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THE SOLUBILIZATION OF DRUG AND EXCIPIENT INTO A HYDROXYPROPYL METHYLCELLULOSE (HPMC)-BASED FILM COATING AS A FUNCTION FOR THE COATING PARAMETERS IN A 24" ACCELA-COTA®

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ABSTRACT

During the aqueous film coating of tablets, components of tablets tend to migrate to the film coating. This migration is enhanced if a component is soluble in the coating solution and also depends on the spray condition used during the coating operation. In this study, a 2^3 orthogonal factorial design was used to study the migration of drug and stearic acid from a tablet to an aqueous-based cellulose coating solution. The independent variables evaluated were atomization air pressure, inlet air temperature, and spray rate. Differential scanning calorimetry was used to quantitate the presence of guaifenesin and stearic acid in the film coating. In the 24" Accela Cota that was used on our experiment, only spray rate and inlet air temperature influenced the migration of drug and stearic acid the film coating.

INTRODUCTION

The use of hydroxypropyl methylcellulose (HPMC) as a film-coating agent first appeared in a patent by Singiser.[1] Low-viscosity HPMCs (3, 6, 15 cps) which were subsequently introduced in 1965, have contributed to the worldwide growth of HPMC as a film-coating polymer.

Numerous authors have described the gradual tendency of industry to switch from coatings with organic bases to those with aqueous bases.[2,3] Today, HPMC-based aqueous films are the first choice for tablet coatings that are designed to mask bitter taste, make tablets more swallowable, impart aesthetic appearance, and identify product. Because the proper ranges of coating conditions for HPMC aqueous-based coatings are rather narrow in comparison with those used for organic solvent coatings, the use of improper coating conditions (those that do not fall within this narrow range) sometimes damages coating batches and makes them unsuitable for reprocessing.[4]

Both Aulton *et al.*[5] and Simpkin *et al.*[6] observed that dissolution of a small amount of excipient or drug from the core tablet to the film may occur during the coating operation. Migration of the excipient or drug to its applied coating may occur over a period of time that follows the coating application. If the drug or excipient is soluble in the coating solution, dissolution occurs during the spray cycle of the coating operation. These authors indicated that the drug or excipient could migrate to and dissolve in the residual coating solvent or in the moisture adsorbed by the coating on storage in environments with high humidity. Okhamafe and York[7] reported that as aspirin tablets degrade, the salicylic acid migrates by a sublimation mechanism to the film coating.

The migration of drug or excipient to the applied film coating may substantially alter the mechanical adhesion and penetration characteristics of the film. Okhamafe and Igbinadolo[8] observed that although the moisture diffusivity of an HPMC film was either lowered or unchanged in the presence of ephedrine hydrochloride or lactose, incorporation of these excipients into the film markedly enhanced the moisture diffusivity of aqueous-based polyvinyl alcohol (PVA) films. Okhamafe and York[9] subsequently used differential scanning calorimetry (DSC) and thermomechanical analysis (TMA) to define the intrinsic changes of the film such as softening, glass transition, temperature, crystallinity, and melting point.

A suitable method to control drug or excipient migration from the core tablet to the film during the coating process has not yet been discovered. To date, the most effective method is to keep the droplet size of the spray mist small and to use a low spray rate.[4]

This study was designed to quantitate the amount of drug and excipient that migrates to an HPMC-based film as a function of the coating parameters for a 24" Accela-Cota.

MATERIALS AND METHODS

Drug Selection

Because the migration of drug from the core tablet to the film coating during aqueous film coating is a function of drug solubility, guaifenesin with an aqueous solubility of 1 g/20 ml was selected.

Tablet Formulation

Guaifenesin was incorporated at a level of 50% w/w into a sustained-release tablet dosage form. The tablets also contained stearic acid (5% w/w), carbomer 934P, compressible sugar, phenylpropanolamine HCl, stearic acid, and zinc stearate.

Tablet Preparation

Three 32-kg batches were prepared in a 2-cu ft V-Blender (Patterson-Kelley Co., East Stroudsburg, PA) that was fitted with an intensifier bar as described below.

1) Guaifenesin, phenylpropanolamine, compressible sugar, carbomer 934P, and stearic acid were passed through an oscillator (Model 43-4, F. J. Stokes, Philadelphia, PA) that was fitted with a 30-mesh screen.

2) The oscillated blend was transferred to a 2-cu ft V-Blender and mixed for five minutes with an intensifier bar.

3) One half of the zinc stearate was added, and the blend was mixed for an additional three minutes, without the intensifier bar.

4) The blend was discharged and passed through a Freund Roller Compactor (Model TF-156, Freund Industries, Tokyo, Japan) that was fitted with ribbon rollers. A compaction force of 2,000 psi and a screw-feed rate of 8 rpm were maintained throughout the run.

5) The compacted ribbons were ground through the oscillator that was fitted with a 12-mesh heavy screen.

6) The granulation and the remaining one half of the zinc stearate were returned to the V-Blender and were mixed for three minutes, without the intensifier bar.

7) The blend was discharged and compressed on a Manesty Beta Press® (Thomas Engineering, Hoffman Estates, IL), which was fitted with an oval-shaped tooling of 0.355-0.700", to a constant weight of 780 mg. Compressional force was maintained at 3-4,000 lbs, and the average tablet hardness was 18-25 SCU.

Film-Coating Selection

A commercially available HPMC-based powder coating system, Dri-Klear® (Crompton and Knowles, Mahwah, NJ), was used. This coating contained hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol, dioctyl sodium sulfosuccinate, and silicon dioxide.

Opaspray® (Colorcon, Inc., West Point, PA) was used to opacify the film. The Opaspray contained hydroxypropyl methylcellulose, SDA alcohol 30, titanium dioxide, and lake dye. Dri-Klear and Opaspray are both proprietary formulations; quantitative formulas were not divulged by either company.

The coating formula used in our study is listed in Table 1.

TABLE 1

HPMC-Based Aqueous Coating Solution

Ingredient	Amount (% w/w)
Dri-Klear	7.8
Opaspray	3.0
Purified Water	89.2
	100.0

The 3.0% Opaspray contained 30.4% solids and, in combination with the 7.8% Dri-Klear, yielded a solution viscosity of 250 cps at 25°C.

Film Preparation

1) The Dri-Klear was added to distilled water and mixed for one hour with a Lightnin® Mixer (Mixing Equipment Co., Rochester, NY).

2) The Opaspray was added to the Dri-Klear and was mixed for 10 minutes before coating; mixing continued throughout the coating process.

Experimental Coating Design

A 2^3 orthogonal factorial design was used to study the coating process parameters. In each of the experiments, the film coating was applied to a 10-kg batch of tablets in a 24" Accela-Cota (Model 24-V, Serial No. 534, Thomas Engineering, Hoffman Estates, IL). The film coating was applied with a single-gun spray system that was located 20 cm from and perpendicular to the rotating tablet bed.

The independent variables evaluated in this study included atomization air pressure, inlet air temperature, and spray rate. Tablet charge, pan speed, nozzle orifice, inlet air-flow rate, and the dew point of the inlet air remained constant. Table 2 shows the experimental design.

Coating Evaluation

1) Visual Appearance

After coating, twenty tablets which were randomly selected from each of the eight lots were examined visually for coating defects such as cracking, bridging, or peeling.

2) Colorimetric Values

After coating, the surface color of the tablets was measured on a McBeth Color-Eye® (Model MC1500S, Newburg, NY). An additional 10 tablets from each lot were randomly selected from four sections of the coating pan for analysis.

TABLE 2

2^3 Experimental Coating Design*

	Experiment							
	1	2	3	4	5	6	7	8
Spray Rate (g/min)	30	30	60	60	30	30	60	60
Inlet Air Temperature (°C)	50	60	50	60	50	60	50	60
Atomization Air Pressure (Bar)	2.0	2.0	2.0	2.0	4.0	4.0	4.0	4.0

* Independent Variables Held Constant:
Tablet Charge; 10.0 kg.
Pan Speed; 11.0 rpm.
Inlet Air-Flow Rate; 320 ft^3/min.
Dew Point of Inlet Air; 10°C.
Nozzle Orifice; 2.2 mm

The L, A, and B values were recorded for four areas of the tablet surface (two on each side). The ΔE (comparison to reference) was then computed for each lot of tablets. Generally, a difference in ΔE value of 2.0 or greater between lots indicates a change in film color which can be perceived by the consumer.

3) Differential Scanning Calorimetry

Guaifenesin and stearic acid in the film coating were quantitated by means of DSC. A scalpel was used to remove the tablet coating from three additional tablets from each lot. The coating was then "cleaned" with a dissecting microscope to make certain all of the remaining tablet had been removed. The flakes of coating were placed in an aluminum sample pan and scanned from 30°C to 100°C at 2°C/min on a Perkin-Elmer DSC-4. Melt areas for guaifenesin and stearic acid were integrated with the Perkin-Elmer Thermal Analysis Data Station. Measured areas were ratioed to the heat of fusion obtained for samples of pure guaifenesin and stearic acid to obtain an assay value.

TABLE 3

Results of Color Comparisons With the McBeth Color-Eye

Experiment	ΔE (Average and S.D. of 40 Observations Per Lot)
1	22.4 ± 0.7
2	22.7 ± 0.8
3	22.1 ± 0.5
4	22.4 ± 0.6
5	21.3 ± 0.9
6	22.2 ± 0.5
7	22.1 ± 0.6
8	22.4 ± 0.6

RESULTS AND DISCUSSIONS

1) Visual Appearance

Tablets from all lots had smooth surface textures with no signs of cracking, bridging, or peeling.

2) Colorimetric Values

Table 3 lists the results of the colorimetric comparisons. The ΔE values were not statistically significantly different among the coated tablets; therefore, variations in tablet color were indistinguishable by the human eye.

TABLE 4

Results of Differential Scanning Calorimetry of the Film Coating

	Experiment							
	1	2	3	4	5	6	7	8
Drug X in the Coating (% w/w)	0.6	2.1	2.1	1.6	0.6	1.2	1.5	1.6
Stearic Acid in the Coating (% w/w)	0.6	0.5	0.7	0.5	0.3	0.5	0.7	0.4

3) Differential Scanning Calorimetry

A precision of 9% RSD (relative standard deviation) was obtained for multiple determinations of guaifenesin. A spiking experiment for guaifenesin over a concentration range of 0-3% to determine recovery from coating samples yielded a correlation coefficient of 0.978.

Table 4 lists the amount of guaifenesin and stearic acid that migrated to the film coating as a function of the coating parameters.

An analysis of variance (ANOVA) was performed with all variables and interaction terms for the DSC data from both guaifenesin and stearic acid. When only spray rate and inlet air temperatures were analyzed together in the model, the p-value was reduced appreciably. For guaifenesin, this p-value was 0.1028 with an r^2 value of 75.5%, and for stearic acid, the p-value was 0.2228 with an r^2 value of 63.0%.

The response surface plot for guaifenesin (Figure 1) shows that at a constant spray rate, the migration of guaifenesin increases as the inlet air temperature increases. At a constant inlet air temperature, the migration of guaifenesin increases as the spray rate increases. These results are consistent

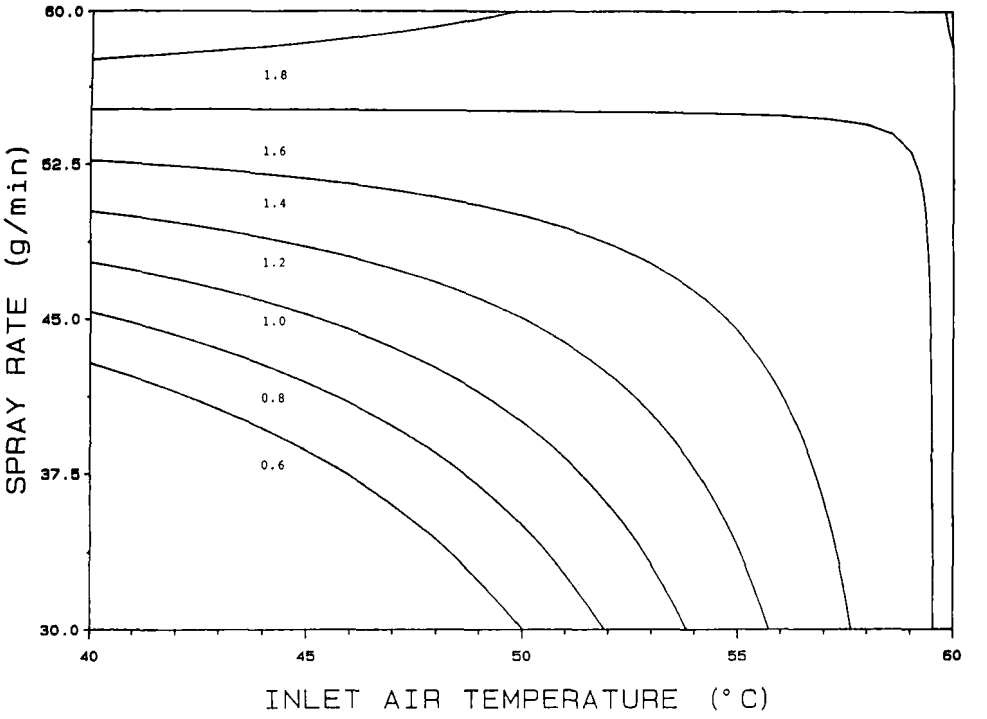

FIGURE 1

Response surface plot of the percent guaifenesin in the film coating as a function of the inlet air temperature and spray rate.

with those reported by both Aulton *et al.*[5] and Simpkin *et al.*[6] who observed that if a drug or excipient is soluble in the coating solution, dissolution occurs during the spray cycle of the coating operation. guaifenesin has a water solubility of 1 g/20 ml of water and surface dissolution is the driving force that controls the rate of migration.

The response surface plot for stearic acid (Figure 2) shows that at a constant spray rate, the migration of stearic acid decreases as the inlet air temperature increases. This finding is inconsistent with previously reported results,[5,6] but can be attributed to the fact that stearic acid reaches its softening

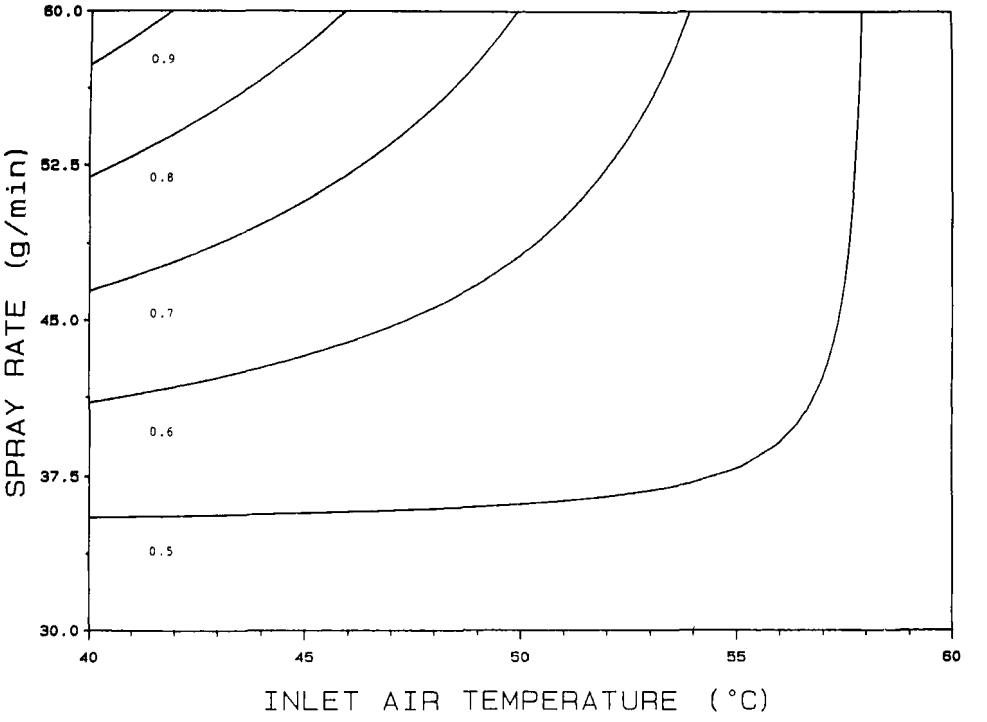

FIGURE 2

Response surface plot of the percent stearic acid in the film coating as a function of the inlet air temperature and spray rate.

point at approximately 45°C. This softening could retard the dissolution of stearic acid to the film coating.

Figure 2 also shows that at a constant inlet air temperature, the migration of stearic acid increases as the spray rate increases. This is consistent with the surface dissolution theory because stearic acid has a solubility of approximately 1 g/20 ml in the SDA alcohol in the Opaspray.

By controlling the inlet air temperature and spray rate it is therefore possible to control the surface dissolution of guaifenesin and stearic acid to the film coating.

4) Theoretical Considerations

The coating solution is sprayed onto the tablets at a constant rate, therefore:

$$dW/dt = k_1 \ (cm^3/sec) \tag{1}$$

where k_1 (g/sec) is the rate constant. The solvent will evaporate at a rate which is proportional to the area (A cm^2) of the tablets, and the vapor pressure, P, of the solvent. Vapor sink is assumed, because the venting is efficient so that no substantial vapor accumulation (as compared to the saturation pressure of the solvent) occurs in the pan:

$$dW/dt = k_2AP \tag{2}$$

where k_2 ($cm^3\ sec^{-1}cm^{-2}Pa^{-1}$) is the mass transfer coefficient, and P follows the Clausius-Clayperon equation:

$$P = \beta exp[-\Delta H/(RT)] \tag{3}$$

where β is a constant, and ΔH is the heat of vaporization, R is the gas constant, and T is the absolute temperature, thus the overall rate of weight increase of liquid is:

$$dW/dt = k_1 - k_2AP = k_1 - k_2A\beta exp[-\Delta H/(RT)] = Q \tag{4}$$

where Q is a constant, given by:

$$Q = k_1 - k_2A\beta exp[-\Delta H/(RT)] \tag{5}$$

To the first approximation of small exponents (i.e., $e(-x) \approx 1-x$)

$$Q = [k_1 - k_2A\beta] + (\phi/T) = \alpha + (\phi/T) \tag{6}$$

where

$$\alpha = [k_1 - k_2A\beta] \text{ and } \phi = k_2A\beta\Delta H/R \tag{7A}$$

(7B)

If, $[k_1 - k_2 A\beta] \ll (\phi/T)$ then Eq. 6 is reduced to:

$$Q \approx \phi/T \tag{8}$$

The amount of "solvent" at time t is then:

$$W = Qt \tag{9}$$

The word solvent is ambiguous in this sense, since the "liquid" will contain ever increasing amounts of solid polymer (which films out, as intended), but is will simply be assumed here that it acts as a liquid layer. It will also be assumed that the solubility, S, of the drug (or tablet excipient) is independent of the amount of polymer present.

The rate of dissolution of the drug into the solvent is given by the Noyes-Whitney equation:

$$dm/dt = kA[S-C] \tag{10}$$

where k is the intrinsic dissolution rate constant (cm/sec), and C is the drug concentration at time t, m is mass of material dissolved[1], i.e., the concentration, C, of the drug in the film is given by:

$$C = m/W \tag{11}$$

Since the tablet area is approximately constant, Eq. 9 may be rewritten:

$$dC/(C-S) = (kA/W)dt \tag{12}$$

which integrates directly (since A is constant) to:

$$C = S[1-\exp\{(-kA/W)t\}] \tag{13}$$

Introducing Eq. 9 gives:

$$C = S[1-\exp(-kA/Q)] \tag{14}$$

[1] This notation is convenient in this setting, although it is different from conventional usage, where m denotes the amount not dissolved.

The amount (Y) dissolved in the "solvent", i.e., eventually in the dried film, is the concentration times the volume, i.e.:

$$Y = CW = S[1-\exp(-kA/Q)]Qt \quad (15)$$

The experiments described here were all carried out at a given spray time, t*. Inserting this in Eq. 12, and noting the exponential simplification for small exponential values it follows that:

$$Y = St^*[Q-kA] \quad (16)$$

where Eq. 6, again, has been utilized. This depends on the length of time of spraying and by virtue of Q, on spraying rate and evaporation rate. The Q and S terms also depend on the temperature for several reasons, and hence the temperature effect is not necessarily predictable from the drug substance (or excipient) to drug substance (or excipient).

To test the self-consistency of the views presented above, the data corresponding to a spray-rate of 45 g/sec were selected. The amount of guaifenesin dissolved is determined graphically from Figure 1 (as a function of temperature) and shown in Table 5.

If Q in Eq. 16 is considerably larger than kA, then the logarithmic transformation of Eq. 16 becomes:

$$Y = St^*\phi/T \quad (17)$$

where use has been made of Eq. 8., Eq. 17 may be written:

$$\ln[YT] = \ln[S] + \ln[t^*\phi] \quad (18)$$

Solubility is a logarithmic function in (1/T), i.e.:

$$\ln[S] = -\Delta H_s/RT + \ln[S_o] \quad (19)$$

where ΔH_s is the heat of solution and $[S_o]$ is a pre-exponential solubility constant. Introducing Eq. 19 into Eq. 18 gives:

$$\ln[YT] = \zeta - \Delta H_s/RT \quad (20)$$

TABLE 5
Amount of Guaifenesin Dissolved in Film as a Function of Temperature at a Spray Rate of 45 g/sec

Temperature (°C)	T (°K)	1000/T	Y
40.8	313.8	3.187	1.0
46	319	3.135	1.2
51	324	3.086	1.4
55.5	328.5	3.044	1.6

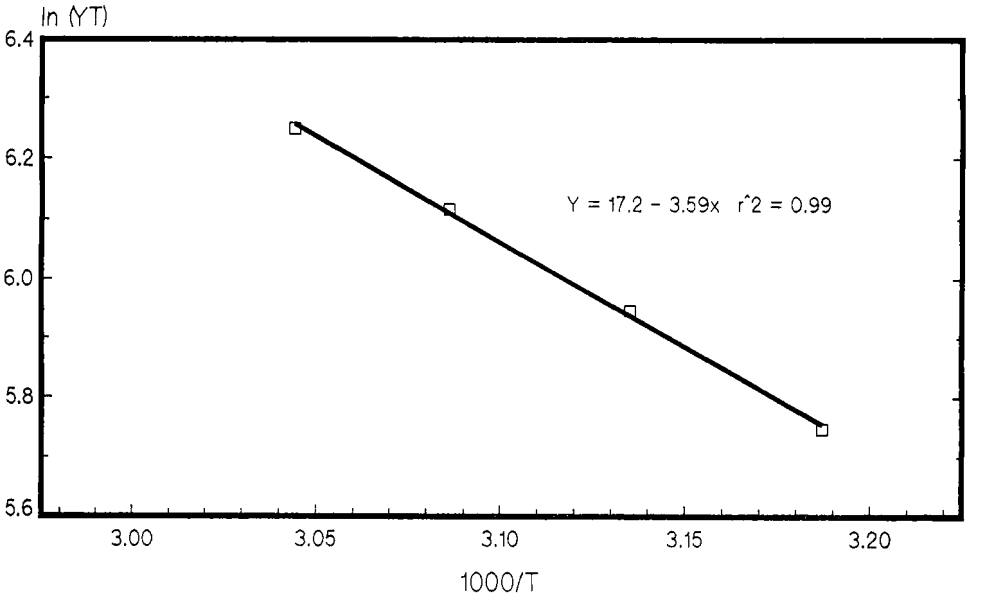

FIGURE 3

A Van't Hoff plot of the amount of guaifenesin dissolved in the film coating as a function of temperature (Eq. 20).

where the constant ζ is given by:

$$\zeta = \ln[t^*\phi S_o] \quad (21)$$

When the data in Table 5 is plotted according to Eq. 18 a straight line ensues, lending credence to the proposed model (Figure 3).

In Chapter 11 of the review text entitled "Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms,"[4] the authors state that dissolution can be minimized by maintaining a small particle size of the spray mist and by using a low spray rate.

In our study, an atomization pressure of 2-4 bar was selected because it represented the typical range currently used to apply aqueous-based films. Our data revealed that atomization air pressure did not significantly affect the migration of guaifenesin and stearic acid to the film, but spray rate and inlet air temperature did have a significant effect.

Prior compatibility studies with DSC indicated that there were no interactions between guaifenesin, stearic acid, and the HPMC-based coating polymer. Because the presence of stearic acid and guaifenesin in the film had no deleterious effect on the film itself (chemical or physical), the only variable that was used to determine the recommended coating process was total processing time. An inlet temperature of 50°C, a spray rate of 60 g/min and an atomization pressure of 2.0 bar were used for subsequent clinical manufacturing.

CONCLUSIONS

1) A relationship exists between the amount of drug and excipient that dissolves to applied film during the coating operation as a result of the spray rate and inlet air temperature.

2) The rate of drug and excipient migration is probably controlled by the solubility of the components in the coating solution.

3) DSC is an easy and accurate analytical test to quantitate the drug and excipients present in a dried film.

4) A simple 2^3 orthogonal factorial design for the variables of inlet air temperature and spray rate, over a range for atomization air pressure of 2-4 bar, can be used to model and predict the extent of migration of a drug and/or excipient to the film coating.

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