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Controlled release pellets by extrusion-spheronization

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Abstract

A radial basket-type extruder and a serrated plate spheronizer were used to prepare spherical pellets with inherent modified-release properties. A Box-Behnken response surface experimental design was employed to address the effects of altering the concentrations of Eudragit RS 30 D, Avicel RC-591, fumaric acid, and acetyltributyl citrate on pelletization of a low density drug. Response surfaces were adequately described by quadratic equations which also contained significant interaction terms. Optimum ingredient concentrations were selected from the response surface equations and validated in subsequent experiments. The models successfully predicted formulation requirements for meeting selected acceptance criteria. Controlled release pellets were produced that met dissolution specifications without subsequent coating.

Key words: Controlled release; Extrusion; Spheronization; Optimization; Pellet

1. Introduction

The objective of this study was to develop high dose pellets with inherent modified release characteristics, without subsequent controlled release coating. Extrusion-spheronization technology was chosen to achieve the objective. Pellet production by extrusion-spheronization was described previously (Conine and Hadley, 1970; Reynolds, 1970; Woodruff and Nuessle, 1972). Attempts have been made to produce slow release pellets by this technology without subsequent coating with limited success. Different Avicel® products (O'Connor and Schwartz, 1985), blends of Avicel products (Ghali et al., 1989a), Avicel and waxes (Ghali et al., 1989b) and a series of release retarding materials (Briquet et al., 1986) were incorporated into pellet formulations to slow drug release. Bioavailability studies of hydrochlorothiazide pellet formulations consisting of Avicel RC-581 (contains 11% NaCMC) did not suggest slow release in vivo (Herman et al., 1988). Incorporation of waxes into a microcrystalline cellulose matrix (Ghali et al., 1989a) resulted in faster release due to matrix interruption. Thermal treatment of the pellets resulted in sustained drug release. Drug

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loading in these cases was low (10%). Several materials failed to retard drug release (Briquet et al., 1986). Carnuba wax was an exception, but was effective only at low drug concentrations. Chitosan and Avicel RC-591 were used as matrix materials for retarding drug release (Goskonda and Upadrashta, 1992). Polymeric dispersions, Aquacoat ECD 30 and Eudragit RS 30 D, were used in combination with Avicel PH-101 or Avicel RC-591 (Goskonda et al., 1992) using acetaminophen and ibuprofen as model drugs. Ibuprofen release was significantly retarded at low drug loading (10%) with higher amounts of polymeric dispersion. Avicel RC-591 aided successful spheronization at higher drug loads and with greater amounts of polymeric dispersions. Bianchini et al. (1992) reported that the release of indobufen could be modified using combinations of pH adjusters and polymeric dispersions with Avicel PH-101 as the spheronizing aid. The extent of slow release was limited (80% in 4 h). A few patents (Heafield et al., 1989; Joshi et al., 1989; Valorose et al., 1989; MacFarlane et al., 1990) also dealt with similar situations.

In the present study, the model drug is zwitterionic (isoelectric point ~ pH 5.5), poorly water soluble, and has low bulk density. Preliminary experiments suggested that sustained release at higher drug loading could be achieved by developing a polymeric pellet matrix and modifying its microenvironmental pH to minimize drug solubility. Screening experiments were conducted according to a Plackett-Burman screening design to isolate critical variables (Goskonda et al., 1994). These experiments were designed to explore the effects of two polymeric dispersions, Aquacoat ECD-30 and Eudragit RS 30 D, on drug release from pellet formulations. Other factors studied were acid type (fumaric acid and succinic acid), acid concentration, plasticizer content (acetyltributyl citrate), and residence time in the spheronizer. The results from these experiments suggested that acid concentration, polymeric dispersion type and concentration, and spheronizing time significantly influenced drug release. Eudragit RS 30 D retarded drug release more than Aquacoat ECD-30 at the tested levels. Inferences from these studies were used to establish the process variable set points and formulation ingredient ranges in the current experiments.

2. Materials and methods

Microcrystalline cellulose (Avicel RC-591, FMC Corp., Philadelphia, PA) was used as the primary spheronizing aid. Eudragit RS 30 D (Rohm Pharm. Tech., Malden, MA) was the polymeric dispersion used in this study. Fumaric acid (Pfizer, New York, NY) was used to alter the pH of the microenvironment. Acetyltributyl citrate (Morflex Chemical Co., Inc., Greensboro, NC) was used as a plasticizer. The model drug (MDL 201,040, Marion Merrell Dow Inc., Kansas City, MO) is zwitterionic (isoelectric point ~ 5.5) and was supplied as a fine powder with a mean diameter of 10–15 μm. It is poorly soluble in water and common alcohols and has low bulk density (0.18–0.21 g/cm^3).

The dry components of each formulation were blended in a planetary mixer (Hobart N-50, Hobart Corp., North York, Ontario) at low speed for 2 min. The required amount of plasticized Eudragit RS 30 D was added to the dry blends. After 1 min of mixing, additional amounts of deionized water were added and mixing continued for an additional 4 min to produce wet granulations. [Additional amounts of water were needed for successful spheronization following extrusion. The diversity of formulation components made it difficult to predict the optimum amount of water for successful completion of the extrusion-spheronization process. The amount of water added (in addition to water from the Eudragit RS 30 D dispersion) was left to the formulator's discretion. When acceptable (spherical) pellets were not obtained, the water content was adjusted, and the batch repeated.] Each wet granulation was passed through a radial basket extruder (Nica Model E-140, Niro-Aeromatic Inc., Columbia, MD) using a 1.2 mm screen with constant feeder (80 rpm) and extruder (30 rpm) speeds. The extrudate was immediately processed in a spheronizer (Nica Model S-320, Niro-Aeromatic Inc., Columbia, MD) at 900 rpm for 15 min. Pellets were dried in a hot air oven at

50°C for 48 h. Each batch size was 0.5 kg and the order of manufacture was random.

In vitro dissolution studies (USP Method II) were performed on pellets from the 14/20 mesh fraction in pH 7.5 phosphate buffer at 100 rpm. Samples were analyzed by UV spectroscopy. Capsule fill weights were determined by hand filling 14/20 mesh pellets into size '0' capsules and calculating the amount of drug using its theoretical fraction for each formulation.

2.1. Experimental design

Prior screening experiments (Goskonda et al., 1994) suggested that acid concentration, polymeric dispersion type and concentration, and spheronizing time significantly influenced drug release. Spheronizer speed, spheronizing time, and batch size are variables that interact and are recommended for further study during scale-up operations. The present work describes investigations on the formulation variables Eudragit RS 30 D, fumaric acid, Avicel RC-591, and acetyltributyl citrate (Table 1). Drug content was used as a float variable, as it did not show a significant effect on responses studied earlier.

A 27-run Box-Behnken design consisting of these four variables at three levels was established using PC-based software (Statgraphics®, Manugistics, Inc., Rockville, MD). Analysis of the data obtained from the design generates a mathematical model with quadratic terms describing non-linear responses. This Box-Behnken design also allows resolution of 2-factor interactions from the main effects of individual variables.

Table 1
Box-Behnken design (randomized)

Run	% Eudragit	% fumaric acid	% Avicel	% plasticizer (ATBC)
1	20	2.5	26.5	0.5
2	20	2.5	30.0	0.0
3	20	4.0	23.0	0.5
4	18	4.0	26.5	0.5
5	20	2.5	23.0	0.0
6	20	1.0	23.0	0.5
7	20	4.0	30.0	0.5
8	18	2.5	26.5	1.0
9	22	2.5	23.0	0.5
10	20	4.0	26.5	0.0
11	22	1.0	26.5	0.5
12	18	2.5	30.0	0.5
13	20	2.5	23.0	1.0
14	20	2.5	26.5	0.5
15	20	1.0	30.0	0.5
16	20	4.0	26.5	1.0
17	22	2.5	26.5	0.0
18	22	4.0	26.5	0.5
19	20	2.5	30.0	1.0
20	20	1.0	26.5	0.0
21	18	2.5	26.5	0.0
22	18	2.5	23.0	0.5
23	18	1.0	26.5	0.5
24	22	2.5	26.5	1.0
25	20	1.0	26.5	1.0
26	22	2.5	30.0	0.5
27	20	2.5	26.5	0.5

3. Results and discussion

Avicel RC-591 allowed the addition of greater amounts of polymeric dispersions and high drug loads while successfully producing spherical pellets. The use of Eudragit RS 30 D as a polymeric matrix and fumaric acid to modify the microenvironmental pH successfully retarded drug release.

Results from the Box-Behnken design are listed in Table 2. Each data point is an average of at least three observations. A typical ANOVA table for % dissolved in 2 h is presented in Table 3. This table indicates that changes in Eudragit, fumaric acid, and plasticizer concentrations have significant effects on the percent dissolved in 2 h. It also suggests the importance of certain interactions (Avicel × Eudragit and plasticizer × Eudragit) and quadratic (fumaric acid, plasticizer, and Eudragit) terms. The data were analyzed using a backward stepwise regression (SAS Institute, Boston, MS) and the following response surface equations were generated. Interaction terms are designated as the product of two factors (e.g., *EA* = Eudragit RS 30 D × Avicel RC-591).

Table 2
Results from the Box-Behnken design

Run	% dissolved in 1 h	% dissolved in 2 h	% dissolved in 4 h	% dissolved in 8 h	capsule fill weight (mg)
1	32.4	46.9	66.7	88.5	255.70
2	31.3	46.1	66.4	88.4	253.02
3	29.6	42.9	61.8	84.8	269.50
4	32.6	47.8	69.4	91.5	264.69
5	30.5	44.7	63.8	86.0	299.57
6	37.1	53.5	73.6	93.2	280.65
7	30.8	45.4	66.7	89.7	239.94
8	35.6	52.1	73.7	93.7	258.96
9	28.1	40.8	58.5	80.6	271.09
10	31.4	46.4	67.5	90.0	274.56
11	35.0	50.6	70.6	91.1	259.83
12	33.8	50.0	71.3	92.8	269.34
13	32.9	47.8	68.0	89.8	289.26
14	28.9	42.0	60.4	83.3	257.55
15	36.8	54.1	75.4	95.1	253.82
16	31.5	45.9	66.4	89.1	261.58
17	26.8	39.6	57.4	79.5	260.84
18	27.1	39.9	58.3	81.6	259.13
19	32.4	48.0	69.0	90.5	247.23
20	38.0	55.4	76.3	95.3	280.18
21	36.4	53.5	75.3	95.1	287.08
22	36.9	53.5	74.9	94.5	294.93
23	42.1	60.3	81.1	98.2	282.78
24	30.9	44.5	63.3	85.1	239.20
25	40.7	58.6	79.3	97.0	264.71
26	30.3	44.2	63.4	85.6	240.00
27	31.0	45.0	64.5	87.9	254.18

Table 3
ANOVA for % dissolved at 2 h

Effect	Sum of squares	DF	Mean Sq.	F ratio	P value
A Eudragit concentration	275.5208	1	275.5208	128.05	0.0000
B fumaric acid concentration	344.5408	1	344.5408	160.12	0.0000
C Avicel concentration	1.7633	1	1.7633	0.82	0.3926
D plasticizer concentration	10.4533	1	10.4533	4.86	0.0478
AB	0.9025	1	0.9025	0.42	0.5362
AC	11.9025	1	11.9025	5.53	0.0366
AD	9.9225	1	9.9225	4.61	0.0529
BC	0.9025	1	0.9025	0.42	0.5362
BD	3.4225	1	3.4225	1.59	0.2312
CD	0.3600	1	0.3600	0.17	0.6940
AA	7.7870	1	7.7870	3.62	0.0814
BB	94.4537	1	94.4537	43.9	0.0000
CC	1.31120	1	1.31120	0.61	0.4583
DD	20.1934	1	20.1934	9.38	0.0098
Total error	25.8208	12	2.1517		
Total (corr.)	788.7918	26			
	$r^2 = 0.967$		$r^2 = 0.93$ (adjusted for degrees of freedom)		

Table 4
Significant results summary from the Box-Behnken design

Variable	% dissolved (1 h)	% dissolved (2 h)	% dissolved (4 h)	% dissolved (8 h)	cap fill weight
Eudragit concentration	+++0	+++0	+0	+0	+
Fumaric acid concentration	+++	+++	+++	+++	+
Avicel RC-591 concentration	+0	+0	+0	+0	+
Plasticizer concentration	+++0	+++0	+++0	+++0	+

+, linear term significant; ++, quadratic term significant; +++, linear and quadratic terms significant; 0, interaction term(s) significant.

% dissolution (1 h)

$$= 264.75 - 14.66E - 8.99F - 3.78A - 27.26P + 0.19EA + 1.23EP + 0.19E^2 + 1.28F^2 + 4.36P^2 \quad (r^2 = 0.94)$$

% dissolution (2 h)

$$= 361.76 - 20.14E - 12.56F - 4.82A - 36.76P + 0.25EA + 1.58EP + 0.26E^2 + 1.8 \times F^2 + 7.12P^2 \quad (r^2 = 0.94)$$

% dissolution (4 h)

$$= 322.11 - 12.074E - 13.66F - 5.8A - 43.3P + 0.30EA + 1.88EP + 1.99F^2 + 7.97P^2 \quad (r^2 = 0.92)$$

% dissolution (8 h)

$$= 291.73 - 9.81E - 10.37F - 4.47A - 38.98P + 0.24EA + 1.75EP + 1.59F^2 + 5.8P^2 \quad (r^2 = 0.90)$$

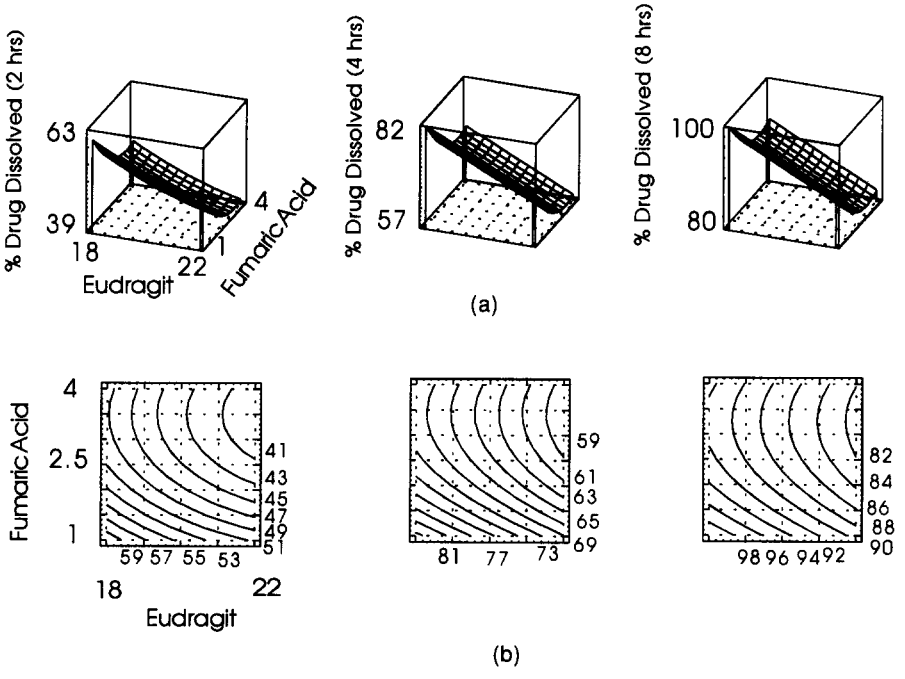

Fig. 1. Estimated response surface (a) and contour plots (b) for % drug dissolved in 2, 4 and 8 h. Constants: Avicel RC-591 = 26.5%; plasticizer (ATBC) = 0.5%.

capsule fill weight (mg)

$$= 514.33 - 5.32E - 2.92F - 4.8A - 15.72P \quad (r^2 = 0.78)$$

where E is the Eudragit RS 30 D concentration and F, P, and A denote concentrations of fumaric acid, plasticizer, and Avicel RC-591, respectively.

The residuals were examined after model development to ensure random distribution. The four variables studied significantly influenced dissolution. The linear, quadratic, and interaction effects of each variable on the responses studied are summarized in Table 4. Response surfaces were plotted for each response using the PC-based Statgraphics program. In Fig. 1, response surfaces (a) and corresponding contour plots (b) show the relationship between the amounts of drug dissolved and amounts of Eudragit and fumaric acid in the formulation. These figures were plotted at constant levels of Avicel RC-591 and plasticizer. These plots show that increasing amounts of Eudragit decrease drug released. Medium amounts of fumaric acid have the greatest effect on retarding the amount of drug dissolved. The plots clearly show the curved relationship between the amount of drug released and the level of fumaric acid used in the formulation.

Since all four variables are included in the regression equations for each response, the plots have been generated for two of the variables, then embedded on axes representing the other two variables. This presentation allows visualization of the changing response surfaces across all four variables (Fig. 2–5). The plots (Fig. 2–4) show that increasing amounts of Eudragit retard drug release. Moving up the column, increasing amounts of plasticizer increase drug release, especially at higher Eudragit concentrations. Larger amounts of Avicel RC-591 at lower concentrations of Eudragit do not influence the amount of drug dissolved. At higher concentrations of Eudragit, increasing Avicel RC-591 increases the amount of drug released. This effect is more pronounced at later dissolution times (4 and 8 h). Overall, high fumaric acid concentrations de-

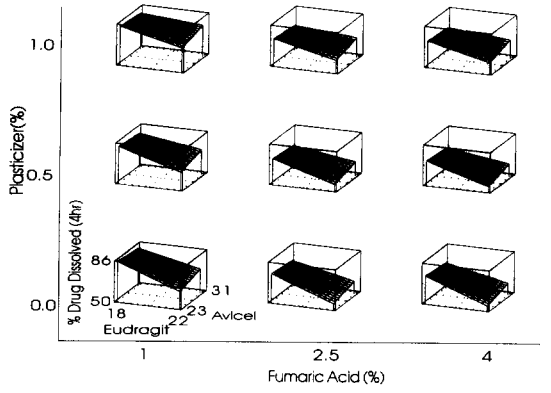

Fig. 3. Estimated response surface plots for % drug dissolved in 4 h.

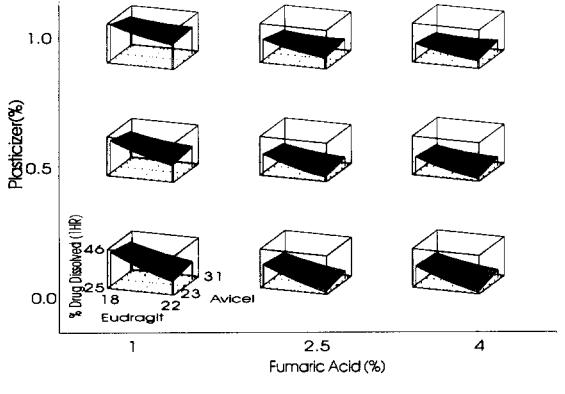

Fig. 2. Estimated response surface plots for % drug dissolved in 1 h.

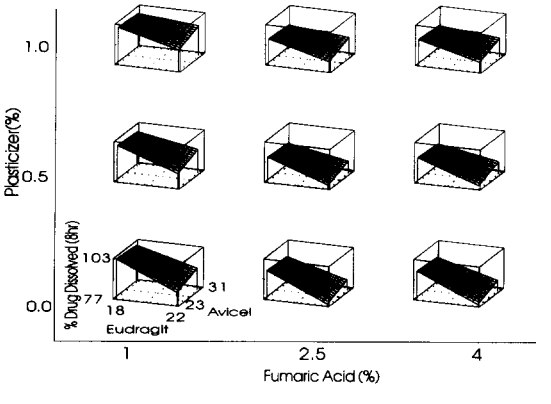

Fig. 4. Estimated response surface plots for % drug dissolved in 8 h.

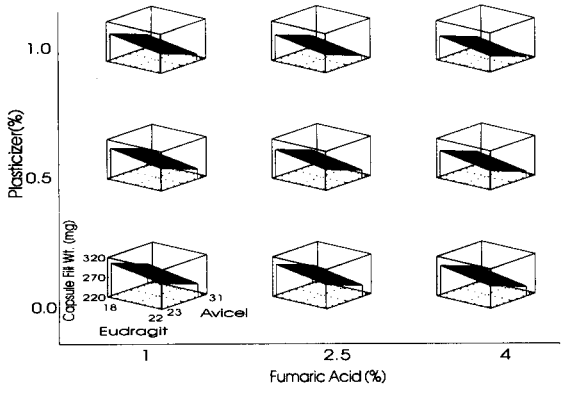

Fig. 5. Estimated response surface plots for capsule fill weights (mg).

crease drug release. In the plot of capsule fill weight (Fig. 5), increasing amounts of all formulation components decreased the net capsule fill weights. This was expected, since the drug was used as float variable in the design. Increasing levels of any other ingredient necessarily decreased the drug content.

Table 5
Experimental runs performed to test the models for lack-of-fit

		Eudragit concentration	Fumaric acid concentration	Avicel RC-591 concentration	Plasticizer concentration
Test 1	(trial 1)	21.8	3.7	24.3	0.2
	(trial 2)	21.8	3.7	24.3	0.2
Test 2	(trial 1)	20.5	3.0	27.0	0.7
	(trial 2)	20.5	3.0	27.0	0.7

3.1. Model testing

To test the empirical mathematical models for lack-of-fit, two additional formulations were prepared in duplicate (Table 5). The formulation

Table 6
Predicted vs actual responses

Test		% dissolved (1 h)	Predicted	95% CI
Test 1	(trial 1)	28.03	28.60%	26.5 –30.7%
	(trial 2)	25.70		
Test 2	(trial 1)	30.60	32.43%	30.35–34.5%
	(trial 2)	29.80		
Test		% dissolved (2 h)	Predicted	95% CI
Test 1	(trial 1)	40.77	39.57%	36.64–42.5%
	(trial 2)	37.55		
Test 2	(trial 1)	44.00	45.34%	42.41–48.27%
	(trial 2)	45.05		
Test		% dissolved (4 h)	Predicted	95% CI
Test 1	(trial 1)	58.80	53.44%	49.52–57.36%
	(trial 2)	54.45		
Test 2	(trial 1)	64.45	61.55%	57.63–65.47%
	(trial 2)	65.40		
Test		% dissolved (8 h)	Predicted	95% CI
Test 1	(trial 1)	82.73	79.85%	76.54–83.16%
	(trial 2)	77.35		
Test 2	(trial 1)	87.25	86.64%	83.33–89.95%
	(trial 2)	87.65		
Test		Capsule fill weight (mg)	Predicted	95% CI
Test 1	(trial 1)	270.8	267.8 mg	251.9–283.7
	(trial 2)	268.8		
Test 2	(trial 1)	271.9	255.9 mg	240–271.8
	(trial 2)	274.9		

Table 7
Sort criteria for determining the optimum formulation

Sort priority	Response	Acceptance level
1	capsule fill weight	≥ 250 mg
2	% dissolved (2 h)	35–45%
3	% dissolved (4 h)	60–90%
4	% dissolved (8 h)	≥ 85%

variable set points for these experiments were different from any of the Box-Behnken design points, but were within the experimental space. These experiments were conducted before the analyses of the Box-Behnken results. Nearly all responses were within the acceptable ranges at the 95% confidence interval (Table 6). These results were satisfactory.

3.2. Optimization

In order to predict results using the models developed, a 'do loop' was created in SAS to solve the prediction equations at 8–10 nested levels of each variable, equally spaced across the experimental range. These calculations resulted in a response matrix containing 8000 data points representing the four-dimensional response surface of the entire factor space. The data were sorted using the criteria in Table 7. About 325 of these 8000 data points met all four criteria. Formulation set points from these 325 points were evaluated and found to be normally distributed. The mean set points were calculated to obtain a set of optimum formulation conditions, providing the best compromised fit to all results (Table 8). The predicted (optimized) formulation is different from the experimental runs of the Box-Behnken design, but is within the experimental space. Two batches using the optimum formulation were subsequently manufactured and the pellets were evaluated for dissolution profiles and capsule fill weights. Results compare favorably with predictions (Table 9).

Table 8
Predicted optimum formulation using sort criteria (set of 325 points)

Statistics	Eudragit	Avicel RC-591	Fumaric acid	Plasticizer (ATBC)
Mean	20.50	25.80	3.40	0.40
Standard deviation	0.32	1.76	0.43	0.25
Standard error	0.02	0.39	0.08	0.13
Median	20.50	25.80	3.40	0.40

Table 9
Predicted and observed results using the optimized formulation

Response	Predicted	Observed (trial 1) ($n = 3$)	Observed (trial 2) ($n = 3$)
Capsule fill weight (mg)	265.1	268.8	266.8
% dissolved (1 h)	31.8	30.00	28.83
% dissolved (2 h)	44.5	43.23	41.69
% dissolved (4 h)	60.8	61.67	60.03
% dissolved (8 h)	85.9	85.87	83.84

4. Conclusions

Pellets with acceptable dissolution profiles were successfully produced, confirming that the concept of producing controlled release pellets without subsequent coating is feasible. Experiments conducted using statistical designs and data analysis allowed the generation of mathematical models which adequately described the release behavior in terms of the levels of the four formulation ingredients studied. Both Eudragit RS 30 D and fumaric acid, at high concentrations, predictably retarded drug release. Optimized formulation concentrations were confirmed in subsequent experiments. The results indicated that moderately high drug concentrations (50% loading) with Eudragit RS 30 D, fumaric acid, and Avicel RC-591 would yield a product with desirable dissolution characteristics without subsequent coating. This process could be cost effective compared to conventional pelletization and overcoating to produce controlled release pellets.

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