FUI x Ed basket method).

For the dissolution tests, each tablet was placed in 750 mL of 0.1 M HCl (pH 1.2) and stirred at 50 rpm and 37°C for 2 hours. Exactly 250 mL of a 0.2 M trisodium phosphate solution was then added to achieve a pH 6.8 value [USP XXIII, method A–Delayed-release (Enteric coated) Articles]. Two-mL samples were taken at selected time intervals and analyzed spectrophotometrically for drug content—DIF: 228 and 252 nm; FLU: 246 and 247 nm; PIR: 339 and 352 nm—for the acidic and neutral pH, respectively. After the samples were taken, they were replaced with the same volume of prewarmed dissolution medium.

RESULTS AND DISCUSSION

Preparation of coevaporates

Tables 1 and 2 summarize the theoretical and actual composition of the prepared solid dispersions. Because of difficulty in collecting all the solid material from the flask after ethanol evaporation, the real amount of drugs determined in each coevaporate was between 75% and 98% of the added amount. For the same reason, production yields ranged between 60% and 100%. However, satisfactory reproducibility of results when repeating the preparations was observed.

Physicochemical characterization of solid dispersions

The physical state of the drugs in the polymer matrices was studied by classical spectroscopic techniques (FT-IR, PXRD, DSC). Physical mixtures with the same composition of coevaporates were tested as reference. In fact, previous observations indicated that most interactions between NSAIDs and Eudragit polymers occurred in solution and not after a simple grinding of the 2 components.

It must be noted that in all the coevaporates each drug was present at a concentration largely overcoming the possible number of "active binding sites" (ie, the ammonium groups) in the polymer networks. For instance, in the 1:5 drug-polymer systems, drug molecules are about 1200-fold more concentrated than in the polymer ammonium groups. Therefore, what has been observed both in the spectroscopic analyses and in the release/absorption studies must be related partially to drug molecules linked to the polymer backbone but mainly to drug molecules or crystals reprecipitated in the Eudragit matrices.

DIF-Eudragit spectroscopic investigation has been discussed in detail in a previous publication [16]. In general, DIF and FLU showed similar behavior, as indicated by spectroscopic data supporting drug-polymer interaction. Although these drugs belong to different chemical classes (salicylates and arylpropionic acid, respectively), they share many phys-

icochemical properties, including molecular weight (250.2 vs 244.27), pK_a (3.3 vs 4.27), logP (4.44 vs 4.16), and log water solubility (6.298 vs 5.414) (values given for DIF and FLU, respectively). Meanwhile, coevaporates loaded with PIR displayed results different from those of DIF and FLU, in terms of PIR interaction with the polymer. PIR has a very different chemical structure and physicochemical properties (eg, pK_a of 6.3, logP of 0.26, log water solubility of 8.451).

However, for all 3 drugs, data indicated that each drug remained in a crystalline form within the polymer network. The preparation conditions used to obtain the solid dispersions did not ultimately result in polymorphic changes or amorphization of drug molecules, their spectroscopic profiles being quite similar to the mere physical mixtures of the 2 components. The progressive disappearance of IR, x-ray, and thermotropic drug signals in coevaporates is more likely to be related to the increasing amount of the polymers, which exert a "diluting" effect on drug signals.

FLU and PIR displayed dissimilar IR spectroscopic behavior (spectra not reported), reflecting their different chemical nature. For FLU, the IR stretching band of the carboxyl group around 1790 cm^{-1} was still visible in the physical mixtures with either RL or RS, while it totally disappeared in the corresponding coevaporates; the latter samples only showed the ester C=O stretching peak of the polymers, around 1730-1735 cm^{-1}. However, the other characteristic peaks of drug molecule were observed in all the IR spectra, like C-F stretching around 1220 cm^{-1}, thus confirming that only the carboxyl group of FLU is involved in the interaction with the polymer reactive sites.

Further indications about the crystalline status of the drug in RS and RL matrices come from DSC and x-ray analyses. Findings of the calorimetric analysis are shown in Figure 1 for FLU/RL systems, the corresponding RS coevaporates showing a very similar behavior. DSC run of the pure drug exhibits a sharp endothermic peak around 115°C, corresponding to the melting point (Figure 1). The dispersion of FLU in the RS and, mainly, in the RL matrix, at both 1:2 and 1:5 weight ratios resulted in

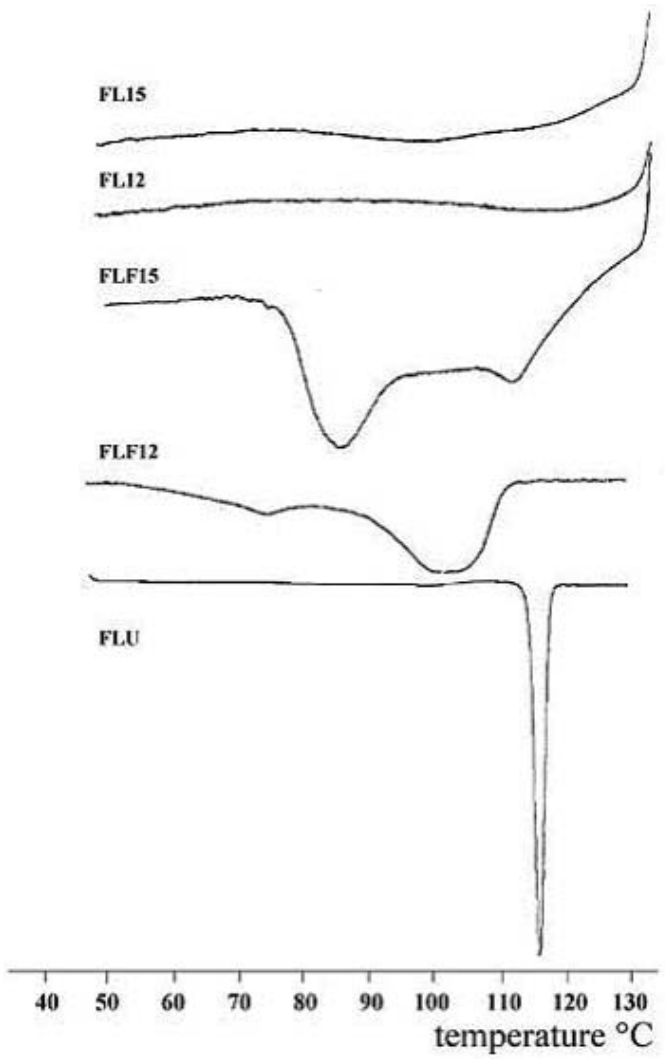

Figure 1. Comparison among DSC thermograms of pure FLU and FLU/RL physical mixtures (FLF) and coevaporates (FL).

a complete suppression of the drug fusion peak (Figure 1), suggesting a homogeneous dissolution of the drug in the polymer. However, the mere physical dispersion of the drug with RS or RL also resulted in a modification of the thermotropic profile (Figure 1). At the lower FLU-polymer ratio a download shift of the drug fusion peak occurred in 2 partially superimposed peaks (centered at 98°C and 106°C, respectively). At the 1:5 weight ratio, such signals were further depressed (FLF15) or even disappeared (FSF15, not shown), leaving a DSC run comparable to that of the corresponding coevaporate. The behavior of FLU in the physical mixture thus indicates that a dilution effect of drug microcrystals within the polymer network is mainly

responsible for the change observed in the calorimetric runs of coevaporates.

As Figure 2 shows, PXRD analysis of pure RS polymer is typical of amorphous materials, whereas the pure drug showed the diffractographic profile of a crystalline product. When the coevaporates prepared with different drug fractions are compared (FS12 and FS15, Figure 2), it is clear that the systems prepared with lower polymer amounts still showed the typical signals of drug crystals, while increasing the RS ratio progressively weakened their intensity. Under the experimental conditions used for the preparation of dispersions, FLU seems, then, able to crystallize in the polymer network when its concentration exceeds the solubility in the polymer itself. However, the crystallinity of the drug in the coevaporates is always less than that observed in the corresponding physical mixtures (cf FSF12 and FSF15, Figure 3). In particular, in both the FS12 and FS15 batches, the measured peak areas accounted for only a residual 10% crystallinity in respect to pure FLU, which is much lower than the amount of drug dispersed in these systems. The corresponding physical mixtures displayed a higher degree of crystallinity in their PXRD spectra, but always lower than the theoretical amount of dispersed drug. Therefore, FLU appears to undergo a microcrystallization in the RS matrix when the drug concentration overcomes its solubility in the polymer, whatever the conditions of their blending (cosolution or dry grinding). From a qualitative point of view, this result is somewhat similar to the one observed for the corresponding DIF-loaded systems [17].

In the FT-IR spectra of PIR/RS and PIR/RL systems (not shown), both coevaporates and physical mixtures showed the two distinct stretching bands of polymer ester C=O (1730-1735 cm^{-1}) and drug amide carbonyl (around 1630 cm^{-1}), along with the other signals typical of PIR [18]. Only signs of hydrogen bond formation were seen around 3400 cm^{-1}.

The absence of significant involvement of PIR functional groups with the 2 polymers was confirmed also by the DSC experiments. Data obtained for the PIR-RL systems are shown in Figure 3;

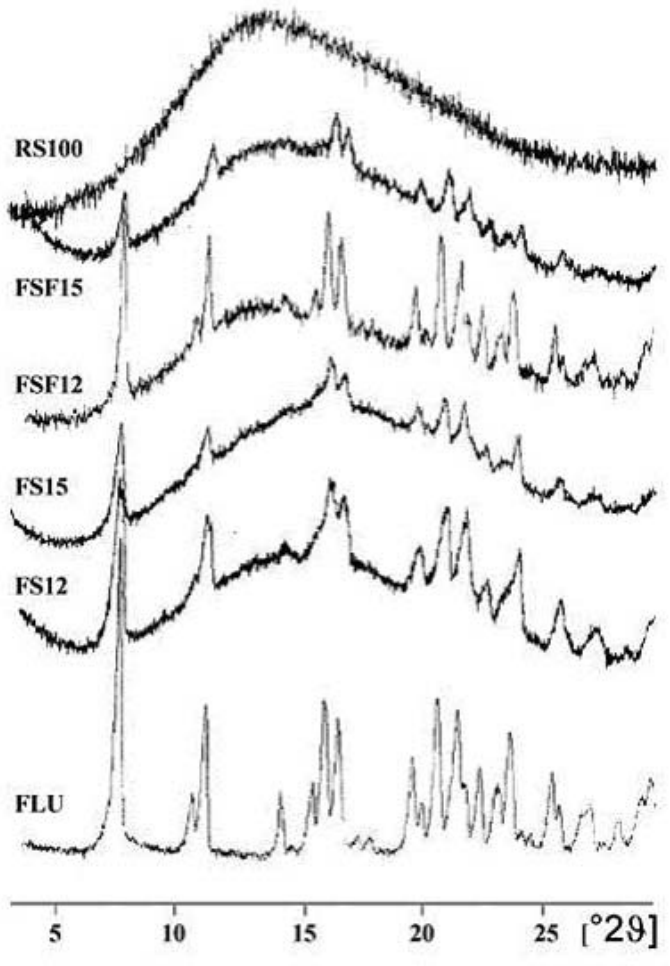

Figure 2. X-ray diffraction patterns of RS100 polymer, pure FLU, and FLU/RS physical mixtures (FSF) and coevaporates (FS).

however, gave similar results. Both PIR/RS and PIR/RL coevaporates, as well as their physical mixtures, had a similar trend, showing a shift of drug melting peak to a broader signal around 180°C, but still more visible than the one observed for FLU and DIF [16] in the same conditions. Once again, the drug-to-polymer ratio strongly accounted for the difference in the shape and intensity of peaks in the various coevaporates.

PXRD spectra of PIR-RS systems also suggested a different interaction between this drug and polymers with respect to the other 2 compounds. In fact, physical mixtures and solid dispersions, prepared with both RL (not shown) and RS (Figure 4) polymers, displayed similar x-ray profiles, with the main signals centered at an angle around 7.95, 14.34,

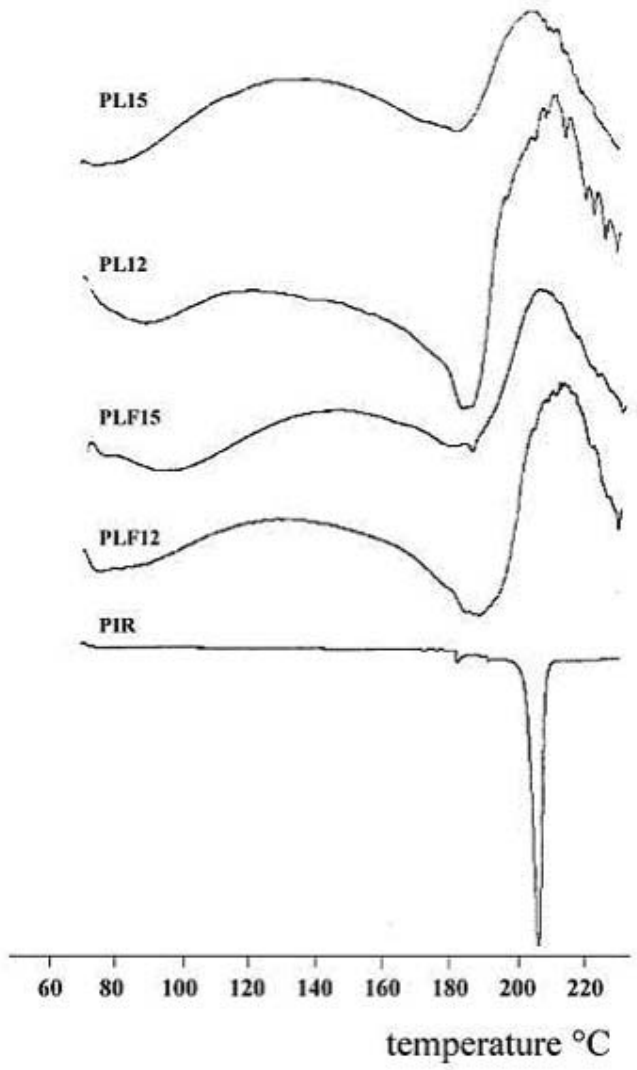

Figure 3. Comparison among DSC thermograms of pure PIR and PIR/RL physical mixtures (PLF) and coevaporates (PL).

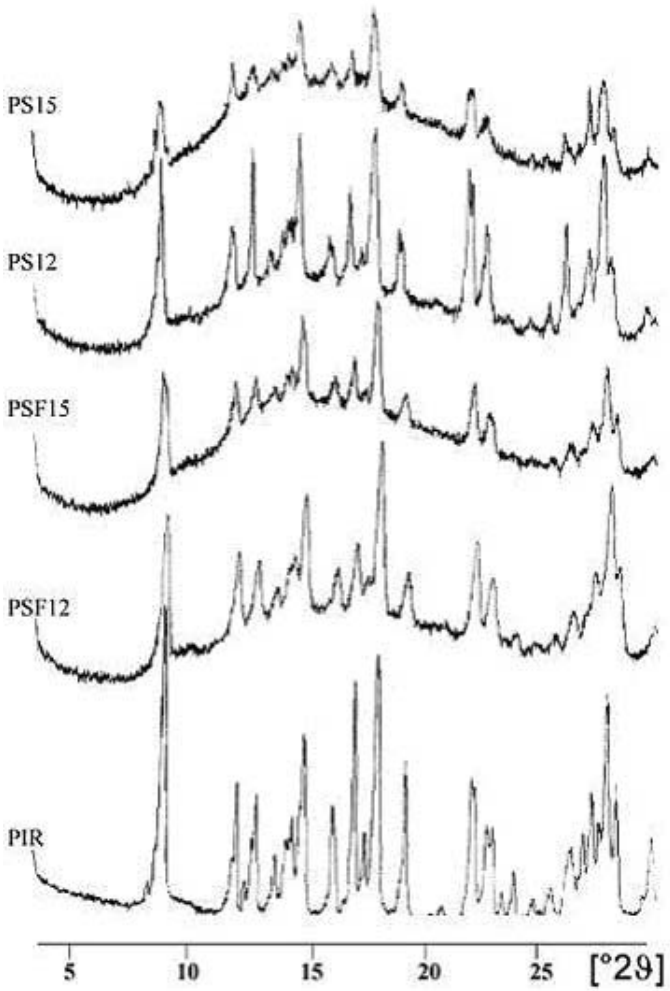

Figure 4. X-ray diffraction patterns of PIR and PIR/RS physical mixtures (PSF) and coevaporates (PS).

17.52, and 27.41 (°2θ). The residual crystallinity calculated from the peak areas versus a calibration curve obtained from increasing amounts of drug to polymers was also comparable for the coevaporates and the corresponding physical mixtures. PIR thereby exhibited a less significant physicochemical interaction with these polymers than DIF and FLU did.

Given all the above investigations, DIF and FLU seem to develop a similar interaction with RS and RL polymers' active sites, but different than that displayed by PIR. The different molecular structures of these agents can, obviously, support our findings. The presence of a carboxyl group more likely than other dissociable acidic ones (like the hydroxy-enolic group in PIR) could help explain the strong interaction with RS and RL polymers' quaternary ammonium centers.

Drug-polymer adsorption

To further evaluate the affinity between the tested molecules and polymers, sorption of drugs onto RS and RL crystals, according to an acid-base chemical classification, was evaluated quantitatively. The ability of Eudragit polymers to adsorb acid drugs from a solution was characterized at pH 7.4. The

ionized acid molecules carried an opposite (negative) charge to that of the ammonium groups linked to thepolymer backbone, allowing electrostatic binding to occur. This was possible because the pH of the dissolution medium was significantly higher than the pK_a of the drugs (about 3.3 for DIF and FLU carboxylic groups, 6.3 for PIR hydroxy-enolic group).

Drug-polymer absorption profiles from a pH 7.4 phosphate buffer are reported in Figures 5-7. RL had a greater absorptive capacity than RS (Figure 5), because of its greater number of quaternary ammonium functions, which act as the activity sites for the electrostatic interactions. The theoretical mechanism of such an interaction was further supported by the adsorption studies carried out in Tris-HCl buffer (pH 7.4), where the adsorption of drugs appeared to be reduced (Figures 5-7). In the last environment, buffer chloride ions compete with drug molecule anions for the active sites in the polymer backbone, thus resulting in a lower adsorption rate of the drugs [9].

As a confirmation of the above-discussed spectroscopic data, in all the adsorption tests PIR was adsorbed less than DIF and FLU. Its hydroxy-enolic group, being not completely dissociated at pH 7.4, reduced the affinity of PIR for these polymers.

Dissolution studies of solid dispersions in simulated gastroenteric environment

The dissolution profiles of active compounds from tablets obtained from pure drug powders or RS and RL coevaporates are plotted in Figures 8-10. The pure drugs displayed a similar behavior, typical of acidic molecules, with only a little amount of drugs dissolved in the external medium during the first 2 hours at pH 1.2. After the pH change to 6.8, the curves showed an almost instantaneous and complete dissolution of the drugs.

The dispersion of the drugs in the polymer matrices strongly influenced their dissolution rate, which appeared slower and more gradual than that of the pure drugs, while increasing the polymer ratios. RL coevaporates usually displayed higher dissolution

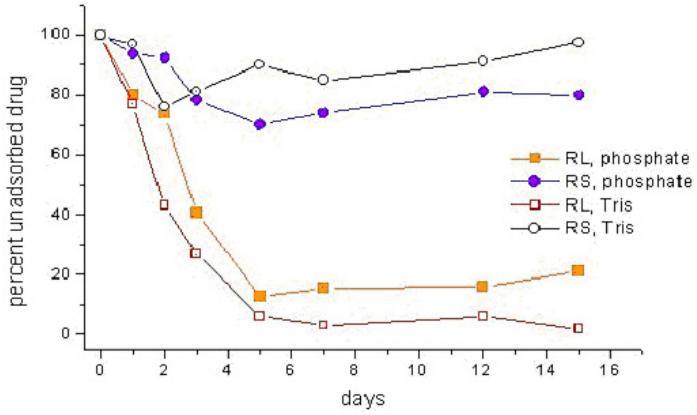

Figure 5. Absorption pattern of DIF from a pH 7.4 phosphate buffer or Tris buffer onto RS and RL particles.

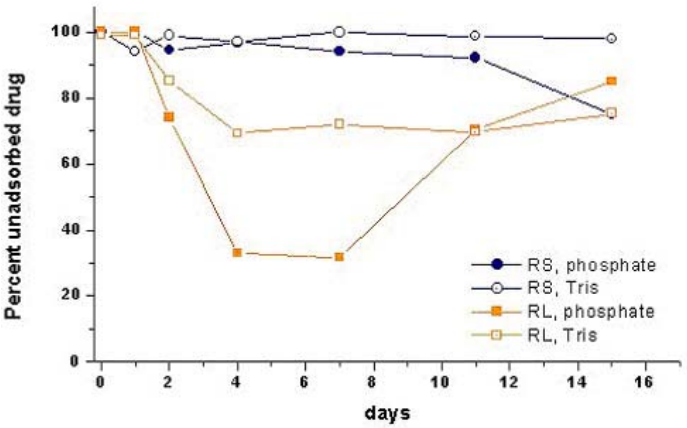

Figure 6. Absorption pattern of FLU from a pH 7.4 phosphate buffer or Tris onto RS and RL particles.

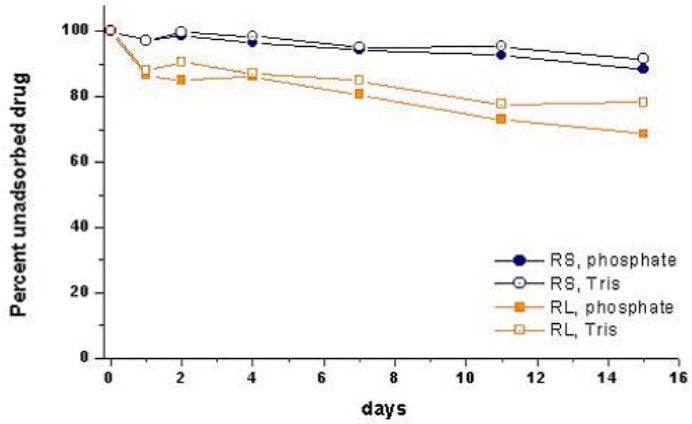

Figure 7. Absorption pattern of PIR from a pH 7.4 phosphate buffer or Tris buffer onto RS and RL particles.

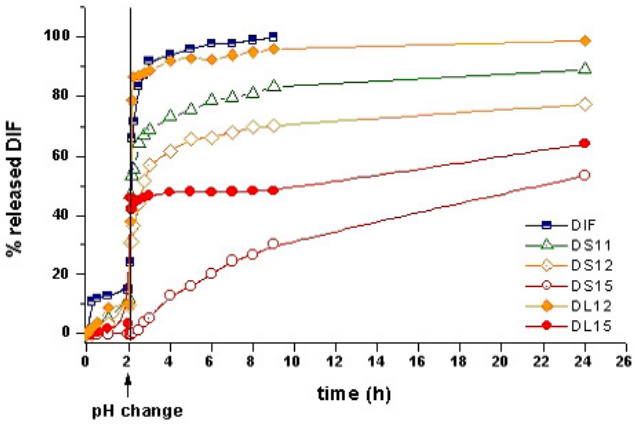

Figure 8. In vitro dissolution pattern of DIF from RS and RL coevaporates in simulated gastroenteric environment (pH 1.2-6.8).

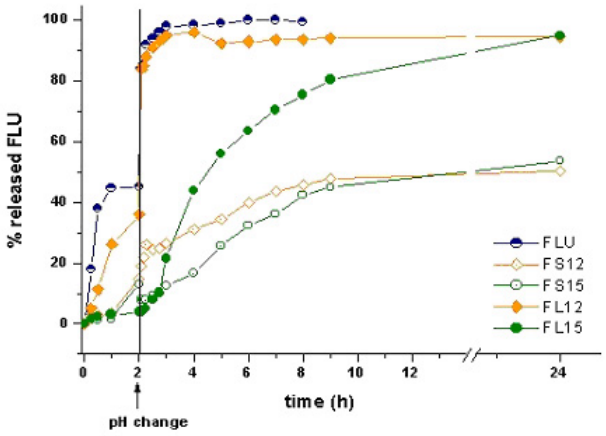

Figure 9. In vitro dissolution pattern of FLU from RS and RL coevaporates in simulated gastroenteric environment (pH 1.2-6.8).

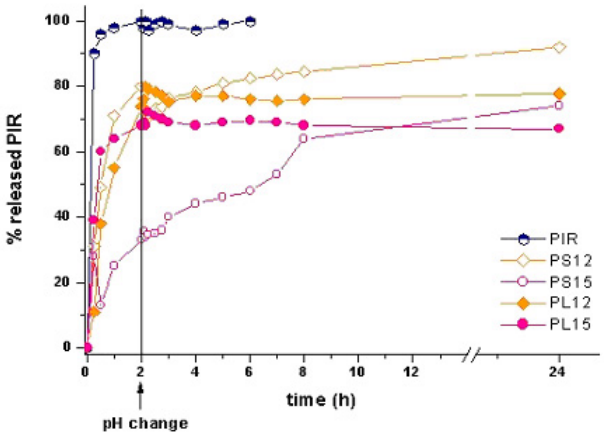

Figure 10. In vitro dissolution pattern of PIR from RS and RL coevaporates in simulated gastroenteric environment (pH 1.2-6.8).

rates than RS coevaporates, because of the greater quaternary ammonium group content in the 2 materials. RS polymer is only slightly permeable to water; hence, drug release is relatively retarded with respect to the freely permeable RL. Increasing the drug-to-polymer ratio (from 1:2 to 1:5) dramatically slowed the release time (see t_{50} values) and the amount of dissolved drugs (Tables 3 and 4). The presence of the polymer, mainly RS, also reduces the massive initial drug dissolution observed immediately after the pH change for pure drug powders.

The significant dissolution observed for most coevaporates containing PIR at pH 1.2 (Figure 10) can be related to the fact that this drug possesses a basic group that becomes protonated at the acid pH and makes the drug readily soluble. However, the RS system at the lower drug-to-polymer ratio (PS15, Figure 10) was able to slow down the diffusion rate of the drug, making it almost independent from the pH value of the external medium.

After 24 hours of dissolution, none of the coevaporates (except for DL12 and FL12) apparently allowed a complete release of the drug into the dissolution medium; they released only 60% to 90% of the initial drug amount in the system (Figures 8-10 and Tables 3 and 4). Such a behavior, which was expected, is due to the fact that the dissolved drug, becoming ionized in the neutral dissolution medium, is readsorbed back onto the polymer particles because of the presence of opposite electrical charges [11, 14]. The phenomenon was proportionally related to the amount of polymer present in each solid dispersion. Thus, the plateau shown by most of the dissolution profiles in Figures 8-10 is related to an equilibrium among the drug release from the coevaporate, its ionization in the dissolution medium, and the saturation of the binding sites on the surface of polymer particles.

The kinetic analysis of the dissolution curves, in agreement with what was previously observed with Tolmetin-RS and -RL systems [17], gave a better fit for the Fickian and dissolutive equations, whereas the first-order and cube-root of time (Hixson-Crowell) analysis fitted more poorly with the experimental data (data not shown). Thus, the various interactions occurring between drugs and polymers

Table 3. Kinetic Data Relative to the In Vitro Dissolution Tests of Eudragit RS100 Coevaporates

System	t_{50} (h)	% Max Dissolved Drug (Plateau)	$t_{plateau}$ (h)	$AUC_{0\rightarrow24h}$ (% x h)
DS11	2.1	89.0	9	1831.1
DS12	2.7	77.6	9	1502.9
DS15	23.7	53.3	9	602.2
FS12	5.9	71.1	24	946.7
FS15	23.5	76.5	24	453.2
PS12	3.4	72.7	48	1543.0
PS15	25.9	63.4	48	754.2

Table 4. Kinetic Data Relative to the In Vitro Dissolution Tests of Eudragit RL100 Coevaporates

System	t_{50} (h)	% Max Dissolved Drug (Plateau)	$t_{plateau}$ (h)	$AUC_{0\rightarrow24h}$ (% x h)
DL12	2.1	99.5	2.6	2038.8
DL15	11.2	68.1	24	1177.3
FL12	2.0	90.2	2.2	2122.6
FL15	4.5	94.0	24	1689.2
PL12	0.2	77.3	3	786.3
PL15	0.8	70.1	3	780.5

led to a complex mechanism of drug release, in which both the drug solubility in the external medium and its diffusion capacity within the polymer network played an important role.

CONCLUSIONS

RS and RL have been often used to obtain controlled drug delivery systems. However, a specific investigation of the possible interactions between these polymers, which contain a low content of ammonium groups, and acidic drugs, like NSAIDs, can be helpful in better understanding their influence on drug incorporation and release, and therefore on drug pharmacological activity itself.

Characterization in the solid state of solid dispersions of RS and RL polymers with 3 different NSAIDs was carried out in order to predict and explain the incorporation and release behavior of these drugs from delivery systems (eg, microparticles) that can be prepared with such polymers for therapeutic purposes. Analytical results indicated that the drug remains in a crystalline form within the polymer network under the preparation conditions employed.

Because of their acidic nature, beside of a mechanical dispersion the tested drugs displayed to interact with Eudragit matrixesby virtue of electrostatic interactions with the ammonium groups present in the polymer backbone. These interactions are stronger for drugs bearing a carboxylic moiety, thus having lower pK_a values, and significantly affect the drug release profile from coevaporates.

Drug leakage can be then modulated on the basis of specific therapeutic needs (ie, a rapid or a sustained-prolonged drug release). In particular, low drug-to-polymer ratios did not appear suitable for preparing useful delivery systems for these drugs, since the strong interactions between them did not allow a significant release of the drug in either neutral or midalkaline dissolution media.

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