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Surface and transport properties of acrylic polymers influencing drug release from porous matrices *

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Summary

Three acrylic/methacrylic esters copolymers with different percentages of hydrophilic groups were used to prepare porous matrices containing aspirin as a drug model. The surface and transport properties of these matrices were studied by measuring the liquid/polymer contact angle and the liquid penetrability, whereas the porous structure was measured by mercury porosimetry. In the case of a non-wetting liquid, such as water, the penetration was found to be controlled by the intraparticle polymer diffusion, whereas for a wetting liquid the penetration was capillary driven.

Consequently the drug release was dependent on the pore structure, i.e. the compaction pressure, in the case of a wetting liquid, whereas no pore structure influence was found in the case of water. Furthermore, whatever the copolymer used or the dissolution medium employed, the drug release was found $\sqrt{t}$-dependent suggesting a drug diffusion only through the interparticle pores.

Introduction

The compaction of a mixture of a drug and a polymer, first proposed by Higuchi (1963) and Desai et al. (1965, 1966a and b), is still one of the most practical

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techniques to obtain oral controlled release tablets. The resulting polymer matrices can be defined as a drug-containing heterogeneous porous systems, either inert (Salomon and Doelker, 1980) or hydrophilic (Buri and Doelker, 1980), in which the voids between the polymer and drug particles form a continuous interconnected network of pores.

The study of such heterogeneous systems has concentrated on analyzing the drug release pattern, with many different mathematical models proposed to interpret the data (Higuchi, 1963; Gurny, et al., 1982; Bamba et al., 1979; Fessi, 1978; Cobby, 1974).

On the other hand, few authors have worked to find the relevance of the physical characteristics (wettability, pore structure) of such porous heterogeneous matrices in the overall process of drug release (Rowe, 1973; Carli and Simioni, 1978 and 1981).

More work has been done to characterize the physical and chemicophysical parameters of the homogeneous matrices, i.e. systems in which the drug is homogeneously dispersed in the polymeric network itself (Flynn, 1974). In such systems the crystallinity of the polymer (Korsmeyer and Peppas, 1981), the cross-linking internodal molecular weight (Reinhart et al., 1981), the porous structure (Miller et al., 1983) and the thermodynamic polymer/solvent interaction (Korsmeyer and Peppas, 1983) have been found to influence the drug release mechanism. Furthermore it was recently pointed out how to exploit such characteristics to obtain a zero-order drug release (Peppas and Franson, 1983) from these homogeneous matrices.

The role of the liquid capillary penetration into the heterogeneous inert matrices (Carli and Simioni, 1978) and of the liquid diffusion through the polymer network in the homogeneous matrices has been investigated (Korsmeyer and Peppas, 1981; Franson and Peppas, 1983), whereas no attempt was carried out to measure the capillary and diffusion phenomena into heterogeneous, hydrophilic and porous matrices.

It is the object of this paper to characterize the basic physical parameters (porous microstructure, surface wettability, and liquid penetrability) of matrix tablets prepared by simple direct compression of mixture of acrylic/methacrylic ester copolymers and a model drug (acetylsalicylic acid) and to relate these parameters to the drug release mechanism. It was decided to use a direct compression technique, with no additives, although the technological properties of such systems were not particularly good, in order to get information which were intrinsic to the polymeric material itself.

Among the different types of acrylic/methacrylic esters copolymers, we decided to study three acrylic resins with a different percentage of hydrophilic quaternary ammonium groups, in order to better point out the relationship between the chemical structure of the polymer on one side and the physical characteristics of the matrix and the drug release mechanism on the other side.

Materials and Methods

Materials

The three copolymers of acrylic/methacrylic esters used were: Eudragit RL, with

10% of hydrophilic quaternary ammonium groups (particle size distribution by Alpine Air Jet Sieve: 33.2% > 125 μm; 42% > 63 μm; 60% > 32 μm); Eudragit RS, with 5% of quaternary ammonium groups (19% > 125 μm; 28.6% > 63 μm; 50% > 32 μm); a special form of Eudragit (Praeparat 281/D: 50% > 125 μm; 71.8% > 63 μm; 74% > 32 μm), with no quaternary ammonium group, similar to the commercialized type E30D, but with a different content of ethyl groups.

All the three polymeric powders were with no additives and were used as received from Rohm Pharma (Darmstadt, F.R.G.).

Acetylsalicylic acid was chosen as the drug model (F.U., Farmitalia Carlo Erba, Italy).

Methods

Matrices were made by directly compressing a uniform aspirin-polymer powders mixture (about 500 mg) containing 10% w/w of the drug, using a compaction machine (Nassovia, F.R.G.) instrumented with piezoelectric loadwashers (Kistler, Switzerland), with a single 13 mm flat-face punch and die.

Liquid/solid contact angles were measured by a Wettability Tester (Lorentzen-Wettre, Sweden) and the method of Mack (1936).

Penetration measurements were carried out using a simple apparatus, elsewhere described (Couvreur et al., 1976); demineralized water saturated with aspirin and a pH 1.2 buffer solution containing 0.1% w/v of sodium laurylsulphate were used as penetration liquids, at room temperature.

Total pore volume and pore size distribution were determined using mercury porosimetry (Mod. 225, Carlo Erba Strumentazione, Italy), with intrusion pressure ranging from 0 to 2000 atm.

Aspirin release rates in 500 ml of distilled water and the surfactant pH 1.2 buffer solution thermostated at 37 °C were determined using the beaker method with mild agitation (40 rpm), as suggested by Sjögren (1971) and exposing a single surface to the dissolution medium. Aspirin was assayed spectrophotometrically (Pye Unicam SP-8-100), following the method of Javaid and Cadwallader (1972).

Results and Discussion

Surface wettability

The surface wettability of the three copolymers was determined by measuring directly the contact angle of water drops placed on the surface of compacts of the polymers. In the direct method it is necessary to correct the data of the apparent contact angles by taking into account the porosity of the surface on which the liquid drop has been placed. This can be conveniently done by using the following equation (Johnson and Dettre, 1969; Carli and Colombo, 1983):

$$\cos \theta_a = (1 - \epsilon)\cos \theta_t - \epsilon \qquad (1)$$

where θ_t is the true contact angle, θ_a is the apparent contact angle and ϵ is the

compact porosity, assumed to be equal to the surface porosity.

In Table 1 the values of the apparent and true contact angles of compacts of the three copolymers prepared at different compaction pressure are reported. It is interesting to observe that all three copolymers were shown to have a non-wettable surface, i.e. a water/solid contact angle higher than 90°. Furthermore the quaternary ammonium groups content (at least in the range studied) seems not to exert a strong influence on the surface wettability of the acrylic/methacrylic ester copolymers: there is only a small increase of the wettability due to the introduction of 5% of hydrophilic groups (103° of water contact angle for Eudragit Special Form compared to 98° for Eudragit RS), but no significant difference was found between the two copolymers with hydrophilic groups.

The water contact angles of the matrices containing 10% w/w of aspirin were also measured: no significant difference was found with the contact angles measured on compacts of the pure copolymers.

Furthermore we measured the contact angle of the pure Eudragit RS compacts prepared at 501.3 $MN \cdot m^{-2}$ with a pH 1.2 buffer solution containing 0.1% w/v sodium laurylsulphate: a value of 58°30′ was found, indicating that this surfactant solution was able to wet the polymer.

Pore structure

In Table 2 are reported the pore structure characteristics, derived by mercury porosimetry, of matrices of the three copolymers prepared at different compaction pressures. The effect of the compaction pressure is similar for the three copolymers, at least in the range 50–200 $MN \cdot m^{-2}$, with Eudragit RS and RL producing less porous matrices and smaller pores and Eudragit Special, on the other hand,

TABLE 1

APPARENT AND TRUE WATER/POLYMER CONTACT ANGLES OF THE THREE ACRYLIC/METHACRYLIC ESTERS COPOLYMERS

Copolymer	N^+ (%)	Compaction pressure ($MN \cdot m^{-2}$)	Compact porosity	Apparent contact angle	True contact angle	Mean true [a] contact angle
Eudragit	0	78.5	0.26	117°05′	105°10′	
Special		86.6	0.22	112°20′	101°49′	103°21′
		157.8	0.18	111°25′	103°03′	
Eudragit RS	5	56.0	0.28	113°02′	98°45′	
		79.8	0.23	109°32′	97°32′	98°08′
		104.9	0.19	107°55′	98°06′	
Eudragit RL	10	54.3	0.30	112°45′	97°08′	
		74.9	0.25	109°52′	96°53′	98°09′
		99.2	0.21	111°12′	101°04′	
		137.2	0.18	106°42′	97°32′	

[a] Derived by the true contact angles at each compaction pressure.

producing more porous compacts with larger pores. These slight differences may be attributed, at least partially, to the different particle sizes of the three polymeric powders. For all three copolymers the increase of the compaction pressure brings about a large reduction of the pore volume and a shift of the pore size distributions towards the smaller sizes, as shown by Fig. 1A, B and C. From such figures it is also possible to observe that all the pore size distribution curves are unimodal, suggesting that the increase of the compaction pressure does not cause any fragmentation of the polymeric particles (Carli et al., 1981).

The porous structure of matrices containing 10% w/w of aspirin was also characterized by mercury porosimetry: the addition of the drug caused only minor modifications of the microstructure of the polymeric matrices.

Penetrability

Fig. 2 shows the double logarithmic plot of the water penetration data of pure Eudragit RS and RL matrices; no water penetration at all was registered for the Eudragit Special Form matrices. This type of plotting has been found (Carli and Simioni, 1979) to be the most suitable to show the variability of the exponent m in the general equation defining the capillary penetration process:

$$V = Kt^m \quad (2)$$

where V is the liquid penetration volume, K a constant, t the time of penetration and m a numerical factor. On the basis of the water contact angle, no capillary penetration can take place in any of the three matrices, the surface of all the three copolymers being highly non-wettable. Thus it seems reasonable to attribute the water penetration found for the Eudragit RS and RL matrices to a liquid transport

TABLE 2

POROUS STRUCTURE CHARACTERISTICS OF MATRICES OF THE ACRYLIC/METHACRYLIC ESTERS COPOLYMERS

Copolymer	Compaction pressure ($MN \cdot m^{-2}$)	Total pore volume (ml/g)	Mean pore [a] radius (μm)
Eudragit	62.7	0.195	10.5
Special	86.7	0.147	8.5
	157.8	0.128	7.7
Eudragit RS	56.0	0.197	5.6
	104.9	0.145	5.1
	492.0	0.082	3.8
Eudragit RL	54.3	0.257	5.8
	99.2	0.180	4.5
	516.1	0.108	3.4

[a] Derived at 50% of the total mercury intrusion volume.

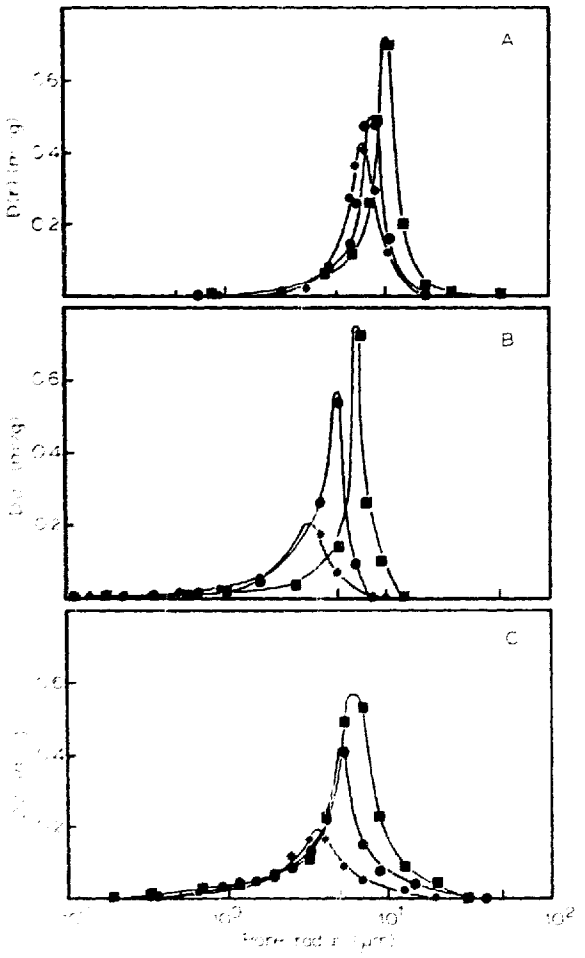


Fig. 1. Effect of compaction pressure on the pore size distribution of matrices of Eudragit Special form (A); ■, 62.7 MN·m^{-2}; ●, 87.7 MN·m^{-2}; *, 157.8 MN·m^{-2}; Eudragit RS (B); ■, 56.0 MN·m^{-2}; ●, 104.9 MN·m^{-2}; *, 492.0 MN·m^{-2}; Eudragit RL (C); ■, 54.3 MN·m^{-2}; ●, 99.2 MN·m^{-2}; *, 516.1 MN·m^{-2}.

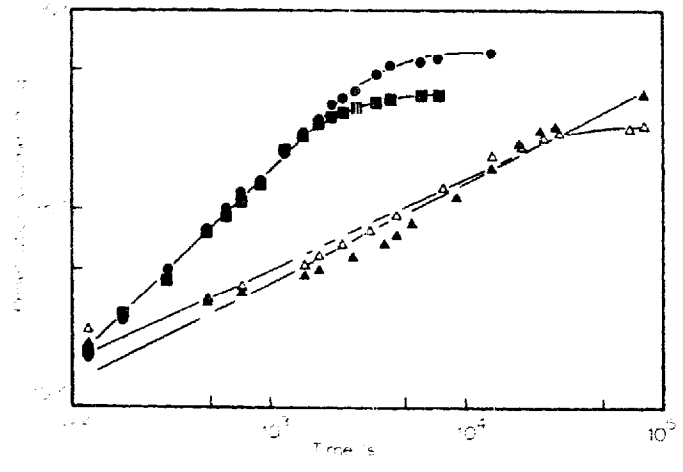


Fig. 2. Effect of compaction pressure on water penetration into Eudragit RS (▲, 56.0 MN·m^{-2}; △, 501.3 MN·m^{-2}) and Eudragit RL matrices (●, 54.3 MN·m^{-2}; ■, 516.3 MN·m^{-2}).

process taking place through the polymer particles. This interpretation is supported by the fact that films of the acrylic/methacrylic copolymers with quaternary ammonium groups have been found (Okor, 1982) to have a strong permeability, related to the content of hydrophilic groups. Furthermore, an analysis of variance of the mean values of the slopes of the double logarithmic plots of the penetration data in the Eudragit RS and RL prepared at the highest and lowest pressure (see Table 3) showed that they do not statistically differ ($t = 0.713$, at $P < 0.001$ and df = 40, for Eudragit RL matrices; $t = 0.878$, at $P < 0.001$ and df = 35, for Eudragit RS matrices). This suggests that the penetration in these matrices is not capillary driven. In fact the authors have shown (Carli et al., 1981) that, for a capillary process, the slopes of double logarithmic plots of penetration data in tablets progressively diminish as the pore size distribution shifts towards the smaller size range. On the contrary, as shown in Table 3, for the Eudragit RS and RL matrices prepared at different compaction pressure all the parameters of the penetration curves remain unchanged, although the porous structure (see Table 2 and Fig. 1) is very different.

It is also interesting to observe that both the penetration rate constant K and the slope m of the double logarithmic plots increase as the hydrophilic quaternary ammonium groups content increases. For the Eudragit Special form matrices, neither a capillary penetration process through the pores nor a transport flow through the particles is registered, due to the non-wettability of the surface and the absence of hydrophilic groups.

TABLE 3

LIQUID PENETRATION CHARACTERISTICS OF ACRYLIC/METHACRYLIC COPOLYMERS MATRICES

Parameters are relative to the general equation $V = Kt^m$ (Carli and Simioni, 1979; Franson and Peppas, 1983)

Liquid	Copolymer	N^+ (%)	Compaction pressure ($MN \cdot m^{-2}$)	m [a]	K [b] ($ml^{1/m}/g^{1/m}s$)	r [c]	F [d]
Water	Eudragit RS	5	56.0	0.504 ± 0.028	$1.925 \times 10^{-6} \pm 1.653$	0.975	333.53(17) [e]
			492.0	0.461 ± 0.015	$1.444 \times 10^{-6} \pm 0.757$	0.991	889.34(18) [e]
	Eudragit RL	10	54.3	0.940 ± 0.039	$1.325 \times 10^{-4} \pm 0.611$	0.983	575.80(22) [e]
			516.1	0.982 ± 0.039	$1.483 \times 10^{-4} \pm 0.639$	0.984	612.67(23) [e]
Sodium lauryl sulphate (0.1 M w/v pH 1.2) solution	Eudragit RS	5	56.0	0.520 ± 0.033 [f]	$2.78 \times 10^{-4} \pm 1.57$	0.982	249.49(4) [e]
			492.0	0.056 ± 0.005 [f]	$1.25 \times 10^{-26} \pm 6.15$	0.980	148.01(6) [e]

[a,b] Derived from the slope and the intercept, respectively, of linear region of double logarithmic plots.

[c] Correlation coefficient at linear region of double logarithmic plots.

[d] Analysis of significance of the linear model.

[e] Degrees of freedom.

[f] Relative to first linear region (capillarity; see Fig. 3).

Finally it remains to be stressed that also in the case of transport flow through the polymer itself, interesting information can be drawn from the values of the slopes of double logarithmic plots (Franson and Peppas, 1983): in the case of m values equal to 0.5, the liquid transport through the polymer is considered to be Fickian, i.e. due to a simple diffusion process of the liquid molecules through the polymer network (Barrie, 1968); if the values of m are equal to 1, the liquid transport is considered to be controlled by a so called Case II mechanism, i.e. a non-Fickian penetration process, in which, the polymer network swells and relaxes as the liquid front advances (Alfrey et al., 1966). In fact the Eudragit RS matrices, presenting a slope of 0.5, did not apparently swell in the 8 h of observation, whereas the Eudragit RL matrices, with a slope of 1, swelled during the penetration process.

In order to confirm the interpretation of the water penetration data reported above, we decided to measure also the penetration rate of a pH 1.2 buffer solution containing 0.1% w/v of sodium laurylsulphate into the Eudragit RS matrices. As we have seen, the polymer presents a contact angle with this surfactant solution smaller than 90°, indicating that a capillary penetration can take place along the interparticle pores. This is indeed the case, as shown in Fig. 3: the penetration pattern of the matrices prepared at the higher compaction pressure dramatically differs from the penetration into the matrices compacted at lower pressure; this is due to the fact that the different porous structure exerts a strong influence on the capillary process. In fact both the m and K values of the penetration rate are considerably reduced by the increase of the compaction pressure (see Table 3). In fact the m values were shown to be statistically different with a high level of significance ($t = 6.701$, $P < 0.001$, df = 12). Furthermore, it is interesting to observe that after the interparticle capillary penetration has completed after 100–300 s, the intraparticle permeation takes place, as suggested by the non-significant difference between the m values of the second stage penetration process in the two differently compacted matrices.

Finally, the water penetration into the matrices containing aspirin was also

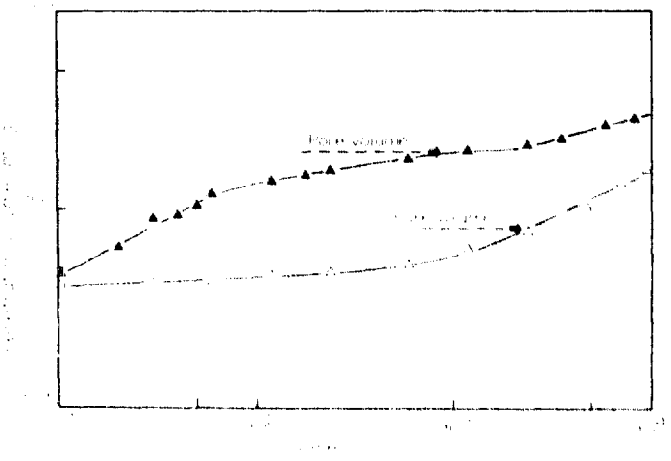


Fig. 3. Effect of compaction pressure on the penetration of a pH 1.2 buffer solution containing 0.1% w/v of sodium laurylsulphate into Eudragit RS matrices (▲, 56.0 MN·m^{-2}; △, 501.3 MN·m^{-2}). Arrows show the total pore volume (by mercury porosimetry) available for capillary penetration.

measured: for both the Eudragit RS and RL the same intraparticle permeation controlled process was found, with no influence of the compaction pressure.

Drug release

As suggested by Korsmeyer et al. (1983) we plotted the drug release data on a double logarithmic plot. As reported in Fig. 4, and on the basis of the considerations pointed out by Korsmeyer et al. (1983), the slope m of such a plot for the Eudragit RL matrices seems to suggest an anomalous Fickian drug diffusion mechanism, whereas for the Eudragit RS and Special the drug diffusion seems to be almost perfectly Fickian.

In order to further investigate the type of drug release mechanism taking place in the acrylic/methacrylic esters copolymers matrices, we plotted the percentage of aspirin undissolved (M) vs time (t) according to four different models.

(1) $100 - M = K_r\sqrt{t}$, the well known Higuchi's model, relative to a drug release process controlled by the diffusion of drug through the pores of the matrix (Higuchi, 1963; Desai et al., 1965, 1966a and b).

(2) $\ln M = -K'_r t$, an exponential model found by Bamba et al. (1979) to fit the release data from gel forming matrices, in which the drug diffuses through a gel barrier.

(3) $\sqrt[3]{100} - \sqrt[3]{M} = K''_r t$, which is relative to a drug release process controlled by the dissolution of the drug particles (Bamba et al., 1979).

(4) $100 - M = K^0_r t$, a zero-order model, which has been found applicable to hydrophobic porous polymeric matrices (Gurny et al., 1982) and to swellable continuous polymeric matrices in which the swelling process is the controlling factor, being much slower than the drug dissolution (Hopfenberg et al., 1981).

As shown in Table 4, for all three copolymers the model with the best linear fitting parameters was the Higuchi's equation, suggesting that the drug release is controlled by the drug diffusion through the matrix pores and not through the

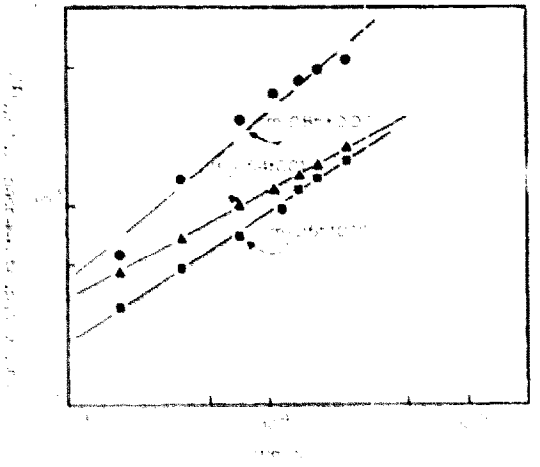


Fig. 4. Double logarithmic plot of aspirin fraction release, in water, from Eudragit RL (●), Eudragit RS (■) and Eudragit Special (▲) matrices. The release not being dependent on compaction pressure, the reported data are the mean of both the compaction pressures.

swollen polymer. The higher significance of the square-root of time model over the other three equations was also tested by a *F*-test, as carried out by Bamba et al. (1979). It is also interesting to observe (see Table 4) that the Higuchi's drug release constant of Eudragit RL matrices is very much higher than those of Eudragit RS and Special Form, which were practically equal; this can be reasonably attributed to the swelling of the polymer particles, leading to breaking and erosion of the matrix structure with consequent enhanced drug release rate and anomalous Fickian behavior.

The diffusion of drug through the polymer itself can be ruled out also by considering that no release rate difference was found between matrices of permeable Eudragit RS and non-permeable Eudragit Special; or by considering that the polymers are completely insoluble, so that also in the case of the most permeable Eudragit RL, the smaller polymer particles remain individually separated, not forming a continuous gel barrier.

TABLE 4

LEAST-SQUARES PARAMETERS OF DIFFERENT MATHEMATICAL MODELS OF DRUG RELEASE FROM ACRYLIC/METHACRYLIC ESTERS COPOLYMERS MATRICES (M = % OF UNRELEASED DRUG; t = TIME, HOURS)

The release not being dependent on compaction pressure, statistical analysis was performed on the data registered at all the compaction pressures.

Mathematical model	Eudragit Special			Eudragit RS			Eudragit RL		
	r^2	F^a	slope	r^2	F^a	slope	r^2	F^a	slope
$100 - M = K_r\sqrt{t}$	0.9967	1791.0	7.7	0.9956	1367.2	7.2	0.9830	347.2	25.7
$\ln M = -K'_r t$	0.9906	630.0	−0.026	0.9910	659.7	−0.023	0.9621	152.4	−0.11
$\sqrt[3]{100} - \sqrt[3]{M} = K''_r t$	0.9891	544.4	0.038	0.9897	577.6	0.035	0.9252	74.3	0.15
$100 - M = K^0_r t$	0.9857	414.2	2.2	0.9869	452.4	2.1	0.9204	69.4	7.3

[a] Analysis of significance of the linear model (for each matrix type the degrees of freedom were 54).

TABLE 5

EFFECT OF COMPACTION PRESSURE ON HIGUCHI DRUG RELEASE RATE CONSTANT FROM EUDRAGIT RS MATRICES IN WATER AND SODIUM LAURYLSULPHATE SOLUTION (0.1% w/v IN pH 1.2 BUFFER)

Liquid	Compaction pressure (MN m^{-2})	Higuchi constant ($h^{-1/2}$)
Water	56.0	6.95 ± 0.24 [a]
	492.0	7.59 ± 0.33 [a]
Sodium laurylsulphate solution	56.0	9.03 ± 0.61 [b]
	492.0	6.58 ± 0.35 [b]

[a] The constants do not statistically differ ($t = 2.406$, at $P < 0.001$, df = 14).

[b] The constants are statistically different ($t = 7.055$, at $P < 0.001$, df = 14).

Finally it was found that the compaction pressure, i.e. the pore structure, does not influence the water drug release rate, (see Fig. 5 and Table 5), as in the case of the permeation rate; on the contrary, in the case of the surfactant solution, the drug release rate is influenced by the compaction pressure (see Table 5): this can be reasonably attributed to the different capillary volume available for the drug diffusion.

On the basis of the results shown, it is possible to conclude that the copolymers with 10% of the hydrophilic groups can lead to higher release rates, whereas the two other copolymers give rise to slower release rates, due to their low swelling (Eudragit RS), or total lack of swelling (Eudragit Special).

Although the Eudragit RL presents a case II (swelling controlled) permeation process, the drug release rate from porous matrices prepared with physical mixture of the drug and this polymer is definitely not constant: this confirms that drug diffusion takes place through the interparticle pores and that the deviation from normal Fickian behaviour is probably due to the swelling and breaking of the pore structure in the course of the release process.

Furthermore, also some general considerations can be made.

(1) A polymer with poor surface wettability can have on the contrary good liquid transport ability. Thus both properties must be characterized in order to properly use the polymer under study in the design of a controlled release system.

(2) Double logarithmic plotting of penetration data into matrices compacted at different pressures allows not only to distinguish between a capillary driven process and a permeation process (see Scheme 1), but also, in the latter case, to further identify the type of diffusion through the polymer network.

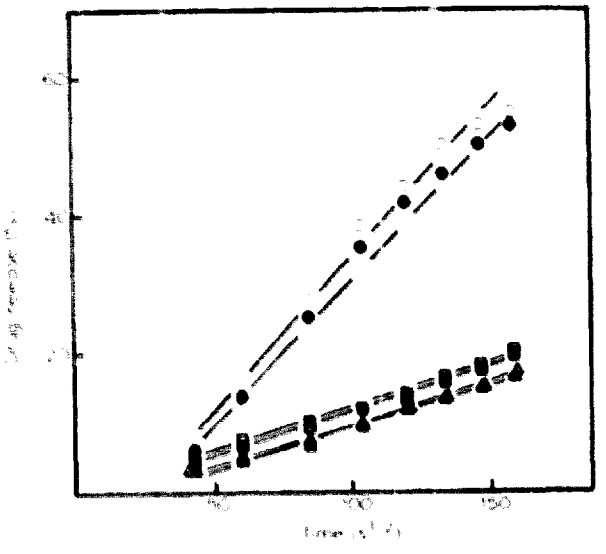
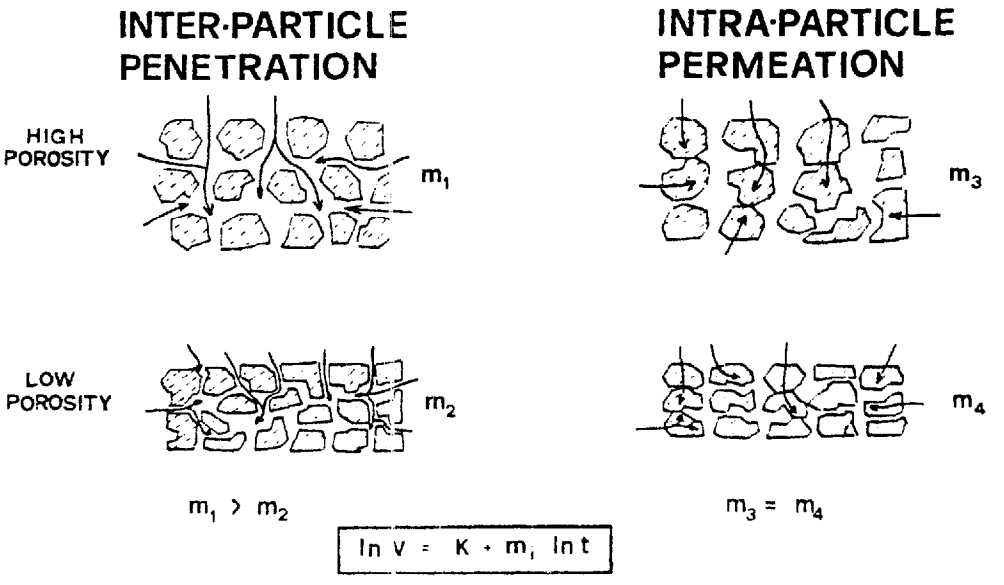


Fig. 5. Aspirin release rate in water (according to Higuchi's equation) of Eudragit RS (▲, 56.0 MN·m^{-2}; △, 491.9 MN·m^{-2}), Eudragit Special (■, 62.7 MN·m^{-2}; □, 157.8 MN·m^{-2}) and Eudragit RL (●, 54.3 MN·m^{-2}; ○, 516.1 MN·m^{-2}) matrices.



Scheme 1. Influence of the porous structure on the value of the exponent m of the liquid penetration volume–time relationship: comparison between the capillary and diffusion processes

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