Research Article

REPARATION OF SOLID DISPERSIONS OF NSAIDS AND ITS MECHANISM OF DRUG POLYMERS INTERACTION

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ABSTRACT:
This work studied the mechanisms of interaction between Eudragit RSPO and RLPO 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 method. 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. The preparative conditions did not induce changes in the crystalline state of the drugs (Amorphization or polymorphic change). RLPO & RSPO coevaporate usually displayed higher dissolution rates. However, the kinetic evaluation of the dissolution profile suggested that both the drug solubility in the external medium and its diffusion capacity within the polymer network are involved. In the sorption experiments, RLPO showed a greater adsorptive capacity than RSPO, 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. DIF and FLU displayed a similar interaction with RSPO and RLPO active sites. PIR's was different .The different molecular structures of these agents can justify such things. 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 RSPO and RLPO 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.

INTRODUCTION:

Eudragit RSPO and RLPO are copolymers of acrylic and methacrylic acid esters that contain a low level of quaternary ammonium groups.RSPO has a lower content of charged groups, thus displaying less water permeability and swellability in comparison with RLPO.

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 (e.g., Micro and Nano-particulate Systems)[1-3].Flurbiprofen-RSPO and -RLPO systems have been proposed, for instance, as films for transdermal delivery[4] & 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 Particularly, the incorporation & release of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) from RSPO & RLPO polymers was shown to

be strongly dependent on the acidic nature of these drugs, which allows chemical interactions, physical interactions, or both to occur (zwitter Ionic adducts, ion pairs, ion exchange resin behavior) with the ammonium group on the RSPO & RLPO backbone.[11,13-15].

Solid dispersions between Diflunisal (DIF) & RSPO or RLPO polymers have been previously described & 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 RSPO & RLPO polymers with DIF or 2 other NSAIDs: Flurbiprofen (FLU) & Piroxicam (PIR).

Solid dispersions of drugs and polymers at different weight ratios were obtained by evaporation of their Ethanol co-solutions. The co-evaporates 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), & Powder X-Ray Diffractometry (PXRD).

To investigate the strength of the interactions occurring between these drugs and RSPO or RLPO 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 co- evaporates.

MATERIALS AND METHODS:

[A] Materials

RS and RL polymers were kindly donated by Röfarma (Gaggiano, Italy). Drugs and Avicel PH-102 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.

[B] Preparation of Drug / Eudragit Solid Dispersions

Drug-polymer coevaporates were prepared by the solvent method.

Drug and polymer (RSPO or RLPO) —-→ Weighed—-→ Dissolved in 50ml Absolute Ethanol—→ Stirring for 4-6 Hrs —-→Removal of Solvent—-→Pulverization of Solid Residue—-→ Triturating to prepare Solid Dispersion

[C] Determination of drug content

Dissolving co evaporates in 5 ml UV grade Methanol

RESULTS :

UV Spectrophotometer Absorbance = DIF (254 nm), FLU (252 nm) & PIR (253 nm).

Results are expressed both as the drug content (mg incorporated drug) and percent incorporation (actual amount of drug in co-evaporates vs the initially added amount).

[D] Preparation of the physical mixtures

For the 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.

Preparation of Co-evaporates

[E] FT-IR spectroscopy

IR spectra of pure drugs & polymers, & of coevaporates and physical mixtures were obtained with spectrophotometer. The scanning range used was 4000 to 500 cm–1 at a scan period of 1 minute.

[F] DSC (Differential Scanning Calorimetry)

Thermal analysis—-→ Differential Scanning calorimeter

The instrument was calibrated with an indium standard.

Temperature Range : 25 to 240°C DIF
25 to 130°C FLU, &
25 to 230°C PIR

[G] X-ray Powder Diffractometry

Diffraction patterns of DIF/ RSPO and FLU/ RSPO systems were recorded. A voltage of 40 kV and a current of 30 mA for the generator were used, with Cu as the tube anode material

[H] Drug-to-polymer adsorption experiments

Drug dissolved in 50 ml pH 7.4 phosphate buffer (0.11M).

UV Absorbance : 252 nm - DIF
247 nm – FLU
& 352 nm – PIR.

[I] In vitro drug dissolution studies in Gastro-enteric environment

Drug dissolution experiments-→ 300-mg tablets :

composition (in weight):

- Co-evaporate: 30% to 50%
- Lactose (Diluent): 20% to 35%
- Avicel PH 102 (disgregant): 30% to 34%
- Magnesium stearate (Lubricant): 1%

DIF: 228 and 252 nm; FLU: 246 and 247 nm; PIR: 339 and 352 nm—for the acidic and neutral pH, respectively.

RESULT AND DISCUSSION:

Tables 1 and 2 summarize the theoretical and actual composition of the prepared solid dispersions. Be-cause of difficulty in collecting all the solid material from the flask after ethanol evaporation, the real amount of drugs determined in each coevaporates 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.

Table 1. Properties of Eudragit RSPO Coevaporates

System In	Drug/RSPO Ratio (wt/wt)	Loading Efficiency (m.g.)		Incorporation	Production Yield (%)
		Theoritical Drug Content	Percent Actual Drug content		
DS11	1:1	50	43	86.0	90
DS12	1:2	33	27	81.8	93
DS14	1:4	20	18	90.0	87.5
FS12	1:2	33	25	75.7	64
FS14	1:4	20	17	85.0	76
PS12	1:2	33	25	75.7	58
PS14	1:4	20	16	80.0	73

Table 2. Properties of Eudragit RLPO Coevaporates

System	Drug/RLPO Ratio (wt/wt)	Loading Efficiency (m.g.)		Percent Incorporation	Production Yield (%)
		Theoritical Drug Content	Actual Drug content		
DL12	1:2	33	28	84.8	86
DL14	1:4	20	18	90.0	66
FL12	1:2	33	29	87.9	93
FL14	1:4	20	17	85.0	70
PL12	1:2	33	27	81.8	72
PL14	1:4	20	16	81.2	69

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

System	t50 (h)	% max Dissolved Drug (Plateau)	tplateau(h)	AUC0-24h (% x h)
DS11	2.1	89.0	9	1830.8
DS12	2.7	77.4	9	1501.9
DS14	23.2	53.1	9	602.4
FS12	5.9	71.0	24	946.3
FS14	23.7	76.3	24	452.8
PS12	3.4	72.7	48	1543.0
PS14	25.4	63.2	48	754.4

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

System	t50 (h)	% max Dissolved Drug (Plateau)	tplateau(h)	AUC0-24h (% x h)
DL12	2.2	99.4	2.6	2038.3
DL14	11.3	68.3	24	1177.1
FL12	2.0	90.2	2.2	2122.6
FL14	4.3	93.0	24	1688.7
PL12	0.2	77.3	3	786.3
PL14	0.8	70.1	3	780.5

Fig 1Comparison among DSC thermograms of pure FLU and FLURL physical mixtures (FLF) and coevaporates (FL)

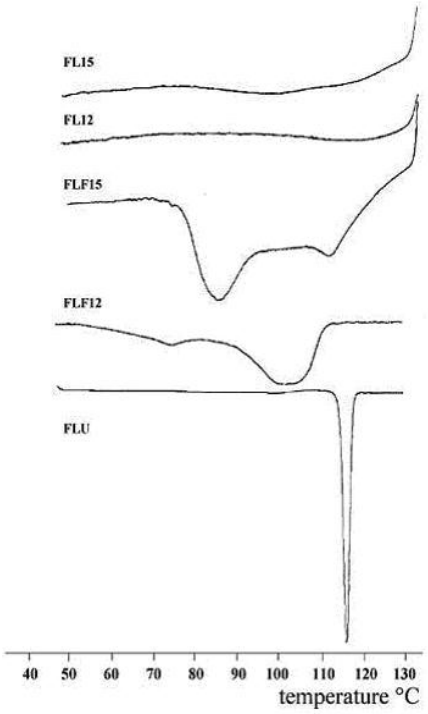


Fig 3Comparison among DSC thermograms of pure PIR and PIRRL physical mixtures (PLF) and coevaporates (PL)

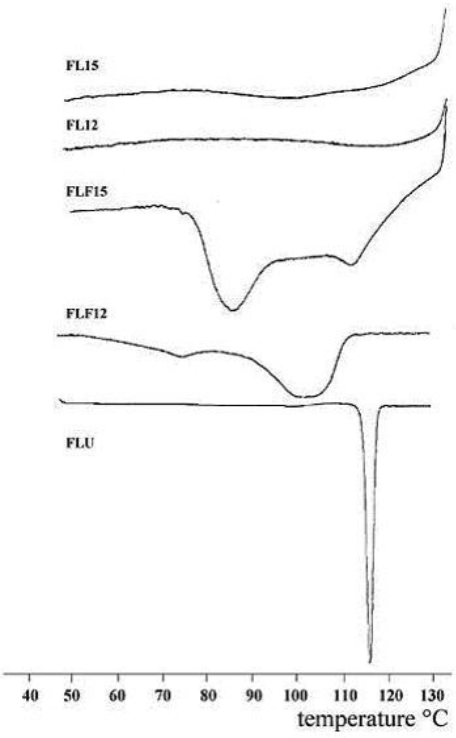


Figure 2. X-ray diffraction patterns of RS100 polymer, pure FLU, and FLURS physical mixtures (FSF) and coevaporates (FS).

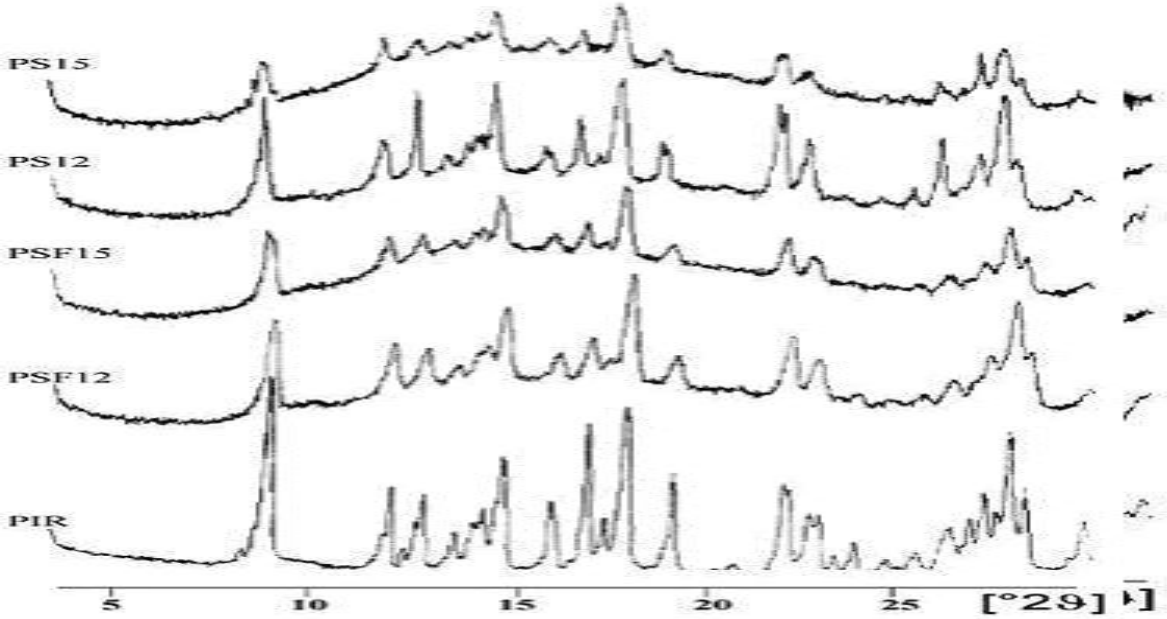


Fig 4X-ray diffraction patterns of PIR and PIRRS physical mixtures (PSF) and coevaporates (PS).

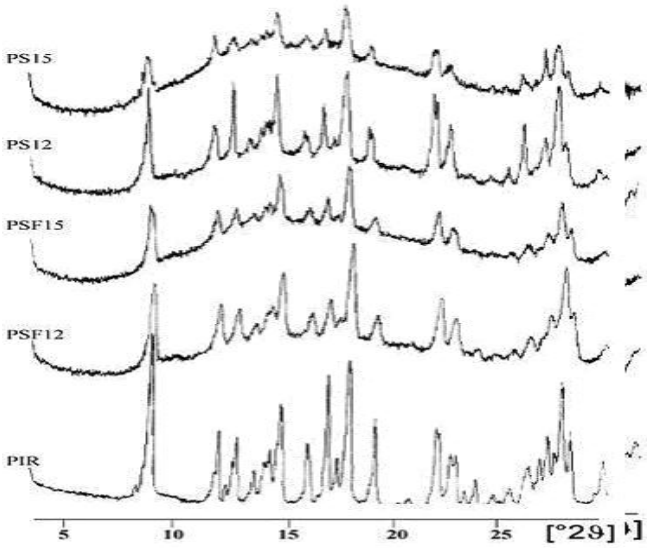


Fig 5 Absorption pattern of DIF from a ph 7.4 phosphate buffer or Tris buffer onto RS and RL particles.

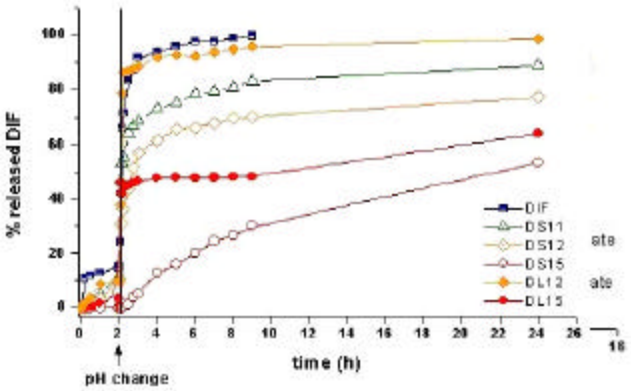


Fig 6 Absorption pattern of FLU from a ph 7.4 phosphate buffer or Tris onto RS and RL particles.

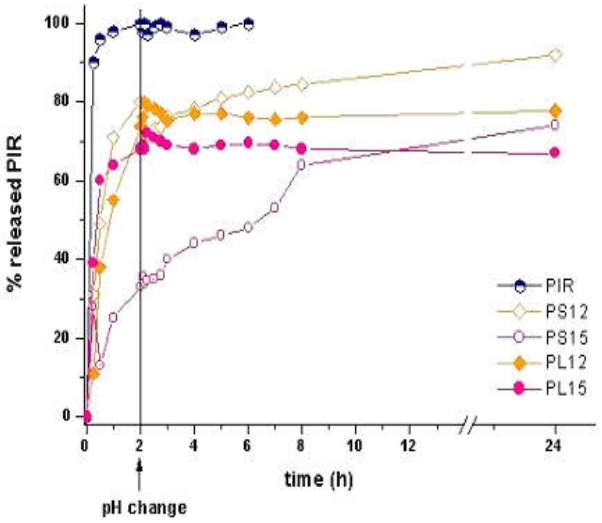


Fig 7 Absorption pattern of PIR from a ph 7.4 phosphate buffer or Tris buffer onto RS and RL particles.

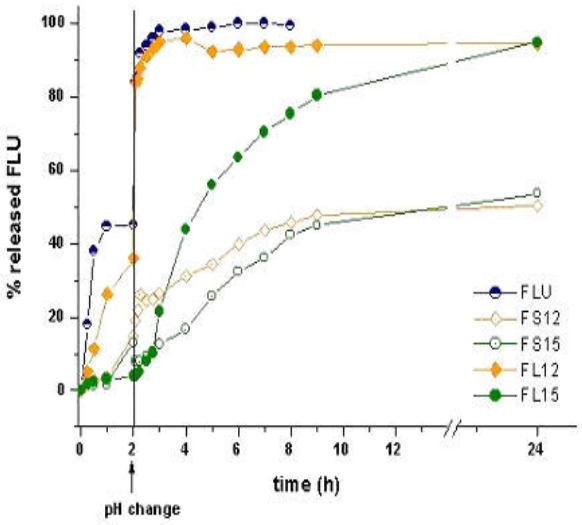


Fig 8 In vitro dissolution pattern of DIF from RS and RL coevaporates in simulated gastroenteric environment (ph 1.2- 6.8

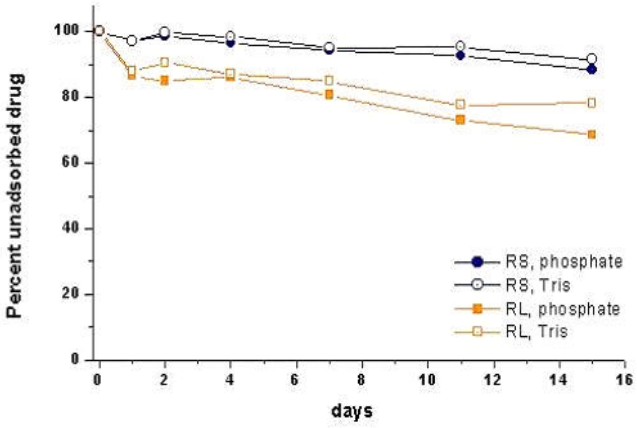


Fig 9 In vitro dissolution pattern of FLU from RS and RL coevaporates in simulated gastroenteric environment (ph 1.2-6.8).

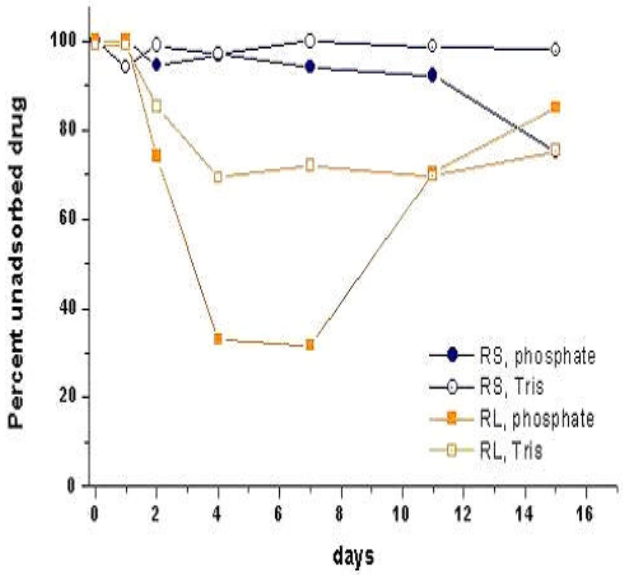
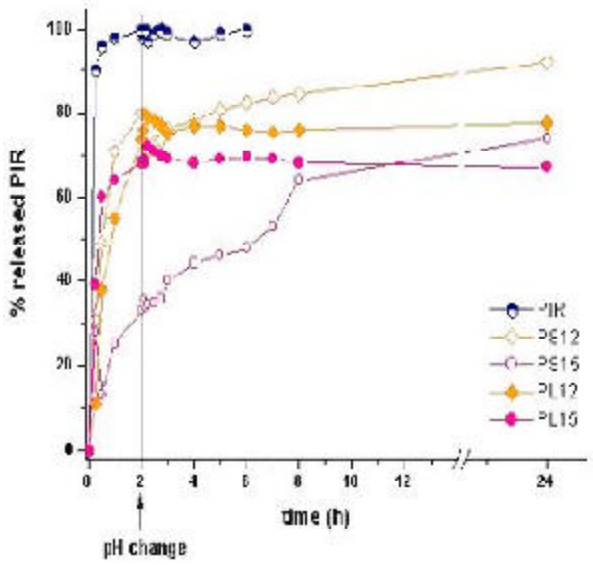


Fig 10 In vitro dissolution pattern of PIR from RS and RL coevaporates in simulated gastroenteric environment (ph 1.2-6.8).



CONCLUSIONS:

RSPO and RLPO 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 there-fore on drug pharmacological activity itself.

Characterization in the solid state of solid dispersions of RSPO and RLPO polymers with 3 different NSAIDs was carried out in order to predict and ex-plain 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 matrixes by 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.

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