Drug Migration during Drying of Tablet Granulations I: Effect of Particle Size of Major Diluent

J. W. WARREN, Jr. [x], and J. C. PRICE

Abstract □ Migration of a water-soluble drug, propoxyphene hydrochloride, during drying of tablet granulations was studied. Wet granulations of the drug were prepared using lactose as the major diluent and corn starch as a disintegrant. Particle-size fractions of lactose ranging from 53 to 177 μm in diameter were employed in different granulations to examine the effect of particle size of the major diluent on drug migration. Determination of drug concentration at various depths in a dried granulation bed was accomplished by using a drying cell consisting of four layers. A numerical coefficient of migration was developed to compare the extent of drug migration in the various lactose granulations. Migration increased with decreasing particle size of the major diluent, lactose. Two factors that may contribute to increased migration with smaller particles are increased entry suction due to decreased intragranular capillary size and increased intergranular contact area.

Keyphrases □ Tablets—effect of particle size of major diluent on drug migration during drying □ Particle size—of major diluent in tablet granulations, effect on drug migration during drying □ Migration, drug—during drying of tablet granulations, effect of particle size of major diluent □ Dosage forms—tablets, effect of particle size of major diluent on drug migration during drying

Drug migration during granulation drying is a relatively new area of investigation. Although migration of water-soluble dyes was studied as early as 1963 (1, 2), reports concerning migration of other granulation components have appeared only since 1971 (3–8).

In a study using 5% (w/w) of the tablet binder povidone in heavy magnesium carbonate, the extent of intragranular povidone migration increased with higher drying temperatures (3). When 2.7% (w/w) warfarin sodium in a wet granulation was studied, the addition of 5% acacia and 15% alginic acid to calcium phosphate reduced drug migration (6). The influence of the volume of solvent on aspirin migration was studied using absolute ethanol as the solvent and 1% (w/w) aspirin in a wet granulation (7). The influence of various drying methods on solute migration was studied with 2.5% (w/w) NaCl in heavy kaolin (8).

Although several factors common to all wet granulations may influence the migration of a soluble drug during drying, the effect of particle size of a major diluent on the extent of drug migration was investigated. Propoxyphene hydrochloride was chosen as a representative drug since it is freely soluble in water and its usual concentration in granulations is higher than other components examined previously.

EXPERIMENTAL

Materials—Propoxyphene hydrochloride, lactose, starch, and magnesium stearate were USP grade and were used without further purification. A single lot of each material was used for all experiments.

Wet Granulation Procedure—The wet granulation formulation (Formula I) used was as follows:

	per tablet, mg	per batch, g
propoxyphene hydrochloride USP	32	48.0
lactose USP	413	619.5
starch USP	50	75.0
magnesium stearate USP	5	7.5
total	500	750.0

Since the major diluent in Formula I was lactose, various particle-size fractions of lactose were collected as follows: Formula I-P1, 100% by weight of the lactose passed a No. 80 (177 μm) U.S. standard sieve but was retained on a No. 100 sieve; Formula I-P2, 100% by weight of the lactose passed a No. 100 (149 μm) U.S. standard sieve but was retained on a No. 140 sieve; Formula I-P3, 100% by weight of the lactose passed a No. 140 (105 μm) U.S. standard sieve but was retained on a No. 170 sieve; Formula I-P4, 100% by weight of the lactose passed a No. 200 (74 μm) U.S. standard sieve but was retained on a No. 270 sieve; and Formula I-P5, 100% by weight of the lactose passed a No. 270 (53 μm) U.S. standard sieve but was retained on a No. 325 sieve. The collected fractions of lactose were incorporated into five granulation batches.

For wet granulation of the five batches, the powders were first passed through a No. 12 U.S. standard sieve (1680 μm) to reduce large agglomerates. The powders were then blended for 15 min at low speed in a planetary mixer[1]. After blending, 150 ml of water was added in portions, approximately 50 ml/addition, to form the wet granulation mass, and the granulation was mixed for an additional 10–12 min.

Wet screening was accomplished by passing the wet granulated mass through a No. 12 (1680 μm) sieve. The wet mass was then placed in a drying cell and dried at 50° for 5 hr in a drying oven[2].

Drying Cell and Sampling Procedure—A drying cell made of acrylic plastic and consisting of four layers, 0.476 cm thick, was used to facilitate the determination of the concentration of propoxyphene hydrochloride at various depths in a granulation bed (Fig. 1). The total height of the cell was 1.90 cm. The cell was open on both ends of the cylinder formed by the layers; the opening was 10.16 cm in diameter. The layers of the cell were secured with screws during the drying process.

When used for migration studies, the drying cell was placed on a drying oven tray lined with porous paper. The granulation in the bottom layer was exposed to the paper during the drying process, which was similar to an actual industrial tray drying process. The wetted granulation, after being wet sieved, was filled into the drying cell with a spatula.

After drying, the top layer of the dried bed was sampled by removing portions of the top cell layer with a flat blade. Three samples were taken from each layer and designated as side 1, side 2, and center. The side 1 sample was taken from an area 3.2 cm from the beginning of air flow across the cell, and the side 2 sample was taken 3.2 cm from the side of the cell cylinder opposite side 1. At this point, the second layer was removed and the granulation was sampled in the same manner. This procedure was repeated for the third and fourth layers.

After mixing the granulation samples, 0.5 g of granulation from each of the 12 samples per cell, three from each layer, was then assayed for propoxyphene hydrochloride content. The average of the three assay results for each layer was used for further calculations and comparisons.

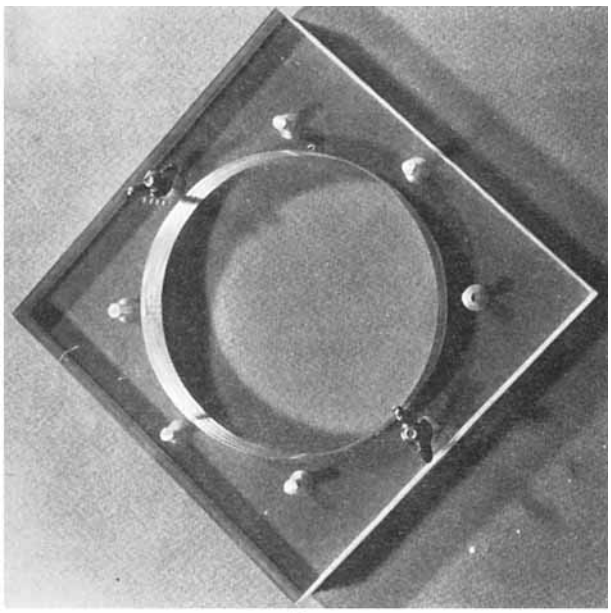
Drug Content Uniformity of Wet Granulations—Drug content uniformity in the wet granulation (Formula I-P1) was determined to establish whether the mixing and granulation wetting process resulted in a uniform mixture. Five random samples (approximately 2 g each) were taken from the wet mass immediately after granulation. After drying for 5 hr at 50°, the samples were assayed for drug.

Determination of Reproducibility of Cell Drying Procedure—To determine the reproducibility of the cell drying procedure, three batches of Formula I-P1 were wet granulated with 150 ml of water/batch; three drying cells from each batch were filled and dried. The top layer was then sampled and assayed, three samples per layer, from each of the nine cells.

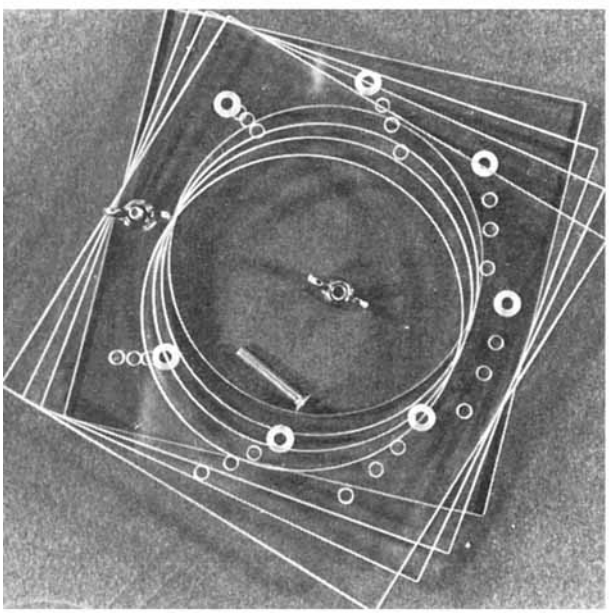
To evaluate cell-to-cell differences within a batch and batch-to-batch differences relative to cells, a nested design analysis of variance was used (9).

Assay for Propoxyphene Hydrochloride—A colorimetric assay (10) was adapted for the determination of propoxyphene hydrochloride in the granulation samples. This method involves the formation of a color

[1] Readco mixer K-20, Read Standard, York, Pa.
[2] Power-O-Matic 60, Blue M Electric Co., Blue Island, Ill.



a



b

Figure 1—*Drying cell assembled* (a) *and partially disassembled to show construction* (b).

complex of bromcresol purple and propoxyphene hydrochloride. A granulation sample, equivalent to approximately 32 mg of propoxyphene hydrochloride, was extracted with 50 ml of methanol by shaking for 1 hr. After shaking, the sample was diluted to 100 ml with methanol. Five milliliters of this solution was diluted to 100 ml with water. Five milliliters of this final solution was then added to 20 ml of bromcresol purple reagent (50 mg of bromcresol purple/liter with 10 ml of acetic acid and sufficient 2 *N* NaOH to adjust the pH to 5.0) in a separator. Finally, 25 ml of chloroform was added.

After agitation for 3 min, a portion of the lower chloroform layer was collected. The absorbance of the collected solution was determined[3] at 405 nm using chloroform as a reference. A blank was prepared by adding 5.0 ml of water to 20 ml of the bromcresol purple solution and following the same analytical procedure. Five milliliters of a standard solution (32 mg of propoxyphene hydrochloride in a 100-ml volumetric flask diluted with methanol) was also carried through the procedure.

Physical Properties of Granulations—As a control measure, the weight of the drying cell contents, bulk density, moisture content, true volume, true density, apparent density, and intraparticle porosity of the granulation in each cell were determined.

The bulk density (grams per cubic centimeter) of the granulation in each cell was calculated using the weight of the drying cell contents and a cell volume of 153.98 cm^3. The moisture content of each granulation was determined using a moisture determination balance[4]. The true volume and the true density of the granulations were determined with an air comparison pycnometer[5].

By using a mercury pycnometer and procedures described by Strickland *et al.* (11), the granule density of each granulation was determined. From the true density and granule density values, the intraparticle porosity of each granulation was calculated.

Data Treatment—To specify the extent to which the drug migrated with a numerical value, the concept of a coefficient of migration was developed.

Since there are four layers in the drying cell, there can be six layer comparison classifications, *i.e.*, a comparative difference, sign ignored, of the average assay values of layer 1 to layer 2, layer 1 to layer 3, layer 1 to layer 4, layer 2 to layer 3, layer 2 to layer 4, and layer 3 to layer 4. These layer differences were determined relative to the amount of drug recovered and potentially present in any two layers. In general, then, the equation for calculating the comparative difference (D) between two layers (j and j') is:

$$D_{j-j'} = \frac{|L_j - L_{j'}|}{\frac{2\sum_{j=1}^{N} L_j}{N}} \qquad \text{(Eq. 1)}$$

where L_j represents the average of three assay values in a given layer, $L_{j'}$ is the average assay value in another layer, $\Sigma_{j=1}^{N}$ is the sum of the average assay values for N layers, and N is the number of layers in the drying cell.

The most divergent system using an open drying cell after drying can be represented as 64, 0, 0, and 64 mg/0.5 g for layers 1, 2, 3, and 4, respectively, where the drug has migrated from the inner layers to the two exposed evaporating surfaces. Again, using Eq. 1, the classification differences would be $D_{1-2} = (64 - 0)/64 = 1$, $D_{1-3} = (64 - 0)/64 = 1$, $D_{1-4} = (64 - 64)/64 = 0$, $D_{2-3} = (0 - 0)/64 = 0$, $D_{2-4} = (0 - 64)/64 = 1$, $D_{3-4} = (0 - 64)/64 = 1$, and total = 4. The coefficient of migration in this example is 4/4 = 1.

If 32 mg of drug/0.5 g of granulation is the theoretical average of the assay values per layer, then the most uniform system in a migration study using an open drying cell after drying can be represented as layer 1 = layer 2 = layer 3 = layer 4 = 32 mg/0.5 g.

With Eq. 1, the classification differences would be zero in all cases and the coefficient of migration would be 0/4 = 0. It follows that as the coefficient approaches one, the extent of migration is greater; as the coefficient approaches zero, the extent of migration is less.

By using the coefficient of migration as a measurement of the total upward or downward movement of drug in the granulation bed, Spearman's rank correlation method (12) was used to test for a significant correlation between the extent of drug migration and particle size of the major diluent.

RESULTS AND DISCUSSION

Drug Content Uniformity of Wet Granulation—The assay values for the five random samples taken from Formula I-P1 were 31.868, 30.800, 30.240, 31.506, and 30.439 mg/0.5 g for Samples 1, 2, 3, 4, and 5, respectively.

The theoretical amount of propoxyphene hydrochloride was 32 mg/0.5 g of granulation. The average value of the five samples was 30.971 mg of propoxyphene hydrochloride/0.5 g of granulation, and the standard deviation was 0.696 mg.

Reproducibility of Cell Drying Procedure—Top drying cell layer assay results of three lactose granulations used to determine the reproducibility of the cell drying procedure are given in Table I.

To evaluate cell-to-cell differences within a batch and batch-to-batch differences relative to cells, a nested design analysis of variance was used (9) (Table II). Since the calculated F value for batches was not significant at $p = 0.01$, there was no significant difference among the top layer assay values of the drying cells when the cells from batches 1, 2, and 3 were compared. Furthermore, because the calculated F value for cells was not

[3] Cary model 118 spectrophotometer, Varian Instrument Division, Palo Alto, Calif.

[4] Ohaus Scale Corp., Union, N.J.

[5] Model 930, Beckman Instruments, Fullerton, Calif.

Table I—Top Drying Cell Layer Assay Results[a] of Three Granulation Batches Used to Determine the Reproducibility of the Cell Drying Procedure

Batch	Sample	Cell 1	Cell 2	Cell 3
1	1	41.83	41.12	41.89
	2	39.12	39.34	38.88
	3	39.74	40.58	40.52
2	1	40.65	41.97	41.16
	2	39.96	39.60	39.11
	3	41.50	38.97	40.47
3	1	40.79	41.53	39.96
	2	39.55	41.28	38.38
	3	39.20	39.09	41.87

[a] Milligrams of propoxyphene hydrochloride/0.5 g of granulation.

Table II—Analysis of Variance to Determine the Reproducibility of the Cell Drying Procedure

Source	Degrees of Freedom	Sum of Squares	Mean Square	*F* Ratio	*F* (0.99)
Batch	2	0.1862	0.0931	0.3645	10.92
Cell (batch)	6	1.5326	0.2554	0.1546	4.01
Error	18	29.7456	1.6525		
	26	31.4644			

significant at $p = 0.01$, there was no significant difference among the three drying cells within a given batch.

Effect of Particle Size on Extent of Migration—A summary of the average assay values for Formulas I-P1–I-P5 is given in Table II. In general, the greatest amount of propoxyphene hydrochloride was found in layer 1 (top layer) in all formulations, and the least amount was found in layer 3. Formula I-P1, containing the largest particle-size lactose, showed the least drug migration.

The percent of the potential amount of propoxyphene hydrochloride depleted from the inner layers of the drying cell, layers 2 and 3, was calculated by dividing the amount of drug potentially present in the inner layers based on the total amount of drug recovered in the four layers (Table III) into the difference of the amount of drug potentially present in the inner layers of the drying cell and the actual amount recovered (Table IV). These data show rather dramatically that drug was transported toward the evaporating surfaces and was readily depleted from the inner layers of the granulation bed.

Water travels through a granulation material by capillary effect in the liquid state and then evaporates when it reaches the evaporating surface (13). It follows that propoxyphene hydrochloride would dissolve in the water and be transported toward the evaporating surfaces; thus, accumulation in layers 1 and 4 occurs when the water evaporates and deposits the drug in the granulation material.

To determine if there was a correlation between the extent of propoxyphene hydrochloride migration and the particle size of the major diluent, lactose, the coefficient of migration for Formulas I-P1–I-P5 was calculated from the results shown in Table III using Eq. 1. By using Spearman's rank correlation method (12), the formulas were ranked from 1 to 5 relative to the decreasing particle size of lactose. Then they were ranked from 1 to 5 relative to an increasing coefficient of migration (Table V).

Table III—Effect of Diluent Particle Size on Propoxyphene Hydrochloride Content[a] of Granulation Layers after Drying

Layer	Formula I-P1	Formula I-P2	Formula I-P3	Formula I-P4	Formula I-P5
1	39.38	37.35	41.35	48.40	48.55
2	29.12	22.74	23.96	22.33	23.06
3	24.12	19.62	17.72	19.76	20.48
4	35.83	35.85	39.02	38.17	39.46

[a] Each value represents an average of three assay determinations of milligrams of propoxyphene hydrochloride/0.5 g of granulation.

Table IV—Effect of Diluent Particle Size on Propoxyphene Hydrochloride Migration from the Inner Layers of the Drying Cell

Formula	Potential Amount in Inner Layers, mg	Amount Recovered from Inner Layers, mg	Amount Depleted from Inner Layers, %
I-P1	64.22	53.24	17.10
I-P2	57.78	42.36	26.69
I-P3	61.03	41.67	31.71
I-P4	64.33	42.09	34.57
I-P5	65.78	43.54	33.81

Table V—Spearman's Rank Correlation Determination for Effect of Particle Size on Extent of Migration

Formula	Particle Size Rank	Coefficient of Migration	Coefficient Rank	d_i	d_i^2
I-P1	1	0.204	1	0	0
I-P2	2	0.287	2	0	0
I-P3	3	0.352	3	0	0
I-P4	4	0.395	5	−1	1
I-P5	5	0.382	4	1	1
					2

$$r_s = 1 - \frac{(6)\sum_{i=1}^{n} d_i^2}{n^3 - n} = 1 - \frac{(6)(2)}{(5)^3 - 5} = 0.900$$

Table VI—Analysis of Variance to Determine the Limit of Migration in a Series of Lactose Granulations

Source	Degrees of Freedom	Sum of Squares	Mean Square	*F* Ratio	*F* (0.99)
Formula	1	3.1191	3.1191	0.4930	8.53
Layer	3	3268.0195	1089.3398	172.1644	5.29
Interaction	3	0.9702	0.3234	0.0511	5.29
Error	16	101.2372	6.3273		
	23	3373.3460			

Table VII—Bulk Density[a], Granule Density[a], and Porosity of Granulations

Formula	Bulk Density, g/cm³	Granule Density, g/cm³	Intraparticle Porosity, %	Moisture Content after Drying, %
I-P1	0.513	1.236	15.8	3.0
I-P2	0.510	1.206	16.3	3.2
I-P3	0.548	1.166	19.1	3.6
I-P4	0.530	1.154	20.3	3.0
I-P5	0.554	1.154	20.7	4.1

[a] Each value represents an average of three determinations.

The critical value for r_s at $n = 5$ is 0.900 at the 0.05 level of significance. The value computed in Table V, $r_s = 0.900$, is significant at the 0.05 level. Thus, a significant correlation existed between the extent of propoxyphene hydrochloride migration and the particle size of lactose. That is, as the particle size of lactose decreased, drug migration increased.

An entry suction tends to draw water from the interior of the granulation bed to the evaporating surfaces where subsequent evaporation occurs (14). It follows that as the radius of the particles is decreased, in this case lactose, the entry suction would increase because of the decreased capillary size. Thus, the resultant capillary forces tending to draw water from the interior of the granulation bed to the evaporating surface are increased as the particle size of lactose is decreased. As the entry suction increases, the movement of water through the bed toward the evaporating surfaces would be enhanced because the capillary state would be more readily maintained between individual granules; therefore, there would be greater potential for propoxyphene hydrochloride to be transported to the outer layers of the drying cell.

As the particle size of lactose is decreased, it is also feasible that an increased fine structure of smaller surface particles of individual granules occurs by increased granule surface contact. Thus, a capillary state would be achieved more easily and intergranular solvent flow would be sustained.

The results from Formulas I-P4 and I-P5 were very close. A two-factor analysis of variance comparing these results is given in Table VI. Since the calculated *F* value for the formulas was not significant at $p = 0.01$, there was apparently no difference in Formulas I-P4 and I-P5. The calculated *F* value for layers was significant, which denotes a layer difference. The interaction *F* value was not significant. It appears that increased migration due to increased capillary flow reached a limit. During the drying process, a point is reached when the capillary water no longer fills the capillary pores; water then evaporates within the granulation bed

and diffuses to the surface as a vapor (13). Thus, regardless of the potential entry suction (14) increasing with decreasing particle size, the amount of migration tends to reach a limit.

Physical Properties of Granulations—The bulk density, granule density, intraparticle porosity, and moisture content of the lactose granulations are given in Table VII. The average bulk density was 0.531 g/cm^3 with a range of 0.510–0.554 g/cm^3. The average moisture content was 3.4% with a range of 3.0–4.1%.

Although the intraparticle porosity increased with a decreased particle size of lactose, the changes in intraparticle porosity did not correlate well with the extent of propoxyphene hydrochloride migration in this series of granulations. Decreased capillary size and increased contact area with decreasing particle size probably are responsible for the observed results.

CONCLUSIONS

Variations in particle size of the major diluent in wet granulations may result in differences in drug content uniformity in different batches of granules. Control of particle size of the major diluent can minimize drug migration and improve product uniformity in some formulations.

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Drug Migration during Drying of Tablet Granulations II: Effect of Binder Solution Viscosity and Drying Temperature

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Abstract □ The effect of binder solution viscosity and drying temperature on the intergranular migration of propoxyphene hydrochloride was studied. Wet granulations containing the drug were prepared using binder solutions with viscosities ranging from 1 to 1000 cps. Temperature studies were conducted using granulations prepared with a 3-cps binder solution and dried at 40, 50, 60, 70, and 80°. Drug migration decreased with increased binder solution viscosity, and insignificant migration occurred in granulations prepared with binder solutions having apparent viscosities above 90 cps. No significant effect on intergranular drug migration was observed within the drying temperature range studied. Tablets compressed from a granulation in which drug migration was high showed a greater tablet-to-tablet drug content variation than a granulation with lower migration, even though each dried granulation was thoroughly mixed before tableting.

Keyphrases □ Tablets—effect of binder solution viscosity and temperature on drug migration during drying □ Viscosity, binder solution—effect on drug migration during drying of tablet granulations □ Drying temperature—tablet granulations, effect on drug migration □ Migration, drug—during drying of tablet granulations, effect of binder solution viscosity and temperature □ Dosage forms—tablets, effect of binder solution viscosity and temperature on drug migration during drying

A study of warfarin sodium migration in wet granulations showed that the addition of 5% acacia and 15% alginic acid to a calcium phosphate granulation reduced drug migration (1). However, the extent of drug migration was not related to binder solution viscosity. Other reports dealt with the influence of solvent volume (2) and various granulation drying methods (3). The effect of drying temperature on intragranular migration of povidone was discussed (4), but apparently no investigations have been reported concerning the effect of drying temperature on intergranular migration. This study concerns the influence of binder solution viscosity and drying temperature on the extent of intergranular migration of a water-soluble drug, propoxyphene hydrochloride.

EXPERIMENTAL

The analytical method for the determination of propoxyphene hydrochloride, the drying cell and sampling procedure, the coefficient of migration, the uniformity of the granulations, and the reproducibility of the granulation and drying procedures were described previously (5).

Materials—Propoxyphene hydrochloride, corn starch, lactose, and magnesium stearate were USP grade. Dibasic calcium phosphate, povidone[1], and hydroxypropyl methylcellulose[2] were NF grade.

Formulations—Two formulations were used. Formula I contained (milligrams per 500-mg tablet): propoxyphene hydrochloride, 32; lactose,

[1] GAF Corp., New York, N.Y.

[2] Methocel E-15, Dow Chemical Co., Midland, Mich.