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RESEARCH PAPER

Production of Carbopol® 974P and Carbopol® 971P Pellets by Extrusion-Spheronization: Optimization of the Processing Parameters and Water Content

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ABSTRACT

Pellets obtained by extrusion-spheronization represent multiparticulate dosage forms whose interest in intestinal drug delivery can be potentiated and targeted through bioadhesive properties. However, adhesion itself makes the process difficult or even impossible. The problem of tackiness encountered with bioadhesive wet masses was previously eliminated by the use of electrolytes such as $CaCl_2$. This approach is known to reduce the viscosity of polyacrylic acids by disturbing the interactions between carboxylate groups on adjacent polymer molecules, thereby decreasing their bioadhesive properties. The present study aimed at producing pellets containing carbomers without addition of electrolytes in order to maintain their bioadhesive potentiality at its maximum. Carbopol® 974P (10%, 15% and 20%) and Carbopol® 971P (10%) were used in combination with Avicel® PH101. The extrusion speed (30, 45, 60, 90, and 150 rpm), spheronizer speed (350, 700, 960, 1000, and 1300 rpm), spheronization time (5, 10, 15, and 20 minutes) and amount of water (45%, 50%, 54%, and 58%) were optimized in order to obtain the highest yield of spherical pellets ranging 710–1000 μm in diameter. For pellets containing 10%, 15% Carbopol® 974P or 10% Carbopol® 971P and 45% water content, 30 rpm extrusion speed, 960 rpm, and 10 minutes spheronization speed and time led to the highest yields and sphericities, respectively, 72% and 0.91, 67% and 0.78, and 76% and 0.80. Production of pellets with 20% Carbopol® 974P could be achieved through the increase of the water content up to 58% and implementation of 30 rpm extrusion speed, 1300 rpm,

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and 10 minutes spheronization speed and time. The yield and sphericity were 42% and 0.78 respectively.

Key Words: Carbopol®; Extrusion-spheronization; Pellets; Yield; Sphericity.

INTRODUCTION

In recent years, oral site-specific drug delivery systems have been devised to improve the absorption of drugs characterized by a poor peroral bioavailability.[1] These strategies are of great interest for oral administration of molecules whose absorption is limited to a specific area of the gastrointestinal tract.[2,3] The drug localization at targeted sites can be achieved through the development of mucoadhesive interactions between the drug carrier system and the intestinal mucosa.[4,5] The concept of bioadhesion, which associates the advantages of extending the residence time of the drug at the absorption site and allowing an intimate contact of the drug with the biological membranes, has been applied to the formulation of a variety of pharmaceutical forms with the aim of targeting different levels in the intestinal tract. Bioadhesive forms intended to reach the small intestine include chitosan microspheres,[6] Prosopis gum granules,[7] and carbomer tablets[8] for theophylline and aminophylline administration, and microdevices with multiple reservoirs providing unidirectional and highly localized release of drugs via lectin/duodenum binding.[9] The colon can be targeted by nonadhesive particles of azocrosslinked polyacrylic acid whose azo network degrades specifically within the colonic environment to produce a mucoadhesive structure.[10] Among these pharmaceutical dosage forms, multiparticulate carriers are favored due to their small size, which is responsible for their easy dispersibility within the intestine with highly inter- and intra-reproducible gastrointestinal transit rate.[11] Multiparticulate dosage forms also cover a larger surface of the mucosa and develop stronger mucoadhesive bindings than single-unit dosage forms.[12] Preference is increasingly given to beads as multiple unit dosage forms instead of tablets because of the greater predictability and reproducibility of their therapeutic effect.[13]

Pellets represent multiparticulate forms with interesting characteristics of sphericity and excellent flow properties, especially when obtained by the extrusion-spheronization process.[14] This pelletization technique is a rapid, straightforward process[15] that represents a method of choice for preparing spheres with a wide range of diameters from tens of micrometers to some millimeters.[16] Among the numerous polymeric substances used as bioadhesives, carbomers are being extensively employed in the formulation development of oral mucoadhesive controlled drug delivery systems.[17] Carbopol® 974P (CP 974P) and Carbopol® 971P (CP 971P) are synthetic, high molecular weight, crosslinked polymers of acrylic acid copolymerized with allyl pentaerythritol, with CP 971P being considerably less crosslinked.[18] Both grades are intended for oral and mucosal applications. While CP 974P exhibits semienteric behavior, which is particularly beneficial in formulations targeted to the intestine, CP 971P provides slower and more linear release profiles than CP 974P throughout the intestinal tract.[18] In a previous study, our laboratory prepared pellets by extrusion-spheronization using different polyacrylic acids and showed that the maximum adhesion occurred below pH 6.8, making these bioadhesive pellets a suitable form for targeting the duodenum.[19]

The use of polyacrylic acids for pelletization poses a number of technological problems due to their tendency to gel, which complicates the extrusion-spheronization process.[20,21] To overcome this obstacle, previous researchers[15,20,21] added electrolytes to the wet masses, such as calcium chloride. This procedure proved successful at eliminating tack for the preparation of chlorpheniramine maleate beads containing up to 40% Carbopol® 974P by extrusion-spheronization.[15] The authors proved that the addition of electrolytes led to a decrease in the bioadhesion properties and the consistency of the used polymers. The efficiency of calcium chloride at reducing the tackiness of wetted CP 974P results from its ability to decrease the interactions between carboxylate groups on adjacent polymer molecules, which leads to a loss of viscosity. As a positive consequence, the manufacture of pellets is facilitated and the yield of production is increased. As a negative consequence, the bioadhesive properties are considerably decreased. The aim of the study reported here was to investigate whether it was possible to produce adhesive pellets containing either CP 971P or CP 974P, by the extrusion-spheronization process without the addition of strong electrolytes in order to maintain the bioadhesive potentiality of the pellets at its maximum. Three process variables—extrusion speed, spheronizer speed, and spheronization time—and one formulation variable—amount of water—were therefore optimized to obtain the highest yield of spherical pellets ranging 710—1000 μm and containing up to 20% polyacrylic acids.

MATERIALS AND METHODS

Pellet Production

Mixtures of CP 974P (10%, 15%, or 20%) or CP 971P (10%) (B.F. Goodrich Chemical Europe N.V., Brussels, Belgium) and Avicel® PH-101 (90%, 85%, or 80%) (FMC Corporation, Palo Alto, USA) with a total weight of 200 g were dry-blended for 10 min and then wetted with an appropriate amount of purified water (ranging from 45% to 58%). Water was added gradually into the mixture at speed setting 1 (lowest speed) and mixing continued for 10 minutes at room temperature in a small-scale planetary mixer (Kenwood Chef, Kenwood Products Ltd., London, United Kingdom). The process was stopped twice to scrape the material adhering to the wall of the bowl and the mixing blade. The wet mass was extruded immediately using an Alexanderwerk extruder (Alexanderwerk AGM/R Remscheid, Germany). The diameter of the dies was 1 mm. The extrusion speeds tested were 30, 45, 60, 90, and 150 rpm. The extrudates were spheronized at 350, 700, 960, 1000, 1300, or 1500 rpm on a Caleva spheronizer (Caleva Process Solution Ltd., Dorset, United Kingdom). Each sample was processed for 5, 10, 15, or 20 min. The pellets were dried in single layers on trays in an oven at 45°C for 24 h. Residual water content present in the pellets after drying was determined by thermogravimetric analysis (Mettler P160N and Mettler LP12, Mettler-Toledo S.A., Viroflay, France) and was below 0.5%. Three batches were prepared for each formulation.

Pellet Characterization

Particle Size Analysis and Yield

The test was carried out as described in the European Pharmacopoeia, 4th Edition. The pellets were thus subjected to particle size analysis using a set of sieves ranging from 90, 125, 180, 250, 355, 500, 710, and 1000 μm. The pellets with a size fraction of 710–1000 μm underwent further investigation. The weight of pellets of usable size was used to calculate the yield of the extrusion-spheronization. The values presented are the means ± SEM (n = three batches for each formulation).

Macroscopic Examination

The appearance of the pellets obtained from each extrusion-spheronization condition was determined by macroscopic examination, and expressed as S for spherical pellets, E for extrudates, or P for powder.

Microscopic Image Analysis

A Nikon video camera (Nikon France SA, Division Instruments, Charenton-le-Pont, France) fitted to a Nikon microscope (magnification 20×) was used to determine the shape of the prepared pellets. The camera was connected to a computer program where image analysis was performed and sphericity or roundness (R) was calculated according to the following equation:[22]

$$R = 4\pi A/C^2$$

where A and C = the area and circumference estimated by the program. For a perfect spherical shape, this value is equal to 1. Twenty measurements taken from samples of each batch were recorded, and the values presented are the means ± standard deviations.

Bulk Density and Tapped Density

The bulk density and tapped density were determined from the weight of a 30-g pellet sample (diameter 710 to 1000 μm) charged into a 100 mL graduated cylinder. The pellets were tapped 500 times and tap density was calculated. The densities were expressed as $g.mL^{-1}$.

Flow Rate

Thirty grams of pellets (diameter 710 to 1000 μm) were filled in a glass funnel with a 6 mm internal stem diameter fixed on a clamp. The time was recorded from when the pellets started to flow until finish. Flow rate was expressed as $g.s^{-1}$.

Optimization of the Extrusion-Spheronization Parameters

Pellets Containing 10% Carbopol® 974P

The variation in the yield, shape, and sphericity of the pellets was investigated as a consequence of

Table 1. Yield of the 10% Carbopol® 974P pellets with diameter ranging from 710 to 1000 µm obtained under each extrusion-spheronization condition (spheronization time: 10 minutes, water content: 45%).

	Extrusion speed (rpm)				
	30	45	60	90	150
Spheronizer speed (rpm)	Yield (%)				
960	72.0±0.02^{a}	70.8±0.01	67.2±0.01	66.1±0.02	51.6±0.02
1000	71.2±0.01^{a}	73.4±0.01	68.9±0.02	63.5±0.02	67.2±0.01
1300	47.0 ±0.01	41.4±0.03	37.4±0.01	27.5±0.01	31.5±0.02
1500	25.5 ±0.02	22.8±0.04	21.0±0.02	20.2±0.04	32.4±0.04

Note: All the yields are statistically different within each extrusion speed value ($P<0.05$ Pairwise multiple comparison by the Tukey test) except for those with the same superscript letter.

processing variables in both extrusion and spheronization stages. Variables were extrusion speed, spheronizer speed, and spheronization time. All the formulations contained 45% water and were repeated three times. Firstly, the extrusion speed was set at 90 rpm, and the influence of the spheronizer speed (350, 700, 960, 1000, 1300, and 1500 rpm) and the spheronization time (5, 10, 15, and 20 min) on the pellet quality was studied. Secondly, the spheronizer speed and spheronization time were set at their optimum values (i.e., 960 rpm and 10 minutes) and four additional extrusion speeds (30, 45, 60, and 150 rpm) were tested.

Pellets Containing 15% Carbopol® 974P or 10% Carbopol® 971P

Once clearly defined with 10% CP 974P, the formulation parameters were applied to 15% CP 974P concentration and to 10% CP 971P.

Pellets Containing 20% Carbopol® 974P

For 20% CP 974P, the extrusion speed, spheronizer speed, and water content had to be optimized again since the parameters optimized with 10% CP 974P did not allow the production of pellets with the correct yield and sphericity. Firstly, four extrusion speeds (30, 45, 60, and 90 rpm) and three spheronizer speeds (350, 960, and 1300 rpm) were tested, the water content being kept at 45%. Secondly, three additional water concentrations (50%, 54%, and 58%) were tested at the lowest extrusion speed (30 rpm) and two spheronizer speeds of 960 and 1300 rpm. All the formulations were submitted to 10 minutes spheronization time, except for the formulation containing 58% water and processed under 1300 rpm spheronizer speed, which was submitted to 5, 10, 15, and 20 minutes spheronization time. Additional extrusion speeds (45, 60, 90, and 150 rpm) were also tested for this formulation.

Table 2. Shape and sphericity (R) of the 10% Carbopol® 974P pellets with diameter ranging from 710 to 1000 µm obtained under each extrusion-spheronization condition (spheronization time: 10 minutes, water content: 45%).

	Extrusion speed (rpm)				
	30	45	60	90	150
Sphe. speed (rpm)	Shape/R				
350	E/0.68±0.012^{a}	E/0.68±0.018^{c}	E/0.69±0.030^{i}	E/0.79±0.039^{n}	E/0.75±0.082^{u}
700	E/0.69±0.012^{a}	E/0.68±0.032^{c}	E/0.69±0.020^{i}	E/0.68±0.016^{n}	E/0.69±0.012^{u}
960	S/0.91±0.012	S/0.80±0.018^{d,e,f}	S/0.80±0.025^{j,k}	S/0.88±0.067^{o,p,q}	S/0.89±0.034^{v,w,x}
1000	S/0.87±0.013^{b}	S/0.84±0.062^{d,g,h}	S/0.85±0.057^{j,l,m}	S/0.90±0.020^{o,r,s}	S/0.84±0.048^{v,y,z}
1300	SP/0.89±0.006^{b}	SP/0.85±0.056^{e,g}	SP/0.89±0.054^{l}	SP/0.88±0.020^{p,r,t}	SP/0.88±0.020$^{w,y,\alpha}$
1500	SP/0.84±0.014	SP/0.79±0.037^{f,h}	SP/0.81±0.050^{k,m}	SP/0.86±0.041^{q,s,t}	SP/0.89±0.033$^{x,z,\alpha}$

Note: All the sphericity values were statistically different within each extrusion speed value ($P<0.05$ Pairwise multiple comparison by the Tukey test) except for those with the same superscript letter. S, Spherical pellets; E, Extrudates; P, Powder; R, Sphericity.

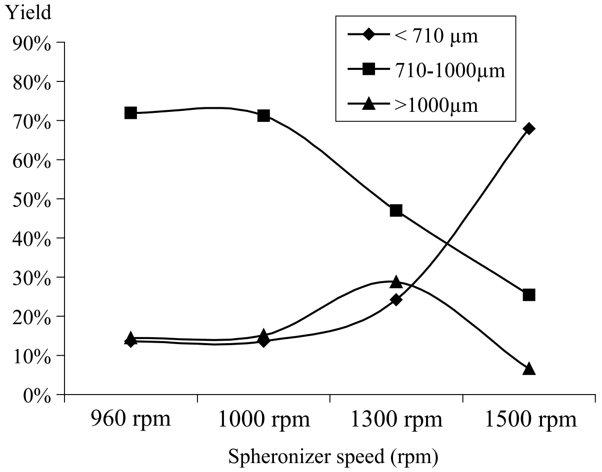

Figure 1. Influence of the spheronizer speed on the yield and diameter of 10% Carbopol® 974P pellets (extrusion speed: 30 rpm, spheronization time: 10 minutes, water content: 45%).

Statistical Analysis

Because of the complex nature of the extrusion-spheronization process and the variation of the component ratio in the pellet formulation, a multifactorial analysis was performed using the Sigma Statistic® software (Statistical Software Version 2.0). The yield and sphericity of pellets with diameter ranging from 710 to 1000 µm obtained under each production condition were used to compare all the results in order to determine the more efficient combination between the extrusion speed, the spheronizer speed, the spheronization time, and the water content. Analysis of variance was carried out, followed by pairwise multiple comparison procedures (Tukey test) in order to isolate the conditions that differed from the others. $P<0.05$ was considered statistically different.

RESULTS AND DISCUSSION

Pellets Containing 10% Carbopol®

Ten percent was the lowest concentration of bioadhesive polymer employed in this work, and the main part of the optimization of the extrusion-spheronization parameters was realized with CP 974P. In preliminary experiments it was determined that the appropriate amount of water ensuring sufficient hydration of the 10% CP 974P/90% Avicel® PH101 mixture was 45%. The influence of the spheronizer speed and the extrusion speed on the yield, shape, and sphericity of the pellets is presented in Tables 1 and 2, the spheronization time being set at 10 minutes. Whatever the extrusion speed, the yield of spherical pellets with diameter ranging from 710 to 1000 µm could not be determined under 350 and 700 rpm spheronizer speeds, since both produced mainly extrudates. The yield measured could not actually be interpreted in terms of pellet production since particles retained by the 710 µm sieve were not spheres but extrudates as expressed by sphericity values of 0.68 to 0.79. Increasing the spheronizer speed produced pellets with a yield closely dependent on the speed value. The highest yields of pellets ranging from 710 to 1000 µm were achieved through 960 and 1000 rpm while spheronizer speeds of 1300 and 1500 rpm produced a poor yield of spherical pellets (min: 20.2%, max: 47.0%) and a high amount of powder. In addition, the highest speed caused frictions that overheated the spheronizer. Figure 1 illustrates the particle size evolution according to the spheronizer speed for the batches processed under 30 rpm extrusion speed. The same increase in the ratio of the finest particles with diameter below 710 µm, concomitant with the drop in the yield of pellets of usable size (710–1000 µm), was observed whatever the extrusion speed (data not shown). Considering the more favorable spheronizer speeds of 960 and 1000 rpm, the statistical analysis showed that the highest yield (72.0±0.02) associated with the best sphericity (0.91±0.012) was obtained at the lowest spheronizer speed of 960 rpm and the lowest extrusion speed of 30 rpm. The influence of the spheronization time on the yield, shape, and sphericity of the pellets produced with the extrusion and spheronizer speeds selected above was then studied

Table 3. The influence of different spheronization times on the yield, shape, and sphericity (R) of the pellets with diameter ranging from 710 to 1000 µm prepared with 30 rpm extrusion speed and 960 rpm spheronizer speed.

Spheronization time (min)	Yield (%)	Shape	R
5	24.2±0.03	E	0.38±0.034
10	72.0±0.02	S	0.91±0.012[a]
15	37.6±0.10	S/P	0.90±0.012[a]
20	27.5±0.20	S/P	0.87±0.008

Note: All the yields were statistically different. The sphericity values were statistically different ($P<0.05$ Pairwise multiple comparison by the Tukey test) except for those with the same superscript letter. S, Spherical pellets; E, Extrudates; P, Powder; R, Sphericity.

(Table 3). Five minutes were not enough to achieve a correct spheronization, and the particles kept an extrudate shape with a poor sphericity of 0.38. Despite a correct sphericity, increasing the spheronization time to 15 and 20 minutes led to the production of a significantly lower yield of pellets ranging 710–1000 µm and a higher amount of larger pellets (>1000 µm: 14% at 10 minutes, 36% at 15 minutes, 46% at 20 minutes). This phenomenon was previously observed by Umprayn, Chitropas, and Amarekajorn,[23] who studied the influence of processing variables on physical properties of pellets made of lactose, microcrystalline cellulose, and various cellulosic products as binders. The authors showed that mean particle size of pellets was increased with increased spheronization time. For example, the mean particle size of pellets containing 1.67% of hydroxypropylcellulose L was 1.01, 1.40, and 1.78 mm, respectively, after 5, 10, and 15 minutes spheronization time. When spheronization time was increased, pellets combined with the fine particles that were produced in the process due to the binding properties of hydroxypropylcellulose L. In our study, the binding properties of CP 974P resulted in the same effect. Considering the four spheronization times tested, 10 minutes was considered as the best spheronization time. Usually, spheronization takes 2–10 minutes between 200–400 rpm speed.[24,25] In our study, the time needed to complete the spheronization process was in the upper range and the spheronizer speed was noticeably higher. This is a common situation in the case of materials for which the deformation process is relatively difficult.[26] Spheronizations at 575 rpm for 30 minutes were also reported by Gomez-Carracedo et al.[21] for preparing Carbopol® 934P pellets. In our study, the optimized parameters for obtaining 10% CP 974P pellets with 90% Avicel® PH101 and 45% water were therefore 30 rpm extrusion speed, 960 rpm spheronizer speed, and 10 minutes spheronization time. The pellets produced under these conditions (Fig. 2A) presented reproducible characteristics of bulk and tapped densities and a rapid flow rate in connection with the sphericity value close to 1 (Table 4). These conditions optimized with CP 974P were successfully applied to the production of pellets with 10% CP 971P. The yield of pellets ranging 710–1000 µm increased about 6% with CP 971P, whereas the sphericity of the pellets decreased about 12%. Awad et al.[19] already noticed a lower yield of extrusion-spheronization with CP 971P than with CP 974P, which may be attributed to the binding

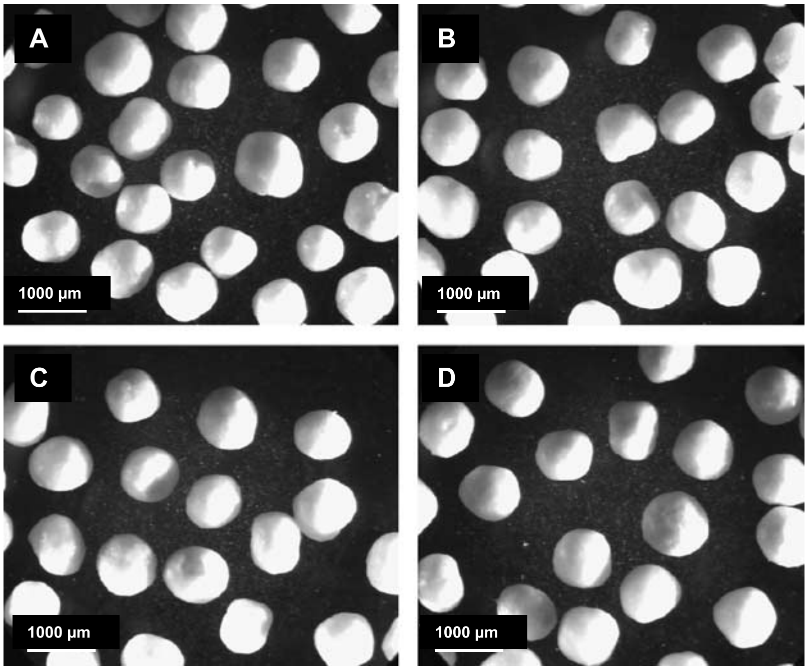

Figure 2. Micrographs of pellets obtained under optimized conditions: **A** = 10% Carbopol® 974P, 30 rpm extrusion speed, 960 rpm spheronizer speed, 10 minutes spheronization time, 45% water content; **B** = 10% Carbopol® 971P, 30 rpm extrusion speed, 960 rpm spheronizer speed, 10 minutes spheronization time, 45% water content; **C** = 15% Carbopol® 974P, 30 rpm extrusion speed, 960 rpm spheronizer speed, 10 minutes spheronization time, 45% water content; **D** = 20% Carbopol® 974P, 30 rpm extrusion speed, 1300 rpm spheronizer speed, 10 minutes spheronization time, 58% water content.

Table 4. Characteristics of Carbopol® pellets with diameter ranging from 710 to 1000 μm produced under optimized conditions.*

	Carbopol® 974P			Carbopol® 971P
	10%	15%	20%	10%
Yield (%)	72.0±0.02	67.0±0.31	42.0±0.38	76.0±0.13
Sphericity (R)	0.91±0.012	0.78±0.046	0.78±0.011	0.80±0.020
Bulk density (g.mL^{-1})	0.50±0.20	0.52±0.10	0.52±0.25	0.47±0.18
Tapped density (g.mL^{-1})	0.53±0.23	0.54±0.32	0.53±0.30	0.51±0.12
Flow rate (g.s^{-1})	7.1±0.41	7.3±0.44	7.1±0.48	6.5±0.34

*30 rpm extrusion speed, 960 rpm spheronizer speed, 10 minutes spheronization time, and 45% water for 10% and 15% Carbopol® 974P pellets and 10% Carbopol® 971P pellets; 30 rpm extrusion speed, 1300 rpm spheronizer speed, 10 minutes spheronization time, and 58% water for 20% Carbopol® 974P pellets.

properties that are noticeably different between both carbomers. However, the characteristics of the 10% CP 971P pellets (Fig. 2B) remained in the same range as those of the 10% CP 974P pellets.

Pellets Containing 15% or 20% Carbopol®

In a previous study, our laboratory observed an increase in the bioadhesive properties of the carbomer pellets when the concentration was doubled from 5% to 10%.[19] This effect, which occurred with polycarbophil and CP 974P (but not with CP 971P), although not statistically significant, led us to test higher amounts of 15% and 20%. Pellets containing 15% CP 974P (Fig. 2C) could be produced using the optimized conditions cited above. However, the yield and sphericity were lowered compared to that of 10% CP 974P pellets (Table 4). The decrease in the percentage of pellets ranging 710–1000 μm mainly benefitted larger pellets whose ratio reached 21% (vs. 14% with 10% CP 974P). This was also observed by Gomez-Carracedo et al.[21] when preparing theophylline pellets with Carbopol® 934. Applying the parameters previously optimized (i.e., 30 rpm extrusion speed, 960 rpm spheronizer speed, and 10 minutes spheronization time) to a higher concentration of 20% CP 974P with a constant amount of water (45%) did not produce spherical pellets with correct yield, shape, and sphericity (Table 5). The yield of 12–14% could not actually be interpreted, since particles passing through the 1000-μm sieve and retained by the 710-μm sieve were not spherical pellets but extrudates as expressed by a sphericity of 0.46–0.53. The remaining particles

Table 5. Yield, shape, and sphericity (R) of the 20% Carbopol® 974P pellets with diameter ranging from 710 to 1000 μm obtained under each extrusion-spheronization condition (spheronization time: 10 minutes, water content: 45%).

	Extrusion speed (rpm)			
	30	45	60	90
Spheronizer speed (rpm)	Yield (%)			
350	ND	ND	ND	ND
960	12.0±0.46	11.0±0.49	10.0±0.32	8.4±0.12
1300	14.0±0.30	13.4±0.25	12.4±0.56	9.7±0.12
Spheronizer speed (rpm)	Shape/R			
350	E/ND	E/ND	E/ND	E/ND
960	E/0.46±0.028	E/0.43±0.005	E/0.49±0.011^{a}	E/0.52±0.015
1300	EP/0.53±0.005	EP/0.55±0.006	EP/0.49±0.005^{a}	EP/0.58±0.015

The yields were statistically different within each extrusion speed value. The sphericity values were statistically different ($P<0.05$ Pairwise multiple comparison by the Tukey test) except for those with the same superscript letter. ND, Not Determined; E, Extrudates; P, Powder.

Table 6. Yield, shape, and sphericity (R) of the 20% Carbopol® 974P pellets with diameter ranging from 710 to 1000 μm according to water amount (extrusion speed: 30 rpm, spheronization time: 10 minutes).

	Water amount (%)			
	45	50	54	58
Spheronizer speed (rpm)	Yield (%)			
960	12.0±0.46	15.6±0.22	19.2±0.14	37.5±0.32
1300	14.0±0.30	20.8±0.30	28.7±0.40	42.0±0.23
Spheronizer speed (rpm)	Shape/R			
960	E/0.47±0.012	E/0.42±0.015	ES/0.56±0.005	S/0.76±0.008
1300	EP/0.53±0.005	E/0.50±0.011	ES/0.67±0.005	S/0.78±0.011

The yields were statistically different within each water percentage. All the sphericity values were statistically different ($P<0.05$ Pairwise multiple comparison by the Tukey test). S, Spherical pellets; E, Extrudates; P, Powder; R, Sphericity.

consisted of larger extrudates (>1000 μm) and finest particles with diameters below 710 μm, more than 40% of each size fraction. Neither the increase in the extrusion speed (45, 60, and 90 rpm), nor the decrease in the spheronizer speed (350 rpm) could improve these results (Table 5). It is well known that the yield of spherical pellets is strongly linked to the percentage of water present in the mixture to be extruded.[27] This parameter is even more crucial when adhesive excipients are used whose tendency to gel hampers the extrusion-spheronization process.[20] In our study, the amount of water appropriate for wetting the powder mass containing either 10% or 15% CP 974P, i.e., 45%, was insufficient with 20% CP 974P. As expected, the increase of the water percentage improved both yield and sphericity values (Table 6). Whereas 50% of water was still insufficient to provide a correct wetting of the powder mass, spherical pellets could be obtained from 54% water content, and the quality of the production reached its optimum with 58% water content. Above this percentage, it was impossible to extrude the wet mass due to its high plasticity. Gomez-Carracedo et al.[21] already underlined the critical point of the correct selection of wetting conditions when using acrylic polymers in the extrusion-spheronization process. They determined the water content to be about three times higher than ours for optimum wetting conditions. However, they combined 40% to 50% Carbopol® 934 with microcrystalline cellulose and added

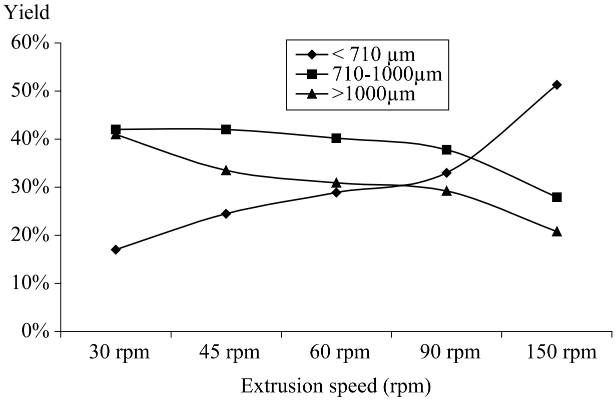

Figure 3. Influence of the extrusion speed on the yield and diameter of 20% Carbopol® 974P pellets (spheronizer speed: 1300 rpm, spheronization time: 10 minutes, water content: 58%).

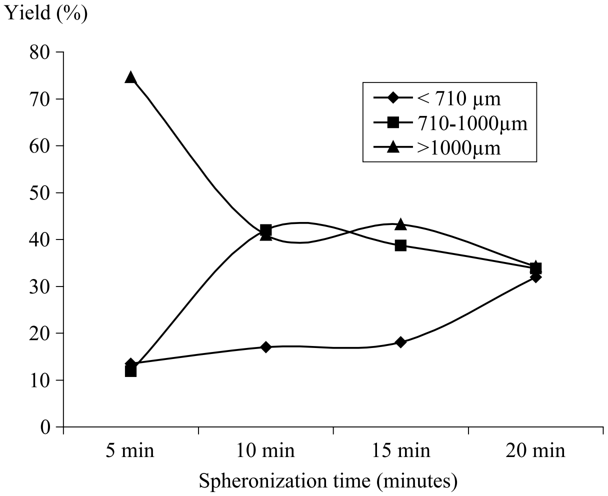

Figure 4. Influence of the spheronization time on the yield and diameter of the 20% Carbopol® 974P pellets (extrusion speed: 30 rpm, spheronizer speed: 1300 rpm, water content: 58%).

$CaCl_2$, which provoked considerable reduction in consistency. In our study, increasing the extrusion speed from 30 to 150 rpm led to a progressive decrease in the 710–1000 μm and above 1000 μm size fractions associated with an increase in the yield of fine particles below 710 μm (Fig. 3). Increasing the spheronization time from 10 to 20 minutes had approximately the same effect, although less pronounced on the 710–1000 μm yield, while 5 minutes led to the production of mainly large particles above 1000 μm (Fig. 4). Consequently, the optimized parameters for obtaining 20% CP 974P pellets with 80% Avicel® PH101 and 58% water were 30 rpm extrusion speed, 1300 rpm spheronizer speed, and 10 minutes spheronization time. Pellets produced under these conditions (Fig. 2D) presented a flow rate, bulk, and tapped densities comparable to those of batches with lower ratios of carbomers (Table 4). The lowest yield among all the formulations, i.e., 42%, expressed the difficulties encountered in the course of the extrusion-spheronization process in connection with the strong adhesive properties of the mixture.

CONCLUSION

The production of bioadhesive pellets containing polyacrylic acids could be of interest for intestinal targeting of drugs, since this form of administration associates the advantages of a multiparticulate carrier with potentially greater predictability and reproducibility of therapeutic effects, and a mucoadhesive carrier allowing the localization of the drug at the site of absorption. However, the adhesive properties of carbomers introduce handling difficulties with techniques involving water like the extrusion-spheronization technique. In this context, the challenge was to prepare bioadhesive pellets without the addition of electrolytes, which previously proved successful at eliminating technological problems but also reduced bioadhesion. This was achieved with 10%, 15%, and 20% carbomers through the optimization of the processing parameters—extrusion speed, spheronizer speed, spheronization time—and the water content leading to acceptable yields up to 76% and sphericity values up to 0.91.

REFERENCES

1. Lambkin, I.; Pinilla, C. Targeting approaches to oral drug delivery. Expert Opin. Biol. Ther. **2002**, *2* (1), 67–73.
2. Bowtle, W.J. Recent developments in oral multiphase and targeting release. Pharm. Sci. Technol. Today **1999**, *2* (1), 32–36.
3. Lavelle, E.C. Targeted delivery of drugs to the gastrointestinal tract. Crit. Rev. Ther. Drug Carr. Syst. **2001**, *18* (4), 341–386.
4. Ahuja, A.; Khar, R.K.; Ali, J. Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm. **1997**, *23* (5), 489–515.
5. Lee, J.W.; Park, J.H.; Robinson, J.R. Bioadhesive-based dosage forms: the next generation. J. Pharm. Sci. **2000**, *89* (7), 850–866.
6. Shimoda, J.; Onoshi, H.; Machida, Y. Bioadhesive characteristics of chitosan microspheres to the mucosa of rat small intestine. Drug Dev. Ind. Pharm. **2001**, *27* (6), 567–576.
7. Attama, A.A.; Adikwu, M.U.; Okoli, N.D. Studies on bioadhesive granules I granules formulated with *Prosopis africana* (Prosopis) gum. Chem. Pharm. Bull. **2000**, *48* (5), 734–737.
8. Prudat-Christiaens, C.; Arnaud, P.; Allain, P.; Chaumeil, J.C. Aminophylline bioadhesive tablets attempted by wet granulation. Int. J. Pharm. **1996**, *141*, 109–116.
9. Ahmed, A.; Bonner, C.; Desai, T.A. Bioadhesive microdevices with multiple reservoirs: a new platform for oral drug delivery. J. Control. Release **2002**, *81*, 291–306.
10. Kakoulides, E.P.; Smart, J.D.; Tsibouklis, J. Azocrosslinked poly(acrylic acid) for colonic delivery and adhesion specificity in vitro degradation and preliminary ex vivo bioadhesion studies. J. Control. Release **1998**, *54*, 95–109.
11. Follonier, N.; Doelker, E. Biopharmaceutical comparison of oral multiple-unit and single-unit sustained release dosage forms. STP Pharm. Sci. **1992**, *2*, 141–158.
12. Peppas, N.A.; Buri, P.A. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J. Control. Release **1985**, *2*, 257–275.
13. Gasconda, S.R.; Hileman, G.A.; Upadrzashta, S.M. Development of matrix controlled release beads by extrusion-spheronization technique using a statistical screening device. Drug Dev. Ind. Pharm. **1994**, *20*, 279–292.
14. Gandhi, R.; Lal Kaul, C.; Panchagnula, R. Extrusion and spheronization in the development of oral controlled-release dosage forms. Pharm. Sci. Technol. Today **1999**, *4* (2), 160–170.
15. Neau, S.H.; Chow, M.Y.; Hileman, G.A.; Durrani M.J.; Gheyas, F.; Evams, B.A. Formulation and process considerations for beads containing

carbopol 974P, NF resin made by extrusion spheronization. Int. J. Pharm. **2000**, *199*, 129–140.

16. Alvarez, L.; Concheiro, A.; Gomez-Amoza, J.L.; Souto, C.; Martinez-Pacheco, R. Effect of microcrystalline cellulose grade and process variables on pellets prepared by extrusion-spheronization. Drug Dev. Ind. Pharm. **2002**, *28* (4), 451–456.
17. Singla, A.K.; Chawla, M.; Singh, A. Potential applications of carbomer in oral mucoadhesive controlled drug delivery system: a review. Drug Dev. Ind. Pharm. **2000**, *26* (9), 913–924.
18. Goodrich, B.F. *Product Information Provided by BF Goodrich*; Cleveland, Ohio, 1995.
19. Awad, G.A.S.; Charrueau, C.A.A.; Allain, P.; Chaumeil, J.C. Formulation and evaluation of bioadhesive pellets containing different carbomers made by extrusion-spheronization. STP Pharm. Sci. **2002**, *12* (3), 157–162.
20. Neau, S.H.; Chow, M.Y.; Durrani, M.J. Fabrication and characterization of extruded and spheronized beads containing Carbopol 974P, NF resin. Int. J. Pharm. **1996**, *131*, 47–55.
21. Gomez-Carracedo, A.; Alvarez-Lorenzo, C.; Gomez-Amoza, J.L.; Martinez-Pacheco, R.; Souto, C.; Concheiro, A. Extrusion-spheronization of blends of carbopol 934 and microcrystalline cellulose. Drug Dev. Ind. Pharm. **2001**, *27* (5), 381–391.
22. Lindner, H.; Kleinebudde, P. Use of powdered cellulose for the production of pellets by extrusion/spheronization. J. Pharm. Pharmacol. **1994**, *46*, 2–7.
23. Umprayn, K.; Chitropas, P.; Amarekajorn, S. Influence of process variables on physical properties of the pellets using extruder and spheronizer. Drug Dev. Ind. Pharm. **1999**, *25*, 45–61.
24. Vervaet, C.; Baert, L.; Remon, J.P. Extrusion-spheronisation. A literature review. Int. J. Pharm. **1995**, *116*, 131–146.
25. Conine, J.W.; Hadley, H.R. Small solid pharmaceutical spheres. Drug Cosmet. Ind. **1970**, *106*, 38–41.
26. Newton, J.M. Extrusion/Spheronization. In *Powder Technology and Pharmaceutical Processes*; Chulia, D., Deleuil, M., Pourcelot, Y., Eds.; Elsevier: New York, 1998; 391–401.
27. Lustig-Gustafsson, G.; Kaur, J.H. The influence of water content and drug solubility on the formulation of pellets by extrusion and spheronisation. Eur. J. Pharm. Sci. **1999**, *8*, 147–152.