Aqueous Ethylcellulose Dispersion of Ethylcellulose. I. Evaluation of Coating Process Variables

Nilesh H. Parikh,[1,2] Stuart C. Porter,[3] and Bhagwan D. Rohera[1,4]

Received May 4, 1992; accepted September 19, 1992

Formulation and process variables play an important role in the film-forming properties of coating polymers. Three selected independent coating process variables, namely, percent solids content in the coating polymeric dispersion, inlet-air temperature, and spray rate of the polymeric dispersion, were investigated in this study to determine their effect on the performance characteristics of tablets coated with a plasticized aqueous ethylcellulose dispersion (Surelease) in a fluid-bed equipment. Response surface methodology (RSM) was utilized to study the complex relationship between these process variables and selected response variables. Three response variables were considered, namely, rate of drug release from the "untreated" coated tablets and the "thermal-treated" coated tablets and microindentation hardness of the untreated coated tablets. A 12-point factorial experimental design was utilized, and three-dimensional (3-D) response surface plots were generated using a second-order polynomial model. The model provided information needed to predict optimal process conditions. Drug release from the coated tablets followed zero-order kinetics. Inlet-air temperature was found to be the most critical process variable for all the three response variables studied. A correlation was observed between the drug release rate and the microindentation hardness of the applied polymeric coat in the case of untreated coated tablets. The 3-D response surface plots indicated that lower rates of drug release from the coated tablets may be obtained by using high inlet-air temperature and low spray rate of the polymeric dispersion during coating.

KEY WORDS: factorial experimental design; response surface methodology (RSM); ethylcellulose; Surelease; ibuprofen; fluid-bed coating; latex film; microindentation hardness; zero-order drug release.

INTRODUCTION

Ethylcellulose is widely used as a dissolution rate-controlling polymer in sustained-release dosage forms (1). While coating with organic polymeric solutions is still widespread, aqueous polymeric dispersions (latexes or pseudolatexes) have drawn much attention due to problems associated with the former coating systems, e.g., high solvent costs, explosion hazards, potential toxicity, and strict air-quality controls set by the EPA (2). As a result, latexes of acrylic polymers (Eudragit by Rohm Pharma) were introduced in the early seventies (3). Later, emulsion/solvent evaporation and phase inversion techniques were utilized to manufacture two pseudolatexes based on ethylcellulose (4,5). These dispersions are widely used to develop coated controlled-release dosage forms (6–14).

Although aqueous coating technology has been known for some time now, the factors affecting film formation from aqueous polymeric dispersions are still not well understood because film formation from these systems is a complex phenomenon (15,16). Drug release from latex-coated dosage forms is strongly affected by variables which influence coalescence of the polymer particles and hence the film formation process (9,10). The effect of process variables, such as coating temperature (11,12), curing conditions (7,12,13), plasticization time (14), and formulation variables, such as type and level of plasticizer (4), and surfactant level (12), must be investigated in order to obtain predictable and reproducible drug release profiles from coated dosage forms. The complex behavior of aqueous coating systems and the multitude of formulation and process variables that may influence this behavior dictate that their effects should be appropriately investigated so that process and formulation optimization can be achieved.

While the need for a curing step has been suggested in the case of dispersion-based coating systems (8,17), no systematic study using an optimization technique has yet been reported which focuses on the effect of product-bed temperature on the performance characteristics of the applied film. Response surface methodology (RSM) has proven to be a useful tool for handling such problems in the area of pharmaceutical product development (18,19). RSM allows the formulator to approximate the true system behavior as a function of the formulation and process variables and to determine the apparent optimal conditions. The use of three-dimensional (3-D) response surface plots allows understanding of the behavior of the system by demonstrating the contribution of independent variables as well as their interactions. These plots also graphically depict maxima and minima in the responses.

The objective of this research was to investigate the effect of three independent coating process variables on the performance characteristics of tablets coated with a commercially available plasticized aqueous ethylcellulose dispersion (Surelease/E-7-7060) and to predict optimal process conditions for coating in a fluid-bed equipment. The three coating process variables selected for the study were percent solids content in the coating polymeric dispersion, inlet-air temperature, and spray rate of the polymeric dispersion since they are likely to have a strong influence on the product-bed temperature and, therefore, possibly on the performance of the coating.

EXPERIMENTAL DESIGN

Factorial experimental design enables the influence of individual variables (main effects) and their interactions to be evaluated simultaneously while using a minimum number of experiments (20). This method has been extensively used in pharmaceutical product development and clinical research (19). On the other hand, central composite design is based on factorial designs with additional points added to estimate the curvature of the respose surface. The model used is typically a second-order polynomial (21).

[1] College of Pharmacy & Allied Health Professions, St. John's University, Grand Central & Utopia Parkways, Jamaica, New York 11439.

[2] Present address: Pharmacy Research and Development, Berlex Laboratories, Inc., Wayne, New Jersey 07470.

[3] Colorcon, West Point, Pennsylvania 19486.

[4] To whom correspondence should be addressed.

0724-8741/93/0400-0525$07.00/0

In the present study, commercially available computer software (ECHIP, Echip, Inc., Hockessin, DE) was used to generate a standard factorial design, perform regression analysis, and generate 3-D response surface plots. The nonrandomized design layout which includes three replicates is shown in Table I. The independent variables considered in this study are also described in this table along with the translation of their coded levels to the experimental conditions. The design was randomized using the software before its execution. A second-order regression model was developed for the various responses in the form shown below:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{33}X_3X_3 \quad (1)$$

where Y_i is the level of response, b_{ij} is the regression coefficient, and X_i is the coded level of the independent variables.

The response variables used to characterize the effect of process variables were the rates of drug release from the coated tablets and the microindentation hardness of the applied polymeric film coat. A standard ECHIP effects table was generated for each response variable to determine the significance of independent variables and to detect the lack-of-fit of a second-order polynomial model. The predictive capability of the model was verified by comparing the predicted and the observed values of the response variable (drug release rates) using experimental conditions that had not been used for the model development.

Table I. ECHIP Standard Factorial Design

	Independent variables in coded form		
Expt No.	Dispersion solids content (X_1)	Inlet-air temperature (X_2)	Spray rate (X_3)
1	−1	−1	−1
2	−1	+1	−1
3	−1	+1	+1
4	+1	+1	+1
5	−1	−1	+1
6	+1	+1	−1
7	+1	−1	+1
8	+1	−1	−1
9	0	−1	0
10	0	0	−1
11	−1	0	+1
12	+1	0	+1
1	−1	−1	−1
2	−1	+1	−1
3	−1	+1	+1

	Level		
Independent variable	Low (−1)	Medium (0)	High (+1)
X_1: dispersion solids content (%, w/w)	5.0	12.5	20.0
X_2: inlet-air temperature (°C)	30	50	70
X_3: spray rate (g/min)	2	6	10

MATERIALS AND METHODS

Materials

Aqueous ethylcellulose dispersion plasticized with glyceryl tricaprylate/caprate (Surelease/E-7-7060) and plasticized hydroxypropyl methylcellulose concentrate (Opadry/YS-1-7006) (Colorcon, West Point, PA), ibuprofen, USP (Ethyl Corp., Baton Rouge, LA), polyvinylpyrrolidone (PVP K29-32, GAF Corp., Wayne, NJ), lactose fast flow, NF (Foremost Whey Products, Baraboo, WI), microcrystalline cellulose, NF (Avicel PH 102, FMC Corp., Philadelphia, PA), and magnesium stearate, USP (Mallinckrodt, Inc., St. Louis, MO), were used as received. All other chemicals were of reagent grade.

Preparation of Ibuprofen and Placebo Tablets

Ibuprofen tablets were prepared by a wet granulation method. Ibuprofen and lactose were mixed together and wet granulated using a 5% (w/w) aqueous solution of PVP in a KitchenAid mixer. The wet mass was passed through a 12-mesh screen by hand and dried in a forced-air oven at 40°C. The dried granules were then milled using a homoloid mill (Model J, The Fitzpatrick Co., Elmhurst, IL) equipped with a No. 2 plate and knives forward configuration. The milled granulation was lubricated with 0.5% (w/w) magnesium stearate for 3 min. The final blend consisting of 60% ibuprofen, 38.5% lactose, 1% PVP, and 0.5% magnesium stearate was then tableted using a partially tooled (4 stations only) 16 stations rotary press (Stokes, Model B-2, Stokes-Merrill, Inc., Bristol, PA) equipped with plain 13/32-in. deep concave punches. The tablet weight was adjusted to yield 200 mg of the drug per tablet. The targeted hardness, determined using a Schleuniger tablet hardness tester (Model 2E-106, Vector Corp., Marion, Iowa), was 8–10 kP. The tablets were then coated using process conditions listed in Tables II and III and used for drug release studies.

Flat-faced tablets of ibuprofen were also prepared for the determination of microindentation hardness of the applied polymeric film coat as a function of the selected process variables. The flat-faced tablets of the same formulation that was tableted on the Stokes press were compressed on a Carver press fitted with a 7/16-in. punch and die set. Tablets weighing 400 mg were compressed at an applied force of 3000 lb and dwell time of 1 sec.

Table II. Coating Conditions for Seal Coating

Parameter	Setting
Batch size[a]	350 g
Nozzle size	0.8 mm
Orifice plate	Type D
Inlet-air flap setting	80–95%
Air atomization	1.5 bar
Spray rate	5–6 g/min
Inlet-air temperature	50°C
Outlet-air temperature	31–33°C
Percent solids content in the dispersion	5% (w/w)
Percent weight increase or coat	2% (w/w)

[a] Deep convex and 200 flat-faced ibuprofen tablets.

Table III. Coating Conditions for Sustained-Release Coating

Parameter	Setting
Batch size	265 g
Nozzle size	0.8 mm
Orifice plate	Type D
Inlet-air flap setting	80–95%
Air atomization	1.5 bar[a]
Spray rate	Variable
Inlet-air temperature	Variable
Outlet-air temperature	Monitored
Percent solids content	Variable
Percent weight increase or coat	3% (w/w)[a]

[a] The values were selected on the basis of the results of preliminary studies.

To conserve the drug, ibuprofen tablets (deep convex and flat-faced) were marked with a water-insoluble ink for ease of separation after the coating operation and mixed with placebo tablets for each coating run. Placebo tablets were prepared by direct compression. Microcrystalline cellulose and lactose were blended in a 0.5-ft^3 twin-shell blender (Patterson Kelly Co., Stroudsburgh, PA) for 15 min followed by blending with 0.5% (w/w) magnesium stearate for 3 min. The final blend was then compressed similarly as ibuprofen tablets.

Coating Formulation and Tablet Coating

The coating formulations were prepared by diluting the plasticized aqueous ethylcellulose dispersion (Surelease) with purified water to the desired percent solids content prior to tablet coating. The diluted dispersions were mechanically stirred for at least 30 min before use for coating, and the stirring was continued during the process.

Tablet coating was carried out in a laboratory-size fluid-bed equipment (Uniglatt, Glatt Air Techniques, Inc., Ramsey, NJ) fitted with a 6-in. Wurster insert. A Masterflex peristaltic pump was used to deliver the polymeric dispersion. Outlet-air temperature was monitored and recorded for each coating experiment.

Seal Coating. A freshly prepared 5% (w/w) aqueous solution of plasticized hydroxypropyl methylcellulose concentrate (Opadry) was used as a seal coat. Before the application of the polymeric dispersion (Surelease), a seal coat was applied to the ibuprofen tablets in order to prevent blocking phenomenon observed in the initial studies. The occurrence of blocking seemed to be related to an interaction between the drug and the polymeric dispersion during application. A 350 g batch of core ibuprofen tablets (deep convex and 200 flat-faced) was seal-coated to a theoretical weight gain of 2% (w/w). The relevant coating parameters are listed in Table II.

Sustained-Release Coating. The polymeric coating (Surelease) was applied to the previously seal-coated tablets (representing a mixture of both convex and flat-faced ibuprofen tablets, and placebo tablets) using the process parameters listed in Table III. The tablets were coated to a theoretical weight gain of 3% (w/w). In order to study the effect of each process variable on the rate of drug release from the coated tablets, no further curing step was conducted after the coating was completed.

Storage and Conditioning of Tablets

Owing to the transparency of the sustained release coat, the ink-marked ibuprofen tablets (deep convex and flat-faced) were easily identified and separated after the coating was completed. The coated tablets were divided into the following two groups to evaluate the effect of curing condition on drug release.

"Untreated" Tablets. A portion of the deep convex tablets along with the flat-faced tablets were stored in a desiccator at room temperature for 10 days prior to conducting drug release studies (deep convex) and microindentation hardness testing (flat-faced).

"Thermal-Treated" Tablets. The remaining coated deep convex tablets were stored at 40°C in a forced-air oven for 36 hr to study the effect of thermal posttreatment on the drug release rate. Based on preliminary studies using thermal analysis, the glass transition temperature, T_g, of the polymeric dispersion (Surelease) was observed to be 35°C (22). The selection of 40°C as the temperature for thermal posttreatment was therefore considered favorable for coalescence of the polymeric coat without imparting tackiness.

In Vitro Drug Release Studies

The *in vitro* drug release studies of the uncoated and coated (untreated and thermal-treated) tablets were performed using the standard USP/NF dissolution apparatus II (Hanson Research Corp., Northridge, CA) interfaced with a Zymate II automated dissolution testing system (Zymark Corp., Hopkinton, MA) and a UV spectrophotometer (Spectronic 601, Milton Roy, Rochester, NY). Nine hundred milliliters of simulated intestinal fluid without enzymes (phosphate buffer, pH 7.2) at 37 ± 0.5°C, as specified in the USP monograph for ibuprofen tablet dissolution test, was used as the dissolution medium. The stirring rate of the paddle was 50 rpm. Due to the relatively higher solubility of ibuprofen in a pH 7.2 medium compared to that in a pH 1.2 medium (23), perfect sink conditions could be maintained. Dissolution samples were withdrawn at 10, 20, 30, 45, and 60 min for the uncoated tablets and at 0.5, 1, 2, 4, 6, 8, 10, and 12 hr for the coated (untreated and thermal-treated) tablets. These samples were analyzed at 221 nm for the drug content. After the assay, dissolution samples were recirculated to their original vessels. The dissolution data represent an average of six determinations. For each dissolution profile, the cumulative amount of drug released was plotted against time using the least-squares linear regression method. The slope of each of the six regressed lines was computed and an average zero-order release rate was determined with the corresponding standard deviation.

Microindentation Hardness Testing

The microindentation hardness test was performed using an ICI pneumatic microindentation hardness apparatus [Research Equipment (London) Ltd., Hampton Hill, Middx, UK]. A sample of 10 coated flat-faced tablets was used for this measurement. The flat-faced tablets were used for this test to restrict the travel of the indenter in the vertical direction only, rather than following the curvature of the substrate which could take place with the curved surface of a

deep convex tablet. The tablets were fixed to the sample holder with a double-sided Scotch tape. A spherical indenter (1.55-mm diameter) was used for indentation under an applied load of 4 g. The indentation and relaxation periods were 1 min each. The vertical movement of the sphere was amplified by a pneumatic amplifier, and the deflections were recorded on a pneumatic chart recorder. Brinell hardness (HB) and elastic modulus (E) of a polymeric film coat can be determined from the distance traveled by the indenter into the film coat under applied load and the distance recovered by the indenter after removal of the load. A typical stress–relaxation curve is shown in Fig. 1. For the present study, only Brinell hardness values were calculated using the following equation (24):

$$HB = \frac{W}{3.147\ D\ h_1} \quad (2)$$

where HB is Brinell hardness (MPa), W is applied load (g), D is diameter of the spherical indenter (mm), and h_1 is depth of penetration under load (μm).

During these determinations, room temperature and relative humidity were controlled (at 20 ± 1°C and 60 ± 2% RH) and monitored.

RESULTS AND DISCUSSION

It has been well established that the mechanisms of film formation from organic solutions and aqueous dispersions are different (15,16). In the case of coatings applied from organic solutions, initial evaporation of the solvent leads to an increase in the concentration of the solution, resulting in increased viscosity of the sprayed film-layer, which eventually brings the polymeric chains in close proximity. Further evaporation of the solvent results in the formation of dense polymeric network providing the coating layer (15). An organic solvent-based coating formulation entails molecular dispersion of the plasticizer in the polymer, a condition which maximizes intermolecular interaction and effective plasticization. On the other hand, the mechanism of film formation from aqueous polymeric dispersions involves an entirely different sequence of events. This process involves deposition of the plasticizer-softened polymer spheres from an aqueous polymeric dispersion in the form of film on the substrate. During drying, water evaporates from the aqueous dispersion, resulting in concentration of the dispersed polymer spheres, which are moved into close contact with one another. This behavior eventually leads to the coalescence of the spheres due to deformation facilitated by capillary forces that are developed in the process and existence of appropriate thermal conditions. The coalescence of latex particles may be incomplete after the coating process and, therefore, a curing step is often recommended to ensure that a continuous, homogeneous film is obtained (10,14,16). It has been reported that employment of a curing step or use of appropriate product-bed temperature during application of the coating has a critical impact on drug release characteristics (11). Achieving complete coalescence of the pseudolatex film during the coating process itself is a key to stabilizing the drug release characteristics. It is possible to stabilize the rates of drug release from the polymeric film-coated substrates provided that optimal process and/or curing conditions are selected which are conducive to initiating the coalescence during the coating process itself.

In the present study, ibuprofen was used as a model drug. Although ibuprofen is relatively insoluble in water (25), being a weak acid it has a solubility of 7045 ± 10 mg/L at 37°C (22) in simulated intestinal fluid without enzymes (phosphate buffer, pH 7.2), which was used as the dissolution medium in this study. With the ibuprofen content of 200 mg/tablet used for *in vitro* dissolution, the total concentration of the drug in the dissolution medium at 37°C (i.e., 200 mg/900 mL) represents approx. 3% of its saturation solubility.

The dissolution data of the uncoated ibuprofen tablets

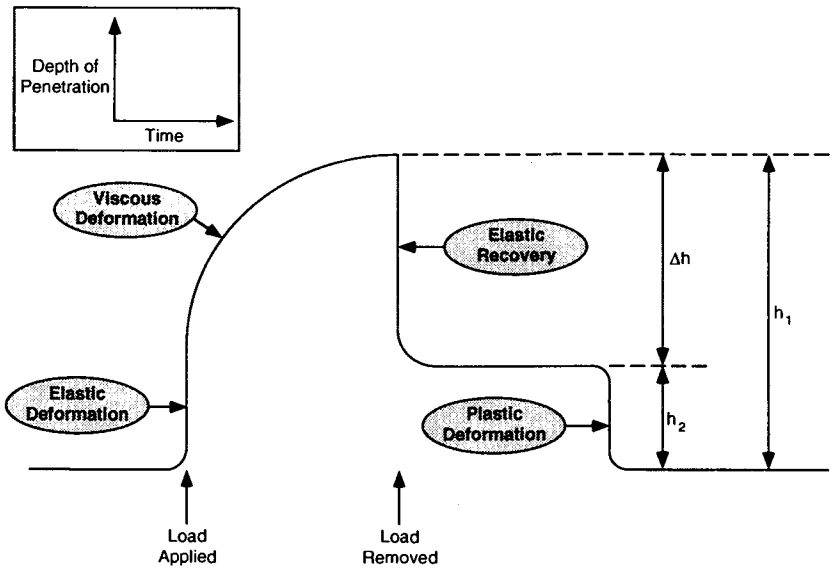

Fig. 1. A typical stress–relaxation curve. h_1 is the depth of penetration under load; h_2 is the depth of penetration after removal of the load; Δh is the recovery on removal of the load.

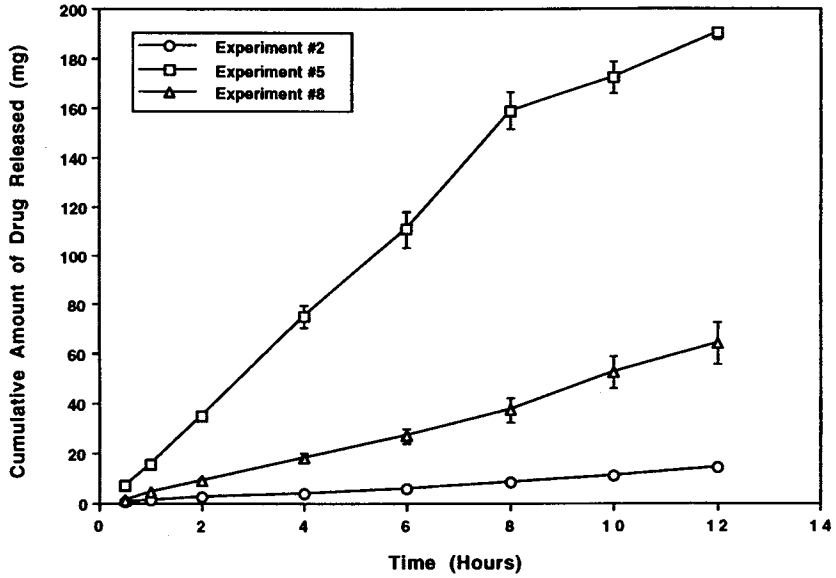

Fig. 2. Drug release profile of the "untreated" coated tablets. Process variables for the coating experiments are listed in Table I.

showed 100% drug release in less than 45 min. Since the core tablet formulation did not have a disintegrant, the tablets disintegrated and dissolved by erosion mechanism. The data in Figs. 2 and 3 illustrate drug release profiles of three lots of "untreated" and "thermal-treated" ibuprofen coated tablets, respectively. The cumulative amount of drug released exhibits a linear relationship with time. The slope of the drug release profile represents zero-order release rate of the drug from the coated tablets. Despite the difference in their slopes, these release profiles show evidence of membrane-controlled (zero-order) release mechanism. Similar release behavior has been reported earlier for dosage forms coated with aqueous polymeric dispersions (26,27). The computed zero-order release rates with the corresponding correlation coefficient values for both untreated and thermal-treated tablets, and Brinell hardness data for untreated tablets along with the outlet-air temperature for each experiment in the proposed design are given in Table IV. These data (with the exception of outlet-air temperature) were further analyzed using a second-order polynomial regression model for each of the responses to determine the significance of the independent variables. The model showed a lack-of-fit for the rate of drug release from the untreated tablets. However, there was no lack-of-fit for the remaining two response variables, i.e., rate of drug release from the thermal-treated tablets and Brinell hardness of the untreated tablets. The use of log transformation for the first response variable, i.e., rate of drug release from the untreated tablets showed no lack-of-fit.

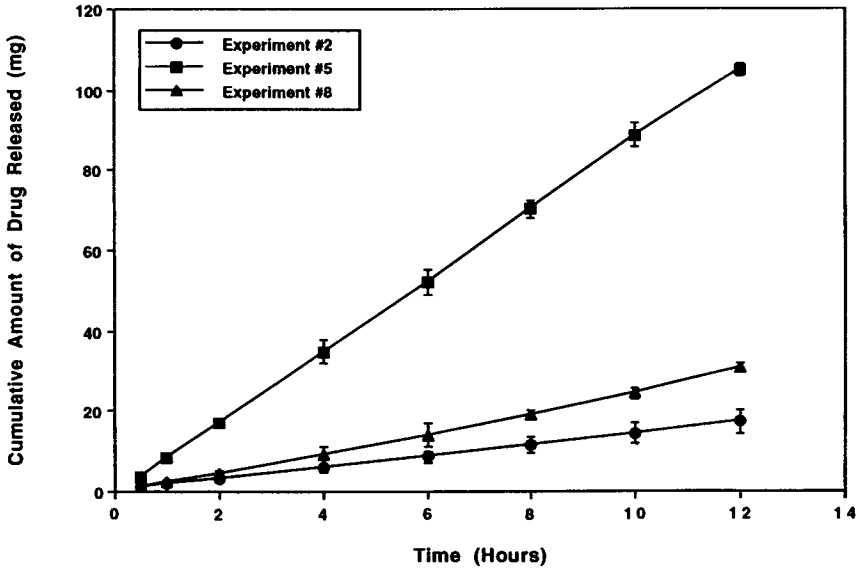

Fig. 3. Drug release profile of the "thermal-treatment" coated tablets. Process variables for the coating experiments are listed in Table I.

Table IV. Response Values and Summary of Regression Results

Expt No.	Drug release rate (mg/hr) (correlation coefficient) "Untreated" tablets (RT)	"Thermal-treated" tablets (40°C)	Brinell hardness (MPa)	Outlet air temp. (°C)
1	20.9 (0.966)	2.9 (0.998)	2.4	28
2	1.4 (1.000)	1.1 (0.988)	4.6	45
3	3.0 (0.997)	4.0 (0.999)	3.9	41
4	7.6 (0.999)	10.7 (0.987)	3.7	41
5	17.8 (0.998)	9.1 (1.000)	2.2	21
6	2.2 (1.000)	2.5 (0.999)	4.2	47
7	17.2 (0.975)	15.3 (0.975)	3.1	26
8	5.3 (0.998)	2.2 (1.000)	3.0	33
9	3.0 (0.999)	2.8 (0.999)	3.7	34
10	1.3 (0.998)	0.6 (0.994)	4.6	36
11	22.2 (0.970)	3.4 (0.998)	3.0	27
12	15.6 (0.979)	10.2 (1.000)	3.2	27
1	19.2 (1.000)	2.4 (1.000)	2.1	29
2	2.0 (0.995)	2.1 (0.984)	5.7	42
3	3.5 (0.985)	4.9 (0.995)	4.2	40

Therefore, for consistency in data analysis, log transformation was used for both release rate response variables even though the second response variable (rate of drug release from the thermal-treated tablets) showed no lack-of-fit when the pure data were used for data analysis. A summary of the final results of regression analysis is given in Table V in the form of an effects table. Unlike other statistical packages, ECHIP's effects table provides estimates of the coefficients of the polynomial model centered and scaled to the units of the independent variable. The asterisks in the "SIGRES" columns indicate the statistical significance of the corresponding effect, while the numerical values indicate the resolution of the data with respect to particular effects. Examination of the effects table (Table V) and response surfaces (Figs. 4–6) indicate phenomenon as described below under individual response variable.

Drug Release from Untreated Tablets

Asterisks in the SIGRES column in Table V for this response variable indicate that inlet-air temperature and spray rate were the significant main effects ($P < 0.01$) with the inlet-air temperature being the most critical. The two-factor interactions between percent solids content*inlet-air temperature and percent solids content*spray rate were significant ($P < 0.05$). The model had a R^2 value of 0.985, i.e., the model accounted for 98.5% of the total variation, which indicates an excellent fit.

Figures 4a–c show 3-D response surface plots for the rate of drug release from the untreated tablets using percent solids content as an off-axis variable. Higher release rates were observed for low inlet-air temperatures and high spray rates, indicating that the coating did not retard the drug release appreciably. The higher release rates may be attributed to the porous and more permeable nature of the films formed under such coating conditions where the existence of low product-bed temperature may not be conducive to optimal film formation. At product-bed temperatures lower than the glass transition temperature of the polymeric dispersion, the polymer chains are immobile, except for movements around the equilibrium position, making it very difficult for the polymer particles to coalesce. In contrast, the release rate decreased dramatically at high inlet-air temperatures and low spray rates since under these conditions, product-bed temperature (as judged from the outlet-air temperature) exceeds the glass transition temperature of the polymeric dispersion (Surelease) and, thus, induces an inherent curing effect during the coating process itself. This may be sufficient to allow the development of capillary forces needed for the deforma-

Table V. Effects Table[a]

Terms in the model	Solids content (% w/w)	Inlet air temp. (°C)	Spray rate (g/min)	Scaled coefficients of release rate of "untreated" tablets	SIGRES	Scaled coefficients of release rate of "thermal treated" tablets	SIGRES	Scaled coefficients of Brinell hardness	SIGRES
0	0	0	0	0.4496		0.2221		3.741	
1	1	0	0	−0.0555	0.2008!	0.1904	*	0.189	1.107!
2	0	1	0	−0.6375	***	−0.1676	*	1.485	**
3	0	0	1	0.3013	**	0.6287	***	−0.618	1.506
4	2	0	0	0.8312	***	0.4149	**	—	—
5	0	2	0	−0.2533	*	0.1308	0.3147	0.055	1.124!
6	0	0	2	−0.2229	*	−0.1193	0.3526	−0.247	1.544!
7	1	1	0	0.2787	**	0.1151	0.2795	−0.746	1.723
8	1	0	1	0.1762	*	0.1211	0.2788	0.143	1.075!
9	0	1	1	0.1093	0.2587	−0.0631	0.2236!	−0.392	1.347!
Residual SD				0.0937		0.1007		0.629	
Replicate SD				0.0705		0.1248		0.465	
Influence				1		0.0939		1	

[a] The term SIGRES refers to the "statistical significance and resolution" of the corresponding scaled coefficients. The sign "!" refers to the extraneous terms in the polynomial model which are statistically insignificant. (*) $P < 0.05$; (**) $P < 0.01$; (***) $P < 0.001$.

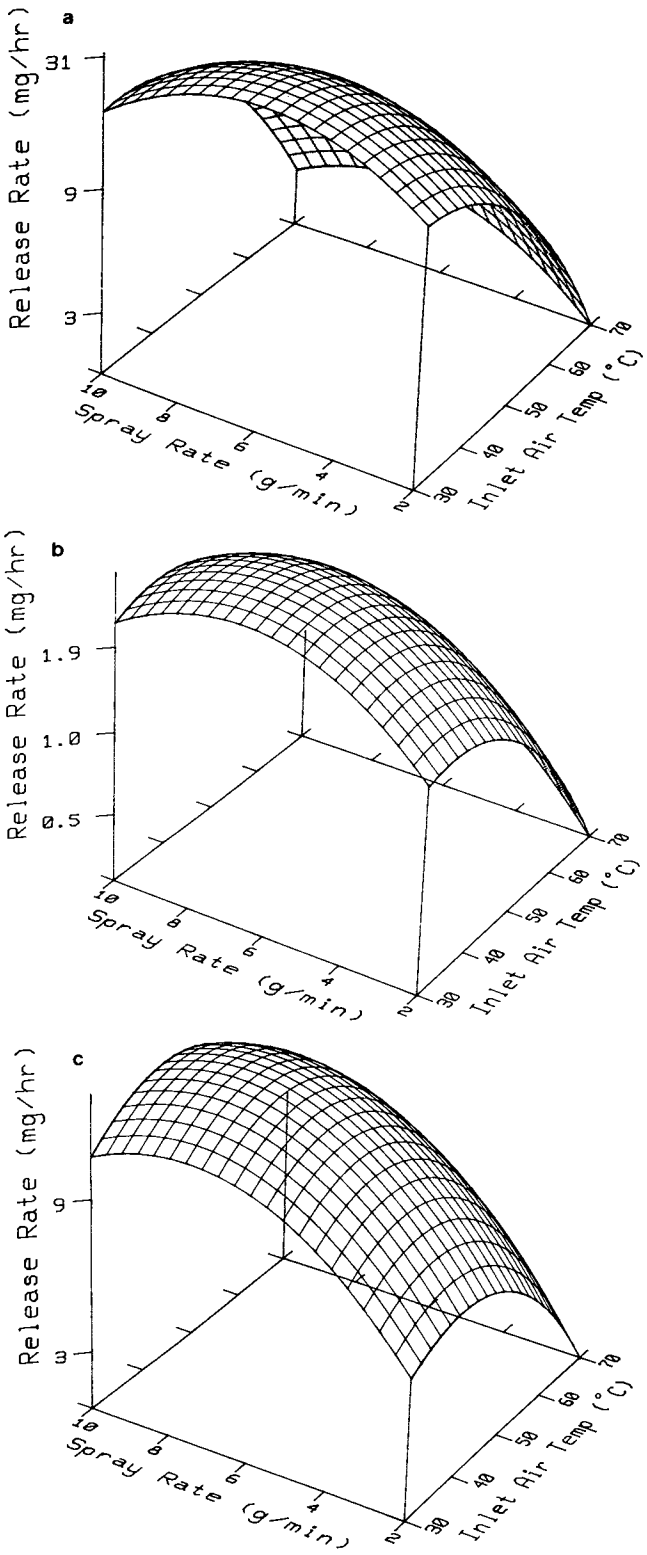

Fig. 4. Response surface plots for the rate of drug release from the "untreated" coated tablets as a function of inlet-air temperature and spray rate at (a) low (5%, w/w), (b) medium (12.5%, w/w), and (c) high (20%, w/w) levels of percent solids content. The percent solids content is an off-axis variable.

tion and fusion of adjacent polymer particles and to induce appreciable mobility of the polymer chain. This results in a continuous, dense, and less permeable coating on the tablets. Similar observations have been reported earlier (11,28).

Drug Release from Thermal-Treated Tablets

In order to prevent the problem of tackiness, which is most likely to occur if the samples are exposed to temperatures much higher than glass transition temperature of the coating polymer, the coated tablets were dried at 40°C, i.e., 5° above the glass transition temperature of the polymeric dispersion (Surelease) (22). This thermal post-treatment step would ensure further gradual coalescence of the films, which were sprayed at suboptimal process conditions.

For the coated tablets that received thermal post-treatment, all main effects for the three independent variables, i.e., percent solids content in the polymeric dispersion, inlet-air temperature, and spray rate, were found to be significant ($P < 0.05$). No significant two-factor interactions were observed, and the model had a R^2 value of 0.975 which indicates an excellent fit.

Figures 5a–c depict 3-D response surface plots for the effect of the three independent variables on the rate of drug release from the thermal-treated tablets. Comparison of the slopes of the individual plots for the thermal-treated tablets (Figs. 5a–c) with those for the untreated tablets (Figs. 4a–c) indicates no significant two-factor interactions between the three independent variables for the rate of drug release from the thermal-treated tablets, which is also evident from the effects table (Table V). In this case, the spray rate seems to be the most significant main effect compared to the other two main effects, since after thermal post-treatment at 40°C, tablets coated at high spray rates (irrespective of inlet-air temperature) had higher release rates. This implies that the conditions of the coating process at high spray rates might not have provided an adequate degree of fusion of polymer spheres resulting in poorly coalesced film. The lowest release rates were obtained for the thermal-treated tablets coated at medium temperatures (i.e., 45–50°C) and low spray rates (i.e., 2–4 g/min). This could be due to the fact that these two process variables might be conducive to the optimal spreading and deposition of dispersion droplets onto the substrate which, upon curing, might form a dense and continuous polymeric network resulting in the lowest release rates.

Microindentation Hardness of Untreated Tablets

Microindentation hardness testing is a static method for the determination of surface properties of a material, especially deformation hardness and elasticity. In the present study, this measurement was performed to characterize and evaluate the Brinell hardness of the polymeric (Surelease) coating as a function of the three independent variables. Brinell hardness number, which indicates resistance to the local permanent deformation, is calculated from the applied load, the diameter of the spherical indenter, and the depth of penetration under the applied load. The greater the depth of penetration, the softer the coating of the tablet. This number has been used to evaluate the effect of plasticizer type and level on the properties of hydroxypropyl methylcellulose films *in situ* on tablets (29).

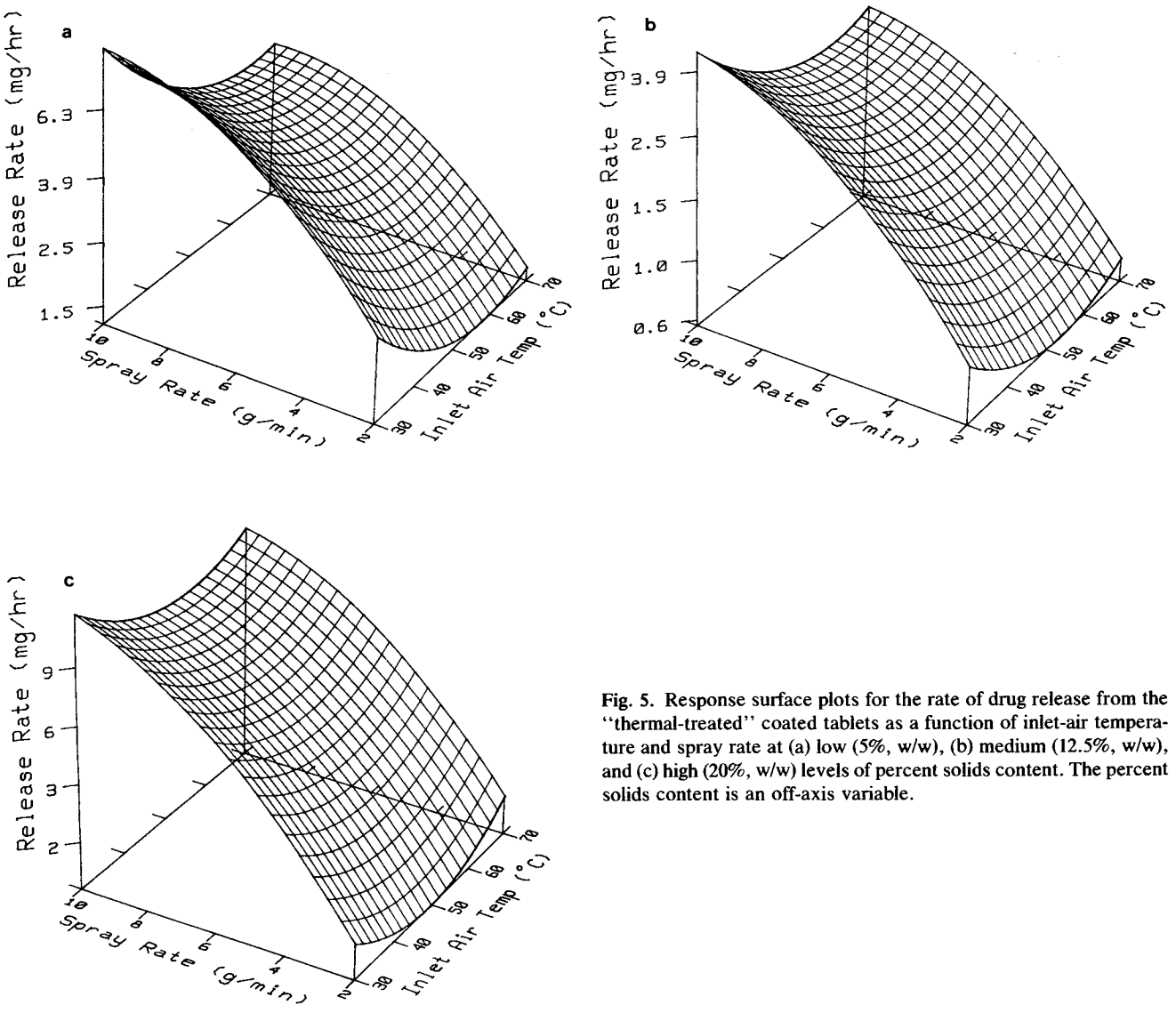

Fig. 5. Response surface plots for the rate of drug release from the "thermal-treated" coated tablets as a function of inlet-air temperature and spray rate at (a) low (5%, w/w), (b) medium (12.5%, w/w), and (c) high (20%, w/w) levels of percent solids content. The percent solids content is an off-axis variable.

For this response variable, only inlet-air temperature showed a significant main effect ($P < 0.01$), and no significant two-way interactions were observed. The fitted model had a lower R^2 value, i.e., 0.82, compared to the other two response variables.

Figures 6a–c represent 3-D response surface plots for Brinell hardness. For consistency and ease of comparison with other response surfaces, percent solids content was kept as an off-axis independent variable. As indicated in the figures, high Brinell hardness values were obtained for high inlet-air temperatures and low spray rates, indicating mechanically stronger films under such coating conditions. Similar observations have been reported earlier where the mechanical properties, measured as fracture stress, fracture strain, and elasticity modulus, of films of DBS plasticized aqueous ethylcellulose dispersions (Aquacoat plasticized with DBS and Surelease/E-7-7050) were determined as a function of coalescence temperature (30). These films were prepared by spraying the polymeric dispersions on a Teflon substrate at a constant inlet-air temperature of 64°C.

Comparison of the results presented in Figs. 4a–c with those in Figs. 6a–c suggests that there is a relationship between Brinell hardness of the applied coating and its drug release characteristics. The polymeric (Surelease) films prepared at product-bed temperatures (as judged by outlet-air temperature) above the glass transition temperature of the coating formulation, i.e., at high inlet-air temperatures, and low spray rates are mechanically stronger, as evident from the maxima of the corresponding response surface, and yield lower drug release rate, as indicated by the minima of the corresponding response surface. A similar relationship between the mechanical properties of a coating and its drug release characteristics has been reported where drug release rates and the fracture stress of ethylcellulose films prepared from organic solvents were investigated (31).

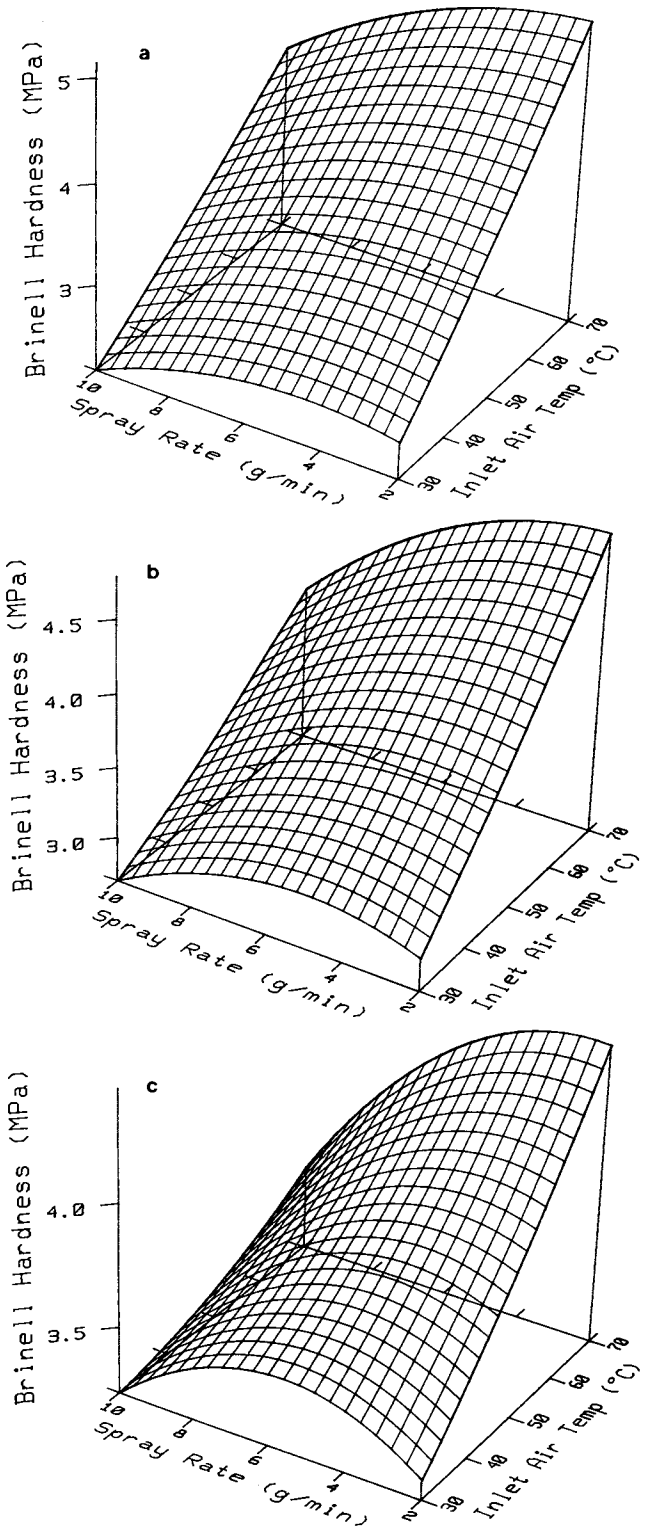

Fig. 6. Response surface plots for Brinell hardness of the "untreated" coated tablets as a function of inlet-air temperature and spray rate at (a) low (5%, w/w), (b) medium (12.5%, w/w), and (c) high (20%, w/w) levels of percent solids content. The percent solids content is an off-axis variable.

Table VI. Results of Verification Experiments

Proposed optimal set of independent variables	
Variable	Level
X_1: dispersion solids content (% w/w)	12.5
X_2: inlet-air temperature (°C)	60.0
X_3: spray rate (g/min)	4.0

Summary of predicted and observed response variables

		Observed*	
Variable	Predicted*	Expt 1	Expt 2
Y_1: Rate of drug release from "untreated" coated tablets (mg/hr)	1.21	1.11	1.35
Y_2: rate of drug release from "thermal-treated" coated tablets (mg/hr)	1.08	1.05	1.20

* The difference between the predicted and the observed values was statistically insignificant (one-way ANOVA, $P > 0.05$).

Verification Experiments

Using the cursor grid on the 3-D response surface plots, predictions of the drug release rates can be made for all experiments having independent variables within the experimental domain defined by the design. In the validation of the predictive capability of this model, levels of independent variables were proposed at which the difference between the predicted rate of drug release from both untreated and thermal-treated tablets was minimal. This is desirable from a practical standpoint since the optimal film formation can be achieved during the coating process itself, and hence the need for thermal post-treatment for curing would be less critical. Two verification experiments were conducted and the rates of drug release from the coated tablets were determined. The proposed levels of the independent variables and the predicted and observed drug release rates are summarized in Table VI. Results in Table VI indicate a good agreement between the predicted and the observed drug release rates. The differences between the predicted and the observed values for both the responses were statistically insignificant (one-way ANOVA, $P > 0.05$).

In summary, this study presents the evaluation of three selected coating process variables for sustained-release applications using response surface methodology. A factorial experimental design has been utilized to study the main effects and two-way interactions which are unlikely to be detected with conventional experimental design by varying one factor at a time. The three selected independent process variables studied (i.e., percent solids content in the polymeric dispersion, inlet-air temperature, and spray rate) are critical for the performance characteristics of tablets coated with the aqueous ethylcellulose dispersion (Surelease/E-7-7060) and, possibly, for other aqueous polymeric dispersions. During the coating process, the application of sufficient thermal energy is critical for optimal film formation, and its magnitude can be controlled by the levels of the

process variables. It is shown that for a given coating formulation, the performance characteristics, as measured by the drug release rate, varied significantly as a function of the process variables. Therefore, in order to achieve the optimal and reproducible drug release rate, the evaluation of coating process variables is extremely critical. A zero-order drug release was obtained from tablets coated with the aqueous ethylcellulose dispersion. A good correlation was observed between the permeability (as judged by the drug release rate) and the Brinell hardness of the polymeric film coat as a function of inlet-air temperature and spray rate.

ACKNOWLEDGMENTS

This paper was abstracted in part from a dissertation submitted by N. H. Parikh to the Graduate Division, College of Pharmacy & Allied Health Professions, St. John's University, in partial fulfillment of the Doctor of Philosophy degree requirements. The authors wish to thank Berlex Laboratories, Inc., Wayne, NJ, for providing laboratory facilities to carry out part of this work, Colorcon, West Point, PA, for their support with this project, and Ethyl Corp., Baton Rouge, LA, for their generous gift of ibuprofen. Mr. R. Messaros of Berlex Laboratories, Inc. is achnowledged for technical assistance in the robotic dissolution.

REFERENCES

1. S. C. Porter. Controlled-release film coatings based on ethylcellulose. *Drug Dev. Ind. Pharm.* 15:1495–1521 (1989).
2. G. S. Banker and G. E. Peck. The new water-based colloidal dispersions. *Pharm. Technol.* 9:55–61 (1985).
3. K. O. R. Lehmann. Chemistry and application properties of polymethacrylate coating systems. In J. W. McGinity (ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications,* Marcel Dekker, New York, 1989, pp. 153–245.
4. C. R. Steuernagel. Latex emulsions for controlled drug delivery. In J. W. McGinity (ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications,* Marcel Dekker, New York, 1989, pp. 1–61.
5. K. L. Moore. Physico-chemical properties of Opadry, Coateric, and Surelease. In J. W. McGinity (ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications,* Marcel Dekker, New York, 1989, pp. 303–315.
6. R. K. Chang, C. H. Hsiao, and J. R. Robinson. A review of aqueous coating techniques and preliminary data on release from a theophylline product. *Pharm. Technol.* 11:56–68 (1987).
7. F. W. Goodhart, M. R. Harris, K. S. Murthy, and R. U. Nesbitt. An evaluation of aqueous film-forming dispersions for controlled release. *Pharm. Technol.* 8:64–71 (1984).
8. M. R. Harris, I. Ghebre-Sellassie, and R. U. Nesbitt. Water-based coating process for sustained release. *Pharm. Technol.* 10:102–107 (1986).
9. I. Ghebre-Sellassie. Recent advances in modified-release coating utilizing aqueous polymeric dispersions. *Proceedings of Pharmaceutical Technology Conference, NJ,* Sep. 26–28, 1988.
10. M. R. Harris and I. Ghebre-Sellassie. Aqueous polymeric coating for modified-release pellets. In J. W. McGinity (ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications,* Marcel Dekker, New York, 1989, pp. 63–79.
11. S. T. Yang and I. Ghebre-Sellassie. The Effect of product-bed temperature on the microstructure of Aquacoat-based controlled release coatings. *Int. J. Pharm.* 60:109–124 (1990).
12. R. Bodmeier and O. Paeratakul. Process and formulation variables affecting the drug release from chlorpheniramine maleate-loaded beads coated with commercial and self-prepared aqueous ethylcellulose pseudolatexes. *Int. J. Pharm.* 70:59–68 (1991).
13. I. Ghebre-Sellassie, U. Iyer, D. Kubert, and M. B. Fawzi. Characterization of new water-based coating for modified-release preparations. *Pharm. Technol.* 12:96–106 (1988).
14. B. H. Lippold, B. K. Sutter, and B. C. Lippold. Parameters controlling drug release from pellets coated with aqueous ethylcellulose dispersions. *Int. J. Pharm.* 54:15–25 (1989).
15. A. Onions. Films from water-based colloidal dispersions. *Manuf. Chem.* 57(3):55–59 (1986).
16. C. Bindschaedler, R. Gurny, and E. Doelker. Theoretical concepts regarding the formation of film from aqueous microdispersions and application to coating. *Labo. Pharma. Probl. Tech.* 31(331):389–394 (1983).
17. *Aquacoat Handbook,* FMC Corp., Philadelphia, PA.
18. R. M. Franz, J. A. Sytsma, B. P. Smith, and L. J. Lucisano. *In-vitro* evaluation of a mixed polymeric sustained release matrix using response surface methodology. *J. Control. Release* 5:159–172 (1987).
19. S. Bolton. *Pharmaceutical Statistics: Practical and Clinical Applications,* Marcel Dekker, New York, 1990.
20. V. L. Anderson and R. A. McLean. *Design of Experiments, a Realistic Approach,* Marcel Dekker, New York, 1974.
21. G. Stetsko. Statistical experimental design and its application to pharmaceutical development problems. *Drug Dev. Ind. Pharm.* 12(8-9):1109–1123 (1986).
22. N. H. Parikh. Factors affecting film forming properties of commercially available aqueous ethylcellulose disperion. Doctor of philosophy thesis submitted to St. John's University, Jamaica, NY, 1993.
23. C. D. Herzfeldt and R. Kummel. Dissociation constants, solubilities and dissolution rates of some selected non-steroidal anti-inflammatories. *Drug Dev. Ind. Pharm.* 9(5):767–793 (1983).
24. M. Aulton. Micro-indentation tests for pharmaceuticals. *Manuf. Chem. Aerosol News.* 47:28–36 (1977).
25. *The Merck Index,* 11th ed., Merck & Co., Inc., Rahway, NJ, 1989, p. 4811.
26. U. Iyer, W. H. Hong, N. Das, and I. Ghebre-Sellassie. Comparative evaluation of three organic solvent and dispersion-based ethylcellulose coating formulations. *Pharm. Technol.* 14(9):68–86 (1990).
27. L. C. Li and G. E. Peck. Water-based silicone elastomer controlled release tablet film coating. V. A statistical approach. *Drug Dev. Ind. Pharm.* 17(1):27–37 (1991).
28. M. Hossain and J. W. Ayres. Variables that influence coat integrity in a laboratory spray coater. *Pharm. Technol.* 14(10):72–82 (1990).
29. R. C. Rowe. The characterization of mechanical strength of the polymeric film coat on tablets. *J. Pharm. Pharmacol.* 28:310–314 (1976).
30. H. Arwidsson. Properties of ethyl cellulose films for extended release. II. Influence of plasticizer content and coalescence conditions when using aqueous dispersions. *Acta Pharm. Nord.* 3(2):65–70 (1991).
31. H. Arwidsson. Properties of ethylcellulose films for extended release. I. Influence of process factors when using organic solutions. *Acta Pharm. Nord.* 3(1):25–30 (1991).