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International Journal of Pharmaceutics 199 (2000) 129–140

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Formulation and process considerations for beads containing Carbopol® 974P, NF resin made by extrusion-spheronization

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Received 11 June 1999; received in revised form 22 December 1999; accepted 4 February 2000

Abstract

Preliminary studies revealed that Carbopol® 974P, NF resin could be incorporated into beads manufactured by extrusion and spheronization, and can slow the release of a highly water soluble drug if calcium chloride was included in the granulating fluid to reduce the tack of the wetted polymer. In this study, the same approach was used to produce high quality chlorpheniramine maleate beads with a prolonged release duration. Because of the complex nature of the extrusion and spheronization process and the various components in the bead formulations, a statistically sound factorial experiment was considered for this study. A one-half fraction of a two level factorial design with three center points was employed to estimate the effects of simultaneously modifying multiple process and formulation variables, including the Carbopol® concentration, calcium chloride concentration, water content, and the spheronization speed and time. Product yield, average bead roundness, and the drug release profile were selected as responses. Increasing the Carbopol® content across the experimental range resulted in a significant ($P < 0.05$) reduction in the percentage drug released at 25, 40, and 60 min. Results suggest that combining the conditions of high Carbopol®, high water, and low calcium chloride levels with low spheronization speeds at long spheronization times produce the highest quality bead with the longest drug release duration.

Keywords: Carbopol; Carbomer; Extrusion-spheronization; Pellets; Beads; Statistical design

1. Introduction

Carbopol® resins are acrylic acid polymers which have a wide variety of applications in the

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PII: S0378-5173(00)00372-0

pharmaceutical and cosmetic industries. Due to gelling and swelling properties, they are mainly used as thickening agents, suspending agents, and emulsifying agents (Carbopol® Resin Handbook, 1993). Carbopol® resins have also been employed in directly compressed matrix tablets to modify drug release (Choulis and Papadopoulos, 1975; Choulis et al., 1976; Elsabbagh et al., 1978; Durrani et al., 1992). Carbopol® 974P, NF resin (Carbopol) in particular has been polymerized in ethyl acetate and is safe for use in most oral dosage forms (Carbopol® Resin Handbook, 1993). Unfortunately, Carbopol becomes tacky when wetted which limits its applications in pharmaceutical dosage forms that require wet massing for manufacture. Preliminary studies have indicated that the tack of wetted mixtures of Carbopol and Avicel PH 101 is greatly reduced in the presence of strong electrolytes. Calcium chloride, in particular, proved to be successful at eliminating tack. This technique was applied in the extrusion and spheronization manufacture of chlorpheniramine maleate beads containing Carbopol, and drug release was prolonged in the presence of Carbopol (Neau et al., 1996).

Extrusion-spheronization has gained attention as a pelletization technology, largely because it is a simple and fast process (Woodruff and Nuessle, 1972; Harrison et al., 1985; Hasznos et al., 1992; Fielden et al., 1993). It has processing advantages with high dose drugs especially when compared to other pelletization techniques, viz. layering, spray congealing, cryopelletization and encapsulation (Hicks and Freese, 1989). The main processing steps are dry powder blending, wet mixing, extrusion of the wet mass, and spheronization of the cylindrical extrudate. It is possible to produce sustained release beads without coating by using the extrusion-spheronization technique (Goskonda et al., 1994).

Because of the complex nature of the extrusion-spheronization process and the number of factors involved in bead formulations containing Carbopol, a statistically sound factorial experiment was considered appropriate for this study. Statistical experimental designs allow the effect of multiple factors to be investigated simultaneously. These designs generate a maximum of information with a minimum of experiments and assist in estimating the main effects of each experimental factor on the product. In later experiments, some formulation and process variables can be fixed at desired levels or eliminated from further consideration.

A two-level half-fractional factorial design with three center points was employed in this study. The effects of Carbopol concentration, calcium chloride concentration, the amount of water used in the wet massing step, and spheronization time and speed on the characteristics of the final products were investigated. Because the Carbopol, water, and $CaCl_2$ concentrations are functionally related, their absolute concentrations in the formulations are necessarily correlated. For purposes of maintaining orthogonality in the design, the levels of water and $CaCl_2$ were varied independently around a nominal concentration described later. As a result, the effects of calcium chloride concentration and water concentration cannot be interpreted in terms of their absolute content in the product. They must be viewed in terms of their deviations from the nominal concentration. The primary objective of this study was to determine how these five factors affect the response variables. Response variables selected for evaluation were the drug release profile at three different time points and various physical characteristics of the beads that could be used to assess the pharmaceutical acceptability of the process, including product yield, bead average diameter and roundness, friability, and tap density.

2. Materials and methods

2.1. Materials

Carbopol® 974P, NF resin (BF Goodrich, Cleveland, OH) was used as a drug release modifying agent. Microcrystalline cellulose (Avicel PH101, FMC Corporation, Philadelphia, PA) was used as the principal spheronization agent. Calcium chloride (Fisher Scientific, Fair Lawn, NJ) was chosen to eliminate tack problems encountered on wet massing. Chlorpheniramine maleate (Napp Chemical Inc., Lodi, NJ) was used as a water-soluble model drug.

2.2. Experimental design

A one-half fraction of a two-level factorial design in five factors and 19 batches that includes three center points (Table 1) was defined using PC-based software (Statgraphics® Plus, Manugistics Inc., Rockville, MD). This resolution V design allows estimation of all the main effects and two factor interactions in half of the experimental runs required for a full factorial design. Interactions of three or more factors are confounded with two factor interactions and are assumed to be insignificant for purposes of this design. Higher order interactions are generally not interpretable, even when they are significant. By adding three center points, it was possible to measure experimental error and to perform an overall test for curvature in the responses.

Formulation and process variables, and the ranges for each, were based on information obtained in preliminary experiments. Carbopol concentration ranged from 5 to 40% (w/w). Low and high levels of spheronization speed were 468 and 1828 rpm, respectively. Spheronization time varied from 5 to 20 min. The minimum amount of calcium chloride required to essentially eliminate tack due to the wetted Carbopol mass, was experimentally determined and is described in Eq. (1):

$$\%\ CaCl_2 \text{ concentration} = 0.635 \times 10^{0.0329C} \quad (1)$$

where C is the percentage of Carbopol in the dry mass. Likewise, the nominal amount of water necessary to allow the wetted mass to be extruded was experimentally determined to be based on R, the ratio of the Carbopol to the Avicel PH101 mass percentages in the formulation, and is described in Eq. (2):

$$\text{millilitre of water} = 310 - 97.4\ R \quad (2)$$

Since the water and calcium chloride levels necessarily varied with the Carbopol content, the study was designed to allow these factors to vary about the nominal concentrations. A low level of calcium chloride corresponds to the value calculated using Eq. (1), and the high level is 1.5 times that value. A low water level was 95% of the volume calculated using Eq. (2), whereas the high level was 105% of the calculated volume. By

Table 1
Half-fractional factorial design with three center points for five variables at two levels

Run	A: Carbopol® (%)[a]	B: $CaCl_2$ (%)[a]	C: water (ml)	D: spheronization speed (rpm)	E: spheronization time (min)
1	22.5	4.36	278	1148	12.5
2	40	13.1	228	1828	5
3	5	1.39	320	468	20
4	5	0.93	320	1828	20
5	5	0.93	320	468	5
6	5	0.93	290	468	20
7	40	13.1	228	468	20
8	40	19.6	210	1828	20
9	40	13.1	190	1828	20
10	22.5	4.36	278	1148	12.5
11	40	19.6	190	1828	5
12	5	1.39	290	1828	20
13	40	19.6	210	468	5
14	5	1.39	320	1828	5
15	5	0.93	290	1828	5
16	40	19.6	190	468	20
17	5	1.39	290	468	5
18	40	13.1	207	468	5
19	22.5	4.36	278	1148	12.5

[a] Percentage of dry mass.

Table 2
Coded half-fractional factorial design with three center points for five variables at two levels

Run	A: Carbopol® (%)	B: CaCl2 (%)	C: water (ml)	D: spheronization speed (rpm)	E: spheronization time (min)
1	0	0[a]	0[d]	0	0
2	+1	−1[b]	+1[e]	+1	−1
3	−1	+1[c]	+1	−1	+1
4	−1	−1	+1	+1	+1
5	−1	−1	+1	−1	−1
6	−1	−1	−1[f]	−1	+1
7	+1	−1	+1	−1	+1
8	+1	+1	+1	+1	+1
9	+1	−1	−1	+1	+1
10	0	0	0	0	0
11	+1	+1	−1	+1	−1
12	−1	+1	−1	+1	+1
13	+1	+1	+1	−1	−1
14	−1	+1	+1	+1	−1
15	−1	−1	−1	+1	−1
16	+1	+1	−1	−1	+1
17	−1	+1	−1	−1	−1
18	+1	−1	−1	−1	−1
19	0	0	0	0	0

[a] 0 level $CaCl_2$ is 1.25 × (the value calculated using Eq. (1)).
[b] −1 level is the value calculated using Eq. (1).
[c] +1 level is 1.5 × (the value calculated using Eq. (1)).
[d] 0 level calculated using Eq. (2).
[e] +1 level is 1.05 × (the value calculated using Eq. (2)).
[f] −1 level is 0.95 × (the value calculated using Eq. (2)).

designing the study in this manner, the assignment of high and low levels to both calcium chloride and water remained independent of the Carbopol and Avicel levels, allowing independent analysis of all factor effects. The coded design in Table 2 illustrates the orthogonality of the main factors. The effects of calcium chloride concentration and water concentration cannot be interpreted in terms of absolute content in the product. They must be viewed in terms of their deviations above or below the relationships described in Eqs. (1) and (2), and are perhaps best interpreted as refinements of those relationships.

2.3. Fabrication and characterization of beads

Carbopol, Avicel PH101 and chlorpheniramine maleate were mixed for 5 min in a Hobart Model N-501 planetary mixer (Hobart Corporation, Troy, OH). The batch size (dry weight) in each experiment was 300 g. The granulating fluid, consisting of calcium chloride dissolved in the required amount of water, was then added. The wet mass was passed through a twin-screw extruder (Fuji Denki Kogyo Co., Osaka, Japan) fitted with a 1.5-mm screen and operated at 50 rpm. The cylindrical extrudate was immediately spheronized in a Q400 Marumerizer (Fuji Denki Kogyo Co., Osaka, Japan) which was operated at the rotational speed and for the duration specified by the design. Beads were collected and air-dried at room temperature for at least 12 h.

Sieve analysis with US standard sieves was used to evaluate product yield. The percentage of the beads found in the 14/20-mesh fraction was reported as the usable yield. Dissolution studies were performed using a USP dissolution apparatus 2 (PharmaTest PTWII, Scientific and Technology Corp., Englishtown, NJ) with a consistent 50-rpm paddle rotation speed. The dissolution

medium was USP standard 0.05-M pH 7.4 potassium phosphate buffer at 37°C. The concentration of chlorpheniramine in the medium was measured by UV analysis at 264 nm using a HP8451A diode array spectrophotometer (Hewlett Packard, Palo Alto, CA). Friability tests were conducted by rotating 50 g of 14/20 mesh beads with 50 glass beads in a Model 10805 friability tester (Vankel Industries Inc., Edison, NJ) for 10 min and then sieving the beads. The percentage of weight lost in the 14/20-mesh fraction was recorded as friability. The density of the beads was calculated by measuring the volume in a graduated cylinder occupied by 80 g of beads after dropping the cylinder from 1.9 cm 20 times. The roundness and the average diameter of more than 800 beads from each batch were evaluated using a Quantimet 500+ image analysis system (Leica Cambridge Ltd., Cambridge, UK). The software reported roundness values, generated using the following expression:

$$\text{Roundness} = \frac{0.9399\,P^2}{4\pi A} \quad (3)$$

where P is the perimeter of the bead image and A is the area determined by the total number of pixels within the feature. The factor 0.9399 corrects the perimeter for the effect of the corners produced by digitization of the image. A roundness value of 1 corresponds to the image of a perfect sphere, and higher values correspond to less spherical images.

3. Results and discussion

Data obtained for each of the evaluated responses are presented in Table 3. Data are reported as the average of three measurements, with the exception of yield, which is a single value for each batch. Neither friability nor tap density varied sufficiently to warrant modeling. Other responses are discussed in detail below. Statistical analyses were performed using the JMP statistical package (SAS Institute, Cary, NC). For each response, a multiple regression model consisting of the appropriate linear and interaction terms was fitted to the data. The models were selected

Table 3
2^{5-1} half-fractional factorial design response values

Run	Released (%)			Yield (%)	Friability (%)	Density (g/ml)	Roundness	Diameter (mm)
	25 min	40 min	60 min					
1	55.0	74.9	89.0	67.8	5.87	0.825	1.14	0.98
2	74.5	94.0	98.0	55.9	3.36	0.814	1.31	0.89
3	58.4	75.2	89.1	88.0	0.0504	0.843	1.14	1.19
4	54.8	70.9	85.2	98.6	0	0.879	1.12	1.16
5	59.2	74.9	88.6	93.8	0.0503	0.851	1.13	1.18
6	67.6	86.4	92.9	94.6	1.29	0.841	1.10	0.95
7	41.7	60.4	75.6	83.7	4.19	0.849	1.17	1.17
8	59.9	83.8	88.6	74.6	4.12	0.883	1.17	1.05
9	55.9	73.9	87.8	87.5	0.304	0.877	1.19	1.16
10	60.5	76.9	88.6	72.4	2.99	0.812	1.13	1.02
11	49.2	72.5	82.8	85.3	2.96	0.888	1.24	1.22
12	74.6	92.4	94.2	80.5	2.80	0.849	1.14	0.88
13	45.6	68.4	82.9	77.4	1.48	0.874	1.21	1.20
14	61.7	78.5	89.3	96.8	0.101	0.864	1.18	1.04
15	73.9	90.6	96.1	78.0	2.91	0.859	1.15	0.90
16	58.7	77.8	90.1	76.3	0.967	0.879	1.18	1.32
17	66.2	82.0	89.7	90.1	0.710	0.835	1.11	1.04
18	58.8	72.4	83.0	83.8	0.305	0.834	1.23	1.23
19	55.2	73.2	90.2	70.7	7.37	0.811	1.16	0.95

Table 4
Stepwise regression results

Release at 25 min		Release at 40 min		Release at 60 min		Yield		Roundness	
Factor	*P*	Factor	*P*	Factor	*P*	Factor	*P*	Factor	*P*
Carbopol-A	0.0007	Carbopol-A	0.0033	Carbopol-A	0.0001	Carbopol-A	0.0113	Carbopol-A	<0.0001
$CaCl_2$-B	0.3681	$CaCl_2$-B	0.5378	$CaCl_2$-B	0.8912	$CaCl_2$-B	0.8333	$CaCl_2$-B	0.7282
Water-C	0.0059	Water-C	0.0065	Water-C	0.0026	Water-C	0.8238	Speed-D	0.0208
Speed-D	0.0064	Speed-D	0.0010	Speed-D	0.0003	Time-E	0.4926	Time-E	0.0019
Time-E	0.2068	Time-E	0.2916	Time-E	0.1037	A × C	0.0368	A × B	0.0703
A × B	0.1115	A × C	0.0008	A × C	0.0014	B × E	0.0236	A × E	0.0313
A × C	0.0071	A × D	0.0245	B × C	0.1741			B × E	0.1524
A × D	0.1374	C × D	0.0111	A × D	0.0017			D × E	0.0703
C × D	0.0103	B × E	0.0004	B × D	0.0010				
B × E	0.0005	C × E	0.0098	C × D	0.0024				
C × E	0.0275	D × E	0.1714	B × E	<0.0001				
				C × E	0.0002				
				D × E	0.0103				
Curvature	0.1154	Curvature	0.0353	Curvature	0.0960	Curvature	0.0014	Curvature	0.0137

using the stepwise regression procedure, with a cutoff *P*-value of 0.25. The selected models were hierarchical in nature, i.e. if an interaction term was deemed appropriate for the model, the associated linear terms were also retained regardless of their individual significance levels. The model terms selected for each response, along with their *P*-values, are presented in Table 4.

Each model was evaluated using the Design-Expert version 5.0.5 (DX-5) statistical software (Stat-Ease Inc., Minneapolis, MN). Standard analyses of the variance (ANOVA) were performed and the models were subsequently tested for lack-of-fit and overall curvature. No significant lack-of-fit was evident in the models presented in Table 4. The *P*-values for tests for curvature are also included in Table 4. Significant curvature would indicate that the data could not be properly described with the simple interaction model employed. Some indication of curvature for all responses was found, suggesting that further experimentation might be required in order to study the curvilinear effects of these factors. A response surface experimental design capable of fully exploring curvilinear effects would be appropriate.

3.1. Dissolution

Dissolution results at the three time points were represented by complex response surfaces. For example, the regression model for dissolution at 40 min (Table 4) includes all the main factors and six significant interaction terms. Carbopol concentration, water deviation from the calculated value, and spheronizer speed main effects were significant. However, these terms were also involved in one or more significant interaction terms. Significant interaction between two factors indicates that the effect of one factor depends on the level of the other factor. In the presence of significant interaction terms involving any of the main effects, no conclusion can be drawn from the main effects alone. The effect of one factor should be examined at each level of the other factors with which it interacts. ANOVA for dissolution at 40 min (Table 5) suggests good fit of this model ($r^2 = 0.96$). However, significant curvature was found ($P = 0.0353$), suggesting that dissolution may be better characterized by a higher order response surface model.

Fig. 1 illustrates the effects on dissolution at 40 min of changing Carbopol concentration and spheronizer speed (and should be interpreted at the 'average' water and $CaCl_2$ content, and at an intermediate spheronizing time). Increasing Carbopol from 10 to 40% reduced the amount of drug released at 40 min by about 10% at slow spheronizer speeds. At higher speeds, this same magnitude of change in Carbopol concentration had little effect on dissolution. Likewise, altering the spheronizer speed at high Carbopol content had a larger effect than did a similar change at low Carbopol content.

Fig. 2 shows the relationship between water concentration and spheronizing time (interpreted at the 'average' Carbopol and $CaCl_2$ content,

Table 5
ANOVA for the 40 min dissolution model

Terms	Estimates	S.E.	t ratio	$P>\|t\|$
Intercept	77.8474	0.6286	123.83	<0.0001
Carbopol-A	−2.9813	0.6850	−4.35	0.0033
$CaCl_2$-B	0.4437	0.6850	0.65	0.5378
Water-C	−2.6188	0.6850	−3.82	0.0065
A × C	3.8687	0.6850	5.65	0.0008
Sph speed-D	3.6937	0.6850	5.39	0.0010
A × D	1.9563	0.6850	2.86	0.0245
C × D	2.3438	0.6850	3.42	0.0111
Sph time-E	−0.7813	0.6850	−1.14	0.2916
B × E	4.2562	0.6850	6.21	0.0004
C × E	−2.4063	0.6850	−3.51	0.0098
D × E	−1.0437	0.6850	−1.52	0.1714
r^2			0.9603	
r^2 adj.			0.8979	
Root mean square error			2.7402	
Mean of response			77.8474	
Observations (or sum weights)			19.0000	

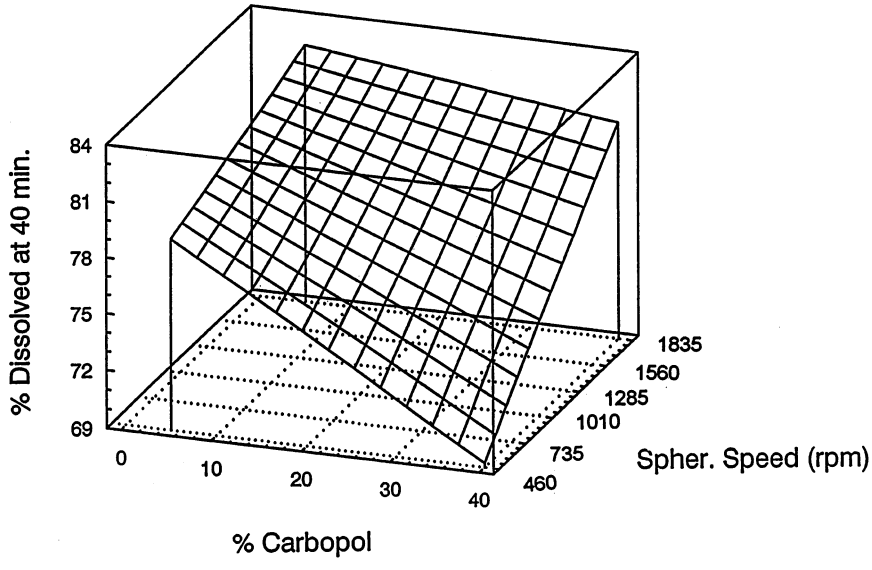

Fig. 1. Effects of changing Carbopol content and spheronizer speed on dissolution at 40 min.

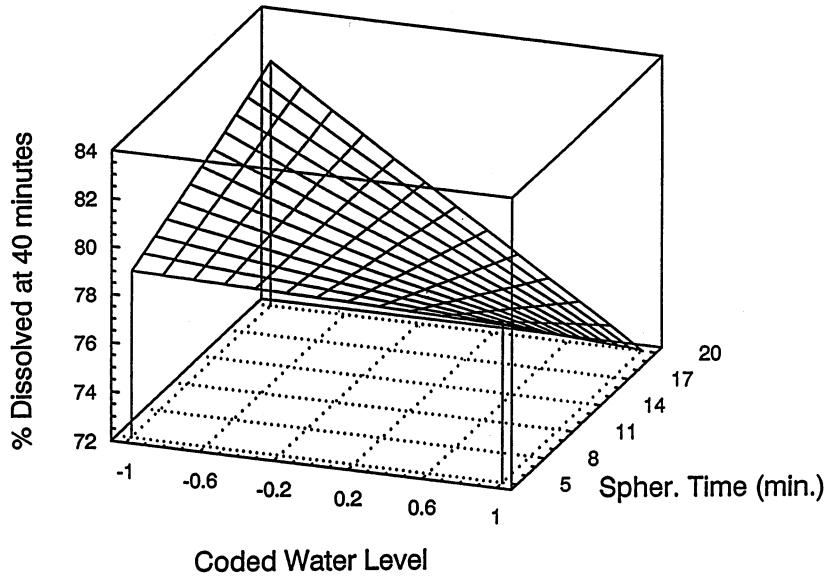

Fig. 2. Effects of changing water content and spheronizing time on dissolution at 40 min.

and at an intermediate spheronizing speed). As the water concentration fell below that predicted in Eq. (2), prolonging spheronizing time caused an increase in the amount dissolved at 40 min. Conversely, as water deviated above the Eq. (2) value, increasing spheronizing time decreased the fraction of drug dissolved.

Fig. 3 illustrates the overall relationship of water, Carbopol, and dissolution at all time points measured. At 40% Carbopol, varying the water content +5% from the Eq. (2) value, had little effect on dissolution. At lower Carbopol content, increasing the water content to the highest level reduced the percent dissolved at 25 and 40 min.

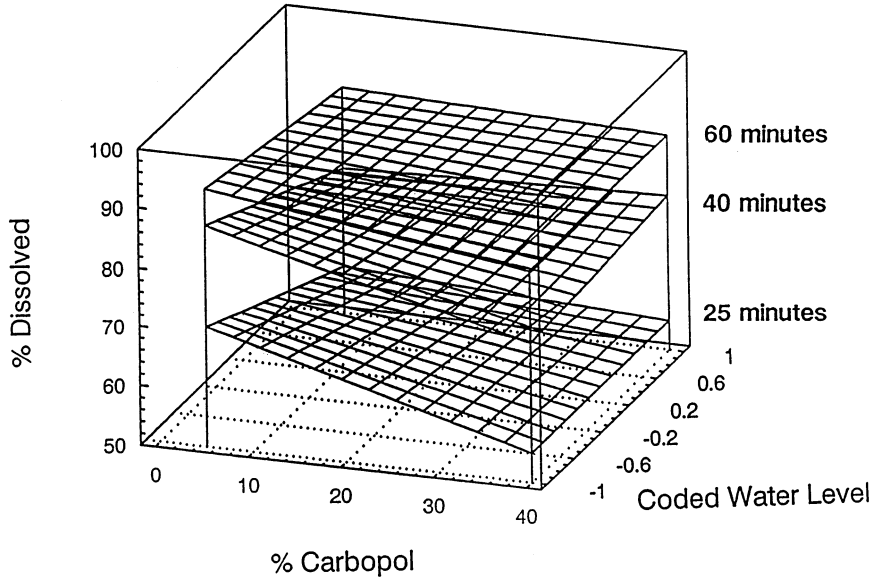

Fig. 3. Effects of changing Carbopol and water content on dissolution.

Combining all main factors and interaction terms, the slowest dissolution can be achieved with high Carbopol and water content, a low salt concentration, and long spheronization time at a low speed.

3.2. Yield

Stepwise regression for the yield response resulted in the model presented in Table 4. The Carbopol main effect was statistically significant. Carbopol–water and $CaCl_2$–spheronization time effects were also significant. ANOVA of the model presented in Table 6 suggests the model does fit the data moderately well ($r^2 = 0.6447$). Curvature is again highly significant ($P = 0.0014$). Thus the simple interaction model supported by this two level factorial design does not adequately describe the yield response surface and a higher order model would be required to fully characterize yield. At the high Carbopol level, the low water concentration resulted in higher yield. However, at the low Carbopol level, the high water concentration produced a greater yield. Overall, high Carbopol content produced lower yield. At the low salt concentration, the longer spheronization time resulted in greater yield, whereas at the high salt concentration, the spheronization time had an opposite effect on yield.

3.3. Roundness

All combinations of formulation components and processing conditions produced beads of acceptable roundness, but roundness can be improved by various means. The model selected using stepwise regression consisted of some interaction effects and all the main effects except water level. This model has a good fit ($r^2 = 0.9076$) but also has significant curvature ($P = 0.0137$). This suggests that improved fit may result from a full response surface model. Significant interaction terms in the model include Carbopol–$CaCl_2$, Carbopol–time and spheronizer speed–time. The roundest beads were produced using formulations with low Carbopol content. As indicated in Table 7, the interaction between salt and Carbopol was significant ($P = 0.0703$). This is evident in Fig. 4, where an increase in salt concentration at low Carbopol content resulted in decreased bead roundness, whereas at high Carbopol content, the opposite effect was seen. The interaction between spheronizing time and Carbopol content was also significant ($P = 0.0313$). Increasing spheronizing time at high Carbopol content improved bead roundness, but at low Carbopol content, it decreased bead roundness. Spheronizing time and speed also interacted ($P = 0.0703$) as illustrated in

Table 6
ANOVA for the yield model

Terms	Estimates	S.E.	t-ratio	$P>\|t\|$
Intercept	81.8842	1.8393	44.52	<0.0001
Carbopol-A	−5.9938	2.0043	−2.99	0.0113
$CaCl_2$-B	−0.4313	2.0043	−0.22	0.8333
Water-C	−0.4563	2.0043	−0.23	0.8238
A × C	−4.7063	2.0043	−2.53	0.0368
Sph speed-E	1.4187	2.0043	0.71	0.4926
B × E	−5.1938	2.0043	−2.59	0.0236
r^2			0.6447	
r^2 adj.			0.4670	
Root mean square error			8.0171	
Mean of response			81.8842	
Observations (or sum weights)			19.0000	

Table 7
ANOVA for the roundness model

Terms	Estimates	S.E.	t-ratio	$P>\|t\|$
Intercept	1.1684	0.0048	242.73	<0.0001
Carbopol-A	0.0394	0.0052	7.51	<0.0001
$CaCl_2$-B	−0.0019	0.0052	−0.36	0.7282
A × B	−0.0106	0.0052	−2.03	0.0703
Sph speed-D	0.0144	0.0052	2.74	0.0208
Sph time-E	−0.0219	0.0052	−4.17	0.0019
A × E	−0.0131	0.0052	−2.50	0.0313
B × E	0.0081	0.0052	1.55	0.1524
D × E	−0.0106	0.0052	−2.03	0.0703
r^2			0.9076	
r^2 adj.			0.8337	
Root mean square error			0.0210	
Mean of response			1.1684	
Observations (or sum weights)			19.0000	

Fig. 5. A combination of low spheronization speed and a long spheronization time produced the most spherical beads.

3.4. Graphic optimization

The goal of this series of experiments was to produce the highest quality bead, based on low roundness scores, high yields, and slow drug release properties. DX-5 has a graphical optimization function that optimizes multiple responses based on a given set of restrictions on the responses. This optimization function was used to explore the factor ranges that will produce beads with the following characteristics: (1) a yield of $>75\%$; (2) a roundness score <1.2; and (3) a percentage released at 15, 40, and 60 min of <45, <65, and $<80\%$, respectively. As seen in Fig. 6, optimum bead production is predicted to occur at the lower right hand corner of the plot, with a high Carbopol and water content, a low $CaCl_2$ concentration, a low spheronizer speed, and long spheronizing times.

In conclusion, beads of acceptable physical characteristics can be produced using extrusion and spheronization with Carbopol® 974P, NF,

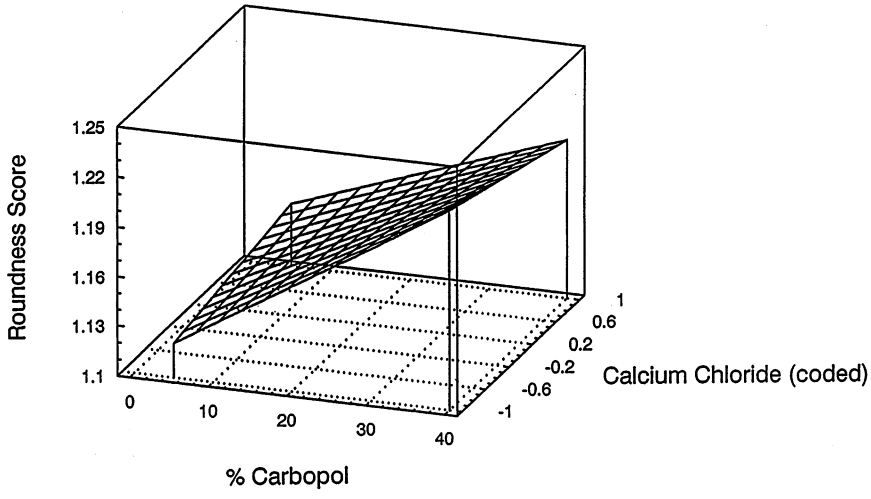

Fig. 4. Effects of changing Carbopol and calcium chloride content on roundness.

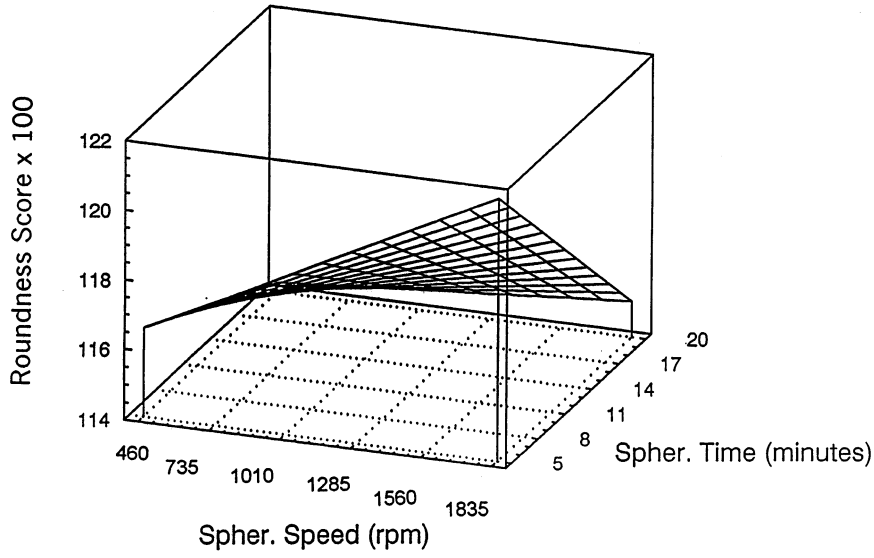

Fig. 5. Effects of changing spheronizing speed and time on roundness.

resin as a release rate-controlling polymer. Increasing the Carbopol content can be a means to slow drug dissolution from the beads. All combinations of formulation components and process conditions produced beads of acceptable roundness. At high Carbopol content, bead roundness can be improved by increasing the salt content and spheronization times. High Carbopol and water content, a low calcium chloride level, low spheronization speed and a long spheronization time period produced the highest quality bead that possessed the longest drug release duration. Complete characterization of factor effects requires additional experiments to model curvilinear responses.

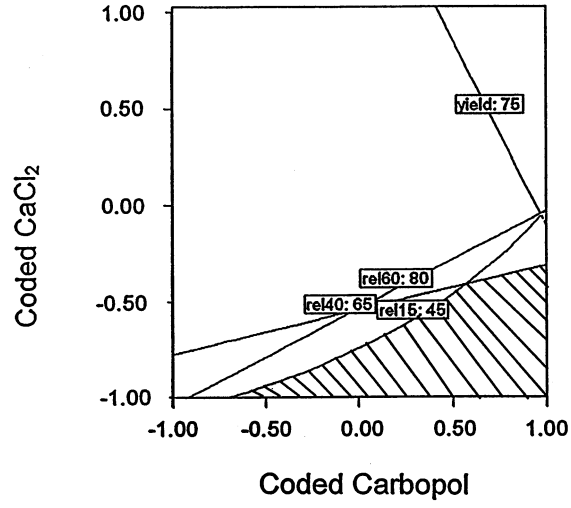

Fig. 6. Graphic optimization of formulation and process variables. For this plot, the water level and spheronizer time were fixed at the highest level and the spheronizer speed was at its lowest level.

Acknowledgements

Chlorpheniramine maleate was a gift from Warner Lambert Co./Parke-Davis, Morris Plains, NJ. The authors gratefully acknowledge Troy Corrigan of Hoechst Marion Roussel, Inc. for instruction in the image analysis technique, and Hoechst Marion Roussel, Inc. for allowing access to their facilities. This work was supported in part by a grant from BFGoodrich Company.

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