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Sustained release solid dispersions of indomethacin with Eudragit RS and RL

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Summary

Sustained release solid dispersions have been investigated using Eudragit RS and Eudragit RL as carriers and indomethacin as a model drug. The solid dispersions were prepared by the solvent method. Up to 30% and up to 20% indomethacin can be dispersed amorphously in Eudragit RL and Eudragit RS, respectively. The release profiles of the drug can be fitted to the square-root of time model. Coevaporates prepared with Eudragit RS give slower release rates than those prepared with Eudragit RL. By increasing the particle size from 100 to 630 μm, the release rate can be reduced. By blending Eudragit RS and Eudragit RL, the kinetics of release can be modulated. There is a linear relationship between the Higuchi rate constant and the percentage of Eudragit RL in a Ind/RS/RL mixture. The influence of pH was studied showing that coevaporates with lower sensitivity to pH variation can be prepared. Interactions between indomethacin and Eudragit RL were investigated and were found to follow a type 1 Langmuir isotherm. The tabletting properties of coevaporates were studied and show no influence of tabletting forces on the Higuchi's release rate constant.

Introduction

Chiou and Riegelman (1971) defined a solid dispersion as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melting, the solvent or the melting-solvent method. The solid dispersion technique was commonly used to enhance the dissolution rate of poorly water-soluble drugs using water-soluble carriers (i.e. PEG, PVP, urea,...) (Ford, 1986). More recently, an increasing interest was shown in the study of solid dispersions using water-insoluble carriers as dispersing agents to produce sustained release forms. Hasegawa et al. (1985a, b and c, 1986) prepared coevaporates of various compounds (nifedipine, digoxin, dipyridamole, griseofulvin,...) using enteric coating agents (HP-50, HP-55, CAP, CMEC, Eudragit L and Eudragit S) as inert carriers. The dissolution behavior of those solid dispersions showed a supersaturation phenomenon at pH 6.8 and no dissolution at pH 1.2. Delayed absorption dosage forms with good bioavailability could then be prepared using this technique.

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Moreover, coevaporates with enteric coating agents improved the chemical stability against acidic hydrolysis as shown for digoxin. Besides, Abd El-Fattah et al. (1984) obtained sustained release forms of pheniramine aminosalicylate using coevaporates with Eudragit S, L, RS and RL. Eudragit S 100 was shown as the more suitable to reduce the release rate. Zierenberg (1986) described an in vivo sustained release action of coevaporates of clonidine prepared with Eudragit E 30D. Solid dispersions of codeine prepared by the melting and the solvent methods were studied by El Gindy et al. (1976, 1980), copolymer of vinyl acetate with 11% crotonic acid (C.A. 11) as well as Eudragit RL were used as dispersing agents. Recently Shaikh et al. (1987) prepared prolonged release solid dispersions of acetaminophen and theophylline with ethylcellulose of various viscosity grades as carrier.

Powder of solid dispersion, granules coated with coevaporates or tablets were mostly studied. In this paper, coevaporates of indomethacin 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 drug-to-polymer ratio, the particle size distribution, the RL-to-RS ratio, the addition of a hydrophilic polymer, the pH, and the interaction between drug and polymers. The influence of tabletting the coevaporate powders was also investigated. Indomethacin (Ind) was used as a model drug; it is a poorly water-soluble, nonsteroidal anti-inflammatory drug containing an acidic function. Its solubility (S) is very dependent on pH variations: pH = 5.1 S = 0.025 g/l; pH = 6.0 S = 0.19 g/l; pH = 7.2 S = 1.6 g/l (Oth and Moës, 1985); $pK_a = 4.0 \pm 0.1$ (Inagi et al., 1981).

Eudragit RS and Eudragit RL are neutral copolymers of poly(ethylacrylate, methylmethacrylate and trimethylammonioethylmethacrylate chloride). These polymers are inert to the digestive tract content, pH independent, and capable of swelling. The RS type of polymer is less permeable to gastric juice than the RL type due to its lower content in quaternary ammonium functions (RS 1/40 ammonium/ester; RL 1/20 ammonium/ester).

Materials and Methods

Materials

Indomethacin (B.P. 80); Eudragit RS 100, RL 100 (Rohm-Pharma); Plasdone K29-32 (Gaf) were used as supplied. Other chemicals were of reagent grade.

Methods

Preparation of Ind/Eudragit coevaporates. Indomethacin and Eudragit RS and/or Eudragit RL and or PVP K 29–32 were dissolved in a suitable ratio in dichloromethane, then the solvent was removed under vacuum in a rotary evaporator at 45 °C. The residue was dried for 24 h under vacuum at room temperature, ground and stored in a dessicator. The different particle size fractions were obtained by sieving (Model A2 Rhewum).

Analysis of the samples. Samples were assayed for Ind using spectroscopy analysis at 322 nm (Hitachi spectrophotometer model 100-60).

X-ray analysis. Powder X-ray diffractometry was carried out with a Philips X-ray Diffractometer, CuK_α radiation (40 kV, 16 MA, slit 1°-1°).

In vitro release studies. USP XX no. 2 dissolution apparatus was used. The stirring rate was 60 rpm. The experiments were carried out at 37 °C. The dissolution media was a 0.1 M phosphate buffer solution used at various pHs and containing 0.05% Tween 20 or the following pH gradient was used with acetic acid 0.05 M, potassium dihydrogen phosphate 0.05 M containing 0.05% Tween 20 and NaOH 4 N or HCl to adjust the pH:

0–0.5 h	pH 1.3
0.5–1 h	pH 5.0
1–4 h	pH 6.3
4–8 h	pH 6.9

The coevaporate powder was spread over the surface of the dissolution liquid. At pre-set intervals, samples of 5 ml were withdrawn through a fritted glass (G3) filter and replaced by an equal volume of fresh test fluid.

Adsorption study. Glass-stoppered tubes containing 25 ml of various Ind solution in 0.1 M phosphate buffer pH 7.2 were rotated with a

known amount of Eudragit, in a water-bath at 37 °C, 30 °C or 25 °C. After equilibrium, the samples were filtered and analyzed for Ind content. The equilibrium was reached in 24 h for the Ind/Eudragit RL system but was never reached even after a week for the Ind/Eudragit RS system. The results were also shown to be reversible and independent of phosphate buffer concentration for the Ind/Eudragit RL system.

Tablets preparation. The following formula was used to prepare tablets at various tabletting forces on an instrumented Courtoy AC27 press (B-Halle).

Coevaporate Ind/RL/RS	
3/3/4 100–200 μm	125 mg
Avicel PH 102 (FMC	
U.S.A.-Philadelphia)	80 mg
Lactose 100 mesh	
(DMV NL-Veghel)	181 mg
AcDiSol (FMC	
U.S.A.-Philadelphia)	12 mg
Magnesium stearate	2 mg
	400 mg

10 mm flat punches were used.

Results and Discussion

The powder X-ray diffraction patterns show no diffraction peaks attributed to indomethacin for coevaporates with maximally 20% of Ind dispersed in Eudragit RS, or maximally 30% of Ind dispersed in Eudragit RL; this implies the absence of apparent crystallinity for Ind in coevaporate systems. By further increasing the Ind content, the coevaporates prepared were no longer amorphous and present definite diffraction peaks. In this study, only the amorphous solid dispersions were investigated.

In vitro release

The release profiles from coevaporates Ind/RL (3 : 7) and Ind/RS (2 : 8) characterized by various particle size distributions are plotted in Fig. 1. The percentage of Ind released in much lower for the solid dispersion prepared with Eudragit RS. Indeed, Eudragit RL has a higher water permeability than Eudragit RS due to the higher quaternary ammonium content of RL. The amounts released for less than 60% Ind can be fitted to the Higuchi square-root of time model. The results are reported in Table 1 and shown in Fig. 2. The data can be linearised over 22 h for the coevaporates prepared with Eudragit RS. The calculated Higuchi constants are much lower for the coevaporates prepared with Eudragit RS than for those prepared with Eudragit RL. The Higuchi constants are strongly affected by the particle size distribution. By reducing the particle size, the release rate increases for both the coevaporates Ind/RL and Ind/RS. This parameter has to be controlled to ensure a good reproducibility of the liberation profiles.

A highly water-soluble polymer can be used to increase the permeability of Eudragit RS to water and then to modify the release profiles of Ind. So coevaporates including various ratios of RL/RS and PVP/RS were prepared. Fig. 3 shows that by changing the RL/RS ratio of the coevaporates, one can modulate the kinetics of release from the solid dispersions. Increasing the Eudragit RL content improved the release rate. The data can be linearised by the Higuchi model and are reported

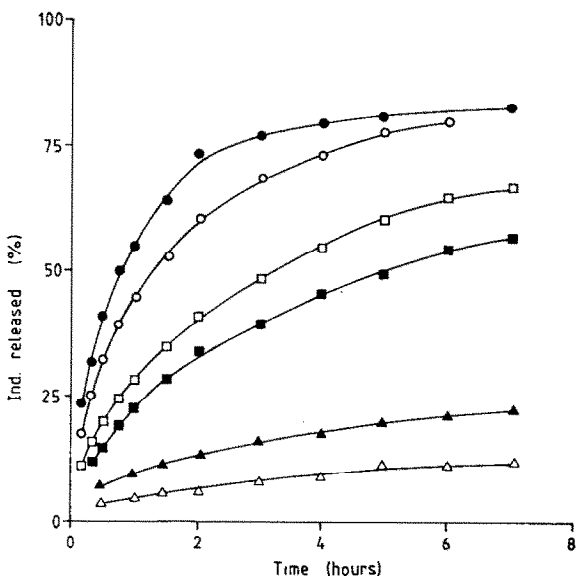

Fig. 1. Influence of particle size of the coevaporates on the percentage of Ind released as a function of time. Coevaporate Ind/RL (3:7): 100–200 μm (●), 200–315 μm (○), 400–500 μm (□), 500–630 μm (■). Coevaporate Ind/RS (2:8): 100–200 μm (▲), 500–630 μm (△).

TABLE 1

Influence of the particle size distribution and Ind/RL or Ind/RS ratios on Higuchi rate constant (K) values and the values of the intercept with the y-axis (b). r is the correlation coefficient

	Particle size (μm)	$K \pm$S.D. ($\% \cdot \sqrt{h}$)	$b \pm$S.D. (%)	r
Ind/RS				
1/9	100–200	7.2±0.1	0.0±0.3	0.998
1/9	500–630	3.5±0.1	0.1±0.2	0.998
2/8	100–200	8.1±0.4	0.9±0.4	0.999
2/8	500–630	4.1±0.3	0.6±0.1	0.997
Ind/RL				
2/8	100–200	48 ±2	3 ±2	0.989
2/8	200–315	40.2±0.7	−1 ±1	0.996
2/8	400–500	28.3±0.7	−1 ±1	0.999
2/8	500–630	23.4±0.3	0 ±1	0.997
3/7	100–200	51 ±2	5 ±3	0.996
3/7	200–315	42.4±0.3	2 ±2	0.997
3/7	400–500	27.6±0.9	2 ±2	0.998
3/7	500–630	23 ±1	0 ±1	0.998

TABLE 2

Influence of Ind/RL/RS ratios on the values of the Higuchi rate constant (K) and the values of the intercept with the y-axis (b). r is the correlation coefficient

Ind/RL/RS	%RL	%RS	$K \pm$S.D. ($\% \cdot \sqrt{h}$)	$b \pm$S.D. (%)	r
2:1:7	12.5	87.5	16.2±0.1	1.9±0.1	0.999
2:2:6	25	75	19.2±0.1	6.0±0.3	0.998
2:3:5	37.5	62.5	23.5±0.1	4.9±0.2	0.996
2:4:4	50	50	27.6±1.2	6.3±0.1	0.997
2:5:3	62.5	37.5	33.9±0.9	5.3±1.2	0.996
2:8:0	100	0	48 ±2	3 ±2	0.989
2:0:8	0	100	8.1±0.4	0.9±0.4	0.999
3:1:6	14.3	85.7	20.3±0.5	2.6±0.2	0.999
3:2:5	28.6	71.4	24.2±0.3	2.5±0.1	0.999
3:3:4	42.9	57.1	29.2±0.3	3.4±0.3	0.996
3:4:3	57.1	42.3	40.5±1.1	0.9±1.2	0.999
3:7:0	100	0	51 ±2	5 ±3	0.996
3:0:7	Non-amorphous				

in Table 2. A linear relationship exists between the percentage of Eudragit RL dispersed in the coevaporates and the Higuchi constant (Fig. 4):

Coevaporates with 20% Ind content

$$K = 0.385(\mathrm{RL}) + 9.4 \quad r = 0.997 \qquad (1)$$

Coevaporates with 30% Ind content

$$K = 0.375(\mathrm{RL}) + 14.8 \quad r = 0.980 \qquad (2)$$

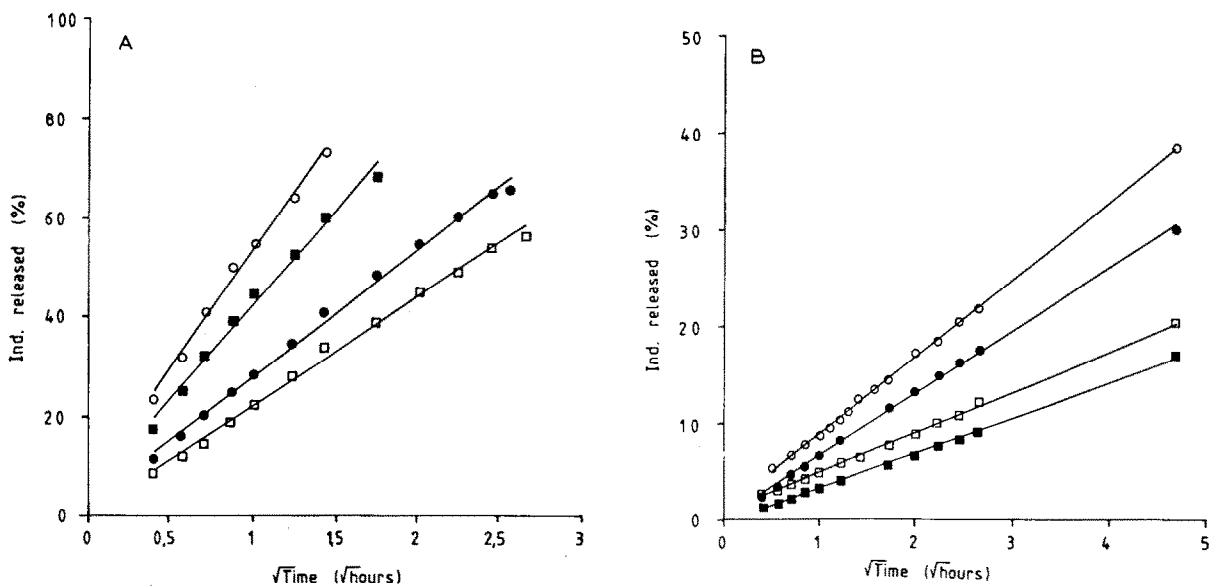

Fig. 2. A: Ind released (%) as a function of the square-root of time. Coevaporate Ind/RL (3:7): 100–200 μm (○), 200–315 μm (■), 400–500 μm (●), 500–530 μm (□). B: coevaporate Ind/RS (2:8) 100–200 μm (○), 500–630 μm (□); coevaporate Ind/RS (1:9) 100–200 μm (●), 500–630 μm (■).

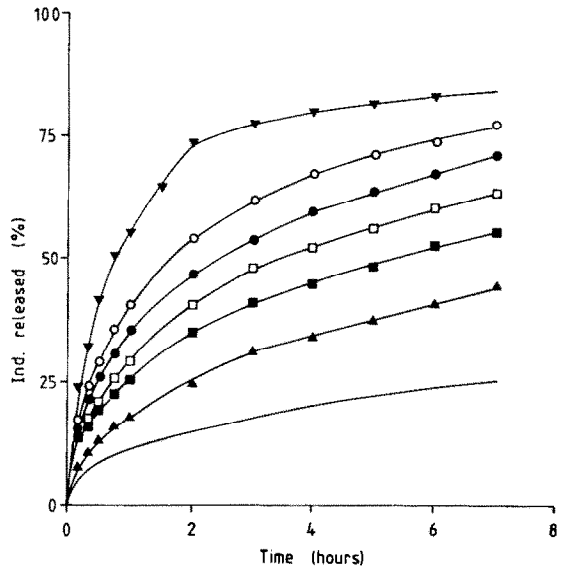

Fig. 3. Influence of RL/RS ratio on the percentage of Ind released as a function of time for various Ind/RL/RS coevaporates. Ind/RL/RS (2:0:8) (———); (2:1:7) (▲); 2:2:6 (■); 2:3:5 (□); 2:4:4 (●); 2:5:3 (○); 2:8:0 (▼).

Using Eqns. 1 or 2, a wide range of the Higuchi rate constants can be selected to obtain the more suitable release profile of the drug.

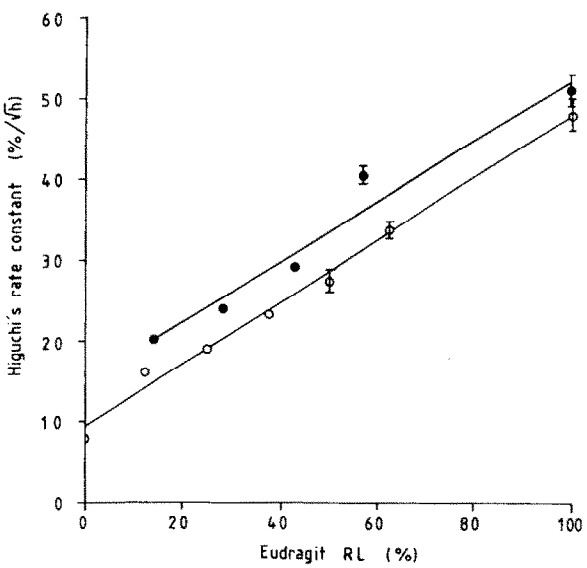

Fig. 4. Linear relationship between Higuchi rate constants and the percentage of Eudragit RL in Ind/RL/RS solid dispersions. Coevaporate Ind/RL/RS at 20% Ind (○) and coevaporate Ind/RL/RS at 30% (●).

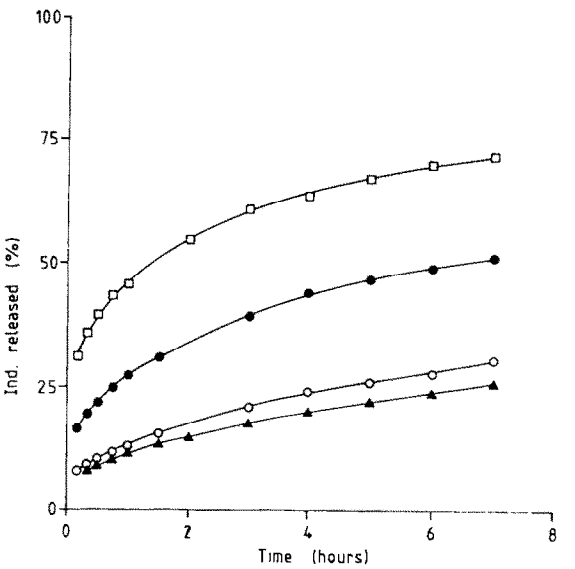

Fig. 5. Influence of PVP/RS ratio on the percentage of Ind released as a function of time. Ind/RS (2:8) (▲); Ind/PVP/RS (2:1:7) (○); Ind/PVP/RS (2:2:6) (●); Ind/PVP/RS (2:3:5) (□).

The addition of polyvinylpyrrolidone (PVP K 29-32) to the coevaporates prepared with Eudragit RS has also been investigated. The percentages of Ind released are reported in Fig. 5. By increasing the PVP content, only the initial amount of Ind released increases but after 2 h the profiles are similar to those obtained with coevaporates prepared with Eudragit RS alone. The blending of Eudragit RS and PVP gives rise to a non-homogenous system characterized by a fast release portion and a slow release portion. Using PVP/RS matrix, the liberation profiles cannot be modulated as well as with the Eudragit RL/RS system.

Indomethacin is a poorly water-soluble drug whose solubility is very pH dependent (Gueurten and Dubois, 1980). The release profiles obtained at pH 7.2, and with a gradient of pHs, are plotted in Fig. 6. For Ind/RL (3:7) coevaporates, the release rate is slower in acidic pH and surprisingly, the reverse is observed for the Ind/RS 2/8 coevaporate where the release rate measured in pH gradient is higher than when measured at pH 7.2. For the coevaporate Ind/RL/RS (3:3:4), the release is not influenced by the modification of pH, indeed there is almost superposition of the

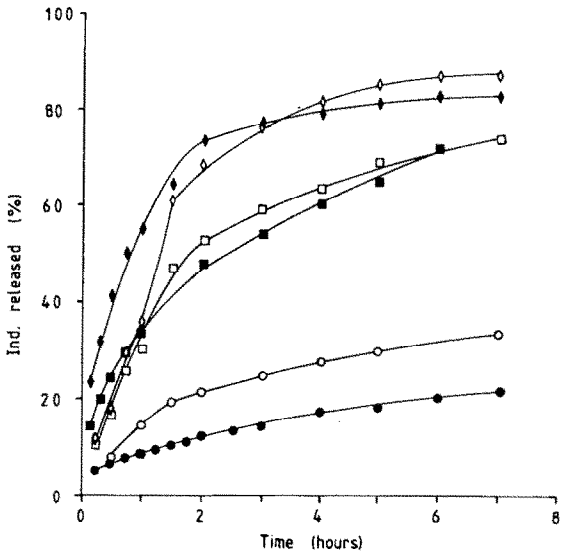

Fig. 6. Comparison of release profiles in pH gradient or at pH 7.2. Ind/RS (2:8) (●); Ind/RL (3:7) (◆); Ind/RL/RS (3':3:4) (■). Open symbols pH gradient; closed symbols pH 7.2.

data obtained at pH 7.2 and with the gradient of pHs ranging from pH 1.3 to 6.9. These results are interesting in view of the very poor solubility of Ind at low pH. For the coevaporate Ind/RL (3:7), the results at low pH can be explained by a water-solubility dependency more than by a permeability dependency. For Eudragit RS, the results can only be interpreted by a modification of the water-permeability according to pH. The water-permeability of coevaporate Ind/RS (2:8) seems to be higher in acidic solutions than in neutral fluids.

Sorption properties of Eudragits RS and RL

In release experiments, the 100% liberation was never achieved. This can be explained by the interaction existing between Ind and the polymers.

The Langmuir plot for indomethacin adsorption on Eudragit RL is shown in Fig. 7. It is a type 1 Langmuir profile that can be linearised by the following equation:

$$C/Y = 1/(b \cdot Y_m) + C/Y_m \qquad (3)$$

where C is the equilibrium concentration in mg of Ind per 100 ml of solution, Y is the amount of Ind in mg adsorbed per gram of polymer; b is a constant and Y_m is the constant giving the maximum drug that 1 g of polymer can adsorb (mg/g polymer) (Martin et al., 1969).

The results obtained at three different temperaturs are shown below

$$37\,^\circ\text{C}: \quad C/Y = 0.028 + 0.00558 \cdot C \quad r = 0.996$$
$$30\,^\circ\text{C}: \quad C/Y = 0.021 + 0.00535 \cdot C \quad r = 0.991$$
$$25\,^\circ\text{C}: \quad C/Y = 0.021 + 0.00570 \cdot C \quad r = 0.984$$

$$37\,^\circ\text{C}: \quad Y_m\ (\text{mg/g}) = 179$$
$$30\,^\circ\text{C}: \quad = 187$$
$$25\,^\circ\text{C}: \quad = 172$$

The interaction between Eudragit RL and Ind is saturable, follows a type 1 Langmuir isotherm, is reversible and not influenced by temperature. The maximum amount of Ind which is adsorbed by 1 gram of Eudragit RL is 180 mg/g. This is equivalent to 75 moles of Ind adsorbed by 1 mole of Eudragit RL. In vitro, the interaction between Eudragit RL and Ind is high enough to avoid 100% release. In vivo, where perfect sink conditions exist, the 100% release should be achieved because the adsorption phenomenon is reversible.

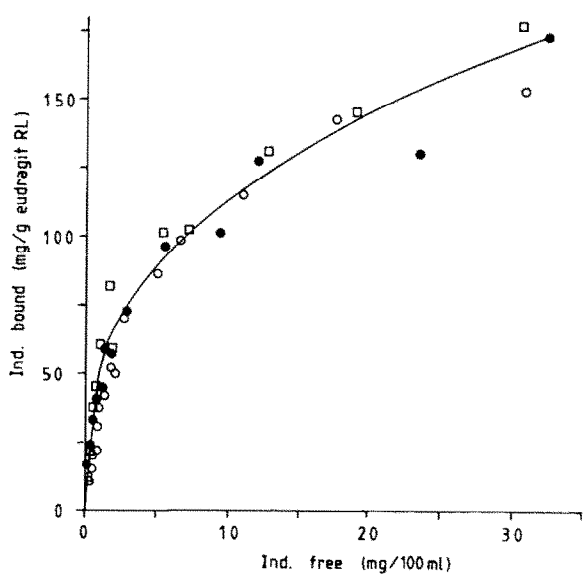

Fig. 7. Langmuir plot for Ind adsorption on Eudragit RL at 25 °C (●); 30 °C (□); 37 °C (○).

TABLE 3

Influence of compression forces on the values of the Higuchi rate constant and the values of the intercept with the y-axis. r is the correlation coefficient

Force (kN)	$K \pm$S.D. ($\% \cdot \sqrt{h}$)	$b \pm$S.D. (%)	r
7.6±0.4	26.4±0.2	9.1±0.1	0.993
11.7±0.3	26.0±0.2	9.8±0.2	0.993
19.3±0.7	26.2±0.1	8.3±0.4	0.994

For Eudragit RS, because of the low permeability of the polymer, the equilibrium was never reached even after a week so the study could not be realised, since Ind is not stable in water for such a long period.

Tabletting properties

Tablets were prepared with the Ind/RL/RS (3 : 3 : 4) coevaporate (sieve fraction 100–200 μm). The release profiles of Ind from tablets prepared at 3 different tabletting forces are reported in Table 3. The Higuchi rate constants are not influenced by the force applied. This means that there is no fusion between the particles of coevaporate during the compression process.

Conclusions

Sustained release forms of Ind can be prepared using coevaporates with Eudragit RL and RS. The particle size distribution of the coevaporates is an important parameter which has to be kept under control. The RL/RS ratio can be optimized to modulate the release profile of the drug. The liberation rate from the coevaporate Ind/RL/RS is less influenced by pH modifications than expected from the solubility data of the active principle. Moreover, the dose is dispersed in many sub-units which is presumably better to achieve less erratic gastric transit times than when it is contained in a monolithic dosage form. Dryable conventional tablets can be prepared easily without influencing the release profile of the drug.

Several points still have to be investigated before proposing the use of such coevaporates:

- the possible modifications of the release kinetics, to avoid too great a decrease of the drug release rate as the liberation proceeds;
- the stability of coevaporates on ageing;
- the in vivo disintegration of tablets and hard gelatin capsules;
- the spreading and the gastric emptying of particles;
- the spreading of the particles in the small intestine and colon.

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