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WATER BASED SILICONE ELASTOMER CONTROLLED RELEASE TABLET FILM COATING IV PROCESS EVALUATION

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ABSTRACT

The processing conditions in an air suspension column were found to be critical in producing controlled release polyethylene glycol-silicone elastomer tablet film coatings. The coating equipment used was also shown to play a major role in determining the permeability of the resultant tablet coatings. This pronounced process dependent phenomenon was explained by the film layering mechanism involved in the formation of the polyethylene glycol containing silicone elastomer coating on tablets.

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INTRODUCTION

In recent years, air suspension coating technique has gained considerable popularity in the application of controlled release aqueous latex and pseudolatex coating on solid dosage forms. The influence of the operation processing variables in an air suspension coating process on the drug release characteristics of the coated products has been shown to be highly significant[1,2,3]. The identification of the critical process variables in a coating operation not only has practical significance, but also furnish valuable information concerning the film formation mechanisms. In this study, process variables which were considered in the coating of potassium chloride tablets using the PEG-silicone elastomer system, included (1) the method for the mixing of coating components, (2) the coating temperature, (3) the solids content of the coating dispersion, (4) the atomization pressure, and (5) the rate of spraying. The scale-up coating involving the use of a whole batch of potassium chloride tablets was conducted using the air suspension column and a side-vented coating pan. The release of potassium chloride from tablets coated in these two different coating machines was compared.

EXPERIMENTAL

Materials:

The coating components and potassium chloride were obtained from the same source as reported previously[4]. Avicel PH 101 was supplied by FMC Corporation.

Methods:

The Effect of Process Variables on Release Pattern:

The coating formulation containing silicone to silica in a ratio of 2 to 1 and 30% PEG 8000 was used for this study. Potassium chloride tablets mixed with

Table 1. Levels for the Process Variables Evaluated in the Air Suspension Column Coating Process.

Variable	Level		
	Low	High	Fixed*
Time of Sonication (minute)	0.0	20.0	10.0
Coating Inlet Air Temperature (°C)	50.0	70.0	60.0
Solids Content of Coating Dispersion (% W/W)	15.0	35.0	25.0
Rate of Spraying (g/min.)	10.0	22.0	16.0
Atomization Pressure (Kp/cm*cm)	1.5	3.5	2.5

* Except for the variable under evaluation, all other variables are fixed at these levels.

1.50 Kg red colored lactose tablets were coated at two levels (high vs. low) of each variable while the other four variables were fixed. The levels for each variable are given in Table 1. For each variable level, two coating batches were prepared. Three coated tablet samples from each batch were tested for the release of potassium chloride in deionized water[4].

Scale Up Coating Using Two Different Machines:

A batch containing only potassium chloride tablets was too dense to be air suspended in the coating column, therefore, potassium chloride tablets formulated with Avicel PH 101 were used for the scale-up coating. Each tablet contained 300 mg of potassium chloride and 150 mg of Avicel PH 101. The tablets were

prepared using a compression granulation method. Potassium chloride powder and Avicel PH 101 were mixed in a laboratory size V-blender[a] for 10 minutes. The powder mixture was roller compacted using the Chilsonator[b] at an air pressure of 28 psi and oil pressure of 640 psi. Granules were formed by breaking the potassium chloride-Avicel compacts through a 16 mesh stainless steel screen on the Stokes oscillating granulator[c]. Tablets which were 7/16 inch standard cup shaped were compressed using a Stokes Model RB2 rotary press[d] run at a speed of 600 tablet/minute. The six-inch Glatt air suspension coating column[e] and the 24-inch Accela Cota perforated side vented coating pan[f] were used in this study. The coating formulation used in this study contained silicone to silica in a ratio of 2 to 1 and PEG 8000 at a loading level of 25%.

Statistical Comparison of the Release Profiles of Potassium Chloride:

Since the same coated tablet sample was used repeatedly for all the sampling time intervals during a dissolution test, the release profiles of potassium chloride from tablets coated at the two levels of each operation variable were compared using the ANOVA statistical model for a repeated measurement design shown as follows[5,6]:

$$Y_{ijkl} = u + F_i + B_{(i)j} + S_{(ij)k} + \delta_{(ij)} + T_l + FT_{il} + BT_{(i)jl} + ST_{(ij)kl} + \epsilon_{(ijkl)}$$

Where Y = the cumulative percent of potassium chloride released from a specific coated tablet at a specific sampling time.

u = the overall mean.

F_i = the process variable effect (i = 1,2).

$B_{(i)j}$ = the coating batch effect (j = 1,2).
$S_{(ij)k}$ = the coated tablet sample effect for F and B equal to i and j (k = 1,2,3).
$\delta_{(ijk)}$ = the restriction error[5].
T_l = the sampling time effect (1 = 1,2,3,4,5,6)
FT_{il}, $BT_{(i)jl}$ and $ST_{(ij)kl}$ are interaction effects for the specific variables and $\varepsilon_{(ijkl)}$ is the random error. Table 2 gives the expected mean squares for

Table 2. Expected Mean Squares for the Statistical Model for the Determination of the Process Variable Effect on the Release Profile of Potassium Chloride from Coated Tablets.

Source of Variation	Degree of Freedom	Expected Mean Squares
Process Variable F_i	1	$\varepsilon^2 + 6\sigma^2_\delta + 6\sigma^2_S + 18\sigma^2_B + 36\phi(F)$
Coating Batch $B_{(i)j}$	2	$\varepsilon^2 + 6\sigma^2_\delta + 6\sigma^2_S + 18\sigma^2_B$
Tablet Sample $S_{(ij)k}$	8	$\varepsilon^2 + 6\sigma^2_\delta + 6\sigma^2_S$
Restriction Error $\delta_{(ijk)}$	0	$\varepsilon^2 + 6\sigma^2_\delta$
Sample Time T_l	5	$\varepsilon^2 + \sigma^2_{ST} + 3\sigma^2_{BT} + 12\phi(T)$
F x T Interaction FT_{il}	5	$\varepsilon^2 + \sigma^2_{ST} + 3\sigma^2_{BT} + 6\phi(FT)$
B x T Interaction $BT_{(i)jl}$	10	$\varepsilon^2 + \sigma^2_{ST} + 3\sigma^2_{BT}$
S x T Interaction $ST_{(ij)kl}$	40	$\varepsilon^2 + \sigma^2_{ST}$
Random Error $\varepsilon_{(ijkl)}$	0	ε^2

this model. In order to have a more sensitive test on the process variable effect, a pooled error term with ten degrees of freedom was obtained by combining the sum of square for the batch effect ($B_{(i)j}$) and the tablet sample effect ($S_{(ij)k}$) following the pooling procedure described by Anderson and McLean[6]. The sum of square for each term in the model was determined using the SAS (Statistical Analysis System) GLM (General Linear Models) program.

RESULTS AND DISCUSSION

The Effect of Sonication of the Coating Dispersion:

The PEG-silicone elastomer dispersion used was a binary dispersion of silicone elastomer and colloidal silica in the continuous phase of an aqueous PEG solution. Due to the multicomponent nature of this system, the degree of mixing of the three components may be critical in achieving reproducible coating results. The comparison between the release profiles for potassium chloride tablets coated with dispersions prepared by 10 minutes of simple stirring using a magnetic stirrer and a stir bar, and 20 minutes of sonication, respectively, is shown in Figure 1. The release profiles and the ANOVA result given in Table 3 indicate that the type of mixing exerted no significant effect on the release pattern of the coated tablets. This result would suggest that simple mechanical stirring is as effective as the sonication in achieving a uniform coating dispersion.

The Effect of Coating Temperature:

In an aqueous film coating process, the coating temperature should be sufficient to produce the most efficient moisture removal but at the same time, not too high to cause spray drying of the coating dispersion. Because of the low melting point of the

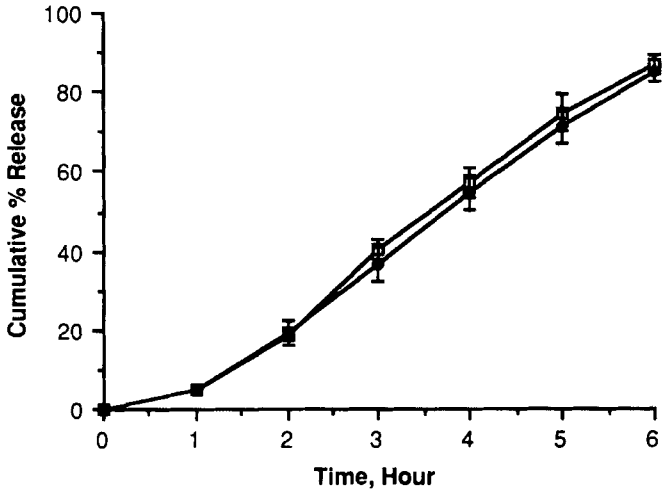

Figure 1. Release Profiles of Potassium Chloride from Tablets Coated with PEG-Silicone Elastomer Dispersions Prepared by Two Different Mixing Methods.
Key: (□) Sonication and (◆) Simple Stir Bar Mixing.

Table 3. Analysis of Variance for the Determination of the Effect of Sonication of Coating Dispersion on the Release Profile of Potassium Chloride from Coated Tablets.

Source	df	SS	MS	F
F_i	1	60.134	60.134	1.255
E*	10	479.294	47.929	-
$\delta_{(ijk)}$	0	-	-	-
T_i	5	59194.454	11838.891	5151.824**
FT_{il}	5	47.263	9.453	4.114**
$BT_{(i)jl}$	10	27.257	2.726	1.186
$ST_{(ij)kl}$	40	91.906	2.298	-
$\epsilon_{(ijkl)}$	0	-	-	-

* Pooled error term from $B_{(i)j}$ and $S_{(ij)k}$ in model.

** Significant at $\alpha = 0.01$ level.

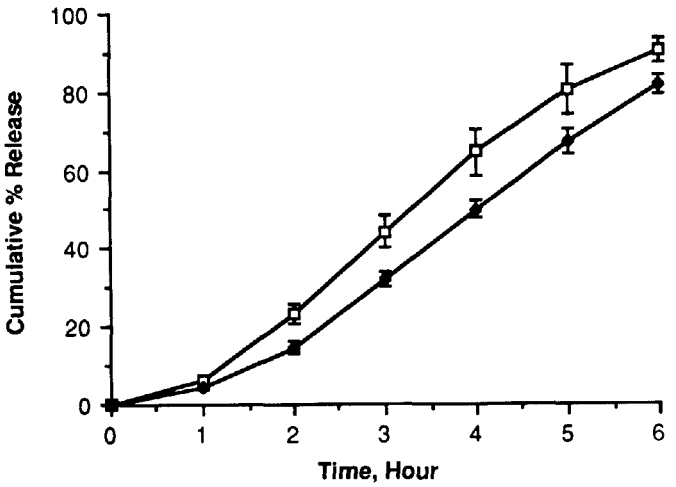

Figure 2. Release Profiles of Potassium Chloride from Tablets Coated with PEG-Silicone Elastomer Dispersions at two Different Temperatures.
Key: (□) 50°C and (◆) 70°C.

PEG's used in the silicone elastomer coating system, the coating temperature may affect the coating results due to the melting of the PEG. Figure 2 shows the release profile of potassium chloride from tablets coated at 50°C and 70°C, respectively. The ANOVA result given in Table 4 concludes that tablets coated at a higher temperature released the active ingredient at a significantly slower rate ($P<0.01$). This temperature dependent phenomenon is probably the result of the melting of PEG 8000 in the silicone elastomer matrix. At an inlet air temperature of 70°C, the surface temperature of the tablets would be high enough to melt the PEG. The increased coating tackiness as indicated by the reduction in the tablet fluidization during the high temperature coating provided the evidence of PEG melting in the coating. Therefore, the

Table 4. Analysis of Variance for the Determination of the Effect of Coating Temperature on the Release Profile of Potassium Chloride from Coated Tablets

Source	df	SS	MS	F
F_i	1	1664.645	1664.645	33.694**
E*	10	494.050	49.405	-
$\delta_{(ijk)}$	0	-	-	-
T_l	5	59317.884	11863.577	3803.648**
FT_{il}	5	275.742	55.148	17.681**
$BT_{(i)jl}$	10	8.613	0.861	<0
$ST_{(ij)kl}$	40	124.764	3.119	-
$\varepsilon_{(ijkl)}$	0	-	-	-

* Pooled error form from $B_{(i)j}$ and $S_{(ij)k}$ in the model

** Significant at $\alpha = 0.01$ level

combined effect of close packing between film layers and enhanced coalescence of silicone elastomer at elevated temperature are responsible for the decrease permeability of the resultant tablet coating.

The Effect of Solids Content of the Coating Dispersion:

The use of coating dispersions with high solids content leads to the reduction in coating time, energy consumption and in labor cost. However, the rheological constraint on the coating system usually precludes the use of concentrated coating dispersion. Also, it is necessary to be aware of the impact of the change of this variable on the properties of the resultant coating. Figure 3 shows the effect of solids content of the coating dispersion on the release

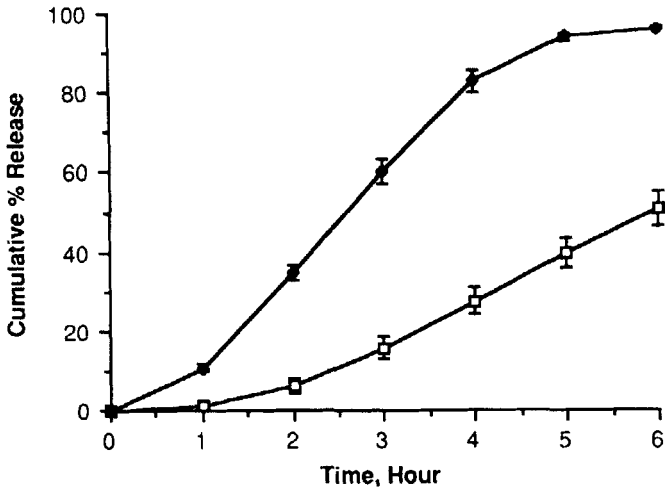

Figure 3. Release Profiles of Potassium Chloride from Tablets Coated with PEG-Silicone Elastomer Dispersions Containing Two Different Solids Contents.
Key: (□) 15% and (◆) 35%.

profiles of potassium chloride from coated tablets. Tablets coated with the 15% dispersion exhibited a significantly slower release rate than those coated with the 35% dispersion ($P<0.01$). This result is explained in light of the film formation mechanism proposed as follows. During a coating process using an air suspension column, the coating dispersion is sprayed onto the tablets which are air suspended inside the center coating chamber. Evaporation of water from the coating dispersions deposited on the tablet takes place as the tablets travel to the top of the fluidized tablet bed and descend by the periphery of the chamber to the bottom of the coating column. Another coating cycle starts as soon as the tablets reenter the coating chamber. The polymer film coating is actually formed by a cyclic film layering process. A further analysis

of the film forming process reveals its dynamic aspect. Within a very short period of time, several events take place concurrently or consecutively, including the wetting of the substrate surface, the spreading of the dispersion, the evaporation of water and the subsequent coalescence of the film formers[8]. In order to ensure a uniform spreading of the coating dispersion, the rate of spreading is particularly important because the rapid evaporation of water would cause the instantaneous gelling of the dispersions and the arrest of spreading. The rate and extent of spreading, which are affected by the surface tension of the coating dispersion and the surface energy of the coating substract, are also controlled by the viscosity of the coating dispersions. Increasing the viscosity greatly increased the time required to reach maximum spreading. Since the viscosity of the 35% coating dispersion was almost six times higher than the 15% dispersion, it is conceivable that the extent of spreading achieved by the concentrated dispersions was much less than that attained by the diluted dispersion. Also, because of the lower water content, droplets of the concentrated dispersions tended to gel at a faster rate, which further reduced the extent of spreading. Furthermore, at the same spraying rate, the same volume of coating dispersion was delivered during each coating cycle; however, for the concentrated dispersions, more coating solids were deposited on the tablet resulting in a thicker film layer. Therefore, with the same coating weight, a tablet film coating consisting of fewer but thicker film layers was produced using the concentrated coating dispersion. A reduction in the number of film layers formed within a tablet coating may reduce the tortuosity of the coating. It was proposed that a concentrated coating dispersion tended to yield a

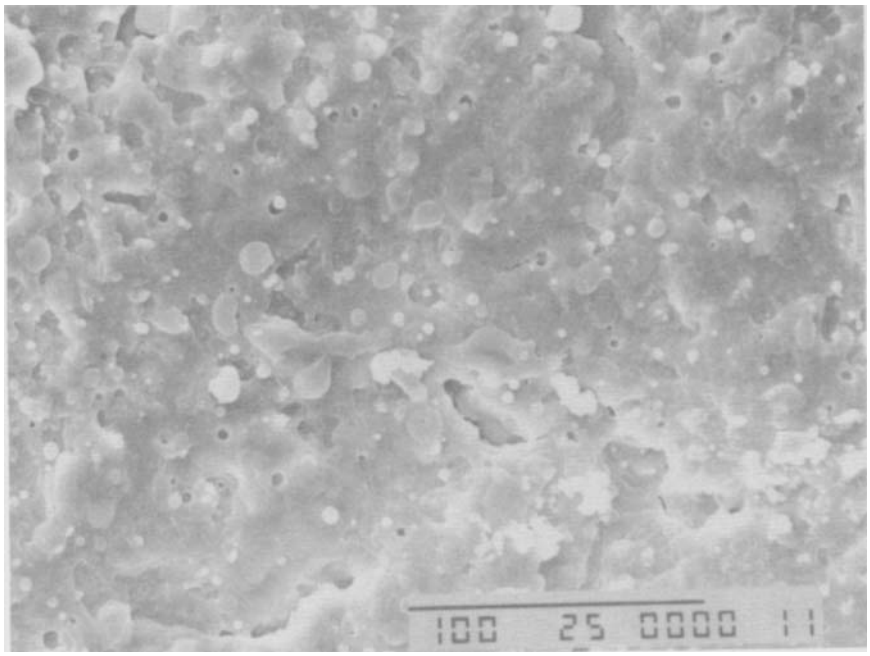

Figure 4. SEM Photomicrographs for Silicone Elastomer Tablet Coating Produced Using a Coating Dispersion with a 35% Total Solids Content. Magnification x 350.

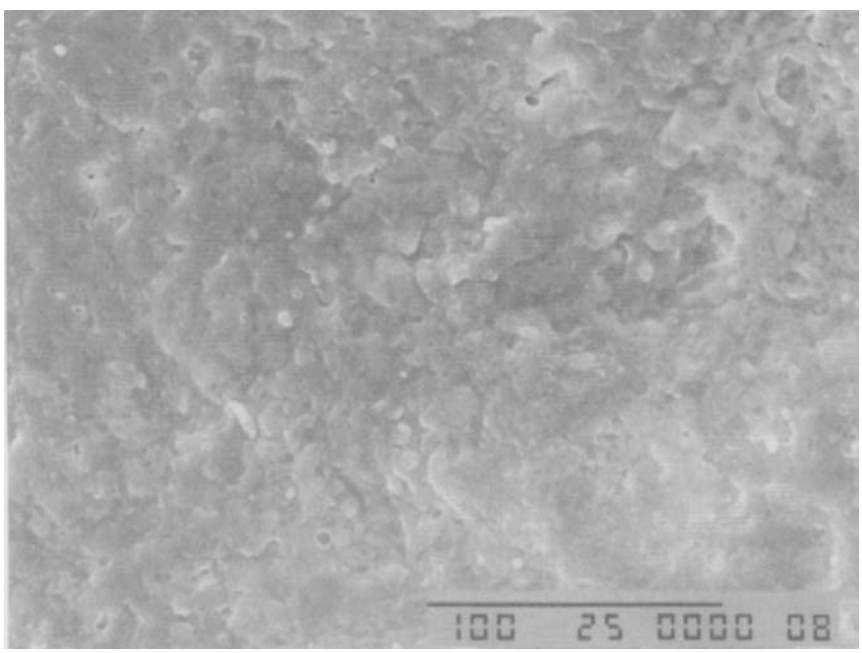

Figure 5. SEM Photomicrographs for Silicone Elastomer Tablet Coating Produced Using a Coating Dispersion with a 15% Total Solids Content. Magnification x 350.

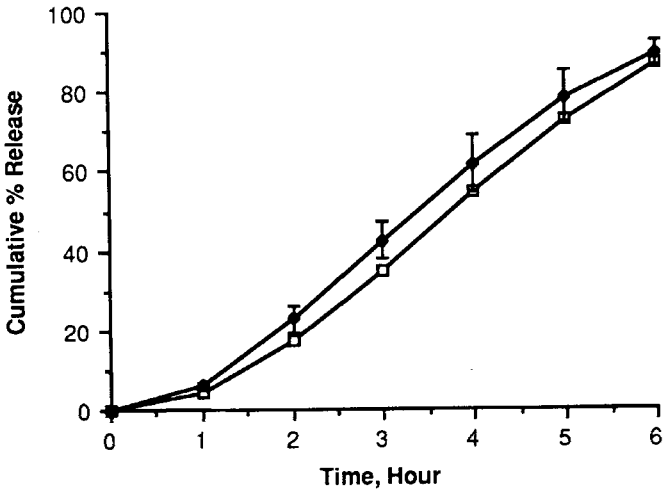

Figure 6. Release Profiles of Potassium Chloride from Tablets Coated with PEG-Silicone Elastomer Dispersions at Two Different Spraying Rates.
Key: (□) 16 g/min. and (◆) 22 g/min.

tablet coating with a more porous and of less continuous nature which accounted for the faster drug release behavior. Figures 4 and 5 show the SEM photomicrographs of the tablet film coating produced by the diluted and concentrated coating dispersions respectively. The relatively more porous surface morphology for the tablet film coating formed by the concentrated dispersion appears to support the above postulation. Additionally, the discrete spherical dried droplets of dispersion formed on the coating surface (Figure 4) also show the evidence of reducing spreading of the concentrated coating dispersion.

The Effect of Spraying Rate:

The effect of coating dispersion spraying rate on the drug release characteristics for the coated tablets is shown in Figure 6. Statistical analysis

demonstrated the significance of this process variable effect ($P<0.01$). The release of potassium chloride from tablets coated at a faster spraying rate was much faster than those coated at a lower spraying rate. It was noted that at a spraying rate of 22 g/min., the coating process was completed in 35 minutes, whereas, 80 minutes of processing time was required for coating conducted at a spraying rate of 10 g/min. At a higher spraying rate, more coating material would be delivered from the nozzle and deposited onto the tablets during each coating cycle. As a result, coating at a faster spraying rate tended to produce a less compact and more porous tablet film coating with fewers film layers and enhanced drug permeability.

The Effect of Atomization Pressure:

The effect of atomization pressure used for producing the coating spray on the release characteristics of coated potassium chloride tablets is illustrated in Figure 7. Statistical analysis indicates that the tablets coated at a high atomization pressure release the active ingredient at a faster rate ($P<0.01$). It is conceivable that at a high atomization pressure finer droplets of the coating dispersion are produced. The resulting tablet coatings should be more continuous and less permeable. However, the result of this study contradicts the above conclusion. Apparently, the droplet size reduction may not be the dominant effect of the atomization pressure in this case. Because of the comparatively low viscosity of the coating dispersion used in this study, it is felt that the degree of droplet size reduction achieved at the high and low atomization pressures was not significantly different. In order to explain the effect of this process variable, a further analysis of the atomization process in the air suspension column is

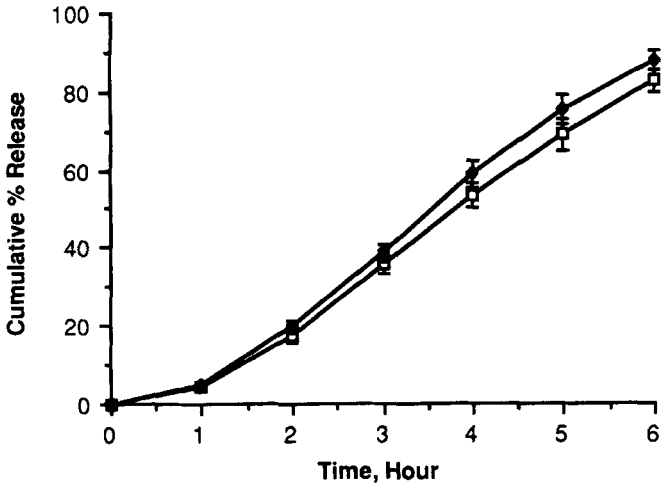

Figure 7. Release Profiles of Potassium Chloride from Tablets Coated with PEG-Silicone Elastomer Dispersions at Two Different Atomization Pressures.
Key: (□) 1.5 Kp/cmxcm and (◆) 3.5 Kp/cmxcm.

necessary. The pneumatic pressure used for atomization is supplied by an external compressed air source. The unheated compressed air is delivered by the distribution tube through the periphery of the spraying nozzle, atomizing the coating dispersion and flowing concurrently with the heated fluidizing air into the coating chamber. When the coating was conducted at a high atomization pressure, the coating chamber probably was flooded with a large volume of cool compressed air which would cause a localized temperature drop. The increased air velocity associated with the high atomization pressure may also produce a negative effect on the spreading of the coating dispersion[9]. It is thought that the combined effect of these two factors may lead to the formation of a more porous and permeable film coating.

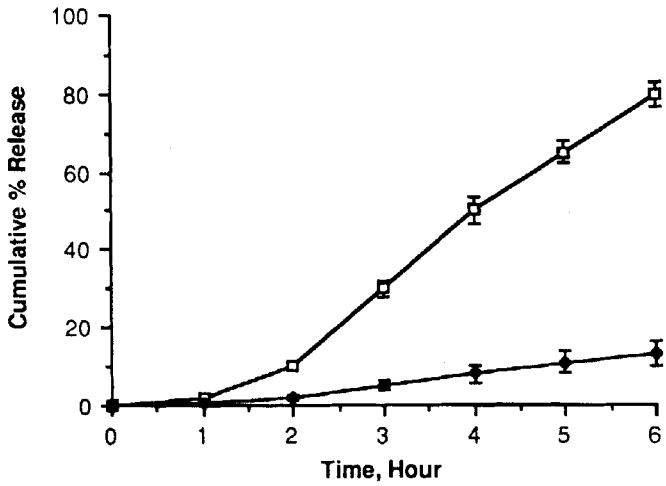

Figure 8. Release Profiles of Potassium Chloride from Tablets Coated with PEG-Silicone Elastomer Dispersions Using Two Different Coating Machines.
Key: (□) Air Suspension Column and (◆) Side Vented Pan.

Scale-Up Coating Studies Using the Air Suspension Coating Column and the Side Vented Coating Pan:

The release profiles of potassium chloride from formulated potassium chloride tablets coated with 25% PEG 8000 loaded silicone elastomer using the 6-inch air suspension column and the 24-inch side vented pan are shown in Figure 8. The column coated tablets exhibited a much faster drug release than the pan coated tablets. This equipment dependent coating phenomenon may be attributed to the difference in the dynamic aspect of the coating process associated with the equipment differences. Since tablets in an air suspension column are fluidized inside the coating chamber by a large volume of hot air, the physical contact between tables with the fluidized tablet bed is somewhat moderate. The SEM photomicrograph for the surface of a column coated tablet is shown in Figure 9. Droplets of dried

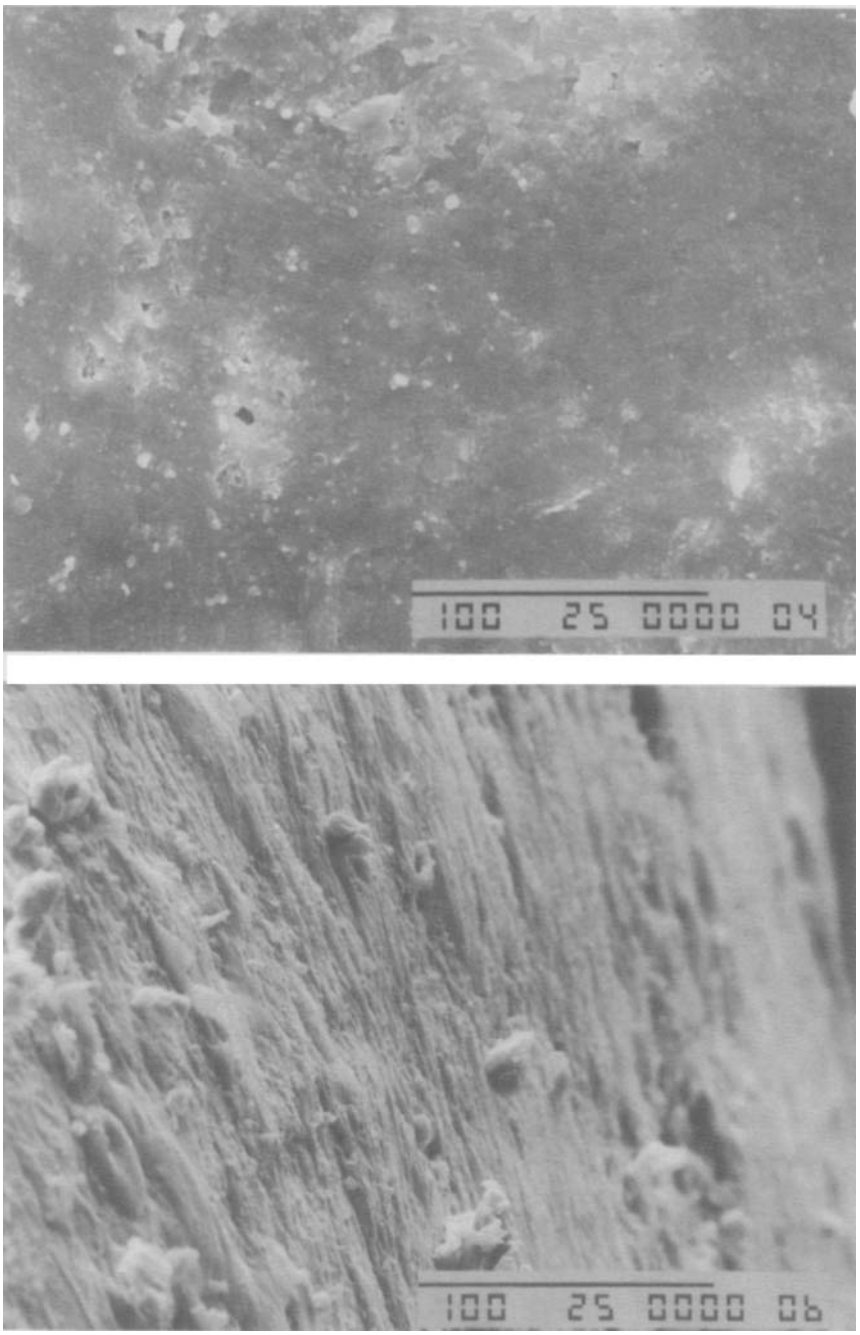

Figure 9. SEM Photomicrographs for a Column Coated Silicone Elastomer Tablet Coating Containing 25% PEG 8000. Key: (A) Surface and (B) Cross-Section. Magnification x 350.

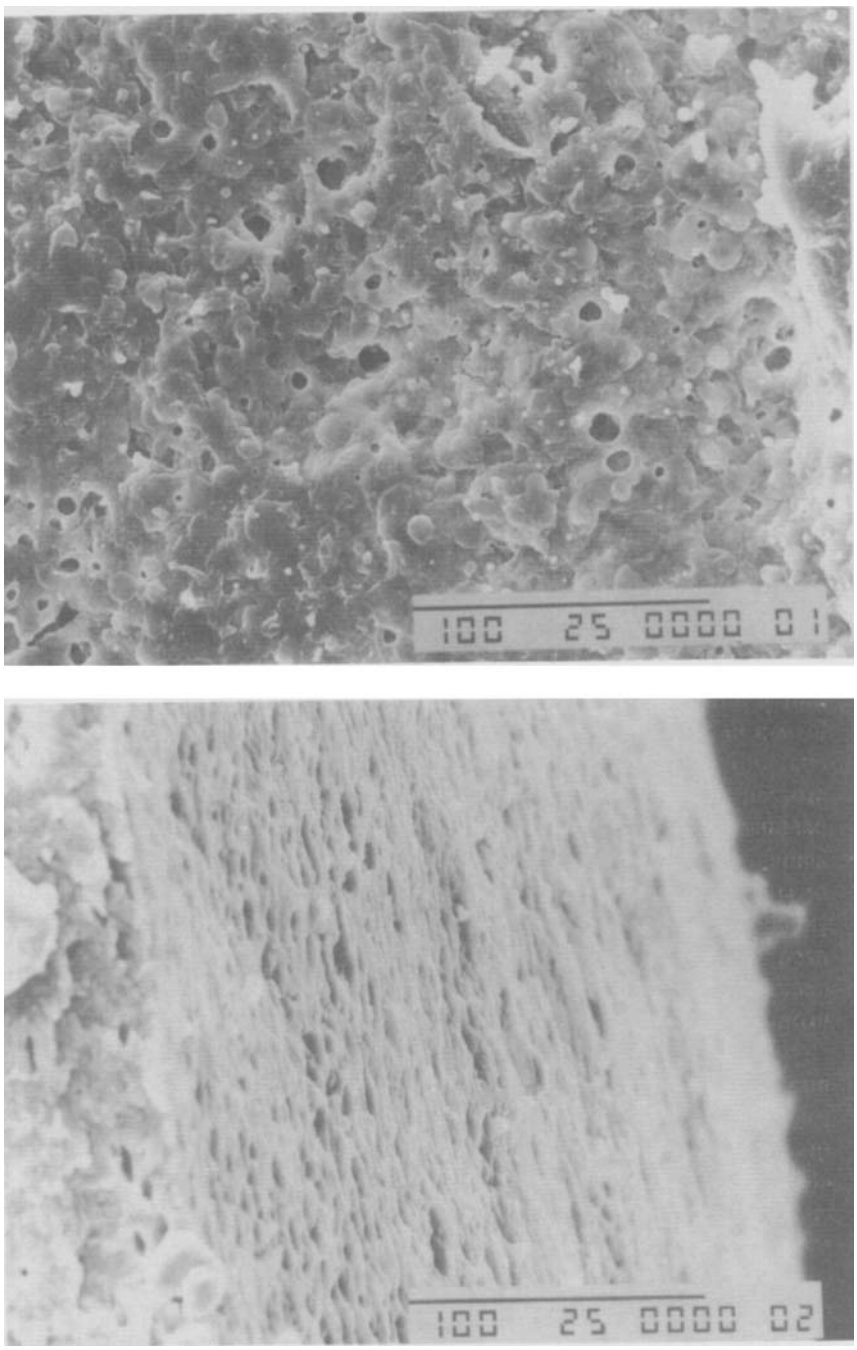

Figure 10. SEM Photomicrographs for a Pan Coated Silicone Elastomer Tablet Coating Containing 25% PEG 8000. Key: (A) Surface and (B) Cross-Section. Magnification x 350.

coating dispersion are seen scattering over the entire surface. The cross section (Figure 9) of the coating shows a film coating layer structure with distinct between layer pores. The granular appearance and the porous layered texture of the coating account for the high drug permeability of the coating.

In a rotating pan, intensive rubbing between tablets takes place in the tumbling tablet bed. As the coating starts, the coating dispersion applied tends to overwet the tablets moving on the surface of the tumbling tablet bed. The tumbling movement of the tablets promotes the distribution of the coating dispersion throughout the entire tablet population. This movement provides a shearing effect which assists the spreading of the coating on the tablet surface. The forced spreading of the coating dispersion apparently leads to the formation of a continuous and coherent tablet film coating as shown in Figure 10. The compact structure of the coating produced by the pan coating process explained the decreased coating permeability.

CONCLUSION

The coating conditions in the air suspension column were found to be critical in producing polyethylene glycol-silicone elastomer coating with reproducible release behavior. Significant process variables including the concentration of the coating dispersion, the temperature of the inlet air, the atomization pressure and spraying rate of the coating dispersion were identified. Significant differences in drug release profiles were also exhibited by tablets coated using an air suspension column and a side vented pan. This processing dependent coating result was

caused by the difference in the dynamic aspects of these two processes. The tablets coated in the pan seem to have an environment producing more spreading of the coating dispersion on the tablet surfaces which resulted in a more continuous and less permeable coating.

ACKNOWLEDGMENT

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NOTES

(a) Twin Shell Dry Blender, the Patterson-Kelly Company, Inc., East Stroudsburg, Pennsylvania.

(b) Chilsonator, Model DM, The Fritzpatrick Company, Elmhurst, Illinois.

(c) Stokes Oscillating Granulator, Model 43A, F.J. Stokes Machine Company, Philadelphia, Pennsylvania.

(d) 24-Inch Acela Cota, Model 24, Thomas Engineering, Inc., Hoffman Estates, Illinois.

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