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MATRIX TABLETS CONTAINING HPMC AND POLYAMIDE 12: COMPARISON OF DISSOLUTION DATA USING THE GOMPERTZ FUNCTION

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INTRODUCTION

There have been several studies reported which have evaluated the controlled drug release from hydrophillic (1,2) or hydrophobic (3) polymeric matrix tablets, but they do not show anything about mixed matrices containing the two kinds of polymeric materials. In a previous paper, we have studied the in vitro dissolution data from mixed matrix tablets containing HPMC and polyamide 12, by means of an analysis of variance of parameters which do not require any model hypothesis. Now the effect on the dissolution profiles of different ratios of the hydrophillic polymer and the hydrophobic one, is evaluated by a mathematical model. The advantage of fittin functions to release data is manifold: that functions can provide a convenient summary of the release process and a stimated release characteristics can be evaluated. Comparison of dissolution profiles under a variety of conditions relation to formulation characteristics and other variations, is usually conducted employing statistical tools such us analysis of variance (4,5).

Then, the aim of this work is to compare dissolution data from matrix tablets containing HPMC and polyamide 12, by means of some parameters derived form Gompertz function. According to the goodness of the fit, this function has been chosen because it is a well-known and widely used mathematical function and it has a very good flexibility. Besides, the parameters derived from it can provide a convenient summary of the release process and a stimated release characteristics can be evaluated. These parameters have a very low standard error and they have a technological meaning, such us cumulative concentration, dissolution time, maximum dissolution rate, relative dissolution rate and so on.

MATERIALS

Polyamide 12 trademark ORGASOL 2002 ES 5 NAT, Atochem.

Hydroxypropylmethyl cellulose trademark PHARMACOAT 615, Shin-Etsu Chemical Co., Ltd.

Metoclopramide dyhydrochloride, Medichem, S.A.

METHODS

-Characterization of active principle.

Qualitative and quantitative analysis of metoclopramide dyhydrochloride, were determined by ultraviolet spectrophotometry at 308 nm (6).

-Tablet manufacture.

Five series of metoclopramide dihydrochloride tablets were formulated with different proportions of polyamide 12 and HPMC, and were compressed by the direct compression method. Table 1 shows the composition of each formulation estudied. The tablets average weight and the hardness were parameters previously defined: 500 mg and 4.5 ± 0.25 Kg respectively. As these technological parameters were kept constant, the differences

TABLE 1. Tablet formulations.
MCP.2HCl (metoclopramide dihydrochloridre).

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

between formulations can be attributed to the different tablets composition.

-Characterization of the tablets.

Tablets were subjected to the following pharmacotechnical tests (Table 2).

Fracture test. Fracture force was measured on six tablets of each formulation, using an Erweka/TBI apparatus.

Uniformity of dosage units. According to USP XXII the uniformity of the compressed tablets was demonstrated by two methods:

Weight variation.- USP XXII requirments comply in all formulations, each one of the ten tablets weight within 85-115% of the mean weight and their coefficient of variation is under 6%

Content uniformity.- All formulations comply with the USP XXII requirment, mean content 15% and coefficient of variation under 6%.

-Dissolution test.

For each formulation six tablets were tested individually in accordance with USP XXII Apparatus I (rotating basket method) at 50 rpm. 900 ml of distilled water were used as dissolution medium. The samples were filtered and metoclopramide

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

FORMULATION	FRACTURE FORCE (kg)	WEIGHT VARIATION (mg)	CONTENT UNIFORMITY (mg)
F1	4.50 (5.55)	494.86 (1.47)	25.21 (0.54)
F2	4.50 (7.84)	493.20 (2.01)	27.46 (1.33)
F3	4.62 (7.48)	507.53 (2.09)	27.33 (3.98)
F4	4.54 (7.23)	506.80 (1.53)	28.34 (3.75)
F5	4.41 (8.43)	509.80 (2.06)	29.95 (3.56)

of an hour intervals during the three first hours, at half hour intervals for the following two hours and finally at one hour intervals for the last three hours of assay.

-Mathematical treatment.

The comparative study of the dissolution process of metoclopramide in water, has been made by a mathematical treatment of the experimental data.

Several sigmoid functions were used to analyze cumulative concentration dissolution curves. Experimental data were fitted by mathematical model using the weighted non-lineal regression program BMDPAR (7) , which estimates the parameters by a pseudo Gauss-Newton algorithm. The weighted function was $\omega_i = 1/y_i^2$ where y_i^2 is the experimental value for i-th observation.

According to the goodness of the fit and to the technological meaning of its paramenters, the Gompertz function (1) was chosen. This function is defined by the following diferential equation:

$$\frac{dC}{dt} = K \cdot C \quad (\ln A - \ln C) \qquad (1)$$

Where indepentent variable is the time and dependent variable is an attribute C that evalues the dissolution process. In this case C represents the cumulative concentration of active

principle, dC/dt represents the absolute dissolution rate and the expression 1/C·dC/dt is the relative dissolution rate, that is generally very adecuated to explain comparative aspects of the dissolution process. K and A are model parameters.

The functional equation that defines the Gompert function is:

$$C = A \exp \left[-B \exp (-K \cdot t) \right] \quad (2)$$

which can also be written:

$$C = P1 \exp \left[-P2 \exp (-P3 \cdot t) \right] \quad (3)$$

This sigmoid function showed a satisfactory kinetic interpretation, since the stimated parameter A (asymptote when $t \longrightarrow \infty$) was closely related to the final dissolution process. About the other two parameters, K is a rate parameter (a high indicating a rapid rise of the function between the two asymptotes and viceversa) and B/K defines the t-value at inflection point. On that point cumulative concentration is given by A/e. The parameter derived from Gompertz function AK/e, is the maximum dissolution rate.

Table 3 shows the technological meaning of Gompertz's model parameters. These parameters are calculated by non-lineal regression methods using computing programs belonging to statistical package BMDP.

The statistical analysis of dissolution data was made by analysis of variance (ANOVA) of Gompertz's model parameters, using the BMDP1V program.

RESULTS AND DISCUSSION

The mean values of cumulative concentration of metoclopramide dissolved in water for the five formulations tested, are shown in table 4.

TABLE 3. Technological meaning of Gompertz's model parameters.

PARAMETER	GOMPERTZ'S MODEL
Cumulative concentration (µg/ml)	C
Final cumulative concentration (µg/ml)	A (P1)
Dissolution time (h)	t
Time on inflection point (h)	β/K (lnP2/P3)
Cumulative concentration on inflection point (µg/ml)	A/e (P1/e)
Time when C = C/2 (h)	t½
Maximum dissolution rate (µg/ml/h)	AK/e (P1P3/e)
Relative dissolution rate (h^{-1})	K (P3)

TABLE 4. Mean values of cumulative concentration of metoclopramide dyhydrochloride dissolved for the five batches of tablets tested.

t (h)	F1	F2	F3	F4	F5
0.25	3.93	6.33	3.86	3.60	2.29
0.5	5.80	8.10	5.40	5.30	3.63
0.75	8.19	10.05	7.07	6.76	5.34
1.00	10.27	11.83	8.64	8.16	6.93
1.25	12.21	13.67	10.14	9.53	8.50
1.50	13.44	15.01	11.37	11.14	9.93
1.75	14.81	16.41	12.59	12.62	11.30
2.00	16.71	17.68	13.64	13.92	12.76
2.25	17.90	18.82	14.63	15.03	14.18
2.50	18.91	19.78	15.56	16.06	15.37
2.75	20.27	20.73	16.40	17.13	16.28
3.00	21.13	21.89	17.25	18.13	17.29
3.50	22.93	23.65	18.62	19.88	19.47
4.00	23.96	25.37	20.00	21.70	21.01
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

Cumulative concentrations dissolved of MCP.2HCl (C) in µg/ml, over the time (t) in hours, were fitted to Gompertz's function, defined by the equation 3 previously shown.

The goodness of the fit was statistically performed by a lack of fit analysis of variance based on replicates. According to F-values, all of them cannot be significant and Gompertz model showed a good fit to all experimental data.

In Table 5 the values of Gompertz's parameters with technological meaning are represented. ANOVA of final cumulative concentration (P1), cumulative concentration on inflection point (P1/e) and maximum dissolution rate (P1P3/e), did not show any high significant differences between formulations.

On the other hand, parameters like time on inflection point (lnP2/P3), mean time ($t_{½}$) and mean relative dissolution rate (P3) were very useful to appreciate differences between formulations.

Figure 1 represents dissolution profiles for each formulation.

Afterwards the results of ANOVA for each parameter are described.

-Time on inflection point . The technological meaning of this point (lnP2/P3 , P1/3) is the time in which the dissolution rate experiments an apreciable change. High significant differences (Table 6) are observed between formulations F1 and F2 with respect to F4 and F5. This seems to point a remarkable influence of the polymers percentage on the active principle's dissolution rate, because F1 and F2 contain 0 and 25% of HPMC respectively, on the other hand F4 and F5 contain that hydrophilic polymer in a percentage of 75 and 100% respectively.

-Mean time . The mean time is the time in which dissolved concentration is a half of final concentration. It can also be observed (Table 7) high significant differences between formulations with low and high content of HPMC.

TABLE 5. Individual values of Gompertz's model parameters which have technological meaning.

	P1	P3	P1P3/e	t½	P1/e	lnP2/P3
F11	25.42	0.86	8.04	1.23	9.35	0.80
F12	33.82	0.73	9.08	2.01	12.44	1.51
F13	21.23	0.62	4.84	1.54	7.81	0.95
F14	29.30	0.91	9.81	1.25	10.78	0.81
F15	29.25	0.74	7.96	1.55	10.76	1.06
F21	31.54	0.48	5.57	1.89	11.60	1.13
F22	29.67	0.48	6.66	1.68	10.91	1.08
F23	32.39	0.62	7.39	1.71	11.92	1.12
F24	32.36	0.55	6.55	1.75	11.90	1.08
F25	33.68	0.54	6.69	1.67	12.39	0.99
F31	29.48	0.61	6.62	1.79	10.85	1.18
F32	32.51	0.65	7.77	1.74	11.96	1.18
F33	16.51	0.54	3.28	1.80	6.07	1.12
F34	24.87	0.67	6.13	1.63	9.15	1.09
F35	18.97	0.53	3.70	2.34	6.98	1.65
F41	24.92	0.37	3.39	3.02	9.17	2.03
F42	34.63	0.51	6.50	2.44	12.74	1.72
F43	36.74	0.50	6.76	2.44	13.52	1.71
F44	32.39	0.59	7.03	2.16	11.92	1.54
F45	28.22	0.62	6.44	1.92	10.38	1.33
F51	31.59	0.56	6.51	2.32	11.62	1.66
F52	30.85	0.73	8.28	1.87	11.35	1.37
F53	32.97	0.64	7.76	2.23	12.13	1.66
F54	26.83	0.63	6.22	2.27	9.87	1.69
F55	18.98	0.65	6.22	2.18	6.98	1.62

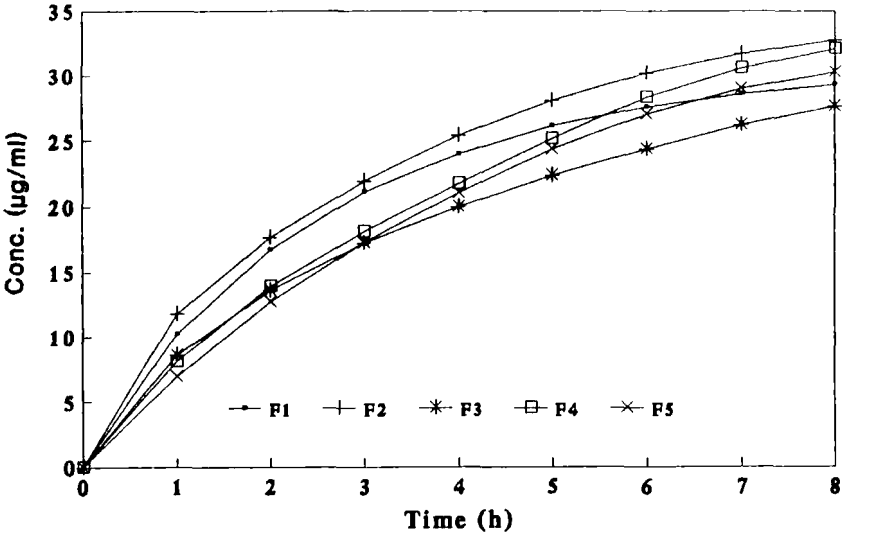

FIGURE 1. Dissolution profiles.

TABLE 6. Test t-Student's matrix values for the equality hyphothesis contrast formulations for the parameter time on inflection point.
NS (non significant)
** ($p \leqslant 0.01$); *** ($p \leqslant 0.001$)

	F1	F2	F3	F4	F5
F1	0.0NS				
F2	-0.03NS	0.0NS			
F3	1.58NS	1.62NS	0.0NS		
F4	4.89***	4.92***	3.30**	0.0NS	
F5	4.74***	4.77***	3.15**	-0.15NS	0.0NS

TABLE 7. Test t-Student's matrix values for the equality hyphothesis contrast formulations for the parameter mean time.
NS (non significant)
* ($p \leqslant 0.05$); ** ($p \leqslant 0.01$); *** ($p \leqslant 0.001$)

	F1	F2	F3	F4	F5
F1	0.0NS				
F2	1.22NS	0.0NS			
F3	2.13*	0.90NS	0.0NS		
F4	5.30***	4.90***	3.18**	0.0NS	
F5	4.20***	2.98**	2.08*	-1.10NS	0.0NS

TABLE 8. Test t-Student's matrix values for the equality hyphothesis contrast formulations for the parameter mean relative dissolution rate.
NS (non significant)
* ($p \leqslant 0.05$); ** ($p \leqslant 0.01$); *** ($p \leqslant 0.001$)

	F1	F2	F3	F4	F5
F1	0.0NS				
F2	-5.13***	0.0NS			
F3	-4.11***	1.03NS	0.0NS		
F4	-5.67***	-0.53NS	-1.56NS	0.0NS	
F5	-2.89***	2.24*	1.22NS	2.78**	0.0NS

-Mean relative dissolution rate . High significant differences are observed (Table 8) between formulation F1 with respect to F2, F3 and F4. This parameter can be compared to a rate constant, therefore it can be said that dissolution rate is different for each formulation studied and it depends on the polymer percentage.

CONCLUSION

The ANOVA results of model parameters suggest that the polymer percentage modify the dissolution behaviour of the different batches of tablets tested.

Moreover this study shows the effectiveness of Gompertz function for the comparison and interpretation of dissolution data in different formulations, because of the technological meaning of its parameters and the magnitude and rate data.

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