International Journal of Pharmaceutics, 95 (1993) 117–125

IJP 03146

Effects of different fillers and wetting liquids on the dissolution behavior of carteolol hydrochloride controlled release inert matrix tablets

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(Received 28 January 1992)
(Modified version received 7 December 1992)
(Accepted 15 December 1992)

Key words: Carteolol hydrochloride; Matrix tablet; Controlled release; Diffusion kinetics; DSC; Affinity constant

Summary

Inert matrix tablets of carteolol hydrochloride were prepared using 50% of Eudragit® RS as a supporting material and a series of fillers: Emcompress®, mannitol, polyethylene glycol 6000 and lactose. Two liquids were used to wet the drug-excipient mixtures: Eudragit® L 12.5% and isopropanol-acetone 6:4 mixture. The affinity of carteolol hydrochloride to the matrix forming material Eudragit® RS (expressed as a K_{aff} value) was calculated: the higher the pH value, the greater was the value of the K_{aff} obtained. Each component of the formulations as well as its presence in the matrix systems was identified by differential scanning calorimetry (DSC). The thermal analysis suggested that no drug-excipient interaction occurs during the preparation process. Finally, the dissolution profiles were studied applying three different kinetic models (zero-order, first-order and Higuchi equation). Controlled release profiles were obtained in all the inert matrix compressed tablets studied with the unique exception of lactose used as a filler. The mechanism of release from the matrices was shown to be diffusion-controlled. The dissolution behavior was found to display a biphasic profile in the case of the lots prepared with Eudragit® L 12.5% as wetting liquid of the formulations. Higuchi release rate constants were also calculated.

Introduction

In recent years, matrix systems as vehicles for drug delivery have been attracting much attention. This interest is due basically to the technological simplicity in comparison with other controlled release systems developed to achieve oral sustained release (Bogentoft, 1982; Buri, 1984).

The materials most commonly employed include a multitude of retardant polymers, waxes, cellulose derivates, high molecular weight alcohols, glycols and hydrogels (Buri and Doelker, 1980; Salomon and Doelker, 1980; Doelker and Buri, 1981). A series of these excipients is mar-

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keted under the trade name of Eudragit® (Liddiard, 1990). Some of them, e.g., Eudragit® RS, have been applied to the preparations of sustained release dosage forms (Cameron and McGinity, 1987). This polymer shows a pH-independent and poor permeability in aqueous solutions, although it has good liquid transport properties.

As a model drug to be carried by inert matrices, we used carteolol hydrochloride (5-[3-*t*-butylamino-2-hydroxy]propoxy-3,4-dihydrocarbostyryl hydrochloride). It has a potent β-adrenergic blocking action (Luther et al., 1986a,b) with appropriate pharmacokinetic and activity profiles to make it a suitable candidate for controlled-release matrix systems (Stoll et al., 1981; Ishizaki et al., 1983). It is readily absorbed from the gastrointestinal tract and is excreted primarily via the kidneys. Peak plasma concentrations usually occur within 1–3 h. The average half-life is 5–6 h (Koch, 1983). Since no literature data on this drug with respect to controlled-release dosage forms were available, initial studies regarding controlled release delivery systems of carteolol hydrochloride have been developed (Rabasco et al., 1990, 1991; Holgado et al., 1991, 1992a,b).

The aim of the present study was to determine the influence of filler excipients (Emcompress®, mannitol, polyethylene glycol 6000, lactose) and wetting liquids (Eudragit® L 12.5% and isopropanol-acetone mixture) on the technological parameters and release behavior of inert matrix carteolol hydrochloride tablets containing the acrylic resin Eudragit® RS as a supporting material.

Materials and Methods

Materials

Carteolol hydrochloride (a gift of Lab. Miquel, Barcelona, Spain) was used as the drug carried by the matrix systems. The supporting material of 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, Tarrasa, Barcelona, Spain) and lactose (Acofarma, Tarrasa, Barcelona, Spain). The two different wetting liquids were Eudragit® L 12.5% (Curtex, Industrias Sintéticas S.A., L'Hospitalet, Barcelona, Spain) and an isopropanol-(Acofarma, Tarrasa, Barcelona, Spain) -acetone (PQS, Sevilla, Spain) mixture 6:4. We used a talc-(Acofarma, Tarrasa, Barcelona, Spain)-magnesium stearate (Acofarma, Tarrasa, Barcelona, Spain) mixture 9:1 as lubricant. All reagents conformed to the European Pharmacopeia.

Determination of the distribution coefficient of the drug between the supporting material and the dissolution medium: K_{aff}

The affinity of carteolol hydrochloride to the supporting material employed (Eudragit® RS) was determined by suspending 5 g of acrylic resin in powdered form for 48 h, at 37°C, in 50 ml of aqueous solutions at known concentration of the drug and the change in absorbance of the solutions was recorded spectrophotometrically (250 nm) (Hitachi, model U-2000). The K_{aff} values express the ratio between the amount recovered in solution after equilibrium was achieved (Zecchi et al., 1986; Holgado et al., 1991).

Dose determination

Nelson's method was used to calculate the amount of carteolol hydrochloride contained in the matrix tablets, which has been previously determined as 30.00 mg (Rabasco et al., 1990; Holgado et al., 1992).

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 and magnesium stearate mixture. The formulations were completed with the appropriate proportion of four different fillers: Emcompress®, mannitol, polyethylene glycol 6000 and lactose. In this work, we have used two different wetting liquids (Eudragit® L 12.5% and isopropanol-acetone 6:4 mixture) to wet the powder mixture. The method of preparation and the wetting pro-

TABLE 1

Composition of the formulations used for preparing the inert matrix compressed tablets

	Lots							
	I	II	III	IV	V	VI	VII	VIII
% drug	10	10	10	10	10	10	10	10
% Eudragit RS	50	50	50	50	50	50	50	50
% lubricant	5	5	5	5	5	5	5	5
% Emcompress	35	–	–	–	35	–	–	–
% mannitol	–	35	–	–	–	35	–	–
% PEG 6000	–	–	35	–	–	–	35	–
% lactose	–	–	–	35	–	–	–	35
ml Eudragit L	10	10	10	10	–	–	–	–
ml isopropanol-acetone 6:4	–	–	–	–	10	10	10	10

cess have been described in a previous paper (Holgado et al., 1992). The formulations employed are listed in Table 1. The biconvex tablets were obtained using an excentric machine (Bonals A-300).

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). Friability was determined on four tablets, tested for 4 min in an Erweka friabilometer (type TAD) set at 25 rpm.

Differential scanning calorimetry (DSC)

DSC analyses were performed to identify any solid state inactivation of carteolol hydrochloride and to detect whether chemical interactions exist between the drug and the excipients (Ford and Timmins, 1989; Stead, 1990). Interactions in the samples are deduced from DSC by changes in thermal events such as the elimination of an endothermic or exothermic peak or the appearance of new peaks.

DSC thermograms were obtained using an automatic thermal analyzer system (Mettler FP80 HT Central Processor and Mettler FP85 TA Cell). The Mettler FP89PS and FP89AT data processing system was connected to the thermal analyzer. Samples of each component of the formulations and of inert matrix tablets before and after the dissolution assay were weighed and sealed into aluminium DSC sample pans. Thermograms were measured from 40 to 320°C at a heating rate of 10°C/min.

In vitro dissolution assay

The dissolution tests were carried out on 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 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 calculated as previously described (Rabasco et al., 1991). Then, data were fitted to three kinetic models: first-order plot, zero-order plot and Higuchi equation. The Higuchi release constants K_r (mg/min$^{0.5}$) for each formulation were then calculated.

Results and Discussion

Determination of K_{aff} values

K_{aff} data, as well as the amount of drug adsorbed on the supporting material (mg drug adsorbed/g Eudragit® RS) at different pH values, appear in Table 2. Fig. 1 shows a semilogarithmic plot of these data. We can assess a linear relationship between the parameters studied in the range of pH tested: the greater the pH values, the higher are the K_{aff} values. This situation is due to the presence of a high proportion of drug in ionized form at low pH values. This form has a higher affinity for the solvent molecules than for the polymer surface (Florence and Attwood,

TABLE 2

Affinity constant data and mg of drug adsorbed per g of acrylic resin at different pH values

pH	K_{aff}	mg drug adsorbed / g Eudragit RS
2.0	0.090	0.068
6.0	0.205	0.136
8.0	0.301	0.185
10.65	0.560	0.287
12.0	0.793	0.354

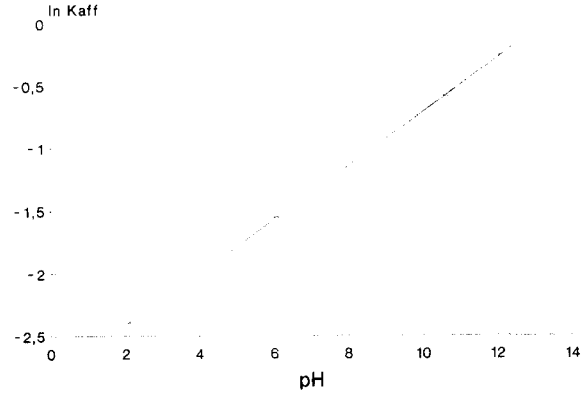

Fig. 1. Semilogarithmic plot of K_{aff} values and amounts (mg) of drug adsorbed per g of Eudragit® RS versus pH.

1988). It was found that the relation between K_{aff} and pH appears to be exponential in the range of pH values which we tested; hence, it can be linearized using the semilogarithmic plot. In Table 3 the more interesting parameters of this curve are listed. These results are similar to those obtained for other β-blockers (Al-Gohary et al., 1988).

Technological parameters of inert matrices

The technological parameters of the compressed tablets are shown in Table 4. As the various technological parameters were kept constant, the differences between lots can be attributed to changes in the formulations. The weight uniformity was evaluated according to the specifications of USP XXII. Thickness, hardness and friability data varied within acceptable values. In relation to hardness and friability data, a clear improvement can be observed by using the isopropanol-acetone mixture in comparison with Eudragit® L, used both as wetting liquids. This fact can be explained by the greater ability of the former vehicle to bind the formulation powder and to facilitate the compacting process.

DSC analysis

DSC thermograms indicated the qualitative composition of the different formulations and verified the identity of each of the components by their thermal properties.

Fig. 2 shows the melting endothermic peaks of carteolol hydrochloride and the different fillers, as well as the acrylic resins, Eudragit® RS and Eudragit® L. It is interesting to note the two peaks of lactose (Fig. 2F): a dehydration endotherm over the temperature range of 140–150°C and a melting endotherm at a temperature of 220°C.

TABLE 3

Multiple linear regression data between ln K_{aff} and pH

Coefficient of determination:	0.9965		Estimation constant term:	−2.8309	
Multiple correlation coefficient:	0.9983		Standard error of estimate:	0.0573	
Source	D.F.	sum of squares	mean of squares	*F*	Prob.
Regression	1	2.81563	2.81563	856.861	0.0000
Residuals	3	0.009856	0.003286		
Total	4	2.82548			
Regression coefficient		standard coefficient	standard error	*T*	Prob.
0.211982		0.9983	0.007241	29.2722	0.0000

TABLE 4

Technological parameters corresponding to the groups of tablets tested: weight (mg) (n = 10), hardness (kp) (n = 5), thickness (mm) (n = 10), diameter (mm) (n = 10), friability (%) (n = 4)

Parameter	Lots	Mean	Standard deviation	Standard error	Coefficient of variation
Weight	I	305.7	2.8991	0.9168	0.9481
	II	302.8	1.1624	0.3676	0.3839
	III	302.2	1.0554	0.3337	0.3493
	IV	302.5	1.6977	0.5369	0.5613
	V	302.8	1.4032	0.4437	0.4633
	VI	301.7	1.3049	0.4126	0.4324
	VII	301.5	0.6342	0.2005	0.2106
	VIII	300.3	0.7846	0.2481	0.2613
Hardness	I	6.40	0.1789	0.0730	2.7951
	II	7.00	0.1789	0.0730	2.5555
	III	7.50	0.4858	0.1983	6.4773
	IV	7.53	0.2733	0.1115	3.6272
	V	8.87	0.1633	0.0667	1.8417
	VI	8.93	0.2066	0.0843	2.3122
	VII	8.83	0.1555	0.0615	1.7044
	VIII	8.33	0.2422	0.0989	2.9065
Thickness	I	4.74	0.0117	0.0048	0.2465
	II	5.02	0.0152	0.0062	0.3018
	III	5.18	0.0256	0.0105	0.4948
	IV	5.00	0.0248	0.0101	0.4968
	V	4.56	0.0163	0.0067	0.3584
	VI	5.06	0.0176	0.0072	0.3476
	VII	5.12	0.0217	0.0088	0.4230
	VIII	4.81	0.0103	0.0042	0.2146
Diameter	I	10.07	0.0098	0.0040	0.0976
	II	10.06	0.0138	0.0056	0.1371
	III	10.06	0.0314	0.0128	0.3121
	IV	10.07	0.0041	0.0017	0.0405
	V	10.06	0.0098	0.0040	0.0977
	VI	10.07	0.0052	0.0021	0.0513
	VII	10.06	0.0052	0.0021	0.0513
	VIII	10.07	0.0052	0.0021	0.0513
			One paddle	Multiple paddles	
Friability	I		0.36	0.36	
	II		0.14	0.17	
	III		0.17	0.19	
	IV		0.28	0.27	
	V		0.21	0.22	
	VI		0.22	0.07	
	VII		0.25	0.25	
	VIII		0.07	0.02	

As examples, Figs 3 and 4 show the DSC thermograms for lots II and VI before (scans A) and after (scans B) the dissolution assay. All the peaks of each component can be verified (scans A); therefore, there were no interactions between the formulation components during the prepara-

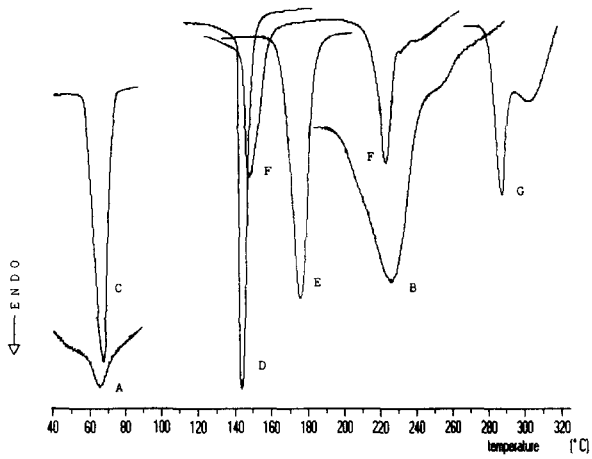

Fig. 2. DSC thermograms of different formulations components: (A) Eudragit® RS, (B) Eudragit® L, (C) PEG 6000, (D) Encompress®, (E) mannitol, (F) lactose, (G) carteolol hydrochloride.

tion process: neither the wetting process nor the compression process has an effect on the initial components of the formulations.

The disappearance of carteolol hydrochloride and mannitol peaks on scans B (Figs 3 and 4) indicates the diffusion of the drug and the filler from the matrix system, in accordance with the later release data. From scan B in Fig. 3, one can also estimate the disappearance of Eudragit® L peak due to the dissolution of the polymer.

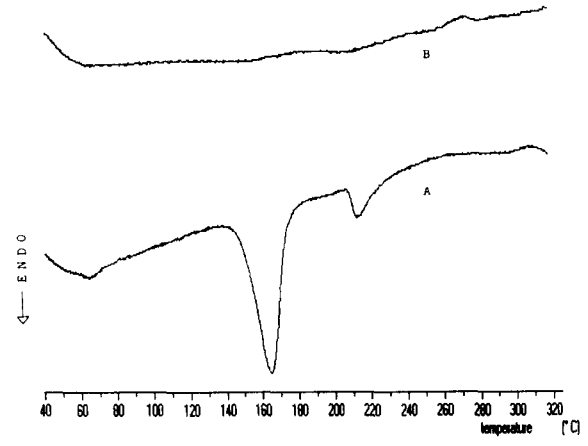

Fig. 3. DSC thermograms of lot II before (A) and after (B) the dissolution assay.

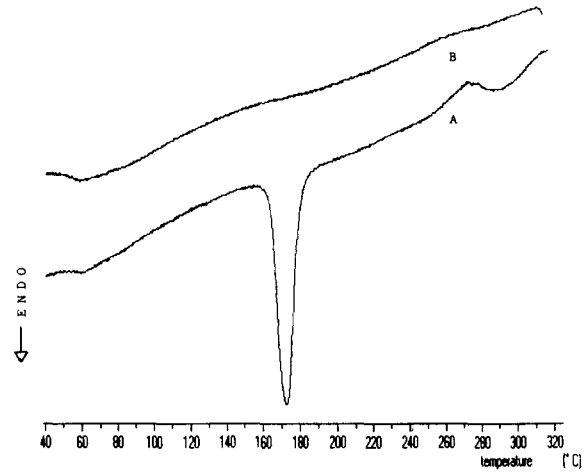

Fig. 4. DSC thermograms of lot VI before (A) and after (B) the dissolution assay.

Release studies

The release kinetics of the eight lots of inert matrix compressed tablets of carteolol hydrochloride were studied according to the procedures described under Materials and Methods. Each experimental run was carried out at least in triplicate. In Figs 5 and 6, the release profiles of the different preparations studied are shown.

Table 5 summarizes the many release parameters obtained after this study.

Each lot of tablets has the same matrix support material (Eudragit® RS), but considering the nature of the liquid used to wet the formulations and the different fillers used, one can ex-

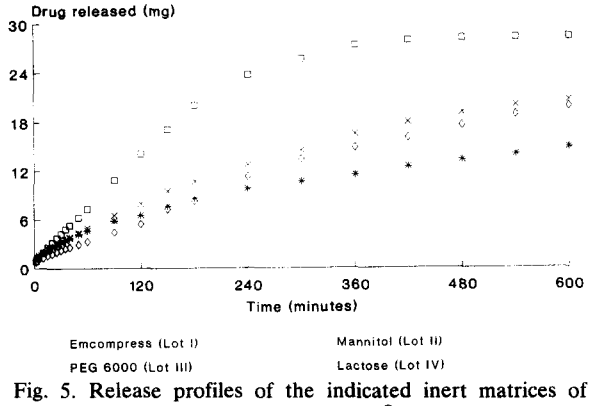

Fig. 5. Release profiles of the indicated inert matrices of carteolol hydrochloride, using Eudragit® L 12.5% as wetting liquid.

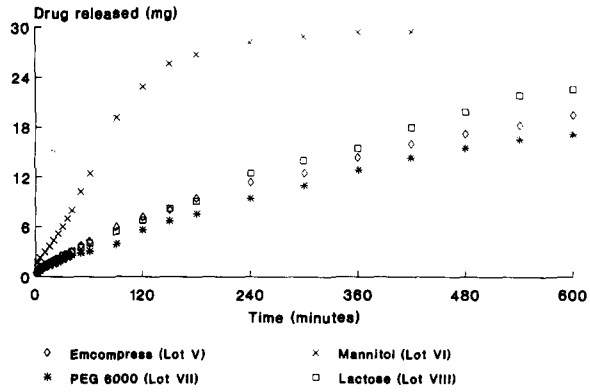

Fig. 6. Release profiles of the indicated inert matrices of carteolol hydrochloride, using isopropanol-acetone 6:4 mixture as wetting liquid.

pect to observe different release behaviour between the various groups of lots.

Therefore, with the use of Eudragit® L (lots I–IV), the release profiles could not be fitted satisfactorily to a given kinetic process among the three kinetic patterns considered here, with the use of Emcompress®, mannitol and PEG 6000. Nevertheless, these formulations could be treated by considering that they exhibit a transition period in the time interval of 120–240 min. This period corresponds to a change in pH of the dissolution medium from 5.8 to 6.8, a pH interval where the solubilization of Eudragit® L results. Before and after this transition period, the best fit of the release kinetics corresponds to the Higuchi model (Table 5), exhibiting two resultant release phases, i.e., different Higuchi rate constants. This last change in the dissolution rate constant is indicative of the presence of a number of discrete changes (dissolution of Eudragit® L, mainly) occurring in the nature of the matrices becoming significant after a particular time during the dissolution rate process. The initial release phase may represent the release of the drug on the surface of the tablet and the drug whose particles are not completely surrounded by the Eudragit® L. The second phase corresponds to the release of drug contained in the matrix network (Chukwu et al., 1991).

In this group of matrix compressed tablets, and considering the different nature of the fillers employed, the use of lactose (lot IV) does not allow an inert matrix to be obtained, as this formulation shows a disintegration process because of its hydrophilic nature. For this reason, we did not continue with its study. In the cases of Emcompress® (lot I) and mannitol (lot II), an increase in the values of the second rate constant was observed, due to the rapid and massive release of these soluble fillers once the Eudragit® L had reached its pH of dissolution and, hence, the binding action of this acrylic resin disap-

TABLE 5

Release parameters tested and correlation coefficients for the three kinetics studied (n = 21)

Lots	Correlation coefficients			Percentage of drug released (t = 600 min)	Higuchi rate constant (mg/min$^{1/2}$)
	First order	Zero order	Higuchi equation		
I [a]	0.9966	0.9951	0.9975	66.93	0.606
	0.9987	0.9977	0.9996		0.932
II [a]	0.9943	0.9920	0.9958	67.00	0.811
	0.9911	0.9792	0.9934		0.892
III [a]	0.9917	0.9891	0.9984	49.46	0.631
	0.9982	0.9989	0.9992		0.611
IV	0.9848	0.9385	0.9829	94.66	–
V	0.9905	0.9860	0.9966	63.80	0.856
VI	0.9417	0.8975	0.9606	88.75	1.821
VII	0.9906	0.9918	0.9927	53.50	0.773
VIII	0.9967	0.9951	0.9904	75.47	–

[a] Groups of tablets with two-phase release profiles.

peared. Lot III (using PEG 6000 as filler) presents a decrease in the rate of the second phase. This situation can be explained by the increase in viscosity in the diffusion channels of the matrix tablets, a phenomenon which implies a diminution in the dissolution process (Salama et al., 1981).

The situation is different with the use of the isopropanol-acetone mixture (lots V–VIII), due to the different structure in the matrix skeleton as a function of the two different wetting liquids used. In these cases, the data presented in Table 5 show the best fit with the Higuchi model, for all the complete release processes. Considering lot VIII (lactose), different release behavior is evident, showing the best fit with the first-order plot. In relation with lot VI, it should be pointed out that with mannitol as a soluble excipient, > 80% of the drug is released within 2 h, without undergoing any disintegration process.

The Higuchi constants exhibit the same sequence in the two groups of tablets (I–III and V–VII): mannitol > Emcompress® > PEG 6000. These rate constants are always greater with the use of isopropanol-acetone mixture in comparison with the mean values of the rate constants corresponding to Eudragit® L. This situation can be explained considering that, in the latter case, the formulations contain another polymer able to delay the release of drug, due to its solubility characteristics.

Considering the final percentage of drug released, in direct relation with the Higuchi rate constant, there is no clear dependence on the hardness data, is accordance with the results reported by others (Cameron and McGinity, 1987). The latter authors did not discover any relation between the amount of drug released, using different fillers, with resultant hardness values greater than 7 kp. These final percentages are not generally greater than 70% at the end of the dissolution assay, because of the intrinsic properties of the diffusion process from inert matrices (Stamm and Tritsch, 1987), and because of the interactions, expressed in terms of the apparent distribution coefficient, of the drug between the supporting material and the amount of drug recovered in solution (K_{aff}).

In relation to the formulation containing mannitol as filler and isopropanol-acetone mixture (lot VI), this presented the highest final percentage of drug dissolved (88.75%). This situation is correlated with a slight modification in the volume of the resultant compressed tablets after the dissolution process, indicative of the lowest regression coefficients for the several kinetic fits and the highest Higuchi rate constant.

We can conclude that inert matrix compressed tablets containing Eudragit® RS as supporting material can produce a delay in the release behaviour of carteolol hydrochloride using Eudragit® L 12.5% as wetting liquid in the formulations, in comparison with organic solvents such as isopropanol-acetone mixture. All the tested formulations can be fitted by a diffusion controlled process, except those containing lactose as filler. The use of acrylic resin Eudragit® L 12.5% as a wetting liquid allows two-phase release profiles to be obtained, where the second phase exhibits a higher Higuchi release rate constant compared with the first. This phenomenon could be considered as a possible mechanism for control of the release of drugs from this type of inert matrices in two phases with different release rates.

Acknowledgement

The present paper is part of a research Project (no. PM90-0151) developed with a grant from the 'Dirección General de Investigación Científica y Técnica (DGICYT)', of the Ministry of Education and Science of Spain.

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