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RESEARCH PAPER

Preparation and Evaluation of Sustained-Release Solid Dispersions of Drugs with Eudragit Polymers

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ABSTRACT

Coevaporates of paracetamol and rifampicin with Eudragit polymers of different natures (anionic, cationic, and zwitterionic) were prepared. Determination of dissolution rate of these coevaporates in dissolution media simulating those of the gastrointestinal tract (GIT) revealed that the release rate of paracetamol is retarded from all the coevaporates studied. In this respect, Eudragit L100-55 shows the highest sustainment of drug release, while Eudragit E100 shows the lowest. Conversely, the release of rifampicin from its coevaporates with the anionic Eudragit S100 polymer is more retarded than the corresponding coevaporate with the zwitterionic Eudragit RL100 or from coevaporates with equal mixtures of the two polymers.

Increasing the polymer weight fraction in rifampicin coevaporates with Eudragit S100 up to 0.5 resulted in a corresponding decrease in the dissolution rate. However, beyond this weight fraction, the polymer effect on the dissolution rate of the drug becomes minimized. The results confirmed that the process of dissolution of the two drugs from their coevaporates is a diffusion-controlled release process.

The biological performance of paracetamol coevaporates was monitored in rabbits; paracetamol level in plasma was found to follow first-order kinetics. For all the investigated paracetamol coevaporates, the peak plasma level was less than 50 μg/ml compared to a value of 60 μg/ml for the drug per se. The coevaporates of the drug with Eudragit L100-55 showed slowest rates of absorption and elimination as well as greatest half-peak and half-life times. Biological performance of rifampicin coevaporates was assessed in human subjects receiving a single oral dose equivalent to 300 mg of the drug. The results depicted sustainment of drug release as a function of polymer weight fraction. A strict correlation was shown

to exist between the total amount of drug excreted during 24 hr post dosing of the coevaporates and its in vitro dissolution rate.

The results depicted that paracetamol can be formulated in the form of a coevaporate with Eudragit L100-55 to prepare a more safe sustained-release formulation with minimal side effects, and also revealed the advantages of administration of rifampicin in the form of a coevaporate with Eudragit S100 (4:1) at a single oral dose equivalent to 600 mg of drug.

INTRODUCTION

The solid dispersion technique was originally utilized to enhance the dissolution rate of poorly water-soluble drugs using water-soluble inert carriers (1,2). However, the same technique was also employed for preparing sustained-release forms of various water-soluble and short-acting drugs using water-insoluble inert carriers (3,4). Examples of such water-insoluble carriers are Eudragits, a group of commercially available acrylate and methacrylate polymers and copolymers available in anionic, cationic, and zwitterionic forms (5).

Paracetamol is a drug with relatively short biological half-life. Conversely, one of its metabolites is hepatotoxic at high concentration levels (6). Accordingly, a sustained-release form of this drug is thought to be worthy of investigation. Administration of rifampicin, which is the most effective drug for treatment of tuberculosis on an intermittent schedule (less than twice weekly) and in daily does of 1200 mg or greater, is associated with frequent side effects, such as a flu-like syndrome with fever, chills, myalgias, eosinophilia, interstitial nephritis, acute tubular necrosis, and hemolytic anemia (7).

A review of the literature revealed that only the two zwitterionic Eudragit polymers, Eudragit RL and Eudragit RS, have been used to prepare prolonged-action microcapsules of paracetamol (8,9), and Eudragit RS100 has been utilized to develop a controlled-release system for rifampicin (10). The objective of this study was to prepare and evaluate controlled-release preparations of paracetamol and rifampicin. For paracetamol, different anionic, cationic, and zwitterionic Eudragit polymers were used. For rifampicin, Eudragit S100 and RL100 were taken into consideration. The former is an anionic copolymer insoluble in acid and water, soluble in intestinal medium from pH 7 upwards. The latter is a zwitterionic copolymer inert to the digestive tract content, independent of pH, and capable of swelling.

EXPERIMENTAL

Materials

Eudragits were gifts from Röhm Pharma GMBH, Darmstadt, Germany. Paracetamol and rifampicin were supplied by El-Nasr Pharmaceutical Chemical Company, Abu-Zaabl, Egypt. Citric acid, disodium hydrogen phosphate, potassium dihydrogen phosphate, trichloroacetic acid, hydrochloric acid, sodium nitrate, sulphamic acid, chloroform, methanol, and sodium hydroxide were all of analytical grade.

Methods

Preparation of Paracetamol Coprecipitates

Sixty grams each of paracetamol and the investigated Eudragit were dissolved in 300 ml of methanol and the solution was transferred to 100 ml distilled water at 5°C while being gently stirred. The precipitate obtained was filtered using Whatman no. 4 qualitative filter paper, spread on a tray, and dried to a constant weight in vacuum at 37°C. The dried samples were milled and screened through a 250-μm mesh sieve.

Preparation of Coevaporates

The minimum amount of methanol needed to dissolve paracetamol or rifampicin and Eudragit polymers was used, then the solvent was removed under reduced pressure in a rotary evaporator at 40 ± 1°C. Further drying was carried out for 5 days under vacuum at room temperature. The residue was ground and the 250 μm particle size fraction was obtained by sieving.

Evaluation of the Prepared Dispersions

Determination of Drug Content

Three samples containing theoretically 5 mg of the drug were taken from each preparation. These samples

were dissolved in methanol and assayed spectrophotometrically for paracetamol at 247 nm or for rifampicin at 476 nm using calibration curves based on standard solutions in methanol. Determination of the drug content in different samples revealed 94–101% of the expected values.

Thin-Layer Chromatography

Thin-layer chromatography (TLC) was carried out for paracetamol dispersions by spotting methanolic solutions for pure drug, coevaporates, and different Eudragits on chromatographic plates of silica gel (G) and developed by solvent system of ethyl acetate:formic acid:methanol:water (65:5:20:10) as described by McGilveray et al. (11). After the plates were dried, they were placed in an iodine tank. Detection of the spots was done by viewing the plate under short UV lamp.

Infrared Spectroscopy

Infrared (IR) spectra of the prepared paracetamol coevaporates were determined using Philips PV 9700 infrared spectrophotometer from potassium bromide disk. The scanning range used was 4000–200 cm^{-1} at a scan period of 7 min with an ordinate expansion of one.

Dissolution Rate Studies

Dissolution experiments were performed using a flow-through apparatus (Desaga, Heidelberg, Germany) with cells 20 mm in diameter supplied with dissolution medium at 37 ± 0.5°C by Desaga peristaltic pump. The dissolution runs were carried out at a flow rate of 5 ml/min. The media selected for determination of dissolution for 8 hr were placed in a buffered solution of pH 1.2 for a period of 2 hr, pH 4.5 for 1 hr, pH 6.8 for 2 hr, and pH 7.4 for 3 hr, simulating in vivo conditions. One hundred fifty milligrams of drug or its equivalent weight of the prepared dispersions was packed in transparent gelatin capsules and their dissolution rate was determined at 37 ± 0.5°C. All of the dissolution runs were replicated six times and the average results were considered.

Bioavailability Studies

Paracetamol

Six male Albino rabbits, average weight 2.75 kg (range 2.5–3 kg) were used. The animals were kept on standard diet during testing periods. The investigated coevaporates were given orally in the fasting state at a dose level of 100 mg/kg body weight in a crossover design system, in such a way that each rabbit received a dose of each preparation at weekly intervals. Blood samples (2 ml each) were collected from the ear vein into heparinized tubes at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hr after administration and immediately centrifuged at 2500 rpm for 10 min; the plasma obtained was kept at −20°C until determination. The drug content in the plasma was determined according to Glynn et al. (12).

Rifampicin

Six healthy human volunteers (30–45 years old) participated in this study. After an overnight fast, a blank urine sample was collected and each subject swallowed a single oral dose of 300 mg of the drug or its equivalent amount of the prepared coevaporates packed in hard gelatin capsules. A crossover design system was followed. Subjects abstained from food for 4 hr post dosing and were asked to ingest 200 ml water hourly. Urine was collected at predetermined time intervals for 24 hr. The urine samples were assayed for their rifampicin content according to the method described by Khalil et al. (13). In a 50-ml separator, 6 ml Sorensen's phosphate buffer (pH 5) was added to 2 ml urine. The diluted urine sample was extracted once with 10 ml chloroform by manual shaking for 10 min. The chloroformic layer was separated and centrifuged. The amount of rifampicin in the chloroformic phase was estimated by measuring its absorbance at 478 nm. The absorbance reading obtained corresponds to intact rifampicin and dexaacetyl rifampicin (total rifampicin), since the latter is the only metabolite extractable with chloroform (14).

RESULTS AND DISCUSSION

The results of TLC analysis of the prepared paracetamol coevaporates revealed the existence of only a single spot for each coevaporate with R_f-value identical to that of the pure drug, except for the coevaporate of the drug with Eudragit L100-55, whereby the spot is not identical with that of the drug. The IR spectra of paracetamol coevaporates were found to be identical with that of the drug, showing the characteristic bands of aromatic ring at 1610 cm^{-1}, carbonyl group at 1660

cm^{-1}, amino group at 3150 cm^{-1}, and the hydroxyl group at 3330 cm^{-1}. This result ruled out any possible interaction between the drug and carrier. However, in the IR spectrum of the paracetamol–Eudragit L100-55 coevaporate, these characteristic bands became more or less shorter and the band at 3150 cm^{-1} disappeared. Both TLC and IR analyses would illuminate a sort of interaction between paracetamol and Eudragit L100-55.

The dissolution efficiency (15) of solid dispersion of paracetamol with Eudragits L100 and S100 prepared by coprecipitation and coevaporation methods was determined and found to be 60 and 70% for paracetamol coevaporate and coprecipitate with Eudragit L100, and 75 and 80% for coevaporate and coprecipitate with Eudragit S100, respectively. This result indicates that the coevaporation technique is more suitable than coprecipitation for preparing sustained-release paracetamol–Eudragit formulations.

Fig. 1 shows that incorporating paracetamol with anionic Eudragit polymers leads to a pronounced retardation in the dissolution rate of the drug. For all of the investigated anionic polymers, the dissolution of the drug is more retarded from the coevaporate compared to the corresponding physical mixture. The retardation in the dissolution rate of the drug induced by these anionic polymers is due to the relatively poor solubility of these substances at pH values lower than 5.5.

The dissolution profiles of paracetamol-Eudragit zwitterionic polymers RS100 and RL100 coevaporates and physical mixtures appear in Fig. 2. The drug release rate from these coevaporates and physical mixtures is lower than that of the drug per se. Also, the release rate from formulation with Eudragit RS is lower than that from the corresponding formulations with RL100. This result is due to the fact that the former polymer contains fewer quaternary ammonium groups than the latter, and consequently is less hydrophilic (16). On the other hand, Eudragit RS100 is water-insoluble and swells in aque-

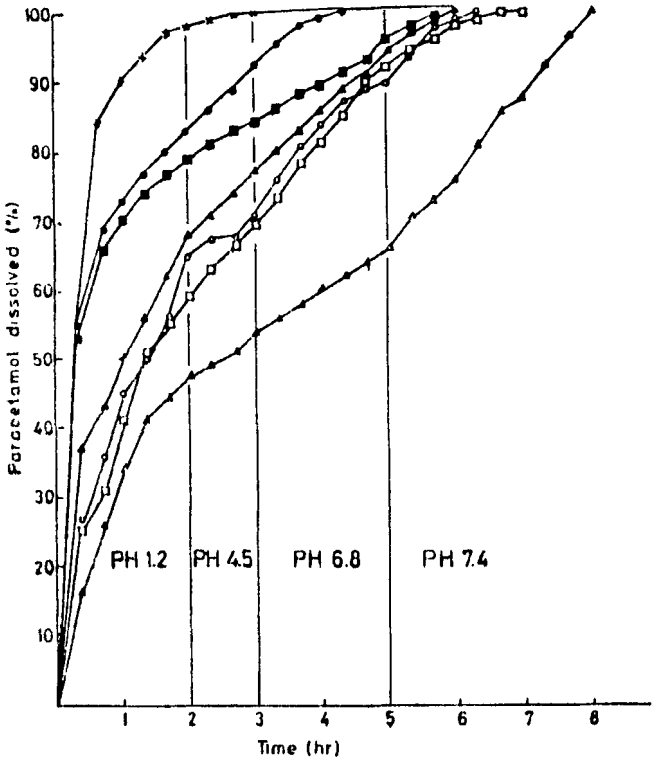

Figure 1. Dissolution profiles of paracetamol coevaporates and physical mixtures with anionic Eudragit polymers. Paracetamol ×—×; paracetamol coevaporates with Eudragits L100-55 Δ—Δ; L100 ○—○; S10 □—□; physical mixtures with Eudragits L100-55; L100 ●—●; S 100 ■—■.

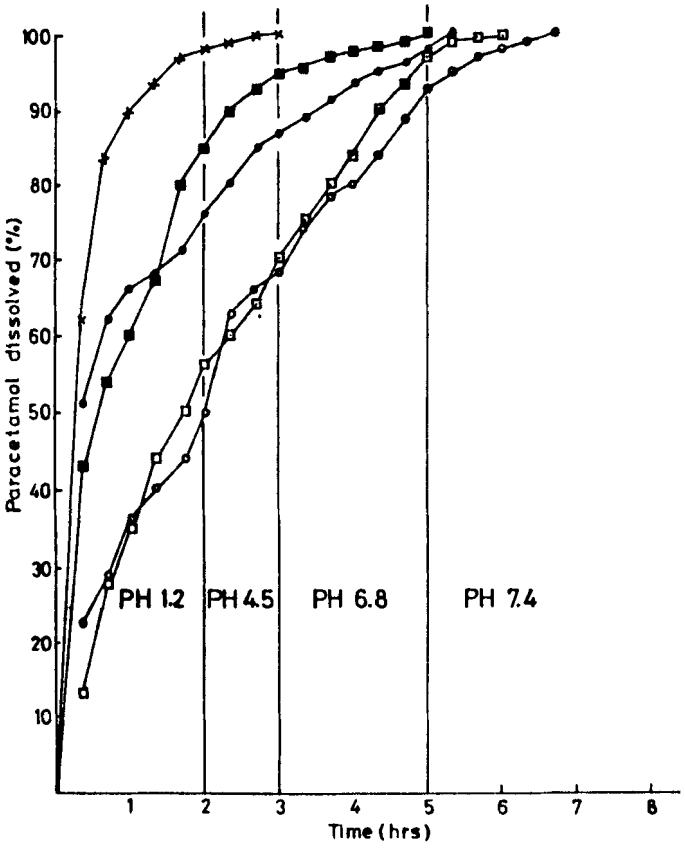

Figure 2. Dissolution profiles of paracetamol coevaporates and physical mixtures with zwitterionic polymers. Paracetamol ×—×; paracetamol coevaporates with Eudragits RS100 ○—○; RL100 □—□; physical mixtures with Eudragits RS100 ●—●; RL 100 ■—■.

ous natural and artificial digestive juices, rendering itself permeable to these liquids (17). The mechanism of drug release would probably be through direct dissolution of partially embedded drug followed by diffusion of embedded drug via the matrix pores.

Because the cationic Eudragit E100 is more or less soluble at pH 12, its effect in retarding the drug release is evidently less than the other investigated polymers. However, incorporation of drug with a mixture of this polymer together with the anionic Eudragit S100 (1:1) augments its retarding effect to some extent (Fig. 3). This is attributed to the fact that Eudragit S100 is soluble at pH 7 or greater.

Data obtained in dissolution medium of pH 1.2 were used to rank the dissolution rates and sustaining efficacies of the prepared paracetamol formulations, since in this dissolution medium nearly 100% of the pure drug is released. The data were analyzed according to different models that are used to obtain dissolution rate constants (Table 1). Among all the models tested, the model for diffusion-controlled release given by Higuchi (18), $[100 - M = K\sqrt{T}]$, appears to provide the best fits for all the investigated formulations (Table 1). This result confirms that the process of dissolution of the drug from these systems is a diffusion-controlled release process. On the other hand, the values of the dissolution rate constant (Table 1) reveal that slowest dissolution rate is obtained from coevaporate of the drug with Eudragit RS100, followed by that with L100-55. However, comparing the values of the dissolution efficiency throughout the entire dissolution time ($DE_{0\text{-}8\ hr}$) shows that the dissolution rate of the drug from its coevaporate or physical mixture with Eudragit L100-55 is evidently lower than from systems containing Eudragit RS100 (Table 2).

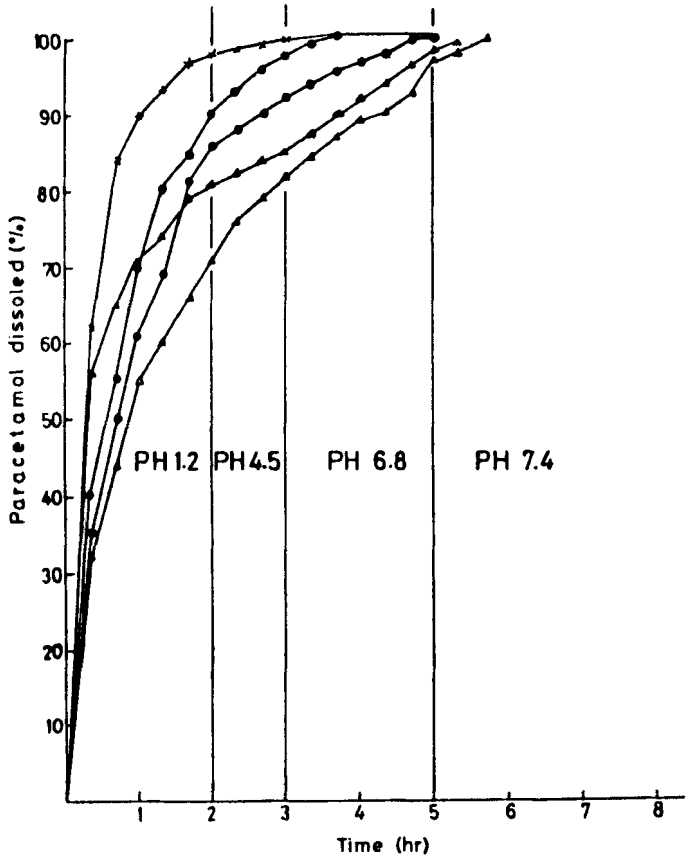

Figure 3. Dissolution profiles of paracetamol coevaporates and physical mixtures with cationic polymer and with 1:1 mixture of Eudragit (E100 + S100). Paracetamol ×—×; paracetamol coevaporates with Eudragits E100 ○—○; E100 + S100 Δ—Δ; physical mixtures with Eudragits E100 ●—●; E100 + S100 Δ--Δ.

The dissolution profiles of coevaporates of rifampicin with Eudragits of different natures appear in Fig. 4. The pH-dependent dissolution characteristics of the drug–Eudragit coevaporates is clearly evident. A more or less significant dissolution takes place for the drug and the drug–Eudragit RL100; higher drug release is observed at pH 1.2 compared to the release at pH 7.4 dissolution medium. It is also clear from the figure that the dissolution rate of rifampicin–Eudragit S100 coevaporate is much lower than that of the coevaporate of the drug with the zwitterionic polymer Eudragit RL100.

These results might be due to the fact that Eudragit RL100 is capable of swelling without disintegration at pH 1.2–7.4 and due to its permeability, diffusion occurs. In the same time, Eudragit S100 is soluble in buffer solution above pH 7.0 and remains intact throughout the dissolution period. Thus, the release rate of the drug from Eudragit S100 coevaporate is less than that from Eudragit RL100 coevaporate. On the other hand, the release of rifampicin from S100 coevaporate might be a diffusion-controlled process. Incorporation of the drug with a mixture of equal amounts of the anionic polymer Eudragit S100 and the zwitterionic polymer Eudragit RL100 inherit to the drug dissolution rate, which is clearly lower than that of the drug, but still higher than that of the drug–Eudragit S100 coevaporate, particularly at the pH range from 1.2 to 6.8. This is also obvious from the data of the dissolution efficiency of these systems calculated from the amount of drug dissolved at different pH values through the entire dissolution run (8 hr).

Table 1

Least Square Parameters of the Model Equations Applied to the Dissolution of Paracetamol Coevaporate and Physical Mixture at pH 1.2

	Coevaporate						Physical Mixture					
	$100 - M = K\sqrt{T}$		$M = KT$		Ln $m = KT$		$100 - M = K\sqrt{T}$		$M = KT$		Ln $m = KT$	
Polymers	r	k	r	k	r	k	r	k	r	k	r	k
Paracetamol + Eudragit L100-55	0.99390	5.042	0.9756	0.318	0.98610	0.047	0.9935	4.751	0.9989	0.307	0.9974	0.0060
Paracetamol + Eudragit L100	0.99640	5.932	0.9798	0.375	0.99490	0.007	0.9921	3.346	0.9694	0.210	0.9979	0.0132
Paracetamol + Eudragit S100	0.99790	5.220	0.9860	0.360	0.98850	0.006	0.9737	3.867	0.9398	0.240	0.9736	0.0080
Paracetamol + Eudragit E100	0.99820	8.279	0.9898	0.515	0.99097	0.016	0.9909	7.852	0.9699	0.494	0.9984	0.0180
Paracetamol + Eudragit L100+S100	0.98790	5.404	0.9571	0.314	0.98135	0.009	0.9912	3.776	0.9703	0.238	0.9912	0.0080
Paracetamol + Eudragit RS100	0.99609	4.166	0.9946	0.268	0.99640	0.004	0.9958	2.879	0.9867	0.183	0.9936	0.0080
Paracetamol + Eudragit RL100	0.99810	6.008	0.9965	0.385	0.99430	0.009	0.9866	6.492	0.9936	0.420	0.9681	0.0120

Table 2

Dissolution Efficiency of Coevaporates and Physical Mixtures of Paracetamol with Different Eudragit Polymers

Systems	Dissolution Efficiency $DE_{0-8\ hr}$	
	Coevaporates	Physical Mixtures
Paracetamol + Eudragit L100-55	60.9	79.43
Paracetamol + Eudragit L100	76.13	89.43
Paracetamol + Eudragit S100	74.86	85.63
Paracetamol + Eudragit E100	85.27	89.79
Paracetamol + Eudragit E100+S100	81.48	86.83
Paracetamol + Eudragit RS100	73.22	86.03
Paracetamol + Eudragit RL100	78.96	87.66
Paracetamol	94.69	

Table 3

Dissolution Efficiency of Coevaporates of Rifampicin with Different Eudragit Polymers

Systems	Dissolution Efficiency $DE_{0-8\ hr}$
Rifampicin + Eudragit RL100 (1:1)	53.99
Rifampicin + Eudragit RL100+S100 (1:1)	40.45
Rifampicin + Eudragit S100 (1:1)	34.24
Rifampicin + Eudragit S100 (1:2)	30.82
Rifampicin + Eudragit S100 (2:1)	48.27
Rifampicin + Eudragit S100 (3:1)	58.69
Rifampicin + Eudragit S100 (4:1)	61.31
Rifampicin	72.41

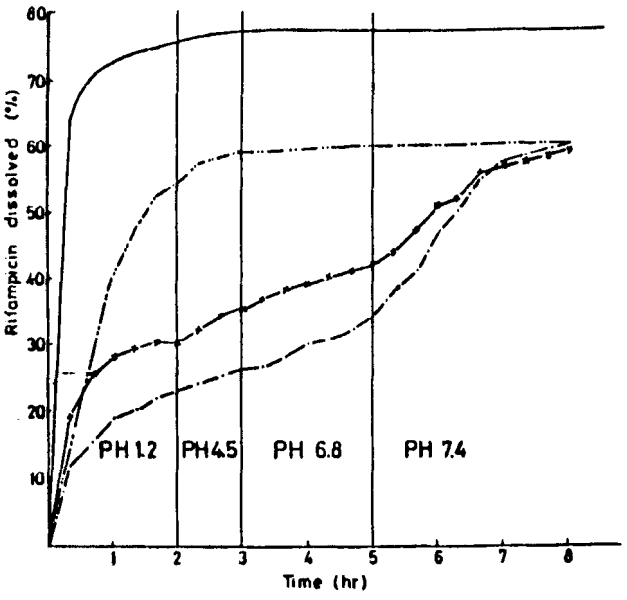

Figure 4. Dissolution profiles of coevaporates of rifampicin with different Eudragit polymers. Rifampicin —; rifampicin coevaporates with Eudragits S100 —·—; RL100 —··—; S100 + RL 100 ×—×.

Eudragit S100 sustains the dissolution of rifampicin as a function of polymer weight fraction (Table 3); increasing polymer weight fraction above 0.5 is not sufficiently influential in sustaining drug dissolution. The kinetics of release of rifampicin from coevaporates containing different weight fractions of Eudragit S100 was studied to determine whether this process is a first-order or a diffusion-controlled process. A plot of percent drug released versus the square root of time revealed a straight-line relationship, indicating that diffusion-controlled mechanism is operative (18).

Bioavailability Studies

Rabbits were chosen as test animals for monitoring the biological performance and assessing the pharamacokinetics of paracetamol coevaporates on the basis of good correlation in gastrointestinal absorption of the drug between rabbits and humans (19). The graphical illustration of the mean values of paracetamol level in plasma after administration of a single oral dose of the investigated coevaporates as a function of time (Fig. 5) reveals a distinct difference between the biological per-

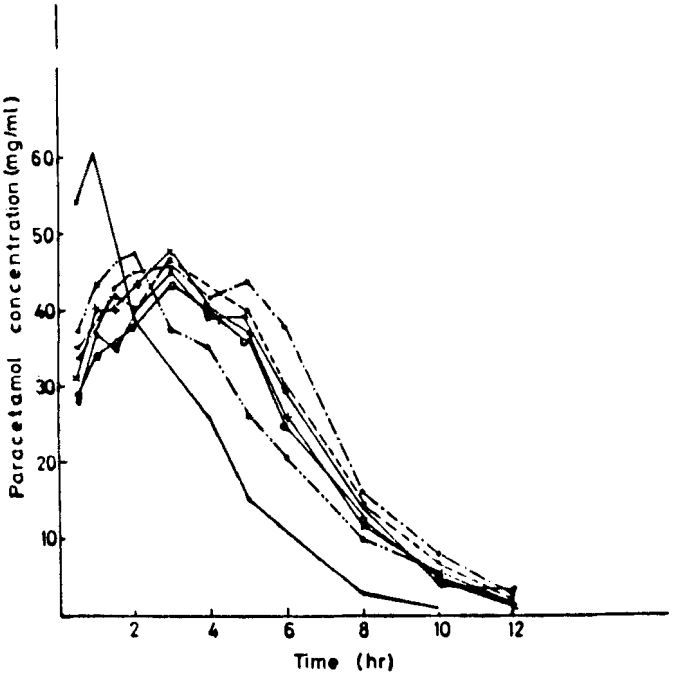

Figure 5. Mean plasma concentration of paracetamol–Eudragit coevaporates in rabbits. Paracetamol —; paracetamol coevaporates with Eudragits L100-55 —·—; L100 ○—○; RS100 — — —; RL100 —×—; E100 —··—; E100 + S100 ●—●.

formance of the coevaporates and the drug per se. This is evident by comparing values of the peak plasma level following administration of the coevaporates, with that following administration of the pure drug; the former value is less than 50 μg/ml, while the latter exceeds 60 μg/ml.

Paracetamol level in plasma was found to follow first-order kinetics. The pharmacokinetic parameters of the investigated preparations were computed and presented in Table 4. The coevaporate of paracetamol with Eudragit L100-55 shows slowest rates of absorption and elimination as well as greatest half-life time value and area under plasma level–time curve.

The biological availability of rifampicin coevaporates with different weight fractions of Eudragit S100 was assessed in human subjects using urine data. The mean values of urinary excretion rate following administration of single oral dose of the different formulae were plotted as a function of time (Fig. 6). Sustainment of drug release from coevaporates is evidently shown by comparing the excretion rate of the coevaporates with that of the drug at time intervals beyond 12 hr post dosing.

The kinetic analysis of the data of excretion rate using the linear regression method showed that it follows first-order kinetics. The pharmacokinetic parameters of different systems were computed (Table 5).

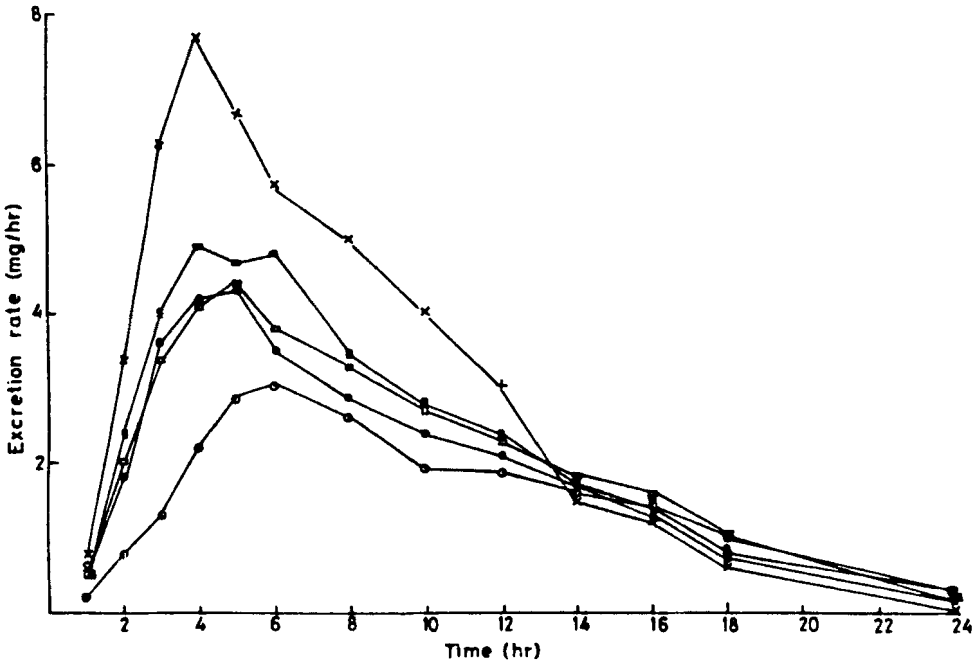

Figure 6. Mean urinary excretion rate of rifampicin–Eudragit S100 coevaporate in human subjects. Eudragit S100 weight fractions: 0.0 ×—×; 0.20 ■—■; 0.25 □—□; 0.33 ●—●; 0.67 ○—○.

Table 4

Pharmacokinetic Parameters of Paracetamol–Eudragit Coevaporates in Rabbits

Parameters	Paracetomol	L100-55	L100	RS100	RL100	E100	E100 + S100
C_{max} ($\mu g \cdot ml^{-1}$)	65.08 + 1.72 (58.0–69.0)	48.80 ± 2.53 40.07–56.55)	46.13 ± 0.97 (45.24–47.71)	45.53 ± 1.90 (40.72–50.57)	47.07 ± 0.60 (45.50–48.91)	50.38 ± 2.340 (44.9–55.34)	44.21 ± 0.89 (41.51–46.71)
t_{max} (hr)	0.92 ± 0.17 (0.5–1.5)	2.67 ± 0.23 (2–3)	3.00 ± 0.71 (2.0–4.0)	3.00 ± 0.283 (2.00–4.00)	3.0 ± 0.00 (3.0–3.0)	1.67 ± 0.13 (1.5–2.0)	2.5 ± 0.25 (2.0–3.0)
$K_e(hr^{-1})$	0.387 ± 0.02 (0.322–0.454)	0.20 ± 0.062 (0.06–0.364)	0.25 ± 0.03 (0.15–0.36)	0.20 ± 0.045 (0.100–0.279)	0.25 ± 0.03 (0.12–0.36)	0.26 ± 0.06 (0.21–0.33)	0.26 +0.06 (0.03–0.37)
$t_{el}^{1/2}$ (hr)	1.81 ± 0.100 (1.526–2.152)	5.72 ± 1.83 (1.904–11.55)	2.85 ± 0.41 (2.60–3.47)	4.66 ± 1.33 (2.35–9.90)	3.36 ± 0.68 (2.15–6.26)	2.72 ± 0.44 (2.12–3.35)	3.38 ± 1.17 (1.88–8.66)
$t_p^{1/2}$ (hr)	2.410 ± 0.25 (1.5–2.90)	6.72 ± 0.215 (6.3–7.2)	5.93 ± 0.57 (5.20–6.80)	6.53 ± 0.200 (5.9–7.20)	6.48 ± 0.24 (5.50–7.0)	5.07 ± 0.36 (4.60–5.60)	6.45 ± 0.22 (5.40–7.50)
$AUC_{0-\infty}$ ($\mu g \cdot ml^{-1}$ hr)	216.08 ± 8.99 (190.81–247.63)	348.022 ± 11.73 (309.71–383.06)	284.6 ± 19.16 (253.80–304.80)	320.79 ± 13.47 (273.30–350.37)	313.44 ± 5.86 (339.76–285.84)	275.27 ± 16.30 (252.21–298.30)	300.45 ±10.16 (269.92–369.43)

All data are the mean ± SE of six experiments; ranges are shown in parantheses.

Table 5

Pharmacokinetic Parameters of Rifampicin-Eudragit S 100 Coevaporates in Human Subjects

Parameters	Rifampicin	Rifampicin-Eudragit S100 1:2	2:1	3:1	4:1
C_{max} (mg·hr^{-1})	8.34 ± 0.36 (8.12-9.01)	3.10 ± 0.62 (2.38-3.47)	4.61 ± 0.64 (3.62-5.22)	4.76 ± 0.062 (3.59-5.44)	5.67 ± 0.87 (4.10-7.0)
t_{max} (hr)	3.33 ± 0.82 (2-4)	(6.0 +0.0) (6-6)	4.83 ± 0.75 (4-6)	4.88 ± 0.64 (4-6)	4.5 + 0.93 (3-6)
K_e (hr^{-1})	0.02 ± 2.97 (0.017-0.025)	0.01 ± 0.0006 (0.009-0.01)	0.011 ± 0.0016 (0.01-0.014)	0.013 ± 0.0018 (0.010-0.015)	0.013 ± 0.0018 (0.010-0.015)
$t_{cl}^{1/2}$ (hr)	3524 ± 4.79 (27.72-40.77)	71.87 ± 4.45 (69.3-77.0)	62.75 ± 8.14 (49.50-69.3)	54.76 ± 9.42 (46.20-69.30)	54.76 ± 8.29 (46.2-69.3)
$t_p^{1/2}$ (hr)	6.95 ± 0.61 (4.5-8.3)	11.56 ± 0.48) (10.5 -12.70)	9.78 ± 1.48 (6.2-15.5)	9.6 ± 0.58 (11.6-8.20)	8.43 ± 0.83 (38.47-62.99)
AUC_{0-24} (mg/hr·hr)	68.48 ± 594 (58.12-74.50)	35.43 ± 4.12 (29.28-37.32)	45.02 ± 7.03 (33.26-54.00)	48.16 ± 13.19 (39.02-59.59)	50.95 ± 9.02 (38.47-62.99)
mg/24 hr	65.96 ± 5.53 (57.08-71.34)	33.69 ± 4.08 (29.28-37.32)	42.03 ± 7.03 (32.03-49.86)	45.16 ± 11.66 (22.0-55.78)	47.58 + 8.021 (36.04-57.70)

Data presented in this table show that incorporation of rifampicin in the form of a coevaporate with Eudragit S100 affects the value of maximum excretion rate to a considerable extent. This reflects a decrease in the value of maximum plasma drug level, which would minimize its side effects.

It can also be seen that increasing the polymer weight fraction leads to an increase in the time for maximum

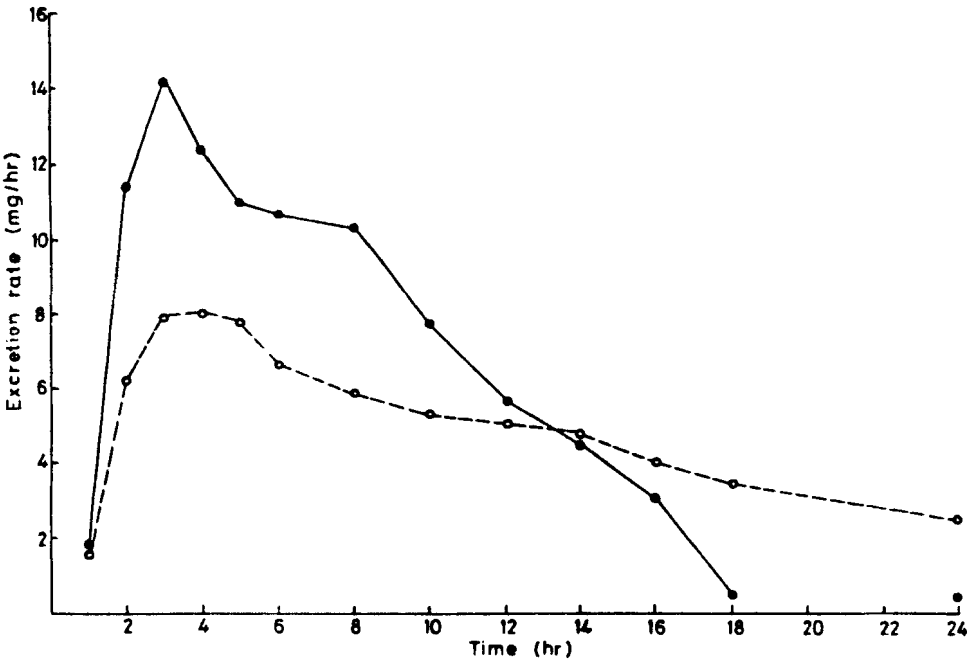

Figure 7. Mean urinary excretion rate of rifampicin-Eudragit S100 coevaporate (1:4) in human subjects receiving a single oral dose equivalent to 600 mg of the drug. Rifampicin ●—●; coevaporates ○—○.

Table 6

In Vitro/In Vivo Correlation for Rifampicin-Eudragit S100 Coevaporates

Polymer Weight Fraction	In Vitro Parameter $DE_{0-8\ hr}$	In Vivo Parameters $AUC_{0-24\ hr}$ (mg·hr^{-1}·hr)	mg/24 hr	C_{max} (mg·hr^{-1})
0.20	61.31	50.95	47.58	5.67
0.25	58.69	48.16	45.16	4.76
0.33	48.27	45.02	42.03	4.61
0.67	30.82	35.43	33.69	3.10
In Vitro/In Vivo correlation coefficient		0.9987	0.9995	0.9820

excretion rate, half-life time, as well as time of half-peak excretion rate, and a decrease in elimination rate constant, indicating an increase in the duration of action of the drug.

Correlation of the in vivo results with the in vitro dissolution results was monitored. For this correlation, the in vitro parameters of dissolution efficiency were correlated to three pharmacokinetic parameters; that is, maximum excretion rate, area under excretion rate versus time curve, and the total amount of rifampicin excreted in 24 hr. The results presented in Table 6 reveal that for the investigated coevaporates, there exists a fair in vitro/in vivo correlation. In this respect, the total amount of drug excreted in 24 hr correlates best with in vitro dissolution parameters.

The bioavailability of a dose equivalent to double the normal dose of rifampicin, i.e., 600 mg, and the equivalent amount of drug (Eudragit S100) (4:1) coevaporate was investigated in human subjects. The graphical representation of the obtained data (Fig. 7) reveals that at 12 hr post dosing, the excretion rate of the coevaporate is evidently higher than that of the drug indicating an increase in bioavailability of the drug and prolongation of its effect. The pharmacokinetic parameters presented in Table 7 reveal an evident increase in the half-life time as well as in the half-peak time of the drug when administered in the form of a coevaporate with Eudragit S100 containing a polymer weight fraction as low as 0.2; both parameters are increased to nearly their double values.

In conclusion, paracetamol can be formulated in the form of a coevaporate with Eudragit L100-55 to prepare sustained-release form of the drug. This form, in addition to possessing longer duration of action compared to the drug of relatively short half-life time, would also minimize the side effects of the drug in virtue of its evidently lower peak plasma level. In virtue of the hepatotoxicity of one of the metabolites of the drug, the suggested formulation would be more safe. The obtained results would illuminate the potential for administration of rifampicin in the form of a coevaporate with Eudragit S100 (4:1) at a single oral daily dose equivalent to 600 mg of the drug.

Table 7

Pharmacokinetic Parameters for Rifampicin-Eudragit S100 Coevaporate (4:1) in Human Subjects Receiving a Single Oral Dose Equivalent to 600 mg of the Drug

Parameter	Drug	Coevaporate
C_{max} (mg·hr^{-1})	14.20 (13.22–15.20)	8.00 (7.60–8.41)
t_{max} (hr)	3.0 (3–3)	4.0 (4–4)
K_e (hr^{-1})	0.023 (0.020–34.65)	0.013 (0.011–0.014)
$t_{el}^{1/2}$ (hr)	30.13 (26.65–34.65)	56.25 (63.0–49.5)
$t_p^{1/2}$ (hr)	9.26 (9.88–8.52)	14.80 (13.80–16.0)
$AUC_{0-24\ hr}$ (mg/hr·hr)	137.88 (127.38–148.37)	114.83 (109.66–120.0)
mg/24 hr	131.35 (123.45–139.24)	111.66 (106.0–117.32)

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