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.

Table I—Binder Solutions Employed to Granulate Formulas I and II[a]

Formula	Molecular Weight of Binder[b]	Total Amount of Aqueous Solution, ml	Apparent Viscosity, cps
I-BV1	—	150	1
I-BV2	10,000	150	3
I-BV3	40,000	150	10
I-BV4	160,000	150	100
I-BV5	360,000	150	1000
II-BV1	—	200	1
II-BV2	10,000	200	3
II-BV3	40,000	200	7
II-BV4	160,000	200	90
II-BV5	360,000	200	600

[a] The amount of binders used was 22.5 g except in Formulas I-BV1 and II-BV1 where none was added. [b] Molecular weights as given by the manufacturer of povidone. Manufacturer code numbers are k-15, k-30, k-60, and k-90 in order of increasing molecular weight.

413; corn starch, 50; and magnesium stearate, 5. Formula II contained (milligrams per 500-mg tablet): propoxyphene hydrochloride, 32; dibasic calcium phosphate, 413; corn starch, 50; and magnesium stearate, 5.

Wet Granulation—Each granulation batch weighed 750 g (1500 tablets). The powders were blended for 15 min at low speed in a planetary mixer[3], and water or binding solution then was added to form the wet granulation mass. Water or binder solution, 150 ml, was added to the lactose granulations (Formula I) and 200 ml was added to the dibasic calcium phosphate granulations (Formula II).

After addition of binder, the granulation was mixed for 10–12 min and wet screened through a No. 12 (1680 μm) U.S. standard sieve. The granulations were collected on porous paper and dried for 5 hr in a drying oven[4]. The drying temperature was 50° for the granulations in the binder solution viscosity studies.

Effect of Binder Solution Viscosity on Migration—Various binder solution viscosities of povidone were achieved by employing molecular weight grades of 10,000, 40,000, 160,000, and 360,000. Each was incorporated at a level of 3% (w/w) in both Formulas I and II. Viscosity measurements were made at 25° with a rotational viscometer[5]. Binder solution formulations and viscosities are given in Table I.

The formulations were wet granulated, placed in drying cells, and dried (5). The coefficient of migration (5) for each formulation was calculated and tested for a significant correlation between the extent of propoxyphene hydrochloride migration and increasing binder solution viscosity using Spearman's rank correlation method (6).

Effect of Temperature on Migration—Formula II, granulated with 22.5 g of povidone of 10,000 molecular weight in 200 ml of water (Formula II-BV2), was used for this study. The viscosity of the solution was 3 cps.

Five granulations, 750 g/batch, were prepared and dried in drying cells at 40, 50, 60, 70, and 80°, respectively. Samples were taken and assayed as described previously (5).

The coefficient of migration for each formulation was calculated and tested for a significant correlation (6) between the extent of propoxyphene hydrochloride migration and increased drying temperatures using Spearman's rank correlation method.

Effect of Extent of Migration on Tablet Content Uniformity—Formula II-BV2, granulated with binder solution having an apparent viscosity of 3 cps, and Formula II-BV5, granulated with binder solution having an apparent viscosity of 600 cps, were used to determine the effect of the extent of migration on the content uniformity of tablets. These formulas were selected because they had shown significant differences in drug migration in the dried granulations. The dried granulations were passed through a No. 20 sieve and mixed for 15 min in a twin-shell blender[6].

Five hundred tablets were compressed from each batch, using a single-station tablet compression machine equipped with 0.952-cm (0.38-in.) standard concave tooling.

The USP content uniformity test was run on tablets from each formulation; 30 tablets were randomly selected from each batch, and 10 individual tablets were assayed from the 30. The average drug content per tablet and the standard deviation were calculated for each batch of assayed tablets.

[3] Readco mixer K-20, Read Standard, York, Pa.
[4] Power-O-Matic 60, Blue M Electric Co., Blue Island, Ill.
[5] Model RVT, Brookfield Engineering Labs., Stoughton, Mass.
[6] Model LB201, Patterson-Kelley Co., East Stroudsberg, Pa.

Table II—Granulation Characteristics as a Function of Binder Viscosity

Formula	Granulation Weight in Cell, g	Bulk Density, g/cm^3	Moisture Content after Drying, %
I-BV1	79.0	0.513	3.0
I-BV2	73.0	0.474	2.7
I-BV3	75.0	0.487	3.0
I-BV4	88.0	0.572	3.8
I-BV5	80.0	0.520	3.4
II-BV1	79.5	0.517	4.0
II-BV2	80.1	0.520	4.0
II-BV3	79.0	0.513	2.5
II-BV4	87.0	0.565	3.0
II-BV5	78.4	0.509	2.5
II-BVE15[a]	83.0	0.539	3.0

[a] Binder viscosity was 600 cps.

Table III—Effect of Binder Solution Viscosity on Propoxyphene Hydrochloride Content[a] of Formula I

Layer	Formula I-BV1	Formula I-BV2	Formula I-BV3	Formula I-BV4	Formula I-BV5
1	39.38	40.61	37.67	33.05	31.02
2	29.12	32.50	31.27	31.83	31.25
3	24.12	24.35	24.70	31.85	31.92
4	35.83	37.40	34.63	31.81	32.12

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

Table IV—Effect of Binder Solution Viscosity on Propoxyphene Hydrochloride Migrated from Inner Layers of Lactose Granulations

Formula	Potential Amount in Inner Layers, mg	Amount Recovered from Inner Layers, mg	Amount Depleted from Inner Layers, %
I-BV1	64.22	53.24	17.1
I-BV2	67.42	56.84	15.7
I-BV3	64.14	55.98	12.7
I-BV4	64.27	63.68	0.92
I-BV5	63.16	63.17	0.00

Characteristics of Granulations—The weight of the granulation contents in each drying cell and the moisture content for each granulation were determined (Table II). The average bulk density for the lactose granulations (Formulas I-BV1–I-BV5) was 0.513 g/cm^3 with a range of 0.474–0.572 g/cm^3. The dibasic calcium phosphate granulations (Formulas II-BV1–II-BV5 and II-BVE15) had an average bulk density of 0.527 g/cm^3 with a range of 0.509–0.565 g/cm^3. The average moisture content of the lactose granulations was 3.2% with a range of 2.7–3.8%; for the dibasic calcium phosphate granulations, the average was 3.2% with a range of 2.5–4.0%.

RESULTS AND DISCUSSION

Effect of Binder Solution Viscosity on Extent of Migration—The average assay values for propoxyphene hydrochloride in the four layers of the dried granulation for Formulas I-BV1–I-BV5 are summarized in Table III. From these data, the percent of the potential amount of propoxyphene hydrochloride depleted from the center section (layers 2 and 3) of each granulation in the drying cell was calculated as previously described (5) (Table IV). Increased binder solution viscosity retarded the depletion of drug from the center section of the granulation bed (Table IV). This result was particularly evident for Formulas I-BV4 (binder solution viscosity of 100 cps) and I-BV5 (binder solution viscosity of 1000 cps), where the percent depletion was virtually equal to zero and rather uniform layers were observed.

With Formulas I-BV1–I-BV3, the entry suction (5, 7) tended to draw water from the interior of the bed to the evaporating surfaces of the drying cell because the binder viscosities were relatively low. However, as the binder viscosities were increased (Formulas I-BV4 and I-BV5), the entry suction could not draw the binder solution to the surface at the rate at which evaporation took place. As the drying process continued, the binder solution was held in the capillaries or pores of the granulation bed and eventually the solvent evaporated from the interior of the bed and dif-

Table V—Effect of Binder Solution Viscosity on Propoxyphene Hydrochloride Content[a] of Formula II after Drying

Layer	Formula II-BV1	Formula II-BV2	Formula II-BV3	Formula II-BV4	Formula II-BV5
1	46.09	46.79	43.98	35.76	30.89
2	23.51	20.82	26.74	28.52	30.59
3	17.26	18.91	24.89	26.79	31.88
4	40.29	42.41	40.37	36.34	31.55

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

Table VI—Propoxyphene Hydrochloride Depleted from Inner Layers of Dibasic Calcium Phosphate Granulations

Formula	Potential Amount in Inner Layers, mg	Amount Recovered from Inner Layers, mg	Amount Depleted from Inner Layers, %
II-BV1	63.57	40.77	35.9
II-BV2	64.47	39.73	38.4
II-BV3	67.99	51.63	24.0
II-BV4	63.71	55.31	13.2
II-BV5	62.46	62.47	0

fused through the bed as a vapor (6, 7). When vapor diffusion occurs from the interior of the bed, it follows that the drug will be deposited from the point of evaporation and more uniform layers will be seen in Formulas I-BV4 and I-BV5.

The average propoxyphene hydrochloride assay values for four layers of Formulas II-BV1–II-BV5 are summarized in Table V. From these data, the amount of propoxyphene hydrochloride depleted from the center section (layers 2 and 3) of each granulation was calculated (Table VI). Increased binder viscosity retarded the depletion of drug from the center section of the granulation bed with Formula II. Relatively uniform layers in Formula II-BV5 (with 600-cps binder solution) can also be attributed to the entry suction concept as explained for the lactose granulations (Formulas I-BV1–I-BV5).

With dibasic calcium phosphate (Formula II), more uniform layers did not occur until 600-cps binder solution was used; with lactose (Formula I), rather uniform layers were observed with 100-cps binder solution. There are three possible reasons for this result.

1. The particle size of the primary excipient, dibasic calcium phosphate (57% passes a No. 325 sieve), in Formula II was smaller than the particle size of the primary excipient, lactose (80% retained by a No. 325 sieve), in Formula I. Therefore, the resultant entry suction (1, 5) for Formula II was greater.

2. The amount of binder solution in Formula II was greater; thus, with more solution to evaporate, more drug was carried to the surface. Also, the larger amount of water (200 ml compared to 150 ml in the lactose formula) resulted in somewhat lower viscosities for the binder solutions.

3. Since the particle size of the dibasic calcium phosphate was smaller than the particle size of the lactose, increased granule surface contact in the dibasic calcium phosphate granulations may have facilitated intergranular solvent flow (5). Therefore, a higher binder solution viscosity would have been required to retard the flow of solvent from the interior of the bed.

To determine if a correlation existed between the extent of propoxyphene hydrochloride migration and increasing binder solution viscosity, the coefficient of migration for Formulas I-BV1–I-BV5 and Formulas II-BV1–II-BV5 was calculated as previously described (5) using Spearman's rank correlation method. The formulas were ranked from 1 to 5 relative to increasing binder solution viscosity and then ranked from 1 to 5 according to the calculated coefficient of migration, with rank 1 representing the smallest coefficient and rank 5 representing the largest (Tables VII and VIII).

The critical value for r_s at $n = 5$ is 0.900 at the 0.05 level of significance. Therefore, the values computed in Tables VII and VIII, $r_s = -0.900$, are significant at the 0.05 level. A significant negative correlation indicates that there was an inverse relationship between the extent of migration and increasing binder solution viscosity. That is, as the binder viscosity increased in both Formulas I and II, the extent of propoxyphene hydrochloride migration decreased.

The ability of a binder solution, other than povidone, to retard the migration of propoxyphene hydrochloride in the granulation bed was also investigated. Formula II was granulated with 8% (w/v) hydroxypropyl methylcellulose. This solution had an apparent viscosity of approximately 600 cps, which was comparable to the povidone apparent viscosity of 600 cps used to granulate Formula II-BV5. The methylcellulose granulation was designated as Formula II-BVE15. The average assay values for Formula II granulated with povidone and methylcellulose, respectively, are given in Table IX.

Table VII—Spearman's Rank Correlation Determination for Effect of Binder Solution Viscosity (Formula I) on Extent of Propoxyphene Hydrochloride Migration

Formula	Binder Viscosity Rank	Coefficient of Migration	Coefficient Rank	d_i	d_i^2
I-BV1	1	0.204	5	−4	16
I-BV2	2	0.199	4	−2	4
I-BV3	3	0.165	3	0	0
I-BV4	4	0.014	1	3	9
I-BV5	5	0.016	2	3	9
					38

$$r_s = 1 - \frac{6\sum_{i=1}^{n} d_i^2}{n^3 - n} = 1 - \frac{6(38)}{(5)^3 - 5} = -0.900$$

Table VIII—Spearman's Rank Correlation Determination for Effect of Binder Solution Viscosity (Formula II) on Extent of Propoxyphene Hydrochloride Migration

Formula	Binder Viscosity Rank	Coefficient of Migration	Coefficient Rank	d_i	d_i^2
II-BV1	1	0.406	4	−3	9
II-BV2	2	0.408	5	−3	9
II-BV3	3	0.260	3	0	0
II-BV4	4	0.141	2	2	4
II-BV5	5	0.018	1	4	16
					38

$$r_s = 1 - \frac{6\sum_{i=1}^{n} d_i^2}{n^3 - n} = 1 - \frac{6(38)}{(5)^3 - 5} = -0.900$$

Table IX—Comparison of Propoxyphene Content[a] of Layers of Dried Granulations Prepared from Different Binder Solutions of Equal Viscosity

Layer	Formula II-BV5, mg	Formula II-BVE15, mg
1	30.89	32.52
2	30.59	31.03
3	31.88	31.03
4	31.55	32.78

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

Table X—Analysis of Variance Comparing Formula II-BV5 with Formula II-BVE15

Source	Degrees of Freedom	Sum of Squares	Mean Square	F Ratio	F (0.99)
Formula	1	2.5020	2.5020	4.7515	8.53
Layer	3	5.8911	1.9637	3.7293	5.29
Interaction	3	5.8082	1.9361	3.6768	5.29
Error	16	8.4250	0.5266		
	23	22.6263			

To compare Formula II-BVE15 with Formula II-BV5, a two-factor analysis of variance was used (Table X). Since the calculated F value for the formula factor is not significant at $p = 0.01$, there is apparently no difference between the extent of migration in Formulas II-BVE15 (with methylcellulose) and II-BV5 (with povidone). Also, since the calculated F value for layers is not significant, there is no apparent difference among the layer assay values within a formulation or when the layers of each formulation are compared. The interaction F value is not significant. Therefore, retardation of migration of propoxyphene hydrochloride appears to be a function of binder solution viscosity rather than a specific binding material.

Effect of Temperature on Migration—The average assay results

Table XI—Effect of Drying Temperature on Propoxyphene Hydrochloride Content[a] of Granulation Layers of Formula II-BV2

Layer	40°	50°	60°	70°	80°
1	45.15	46.09	48.02	48.65	43.18
2	21.01	23.51	24.46	21.99	26.23
3	19.65	17.26	19.47	19.35	21.40
4	40.70	40.29	38.92	39.66	38.03

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

Table XII—Spearman's Rank Correlation Determination for Effect of Temperature on Extent of Propoxyphene Hydrochloride Migration in Formula II

Drying Temperature	Temperature Rank	Coefficient of Migration	Coefficient Rank	d_i	d_i^2
40°	1	0.380	2	−1	1
50°	2	0.408	5	−3	9
60°	3	0.382	3	0	0
70°	4	0.407	4	0	0
80°	5	0.299	1	4	16
					26

$$r_s = 1 - \frac{6\sum_{i=1}^{n} d_i^2}{n^3 - n} = 1 - \frac{6(26)}{(5)^3 - 5} = -0.300$$

for Formula II granulated with 3-cps povidone and dried at 40, 50, 60, 70, and 80° are summarized in Table XI.

To test for a significant correlation between the extent of migration and increased drying temperatures, the coefficient of migration for the granulation dried at each temperature was calculated. By using Spearman's rank correlation method, the results at each temperature were ranked from 1 to 5 relative to increased drying temperature, with rank 1 representing the smallest coefficient of migration and rank 5 representing the largest (Table XII).

The critical value for r_s at $n = 5$ is 0.900 at the 0.05 level of significance. The r_s value of −0.300 computed in Table XII is not significant. There apparently is not a significant correlation between the extent of intergranular migration of propoxyphene hydrochloride and increasing drying temperature.

Travers (3), investigating the intergranular migration of sodium chloride, explained that heat transfer by convection is slow and, therefore, evaporation is also slow enough to maintain a solvent flow to the evaporating surfaces. Since heat transfer, which occurs by surface absorption, is slow, the capillary state or film continuity is maintained between individual granules. As the capillary state is maintained and solvent flow continues toward the evaporating surfaces, the solute is transported with the solvent and the solute concentration reaches a maximum near the evaporating surfaces of the granulation bed. Between 40 and 80°, heat transfer and subsequent evaporation were apparently slow enough to maintain a solvent flow to the evaporating surfaces of the top and bottom layers. Consequently, migration of propoxyphene hydrochloride was not significantly different among the temperatures employed.

Effect of Extent of Migration on Tablet Content Uniformity—The final phase of this study was to determine the effect of migration on the content uniformity of tablets. Formula II-BV2, which exhibited considerable drug migration, and Formula II-BV5, which showed little migration, were used.

The assay values for the 10 tablets from Formula II-BV2 are given in Table XIII. The average assay value was 30.661 ± 1.458 (*SD*) mg of propoxyphene hydrochloride/tablet. The range was 88.1–102.6% of theory (32 mg of propoxyphene hydrochloride/tablet). The average tablet weight was 0.506 ± 0.05 (*SD*) g.

The assay values for the 10 tablets from Formula II-BV5 are given in Table XIV. The average assay value was 31.981 ± 0.626 (*SD*) mg of propoxyphene hydrochloride/tablet. The range was 96.1–102.4% of theory (32 mg of propoxyphene hydrochloride/tablet). The average tablet weight was 0.496 ± 0.04 (*SD*) g.

Both tablet batches conformed to the USP content uniformity test, and the data were not significantly different when tested statistically. However, the range of assay values was greater in the granulation exhibiting the greatest drug migration, in line with previous results (1). Content uniformity of tablets made from granulations showing a large amount of migration can be expected to be highly dependent on how well the granulation has been mixed after drying; less thoroughly mixed granulations should show greater variation.

Table XIII—Propoxyphene Hydrochloride Content of Tablets Made from Formula II-BV2 (Granulated with 3-cps Binder Solution)

Tablet Number	Tablet Weight, g	Theoretical Amount per Tablet, mg	Amount Recovered per Tablet, mg	Difference, mg
1	0.502	32.13	28.18	3.95
2	0.500	32.00	30.40	1.60
3	0.514	32.90	30.36	2.53
4	0.508	32.51	30.53	1.98
5	0.507	32.45	30.99	1.46
6	0.504	32.26	32.85	0.59
7	0.512	32.77	31.73	1.04
8	0.502	32.13	28.43	3.70
9	0.506	32.38	31.28	1.11
10	0.510	32.64	31.87	0.77

Table XIV—Propoxyphene Hydrochloride Content of Tablets Made from Formula II-BV5 (Granulated with 600-cps Binder Solution)

Tablet Number	Tablet Weight	Theoretical Amount per Tablet, mg	Amount Recovered per Tablet, mg	Difference, mg
1	0.500	32.00	30.75	1.25
2	0.498	31.87	32.78	0.91
3	0.493	31.55	31.51	0.04
4	0.504	32.26	32.43	0.17
5	0.499	31.94	31.95	0.01
6	0.493	31.55	31.58	0.03
7	0.491	31.42	32.19	0.77
8	0.493	31.55	31.58	0.03
9	0.495	31.63	32.57	0.89
10	0.501	32.06	32.47	0.41

CONCLUSIONS

Drug migration during drying of wet granulations was found to be a significant problem with a soluble drug, propoxyphene hydrochloride, formulated with at least two types of diluents (lactose and dibasic calcium phosphate). A drying temperature of 40–80° appears to have little effect, but an increase in binder solution viscosity can minimize migration with either diluent.

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