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Influence of diluents and manufacturing method on the in vitro dissolution of carteolol hydrochloride matrix tablets

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Abstract

The release behaviour of carteolol hydrochloride matrix tablets was investigated as a function of filler nature (Emcompress®, mannitol, PEG 6000 and lactose), type of wetting liquid (Eudragit® L 12.5% and isopropanol-acetone mixture 6:4) and mode of filler incorporation. The values of the technological parameters suggest that hardness was the most significantly affected by the three formulation factors considered. The strongest influence over the technological parameters was exerted by the mode of filler incorporation. The kinetic data conformed with the Higuchi square root equation, except for the lots containing mannitol and isopropanol-acetone mixture that conformed to a first-order plot. The lot containing Emcompress® and isopropanol-acetone mixture displayed acceptable linearity with both plots. Therefore, a non-linear regression procedure and reduced time method were used to define with precision the kinetic model followed by this formulation. Release parameters such as the Higuchi rate constant, t_{50} and dissolution efficiency were calculated. Lots containing mannitol presented more rapid release rates due to the high solubility of this filler. On the other hand, the use of PEG 6000 as diluent significantly decreased drug release. The influence of technological parameters on the release of these systems was also examined, an inverse relationship between hardness and dissolution efficiency being found.

Keywords: Carteolol hydrochloride; Matrix tablet; Filler nature; Wetting liquid; Filler incorporation; Nonlinear regression; Reduced time

1. Introduction

Matrix systems appear to be one of the most attractive approaches from an economic as well as from the process development and scale-up points of view. The most important variable in these systems is the rate at which the drug substance is released. In the preparation and study of matrix tablets it was thought that there are diverse factors controlling drug release: particle size of drug and excipients, compression force, nature of polymer support and diluents.

One of the factors also affecting both drug dissolution in vitro and bioavailability in vivo is granulating or wetting of the forming components

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and the variables associated with them (Delacourte et al., 1992; Sarisuta and Mahahpunt, 1994).

The principal objective of this work and as a part of our continuing study of the release behaviour of carteolol hydrochloride matrix systems (Rabasco et al., 1991; Holgado et al., 1992; Caraballo et al., 1993, 1994; Fernández-Arévalo et al., 1993) was to examine the effect of various diluents and the mode of incorporation of these substances on the release behaviour of these systems. Consequently, two methods for incorporating the filler into the polymeric matrices were adopted: in a previous paper (Fernández-Arévalo et al., 1993), all the components of the matrices (drug, polymer and diluents) were moistened by two wetting liquids (Eudragit® L 12.5% and isopropanol-acetone mixture 6:4) whereas in this study, the different fillers were incorporated once the powder mass of tablets (drug and polymer) had been wetted and dried.

Hence, the formulation factors considered in this paper were: (i) the nature of the filler: Emcompress®, mannitol, PEG 6000 and lactose; (ii) the nature of the wetting liquid: Eudragit® L 12.5% and isopropanol-acetone mixture 6:4; and (iii) the mode of filler incorporation: (a) wetting of the total powder mass of tablets and (b) wetting of the drug-polymer mixture, including the different filler subsequently.

2. Experimental

2.1. Materials

Carteolol hydrochloride, used as drug carried by the matrix systems, was a gift of Lab. Miquel (Barcelona, Spain). The supporting material for the inert matrix tablets was the acrylic resin Eudragit® RS 100 (Curtex, Industrias Sintéticas S.A., L'Hospitalet, Barcelona, Spain). The fillers used were: Emcompress® (Glyco Ibérica S.A., Gavá, Barcelona, Spain), mannitol (Acofarma, Tarrasa, Barcelona, Spain), polyethylene glycol 6000 (Acofarma) and lactose (Acofarma). The two different wetting liquids used were Eudragit® L 12.5% (Curtex) and an isopropanol (Acofarma)-acetone (PQS, Sevilla, Spain) mixture (6:4). A talc (Acofarma)-magnesium stearate (Acofarma) mixture (9:1) was used as lubricant. All reagents conformed to the European Pharmacopoeia.

Table 1
Composition of the formulations employed

Lots	Wetting liquid	Filler
1	Eudragit® L 12.5%	Emcompress®
2		mannitol
3		PEG 6000
4		lactose
5	Isopropanol-acetone mixture	Emcompress®
6		mannitol
7		PEG 6000
8		lactose

2.2. Preparation of inert matrix tablets

Compressed matrix tablets, each weighing 300 mg, were formulated to contain 10% carteolol hydrochloride, 50% Eudragit® RS and 5% talc-magnesium stearate mixture. The formulations were completed with the appropriate proportion of the four different fillers indicated in section 2.1. The method of preparation and the wetting process have been described in a previous paper (Holgado et al., 1992). The formulations employed are listed in Table 1.

2.3. Technological study of inert matrix tablets

The weight was determined on 10 tablets using an electronic balance (Mettler, type AE-50). Thickness and diameter were evaluated using a precision micrometer (Export-Pel) on 10 tablets. Hardness was measured on five tablets using a Schleuniger durometer (model 2E/205).

The formulations were established to allow the effects of formulation factors to be tested in a $2 \times 2 \times 4$ factorial design. This study was completed with a correlation test according to the technological parameters.

2.4. In vitro dissolution assay

The dissolution tests were carried out in the USP XXII rotating basket apparatus (Turu Grau,

model D-6) at 37 ± 0.5°C at a speed of 50 rpm. 700 ml of simulated gastric fluid without enzymes was employed as the initial dissolution medium. This medium was modified, by adding 4 N NaOH solution, to obtain the following pH values:

t (h)	0–1	1–2	2–3	> 3
pH	1.2	1.9	5.8	6.8

Sink conditions were maintained throughout the runs. The cumulative amounts were spectrophotometrically calculated (250 nm) as previously described (Rabasco et al., 1991). Then, data were fitted to three kinetic models: first-order plot, zero-order plot and the Higuchi equation.

Table 2
Technological parameters of tablets tested

Parameter	Lots	Mean	SD	CV	e	Mean [a]
Weight	1	300.9	1.190	0.395	0.376	305.7
	2	301.4	0.705	0.234	0.223	302.8
	3	300.9	0.879	0.292	0.278	302.2
	4	301.4	1.029	0.341	0.335	302.5
	5	301.2	1.273	0.422	0.402	302.8
	6	301.0	1.179	0.392	0.373	301.7
	7	299.7	0.729	0.243	0.230	301.5
	8	300.6	0.381	0.126	0.120	300.3
Hardness	1	5.10	0.228	4.471	0.093	6.40
	2	4.93	0.163	3.310	0.066	7.00
	3	5.30	0.209	3.957	0.085	7.50
	4	5.27	0.244	4.630	0.100	7.53
	5	7.23	0.150	2.081	0.061	8.87
	6	6.91	0.266	3.845	0.108	8.93
	7	6.33	0.242	3.824	0.098	8.83
	8	6.11	0.160	2.619	0.065	8.33
Thickness	1	5.20	0.044	0.860	0.018	4.74
	2	5.04	0.011	0.231	0.004	5.02
	3	5.40	0.016	0.302	0.006	5.18
	4	5.05	0.014	0.280	0.004	5.00
	5	5.18	0.014	0.273	0.006	4.56
	6	5.07	0.007	0.139	0.003	5.06
	7	5.36	0.014	0.264	0.006	5.12
	8	5.10	0.023	0.447	0.009	4.81
Diameter	1	10.01	0.012	0.120	0.004	10.07
	2	10.01	0.009	0.098	0.004	10.06
	3	10.02	0.007	0.075	0.003	10.06
	4	10.03	0.006	0.063	0.003	10.07
	5	10.03	0.003	0.032	0.001	10.06
	6	10.02	0.007	0.071	0.003	10.07
	7	10.03	0.006	0.063	0.003	10.06
	8	10.03	0.011	0.114	0.005	10.07

Technological parameters of tablets: weight (mg) ($n = 10$); hardness (Kp) ($n = 5$); thickness (mm) ($n = 10$); diameter (mm) ($n = 10$). SD, standard deviation; CV, coefficient of variation; e, standard error. [a] Mean values of tablets containing wetted fillers.

Table 3
Multifactorial analysis of technological parameters

Parameter	Source of variation	F	P
Weight	*A*	6.2001	0.0154
	B	26.0249	< 0.0001
	C	11.8162	< 0.0001
	AB	7.8045	0.0069
	AC	15.1111	< 0.0001
	BC	9.1913	< 0.0001
	ABC	8.5274	< 0.0001
	global	11.5944	
Hardness	*A*	1633.06	< 0.0001
	B	3728.16	< 0.0001
	C	17.3579	< 0.0001
	AB	0.36125	0.5499
	AC	63.4679	< 0.0001
	BC	7.99458	0.0001
	ABC	6.07458	0.0011
	global	376.418	
Thickness	*A*	10.5978	0.0018
	B	41.0812	< 0.0001
	C	42.4939	< 0.0001
	AB	79.3911	< 0.0001
	AC	15.3163	< 0.0001
	BC	1.1421	0.3389
	ABC	11.6585	< 0.0001
	global	22.7475	
Diameter	*A*	10.0000	0.0024
	B	722.500	< 0.0001
	C	7.5000	0.0002
	AB	10.0000	0.0024
	AC	1.6667	0.1830
	BC	4.1667	0.0093
	ABC	5.0000	0.0035
	global	54.0000	

A, type of wetting liquid; *B*, mode of filler incorporation; *C*, type of filler.

3. Results and discussion

3.1. Technological parameters of inert matrices

The technological parameters of tablets obtained experimentally are shown in Table 2 (for tablets containing moistened fillers only the mean values are indicated). The observed differences between tablets can be explained on the basis of

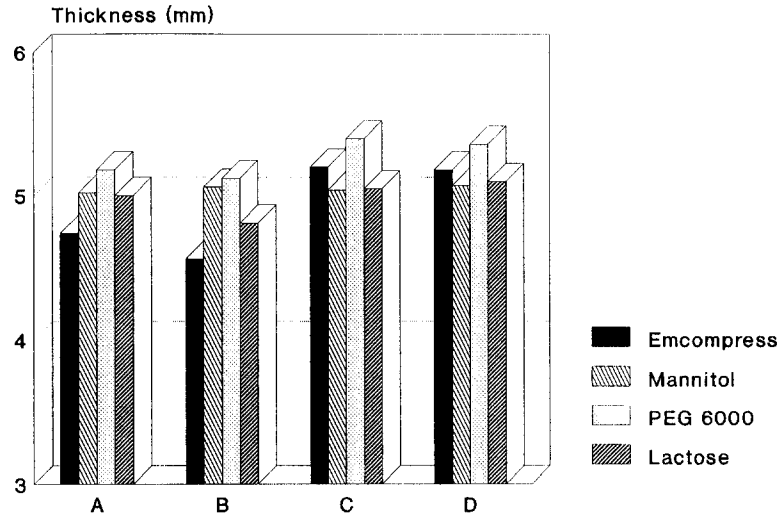

Fig. 1. Thickness (mm) data. (A) Matrix tablets containing Eudragit® L, wetted filler; (B) matrix tablets containing isopropanol-acetone mixture, wetted filler; (C) matrix tablets containing Eudragit® L, no wetted filler; (D) matrix tablets containing isopropanol-acetone mixture, no wetted filler.

changes in the formulations' composition, as the diverse technological conditions were kept constant. The weight uniformity was evaluated according to the specifications of USP XXII. Thickness, hardness and friability data varied within acceptable values.

In relation to thickness and hardness data, it is interesting to note the results obtained, which are shown in Fig. 1 and 2. In formulations containing no wetted fillers, greater thickness values are reached due to the lower compaction between the particles forming the tablets. On the other hand, formulations present the same sequence of values as a function of the mode of filler incorporation. With respect to the nature of the wetting liquid, tablets containing Eudragit® L exhibit

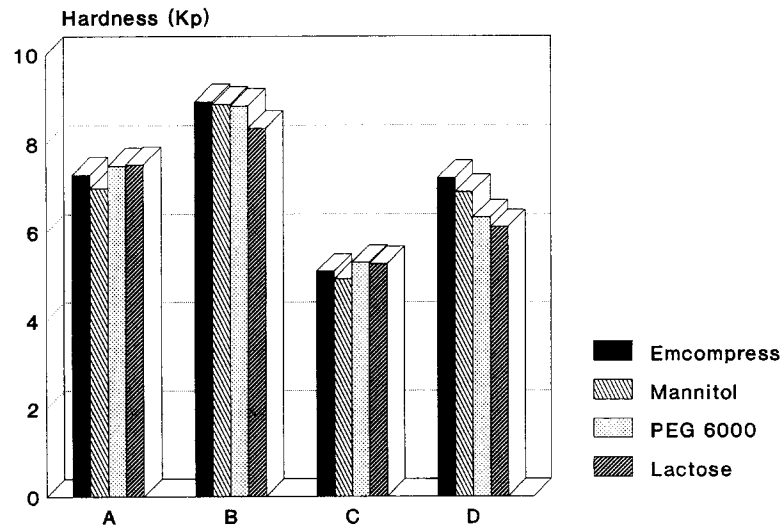

Fig. 2. Hardness (Kp) data. (A) Matrix tablets containing Eudragit® L, wetted filler; (B) matrix tablets containing isopropanol-acetone mixture, wetted filler; (C) matrix tablets containing Eudragit® L, no wetted filler; (D) matrix tablets containing isopropanol-acetone mixture, no wetted filler.

slightly greater thickness values than those containing isopropanol-acetone mixture, since in the former case a new component in the formulation (Eudragit® L polymer) is incorporated. In all cases, PEG 6000 yields the highest thickness values.

Concerning the hardness data, no wetting of fillers produces a clear diminution in hardness values. In such a way, wetting liquids act as binder substances which allow considerable contact between the particles, achieving an increase in the compression efficiency. All these circumstances can be summarized in two significant facts: tablets containing wetted fillers present lower thickness values and the highest hardness values. On the other hand, the isopropanol-acetone mixture seems to display a high binding capacity, producing tablets with more cohesiveness between the particles. Wetting the formulation with this liquid, which is capable of partially dissolving the polymeric support, improves the strength properties of tablets. On this occasion, formulations demonstrated the same sequence of values as a function of the wetting liquid type.

In Table 3 one can observe the analysis of variance of each parameter tested: with few exceptions, the considered variables, independently and their interactions, present an influence with statistical significance over the technological characteristics of the tablets. The data suggest that hardness was the most significantly affected by the three variables considered, since this parameter is directly associated with the degree of cohesion between particles integrating powders. Otherwise, the strongest influence over the technological parameters was exerted by the mode of filler incorporation. No interesting correlation was found between the technological parameters of matrix tablets.

3.2. Release profile studies

The release kinetics of the carteolol hydrochloride matrix tablets were studied according to the procedures described in section 2. Each experimental run was carried out at least in triplicate. As the matrix support material is the same for all the formulations, one can expect different release behaviour as a function of the type of wetting liquid, filler nature and mode of filler incorporation.

Table 4
Correlation coefficients according to the indicated kinetic models

Lots	n	Zero order	First order	Higuchi
1	22	0.9683	0.9804	0.9897
2	22	0.9627	0.9842	0.9924
3	22	0.9597	0.9757	0.9931
5	22	0.9523	0.9909	0.9950
6	19	0.9617	0.9918	0.9772
7	22	0.9517	0.9897	0.9973

Tables 4 and 5 summarize the correlation coefficients according to the studied kinetics and the release parameters obtained in this section corresponding to the formulations containing no wetted fillers. Those corresponding to the tablets containing wetted fillers have been reported previously (Fernández-Arévalo et al., 1993). Data for tablets containing lactose as filler (lots 4 and 8) are not shown because those formulations underwent a disintegration process and no controlled release action was achieved.

In comparison with lots reported previously (Fernández-Arévalo et al., 1993), these formulations did not show a biphasic release behaviour and successful fittings for the whole release process could be achieved. In all cases studied, except for the formulation containing mannitol and isopropanol-acetone mixture (lot 6), the best fitting was obtained with the Higuchi model. Thus,

Table 5
Release parameters obtained

Lots	K_H (mg/min$^{1/2}$)	t_{50} (min)	Amount of released drug (%)	DE (%)
1	0.809	417.69	56.67	38.66
2	0.871	349.55	62.03	42.69
3	0.640	638.71	46.97	32.68
5	1.004	203.15	81.73	56.97
6	–	84.77	98.19	85.56
7	0.988	212.50	78.31	56.05

K_H, Higuchi rate constant; t_{50}, time necessary to dissolve 50% of drug content; DE, dissolution efficiency.

these results appear to indicate that the release mechanism of these matrices was via diffusion control.

A good fitting to the first-order model was also presented by lot 5. This situation was similar to those found by Benita and Donbrow (1982), Donbrow and Benita (1982), Uko-Nne et al. (1989), Biswanath et al. (1990) and Al Gohary et al. (1991). To distinguish between the two release mechanisms, Schwartz et al. (1968) applied differential rate mathematical treatments. Although this is mathematically legitimate, Benita et al. (1984) prefer to use a more valid test for drug release from matrices, since the differential rate test suffers from a lack of accuracy due to the transformation performed on the initial kinetic parameters by linearization and differentiation of the original curve.

Thererfore, to identify exactly the release mechanism of this formulation, a non-linear regression method has been used. By means of the two different values of AIC obtained (Akaike, 1976), −4.8927 and −43.4636, corresponding to the first-order model and Higuchi equation, respectively, it can be deduced that the release mechanism of lot 5 follows the Higuchi kinetic model.

Another tool used to distinguish between both types of kinetic models is the parameter referred to as the 'reduced time' proposed by Chukwu et al. (1991). It can be defined as:

$$T_r = t/T_s$$

where, T_r is the reduced time, t denotes time, and T_s is the time necessary to dissolve a defined amount of drug.

In this case, the t_{50} value has been chosen as T_s. The reduced time plot is used to compare an entire dissolution process where a single equation cannot satisfactorily describe the whole process. If dissolution proceeds by the same release mechanism in different batches, but differs only in rate from one another, the plots of amount released against reduced time should be perfectly superimposed upon each other.

Fig. 3 shows the released amounts of drug as a function of reduced time for the dissolution profile data for lots 5–7. The dissolution rate curves corresponding to Emcompress® and PEG 6000 are perfectly superimposed, showing that the release behaviour of these formulations can be described by the same mechanism, namely, the Higuchi model. In contrast, the lot containing mannitol demonstrates a different profile, indicating that the first-order plot can be assumed as a kinetic model describing the release process.

Along the lines of the results obtained, it can be deduced that the compression of these formu-

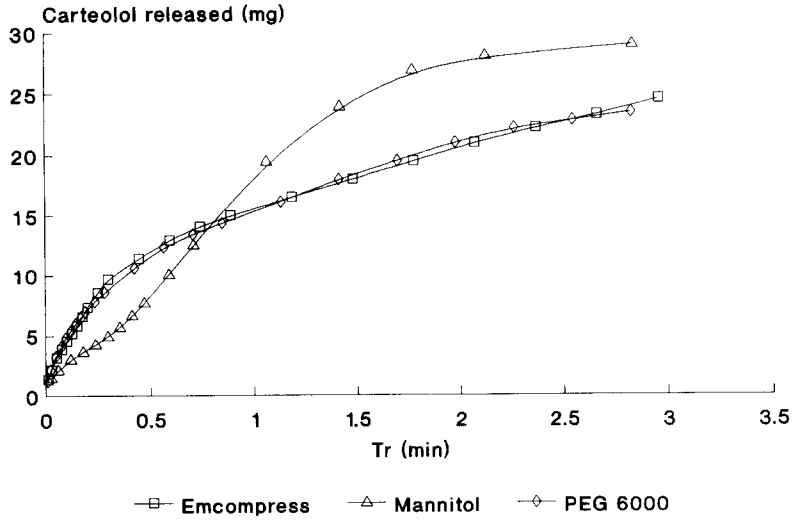

Fig. 3. Carteolol released (mg) as a function of reduced time (min). Lots 5–7.

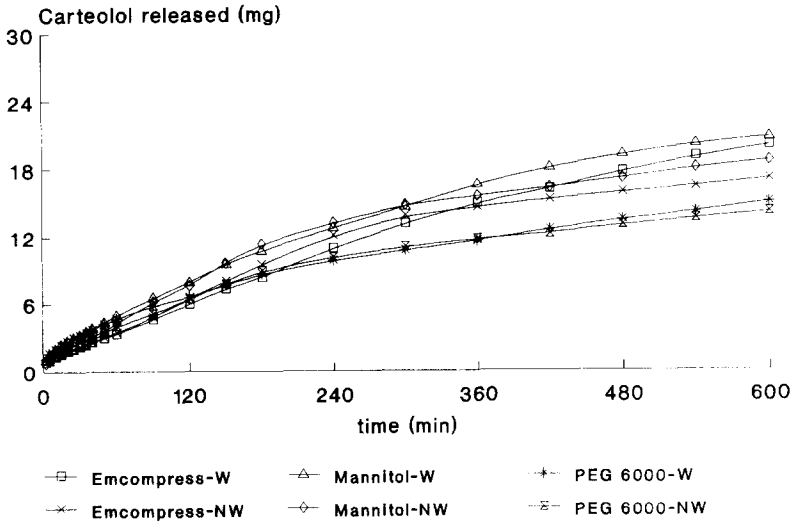

Fig. 4. Carteolol released (mg) as a function of time (min). Matrix tablets containing Eudragit® L. W, wetted filler; NW, no wetted filler.

lations, except those containing mannitol as filler and isopropanol-acetone mixture as wetting liquid, gives rise to the formation of an inert matrix structure where drug is uniformly distributed inside the polymeric support. On the other hand, in contrast to those formulations containing moistened fillers (Fernández-Arévalo et al., 1993), these matrix tablets did not show biphasic release processes. Hence, the first difference found between the two methods used for incorporating the filler in the polymeric matrices was that no wetting of fillers allows obtaining of matrices displaying single-phase release processes.

3.3. Influence of formulation factors

Fig. 4 and 5 show the release profiles corresponding to the lots tested and those previously

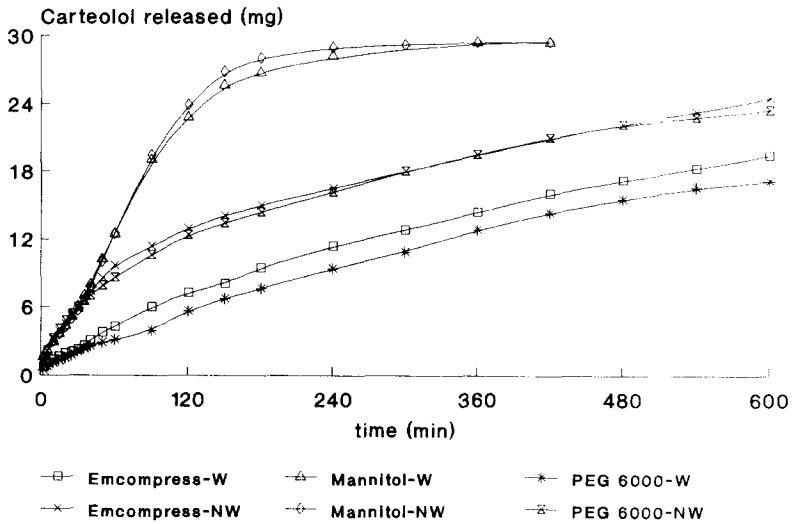

Fig. 5. Carteolol released (mg) as a function of time (min). Matrix tablets containing isopropanol-acetone mixture. W, wetted filler; NW, no wetted filler.

reported (Fernández-Arévalo et al., 1993) as a function of the type of wetting liquid.

Concerning Eudragit® L, a slight decrease in the release rate of lots containing no wetting fillers was evident. To explain this situation, two different factors may be considered. Firstly, when the filler is not wetted the relative proportion of resin to drug increases, giving rise to a decrease in the release rate of the process. Secondly, the formation of channels inside the matrix due to the rapid dissolution of fillers is favoured, yielding a more rapid release process. Therefore, the slight difference observed in the release profiles is produced by the opposing actions of both circumstances, the retardant effect of resin having priority over drug.

In contrast, the use of isopropanol-acetone mixture implies the reverse of the situation and greater differences. The use of wetted diluents suggests the formation of a more compacted matrix structure allowing a slower drug release. Lots containing mannitol present more rapid release rates due to the high solubility of this excipient.

It is interesting to note that the release profiles of lots 5 and 7, as a function of square root of time, can be considered as having two phases. The diffusion rate and the duration of both phases are different as a function of the type of filler and method of manufacture (Table 6).

Table 6
Study of diffusion process

		Phase 1	Phase 2
Lot 5	t (min)	0–60	60–540
	r	0.9919 ($n = 10$)	0.9995 ($n = 12$)
	K_H (mg/min$^{1/2}$)	1.308	0.858
Lot 7	t (min)	0–90	90–480
	r	0.9999 ($n = 12$)	0.9965 ($n = 10$)
	K_H (mg/min$^{1/2}$)	1.167	0.861

Duration, regression coefficients and Higuchi rate constants of both considered phases are given.

The first phase of lot 5 is shorter (approx. 30 min) than that corresponding to lot 7. This circumstance can be attributed to the rapid dissolution of Emcompress® in acid medium (Bryan and McCallister, 1992; Lin and Lin, 1993). The progressive dissolution of PEG 6000 yields an increase in viscosity of the matrix channels acting as a barrier that decreases the drug release rate in this first step. On the other hand, the second phase demonstrates release rates similar to but lower than those found in the first phase. This circumstance is directly in relation with the gradual depletion of matrix systems (Ahmed et al., 1992; Abdel-Rahman et al., 1992). This change in rate is due to a modification of the release process itself. It appears when the matrix tablet has

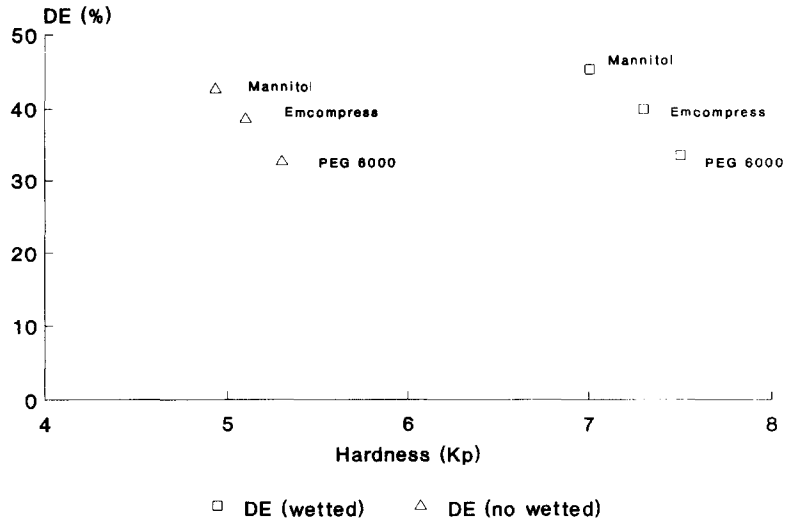

Fig. 6. Dissolution efficiency (%) as a function of hardness (Kp). Matrix tablets containing Eudragit® L.

been completely penetrated by the dissolution liquid (Çapan, 1989).

In relation with the nature of the filler, it can be seen that the use of Emcompress® and PEG 6000 allows formulations to be obtained fitting the Higuchi model, without considering the type of wetting liquid and methods of manufacture. On the other hand, it is interesting to note the retardant nature of PEG 6000, decreasing significantly drug release in all formulations containing it. This excipient, due to its water-soluble nature, is usually used as an agent in acrylic polymer films to modify their release properties. Hence, an increase in matrix permeability (creation of new channels and pores) could be expected; apparently, this did not occur. Muhammad et al. (1991) suggest that this phenomenon can be produced by a change, without explaining its nature, in the properties of the acrylic resin supporting matrix systems as a result of the presence of PEG 6000.

To complete the present study, a comparative analysis between the technological characteristics and release parameters has been accomplished. Fig. 6 shows the relation established between dissolution efficiency and hardness in matrix tablets containing Eudragit® L as wetting liquid. Two different zones may be appreciated: formulations with no wetted diluents (hardness values between 4 and 6 Kp) and those with wetted fillers (hardness data between 6 and 8 Kp). Considering each group of formulations, an inverse relationship between dissolution efficiency and hardness has been found. Furthermore, tablets more resistant with similar release characteristics are obtained when fillers are wetted. The wetting process allows the formation of more compacted systems, however, this increase in hardness seems to affect the final release characteristics slightly. From these results it can be deduced that the release process of formulations containing Eudragit® L as wetting liquid can be influenced by the filler nature (finding the same sequence in both cases) and not by the hardness values of these matrix tablets.

When the isopropanol-acetone mixture was used, no interesting relationship between dissolution efficiency and hardness was found, i.e., the release characteristics of these types of formulations are strongly influenced by the structural properties of these systems.

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