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RESEARCH PAPER

# Extrusion-Spheronization of Blends of Carbopol 934 and Microcrystalline Cellulose

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**ABSTRACT**

*We evaluated the effects of several process variables on the pharmaceutical and drug release properties of extrusion-spheronization pellets of blends of Carbopol 934 and microcrystalline cellulose (MCC) containing a high proportion of Carbopol. The model drug was theophylline. Rheological monitoring during mixing was by mixer torque rheometry. Carbopol:MCC blends wetted with a $CaCl_2$ solution showed different rheological behavior compared to blends with a high proportion of MCC wetted with water only. In contrast to previous suggestions, the optimal wetting point for extrusion did not coincide with the point of peak torque, but occurred just beyond this point, at much lower torque. The influence of process variables on blend properties was investigated with a three-variable factorial design (Carbopol:MCC ratio, wetting liquid proportion, $CaCl_2$:Carbopol ratio), and the influence of process variables on pellet properties with a four-variable design (the variables listed plus extrusion screen hole diameter). Blend torque values were strongly influenced by $CaCl_2$ proportion, while mean pellet diameter was influenced by Carbopol:MCC ratio. Mean pellet diameter also differed depending on whether the pellets contained theophylline. The observed among-formulation differences in theophylline release kinetics were largely explained by differences in pellet size and*

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*theophylline hydration state. Compaction of pellets to form tablets markedly modified the drug release profile, making it biphasic.*
***Key Words:*** *Carbopol 934; Extrusion-spheronization; Microcrystalline cellulose; Mixer torque rheometry; Pellets; Theophylline.*

## INTRODUCTION

Multiparticulate systems comprised of pellets obtained by extrusion-spheronization have acquired considerable relevance as oral dosage forms over the last few years (1). In controlled release, the use of pellets has important advantages, such as allowing the formulation of incompatible drugs or drugs that require different release patterns in a single dosage unit (2). Furthermore, extrusion-spheronization pellets have a spherical shape (leading to excellent flow properties and a high packing ratio) and low friability, making them particularly suitable for incorporation into hard capsules or coated forms (3). Finally, in comparison with monolithic forms, pellet-based forms may reduce the likelihood of burst effect and minimize inter- and intraindividual variability in gastrointestinal transit (4).

The acrylic polymers, common components of hydrophilic matrix tablets (5–8), are potentially useful excipients for obtaining controlled-release pellets, although their use presents a number of technological problems derived from their tendency to gel, which complicates the extrusion-spheronization process (9). As a consequence, the correct selection of wetting conditions is critical. Mixer torque rheometry is very useful for monitoring and end point determination in the wetting of blends based on microcrystalline cellulose (MCC) (10); however, this technique has not been tested for systems with high proportions of acrylic polymers. Furthermore, it has mainly been used for monitoring conventional granulation processes (10), and its usefulness in extrusion-spheronization has not yet been studied. On the other hand, the small size of extrusion-spheronization pellets could limit their usefulness for formulating drugs that are highly water soluble. In view of these observations, the aims of the present study were (1) to assess the usefulness of mixer torque rheometry for determination of optimal wetting point during mixing of Carbopol:MCC blends for extrusion-spheronization, (2) to investigate the influence of different process variables on the properties of pellets obtained by extrusion-spheronization of Carbopol:MCC blends, (3) to investigate the suitability of such pellets for controlled release of theophylline, and (4) to investigate the effects on theophylline release of direct compression of the pellets to form tablets (11,12).

## EXPERIMENTAL

### Materials

Microcrystalline cellulose (Avicel® PH-101, FMC, Philadelphia, PA, batch 6703 C); Carbopol® 934 (BF Goodrich Europe, Brussels, Belgium, batch KK79KA975); $CaCl_2$ $2H_2O$ (Merck, Darmstadt, Germany, batch TA882282); and anhydrous theophylline (Sigma-Aldrich Chemie, Steinheim, Germany, batch 97F-0733) were used.

### Methods

#### Preparation and Rheological Characterization of Carbopol Dispersions

Carbopol dispersions (0.5% w/v) were prepared in distilled water or in $CaCl_2$ solution (0.145% or 0.19% w/v) to obtain a $CaCl_2$/Carbopol ratio of 0.29 or 0.38. To prepare the dispersions, 1 g of Carbopol was added to 200 ml with stirring for 4 h at 500 rpm in a RW 20 DZM Janke and Kumkel (Germany) mixer.

The rheological characterization of the dispersions was carried out at 25°C in a Rheolyst AR-1000 N rheometer (TA Instruments, UK) equipped with an AR 2500 data analyzer and a thermostated concentric-cylinder adapter. Rheograms were fitted with the Ostwald equation (13):

$$\eta = m \cdot \dot{\gamma}^{n-1} \tag{1}$$

where $\eta$ represents the viscosity, $\dot{\gamma}$ is the shear rate, $m$ is the consistency, and $n$ is the power law index, with the values of $m$ and $n$ obtained by fitting.

To determine the linear viscoelastic range, a test was run with a fixed frequency of 0.15 Hz while a strain sweep was performed. Oscillatory shear tests were carried out within the linear viscoelastic range, with frequency sweeps over the range 0.008–8 Hz for the determination of the storage modulus $G'$, the loss modulus $G''$, and the dynamic viscosity $\eta'$:

$$G' = \frac{\tau_0}{\gamma_0} \cdot \cos \delta \tag{2}$$

$$G'' = \frac{\tau_0}{\gamma_0} \cdot \sin \delta \tag{3}$$

$$\eta' = \frac{\tau_0}{\gamma_0 \cdot \omega} \cdot \sin \delta \quad (4)$$

where $\tau_0$ represents the amplitude of the stress applied, $\gamma_0$ is the amplitude of the resulting strain, $\delta$ is the phase angle, and $\delta$ is the angular frequency. Creep recovery profiles were obtained by the application of 0.1 Pa for 5 min, and compliance values were calculated as the ratio of strain to shear stress (14).

### Carbopol Heat of Hydration Solution

The hydration solution heat of Carbopol at 25°C was determined in triplicate in a Tronac 458 (Tronac, Inc., USA) isoperibol titration calorimeter (15). In these assays, the test dispersion was 0.1 g of dried Carbopol (70°C, 12 h) in 50 ml of distilled water or $CaCl_2$ solution (at a concentration to give a final $CaCl_2$:Carbopol ratio of 0.38).

### Preparation and Wet Massing Studies of Carbopol:Microcrystalline Cellulose (50:50) Systems

To characterize the wetting of Carbopol:MCC systems, 50:50 (w/w) blends were prepared after excluding Carbopol particles larger than 1 mm (no. 18 ASTM screen). The electrolyte quantities necessary to obtain a final $CaCl_2$:Carbopol ratio of 0.29 were dissolved in 80–220 ml of distilled water, and this solution was then added to 100 g of dry mixture. The wet mass was stirred in a Heidolph RARF50 (Germany) mixer at 125 rpm for 1 h. Mean torque values were measured in triplicate in a mixer torque rheometer (Caleva, UK). Shaft speeds were 52 and 104 rpm, and the blends were stirred for 30 s before taking readings. From the results, plots of torque against electrolyte solution volume were obtained (16).

### Preparation and Characterization of Carbopol: Microcrystalline Cellulose and Carbopol–Microcrystalline Cellulose–Theophylline Pellets

Extrusion-spheronization was used to make 36 formulations of Carbopol:MCC pellets, following a $2 \times 3 \times 3 \times 2$ factorial design for four variables: Carbopol:MCC ratio (1 or 1.5) (A); $CaCl_2$:Carbopol ratio (0.29, 0.335, or 0.38) (B); volume of wetting water (1.4, 1.5, or 1.6 ml per g of Carbopol:MCC blend) (C); and extrusion screen hole diameter (1 or 2 mm) (D). Screen thickness in both cases was 1 mm. In addition, 8 formulations of anhydrous theophylline pellets were made with a Carbopol:MCC ratio of 1.5 w/w following a $2 \times 2 \times 2$ design for two variables: 1.4 or 1.6 ml of $CaCl_2$ solution per gram of Carbopol:MCC blend to obtain a final $CaCl_2$:Carbopol ratio of 0.29 or 0.38 (B); and extrusion screen hole diameter of 1 or 2 mm (D). The proportion of theophylline was in all cases 20% w/w. Prior to extrusion-spheronization, all 44 formulations were characterized rheologically, with statistical analysis in accordance with the corresponding $2 \times 3 \times 3$ (A × B × C) or $2 \times 2$ (B × C) factorial design.

The procedure was as follows:

#### *Preparation of the Wet Masses*

Carbopol, MCC, and when necessary, theophylline were mixed in a mortar. $CaCl_2$ solutions at appropriate concentrations were then incorporated, and the blends were stirred at 125 rpm for 1 h in a Heidolph RARF50 (Germany) mixer.

#### *Mixer Torque Rheometry of Blends*

The consistency of the wet masses (30 g) was measured in triplicate using the procedure described above concerning the 50:50 Carbopol:MCC systems.

#### *Pellet Manufacture*

Extrusion of the wet masses was done with a screen extruder (Caleva model 10, UK; screen hole diameter 1 or 2 mm, thickness 1 mm), and spheronization was performed with a Caleva spheronizer (model 120, UK; 575 rpm, 30 min). The masses were dried in an air oven at 40°C for 24 h. Pellet residual humidity was determined by thermogravimetric analysis (TA-50 Shimadzu, Japan) at a heating rate of $10°C \cdot min^{-1}$ over the range 25°C–105°C.

#### *Pellet Characterization*

Pellets were characterized as follows:

*Pellet size and shape* For each formulation, the images of at least 300 particles (Olympus SZ60, Japan, stereomicroscope equipped with a VGA24 video camera linked to PC Image software, version 2.1) were digitalized for estimation of circularity (17) and mean Feret diameter (assuming a normal distribution). For each particle, the mean Feret diameter was estimated as the mean of 64 random measurements of Feret diameter.

*Friability* For friability, 5-g samples were tested in a friabilometer (Erweka TAB, Germany; 20 rpm, 30 min) with glass pearls 4 mm in diameter (100 units). The glass

pearls were then removed, and the pellets were sieved through a 250-μm screen to remove fine particles, with friability estimated as percentage weight loss (18).

*X-ray diffractometry* Pellet spectra were recorded on a Philips PW 1710 (Netherlands) diffractometer using $CuK_\alpha$ radiation and scanning from 5° to 50° 2θ at a rate of 1.5° 2θ · $min^{-1}$.

*Dissolution test* Drug release profiles for 500 mg of pellets (100 mg theophylline) were determined in triplicate using a USP 23 type II apparatus (50 rpm, 900 ml of distilled water, 37°C). Theophylline was determined spectrophotometrically at 271 nm, and the equation of Ford et al. (19) was fitted to the release profiles:

$$Q = K \cdot (t - l)^n \quad (5)$$

where $Q$ is the percentage of dissolved drug at time $t$, $l$ is the lag time, and $K$ and $n$ are constants that provide information about the rate and mechanism of drug release.

### Manufacture and Characterization of Tablets of Theophylline Pellets

Eight theophylline tablet formulations (theophylline 100 mg, tablet 500 mg) were prepared by direct compression of theophylline pellets using a Bonals B-MT (Spain) eccentric press (manual filling of the die, flat punch 9 mm in diameter, 354 MPa pressure, 52% volumetric reduction). Drug release profiles were then characterized by the procedure described above.

### Statistical Analysis

The influence of process variables A–D on the properties of blends and pellets was investigated by stepwise multiple regression, with the candidate independent variables being those variables or cross terms found to have a significant effect ($\alpha < .05$) in analysis of variance (20). All analyses were performed with Statgraphic statistical software.

## RESULTS AND DISCUSSION

### Rheological Behavior of Carbopol Aqueous Dispersions

It has been shown previously that electrolytes can modify the swelling behavior of poly(acrylic acid) derivatives (21) and the viscosity of their aqueous dispersions (22). We evaluated the effects of incorporation of $CaCl_2$ on the rheological behavior of Carbopol aqueous dispersions to assess whether this electrolyte facilitates the extrusion-spheronization of Carbopol:MCC blends with a high proportion of Carbopol. Flow and creep recovery rheograms for 0.5% aqueous dispersions of Carbopol at 25°C, with or without $CaCl_2$, are shown in Fig. 1; the corresponding values for consistency $m$ and power law index $n$ are summarized in Table 1.

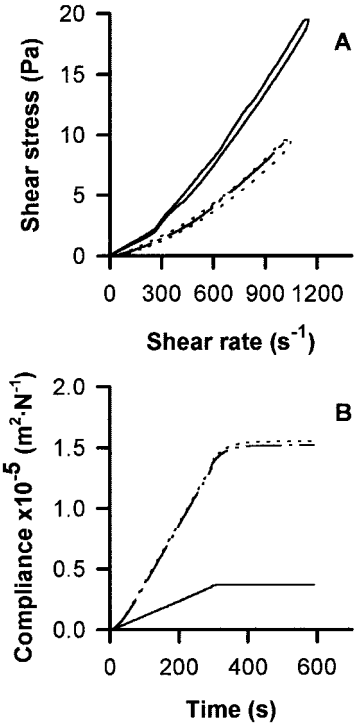


**Figure 1.** Rheograms of 0.5% dispersions of Carbopol at 25°C, in water or in the presence of $CaCl_2$ (A, flow; B, creep recovery; —, water, – –, $CaCl_2$:Carbopol ratio of 0.38; — –, $CaCl_2$:Carbopol ratio of 0.29).

All the dispersions evaluated were shear-thickening viscous systems (14), with the compliance attained in the creep process being maintained throughout the recovery phase (Table 1). The shear-thickening behavior can been explained by the fuzzball structure of the unneutralized polymer: At lower shear rates, the macromolecules are coated by water, which acts as a glidant and makes their relative displacements easier; at higher shear rates, this coating disappears, and the macromolecules thus become more compact and more flow resistant (23).

The incorporation of $CaCl_2$ provoked considerable reduction in consistency, suggesting that the macromolecules adopt a less expanded disposition due to competition between ions and the polymer for the water molecules. Isoperibol microcalorimetry measurements

***Table 1***

*Values of Consistency (*m*), the Power-Law Index (*n*) and Compliance Obtained for Aqueous Carbopol Dispersions in the Absence and Presence of $CaCl_2$*

| Assay | Parameters | Water | $CaCl_2$:Carbopol Ratio = 0.29 | $CaCl_2$:Carbopol Ratio = 0.38 |
|---|---|---|---|---|
| Flow | $m$ (Pa · $s^n$) | $1.087 \cdot 10^{-3}$ | $1.714 \cdot 10^{-4}$ | $3.834 \cdot 10^{-4}$ |
| | $n$ | 1.394 | 1.576 | 1.460 |
| | $r$ | 0.9949 | 0.9788 | 0.9767 |
| Creep | Compliance ($m^2 \cdot N^{-1}$) | 35,900 | 138,200 | 140,100 |

corroborated this assumption: The heat of hydration solution for Carbopol in water is −26,170 ($n$ = 3, standard deviation [SD] = 1417) J · $kg^{-1}$, versus −22,667 ($n$ = 3, SD = 542) J · $kg^{-1}$ in $CaCl_2$ solution ($CaCl_2$:Carbopol ratio 0.38).

Carbopol dispersions showed linear viscoelastic behavior at stress amplitudes of up to 0.5 Pa, and all oscillatory shear tests and creep recovery tests were therefore carried out at the lower stress amplitude of 0.1 Pa. The oscillatory shear tests, in which elastic responses were not observed, confirmed the viscous character of all the dispersions. $CaCl_2$ also had an effect on viscosity, as shown by the viscous module and the dynamic viscosity values (Fig. 2). These results indicate that incorporation of $CaCl_2$ will improve Carbopol:MCC blends for extrusion-spheronization not only as a consequence of its effect on the tack of the wet acrylic polymer (9), but also because it reduces viscosity and increases fluency, which should facilitate the extrusion-spheronization process.

## Mixer Torque Rheometry

### Wet Massing Studies of Carbopol: Microcrystalline Cellulose Blends

Mixer torque rheometry was used first to determine the optimum wetting point by measuring the consistency of Carbopol:MCC mixtures after wetting with different proportions of liquid. Figure 3 shows the rheological profile for the 50:50 Carbopol:MCC mixture using a $CaCl_2$ solution as wetting liquid ($CaCl_2$:Carbopol ratio 0.29). This profile is narrower and sharper than those obtained previously for binder:MCC mixtures containing low proportions of other (non-Carbopol) binders (24), suggesting that the wetting process occurs in a different way as a consequence of the water-Carbopol interaction, despite the fact that the presence of electrolytes can be expected to hinder polymer swelling. It has been suggested (10) that the capillary state in agglomeration (as indicated by peak torque) is the optimal wetting point for pellet formulation. However, we found that the mass obtained at peak torque (1 ml of water per gram of dried mixture), although appearing homogeneously wetted, did not form pellets, perhaps due to inadequate plasticity. A wetting liquid proportion between 1.4 and 1.6 ml · $g^{-1}$, which gave lower torque values, was found to be adequate for subsequent extrusion-spheronization.

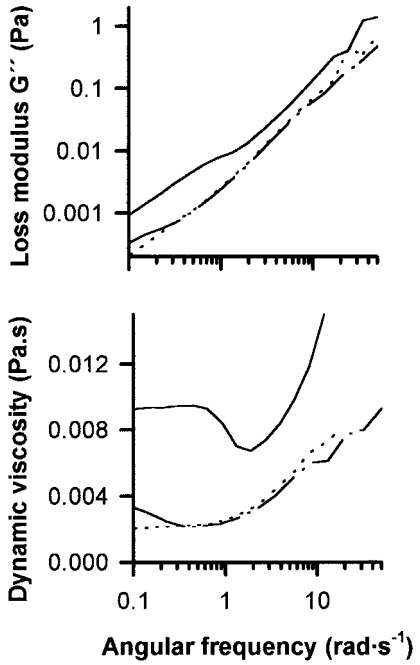


**Figure 2.** Oscillatory shear profiles of 0.5% dispersions of Carbopol at 25°C in water or in the presence of $CaCl_2$ (—, water; – –, $CaCl_2$:Carbopol ratio of 0.38; — –, $CaCl_2$:Carbopol ratio of 0.29).

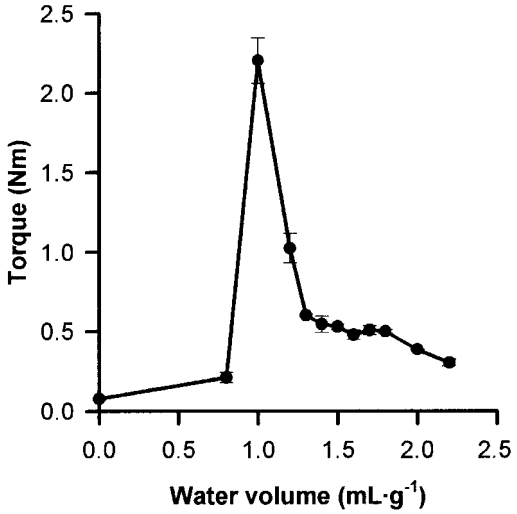


**Figure 3.** Dependence of mean torque values of 50:50 Carbopol:MCC blends on the volume of water incorporated ($CaCl_2$:Carbopol ratio of 0.29).

## Influence of Process Variables on the Rheology of the Carbopol:Microcrystalline Cellulose Blends

### *Carbopol:Microcrystalline Cellulose Blends*

Mean torque values for the wetted masses are shown in Table 2. All wetted masses, over a wide range of mean torques, were satisfactory for obtaining pellets. Stepwise regression analysis with mean torque value as the dependent variable indicated a complex influence of all three process variables considered (A = Carbopol:MCC ratio; B = $CaCl_2$:Carbopol ratio; C = wetting liquid proportion):

$$\begin{aligned} \text{Mean torque (Nm)} &= 3.53 - 9.04 \cdot A \\ &\quad + 4.67 \cdot A \cdot C \\ &\quad + 18.52 \cdot A \cdot B \\ &\quad - 5.72 \cdot B \cdot C \\ &\quad - 8.79 \cdot A \cdot B \cdot C \\ r^2 &= 0.7230, \\ F_{5,102} &= 56.86,\ \alpha < .01 \end{aligned} \tag{6}$$

### *Carbopol:Microcrystalline Cellulose:Theophylline Blends*

Table 3 shows torque values for the Carbopol:MCC:theophylline blends prepared at the lowest and highest Carbopol proportions. The incorporation of theophylline decreases the consistency of the blend, presumably as a consequence of competition with Carbopol for water of hydration. Stepwise regression analysis with mean torque as the dependent variable showed that both $CaCl_2$:Carbopol ratio (B) and wetting liquid proportion (C) had significant effects:

$$\begin{aligned} \text{Mean torque (Nm)} &= 0.38 + 1.10 \cdot B \\ &\quad - 0.99 \cdot B \cdot C \\ r^2 &= 0.8600, \\ F_{2,21} &= 71.62,\ \alpha < .01 \end{aligned} \tag{7}$$

## Influence of the Process Variables on the Properties of the Carbopol: Microcrystalline Cellulose Pellets

Carbopol:MCC blends and Carbopol:MCC:theophylline blends were used to prepare pellets following the procedure outlined above. The spheronization conditions were selected to obtain spherical pellets. The time needed to complete the spheronization process was in the upper limit of the range usually required for this process. This is a common situation in the case of materials for which deformation process is relatively difficult (25). The influence of process variables on pellet properties was studied with a factorial design comprising the three factors considered previously (A, B, and C) and a fourth factor (D = extrusion screen hole diameter).

### Carbopol:Microcrystalline Cellulose Pellets

Pellet diameter was significantly affected not only by screen hole diameter (as expected), but also by Carbopol:MCC ratio. This was attributable to the binding character of acrylic polymers like Carbopol (26):

$$\begin{aligned} \text{Mean Feret diameter } (\mu\text{m}) &= 347.74 \\ &\quad + 133.31 \cdot D \\ &\quad + 275.67 \cdot A \cdot D \\ r^2 &= 0.9214, \\ F_{2,33} &= 206.21,\ \alpha < .01 \end{aligned} \tag{8}$$

Pellet shape varied little, with circularity values in all cases being at least 0.75 (Table 2). Stepwise regression analysis revealed statistically significant effects of three of the variables considered, although the low $r$ value means that the regression equation has no real predictive value:

***Table 2***

*Torque Values for Wet Carbopol-MCC Masses and Characteristics of Carbopol-MCC Pellets*

| Carbopol/MCC | Water Volume ($ml \cdot g^{-1}$) | $CaCl_2$:Carbopol | Torque (Nm) | Screen Holes (mm) | Mean Diameter (μm) | Circularity |
|---|---|---|---|---|---|---|
| 1 | 1.4 | 0.29 | 0.605 (0.053) | 1 | 708 (350) | 0.77 (0.15) |
| | | | | 2 | 1314 (522) | 0.77 (0.15) |
| 1 | 1.5 | 0.29 | 0.503 (0.036) | 1 | 650 (371) | 0.83 (0.15) |
| | | | | 2 | 1234 (470) | 0.81 (0.15) |
| 1 | 1.6 | 0.29 | 0.567 (0.021) | 1 | 744 (347) | 0.80 (0.15) |
| | | | | 2 | 1173 (560) | 0.80 (0.15) |
| 1 | 1.4 | 0.335 | 0.432 (0.039) | 1 | 839 (390) | 0.80 (0.15) |
| | | | | 2 | 1097 (616) | 0.81 (0.16) |
| 1 | 1.5 | 0.335 | 0.034 (0.024) | 1 | 714 (315) | 0.82 (0.15) |
| | | | | 2 | 1084 (434) | 0.82 (0.15) |
| 1 | 1.6 | 0.335 | 0.310 (0.026) | 1 | 752 (329) | 0.82 (0.15) |
| | | | | 2 | 1155 (558) | 0.81 (0.16) |
| 1 | 1.4 | 0.38 | 0.303 (0.020) | 1 | 768 (355) | 0.83 (0.15) |
| | | | | 2 | 1253 (521) | 0.83 (0.14) |
| 1 | 1.5 | 0.38 | 0.278 (0.018) | 1 | 664 (305) | 0.85 (0.14) |
| | | | | 2 | 1121 (422) | 0.84 (0.14) |
| 1 | 1.6 | 0.38 | 0.248 (0.014) | 1 | 839 (345) | 0.82 (0.17) |
| | | | | 2 | 1121 (357) | 0.88 (0.13) |
| 1.5 | 1.4 | 0.29 | 0.163 (0.047) | 1 | 931 (367) | 0.75 (0.14) |
| | | | | 2 | 1569 (602) | 0.76 (0.15) |
| 1.5 | 1.5 | 0.29 | 0.165 (0.008) | 1 | 961 (369) | 0.76 (0.15) |
| | | | | 2 | 1363 (457) | 0.82 (0.14) |
| 1.5 | 1.6 | 0.29 | 0.628 (0.038) | 1 | 911 (340) | 0.77 (0.14) |
| | | | | 2 | 1358 (560) | 0.77 (0.14) |
| 1.5 | 1.4 | 0.335 | 0.185 (0.026) | 1 | 867 (318) | 0.78 (0.15) |
| | | | | 2 | 1550 (588) | 0.76 (0.17) |
| 1.5 | 1.5 | 0.335 | 0.265 (0.025) | 1 | 861(336) | 0.78 (0.16) |
| | | | | 2 | 1384 (569) | 0.78 (0.16) |
| 1.5 | 1.6 | 0.335 | 0.243 (0.015) | 1 | 957 (420) | 0.77 (0.16) |
| | | | | 2 | 1389 (495) | 0.82 (0.15) |
| 1.5 | 1.4 | 0.38 | 0.291 (0.021) | 1 | 868 (329) | 0.77 (0.17) |
| | | | | 2 | 1456 (481) | 0.78 (0.17) |
| 1.5 | 1.5 | 0.38 | 0.252 (0.018) | 1 | 927 (347) | 0.75 (0.17) |
| | | | | 2 | 1261 (494) | 0.76 (0.17) |
| 1.5 | 1.6 | 0.38 | 0.242 (0.012) | 1 | 894 (336) | 0.81 (0.16) |
| | | | | 2 | 1572 (610) | 0.76 (0.17) |

Values are means with standard deviations in parentheses.
MCC, microcrystalline cellulose.

$$\text{Circularity} = 0.81 - 0.09 \cdot A + 0.18 \cdot B \cdot C \qquad (9)$$
$$r^2 = 0.5889,\ F_{2,33} = 26.07,\ \alpha < .01$$

None of the formulations tested showed appreciable friability. To detect possible structural modifications derived from the manufacturing process, the pellets were analyzed by X-ray diffractometry. All formulation showed the characteristic diffraction patterns of MCC (peaks at 15° and 22.6° 2θ). This fact indicated that the crystallinity of MCC was not modified by the process (27).

### Theophylline Pellets

The blends containing theophylline gave bigger pellets, doubtless due to the high water solubility of the drug,

***Table 3***

*Torque Values for Wet Carbopol-MCC-Theophylline Masses and Characteristics of Carbopol-MCC-Theophylline Pellets*

| Theophylline[a] | Carbopol/MCC | Water Volume[b] | $CaCl_2$:Carbopol | Torque (Nm) | Screen Holes, mm | Mean Diameter (μm) | Circularity |
|---|---|---|---|---|---|---|---|
| 25 | 1.5 | 1.4 | 0.29 | 0.291 (0.014) | 1 | 964 (316) | 0.79 (0.16) |
| | | | | | 2 | 1389 (563) | 0.82 (0.16) |
| 25 | 1.5 | 1.6 | 0.29 | 0.245 (0.013) | 1 | 988 (280) | 0.83 (0.14) |
| | | | | | 2 | 1683 (466) | 0.79 (0.16) |
| 25 | 1.5 | 1.4 | 0.38 | 0.275 (0.018) | 1 | 1115 (365) | 0.83 (0.15) |
| | | | | | 2 | 1714 (451) | 0.83 (0.14) |
| 25 | 1.5 | 1.6 | 0.38 | 0.191 (0.013) | 1 | 1769 (470) | 0.78 (0.15) |
| | | | | | 2 | 2496 (515) | 0.85 (0.05) |

Values shown are means with standard deviations in parentheses.
MCC, microcrystalline cellulose.
[a] Grams per 100 g of carbopol:MCC blend.
[b] Milliliters per gram of carbopol:MCC blend.

which was present at a high proportion in all the mixtures tested (28). Stepwise regression analysis revealed statistically significant effects of all three variables considered:

$$\begin{aligned} \text{Mean Feret diameter} \\ (\mu\text{m}) &= -727.52 \\ &\quad + 2638.15 \cdot B \cdot C \\ &\quad + 1216.19 \cdot B \cdot C \cdot D \qquad (10) \\ r^2 &= 0.8641, \\ F_{2,5} &= 23.25,\ \alpha < .01 \end{aligned}$$

Circularity values in all cases were greater than 0.78 (Table 3), and none of the formulations showed detectable friability. X-ray diffractograms showed the characteristic peaks of MCC at 15° and 22.6° 2θ and of anhydrous theophylline at 7°, 12°, and 25° 2θ in all formulations. In addition, the diffractograms of pellets manufactured with the highest wetting liquid proportion (1.6 ml · $g^{-1}$) and the highest $CaCl_2$:Carbopol ratio (0.38) likewise show the characteristic peaks of the theophylline monohydrate at 9°, 11°, and 27° 2θ, indicating partial dissolution of the theophylline in water during the wetting step, providing the necessary supersaturation for the nucleation and growth of monohydrate crystals (29). During the drying process, the monohydrate will be partially dehydrated to the anhydrous form (30); the proportion of the monohydrate that is dehydrated will depend on the affinity of the excipients for water, on the volume and composition of the wetting liquid, and on the dimensions and structure of the pellets.

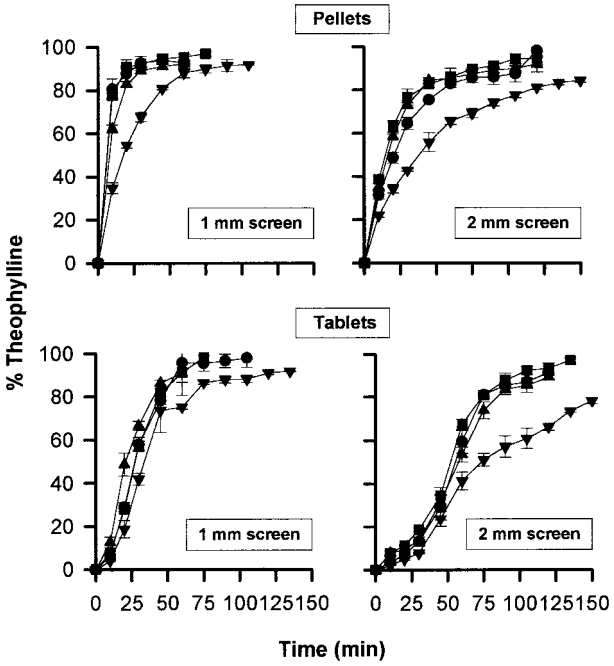


**Figure 4.** Theophylline release profiles for pellets and compacted pellet tablets obtained under the following conditions: ● wetting liquid proportion 1.4 ml · $g^{-1}$, $CaCl_2$:Carbopol ratio 0.29; ■ wetting liquid proportion 1.6 ml · $g^{-1}$, $CaCl_2$:Carbopol ratio 0.29; △ wetting liquid proportion 1.4 ml · $g^{-1}$, $CaCl_2$:Carbopol ratio 0.38; ▼ wetting liquid proportion 1.6 ml · $g^{-1}$, $CaCl_2$:Carbopol ratio 0.38.

***Table 4***

*Values of the Parameters of the Equation of Ford et al. (Eq. 5, See Text) Fitted to the Theophylline Release Profiles for Pellets and Compacted Pellet Tablets*

| Formulation | | | Pellets | | | Tablets | | | |
|---|---|---|---|---|---|---|---|---|---|
| Water Volume ($ml \cdot g^{-1}$) | $CaCl_2$:Carbopol | Screen Holes (mm) | $K$ ($min^{-n}$) | $n$ | $r$ | $K$ ($min^{-n}$) | $l$ (min) | $n$ | $r$ |
| 1.4 | 0.29 | 1 | 58.36 | 0.1200 | 0.9958 | 65.43 | 29.75 | 0.0875 | 0.9611 |
| | | | 79.22 | 0.0460 | 0.9974 | 53.72 | 27.67 | 0.1462 | 0.9654 |
| | | | 68.41 | 0.0780 | 0.9994 | 56.45 | 29.23 | 0.1404 | 0.9871 |
| 1.4 | 0.38 | 1 | 41.12 | 0.2104 | 0.9908 | 40.17 | 19.81 | 0.2021 | 0.9740 |
| | | | 44.12 | 0.1909 | 0.9934 | 37.98 | 19.59 | 0.2249 | 0.9849 |
| | | | 45.36 | 0.1809 | 0.9915 | 32.86 | 19.53 | 0.2652 | 0.9835 |
| 1.6 | 0.29 | 1 | 65.33 | 0.0948 | 0.9964 | 40.42 | 25.53 | 0.2111 | 0.9619 |
| | | | 65.73 | 0.0906 | 0.9971 | 43.25 | 26.28 | 0.2177 | 0.9957 |
| | | | 64.74 | 0.1006 | 0.9986 | 59.05 | 29.00 | 0.1411 | 0.9923 |
| 1.6 | 0.38 | 1 | 18.04 | 0.3650 | 0.9824 | 40.96 | 29.16 | 0.1791 | 0.9872 |
| | | | 20.28 | 0.3382 | 0.9853 | 49.48 | 29.52 | 0.1336 | 0.9929 |
| | | | 20.72 | 0.3398 | 0.9841 | 66.95 | 30.00 | 0.0664 | 0.9788 |
| 1.4 | 0.29 | 2 | 19.64 | 0.3368 | 0.9885 | 13.81 | 28.85 | 0.4304 | 0.9741 |
| | | | 16.56 | 0.3717 | 0.9857 | 8.30 | 28.60 | 0.5496 | 0.9706 |
| | | | 17.14 | 0.3664 | 0.9850 | 9.38 | 28.79 | 0.5192 | 0.9546 |
| 1.4 | 0.38 | 2 | 25.28 | 0.2918 | 0.9674 | 7.77 | 27.70 | 0.5492 | 0.9872 |
| | | | 26.18 | 0.2711 | 0.9745 | 7.70 | 27.95 | 0.5566 | 0.9765 |
| | | | 24.36 | 0.2949 | 0.9796 | 11.44 | 28.71 | 0.4710 | 0.9809 |
| 1.6 | 0.29 | 2 | 26.84 | 0.2732 | 0.9793 | 14.78 | 28.70 | 0.4133 | 0.9753 |
| | | | 28.58 | 0.2618 | 0.9818 | 15.15 | 28.56 | 0.4148 | 0.9557 |
| | | | 26.99 | 0.2740 | 0.9779 | 16.19 | 28.72 | 0.3938 | 0.9797 |
| 1.6 | 0.38 | 2 | 15.06 | 0.3332 | 0.9755 | 6.74 | 28.95 | 0.5020 | 0.9894 |
| | | | 15.75 | 0.3260 | 0.9803 | 9.16 | 29.49 | 0.4390 | 0.9934 |
| | | | 16.49 | 0.3179 | 0.9726 | 10.54 | 29.55 | 0.4146 | 0.9946 |

All the theophylline pellets were made with the same Carbopol:MCC ratio; however, the proportion of water, the proportion of electrolyte, and the diameter of the screen holes used in the extrusion were different. Obviously, the hydration of theophylline will become increasingly easier as the proportion of water incorporated increases. On the other hand, the proportion of electrolyte and the surface/volume ratio of the pellets must have a marked effect on the water lost during drying, explaining the presence of theophylline monohydrate in the formulations prepared with the highest proportion of $CaCl_2$ and using a screen with holes with a diameter of 2 mm.

Figure 4 shows the theophylline release profiles for the pellets. Dissolution rates are quite high and are strongly influenced by the manufacturing conditions. Since the pellets have a high content of Carbopol that provides matrix characteristics, the equation of Ford et al. (19) was used to analyze the drug release profiles. This equation has been applied previously to establish the mechanism of release of different types of drugs from compacted hydrophilic matrices. The results of fitting Eq. 5 are shown in Table 4. The $n$ values obtained indicate that the principal mechanism of drug release is Fickian diffusion (31), and the $K$ values reflect a decrease in release rate when pellet size increases, independent of the volume of wetting liquid or of electrolyte incorporated into the formulation. The results of fitting Eq. 5 are shown in Table 4. The presence of theophylline monohydrate, with lower water solubility than the anhydrous form, may contribute to delaying drug release from formulations manufactured with higher wetting liquid proportion (1.6 ml/g) and the higher $CaCl_2$:Carbopol ratio (0.38) (32).

### Theophylline Release from Compacted Pellet Tablets

The compaction of theophylline pellets led to a reduction in drug release rates (Fig. 4). From a kinetic point of view, the most important difference was that tablets showed a biphasic profile, with an initial slow release step that lasted 30 min and the quantitatively more important fast-release step. This behavior is reflected in the significant time lags obtained fitting Eq. 5 to the drug release profiles (Table 4). The principal release control process is initiated with a delay as a consequence of the time needed for tablet disintegration and regeneration of the original pellets. It is interesting to note that, during the slow phase, the drug is released at a constant rate. The lag time values obtained from the kinetic model are closely related to the size of the pellets and consequently to the diameter of the screen holes, which is explained by the influence of this parameter on the disintegration of the tablets. The principal mechanism of drug release is again Fickian diffusion, and the release rate decreased with increasing pellet size.

## CONCLUSIONS

The results obtained indicate that the peak torque value (obtained at 1 ml of water per gram of dried blend) is not the optimum wetting point for the extrusion-spheronization of Carbopol:MCC blends with high proportions of the acrylic polymer. The optimum wetting point for this process, in fact, was obtained with about 1.5 ml of water per gram. The incorporation of $CaCl_2$ into the wetting liquid led to appreciable modifications in the behavior of the blends due to its influence on the viscosity of the aqueous dispersions of the acrylic polymer, attributable in turn to the high capacity of $CaCl_2$ to compete for water molecules, decreasing the hydration of Carbopol. Pellet size is determined by the electrolyte and polymer proportions in the mixture, the amount of water incorporated at the wetting step, and the size of the holes in the screen used for the extrusion. The drug release rate depends on pellet size and on Carbopol:$CaCl_2$ ratio, which also affect whether monohydrate theophylline remains after the drying process. Finally, compaction of the pellets to form tablets leads to a marked delay in the dissolution process and could constitute an additional way of controlling the drug release.

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## REFERENCES

1. Vervaet, C.; Baert, L.; Remon, J.P. Int. J. Pharm. **1995**, *116*, 131–146.
2. Nesbitt, R. U. Drug Dev. Ind. Pharm. **1994**, *20*, 3207–3236.
3. Lundqvist, A.E.K.; Podczeck, F.; Newton, J.M. Int. J. Pharm. **1997**, *147*, 95–107.
4. Porter, S.C.; Ghebre-Sellassie, I. Key Factors in the Development of Modified-Release Pellets. In *Multiparticulate Oral Drug Delivery*; Ghebre-Sellassie, I., Ed.; Marcel Dekker: New York, 1994; 217–284.
5. Pérez-Marcos, B.; Iglesias, R.; Gómez-Amoza, J.L.; Martínez-Pacheco, R.; Souto, C.; Concheiro, A. J. Controlled Release **1991**, *17*, 267–276.
6. Pérez-Marcos, B.; Gutierrez, C.; Gómez-Amoza, J.L.; Martínez-Pacheco, R.; Souto, C.; Concheiro, A. Int. J. Pharm. **1991**, *67*, 113–121.
7. Pérez-Marcos, B.; del Caño, O.; Gómez-Amoza, J.L.; Martínez-Pacheco, R.; Souto, C.; Concheiro, A. STP Pharm. Sci. **1995**, *2*, 105–109.
8. Dittgen, M.; Durrani, M.; Lehmann, K. STP Pharm. Sci. **1997**, *7*, 403–437.
9. Neau, S.H.; Chow, M.Y.; Durrani, M.J. Int. J. Pharm. **1996**, *131*, 47–55.
10. Parker, M.D.; Rowe, R.C.; Upjohn, N.G. Pharm. Tech. Int. **1990**, *2*, 50–64.
11. Nicklasson, F.; Johansson, B.; Alderborn, G. Eur. J. Pharm. Sci. **1999**, *7*, 221–229.
12. Nicklasson, F.; Johansson, B.; Alderborn, G. Eur. J. Pharm. Sci. **1999**, *8*, 11–17.
13. Ostwald, W. Colloid-Z **1925**, *36*, 99–117.
14. Scharmm, G. Aspects of Viscometry. The Measurement of the Elastic Behaviour of Visco-Elastic Fluids. In *A Practical Approach to Rheology and Rheometry*; HAAKE: Karlsruhe, 1994; 13–22, 77–126.
15. Tronac, Inc. *Isoperibol Titration Calorimeter. Instruction and Service Manual*; Tronac Inc.: Oren, UT, 1992.
16. Rowe, R.C. Pharm. Tech. Eur. **1996**, *8*, 30–48.
17. Exner, H.E.; Link, E. Powder Metall. Int. **1977**, *9*, 131–133.
18. Shah, R.D.; Kabadi, M.; Pope, D.G.; Augsburger, L.L. Pharm. Res. **1995**, *12*, 496–507.
19. Ford, J.L.; Mitchell, K.; Rowe, P.; Armstrong, D.J.; El-

liott, P.N.C.; Rostron, C.; Hogan, J.E. Int. J. Pharm. **1991**, *71*, 95–104.
20. Walpole, W.E.; Myers, R.H. Multiple Linear Regression. In *Probability and Statistics for Engineers and Scientists*; Macmillan: New York, 1989; 401–462.
21. Kriwet, B.; Kissel, T. Int. J. Pharm. **1996**, *127*, 135–145.
22. Bonner, M.C.; Jones, D.S.; Woolfson, A.D. J. Pharm. Pharmacol. **1997**, *49* Suppl. 4, 74.
23. Barry, B.W.; Meyer, M.C. Int. J. Pharm. **1979**, *2*, 1–25.
24. Parker, M.D.; York, P.; Rowe, R.C. Int. J. Pharm. **1990**, *64*, 207–216.
25. Newton, J.M. Extrusion/Spheronisation. In *Powder Technology and Pharmaceutical Processes*; Chulia, D., Deleuil, M., Pourcelot, Y., Eds.; Elsevier: New York, 1998; 391–401.
26. Vila-Jato, J.L.; Concheiro, A.; Seijo, B. Drug Dev. Ind. Pharm. **1987**, *13*, 1315–1327.
27. Kumar, V.; Kothari, S.H. Int. J. Pharm. **1999**, *177*, 173–182.
28. Lustig-Gustafsson, C.; Kaur Johal, H.; Podczeck, F.; Newton, J.M. Eur. J. Pharm. Sci. **1999**, *8*, 147–152.
29. Zhu, J.; Yuen, C.; Grant, D.J.W. Int. J. Pharm. **1996**, *135*, 151–160.
30. Phadnis, N.V.; Suryanarayanan, R. J. Pharm. Sci. **1997**, *86*, 1256–1263.
31. Peppas, N.A. Pharm. Acta Helv. **1985**, *60*, 110–111.
32. Alvarez-Lorenzo, C.; Gómez-Amoza, J.L.; Martínez-Pacheco, R.; Souto, C.; Concheiro, A. Drug Dev. Ind. Pharm. **2000**, *26*, 13–20.