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ELABORATION AND TECHNOLOGICAL CHARACTERIZATION OF INERT MATRIX TABLETS OF CARTEOLOL HYDROCHLORIDE

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ABSTRACT

An original method for elaborating inert matrix tablets made with different types and proportions of Eudragit is presented. The influence of various formulation factors on technological properties of these matrix tablets were tested.

INTRODUCTION

Carteolol hydrochloride is a newly developed beta blocker. It has appropriate pharmacokinetic and activity profiles to make it a suitable candidate for controlled-release matrix systems [1 - 6]. As a support for these matrices we have used acrylic resins of the type Eudragit [7 - 10]. In this work, we propose a new technique for the elaboration of inert matrices and we test the influences of type and proportion of Eudragit and presence of lubricant over the compressed tablets technological parameters. This study is completed with a disintegration assay to differenciate those formulations that could be considered as matrix tablets. These formulations will be tested in a further work with a dissolution study.

EXPERIMENTAL

Materials

The matrix forming materials were:

* Drug: Carteolol hydrochloride (Lab. Miquel, Barcelona). Carteolol hydrochloride, 5 - (3 - tert - butylamino - 2 - hydroxy) - propoxy - 3, 4 -dihydrocarbostyril hydrochloride. is a beta-blocking drug having a 3,4-dihydrocarbostyril skeleton [1, 11].

* Excipients:

Polymer: Acrylic resins including Eudragit RL, RS, L 12.5 % and S 12.5 % (Curtex,

Industrias Sintéticas S.A., L'Hospitalet, Barcelona) [12].

Filler: Emcompress (R) (Glyco Ibérica S.A., Gavá, Barcelona).

Lubricants: Talc:Magensium stearate (9:1) (Acofarma, Tarrasa, Barcelona).

Dose determination

Nelson's method [13] has been used to determine the dose in carteolol hydrochloride contained in matrix tablets. Using its pharmacokinetic data [1], the usual dose of the drug (20 mg), its therapeutic concentration (20 ng/mL) and the time period we want to mantain the plasmatic concentration (12 h), we can determine the total dose of carteolol hydrochloride as 30.0017 mg.

Preparation of tablets

Matrix tablets, weighing 300 mg each, were formulated to contain 10 percent carteolol hydrochloride. The formulations used are shown in table 1, keeping as a constant the diverse technological conditions. The solid components of tablets were weighed (Mettler, type AE-50) and homogeneously mixed. 12.5 % solution of Eudragit L or S and 1 mL of acetone (PQS, Dos Hermanas, Sevilla) were included with constant kneading. The resultant wet mass was dried at 37 °C (Selecta, mod. 204) for 48 hours. The mass was then crushed and screened (C.I.S.A.) adequately. The sorted powder was in the 25 and 500 μ size particles range. The formulations were compressed on a excentric machine (Bonals A-300), using 10 mm concave punches. 100 tablets were elaborated for each of the 18 lots mentioned before.

Technological parameters of tablets

The external aspect of the tablets has been determined. The weight variation was evaluated individually on 10 tablets of each formulation (Mettler, type AE-50). Thickness and diameter were determined using a precision micrometer (Export-Pel, 0.05 mm) on 10 tablets. Hardness was measured on 5 tablets using a Schleuniger durometer (mod. 2E/205). Friability was determined on 4 tablets, tested for 4 min in a Erweka (type TAD) friabilometer set at 25 r.p.m. Disintegration time was evaluated on 6 tablets (Erweka disintegration apparatus, mod. ZT3), using the artificial gastric medium indicated in USP XXI [14].

Statistical analysis of technological parameters

The formulations were established to allow the effects of formulations factors to be tested in a 2 x 3 x 2 factorial design. This study was completed with a corelation test according to the technological parameters.

TABLE 1

Formulations of tablets used.

LOTS	Eudragit RL (%)	Eudragit RS (%)	Eudragit L 12.5 %	Eudragit S 12.5 %	Lub. (%)
1	40	--	+		5
2	60	--	+		5
3	80	--	+		5
4	40	--	+		0
5	60	--	+		0
6	80	--	+		0
7	40	--		+	5
8	60	--		+	5
9	80	--		+	5
10	--	40	+		5
11	--	60	+		5
12	--	80	+		5
13	--	40		+	5
14	--	60		+	5
15	--	80		+	5
16	--	40		+	0
17	--	60		+	0
18	--	80		+	0

RESULTS AND DISCUSSION

Technological characteristics

Every lot containing lubricant shows white colour and a polished and bright surface. On the contrary, those without lubricating mixture show a dull aspect; inside this group, those containing 80 % of powdered Eudragit show fissures and erosion on the edge after a period of time. The weight uniformity was evaluated according to the specifications of USP XXI [15]. Thickness, diameter, hardness and friability data oscillated inside acceptable values. The thickness of tablets was seen to be mainly dependent on the concentration of acrylic resins: a plot of the thickness vs the percentage of polymer is represented in figure 1. The effect of varying concentrations of acrylic resin on hardness is shown in figure 2. We can estimate a

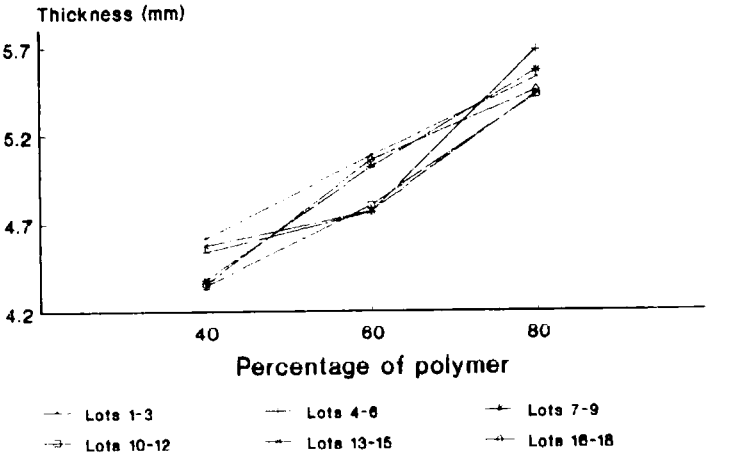

FIGURE 1
Thickness mean values (mm) vs percentage of polymer

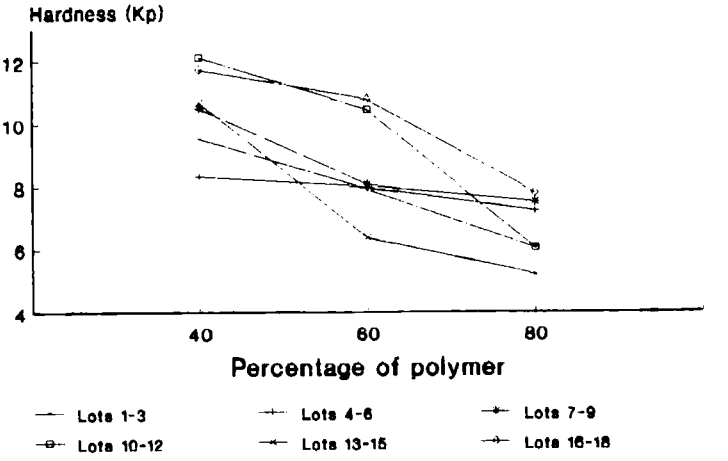

FIGURE 2
Hardness mean values (Kp) vs percentage of polymer

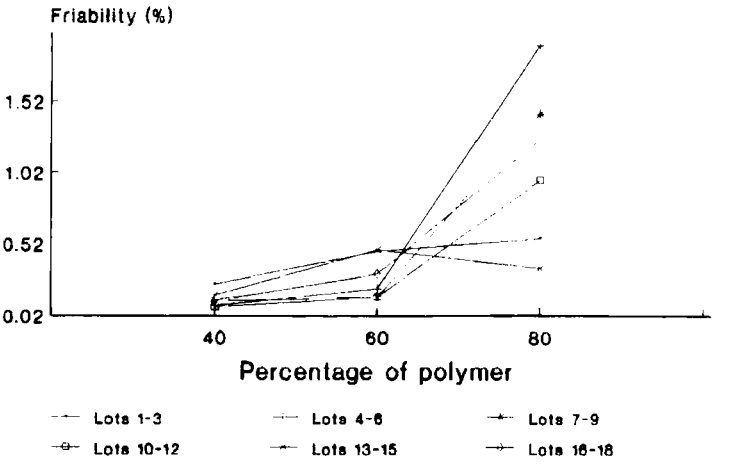

FIGURE 3
Friability mean values (%) vs percentage of polymer

clear diminution in hardness while increasing proportion of Eudragit. Tablets made with 80 % of polymer show the lowest hardness values. A graph of friability vs polymer concentration is shown in figure 3. The results reveal that friability exhibits a linear relationship with the proportion of resin. The biggest difference appears between 60 - 80 % of Eudragit.

Disintegration assay

This assay has been carried out in order to determine which of the formulations proposed can become authentic matrices, taking into account that the total lack of disintegration is one of the first requisites that every matrix must accomplish. The disintegration assay was tested during 600 minutes, time period for the later dissolution assay. The disintegration time data are presented in table 2. The formulations containing Eudragit RL and 12.5 % L mixture show a disintegration time inferior to 60 min. The table reveals a great inversed relationship between disintegration time and percentage of polymer. This situation is due to the higher Eudragit RL permeability, so that an increase in its concentration favours the tablet wettability. The inclusion of lubricant in lots 1 - 3 has not kept the matrix skeleton intact, although it has succeeded in delaying disintegration. All tablets containing Eudragit RS and Eudragit RL - 12.5 % S mixtures exceeded the assay time without undergoing any disintegration process. These results suggest that these no disintegrated tablets can be considered as potential matrix tablets, circumstance that will be the objective of a next work.

TABLE 2

Disintegration data (min). Mean values (x), standard deviations (SD), variation coefficients (CV) and standard error (e).

Lots	x	SD	CV	e
1	22.08	0.1547	0.7006	0.0632
2	12.16	0.1636	1.3455	0.0668
3	5.10	0.0922	1.8070	0.0376
4	10.08	0.1030	1.0220	0.0420
5	6.03	0.1038	1.7214	0.0424
6	4.07	0.0738	1.8142	0.0301
7 - 18	> 600			

TABLE 3

Multifactorial analysis of technological characteristics.

A = Eudragit B = Percentage of polymer C = Lubricant

		WEIGHT		THICKNESS		DIAMETER		HARDNESS	
SOURCE	D.F.	F	PROB.	F	PROB.	F	PROB.	F	PROB.
A	1	0.2098	0.6478	27.6429	0.0000	3.4319	0.0667	26.2192	0.0000
B	2	23.8498	0.0000	1061.80	0.0000	85.5336	0.0000	173.897	0.0000
C	1	47.1794	0.0000	2.3171	0.1309	95.4771	0.0000	64.6422	0.0000
AB	2	9.3154	0.0002	4.8324	0.0098	90.9909	0.0000	15.7258	0.0000
AC	1	11.6835	0.0009	4.8161	0.0303	6.6514	0.0113	75.1493	0.0000
BC	2	7.5655	0.0008	18.2389	0.0000	7.6805	0.0008	33.3889	0.0000
ABC	2	49.2589	0.0000	48.4206	0.0000	65.2352	0.0000	9.2396	0.0002
GLOBAL	11	21.7295	0.0000	209.216	0.0000	54.9490	0.0000	57.3193	0.0000
TOTAL	119								

TABLE 4

Correlation matrix of parameters tested.

Weight	1				
Thickness	-0.1602	1			
Diameter	0.1475	0.1763	1		
Hardness	-0.0193	-0.7297	0.0033	1	
Friability	-0.1977	0.7390	0.3047	-0.3976	1
	Weight	Thickness	Diameter	Hardness	Friability

Statistical treatments

In table 3 we can observe the analysis of variance of each parameter tested: with few exceptions, the considered variables, independently and their interactions, present influence with statistical significance on the technological characteristics. Data suggest that thickness was not significantly affected by the lubricant. Neither weight nor diameter were influenced by the type of polymer; on the last two factors the greatest influence was exerted by the presence of lubricant. Otherwise, we have found the biggest influence of proportion of Eudragit over thickness and hardness because both characteristics are directly associated with the cohesion degree between particles integrating powders. In relation to weight, there is statistical significance on the different variables (with relatively low F values). This result is not considered to be an impediment according to the specifications of USP XXI. In relation to the correlation study, table 4 expresses the correlation matrix about matrix tablets. We can value correlation coefficients with statistical significance between thickness and friability (direct relation) and between thickness and hardness (inverse relation), due to the smaller compaction that these tablets have.

As a summary, we can point out that a clear increase in tablets thickness and friability and a diminution in hardness have been observed with increasing percentage of resin. Formulations containing Eudragit RL and 12.5 % L mixture do not originate matrix tablets. Finally, we have obtained matrix tablets employing Eudragit (R) RS, both with Eudragit (R) 12.5 % L and 12.5 % S.

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