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Preparation and characterization of Furosemide-Eudragit controlled release systems

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Abstract

Solid dispersions and physical mixtures were prepared and characterized by X-ray diffraction, infrared spectroscopy, electronic microscopy and dissolution rate studies. The characterization with X-ray diffraction showed a transition from the crystalline to the amorphous phase. A new phase near 50% Furosemide concentration with both types of carriers was present. From infrared spectroscopy strong interactions between amine and carbonyl groups from both the Furosemide and the polymers were found. Electronic microscopy analysis showed that the Furosemide changed its crystalline habit from needle to a new spherical phase, with diameter near to 1 μm. Solid dispersions were prepared in order to modify the system characteristics. The Furosemide dissolution rate was determined in order to follow the behavioural changes of the system. Scanning electron microscopy showed the presence of micro spheres within the polymeric matrix, and the channels formed due to the Furosemide dissolution inside the Eudragit: this fact modified the release pattern of the Furosemide system.

Keywords: Furosemide solid dispersions; Infrared spectroscopy; X-ray diffraction patterns; Crystals; Dissolution rate; Eudragit

1. Introduction

Cardiovascular and heart failure are among the most common diseases in modern times. Several drugs have been used to control these diseases. In the last few years controlled release systems have become increasingly important, because these systems can maintain the pharmacological effect for an appropriate extended time.

Controlled release therapeutic systems present some advantages over traditional pharmaceutical preparations due to the fact less active drug is necessary for similar results and consequently less secondary effects are present. In this way the drug is more efficiently used.

There are different ways to modify the drug solubility such as crystal modifications, drug solubility modifications, quelation induced products, prodrug or probiotic use, etc. (Robinson and Lee, 1987).

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It is possible to design systems with continuous and uniform delivery of the drug. The ways to produce controlled release include micro-encapsulation, film coating, polymeric matrixes and solid dispersions. The use of solid dispersions is an alternative frequently employed in modifying drug solubility. The term solid dispersion was initially used by Sekiguchi and Obi (Sekiguchi and Obi, 1961) and is applied to systems in which the drugs are homogeneously dispersed within a carrier. The methodology to make solid dispersions includes co-fusion, co-dissolution in a proper solvent or a mix of both (Majerson and Gibaldi, 1966; Doherty and York, 1969; Bloch and Speicer, 1971; Chiou and Riegelman, 1971; Rubinstein, 1987; Ashimada, 1988; Sushama and Lloyd, 1989; Ansel and Popovich, 1990; Serajuddin Abu, 1990; Hiroshi, 1991).

The use of hydrophobic carriers in controlled release includes polymers such as ethyl cellulose, cellulose acetate phthalate, waxes and methacrylic acid copolymers.

Furosemide 5-(aminosulfonyl)-4-chloro-2-[(furanylmethyl)amino]benzoic acid is a diuretic and antihypertensive drug, practically insoluble in water. The purpose of the present paper is to describe the preparation of and characterize solid dispersions of Furosemide with Eudragit RL and RS, achieving controlled dissolution profiles with different carrier concentrations.

The goal was to change the Furosemide crystallographic habit by obtaining a modification in the dissolution pattern and a controlled release of the drug from a matrix system. Due to the fact that in oral administration the Furosemide therapeutic effect is very fast and intense, we tried to decrease and control that effect by making solid dispersions.

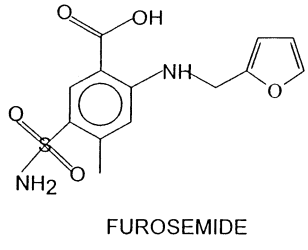
Table 1
Final volume and Furosemide composition of different samples

Composition (% Furosemide)	Final volume (ml)	Solvent evaporation time (days)
100	90.9	2.0
90	83.5	1.7
80	76.1	1.0
70	68.6	1.0
60	61.2	1.0
50	53.8	1.0
40	46.4	1.0
30	38.9	1.0
20	31.5	1.0
10	24.1	1.0
0	16.7	1.0

Table 2
Angles of Furosemide and solid dispersion peaks

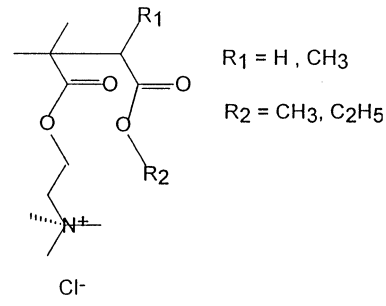
Furosemide	New peaks
24.8	18.7
22.9	22.0
21.3	20.0[a]
18.9	
18.1	

[a] This peak disappears at concentrations above 50%.



FUROSEMIDE

Fig. 1. Furosemide and Eudragit molecules scheme, part 1.



Monomer of Eudragit RL or RS

Fig. 2. Furosemide and Eudragit molecules scheme, part 2.

2. Materials and methods

2.1. Materials

Furosemide was purchased from Hoechst, and used after re-crystallization in hot methanol and allowed to stand at room temperature (slow re-crystallization). The methanol and the carriers, Eudragit RL and RS, were analytical reagent grade.

2.1.1. Preparation of solid dispersions

A random block model was employed for preparing solid dispersions. Methanolic solutions of the Furosemide (22 g/l) and carriers (12 g/l; Eudragit RL or Eudragit RS) were used to prepare the dispersions in order to obtain similar drug batches (Table 1). The lot size was 2 g and the crystal size of carrier was between 60 and 80 mesh. Finally, the solvent was allowed to evapo-

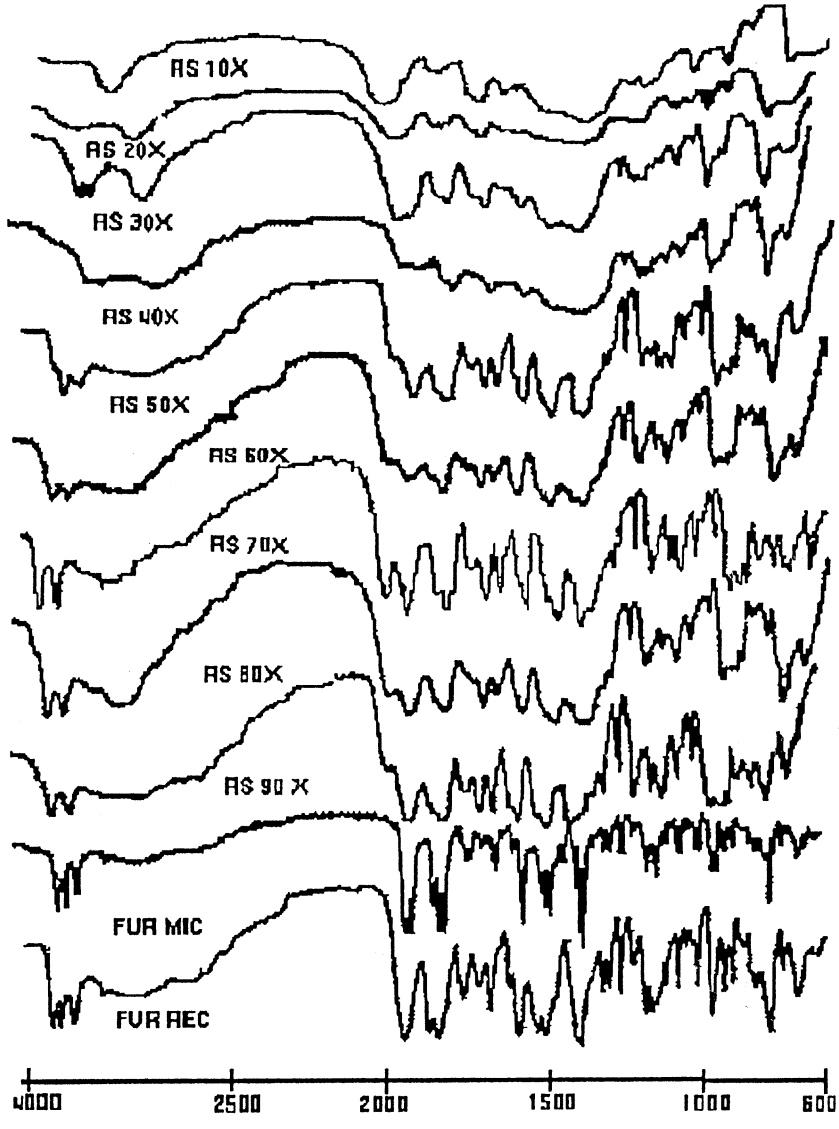


Fig. 3. Infrared spectra of Furosemide-Eudragit RS solid dispersions at different concentrations and micronised and re-crystallized Furosemide.

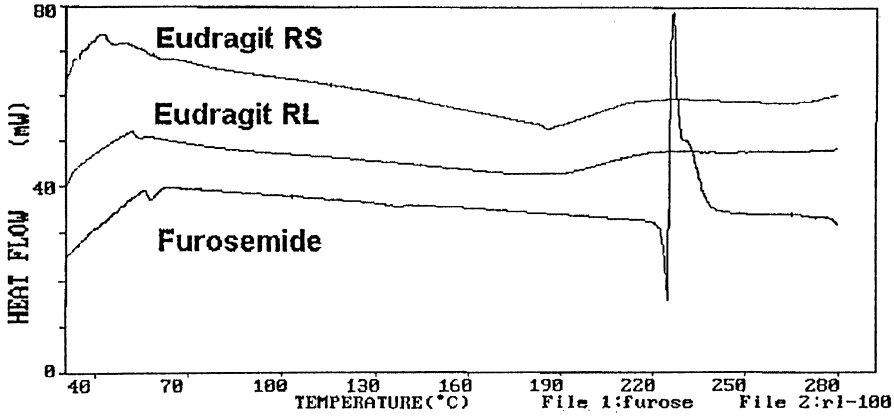


Fig. 4. Thermal behavior of Furosemide, Eudragit RL and RS.

rate at room temperature without stirring. For the dissolution kinetic study 80, 70, 60 and 40% (w/w) mixtures were used. As a control system physical mixtures with the same concentrations were prepared by mixing for 10 min.

An X-ray diffractometer, model Kristalloflex D5000 (Siemens) was used in the range 2.5–50° of 2θ. The working conditions were: Cu Kα radiation, 30 kV and 20 mA, at a 0.1°/seg rate and collimators 2,2,2,0.6.

Tablets for IR analysis were made with KBr and analyzed with an IR Perkin Elmer model 1330, in the range from 4000 to 600 cm^{-1}.

Samples weighing between 2 and 3 mg in sealed pans with heating rate of 20°C/min in the range 30–290°C for the thermal analysis were employed with a DSC-7 Perkin Elmer Thermal Analyzer.

2.1.2. Optical microscopy

A Zeiss microscope with photographic camera attached was used with the samples at 16, 40 and 100 ×.

For the scanning microscopy study an electronic microscope, Jeol JMS 25 SII, was used.

2.1.3. Matrix preparation

Solid dispersions and physical mixtures were milled and solid particles between 60 and 80 mesh were separated and 150-mg samples were compressed at 5000 psi. Tablets with 6-mm diameter were obtained for the dissolution studies.

2.1.4. Furosemide dissolution rate

One face of the tablets was used for the dissolution test (Wood's modify device) in NaOH 0.02 N solution at 37°C and 50 rpm. The tests were conducted three times in a random sequence model in order to obtain the dissolution rates for the different systems

3. Results

The micronised and re-crystallized Furosemide diffraction patterns clearly show the crystalline character of both materials given by different

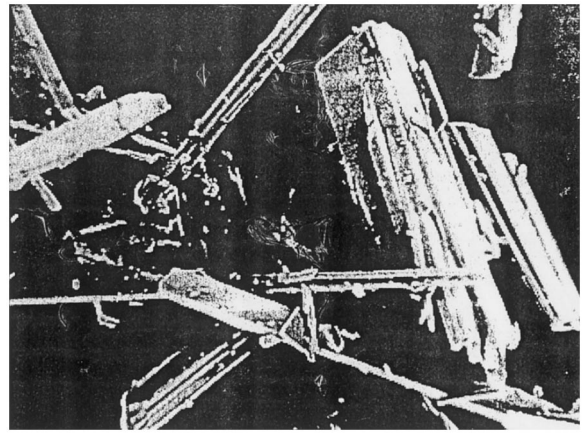


Fig. 5. Scanning electronic micrograph of Furosemide needle crystals (200 ×).

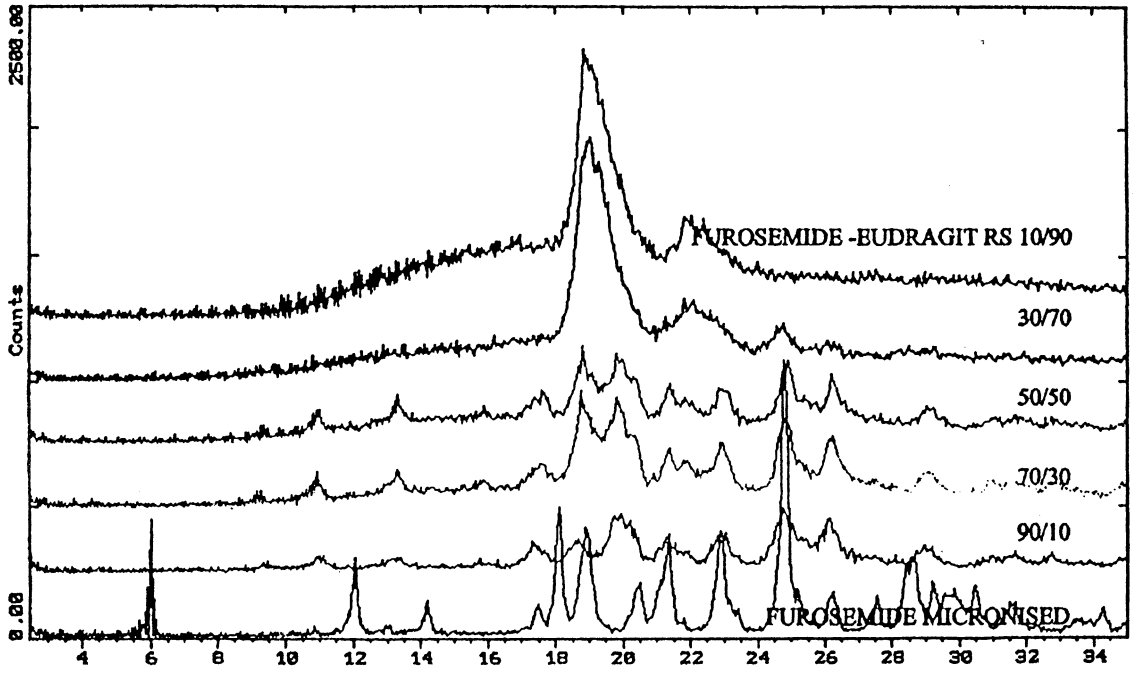


Fig. 6. X-ray diffraction patterns of micronised Furosemide and Furosemide-Eudragit system at different concentrations.

peaks at fixed angles. On the other hand, the Eudragit carrier showed an amorphous character as observed by the lack of defined peaks in the X-ray patterns. Electronic microscopy confirmed the crystalline character of Furosemide and the amorphous character of the carriers.

The Furosemide diffraction peaks obtained are similar to form I of previous reports (Matsuda and Tatsumi, 1990). Form I presented three main peaks at 24.8, 21.3 and 22.9° of 2θ values with 100, 46 and 40% of intensity, respectively.

In Table 2 the résumé of the modification of the peaks is presented. From the Furosemide-Eudragit RL or RS physical mixtures, no significant crystalline differences could be detected between them from the diffraction patterns.

Furosemide and Eudragit molecules are presented in Figs. 1 and 2. It is worth observing the amine and carbonyl groups that are probably interacting physically which is the cause of the change in the crystalline habit of the system studied.

From IR spectroscopy, some changes in the spectrum could be observed, as shown in Fig. 3, when the concentration of carrier was increased; the disappearance of the amine group signal (3400 cm^{-1}) and the translation of the signal from the carbonyl group (1900 cm^{-1}) were observed.

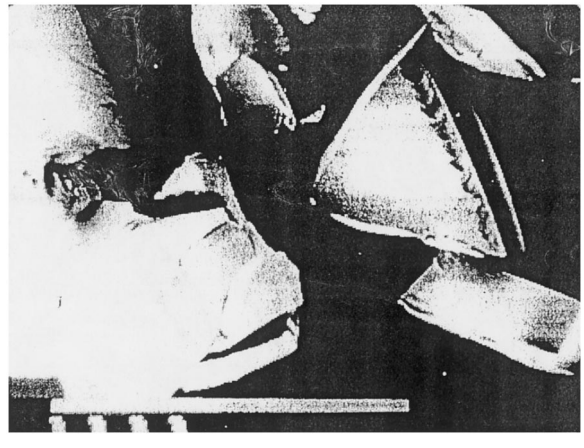


Fig. 7. Scanning electronic micrograph of amorphous Eudragit RL 45X.

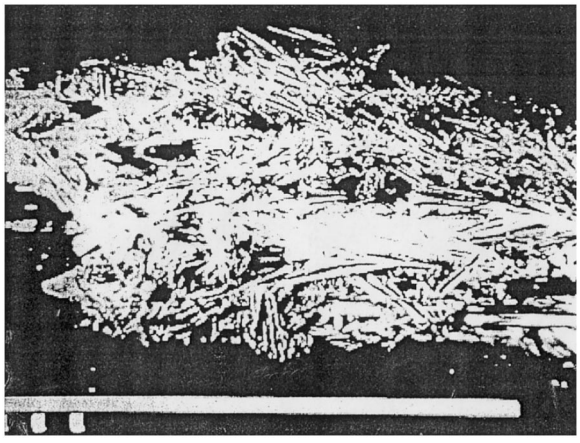


Fig. 8. Scanning electronic micrograph of Furosemide-Eudragit RS solid dispersions at medium concentration of carrier (40%) (700 ×).

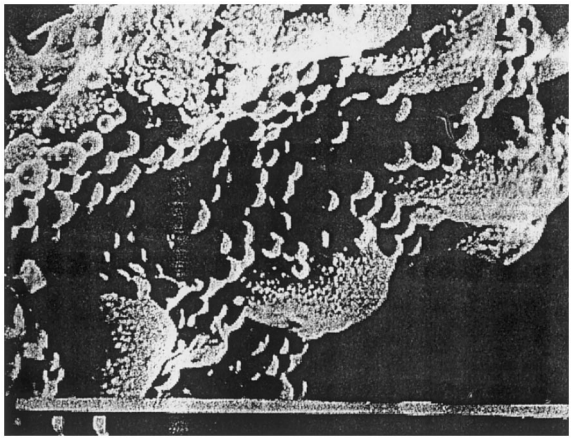


Fig. 9. Scanning electronic micrograph of Furosemide-Eudragit RS solid dispersions at higher concentration of carrier (70%) (700 ×).

4. Discussion

DSC results showed that Furosemide melted with decomposition at 217°C; however, the acrylic resin Eudragit carriers do not present any thermal transition in the experimental conditions, as can be observed in Fig. 4. So, these facts confirm that Furosemide presented a needle crystallographic habit as shown in Fig. 5. The crystalline character of the Furosemide and the amorphous habit of the carriers were determined by X-ray diffraction patterns presented in Fig. 6.

The X-ray diffraction patterns of micronised and re-crystallized Furosemide, Eudragit RL and Eudragit RS are shown in Fig. 6. The micronised and re-crystallized Furosemide diffraction patterns show clearly the crystalline character of both materials given by different peaks at fixed angles. On the other hand, the Eudragit carrier shows an amorphous character as observed by the lack of defined peaks in the X-ray patterns. Electronic microscopy confirmed the crystalline character of Furosemide and the amorphous character of the carriers.

X-ray diffraction patterns showed that original Furosemide was crystalline as can be observed from Fig. 5, but on the other hand Eudragit RL and RS were amorphous. These changes probably are caused by the chemical groups interactions between the Furosemide and carrier molecules; this fact could be better explained by observing the diffraction patterns. In the range studied some Furosemide disappeared and new peaks were formed. Thus a new phase is possible, since the new peaks do not fit to the original peaks of Furosemide or to those of carriers.

Electronic microscopy micrographs and X-ray diffraction patterns showed that the Furosemide crystalline habit changed to a new spherical phase and this type of solid was found with a diameter near to 1 μm, as shown in Fig. 7. The number of spherical particles increased as the Eudragit concentration was increased. Besides, at the lower concentration of Eudragit, Furosemide needle crystals were still observed, however, at higher Eudragit concentration the Furosemide needle crystals were not present (Figs. 8 and 9)

The modifications in IR spectra probably originated due to the following facts. The Furosemide amine group had a strong interaction with the carrier carbonyl group. Also the Furosemide carbonyl group had an interaction with the carrier amine group forming hydrogen bonds that modified the original Furosemide or the carrier IR spectra. These interactions were made while the molecules were in solution. That is when the distances between the molecules were so small that association between the functional groups is possible. The differences between both polymers

RS and RL were due to the different amounts of amine and carbonyl groups on the molecules. Besides, the C-H signal in the IR spectrum from the carrier could be observed due to the carrier high molecular weight.

The exact concentration range in which the phase transition was detected requires further research.

The dissolution test results are presented in Figs. 10–13. The dissolution rate of milled Furosemide was twice as high as that of pure recrystallized Furosemide because, as expected, the exposed surface by the Furosemide milled dissolution was increased by the particle size reduction and because the defects in that material enhanced the solubility of Furosemide. The solid dispersions (SD) dissolution profile was lower than that of the physical mixtures (PM) due to the fact that the Eudragit acted like a shield avoiding the Furosemide dissolution because the polymer has very low permeability and solubility in aqueous solutions. Similar results were obtained when solid dispersions were prepared with Eudragit RL (Fig. 12) and Eudragit RS (Fig. 13).

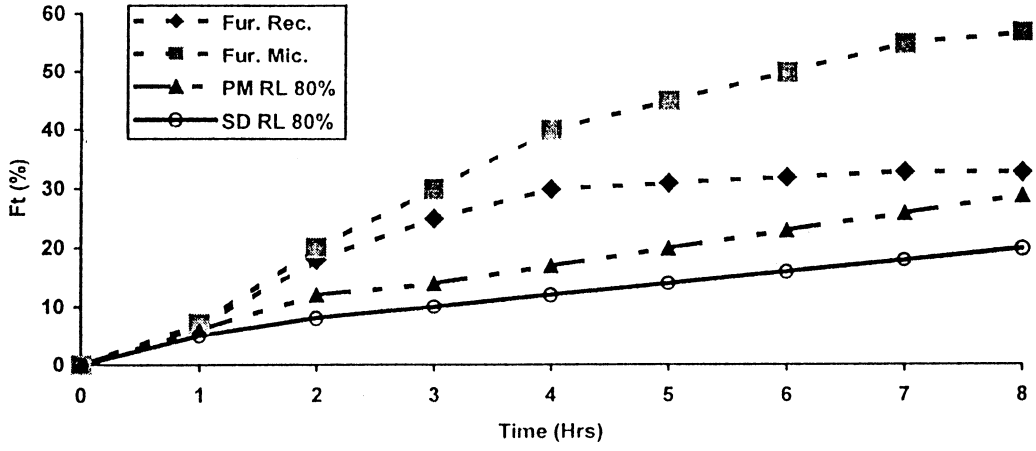


Fig. 10. Comparative dissolution profile between physical mixture (PM), solid dispersion (SD), Eudragit RL with re-crystallized Furosemide (Fur Rec.) and micronised Furosemide (Fur Mic).

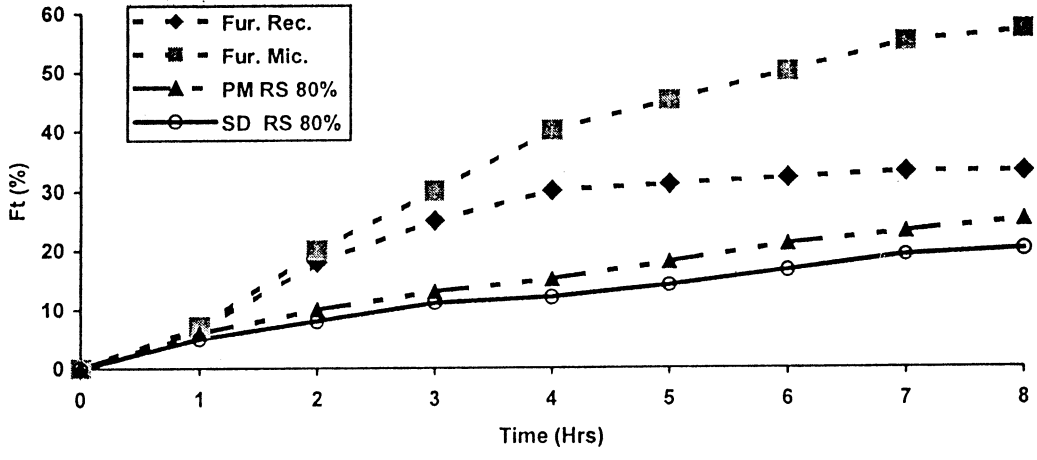


Fig. 11. Comparative dissolution profile between physical mixture (PM), solid dispersion (SD), Eudragit RL with re-crystallized Furosemide (Fur Rec.) and micronised Furosemide (Fur Mic).

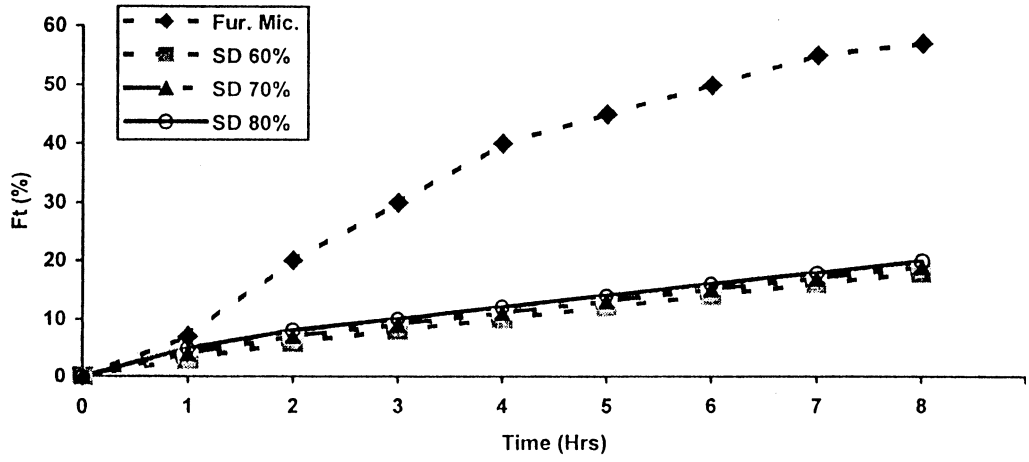


Fig. 12. Comparative dissolution profile of solid dispersions of Eudragit RL and micronised Furosemide (Fur Mic.)

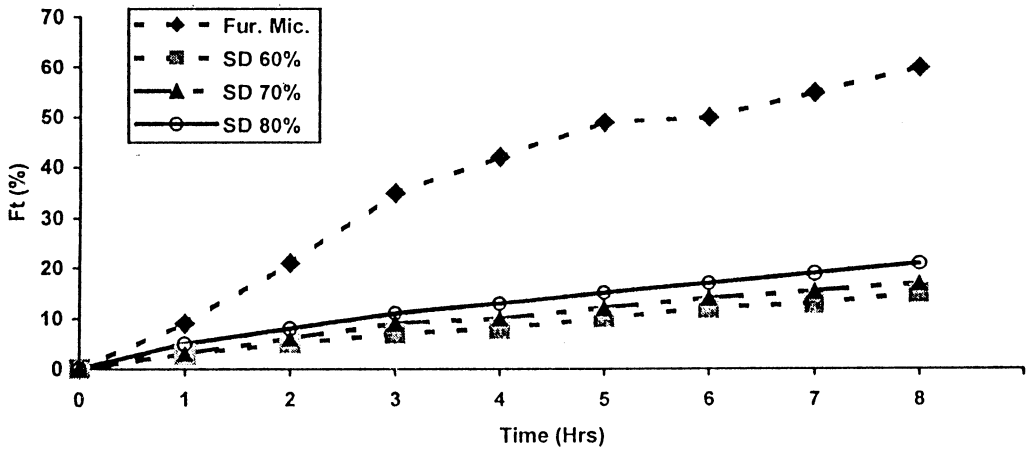


Fig. 13. Comparative dissolution profile of solid dispersions of Eudragit RS and micronised Furosemide (Fur Mic.)

Table 3
Least square regressions for solid dispersions with zero order kinetic

Carrier	% Drug	Slope	Intercept	R^2	% Release at 8 h
RL	80	1.86571	6.3690	0.9947	20.17
	70	1.27848	5.6959	0.9876	15.36
	60	0.97419	5.5864	0.9954	13.08
	40	0.57868	7.6022	0.9891	12.27
RS	80	1.63999	6.2652	0.9854	19.27
	70	1.20277	5.7392	0.9755	14.39
	60	0.98187	5.2507	0.9807	12.09
	40	0.50339	7.3584	0.9646	11.22

The dissolution profiles were analyzed by least square linear regression: the solid dispersion systems have a better fit than those of the physical mixtures. The statistical parameters are shown in Table 3.

Although both solid dispersions have significant reductions in the Furosemide dissolution profiles each system behaves in a characteristic way depending on the Eudragit RL or RS concentration used. However, the solid dispersion composition had an important effect on dissolution profile due to the fact that the polymer concentration controlled the dissolution rate. When the Furosemide concentration increased the dissolution rate was higher, so the dissolution rate was controlled by the composition of the polymer and the polymer concentration within the matrix (Figs. 12 and 13).

5. Conclusions

The Eudragit RL or RS are appropriate carriers to obtain a controlled release system with Furosemide as the drug to be delivered. At different carrier concentrations, modifications of the Furosemide crystalline habit were observed.

There seems to be a strong interaction between the functional groups of both components. It may be due to hydrogen bonds, which could be the reason for the spherical crystallization. However inside the matrix, the formation of channels showed that this effect is a superficial one between the Furosemide spheres and the polymer matrix since the drug keeps its chemical structure and potency.

The Furosemide system studied seems to be appropriate to use for the delivery of low solubility drugs due to channel formation when the carrier is dissolved.

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