where:

A = specific activity of radioactive morphine standard (counts/min./mg.)
B = specific activity of isolated morphine
C = amount of radioactive morphine standard added to the opium sample (mg.)
D = amount of opium used for extraction (mg.)

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Migration of Potent Drugs in Wet Granulations

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Abstract □ Sodium warfarin tablets prepared by a wet granulation method were shown to be unsatisfactory as to content uniformity due to the migration of the drug substance during the drying period. By using a TLC method, additives were selected which inhibited the migration of the drug substance. The use of these additives with sodium warfarin gave satisfactory tablets as to content uniformity when a wet granulation method was employed.

Keyphrases □ Tablets, content uniformity—migration during drying of water-soluble drug in wet granulations, evaluation of additive inhibitors □ Content uniformity, tablets—migration during drying of water-soluble drug in wet granulations, evaluation of additive inhibitors □ Migration of drugs in wet granulations—evaluation of additive inhibitors □ Sodium warfarin tablets—additive inhibition of drug migration in wet granu'ations □ Wet granulations—inhibition of water-soluble drug migration, evaluation of additives □ TLC—evaluation of additives for inhibition of sodium warfarin migration in wet granulations

Compressed tablets are one of the most widely used dosage forms for the administration of orally effective therapeutic agents. Among the requirements for a satisfactory tablet, content uniformity is of prime importance (1–4). Uniformity of the drug substance is dependent on the uniform distribution of the active ingredient, or ingredients, throughout the tablet, as well as maintaining a constant tablet weight (5). Some compendia

Table I—Amount of Sodium Warfarin (Milligrams) Found in Different Layers of Samples Removed from Dried Granulation of Batch A

Sample	Top Layer	Middle Layer	Bottom Layer
1[a]			
a	1.74	1.03	1.71
b	1.74	1.04	1.68
2[b]			
a	2.32	1.40	2.25
b	2.25	1.54	2.19

[a] Sample taken from center of granulation bed. [b] Sample taken from side of granulation bed.

assume that uniform drug distribution does exist within tablets and employ the criterion of tablet weight variation as a control for uniformity of drug substance dosage. However, undetectable variations in the active ingredient when combined with variations in tablet weight can result in differences in dosage greater or smaller than desirable (6).

The tolerances of potency as stated in the compendia should be indicative of the average potency of a batch of tablets. As indicated by Train (7), it is realized that the content of each tablet is of primary importance and not a good estimate of the mean content of a large number of tablets. In assaying individual tablets from 12 commercial products, Moskalyk *et al.* (5) found that four failed to comply with USP tolerance for potency. There appeared to be a general trend for the tablets to become increasingly more uniform as their weight increased. They concluded that greater variations would be found in lighter tablets, especially in those containing a relatively small proportion of active ingredient. Since these tablets usually contain a potent drug substance, the need for more effective control over dosage variability was indicated.

Uniformity of composition in a tablet prepared by wet granulation is the same as in the initial powder blend unless demixing occurs during handling, prior to or during the wet granulation step, or a drug-soluble granulating agent is used which may change the uniformity. In the latter case it would be expected that if any drug substance migration occurs during wet granulation, it would be more prominent and of greater importance in the case of a solvent-soluble, low dosage drug. When water-soluble dyes are used in tablet preparation in procedures involving wet granulation, the migration of the colorant can readily be noted both in the granulations and the compressed tablets. The degree to which color migration occurs depends on several factors such as the water solubility of the colorant, the conditions under which the granulation is dried, and the excipients present (8, 9).

To confirm the occurrence of migration of a solvent-soluble drug, compressed tablets of sodium warfarin were made using a wet granulation method. Sodium warfarin was selected as the substance for investigation due to its high water solubility and the importance of well-controlled dosage in its therapeutic use (10, 11).

It is reasonable to expect that the extent of migration of a water-soluble drug during drying of the granulation is influenced not only by drying conditions but also by the additives present in the granulation. By using a TLC technique, additives were evaluated for their ability to retard the migration of sodium warfarin. In applying this technique, plates of the additives were prepared and the additives served as the substrates.

Table II—Fraction of Theoretical Sodium Warfarin Content Found in Individual Tablet Samples Removed from Successive 1000-Tablet Lots of Batch A

Lot	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5
I (1–1000)	0.93	0.96	0.76	1.23	1.20
II (1001–2000)	0.84	0.83	0.60	1.11	1.18
III (2001–3000)	0.78	0.81	1.08	1.16	0.57
IV (3001–4000)	0.80	0.83	0.66	0.87	1.13
V (4001–5000)	0.68	0.57	0.74	0.54	1.02
VI (5001–6000)	1.07	1.00	0.80	1.13	0.54
VII (6001–7000)	0.91	0.77	0.88	1.12	0.81
VIII (7001–8000)	0.79	0.90	0.87	1.04	0.76
IX (8001–9000)	0.77	0.64	0.97	0.73	0.71
X (9001–10,000)	0.77	1.26	0.80	0.95	0.84

On the basis of results obtained from the TLC studies, a group of additives were selected and sodium warfarin tablets again were prepared using a wet granulation method. The uniformity of drug substance within individual tablets would indicate that migration of solvent-soluble drug during drying of a wet granulation can be reduced by the proper selection of additives.

EXPERIMENTAL

Materials—The materials used were sodium warfarin USP[1], dibasic calcium phosphate NF[2], starch USP[3], magnesium stearate USP[3], acacia USP[4], and alginic acid food grade[5].

Tablet Preparation—By using wet granulation methods, two batches of 10,000 compressed tablets containing 2 mg. sodium warfarin were prepared according to the following formulas:

Per Tablet (mg.)	Ingredients	Per Batch of 10,000 (g.)
	Batch A	
2.0	sodium warfarin USP	20.0
67.0	dibasic calcium phosphate NF	670.0
4.5	starch USP	45.0
0.25	starch USP (as 10% w/v starch paste)	2.5
0.75	magnesium stearate USP	7.5
	Batch B	
2.0	sodium warfarin USP	20.0
67.0	dibasic calcium phosphate NF	670.0
13.0	alginic acid	130.0
0.25	acacia USP (as 10% w/v solution)	2.5
0.9	magnesium stearate USP	9.0

[1] Endo Laboratories, Garden City, L.I., N. Y.
[2] Mallinckrodt Chemical Works, St. Louis, Mo.
[3] Amend Drug and Chemical Co., New York, N. Y.
[4] S. B. Penick & Co., New York, N. Y.
[5] Kelco Co., Clark, N. J.

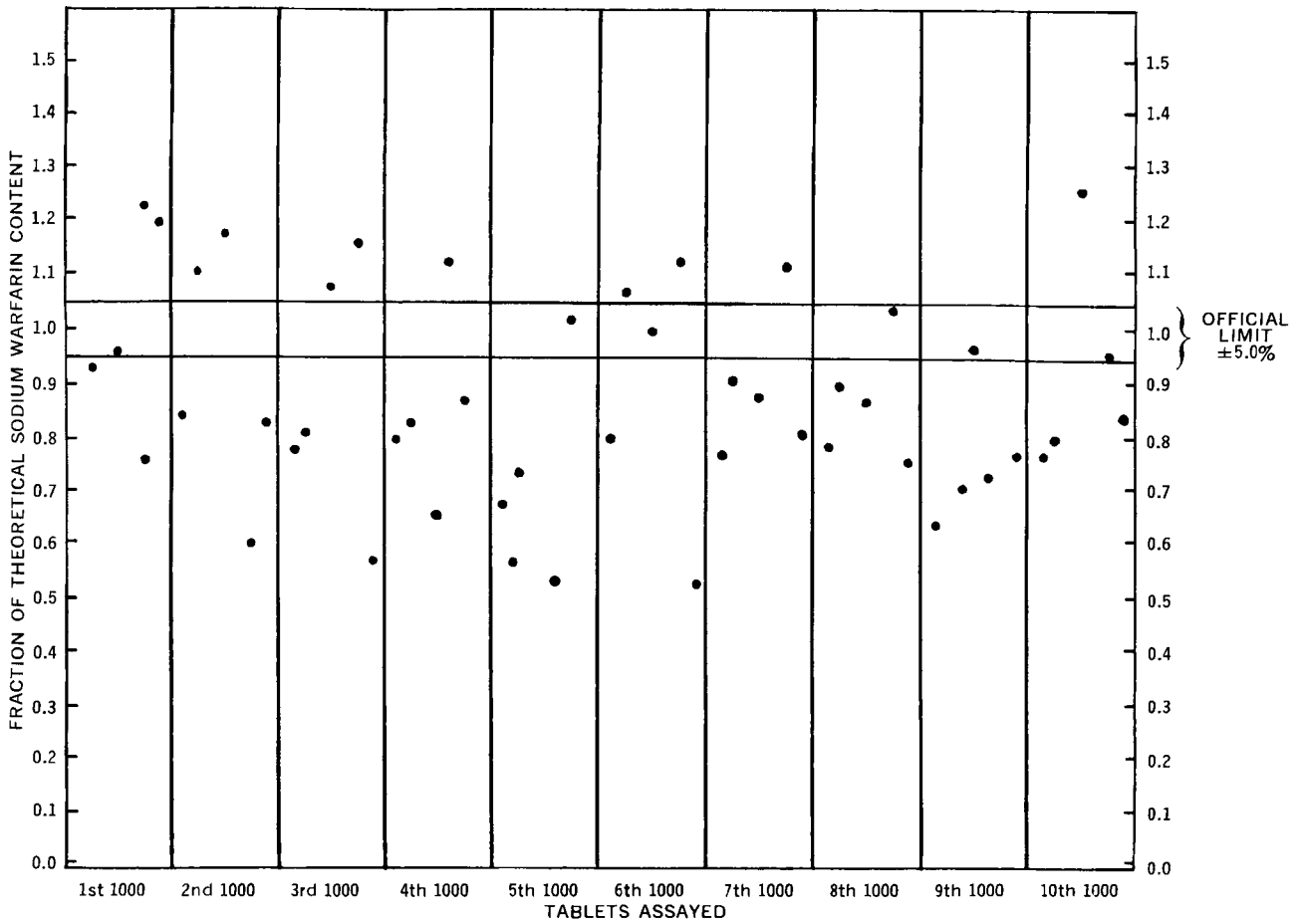

Figure 1—*Distribution of sodium warfarin in individually assayed tablets (Batch A).*

The materials were blended using a twin-shell blender[6], and uniform blending was confirmed by assaying for sodium warfarin. The powders were mixed with starch paste or acacia solution, depending on the batch being prepared, and the wet granulation was passed through a No. 8 screen and dried in a layer, 1.27 cm. (0.5 in.) thick, at 65–70° for 16–18 hr. in a tray shelf dryer[7]. After passing through a No. 20 screen, the granulation was blended with the lubricant using the twin-shell blender. The tablets were compressed on a single-punch machine[7] using a 0.64-cm. (0.25-in.) punch of standard curvature. Each 1000 tablets were collected separately and labeled successively for each batch.

Tablet Characteristics—The thickness and hardness of the tablets prepared were determined using a thickness gauge[8] and a hardness tester[7], respectively. The values reported represent average values of 10 determinations on tablets selected at random. Disintegration times were done according to the USP procedure (12). The weight variation test, as defined by the USP, was done for 20 tablets from each 1000 tablets compressed for each 10,000 tablet batch (12). From each batch, 30 tablets were selected at random and their weights were subjected to a statistical analysis.

Sodium Warfarin, Assay Method—For individual tablets containing 2 mg. sodium warfarin, the following assay procedure was used. The tablet was powdered and transferred carefully to a volumetric flask. The sodium warfarin was extracted with 20 ml. sodium hydroxide solution (1 in 2500) by shaking for 15 min. The solution was filtered through paper, and the first few drops of the filtrate were discarded. Ten milliliters of the filtrate was transferred to a 125-ml. separator and 2 ml. water was added. The solution was adjusted to pH less than 3 (pH indicator paper) with hydrochloric acid. The aqueous solution was extracted with one 25-ml. and two 15-ml. portions of chloroform; the chloroform extracts were filtered through a pledget of cotton into a 100-ml. volumetric flask. The pledget was rinsed, and chloroform was added to bring the volume to 100 ml. The absorbance of the solution at 307 nm. was determined, using chloroform as the blank, using a spectrophotometer[9]. The quantity of $C_{19}H_{15}NaO_4$ was calculated by the formula: mg. = 2 (A at 307 nm. ÷ 0.311). This method of assay was evaluated, and reproducible results were obtained. For both batches, five tablets were selected at random from each lot of 1000 tablets and assayed individually.

Migration of Drug Substance—After blending the ingredients in the tablet formulations, two samples were taken and the amount of drug substance was determined to confirm the uniform composition of the mixture. An amount of powder representing theoretically 2 mg. of drug substance was taken and assayed by the procedure already described. Following drying of the wet granulations, two samples, approximately 2.54 cm. (1 in.) long and 2.54 cm. (1 in.) wide, were taken from two locations. Each sample was divided into three portions, representing the top, middle, and bottom layers of the dried granulations. From these materials, an amount of powder representing theoretically 2 mg. of drug substance was taken and assayed by the procedure already described.

TLC—Glass plates (20 × 20 cm.) were thoroughly cleaned and dried. An even, uniform suspension or slurry of the material, *i.e.*, additive to be evaluated, was prepared; layers 250 μ thick were spread with the aid of a layer spreader. The plates were allowed to dry at room temperature and were subjected to 95–105° for 45–60 min. before use. A standard solution of sodium warfarin was prepared and, with the aid of a micropipet, 10 μl. was spotted. An ascending chromatographic technique was used, with water as the solvent. The ability of sodium warfarin to fluoresce in UV light was used as the means of detection and determination of the R_f values.

[6] Patterson-Kelley Co., East Stroudsburg, Pa.
[7] Model E, Stokes Division, Pennwalt Corp., Philadelphia, Pa.
[8] B. C. Ames Co., Waltham, Mass.
[9] Hitachi-Perkin-Elmer, model 139.

Table III—R_f Values for Sodium Warfarin on Additive Substrates, Using Water as the Solvent

Additive	R_f Value
Dibasic calcium phosphate	0.50
Calcium sulfate	0.72
Lactose	0.54
Calcium phosphate + starch (9.2%)	0.63
Starch	0.68
Calcium phosphate + veegum-F (5%)	0.70
Calcium phosphate + alginic acid (15%)	0.00
Calcium phosphate + acacia (5%)	0.41
Calcium phosphate + acacia (5%) + alginic acid (15%)	0.00

Table IV—Amount of Sodium Warfarin (Milligrams) Found in Different Layers of Samples Removed from Dried Granulation of Batch B

Sample	Top Layer	Middle Layer	Bottom Layer
1	1.99	1.99	1.93
2	1.90	1.82	1.80

The plates were placed in a UV cabinet[10], and the R_f values were measured.

RESULTS AND DISCUSSION

Migration of Sodium Warfarin—Following wet granulation and drying of a formulation (Batch A) containing sodium warfarin, it was shown that the granulation was no longer uniform as to sodium warfarin content (Table I). Migration of the drug substance had occurred during drying. Sodium warfarin, being highly water soluble, followed the solvent as it moved upward and downward during the drying period. Higher concentrations of the drug were found in the outer layers, with a reduced amount toward the center as compared with the initial blended material. Individual assays on the tablets compressed from this granulation demonstrated that migration of the drug substance during drying resulted in uneven drug distribution in the tablets. Of the 50 tablets assayed individually, only six tablets (12%) fell within the acceptable USP limits. The remainder of the tablets were outside of official limits (Table II and Fig. 1).

Application of TLC—After confirming the occurrence of migration, it was reasonable to assume that if the drug substance had more affinity for the additives than the solvent, or if the additives had the ability to adsorb the drug, then migration of the drug would be inhibited during drying. Randerath (13) observed that the adsorption of the drug substance on the substrate, or the affinity of the substrate toward the drug substance, has a major effect on the R_f value. In TLC the greater the affinity the substrate has for the drug, the less it migrates, giving a smaller R_f value. TLC appeared to be a suitable means for evaluating additives as to their drug migration inhibitory properties.

Since sodium warfarin exhibited the lowest R_f value on calcium phosphate (among the three diluents evaluated), it was assumed that calcium phosphate has more drug migration inhibitory characteristics than the other diluents evaluated (Table III). In spite of the fact that calcium phosphate was used in the Batch A granulation, migration had occurred. The presence of starch in the granulation reduced the drug migration inhibitory properties of calcium phosphate.

Chromatographic results of calcium phosphate plus alginic acid (15%) showed that alginic acid has a drug migration inhibitory effect; with calcium phosphate, it imparts the same characteristic to the mixture. A 15% concentration of alginic acid was used because it was an effective disintegrator at this concentration.

[10] Chromato-Vue, Ultra-Violet Products, San Gabriel, Calif.

Table V—Fraction of Theoretical Sodium Warfarin Content Found in Individual Tablet Samples Removed from Successive 1000-Tablet Lots of Batch B

Lot	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5
I (1–1000)	0.99	1.00	0.97	0.99	0.97
II (1001–2000)	1.02	1.02	0.96	0.97	0.96
III (2001–3000)	0.95	0.98	1.00	0.95	1.03
IV (3001–4000)	0.99	0.99	1.03	1.05	1.03
V (4001–5000)	1.05	1.00	1.00	1.00	1.05
VI (5001–6000)	0.98	1.00	1.00	1.00	1.00
VII (6001–7000)	1.08	1.01	0.99	1.00	0.99
VIII (7001–8000)	1.01	1.04	1.05	1.05	1.05
IX (8001–9000)	1.05	1.01	1.05	1.03	1.05
X (9001–10000)	1.01	1.04	1.03	1.00	0.99

Granulation with Selected Additives—Following wet granulation and drying of a formulation containing sodium warfarin and additives selected for their drug migration-inhibitory properties (Batch B), the granulation remained uniform with respect to distribution of drug substance during drying (Table IV). The sodium warfarin content of tablets prepared from this granulation, as determined by individual tablet assays, confirmed the lack of migration in the granulation during drying (Table V and Fig. 2). Eighty-eight percent of the tablets fell within acceptable USP limits.

Although falling within the official limits for disintegration, this batch of tablets (Batch B) showed a longer disintegration time (Table VI). This is due to the stronger binding action of the acacia as compared with starch. The study is being continued to obtain the dissolution time for Batch B and to determine the biological availability of the drug in animals receiving the tablet with the selected additives.

CONCLUSIONS

Migration of a soluble drug substance with the solvent during drying of a wet granulation results in an uneven distribution of the drug substance within the granulation. Sodium warfarin uniformly distributed in a granulation prior to drying was shown to migrate

Table VI—Physical Characteristics of Compressed Tablets Containing Sodium Warfarin

Characteristic	Batch A	Batch B
Punch	0.63 cm. (0.125 in.); standard curvature	0.63 cm. (0.125 in.); standard curvature
Hardness	4.0 kg. (Stokes)	4.3 kg. (Stokes)
Thickness	0.18 cm. (0.072 in.)	0.22 cm. (0.085 in.)
Disintegration time (USP)	10–12 sec.	16–18 min.
Weight variations	Conform with USP limits, 76.7 mg., 10%	Conform with USP limits, 82.4 mg., 10%
Average weight	73.6 mg.	82.4 mg.
Standard deviation	1.52	3.0
Tablet weight range	70–76 mg.	80–89 mg.

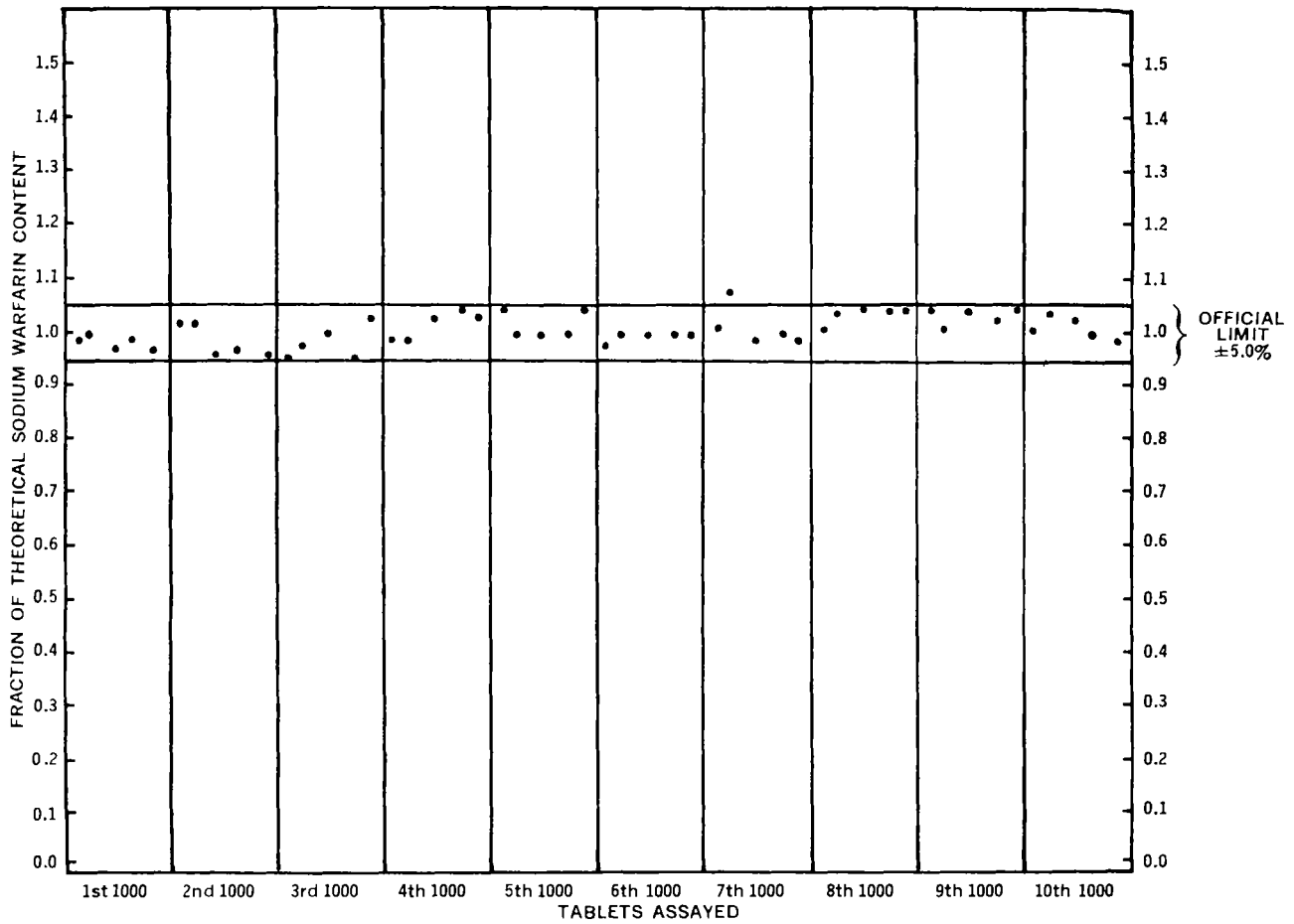

Figure 2—*Distribution of sodium warfarin in individually assayed tablets (Batch B).*

with the solvent. When assayed individually, tablets compressed from the dried granulation showed a wide variation in drug substance content; only 12% was within the official limits.

TLC was utilized to evaluate the ability of tablet additives to inhibit the migration of sodium warfarin. The R_f values for sodium warfarin were determined, using various tablet additives as substrates. The movement of the drug substance was detected by its fluorescence in UV light.

Using those materials as additives on which sodium warfarin had the lowest R_f values, another batch of sodium warfarin tablets was prepared by the same technique as was previously employed. Migration of the drug substance within the granulation was reduced, and the content uniformity of the compressed tablets, when assayed individually, was found to be satisfactory.

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