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A METHOD OF COATING NON-UNIFORM GRANULAR PARTICLES

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ABSTRACT

A method was developed for coating non-uniform granular particles in a uniform and controlled manner. Specific surface area was calculated based on the sieve-analysis data of uncoated theophylline granules which was used as the model compound. Theophylline granules were coated with different amounts of Eudragit® L30D utilizing a Wurster coating apparatus. The in-vitro dissolution rate profiles of several batches were determined. Standard dissolution curves were established based on the amount of Eudragit® L30D applied per unit area of theophylline granules. Using these curves as a standard, a prediction of dissolution rate could be made based on the knowledge of specific surface area of the theophylline granules and the amount of coating applied.

INTRODUCTION

Film-coated tablets can be prepared by depositing one or more film-forming polymers onto the core surface using different types of equipment and a wide variety of coating procedures. These processes are easily controlled and are well defined due in large measure to the nature of the particular tablet formulation. Tablets of a given formulation are compressed to a specific set of requirements (i.e., thickness, shape and weight). Therefore, each batch of tablets of a given weight will have a uniform apparent surface area to be coated. In addition, if there is uniform spraying/tumbling in the equipment, each tablet in the coating operation at any particular time should be representative of every other tablet. Therefore, the amount of coating applied is easily determined during the process by monitoring the weight gain of a group of tablets undergoing the coating operation (1). Usually the finished tablet contains no more than 2 to 5 percent by weight of the coating material (2).

Non-uniform granular systems can be coated with film-forming polymers as well (3,4). It is very difficult to monitor the weight gain during such a process because each particle is irregularly shaped and the weights of the particles are not uniform. Even if the particles were uniform, it would present a challenge to the formulator to

weigh a representative number of particles to monitor the weight gain during the process. Therefore, in a multi-particulate coating operation, the formulator does not have the convenience of being able to monitor the amount of coating applied per unit surface area by using the weight gain measurement. For this reason, most processes dealing with coating multiparticulate granular substances usually employ two concurrent methods to control the process: (1) use a narrow sieve fraction of the uncoated granules; and, (2) apply a fixed weight of polymeric substance by using a specific amount of coating suspension or solution (3,4). The former method is not cost effective because not all of the raw material can be utilized from a given batch. In addition, there is a possibility that variation in surface area can occur between two lots of granular material that meet a given mesh fraction specifications. For example, if two lots are labelled as 12/20 mesh material, one could be 12/14 mesh while the other could be 18/20 mesh. Most of the time the latter method is effective. However, if there is skewing of the mesh fraction as already mentioned, there is a possibility that the coating operation will result in a product that could be out of specification. It is the purpose of this report to show a convenient means of coating non-uniform granular particles in a uniform fashion and to

use the method as a tool to determine the amount of coating to apply.

EXPERIMENTAL

Materials

Theophylline anhydrous granules[a,b] and talc[c] were USP grade. Polyethylene glycol 8000[d] and xanthum gum[e] (Keltrol®) were NF grade. The coating system contained Eudragit® L30D[f] which consisted of a copolymer of acrylic-methacrylic acid and acrylic-methacrylic acid methyl or ethyl esters. All reagents were analytical grade or better.

Equipment

The coating experiments were conducted using two different air suspension coating columns[g,h].

The dissolution tests were conducted using apparatus II, USP XXI/NF XVI with paddle. Agitation speed of 50 rpm was used in this study. Five hundred milligrams of coated granules were used with 900 mL of dissolution medium at 37°C. The dissolution medium consisted of a pH 3.0 phosphate buffer. Samples were removed at suitable time intervals. The collected samples were assayed spectrophotometrically using a Beckman DU®-6 spectrophotometer[i] at 271 nm for theophylline content.

Sieve-Analysis

The size distribution of the theophylline granules was evaluated by a sieve-analysis technique using a set of U.S.

TABLE I

Composition of Coating Dispersion

	Percent w/w
Eudragit® L30D (Solid Content)	53.7
Talc, USP	40.6
Polyethylene Glycol 8000, NF	5.3
Keltrol® (food grade)	0.4
Distilled Water	q.s.

standard sieves, namely #20, #30, #40, #50, #60 and base pan. The sieving load was 100 grams. The sieve nest was shaken using an automatic shaker for ten minutes. The net weight that was retained on each sieve was then determined and recorded. Duplicate samples were run for each batch of theophylline. The average values were used for the calculation of particle size distribution.

True Density

The true density of each sample of theophylline granules was determined by using a solvent displacement method.

Coating Operation

A predetermined amount of theophylline granules was coated in an air-suspension column using an Eudragit® L30D dispersion. The composition for the dispersion is presented in Table I. Different amounts of the Eudragit® L30D coating were applied to the theophylline granules by spraying predetermined amount of the coating dispersion onto the theophylline granules. Samples were taken at appropriate

intervals. In all, a total of 36 samples were collected for testing and evaluation of the results.

THEORETICAL

Calculation of Surface Area

Surface area can be related to particle size by plotting particle size versus cumulative weight percentage oversize from sieve analysis data on a logarithmic-probability grid. Linearity of this plot, shown in Figure 1, is indicative of a log-normal distribution (5). The geometric mean diameter (dg) can be determined directly from the plot by determining the particle size which corresponds to the 50 percent probability value. The geometric standard deviation (σg) for each log-normal distribution material can be calculated from the equation:

$$\sigma g = \frac{84.13\% \text{ size}}{50\% \text{ size}}$$

where the numerator value is the extrapolated value at 84.13% oversize from Figure 1.

The calculation of specific surface area from a log-normal distribution has been reported by Herdan (5), based on an equation derived by Hatch and Choate (6). For a size distribution by weight, the equation for mean volume-surface diameter (d_{VS}) was expressed by Parrott (7) as:

$$\log d_{VS} = \log dg - 1.151 \log^2 \sigma g$$

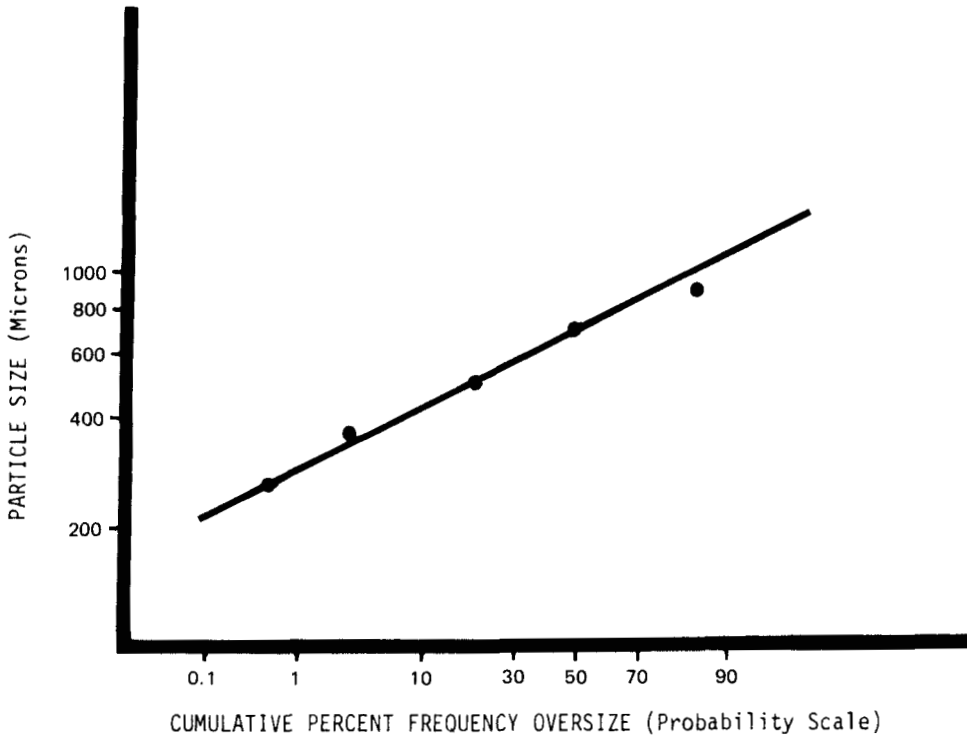

FIGURE I
Plot of Log-Normal Size Distribution for Theophylline Granules

Assuming the particles were spherical, the specific surface area (SA) was expressed by Martin, et al (8) as:

$$SA = \frac{6}{\rho d_{vs}}$$

where ρ = true density

RESULTS AND DISCUSSIONS

A series of coating experiments were carried out with eight different batches of theophylline granules. The granules were coated in an Aeromatic S-4 column with the formula given in Table I.

Particle size distribution and the true density of each of the eight batches of theophylline granules were determined. The geometric mean diameter and the specific surface area for each of these batches were then calculated (Table 2). Different amounts of the coating suspension were applied to each of the eight batches of the theophylline granules. At various time intervals throughout each of the eight coating cycles, samples were withdrawn and the amount of coating applied per unit area (cm^2) was calculated. The maximum amount applied on each of the eight batches is presented in Table 2.

A graph of percent of theophylline released versus the amount of Eudragit® L30D applied per cm^2 of theophylline granules for all 36 samples was constructed (Figure 2). The three curves show the percent theophylline released at three different time intervals; namely, 1, 2 and 3.5 hours. Using these curves as a standard and knowing the surface area of any batch of theophylline, the desired dissolution rate profile could be obtained.

To test this hypothesis, two lots of theophylline granules, having specific surface area of 97 and 65 cm^2/g respectively, were coated with the same amount of coating suspension of the formula in Table 1. The data showed dramatic differences in dissolution profile between these two batches of coated granules (Figure 3). This experiment

TABLE 2

Physical Parameters of Theophylline Granules Used in this Study

Theophylline Lot No.	Geometric Mean Diameter (microns)	True Density (gm/cc)	Specific Surface Area (cm^2/g)	Maximum Solid Applied per Unit Surface Area (mg/cm^2)
1*	740	1.420	64.41	1.013
1*	700	1.450	65.16	1.036
1*	720	1.470	61.56	0.846
2	780	1.430	58.03	0.898
3	720	1.430	61.88	0.842
4	730	1.466	61.18	1.209
5*	760	1.465	60.23	1.229
5*	760	1.465	60.23	1.336

* Different drums from the same lot of theophylline granules.

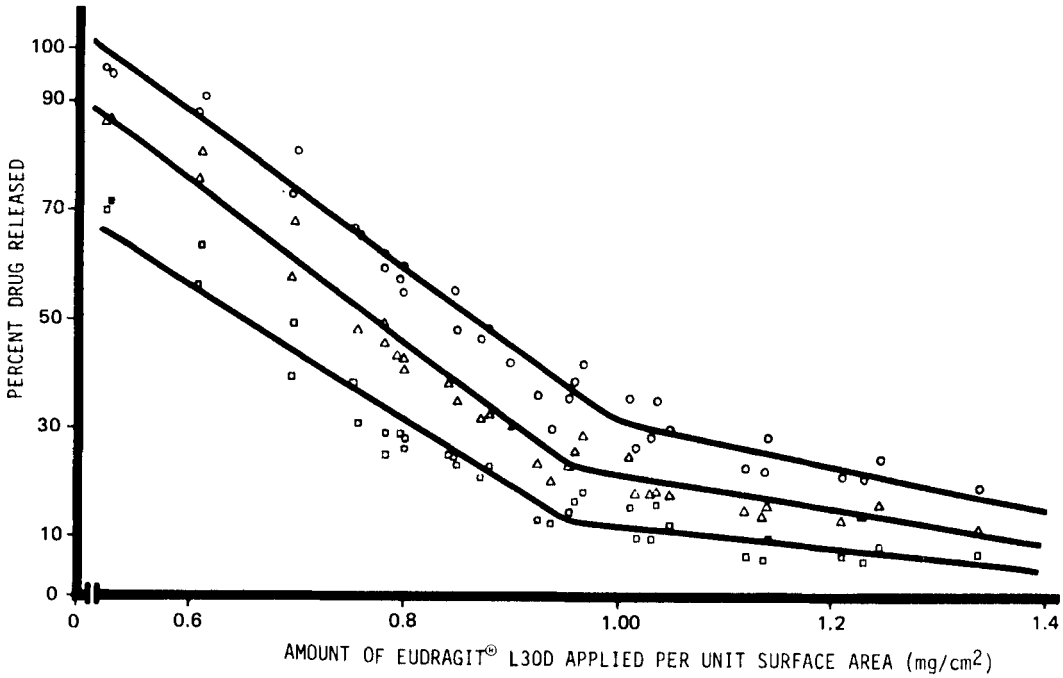

FIGURE 2
Percent of Theophylline Released Versus Amount of Eudragit® L30D Applied per Unit Surface Area (mg/cm^2). [Key: □ -First Hour Interval, △ -Second Hour Interval, O-Three and One Half Hour Interval].

pointed out that the specific surface area of raw material should be closely monitored so as to obtain a consistent coating in order to control the release rate. However, sufficient data should be generated for a specific formulation so as to establish a standard correlation of the variables involved which in turn can be utilized to obtain a batch to batch uniformity.

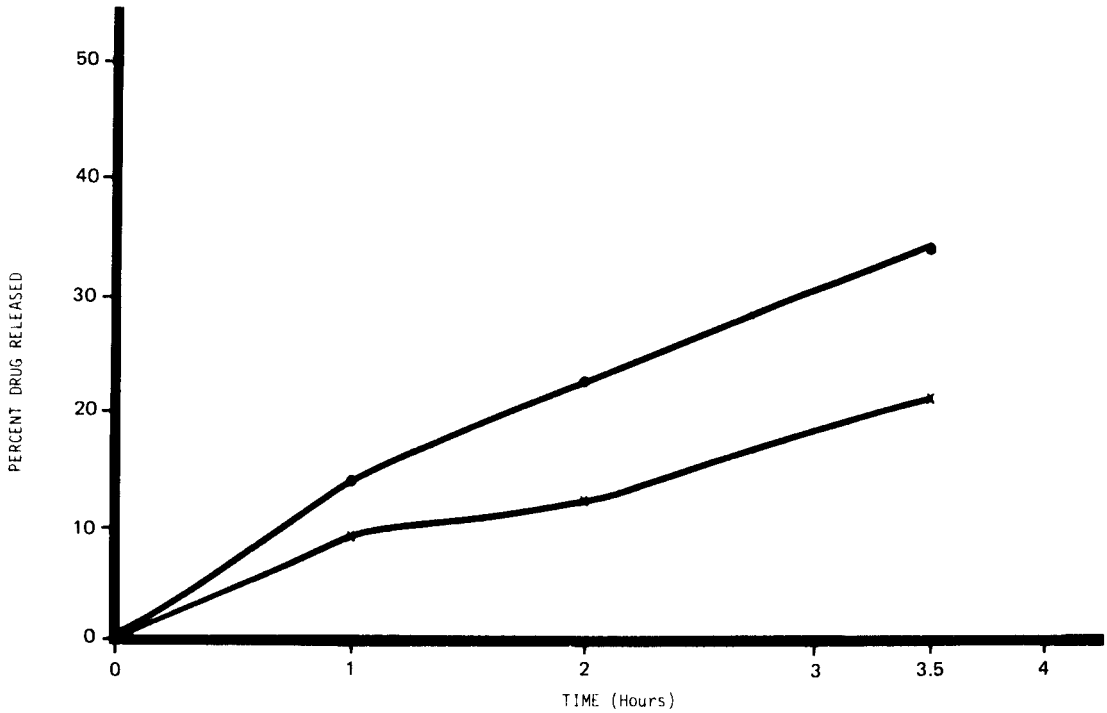

FIGURE 3
Dissolution Profile of Samples from Batches Prepared with Two Different Lots of Theophylline Granules Coated with the Same Levels of Eudragit® L30D Polymer Contents Using 18 Inch Wurster Coater Fitted on to Glatt GPCG 60/100. [Key: X-Batch 1 (Specific Surface Area of Theophylline: 65 cm^2/g), O-Batch 2 (Specific Surface Area of Theophylline 97 cm^2/g)].

CONCLUSION

Based on the data and discussion presented in this paper, it is apparent that this approach allows the use of granules from any batch of material to be coated in a uniform manner, as long as the specific surface area of the granules of raw material can be determined. In other words, the specific

surface area of the raw material should be closely monitored in order to achieve a consistent coating process.

Since raw materials could exhibit significant specific surface area variability on a batch to batch basis, and even on a drum to drum basis within a batch, the experimental approach presented in this paper can be used to minimize the effect of those variations on the final coating process. A standard plot of percent drug released versus amount of polymer applied per unit area of raw material can be utilized to estimate the desired dissolution rate profile.

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FOOTNOTES

a. Boehringer-Ingelheim, New York, NY.

b. Knoll Fine Chemicals, New York, NY.

c. Charles B. Chrystal Company, Inc. New York, NY.

d. Union Carbide Corp. Danbury, CT.

e. Kelco, Inc., Rahway, NJ.

f. Rohm Tech Inc., Malden, Massachusetts.

g. 18" Wurster Coater in a Glatt Powder Coater/Granulator 60/100; Glatt Air Technique, Inc., Ramsey, NJ.

h. Aeromatic Coater, Model #S-4, Aeromatic Inc., Towaco, NJ 07082.

i. Smith Kline Beckman Inc., Philadelphia, PA.

j. Pulverit Comminution Equipment, Type RP-3020, Geoscience Instrument Corporation, New York, NY.

REFERENCES

1. S. C. Porter, C. H. Bruno and G. J. Jackson, in "Pharmaceutical Dosage Forms:Tablets", H. A. Lieberman and L. Lackman, eds., Vol. 3. Dekker, NY, 1980, P. 73.

2. J. R. Ellix, E. B. Prillig and A. H. Amann, in "The Theory and Practice of Industrial Pharmacy", L. Lachman, H. A. Lieberman and J. L. Kanig, ed., Lea & Febiger, Philadelphia, 1976, P. 359.

3. F. W. Goodhart, M. R. Harris, K. S. Murthy and R. U. Nesbitt, Pharmaceutical Technology, April, 64 (1984).

4. A. M. Mehta, M. J. Valazza and S. E. Abele, Pharmaceutical Technology, April, 46 (1986).

5. G. Herdan, "Small Particle Statistics", Butterworths, London, 1960.

6. T. Hatch and S. Choate, J. Franklin Inst., 207, 369 (1933).

7. E. L. Parrott, in "The Theory and Practice of Industrial Pharmacy", L. Lachman, H. A. Lieberman and J. L. Kanig, ed., Lea & Febiger, Philadelphia, PA 1976, p. 466.

8. A. N. Martin, J. Swarbrick and A. Cammarata, in "Physical Pharmacy", 2nd ed., Lea & Febiger, Philadelphia, 1969, p. 468.