Processing Considerations for an EC Latex Coating System: Influence of Curing Time and Temperature

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The influence of curing time and curing temperature for a commercially available ethylcellulose latex coating dispersion (Aquacoat®) were evaluated using response surface methodology. Levels for the factor curing time ranged from 30 to 300 minutes while levels for curing temperature ranged from 45° to 75°C. Responses, A, κ, and γ, were derived from regression analysis of the dissolution profiles and correspond to the maximum amount of drug released over the 12 hour sampling period, the rate of release, and the inflection point of the dissolution profile, respectively. The nature of the response surface was dramatically influenced by the plasticizer incorporated into the coating formula. When dibutyl sebacate was employed as the plasticizer, faster release resulted (higher A and κ values, lower γ values) when samples were exposed to higher curing temperatures or were stored for longer periods of time. Paradoxically, when tributyl citrate was used as the plasticizer, slower release resulted when samples were exposed to more rigorous conditions. Overall, curing temperature had a more dramatic effect than curing time.

KEY WORDS: response surface methodology; Aquacoat®; ethylcellulose; film coating; latex; curing; further gradual coalescence.

INTRODUCTION

The process of film formation from latex coating systems involves the following three steps: the evaporation of water, coalescence of latex particles and interdiffusion of polymer chains among adjacent particles (1). The last step has also been referred to as "further gradual coalescence" (2) or "curing" (3). For the pharmaceutical unit operation of coating, the first two steps take place during the application of the coating dispersion to a substrate material using equipment which is efficient in terms of high rates of heat and mass transfer. Work by Parikh *et al.* suggests that further gradual coalescence also takes place to a certain extent during this application process as slower release profiles result following processing at higher temperatures. However, a recommended procedure used to assure the completion of coalescence is to expose the product to elevated temperatures following the application process either in the coating machine using a process known as post-coating fluidization (3) or by placing the samples into an oven (5-6).

Certain latex systems have been characterized with respect to the curing stage and it has been possible to quantify the completion of this final step of film formation using sophisticated techniques such as small angle neutron scattering (SANS) (1) or a nonradiative direct energy transfer technique (7).

However, limited published studies have addressed the curing processing step for the commercially available ethylcellulose latex coating systems. Nevertheless, in light of the advantages which these systems offer over solvent-based coating systems (reduced toxicity and environmental contamination and a decreased threat of explosion) and because the curing step may have an impact on the final product by influencing release profiles, it is necessary to gain an improved understanding of the influence of two key processing variables associated with further gradual coalescence: curing time and curing temperature.

An approach frequently used for the modelling of pharmaceutical processes, which may be applied to the curing process, is response surface methodology. Data generated using various experimental designs have been depicted graphically through the generation of response surfaces which can give the investigator visual confirmation of the nature of experimental results (4, 8-10). A central composite design is often preferred since curvature, a phenomena associated with many pharmaceutical processes, can be modelled with a minimal number of experiments (11). Key features of this design are that it is rotatable, orthogonal and has uniform precision if a sufficient number of center point replicates are performed (12).

In the following work response surface methodology was used to study the two factors, curing time and curing temperature, for modified release spheres coated with a barrier layer consisting of Aquacoat® and either tribuyl citrate (TBC) or dibutyl sebacate (DBS) as the plasticizer.

MATERIALS AND METHODS

Materials

All materials were used as received. Aquacoat® was obtained from FMC Corporation (Newark, DE). The plasticizers used in the modified release coating layer were tributyl citrate (TBC)(Morflex, Inc., Greensboro, NC) and dibutyl sebacate (DBS) (Sigma Chemical Co., St. Louis, MO). The model drug used was propranolol HCl (Wyckoff Chemical Co., South Haven, MI). HPMC (Methocel® E5 Premium, Dow Chemical Co., Midland, MI) and PEG 400 (Union Carbide, Danbury CT) were also used in the formula. The substrate material used was sugar spheres, NF (Nu-Pareil® PG, size 14-18 mesh) obtained from Crompton & Knowles Corporation (Pennsauken, NJ).

Preparation of Drug Loaded Modified Release Spheres

Drug containing modified release spheres consisted of non-pareil seeds onto which two coating layers were applied. The formulation of the first (drug loading) coating layer applied consisted of Methocel® E5 (72 g), propranolol HCl (24 g), PEG 400 (7.2 g) and distilled water (940 g). After drug

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loading, a modified release coating layer was applied which consisted of Aquacoat® plus a plasticizer (TBC or DBS) (Table I). The amount of plasticizer (25% or 30%) was determined based on the weight of ethylcellulose in the Aquacoat® formula (27% EC). A 5% (weight increase) coating level was used. Processing conditions for both coating layers are presented in Table II. Once prepared, samples (20 g) were removed and were placed in Nalgene® bottles and were exposed to the various curing conditions described below. Curing took place in an oven.

Following the curing process, the dissolution profiles of the samples were determined using the USP XXII rotating basket method. The basket rotation speed was fixed at 100 rpm and media used was diluted HCl. Samples (10 ml) were withdrawn at the following times: 15 and 30 minutes, 1, 2, 4, 6, 8, 10 and 12 hours and were analyzed spectrophotometrically (DU®70 Spectrophotometer, Beckman Instruments, Fullerton, CA) using a wavelength of 289 nm.

Parameterization of Dissolution Data

Each dissolution profile was fit to equation 1 using SAS (SAS institute, Inc., Cary, NC). The coefficients obtained, A, κ, and γ, were used as the response values in the central composite design.

$$\%released = Ae^{-e^{-\kappa(t-\gamma)}} \quad (1)$$

Curing of Spheres: Central Composite Design

A central composite design was used to study two factors, curing time (T_1) and curing temperature (T_2). The experiments performed, in coded form and with the corresponding levels, are presented in Table III. Experiments 1-6 (4 factorial runs and 2 center point replicates) were carried out initially and the data were fit to a first order model (equation 2) were Y_i represents the response, b_k represent regression coefficients and T_j represents the level of each factor for a given experimental run.

$$Y_i = b_0 + b_1T_1 + b_2T_2 + b_3T_1T_2 \quad (2)$$

If significant lack of fit was determined for the first order model, the remaining seven experiments were completed (4 axial points and 3 more center point replicates) as all 13 runs are required to satisfy the number of degrees of freedom needed to add second order terms (for curvature) to the model (equation 3).

$$Y_i = b_0 + b_1T_1 + b_2T_2 + b_3T_1T_2 + b_4T_1^2 + b_5T_2^2 \quad (3)$$

Using the regression data for the three responses, determined for each formula, response surfaces were generated using a statistical software program (ECHIP, Echip Inc., Hockessin, DE).

Table I. Composition of Modified Release Spheres

Ingredient	Grams	
	Formula I (DBS 30%)	Formula II (TBC 25%)
Aquacoat®	66.7	66.7
Plasticizer	5.4	4.5
Water	45.5	45.5
Drug loaded Nu-Pareil® spheres	400.0	400.0

Table II. Conditions for Applying the Drug Containing Layer and the Modified Release (MR) Coating Layer Using the Glatt GPCG-1 Fluidized Bed Coating Machine (Wurster Configuration)

	Drug layer	MR layer
Inlet air temperature, °C	55	52
Product bed temperature, °C	40–43	36–38
Spray nozzle diameter, mm	1	1
Spray nozzle pressure, bar	2	1.2
Dispersion flow rate, g/min	8.5	11.2
Distributor plate type	C	C
Pressure drop across chamber, kPa	1	1

RESULTS AND DISCUSSION

Figure 1 illustrates typical dissolution profiles and predicted profiles obtained using equation 1. This equation, known as the Gompertz equation (13), was used because of the sigmoidal shape of the dissolution curves. Other relationships (first order, square root of time, etc.) were not used as higher residual error and greater lack of fit was found. By using the Gompertz equation, all of the data points of the dissolution profile could be used for fitting the equation rather than a hand-picked portion of the curve.

Table III. Central Composite Design in Randomized Coded Form with Actual Levels in Brackets

Run number	Factors	
	Curing time (minutes)	Curing temperature (°C)
1	−1 (70)	1 (71)
2	1 (260)	1 (71)
3	−1 (70)	−1 (49)
4	1 (260)	−1 (49)
5	0 (165)	0 (60)
6	0 (165)	0 (60)
7	0 (165)	$\sqrt{2}$ (75)
8	$\sqrt{2}$ (300)	0 (60)
9	0 (165)	0 (60)
10	$-\sqrt{2}$ (30)	0 (60)
11	0 (165)	$-\sqrt{2}$ (45)
12	0 (165)	0 (60)
13	0 (165)	0 (60)

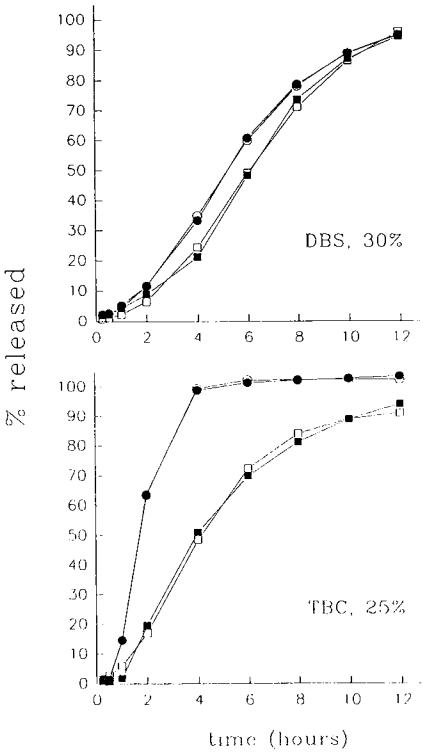

Fig. 1. Examples of actual (solid symbol) and predicted (hollow symbol) release profiles for modified release spheres prepared using Aquacoat®. ●/○: best fit, ■/□: worst fit.

Best and worst case fits are illustrated based on the mean square residual (MSE) results obtained using the PROC NLIN procedure in the SAS package. For samples prepared using DBS (30%) as the plasticizer, the best and worst case MSE values were 0.70 and 5.56, respectively. For samples prepared in which TBC (25%) was used as the plasticizer, best and worst case MSE values are 0.71 and 9.75, respectively. Using parameters obtained by fitting the data is preferred to using individual data points taken from the graph as the fit parameters are determined using all of the data from the graph. Further, the parameters are meaningful. Parameter A corresponds to the maximum amount of drug released over the 12 hour sampling period, κ corresponds to the release rate, and γ corresponds to the inflection point of the dissolution profile. In general, higher γ values correspond to slower release rates.

Tables IV and V represent the regression results for the curing response surface for beads prepared using DBS (30%) and TBC (25%), respectively. First order regression was sufficient to characterize the response surface for the coating in which DBS was used as the plasticizer (Table IV). Lack of fit was found for parameter A only so the additional experiments necessary for determining higher order terms were not performed. The regression results (Table V) generated for the samples in which TBC was used as plasticizer are second order as significant lack of fit was found when the data (runs 1-6) were fit using a first order model. While the second order regression equation used to characterize the curing data for the samples prepared using TBC shows a high R^2 value, the LOF for all three parameters is significant. The reason for the high LOF is due to the high reproducibility of

Table IV. First Order Regression Analysis Results for A, κ, and γ (Formula I, DBS 30%)

Parameter	Estimates for measured responses		
	A	κ	γ
R^2	0.6670	0.9628	0.9701
Intercept	−19.42	0.105	4.952[a]
T_1 (time)	0.158	−0.0007	0.024[a]
T_2 (temperature)	1.929	0.0029	0.011
$T_1 * T_2$ (time * temperature)	−0.0027	0.00001	−0.0004[a]

[a] Term is significant at α = 0.05.
R^2, coefficient of determination.

the center point. Overall, curing temperature had a more dramatic effect than curing time. This conclusion based on the overall significance of the terms T_2 (temperature) and the lack of significance of T_1(time).

Observation of the response surfaces for the parameters A, κ, and γ reveals that at least two types of phenomena result following the curing of Aquacoat®. Contrasting response surfaces for the parameter, κ, are typical (Figure II). For samples in which DBS was incorporated as the plasticizer, parameters A and κ are higher with increases in curing time and temperature while γ decreases. These results reflect an increase in the amount released over the 12 hour sampling period, an increase in the release rate and a reduction in the time corresponding to the inflection point of the dissolution profile, respectively. Results obtained for the samples in which TBC was used as the plasticizer are the opposite; the amount of release over the 12 hour sampling period and the release rate decrease with longer curing times and higher curing temperatures while the dissolution curve inflection point occurs at a later time.

These results imply that different types of phenomena occur depending on the type and/or the amount of plasticizer used. Since faster release is obtained following storage of DBS samples, these results reflect the presence of excessive plasticizer in the film coating. This plasticizer may be squeezed out of the coating. The migration of the plasticizer to the surface of the barrier coating from the bulk of this coating layer may be more dramatic at higher curing temper-

Table V. Second order regression analysis results for A, κ, and γ (Formula II, TBC 25%)

Parameter	Estimates for measured responses		
	A	κ	γ
R^2	0.9496	0.9838	0.9682
Intercept	118.6[a]	8.997[a]	−9.131[a]
T_1 (time)	−0.082	−0.0020	0.010
T_2 (temperature)	0.268	−0.245[a]	0.289[a]
T_1^2 (time^2)	0.0003[a]	0.000005[a]	−0.00002[a]
T_2^2 (temperature^2)	−0.0084	0.00179[a]	−0.002[a]
$T_1 * T_2$ (time * temperature)	−0.0006	−0.000007	−0.0001

[a] Term is significant at α = 0.05.
R^2, coefficient of determination.

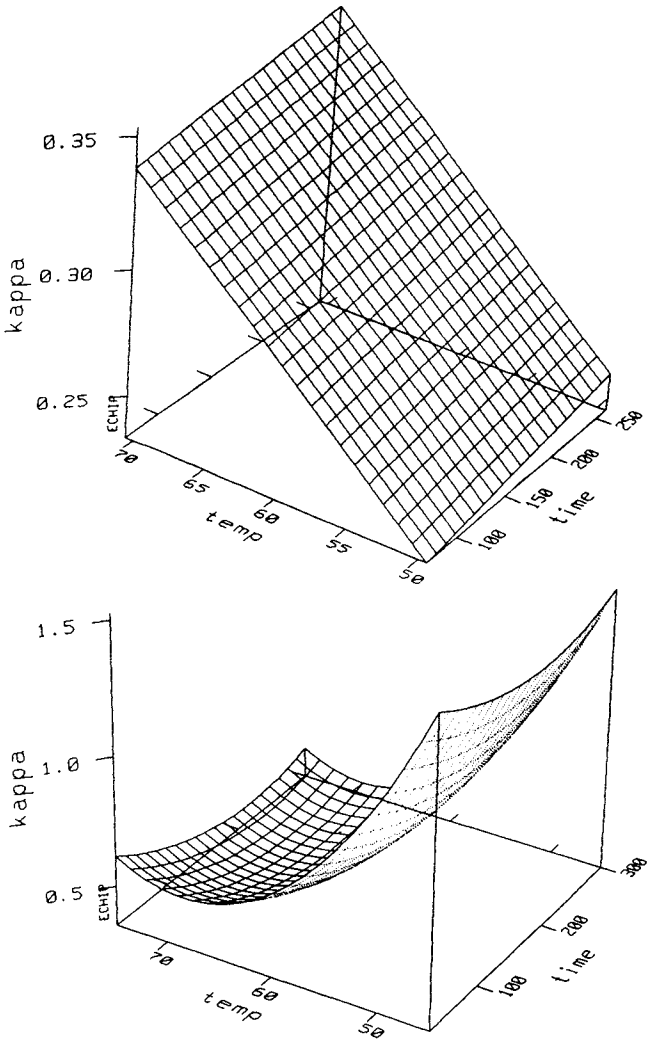

Fig. 2. Response surface plots representing the effect of curing time and curing temperature on the dissolution curve parameter, κ, for samples prepared using Aquacoat® and DBS, 30%, (left) or Aquacoat® and TBC, 25%, (right).

atures or following longer storage times. The drug may also become solubilized in the plasticizer at higher curing temperatures. However, Ozturk *et al.* (14) determined that the solubility of another hydrochloride salt, phenylpropanolamine HCl was quite low in DBS. Further, the increase in the release rate was not observed for samples prepared with TBC as the plasticizer even though TBC and DBS have similar solubility parameter values (15-16). Finally, the samples stored at higher curing temperatures became very soft. This softening may have lead to picking of the barrier coating layer from adjacent spheres (17). The extent of such picking could be influenced by the longer curing times and higher curing temperatures.

Alternative explanations may be used to describe the behavior observed for samples prepared using TBC. Here, the increase in curing time and temperature leads to a reduction in release rate. Thus, further gradual coalescence occurs to a greater extent at higher curing temperatures. Such results may be correlated with findings for free films of Aquacoat® prepared with TBC as the plasticizer which showed

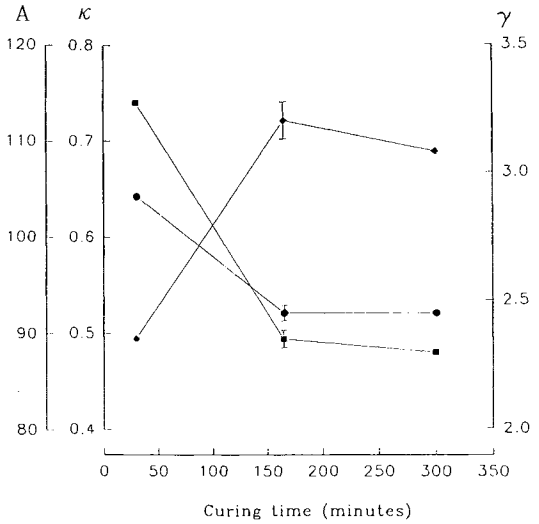

Fig. 3. The effect of curing time (minutes) on the dissolution profile parameters A: ●, κ: ■, γ: ◆.

greater elongation following exposure to higher curing temperatures (18).

Associated with the variable time is a maximization/minimization of a particular response. Considering a 2D depiction of the results obtained at 60°C (Figure III), A and κ are minimized and γ is maximized following storage for 165 minutes; no further change is effected by prolonging storage to 300 minutes. Thus, the completion of coalescence at a given temperature is time dependent. Such time dependence reflects a limitation of the heat transfer rate into the stored sample. Nevertheless, while the extent of coalescence at a given temperature may peak with time, the results of the experiments involving samples prepared using TBC (25%) suggest that yet more curing is still possible if the temperature is raised further (Figure IV). The implication of this finding is that samples ought to be cured at a temperature above any possible storage condition which may be encountered.

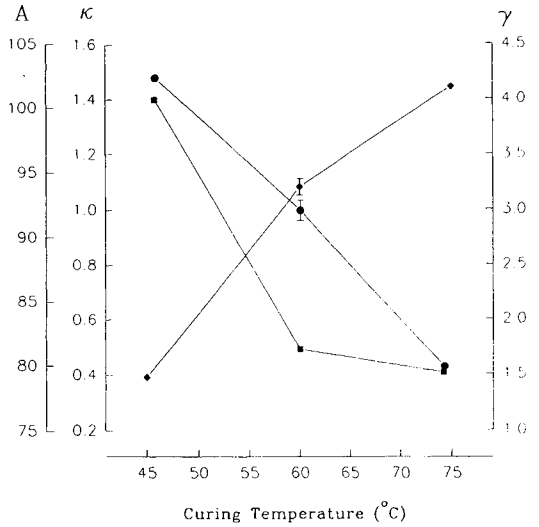

Fig. 4. The effect of curing temperature (°C) on the dissolution profile parameters A: ●, κ: ■, γ: ◆.

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