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Usefulness of certain varieties of Carbomer in the formulation of hydrophilic furosemide matrices

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Summary

This paper deals with the evaluation of the possible use of three types of Carbomer, with different molecular weights, in the formulation of hydrophilic furosemide matrices. To this purpose the effects of the most outstanding elaboration variables; type and proportion of polymer and maximum compression force on the mechanical and release characteristics of tablets are studied. The factorial designs that were used as the basis for the development of this study have made it possible, through the respective ANOVA, to identify the factors having a significant effect on the properties of the tablets. Among the effects observed, which were quantified by sequential multiple linear regression, with acceptable adjustment levels, one of the most noteworthy is the effect that the maximum compression force has on the dissolution efficiency of furosemide from the formulations, regardless that variety of Carbomer employed. In all cases, the furosemide dissolution profiles, whose dependency on the microporous structure has been discussed, were fit to a zero order releasing kinetics, pointing to an erosion mechanism.

Introduction

When an oral sustained release formulation is being designed, the hydrophilic matrices present an interesting alternative to other monolithic or multiparticulate pharmaceutical dosage forms. Among the many advantages, the following stand out: their simple elaboration process and low production cost; the possibility of large proportions of the drug being added and the wide range of release profiles offered (Buri and Doelker, 1980; Alderman, 1984; De Haan and Lerk, 1984; Doelker, 1985).

In the formulation of hydrophilic matrices, a wide range of polymers (Buri and Doelker, 1980) is employed among which the group of acrylic acid derivatives, known officially as Carbomer (American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, 1986) or by their commercial name Carbopol^{R} (BFGoodrich, Cleveland, OH) is included.

Several papers dealing with these products have been published, demonstrating their utility in achieving sustained release with diverse active

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principles, although they center exclusively on the 934 variety (Choulis and Papadopoulos, 1975; Salib et al., 1983; Agabeyoglu, 1986; Graf et al., 1986; Malley et al., 1987; Bulut-Oner et al., 1989; Çapan et al., 1989). Recent research has shown the possibilities that are offered by controlling the release of hydrosoluble substances when used in conjunction with hydroxypropyl cellulose in the elaboration of matrices (Satoh et al., 1989). Their practical value is evident from the great number of patents for sustained release formulations, some of which have been registered in the last few years (DeCrosta et al., 1987; Ueda et al., 1987; Hirofumi et al., 1988).

However, despite the potential interest this group of products holds, at the present time the information on the effect the elaboration variables have on the characteristics of the tablets is very limited.

This article presents the results of a study in order to make a preliminary evaluation of the possibilities offered by several varieties of Carbomer with different molecular weights in the formulation of sustained release tablets with low soluble active principles. The mechanisms involved in release, as well as the effect of the most significant technological variables on this process for each variety selected, are also discussed.

Materials and Methods

Active principle and excipients

Furosemide USP, BP (C. Barcia, batch 0053); Carbomer 934 NF (Carbopol^R 934, Escuder, batch 043); Carbomer 940 NF (Carbopol^R 940, Escuder, batch 072); Carbomer 941 NF (Carbopol^R 941, Escuder, batch 005); Lactose USP, BP (C. Barcia, batch 872); Magnesium Stearate USP, BP (C. Barcia, batch 832); Polyvinylpyrrolidone 40 000 USP, BP (C. Barcia, batch 841-A).

Formulations

Twelve furosemide tablet formulations were elaborated using the conventional wet granulation method. In order to do this, a furosemide lactose granulate (40 : 60), using a polyvinylpyrrolidone 40 000 aqueous dispersion as wetting liquid, was prepared. The amount of binder comprised 1.1% of the granulated mass. The granulate was mixed with the Carbomer for 20 min in a Turbula T2C mixer at 30 rpm. Next, 0.5% magnesium stearate was added and then mixed for another 5 min. Finally it was compressed using flat teflon punches, 12 mm in diameter in an excentric press (Korsch EKO), equipped with a pressure recording system (Martínez-Pacheco et al., 1985). In all cases tablet weight was adjusted so that furosemide content was 100 mg. The formulations that were elaborated will be referred to henceforth by the letters A, B or C, depending on whether they contain Carbomer 934, 940 or 941. The subscripts show the ratio of polymer (20 or 40%), and the maximum compression force applied during the compression cycle (4000 or 16 000 N), respectively.

Tests

The tablets from each formulation, obtained using the process described above, were subjected to the following tests;

Furosemide content. The spectrophotometric procedure described in the USP XXI was applied.

Crushing strength. Six tablets were tested using an Erweka TB24 durometer.

Friability. Weight loss was determined for 10 tablets in an Erweka TAP apparatus at 20 rpm for 15 min.

Dissolution rate. The furosemide dissolution rate was determined for 6 tablets using the USP XXI apparatus II. In order to keep tablets on the bottom of the tray so that they would not float during the tests, they were placed in parallelepiped stainless steel mesh baskets 1.6 mm DIN, $2.8 \times 2.8 \times 1.1$ cm. Blade turning speed was 150 rpm. Phosphate buffer pH = 5.8 was used as dissolution medium. The amount of furosemide dissolved at pre-established sampling times was ascertained using the same procedure applied for determining the active principle. The parameter used to characterize the curves obtained was the dissolution efficiency between 0 and 8 h (Khan, 1985).

Porosity. The microporous structure analysis of the tablets was carried out using mercury intrusion porosimetry (Micromeritics 9305). The measurements were extended to a pressure of 25 000

Psi. In all cases pore size population was fit to a log-normal distribution. Total porosity as well as the mean and standard deviation of the corresponding distribution were employed for characterizing formulations. Three assays were carried out for each formulation.

Experimental design and statistical analysis

The composition and elaboration conditions of the different formulations define a factorial design for two variables—maximum compression force applied during the compression cycle (MCF) and Carbomer percentage (CP)—at two levels for each of the varieties of Carbomer selected.

The results of the different assays were subjected to two-way ANOVA, corresponding to the experimental design used to identify the formulation variables responsible for the differences observed. The equations needed to construct the response surfaces were fit using a stepwise multiple linear regression program, BMDP.P2R (Dixon, 1983), introducing terms that proved significant in the ANOVAS.

Results and Discussion

Table 1 shows mean values obtained from the different assays done on the tablets. The results from the test on active principle content have been omitted, which in all cases were fit to the standards set in the USP XXI.

As far as mechanical properties are concerned, all the formulations show acceptable characteristics, as can be easily deduced from the results.

If the ANOVA results compiled in Table 2 are examined, it is possible to detect a similarity of dependence on the variables under study for the three varieties of Carbomer. The following equations fitted using stepwise multiple linear regression, allow one to quantify these effects:

Carbomer 934:

Crushing strength

$$= -88.00 + 5.20 \times CP + 1.54 \times 10^{-2} \times MCF - 3.38 \times 10^{-4} \times CP \times MCF \quad (1)$$

$[R = 0.9636;\ P > 99\%]$

Carbomer 940:

Crushing strength

$$= -42.78 + 3.80 \times CP + 1.18 \times 10^{-2} \times MCF - 2.33 \times 10^{-4} \times CP \times MCF \quad (2)$$

$[R = 0.9890;\ P > 99\%]$

TABLE 1

Tablet test results

Formulation	Crushing strength (N)	Friability (%)	Dissolution efficiency (%)	Porosity (%)	Pore mean diameter (μm)
A_{11}	50.8	0.37	16.2	32.7	0.22
A_{12}	147.9	0.06	53.1	11.9	0.06
A_{21}	127.5	0.05	31.1	32.2	0.11
A_{22}	150.0	0.15	41.8	13.6	0.04
B_{11}	62.1	0.19	26.6	28.1	0.18
B_{12}	148.3	0.18	42.7	16.8	0.08
B_{21}	119.6	0.04	16.0	34.5	0.11
B_{22}	150.0	0.18	19.6	13.0	0.04
C_{11}	43.9	0.25	3.8	28.8	0.32
C_{12}	145.8	0.20	5.8	12.2	0.08
C_{21}	129.2	0.03	1.4	31.5	0.17
C_{22}	150.0	0.04	1.9	12.8	0.05

TABLE 2

Values of F obtained for the different parameters in the analysis of variance (C.S., crushing strength; D.E., dissolution efficiency; P, porosity; M.P.D., mean pore diameter)

Parameter	Variety of carbomer	Proportion of carbomer (CP)	Compression force (MCF)	Interaction (CP×MCF)
C.S. [a]	934	75.91 [c]	175.03 [c]	68.09 [c]
	940	154.16 [c]	599.39 [c]	137.28 [c]
	941	114.79 [c]	225.63 [c]	92.87 [c]
D.E. [a]	934	0.21	37.22 [c]	11.24 [c]
	940	37.80 [c]	12.90 [c]	5.18 [d]
	941	42.51 [c]	6.71 [d]	2.50
P [b]	934	4.04	542.11 [c]	0.01
	940	1.63	474.27 [c]	54.70 [c]
	941	2.25	264.51 [c]	1.04
M.P.D. [b]	934	23.32 [c]	90.67 [c]	8.95 [d]
	940	82.63 [c]	186.53 [c]	4.04
	941	23.32 [c]	90.67 [c]	8.95 [d]

[a] 1 and 20 d.f.
[b] 1 and 8 d.f.
[c] Significant at 0.01 level.
[d] Significant at 0.05 level.

Carbomer 941:

Crushing strength

$$= -92.85 + 5.38 \times CP + 1.48 \times 10^{-2} \times MCF - 3.26 \times 10^{-4} \times CP \times MCF \quad (3)$$

$[R = 0.9841;\ P > 99\%]$

The surface responses based on these equations (see Fig. 1) clearly show that the three varieties of polymer have similar behavior. The increase in crushing strength that was observed in the tablets as the proportion of polymer rises, can be explained by the well-known effectiveness of Carbomer as a binder (Concheiro et al., 1987).

The application of the stepwise multiple linear regression program BMDP.P2R to the results obtained from the friability test demonstrate that the controlled variables have no appreciable effects, except on tablets elaborated with variety 941, for which the following equation was obtained:

$$\%\ \text{Friability} = 0.4150 - 0.0095 \times CP \quad (4)$$

$[R = -0.9825;\ P > 95\%]$

This equation demonstrates that the proportion of Carbomer has an effect of a very small scope. Perhaps the reason for this strong independence lies in the extremely reduced values for weight loss caused by friability, which were found for all the formulations.

Given the purpose of this study, the aspect which holds the greatest interest is the dissolution rate of furosemide. As regards this aspect, the behavior of the formulations is highly varied and covers a wide range of possibilities, as seen in Figs. 2–4. However, despite the diversity found in the dissolution rate of furosemide, we observed that the profiles fit a type of kinetics that is clearly constant. In all cases, the fit that was obtained by assimilating the results to zero order kinetics proved more satisfactory than the one observed for the remaining commonly used models, and particularly for the classical Higuchi's square root kinetics. In Table 3 the goodness of fit of the experimental results to the model above can be verified. This suggests that the predominant mechanism controlling drug release is the superficial erosion of the matrix and not a Fickian diffusion process. The low hydrosolubility of the furosemide must also greatly contribute to this. The important role that the solubility of the drug plays in its release behavior was pointed out by Alderman (1984) and confirmed by Ford et al. (1987) and Ranga Rao et al. (1987) using a number of drugs added to cellulose ether matrices.

In order to evaluate the effect of the technological factors under study on the dissolution rate of furosemide, dissolution efficiency was chosen as the parameter representative of the process. A model-independent parameter was preferred in order to demonstrate the difficulties entailed in the statistical processing with constants with an associated estimation error. On the other hand, dissolution efficiency contributes information sim-

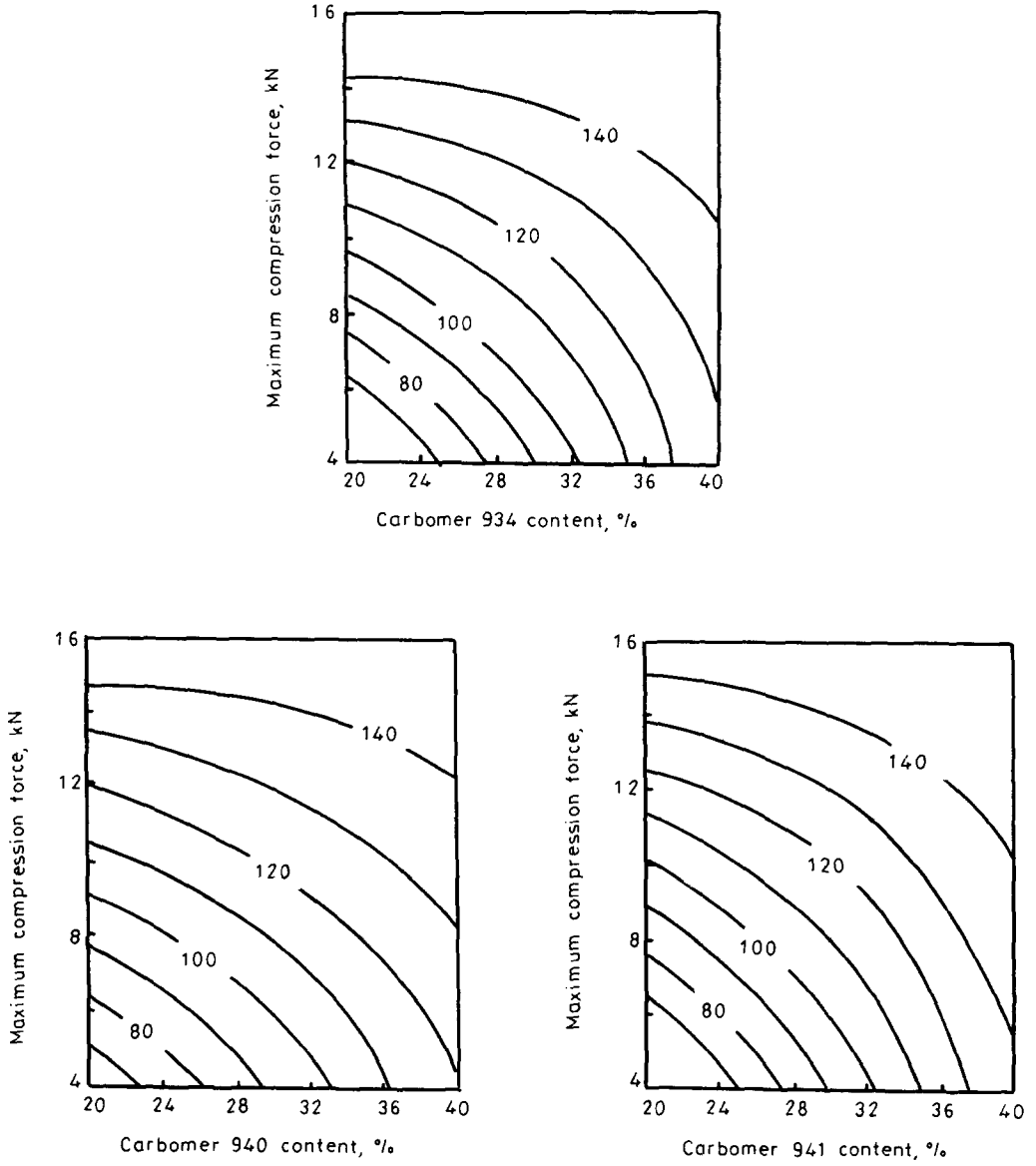

Fig. 1. Response surfaces corresponding to the crushing strength parameter.

ilar to the rate constant, since, as was mentioned earlier, dissolution profiles acceptably fit zero order kinetics.

Inspection of dissolution profiles corresponding to the three varieties of Carbomer studied gives evidence of very marked differences in their be-

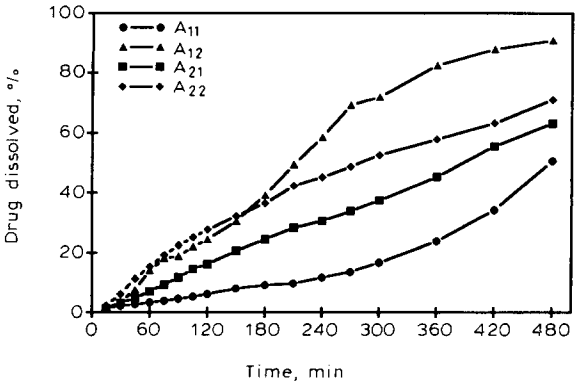

Fig. 2. Mean dissolution profiles corresponding to the formulations elaborated with Carbomer 934.

havior. The ANOVA results (Table 2) confirm these differences, which become clear in the equations fit using multiple stepwise regression:

Carbomer 934:

Dissolution efficiency

$$= 0.1572 + 1.98 \times 10^{-5} \times \text{MCF} \quad (5)$$

$[R = 0.7367;\ P > 99\%]$

Carbomer 940:

Dissolution efficiency

$$= 0.1806 + 3.09 \times 10^{-5} \times \text{MCF} - 7.56 \times 10^{-7} \times \text{MCF} \times \text{CP} \quad (6)$$

$[R = 0.8468;\ P > 99\%]$

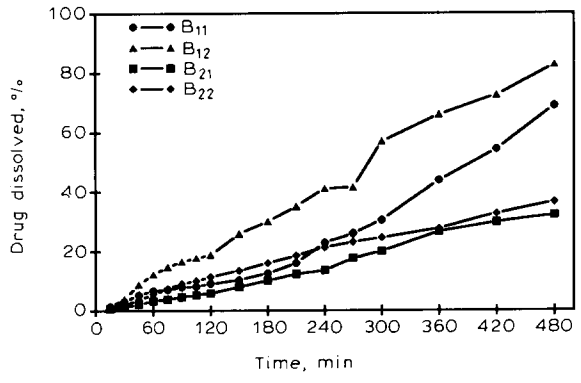

Fig. 3. Mean dissolution profiles corresponding to the formulations elaborated with Carbomer 940.

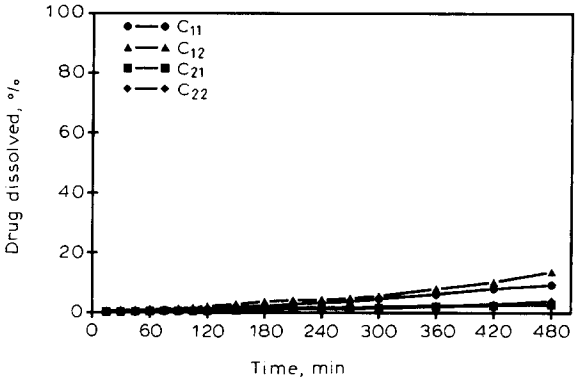

Fig. 4. Mean dissolution profiles corresponding to the formulations elaborated with Carbomer 941.

Carbomer 941:

Dissolution efficiency

$$= 0.0687 - 0.0016 \times \text{CP} + 1.04 \times 10^{-8} \times \text{MCF} \quad (7)$$

$[R = 0.8284;\ P > 99\%]$

In spite of the diversity in behavior discussed earlier, we observed a significant effect of maximum compression force on the three varieties (Fig. 5). The fact that any increase in maximum compression force results in a rise in the dissolution

TABLE 3

Results obtained by fitting dissolution data for the formulations studied to zero order kinetics (1, 15 d.f.)

Formulation	R	F	K (mg min^{-1})
A_{11}	0.9232	86.6 [a]	0.0170
A_{12}	0.9848	482.9 [a]	0.2175
A_{21}	0.9971	2597.1 [a]	0.1251
A_{22}	0.9885	693.3 [a]	0.1608
B_{11}	0.9588	171.0 [a]	0.1179
B_{12}	0.9957	1718.7 [a]	0.1738
B_{21}	0.9870	567.0 [a]	0.0602
B_{22}	0.9932	1091.7 [a]	0.0816
C_{11}	0.9882	627.4 [a]	0.0169
C_{12}	0.9734	271.2 [a]	0.0228
C_{21}	0.9842	463.8 [a]	0.0053
C_{22}	0.9715	251.8 [a]	0.0080

[a] Significant at 0.01 level.

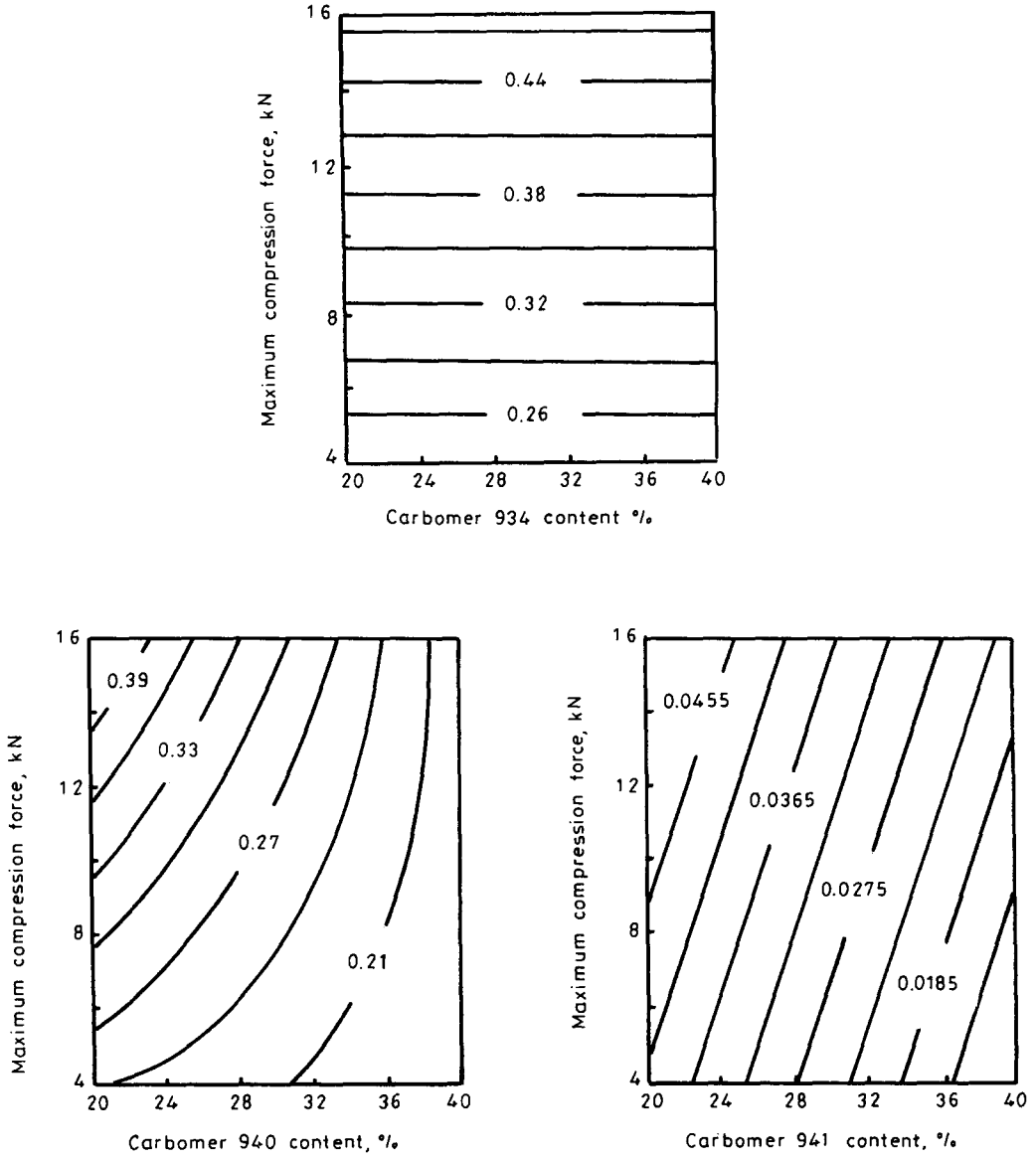

Fig. 5. Response surfaces corresponding to the dissolution efficiency parameter.

rate demonstrates that the three varieties of Carbomer behave in a clearly different manner than cellulose ethers. The latter have shown no appreciable effects for this variable (Salomon et al., 1979; Boymond et al., 1981; Korsmeyer et al., 1983; Nakano et al., 1983).

However, the results obtained here contradict in part those of Choulis and Papadopoulos (1975) who, in their studies on matrices elaborated with the 934 variety, did not find any substantial maximum compression force effects between 4000 and 23000 N on the dissolution rate of quinine sulphate. These differences in behavior may be attributed to the solubility differences of the two active principles added and to the presence of other additives in the formulations.

As regards the furosemide dissolution profiles for each Carbomer variety selected, it is important to underline the following remarks:

Variety 934, commonly used in oral preparations, provides the widest range of modulation possibilities by controlling the technological variables. The results of the corresponding ANOVA demonstrate a clearly significant effect on dissolution efficiency of maximum compression force and of the interaction between maximum compression force and proportion of Carbomer. Nevertheless, the fact that interaction term was not included in the equation fitted by regression, indicates the small contribution of this term to explain the effects observed (see response surface in Fig. 5).

Despite the statistical significance of the ANOVA terms for the 940 variety, the proportion of polymer added to the matrix is the variable having the most important effects in quantitative terms. In this case the effects of maximum compression force attenuate as the proportion of Carbomer increases (see response surface in Fig. 5).

Lastly, the results obtained for the 941 variety show that, in spite of the significance of some ANOVA terms, the effects on the dissolution rate have very little quantitative importance within the range studied. It must be remembered that in all cases, dissolution rate is extremely slow.

Mercury intrusion porosimetry studies were carried out for the purpose of determining the effect of the microporous tablet structure on the furosemide release characteristics, and to attempt an interpretation of the mechanisms involved in this process. For all the formulations an excellent fit of the experimental data to the log-normal distribution function was obtained.

The ANOVAS (Table 2) corresponding to the total porosity parameter shown in Table 1 indicate that the maximum compression force is the variable that has major control over the scope of this parameter. Under these conditions and considering the dependencies for dissolution efficiency discussed earlier, we are led to believe that correlations between porosity and dissolution rate exist. However, we only observe a certain correlation ($R = 0.9007$ and $F = 8.95$ with 1 and 2 d.f.) in the case of formulations elaborated with Carbomer 934, where the proportion of Carbomer as a variable is also significant. Similar conclusions have been drawn using the pore diameter parameter.

These results decisively show that variables associated with the type and proportion of Carbomer, with insignificant effects on porosity, play an important role in the release characteristics of the active principle. As has been pointed out for other groups of polymers, one of the major characteristics is the viscosity of the hydrogels produced. However, the quantification of this type of effect entails considerable difficulties of a practical nature. Therefore, it is important to emphasize the fact that the 941 variety, which only produces higher viscosities than the other two (934 and 940) when the hydrogels formed contain low proportions of polymer, is the one that shows the slowest release profiles. This tablet behavior, which is logical if we accept the fact that the deciding release mechanism is erosion, suggests that it would be desirable to use viscosity data measured in such conditions, if predictions are to be made.

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