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IN VITRO STUDY OF MIXED CONTROLLED RELEASE MATRIX TABLETS CONTAINING HMPC AND POLYAMIDE 12

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INTRODUCTION

In recent years there has been a growing interest, in the subject of drug delivery and the design and evaluation of controlled release systems (1,2,3). Probably the simplest and least expensive way to control the release of an active agent, is to disperse it in an inert polymeric matrix (4,5,6) . In polymeric systems, the active agent is physically blended with the polymer powder and then fused together by compression moulding, which is a common process in the Pharmaceutical Industry (7,8,9).

This study deals with oral dosage forms in matrix type tablets, which associate two kinds of polymeric materials, one hydrophobic and the other hydrophylic, looking for relationships between formulation and pharmacotechnical variables. Dissolution rates of these different formulations have been the comparative term. The results obtained have allowed to quantify the influence of the polymer percentage in the dissolution rate of the active agent, when two excipients with

different forms of release are associated. The comparative study of the dissolution process has been performed by a mathematical treatment of the experimental data, based on two procedures: statistical study of the dissolution profiles (this enables to know the qualitative behaviour of release) and analysis of variance of parameters which do not require any model hypothesis (dissolution efficiency, area under the dissolution curve and cumulative concentration of active agent dissolved within 8 hours).

MATERIALS

The hydrophilic polymer chosen has been the hydroxypropylmethilcellulose (HPMC) with high viscosity, and polyamide 12 trademark ORGASOL 2002 ES 5 NAT, as hydrophobic polymer. The active agent tracer has been metoclopramide hydrochloride (MCP.HCl) since it is specially appropiate for its administration as controlled release dosage forms, due to its physicochemical properties and its therapeutical interest.

To carry out this experimental study, five batches of matrix tablets of metoclopramide hydrochloride were made with different proportions of HPMC and ORGASOL 2002 ES 5 NAT. Both excipients are for direct compression. A batch of reference tablets with AVICEL PH-101 as conventional excipient, was made too. Table 1 shows the composition of the different matrix tablets formulations studied.

METHODS

The following pharmacotechnical parameters of the tablets have been determined:

1. Compression ratio.

This is a parameter which evaluates the compression degree which takes place in a material, and it is expressed by the following equation:

TABLE 1. Tablet formulations.

FORMULATION	ORGASOL%	HPMC%	MCP.2HCl (mg)
F1	100	0	30
F2	75	25	30
F3	50	50	30
F4	25	75	30
F5	0	100	30

$$Rc = \frac{hr}{H}$$

Rc = compression ratio.

hr = actual height of the tablet.

H = height of the die's force.

The compression ratio mean values for each batch are shown in table 2.

2. Fracture test.

It has been intended to have fracture force approximately the same in all the batches of tablets, in order to keep constant this parameter. Table 2 shows the results obtained in each batch.

3. Uniformity of dosage units.

The uniformity of dasage units has been demonstrated according to U.S.P XXII. Mean values of weight variation and content uniformity are shown in table 2.

4. Dissolution rate.

An apparatus type 1 of U.S.P XXII at 50 rpm was used to carry out dissolution rate tests. Six tablets from each batch were tested, using 900 ml of distilled water as dissolution medium. The tests have lasted 8 hours.The samples were filtered and then their concentrations were determined by ultraviolet spectrophotometry at 308 nm wavelength.

RESULTS AND DISCUSSION

The comparative study of the dissolution process of metoclopramide in water, in the different batches of tablets

TABLE 2. Mean values and coefficient of variation of the pharmacotechnical tablets parameters.

FORM.	Rc	FRACTURE FORCE (kg)	WEIGHT VARIATION (mg)	CONTENT UNIFORMITY (mg)
F1	0.467	4.50 (5.55)	494.86 (1.47)	25.21 (0.54)
F2	0.445	4.50 (7.84)	493.20 (2.01)	27.46 (1.33)
F3	0.408	4.62 (7.48)	507.53 (2.09)	27.33 (3.98)
F4	0.375	4.54 (7.23)	506.80 (1.53)	28.34 (3.75)
F5	0.380	4.41 (8.43)	509.80 (2.06)	29.95 (3.56)
F6	0.303	4.58 (7.49)	488.70 (2.99)	28.22 (1.94)

tested, has been made by a mathematical treatment of the experimental data, based on two procedures: statistical study of the dissolution profiles and analisys of variance (ANOVA) of parameters which do not require any model hypothesis.

1. Release profiles.

The dissolution curves of each tested batch are compared by statistical parameters such as variance and coefficient of variation of cumulative concentration dissolved of active component. Figure 1 represents the dissolution profiles.

Table 3 shows the mean values of cumulative concentration of metoclopramide dissolved in water, for the six batches of tablets tested.

It can be observed that F6 formulation presents dissolution kinetics very different from the other formulations. Formulation F1 shows faster dissolution rate at the begining of the process but later on, the rate decreases and by the end of the process, the active agent is not completely released. This may be explained because orgasol tablets are slightly erosiones on their surface and so the active agent placed in this area, is inmediately released to the dissolution medium. However, a portion of active agent is not released due to the difficulty of the dissolution liquids to penetrate into the internal nucleus of

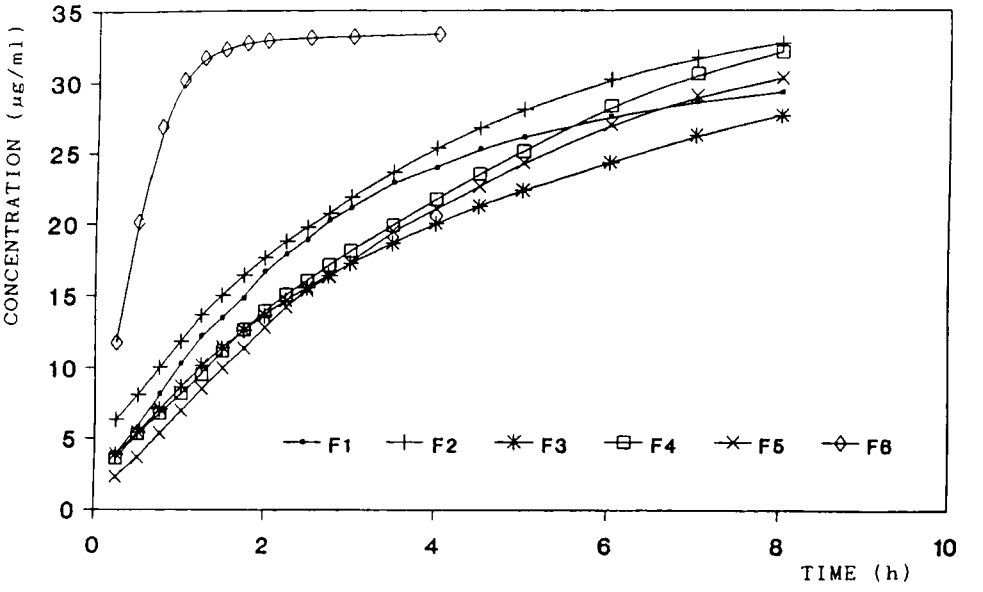

FIGURE 1. Cumulative concentration vs time.

TABLE 3. Mean values of cumulative concentration.

t (h)	F1	F2	F3	F4	F5	F6
0.25	3.93	6.33	3.86	3.60	2.29	11.76
0.5	5.80	8.10	5.40	5.30	3.63	20.16
0.75	8.19	10.05	7.07	6.76	5.34	26.90
1.00	10.27	11.83	8.64	8.16	6.93	30.17
1.25	12.21	13.67	10.14	9.53	8.50	31.71
1.50	13.44	15.01	11.37	11.14	9.93	32.31
2.00	16.71	17.68	13.64	13.92	12.76	32.93
2.25	17.90	18.82	14.63	15.03	14.18	
2.50	18.91	19.78	15.56	16.06	15.37	33.10
2.75	20.27	20.73	16.40	17.13	16.28	
3.00	21.13	21.89	17.25	18.13	17.29	33.17
3.50	22.93	23.65	18.62	19.88	19.47	
4.00	23.96	25.37	20.00	21.70	21.01	33.35
4.50	25.18	26.78	21.23	23.51	22.59	
5.00	26.12	28.09	22.36	25.13	24.31	
6.00	27.57	30.21	24.32	28.34	27.00	
7.00	28.58	31.72	26.21	30.58	29.01	
8.00	29.30	32.73	27.66	32.08	30.27	

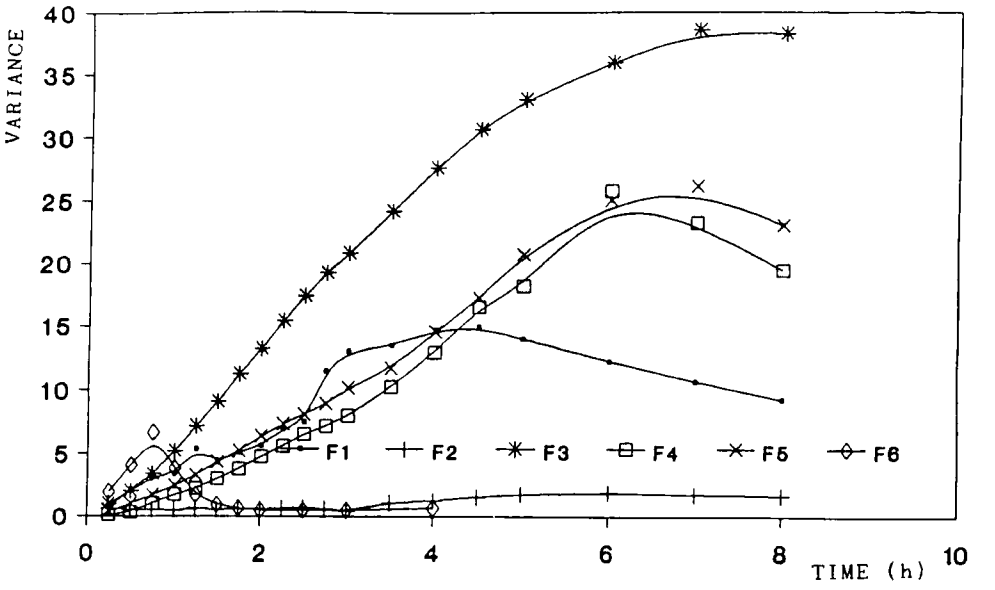

FIGURE 2. Variance vs time.

the tablets. Formulation F2 shows more homogeneous kinetics, obtaining higher concentrations than the other formulations during all the dissolution process. Formulations with 50, 75 and 100% HPMC, do not present differences in the dissolution kinetics until 4-5 hours.

Variances of cumulative concentration versus time show more remarkable differences (figure 2).

Formulation F2 presents small and constant variance with time. Variance values for formulation F1 increase up to a maximum and then they decrease. After this maximum, erosion phenomena of the tablets probably cease, and then the release becomes constant. Formulation F3 shows variances which increase with time, this explains the differences among the disgregation times in the various tablets tested. In relation to formulations F4 and F5 , these tablets swell up and after 6-7 hours they finally disgregate, when the maxima in variance are

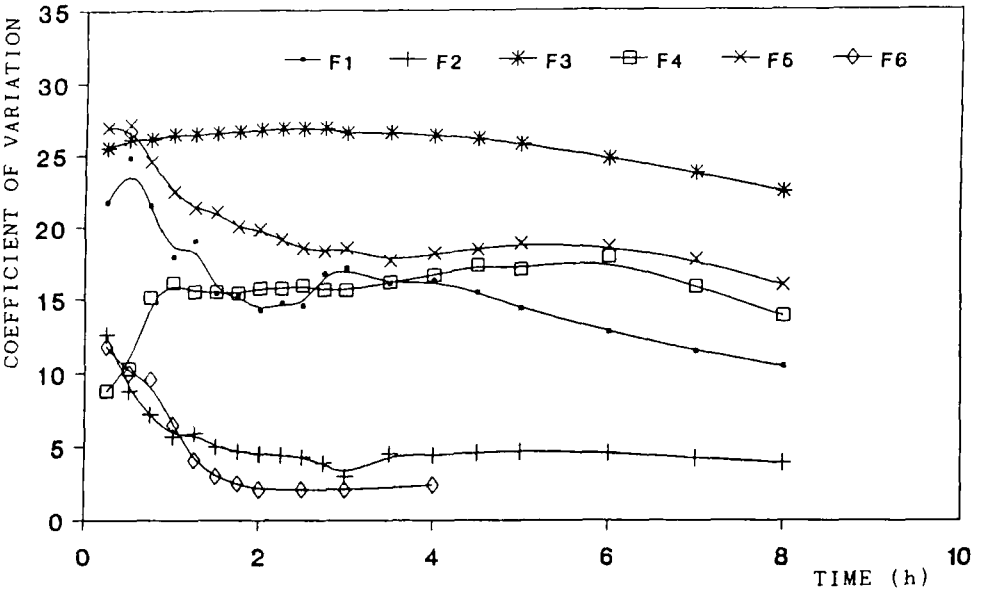

FIGURE 3. Coefficients of variation vs time.

observed. This can also be noticed when coefficients of variation are represented (figure 3).

For F2 at short times, the coefficient of variation is high, but decreases as the dissolution process stabilizies. F3 shows the highest coefficient of variation, but practically constant with time, due to the differences in the disgregation times of the tablets. The other formulations have coefficientes of variation independent with time, approximately in 1-2 hours.

2. ANOVA of independent paramenters.

The following parameters have been studied: dissolution eficiency (10), area under the dissolution curve and cumulative concentration within 8 hours.

High significant differences are observed between formulation F1 and those with 50% HPMC or more. F2 presents similar behaviour to F1, showing high significant

TABLE 4. Test t-Student's matrix values for the equality hyphothesis contrast formulations for the parameter dissolution efficiency.
NS (non significant); * ($p \leqslant 0.05$); *** ($p \leqslant 0.001$)

	F1	F2	F3	F4	F5
F1	0.0NS				
F2	-1.17NS	0.0NS			
F3	-3.75***	-2.58*	0.0NS		
F4	-5.49***	-4.32***	-1.74NS	0.0NS	
F5	-5.34***	-4.17***	-1.59NS	0.14NS	0.0NS

TABLE 5. Test t-Student's matrix values for the equality hyphothesis contrast formulations for the parameter area under the dissolution curve.
NS (non significant); * ($p \leqslant 0.05$)

	F1	F2	F3	F4	F5
F1	0.0NS				
F2	-0.06NS	0.0NS			
F3	-2.28*	-2.23*	0.0NS		
F4	-1.69NS	-1.63NS	0.59NS	0.0NS	
F5	-2.31*	-2.25*	-0.02NS	-0.61NS	0.0NS

TABLE 6. Test t-Student's matrix values for the equality hyphothesis contrast formulations for the parameter cumulative concentration.
NS (non significant)

	F1	F2	F3	F4	F5
F1	0.0NS				
F2	1.26NS	0.0NS			
F3	-0.61NS	-1.87NS	0.0NS		
F4	1.02NS	-0.24NS	1.63NS	0.0NS	
F5	0.35NS	-0.91NS	0.96NS	-0.67NS	0.0NS

differences with respect to formulations F4 and F5 too. This seems to point out a remarkable influence of the proportion of polymers on the active agent dissolution rate. Table 5 represents the ANOVA results for the area under the dissolution curve variable. If we compare these results with the former ones, we can appreciate that the dissolution efficiency variable is more adequate for comparing the different formulations.

Finally the cumulative concentration within 8 hours, has been studied. Table 6 shows the analysis of variance of this parameter. There are no significant results, therefore this parameter is of no use to appreciate differences in the dissolution kinetics of the active component.

CONCLUSIONS

The matrix tablets studied present dissolution profiles different to the reference tablets, and may be considered as controlled release formulations.

The dissolution kinetics are markedly different for the various formulations studied, depending in each case on the proportion of excipients.

The dissolution efficiency paramenter is very useful to study this type of formulations and to estimate the probable differences in the dissolution rate of the active agent.

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