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INVESTIGATION OF CONTROLLED RELEASE SOLID DISPERSION OF NAPROXEN USING EUDRAGIT RS AND RL POLYMERS

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تم فى هذا البحث صياغة وتقييم المشتتات الصلبة والمحتوية على عقار النبروكسين وبوليمر الايدراجيت رس١٠٠ أو الايدراجيت رل١٠٠ كمواد حاملة للعقار ، وقد تمت صياغة مشتتات النبروكسين الصلبة بإستخدام طريقة تبخير المذيب.

أظهرت نتائج البحث أن كمية النبروكسين المنطلقة من المشتتات الصلبة تتبع معادلة هيجوشى للانتشار المنتظم وأن معدل انطلاق العقار من المشتتات الصلبة المحتوية على الايدراجيت رس١٠٠ كان أقل من مثيله بالنسبة للمشتتات الصلبة والمحتوية على الايدراجيت رل١٠٠. وقد أظهرت الدراسة أنه يمكن التحكم فى ميكانيكية انطلاق العقار وذلك عن طريق التغيير فى النسبة البوليمرية لكل من بوليمرات الايدراجيت رس١٠٠ والايدراجيت رل١٠٠.

لوحظ من الدراسة أيضا وجود نقصان واضح فى معدل انطلاق عقار النبروكسين وذلك عند زيادة حجم الجزئيات للمشتتات الصلبة وأنه يوجد علاقة خطية بين القيمة اللوغاريتمية لثابت انطلاق عقار النبروكسين وكمية الايدراجيت رل١٠٠ الموجودة فى المشتتات الصلبة والمكونة من عقار النبروكسين/الايدراجيت رس١٠٠/الايدراجيت رل١٠٠ مما يؤكد أن انطلاق عقار النبروكسين من هذه المشتتات الصلبة يتبع معادلة هيجوشى للانتشار المنتظم.

وقد أظهرت النتائج المستقاه من هذه الدراسة أن إدماج البولى فينيل بيروليدون فى هذه المشتتات الصلبة والمحتوية على الايدراجيت رس١٠٠ أدى إلى تحسين وزيادة معدل أنطلاق عقار النبروكسين.

Naproxen was used as a model drug and Eudragit RS and RL were used as inert carriers in an attempt to study the controlled release solid dispersion. Naproxen solid dispersion was prepared using solvent evaporation technique. IR study illustrated Naproxen/Eudragits interaction. Dissolution-rate studies showed that the amounts of Naproxen released were found to be fitted to the Higuchi-Square root of time model. the study proved that the solid dispersions composed of Eudragit RS exhibited slow release rates when compared with those composed of Eudragit RL. By a simple modification in the polymeric ratio of both Eudragit RS and Eudragit RL, the kinetics of release can be modulated. A marked reduction in the magnitude of release rates was observed upon increasing the particle size. It was found that there was a linear relationship between the logarithmic value of release rate constant and the fraction of Eudragit RL in the coevaporate composed of Naproxen/RS/RL. This finding was a confirmatory indication that the release was following Higuchi-diffusion model. The study also proved that the compression forces had no effect on the release rate constant. The incorporation of polyvinylpyrrolidone in the coevaporates containing Eudragit RS improved and increased the release profile of Naproxen.

INTRODUCTION

Naproxen is poorly water soluble, non-steroidal anti-inflammatory drug, containing an acidic function. It is, like other drugs of its class, not free of side effects. The side effects of these drugs, such as gastrointestinal bleeding and ulcers, may result in hospitalization. The

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controlled delivery system reduce the dose and/or the frequent of administration or application, and also reduce the possibility of side effects.[1,2]

Several investigators[3-7] demonstrated that the formation of solid dispersion in the form of coevaporate or coprecipitate of relatively water insoluble drugs with various pharmacologically inert polymers can increase significantly their release rates. However, the use of polymeric materials, especially Eusdragit RS or RL, as carriers in the coevaporate solid dispersions has received limited attention in the literature.[8-11]

In this paper, coevaporates of Naproxen with Eudragit RL, RS or a blend of both polymers were investigated. The effects of various parameters on the release profiles of coevaporates were studied as the particle size distribution, Eudragit RL to RS ratio, the addition of a hydrophilic polymer and the influence of compression forces. Naproxen was used as a model drug,

Eudragit RS and Eudragit RL are copolymerizates based on esters of acrylic and methacrylic acids with a low content of quaternary ammonium groups. The ammonium groups are present as salts, and they are responsible for the permeability which is independent of pH in the physiological region. The molar ratio of these hydrophilic components to the other neutral methacrylic acid esters is 1:20 for Eudragit RL (high permeability), and 1:40 for Eudragit RS (low permeability). These polymers are inert to the digestive tract content, pH independent, and capable of swelling.[12]

EXPERIMENTAL

Materials

Naproxen (kindly provided by Miser Co. for Pharm. Ind., Cairo, Egypt); Eudragits RS100 and RL100 (Rohm Pharma GMBH, Darmstadt, West Germany); Polyvinyl-pyrrolidone (K-30) supplied by the General Aniline and Film Corp., New York, USA). Other chemicals were of reagent grade.

Equipments

- Sieve shaker, RX-86-1 (Cole-Parmer Instrument Co., USA).
- Spectrophotometer, UV-1601 (Shimadzu Co., Japan).
- pH-meter, Ama digital (Ama, Germany).
- Dissolution-test apparatus, SR11 6-flask (Hanson research, USA).

Methods

Preparation of Naproxen/Eudragits coevaporates

Naproxen and Eudragit RS and/or Eudragit RL and/or PVP (K-30) were dissolved in the specified ratio in methylene chloride and the solvent was allowed to be removed by evaporation at room temperature and complete drying of the product was attained by desiccation for 3-5 days. The solid dispersion obtained was then powdered and the different particle size fractions were obtained by sieving.

The effect of particle size distribution was the first one of the objectives of this study. Three types of coevaporates with different particle size distributions were prepared, Accordingly, Naproxen/RL (3:7) coevaporates of particle size distributions, 100-200, 200-315, 400-500 and 500-630 μm were prepared. Naproxen/RS (2:8) coevaporates of particle size distributions, 100-200 and 500-630 μm and Naproxen/RS (1:9) coevaporate of particle size distributions, 100-200 and 500-630 μm were also prepared.

To investigate the effect of modification in the Eudragit RL/RS ratio on the release profile of Naproxen, coevaporates of Naproxen/RL/ RS (2:0:8), (2:1:7), (2:2:6), (2:3:5), (2:4:4), (2:5:3) and (2:8:0) were prepared. All these coevaporates had the same particle size distribution (100-200 μm) and also the same drug content (20% w/w). The addition of polyvinylpyrrolidone (PVP) to the coevaporates prepared with Eudragit RS has also been investigated by preparing coevaporates; Naproxen/PVP/RS (2:0:8), (2:1:7), (2:2:6) and (2:3:5). The four coevaporates were of the same particle size distributions (100-200 μm) and drug content (20% w/w).

To study the effect of compression forces on the release profile of naproxen, three coevaporates of Naproxen/RL/RS (2:5:3) of 100-200 μm particle size were prepared. The drug content in each of these coevaporates was 20% w/w. The following formula was used to prepare tablets at various tabletting forces:

Coevaporate of Naproxen/RL/RS (2:5:3)	
100-200 μm	125 mg
Avicel	80 mg
Lactose	181 mg
Magnesium stearate	2 mg
	388 mg

Preparation of coevaporates and physical mixtures

Coevaporates and physical mixtures of Naproxen and Eudragit RS or Eudragit RL were prepared in ratio 1:1 to study the drug/polymer interaction by IR-spectroscopy.

IR-Spectroscopy studies

IR spectra of the dried samples were obtained with an infra-red spectrophotometer using KBr pellets prepared at a pressure of 6 tons.

In Vitro release studies of the prepared coevaporates

A weighed sample of each coevaporate corresponding to 100 mg of the drug was spread over the surface of the dissolution medium (Sorensen's phosphate buffer, pH 7.4) previously warmed to 37°C. The dissolution process was conducted in a thermostatically controlled dissolution apparatus at 37°C and the rotation was at rate of 60 rpm. At each specified time interval, samples of 5 ml were withdrawn through a non-absorbable cotton wool piece as a filter and replaced with an equal volume of previously warmed fresh phosphate buffer. The withdrawn samples were analyzed spectrophotometrically at 271 nm after suitable dilution with the buffer. A blank was used to cancel the possible interference of Eudragit polymers or other additives. Dissolution rate studies were conducted duplicate.

RESULTS AND DISCUSSION

IR-Spectra studies

IR spectra showed more evidence of drug/polymers interactions. Figures (1) and (2) showed the wavelengths of some characteristic bands for Naproxen, Eudragits, coevaporates and physical mixtures. The physical mixtures showed spectra corresponding to superposition of their parent products with slightly decrease in intensities of bands. In coevaporates, the characteristic bands were disappeared. These results indicate the presence of interaction between the drug and the Eudragits.

Dissolution studies

From the obtained results, it is obvious that the release rate constants are strongly affected by the particle size distribution. By decreasing the particle size, the release rate constant increases for both coevaporates Naproxen/RL and Naproxen/RS. Therefore, the particle size must be adequately controlled to improve and optimize the release profile of naproxen. It has been noted that there was a direct proportionality between the values of half-life times and the particle size distribution. The data of the release profile from the coevaporates were listed in Table (1) and graphically represented by Figures (3) and (4).

Table (2) and Figure (5) illustrate the release rate data of Naproxen from its coevaporates Naproxen/RL/RS (2:0:8), (2:1:7), (2:2:6), (2:3:5), (2:4:4), (2:5:3) and (2:8:0) respectively. The drug content in all of these coveaporates was 20% and the particle size was 100-200 μm. The addition of highly permeable polymer e.g. RL100 can be used to increase the permeability of Eudragit RS to water and then to modify the release profiles of naproxen. It was evident that increasing Eudragit RL content improved and increased the release rate and by changing the RL/RS ratio of the coevaporate, the kinetics of Naproxen release from its coevaporates can be modulated. It was observed that there was a linear relationship between the fraction of Eudragit RL dispersed in the coevaporate and the logarithmic value of corresponding release rate constant. This relationship is graphically represented by

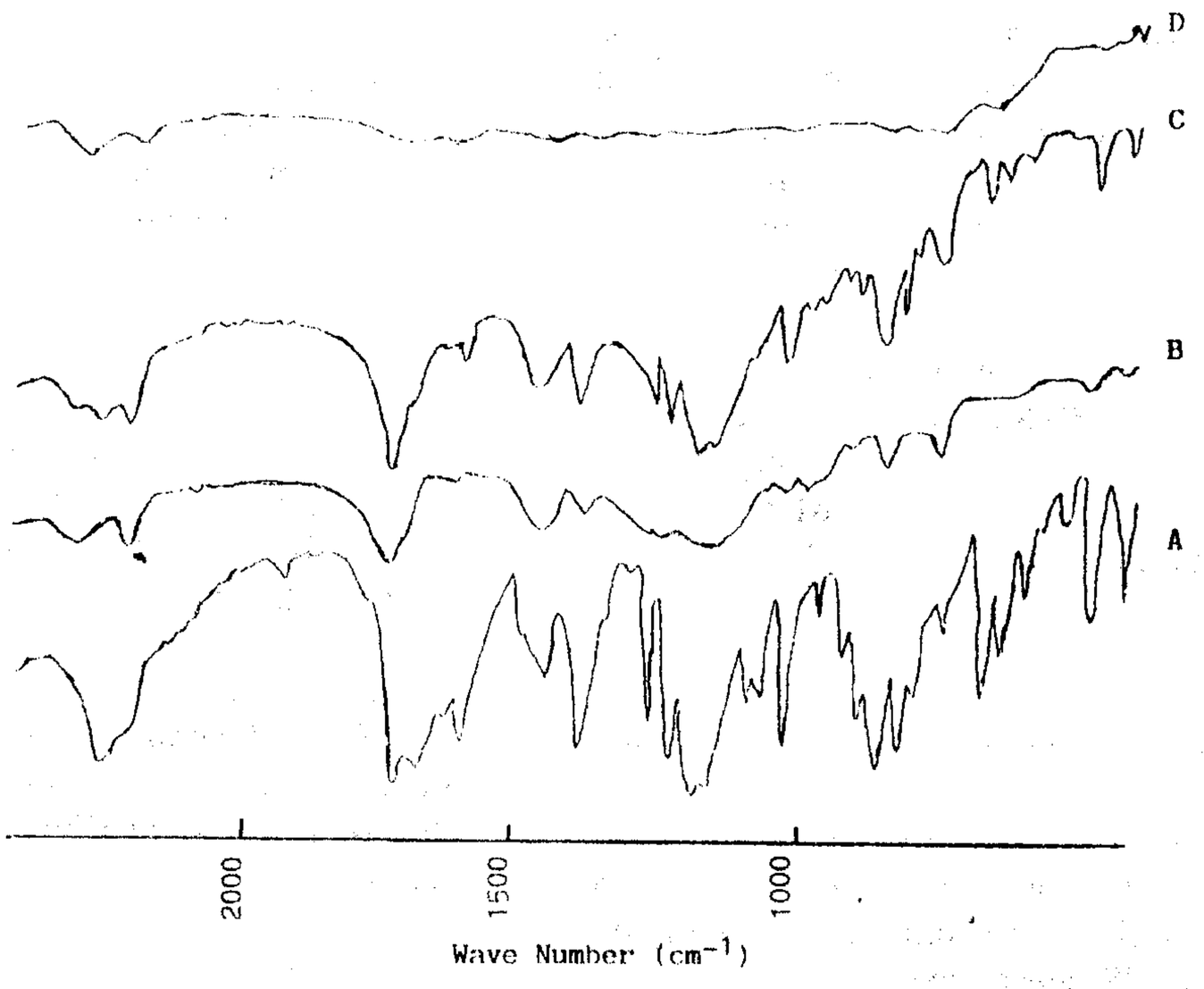

Fig. 1: IR spectra of 1:1 w/w Naproxen/Eudragit RS systems: (A) Naproxen, (B) Eudragit RS, (C) Physical mixture and (D) Coevaporate.

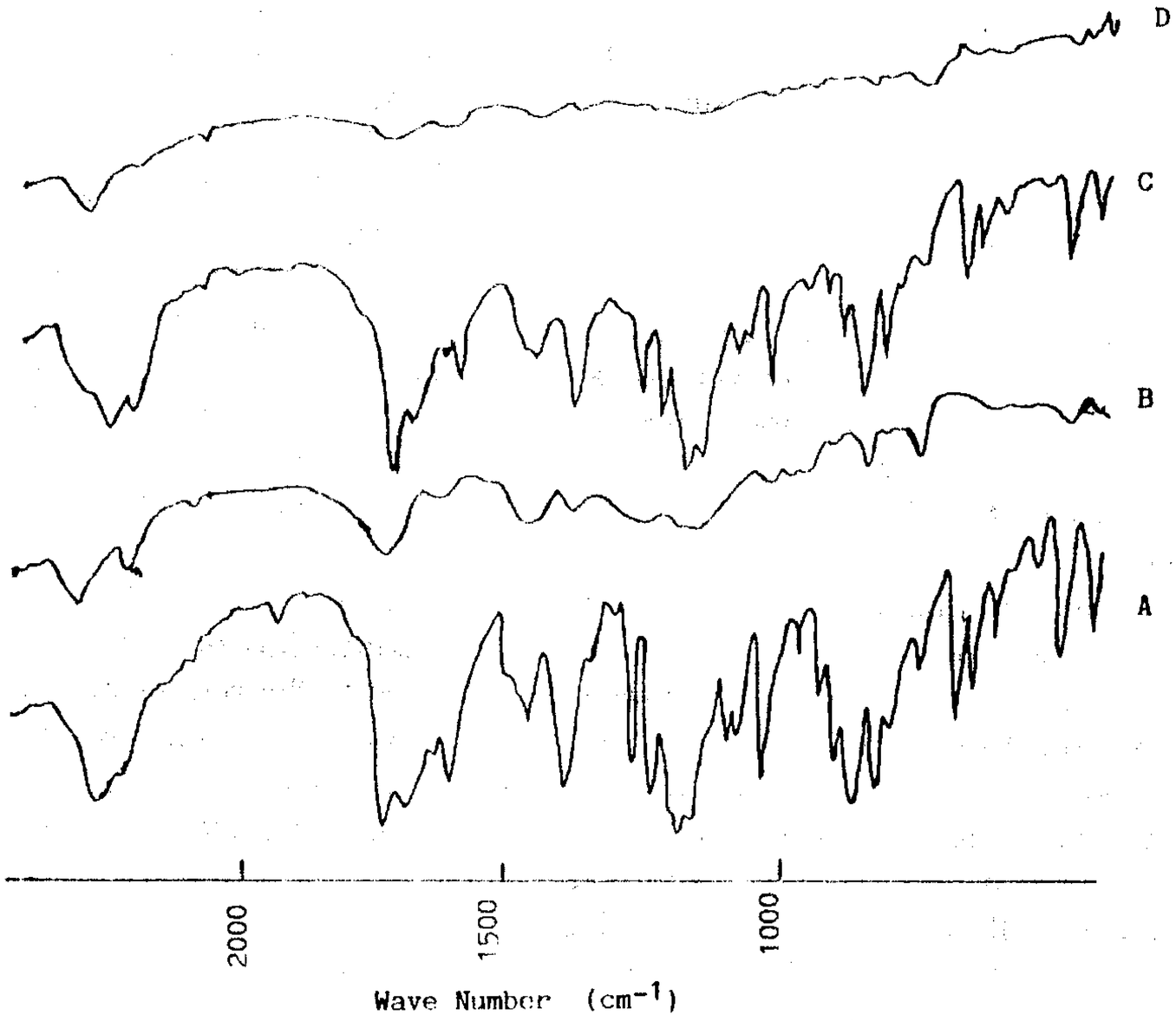

Fig. 2: IR spectra of 1:1 w/w Naproxen/Eudragit RL systems: (A) Naproxen, (B) Eudragit RL, (C) Physical mixture and (D) Coevaporate.

Table 1: Effect of partical size distribution on release rate constant (K) half-life ($t_{½}$), (t_{lag}), interecpt with Y-axis (A) and correlation coefficient (r) for various drug / polymer coevaporates at different particle size. (Higuchi-diffusion model).

Coevaporate	Particle size (μm)	Release Rate constant (K) (%/√h)	Half-Life (t½) (hr)	Correlation coefficient (r)	A (%)
Napr. : RL 100 3:7	100-200	39.332	1.130	0.994	8.159
	200-315	34.320	1.86	0.999	3.045
	400-500	24.834	3.76	0.997	1.828
	500-630	20.897	5.71	0.999	0.099
Napr. : RS 100 2:8	100-200	5.508	68.99	0.996	4.255
	500-630	3.993	144.36	0.999	2.028
Napr. : RS 100 1:9	100-200	4.943	101.4	0.995	0.226
	500-630	3.213	247.73	0.992	0.539

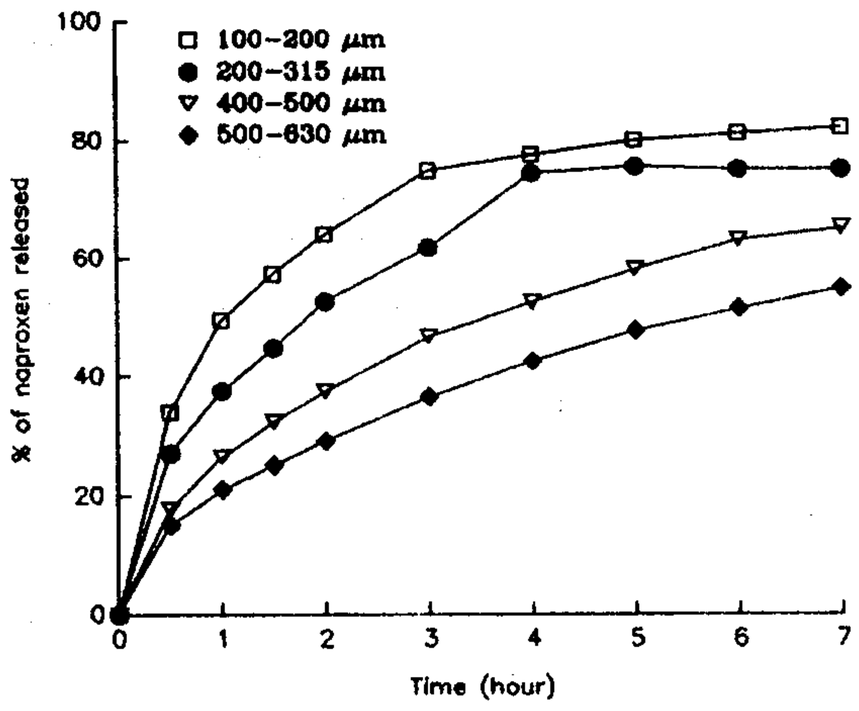

Fig. 3: Drug release profile of Naproxen/RL coevaporate (3:7) at different particle size distribution.

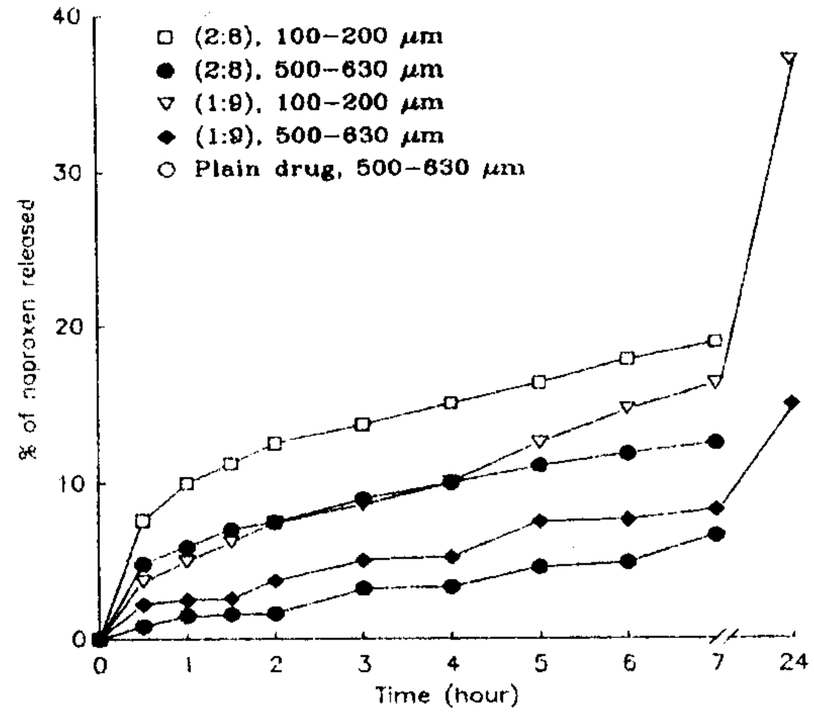

Fig. 4: Drug release profile of Naproxen/RS coevaporate (2:8) and (1:9) at different particle size distribution.

Table 2: Effect of modification in polymeric ratio an release rate constant (K) half-life ($t_{½}$), and correlation coefficient (r) for various Naproxen / RL / RS coevaporates at different RL / RS ratios (Higuchi-diffusion model).

Coevaporate Nape./ RL / RS	Fraction of Eudragit RL 100	Release Rate constant (K) (% √h)	Log Release rate constant log k (%√h)	half-life t½ (hr)	Correlation coefficient (r)
2:0:8	0.00	5.553	0.745	68.23	0.997
2:1:7	0.10	14.830	1.171	9.86	0.992
2:2:6	0.20	15.423	1.188	6.46	0.992
2:3:5	0.30	19.250	1.284	3.98	0.994
2:4:4	0.40	22.313	1.349	3.12	0.994
2:5:3	0.50	33.420	1.524	1.93	0.944

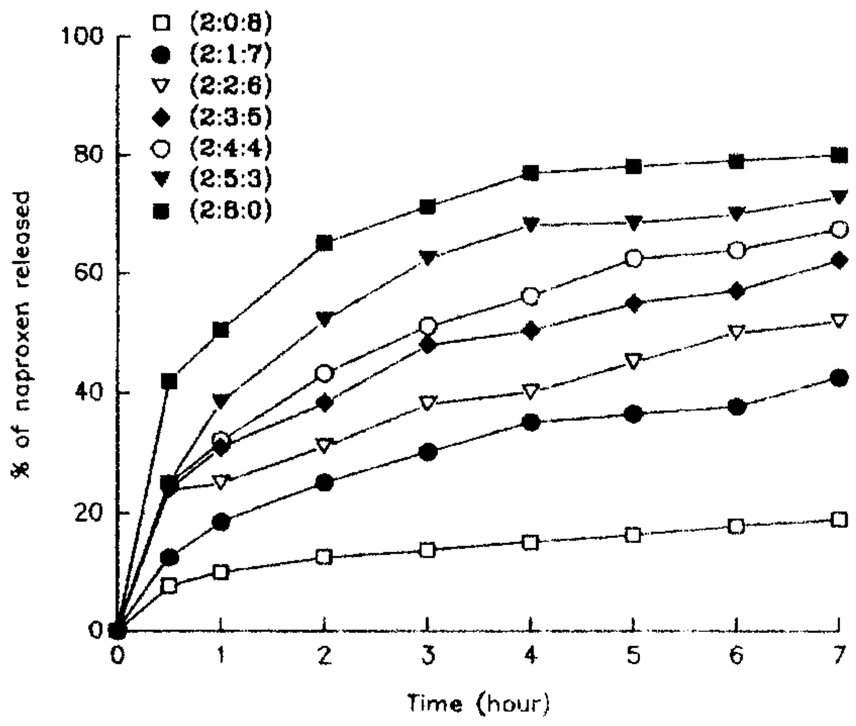

Fig. 5: Drug release profile of Naproxen/RL/RS coevaporate at various RL/RS polymeric ratios.

Figure (6). The logarithmic values of the obtained release rate constants and the corresponding fractions of Eudragit RL100 can be fitted to the linear regression program, from which the slope and Y-intercept can be obtained. So, by using the following equation, a wide range of the Higuchi release rate constants can be selected to obtain the more suitable release profile of Naproxen:

$$\log K = 1.293\ (RL) + 0.887 \qquad r = 0.996$$

In an attempt to investigate another water-soluble polymer e.g. PVP when added to the coevaporate prepared with Eudragit RS, it was found that by increasing the PVP content, there was a remarkable increase in the amount of Naproxen released. The modification in PVP/RS ratio gave rise to a non-homogenous system characterized by a fast release first portion and a slow release last portion. It has been noticed that all coevaporates containing PVP showed a considerable increase in the initial amount of Naproxen released when compared with Naproxen/ RL/RS coevaporates. Table (3) and Figure (7) illustrated the release rate data of Naproxen from its four coevaporates, Naproxen/PVP/RS (2:0:8), (2:1:7), (2:2:6) and (2:3:5).

Naproxen tablets were prepared from Naproxen/RL/RS (2:5:3) coevaporate with a particle size 100-200 μm. Table (4) demonstrates the release profile of Naproxen from tablets prepared at three different compression forces. It was found that the release rate constants are not affected by the applied compression forces, and this can be explained on the basis that there is no fusion occurring between the particles of coevaporates components during the compression process.

Table 3: Effect of incorporation of polyvinylpyrrolidone (PVP) on release rate constant (K) half-life ($t_{½}$), and correlation coefficient (r) in various Naproxen / PVP / RS coevaporates (Higuchi-diffusion model).

Coevaporate Nape./ PVP / RS	Release rate constant (K) (%/√h)	half-life $t_{½}$ (hr)	Correlation coefficient (r)
2:0:8	5.553	68.23	0.996
2:1:7	7.124	43.30	0.995
2:2:6	15.373	7.31	0.995
2:3:5	17.879	1.69	0.995

Table 4: Effect of compression forces (KN) on release rate constant (K) half-life ($t_{½}$), and correlation coefficient (r) for tables prepared with Naproxen / RL / RS (2:5:3) coevaporates using different compression forces:

Force (KN)	Release rate constant (K) (%/√h)	half-life $t_{½}$ (hr)	Correlation coefficient (r)
8	33.420	1.93	0.994
12	33.431	1.93	0.994
20	33.862	1.93	0.996

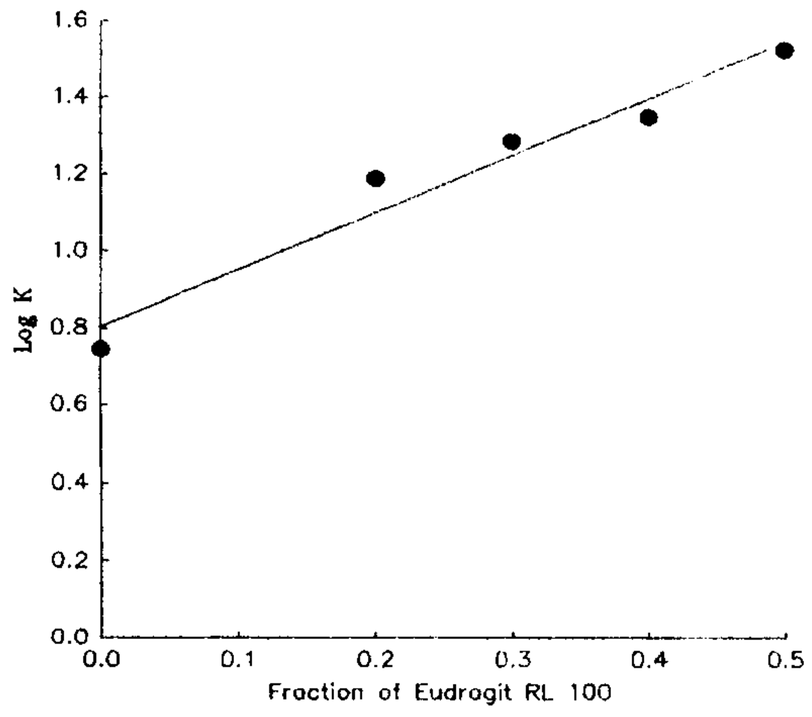

Fig. 6: Linear relationship between log values of Higuchi release rate constants and fraction of Eudragit RL 100 in Naproxen/RL/RS coevaporate at 20% w/w drug cotent and 100-200 μm particle size distribution.

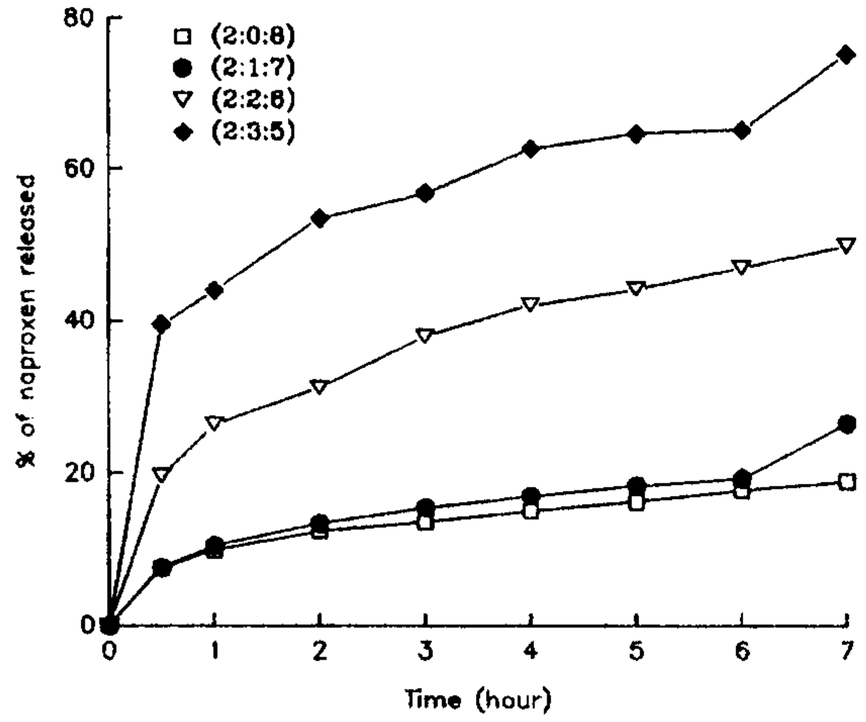

Fig. 7: Effect of PVP/RS ratio on the % of Naproxen released as a function of time.

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