served between FD&C Red No. 2 and PEG 6000, and can be explained similarly on the basis of adsorption phenomenon. On an average, 700 equivalents of oxyethylene linkages are required to solubilize 1 mole of FD&C Red No. 1, and 450 equivalents to solubilize 1 mole of FD&C Red No. 4.

Filmcoating Studies.—The relative uniformity of color produced by formulations YI (FD&C Yellow No. 5) and RI (FD&C Red No. 2) contrasted with the highly mottled appearance produced by formulations YII (FD&C Yellow No. 5) and RII (FD&C Red No. 2) substantiates the hypothesis presented earlier that to achieve uniform color coverage the dye must be brought into solution. However, the results shown by formulations YIV (FD&C Yellow No. 5) and RIV (FD&C Red No. 2) do not substantiate this hypothesis. Although here the amount of dye is in excess (same as in YII and RII, respectively), the presence of titanium dioxide helps to prevent the expected mottled appearance of the tablets.

Study of the Function of Titanium Dioxide in the Filmcoating Formulation.—The results obtained in the study designed to evaluate the function of titanium dioxide in the filmcoating formulation showed no change in the adsorption curve patterns obtained for PEG 6000–dye interactions. Hence, it is concluded that titanium dioxide does not act as an adsorbent for the dye or PEG 6000 and thus does not aid in preventing mottling by an adsorption process. Furthermore, the studies show that the titanium dioxide does not act in any way to affect the interactions between the dyes and PEG 6000. However, the results in the filmcoating studies show that even when the dye was not completely solubilized by PEG 6000, the mottling was considerably reduced by the addition of titanium dioxide to the filmcoating formula. Therefore, it is concluded that the presence of titanium dioxide promotes color uniformity simply due to "mechanical effect" of its bulk; that is, the larger number of titanium dioxide particles present tends to mechanically prevent the aggregation of the dye particles.

CONCLUSIONS

The results of the present investigation have demonstrated: (*a*) PEG 6000 interacts with the dyes tested (FD&C Red No. 1, 2, and 4; FD&C Yellow No. 5; and FD&C Blue No. 1). The interaction (adsorption of PEG 6000 onto the solid dye) results in solubilization of the dyes which are almost insoluble in the solvent system used (65% acetone and 35% absolute ethanol). (*b*) No interaction is observed between CAP and the dyes tested. (*c*) Presence of titanium dioxide does not alter or affect the adsorption of PEG 6000 onto dyes.

Thus, in a typical basic filmcoating formulation containing dye, PEG 6000, CAP, and titanium dioxide in the nonaqueous solvent system, the interaction between PEG 6000 and dyes plays a significant role in affecting the uniformity of color. In order to assure maximum color uniformity, the amount of dye in a filmcoating formulation should not exceed the amount capable of being brought into solution by PEG 6000. The purely mechanical effect of titanium dioxide in preventing the aggregation of dye particles also plays a significant role in achieving color uniformity.

The information provided by this study gives some insight into methods that may be employed in formulating filmcoating solutions on the basis of scientific data rather than by the use of purely empirical techniques.

REFERENCES

(1) Gross, H. M., and Endicott, C. J., *Drug Cosmetic Ind.*, **86**, 170(1960).
(2) Higuchi, T., and Lach, J. L., *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 465(1954).
(3) Barrow, G. M., "Physical Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1961, p. 631.

Experiences in Development of Directly Compressible Tablets Containing Potassium Chloride

By JACK LAZARUS and LEON LACHMAN

The influence of particle size distribution, particle shape, apparent bulk density, moisture content, additives, and punch shape on the directly compressible characteristics of potassium chloride were investigated. The relative weight and drug variability of hydrochlorothiazide–potassium chloride tablets prepared by direct compression were compared with those prepared by customary wet granulating techniques.

ACCORDING TO the literature (1, 2) it should be possible to directly compress crystals belonging to the cubic system into conventional flat-faced or biconvex tablets. Potassium chloride crystals fall under this classification and can normally be directly compressed into such tablets. However, when the tablet shape is altered, not all batches of U.S.P. potassium chloride crystals obtained from different suppliers could be directly

Received April 28, 1966, from the Research Department, Ciba Pharmaceutical Co., Summit, N. J.
Accepted for publication July 7, 1966.
Presented to the Industrial Pharmacy Section, A.PH.A. Academy of Pharmaceutical Sciences, Dallas meeting, April 1966.
The authors express their appreciation to Mr. James B. Smith for his analytical assistance.

compressed to produce tablets with satisfactory physical properties. The term "directly compressed" as used in this text refers to the compression of a mixture of materials which have been subjected to thorough mixing prior to compression in order to obtain a uniform distribution of components of the mixture. By this process, treatments, such as drying the wet granulation, rescreening, and lubricating are not necessary.

Several physical factors appear to influence the direct compression of potassium chloride crystals into modified ball-shaped tablets. This report will relate findings on the influence of particle size distribution, particle shape, apparent bulk density, moisture, drug, and lubricant on the compaction characteristics of potassium chloride crystals.

EXPERIMENTAL

Formulations.—The formula used for screening the direct compressibility of potassium chloride crystals was:

	1000 Tablets
Potassium chloride crystals	1000 Gm.
Stearic acid, powdered	5

Pass the potassium chloride crystals and the stearic acid through a No. 30 mesh stainless steel screen and mix well.

Wet Granulation Formula	1000 Tablets
Potassium chloride crystals	1000 Gm.
Hydrochlorothiazide crystals	50
Gelatin	10
Stearic acid, powder	5

Pass the potassium chloride and hydrochlorothiazide through a No. 30 mesh stainless steel screen and mix well. Dissolve the gelatin in a suitable quantity of deionized water and granulate. Screen the granulation to break up the lumps, dry on trays in a circulating air oven, rescreen, and lubricate.

Direct Compression Formula	1000 Tablets
Potassium chloride crystals	1000 Gm.
Hydrochlorothiazide crystals	50
Polyethylene glycol 6000, powdered	5
Deionized water	1.0 ml.
Colloidal silica	5 Gm.
Stearic acid	5
Talc	10

Pass the potassium chloride, hydrochlorothiazide, and the polyethylene glycol 6000 through a No. 30 mesh stainless steel screen. Mix well and then spray in the water by means of an atomizer or a pressure-actuated spray nozzle. Mix well, then add the colloidal silica, stearic acid, and talc. Mix until blended. The granulation is now ready for compression.

Compaction.—A four-station, single-rotary Colton 204 tablet press, using $^{15}/_{32}$ in. modified ball stainless steel punches, was used to screen the direct compressibility of the different batches of potassium chloride crystals. The batch of crystals which compressed satisfactorily was then formulated with hydrochlorothiazide. The mixtures which produced satisfactory tablets on the Colton 204 were scaled up for compression on a 27-station, double-rotary tablet press. The production-size batches were sufficient to make 240,000 tablets and were compressed on a Stokes 541 double-rotary press, operating at a speed that produced 2000 tablets/min.

The four-station, single-rotary press was used rather than a single-punch machine for the screening studies in order to more closely approximate the compression force distribution encountered when the tablets are compressed in production on a larger rotary press. Furthermore, in a single-punch machine, the lower punch is stationary and only the upper punch exerts the pressure at the time of maximum compression. In a rotary press, both the upper and lower tablet punches approach one another simultaneously up to the point of maximum pressure. Consequently, the strains induced in tablets produced on a single-punch machine would be different than those obtained from a rotary press.

For this investigation, modified ball-shaped tablets were chosen since such tablets provide a minimum volume for a heavy tablet and a narrow edge which facilitates the application of a coating onto the tablets. A tablet compressed with standard concave punches or extra deep concave punches would have a wider edge which is not so easily coated. Figure 1 shows a composite photo of these different shaped tablets.

Friabilator.—A modified Roche friabilator (3) was employed to determine the resistance of the tablet to breaking. Both a plastic and stainless steel frame were used initially for tumbling the tablets. The plastic frame was selected for use after the initial evaluations since it was found that each frame gave comparable results. Twenty tablets were placed in the friabilator which was then set in motion and timed. The test was terminated when one or more tablets were broken. Four minutes was the minimum acceptable time based on experience gained in spray coating of these tablets.

Particle Size Distribution.—Two hundred grams of potassium chloride crystals were sized on 8-in. diameter stainless steel screens (U. S. sieve series) using a Rotap sieve shaker operating for 20 min. The per cent of the crystals retained on each screen was then determined.

Apparent Bulk Density.—A weighed sample of crystals was placed into a graduated cylinder and tamped a given number of times from a uniform height. The volume of the crystals in the cylinder was used to estimate the apparent bulk density.

Moisture Determination.—The potassium chloride crystals were placed into weighing bottles fitted with ground-glass covers and weighed on a Mettler semimicro analytical balance. The bottles were previously exposed to 175° for 20 hr. The samples of crystals were placed in an oven set at 105 ± 1° for 2 hr. to remove surface moisture. The bottles were then stoppered, placed into a desiccator, and weighed when at room temperature. After weighing, the bottles were transferred to the 175 ± 1° for 20 hr., after which they were stoppered, cooled in a desiccator until at room temperature, and reweighed.

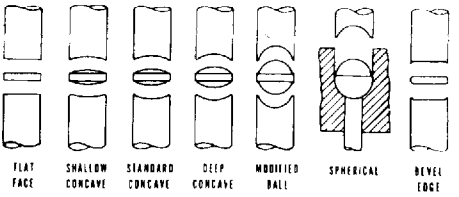

Fig. 1.—Concave punches used in tablet manufacturing.

TABLE I.—MAXIMUM SAFE PRESSURE IN TONS ON TABLET MACHINE PUNCHES[a]

Punch Diam. Fraction	Area of Punch Face, sq. in.		Max. Safe Pressure, Tons—Flatface or Std. Concave Punches	Max. Safe Pressure, Tons—Bevel-Edge Modified Ball or Carbide Tipped Punches
$^{12}/_{32}$	.3750	.1105	5.6	2.2
$^{13}/_{32}$	.4063	.1295	6.6	2.6
$^{14}/_{32}$	.4375	.1506	7.7	3.1
$^{15}/_{32}$	.4688	.1726	8.8	3.5

[a] F. J. Stokes Corp., Philadelphia, Pa.

Microscopic Examination.—The deformation of crystals following compression into modified ball-shaped tablets was evaluated microscopically. The potassium chloride crystals were lubricated with stearic acid, mixed with a small quantity of activated charcoal, and compressed. The tablets were then cut in half and examined under low power magnification.

Sampling Procedure for the Determination of Inter-Unit Tablet Variability.—Six individual batches of the directly compressible formulation of potassium chloride with hydrochlorothiazide, sufficient to make 240,000 tablets per batch, were prepared and individually processed. Three batches were selected for statistical analysis of the inter-unit variability in tablet weight, drug content, and per cent of drug. Four samples of approximately 100 tablets each were taken systematically at 30-min. intervals from each side of the double-rotary tablet press during the compression operation. The initial sample was taken 30 min. after starting compression. During this period, the production personnel made the routine weight adjustments on the machine which may not have been the same in number or in time for the three batches that were analyzed, nor were they the same for each side of the tablet press. Ten tablets were randomly selected from each sample, individually weighed, and each was placed into a coded bottle, which identified the tablet as to batch, time of sampling, side of machine from which sample was taken, and weight of tablet. Four tablets were randomly selected from each set of 10 tablets for analysis of drug content per tablet. A table of random numbers was employed to facilitate random selection.

RESULTS AND DISCUSSION

The failure of some crystals to compact favorably when compressed into modified ball-shaped tablets may be due to the amount of pressure which can safely be applied to the tablets and to the distributions of the forces in the tablet itself. Table I shows the maximum safe pressure which may be applied with different shaped tablet punches. It will be noted that less than half the amount of pressure can be applied safely when using modified ball punches than when using flat-faced or standard concave punches.

Seth (2) stated that deeply biconvex tablets show a greater tendency toward capping because the applied pressure is not uniformly distributed throughout the tablet granulation in the die cavity during compression. As a result, the more deeply biconvex-shaped tablets are, in general, relatively weaker in strength than flat-faced or conventional biconvex tablets. Because of the convexity of the tablet, the pressures reaching the center of the tablet at its maximum diameter would be expected to be a minimum.

Modified ball-shaped tablets which showed poor friability were split in half and examined under low-

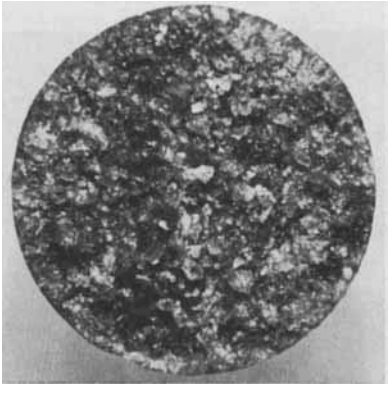

Fig. 2.—Section of compressed tablet of potassium chloride with stearic acid. Carbon has been added to help visualize the crystal boundaries.

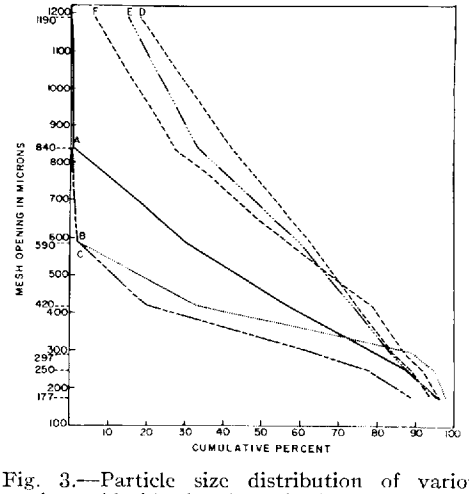

Fig. 3.—Particle size distribution of various potassium chloride batches sized on U. S. sieve series screens.

Fig. 4.- Potassium chloride crystals, batch D.

Fig. 5.—Potassium chloride crystals, batch E.

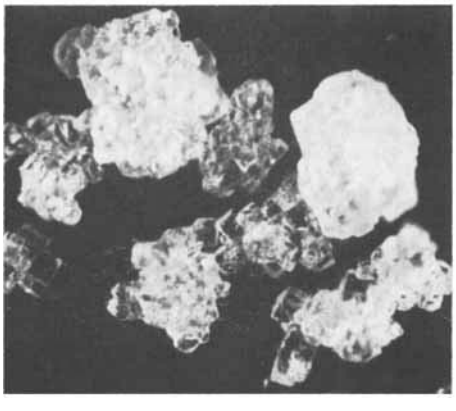

Fig. 6.—Potassium chloride crystals, batch F.

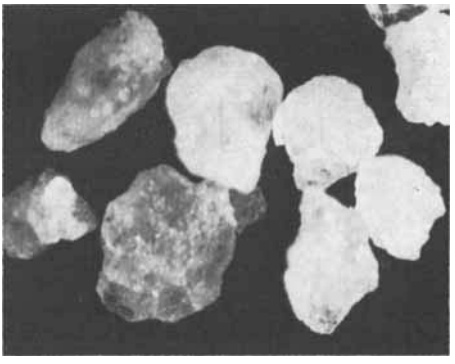

Fig. 7.—Potassium chloride crystals, batch A.

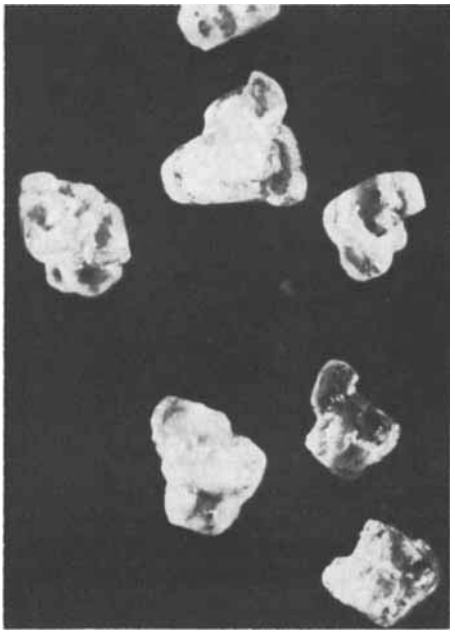

Fig. 8.—Potassium chloride crystals, batch B.

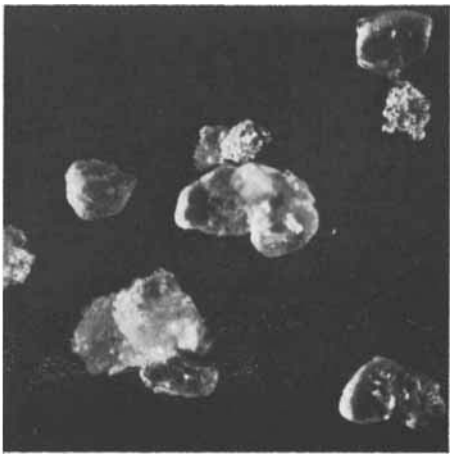

Fig. 9.—Potassium chloride crystals, batch C.

power magnification as shown in Fig. 2. Batch B crystals were used to make the tablet shown in the figure. The crystals at the edges of the tablet, *i.e.*, those crystals in close proximity to the punch face, showed the greatest modification in shape due to the pressure exerted. The crystals in the center of the tablet showed little or no modification from their original shape, indicating that the pressures exerted on the granulation bed were not uniform, a finding which was not unexpected due to the curvature of the punch faces.

Particle Size Distribution.—The particle size distribution of the several batches of potassium chloride crystals is presented in Fig. 3, and it can be seen that there exists a wide range of sizes in the batches. The directly compressible crystals were at least 650 μ or larger at the fiftieth percentile, while the largest crystals at this percentile for those batches that did not exhibit directly compressible properties were no more than 450 μ in size. Approximately 75% of the crystals from the directly compressible batches were 420 μ or larger, while approximately 75% of the nondirectly compressible crystals were 297 μ or larger.

Particle Shape and Appearance.—Examination of the crystals under low-power magnification revealed differences in the appearance and shape of the crystals. The directly compressible crystals (Figs. 4, 5, and 6), batches D, E, and F, respectively, were irregular in shape, frequently having straight jagged edges, often transparent, and appearing to be built up in the form of clusters as a result of growing together in irregular clumps. Other crystals were cubic units built-up in almost pyramid fashion by what appears to be fusion of adjacent crystals. The nondirectly compressible crystals (Figs. 7, 8, and 9), batches A, B, and C, respectively, frequently had rounded surfaces and appeared to lack distinct crystal faces. In addition, these crystals were usually translucent and occasionally opaque in appearance.

Apparent Bulk Density.—The apparent bulk density of the crystals corresponded fairly closely to the particle size distribution of the crystals as shown in Table II. The bulk density represents the packing tendency of the crystals and is a function of the crystal size distribution and the irregularities of the crystal shape. The larger crystals and the highly irregular crystals provide fewer contact points between crystals and create greater void spaces; and if these voids are not filled in by the smaller crystals in the distribution, a low apparent bulk density value will be obtained. It was observed that those crystals which had an apparent bulk density above 1.0 could not be directly compressed.

Moisture Content of Crystals.—When sodium chloride and potassium chloride are crystallized from solution, some water of crystallization may be occluded in the crystals. Smith and co-workers (4) dried sodium chloride and potassium chloride crystals at 140° and then heated them at 550° for 1 hr. A loss in moisture was recorded at the latter temperature. A further loss in occluded moisture was observed when the crystals were heated for 20 min. at 900° which is more than 100° above the fusion point of the crystals. For example, they reported a loss of 0.156% water at 550° and an additional loss of 0.064% water at 900° for potassium chloride crystals prepared by slow evaporation on a hot plate followed by drying to remove surface moisture. In addition, they found that the amount of water occluded varied with the method of precipitating the salts.

The various batches of potassium chloride in the present study were evaluated for the possible presence of occluded moisture, first by drying the crystals at 105° and then at 175° for 20 hr. The 175° temperature was selected because of convenience, no special precautions were necessary to guard against loss by decrepitation, and significant results were apparently attained at this temperature. The data obtained from these drying studies are summarized in Table III. Samples A, B, and C represent crystals which could not be directly compressed or could they be compressed when wet granulated. Samples D, E, and F were directly compressible.

The loss of moisture at 175° was, as one would expect, higher than at 105° which is the usual temperature for removing surface moisture. The loss at 175° which is represented by the difference between total loss of 175° and the observed loss at 105° was generally higher for the directly compressible crystals than for the others.

To determine whether the per cent of occluded water within the crystals varied with the particle size of the crystals, a similar study was performed on different size crystals from several batches, and the results are presented in Table IV. The data in the table indicate that there were generally greater losses in moisture from the larger size crystals than from the smaller crystals. This moisture is not apparently surface moisture because if it were, the small crystals, which have a larger surface area, would be expected to exhibit a greater loss on heating.

The higher percentage of moisture in the larger crystals may be one of the factors that contribute to the compressibility of these crystals. Although these moisture values are small in magnitude, they appear to be of significance when used as a measure

TABLE II.—SUMMARY OF DATA ON VARIOUS POTASSIUM CHLORIDE BATCHES

Sample	Particle Size, mμ		% Loss at 175°	Bulk Density	Hardness	Friability
	50% Up To	50% From				
A	450	450–850	0.01	1.06	7	<2.5 min.
B	360	360–580	0.02	1.10	7	<3
C	320	320–580	0.04	1.14	6	<3
D	730	730–1200	0.05	0.86	13	>10
E	670	670–1200	0.05	0.88	14	>10
F	650	650–1200	0.08	0.92	12	>10

TABLE III.—LOSS OF MOISTURE IN PER CENT AT 105 AND 175° IN VARIOUS SAMPLES OF KCl CRYSTALS[a]

Sample	Loss at 105°	Total Loss at 175°	Difference
A	0.02	0.03	0.01
B	0.01	0.03	0.02
C	0.08	0.12	0.04
D	0.01	0.06	0.05
E	0.01	0.06	0.05
F	0.02	0.10	0.08

[a] Each value represents an average of five determinations. Sample weight ranged from 0.9000 to 4.5000 Gm.

TABLE IV.—MOISTURE LOSS AT 175° OF DIFFERENT BATCHES OF SIZED CRYSTALS OF KCl

	Crystal Size Retained on Screen—		
Sample	No. 20 Mesh, %	No. 30 Mesh, %	No. 60 Mesh, %
A	0.01	0.01	0.00
B	...	0.04	0.01
C	...	0.02	0.01
D	0.09	0.06	0.01
E	0.04	0.03	0.01
F	0.07	0.04	0.02

TABLE V.—EFFECT OF LUBRICANTS ON THE PHYSICAL PROPERTIES OF POTASSIUM CHLORIDE TABLETS

Lubricant	Concn., %	Hardness[a]	Friabilator, min.	Thickness, mm.
KCl + stearic acid	0.5	12	>10	7.9
KCl + magnesium stearate	0.5	5	< 1	7.9
KCl + calcium stearate	0.5	6	< 1	7.9

[a] Hardness was measured on a Strong-Cobb hardness tester, modified so that it was actuated by air pressure rather than the manually operated lever.

TABLE VI.—TYPICAL TABLET PROPERTIES FOLLOWING THE ADDITION OF HYDROCHLOROTHIAZIDE

Formula	1 Tablet, mg.	1 Tablet, mg.
Potassium chloride	1000	1000
Stearic acid	5	5
Hydrochlorothiazide	...	50
Tablet Properties		
Tablet diameter	15/32 in.	15/32 in.
Tablet thickness	7.9 mm.	8.0 mm.
Tablet shape	Modified ball	Modified ball
Hardness	12	9
Friabilator	>10 min.	3.0 min.

of water of occlusion and are in the same order of magnitude as reported by Smith *et al.* (4).

It is reasonable to assume that the loss in weight observed after heating the crystals represents moisture since the crystals are obtained by evaporation from water. Examination of the crystals, before and after heating, under low-power magnification, preferably with the stereomicroscope, will reveal an apparent increase in the number of air bubbles or cavities following the heat treatment. The air bubbles will be more obvious with crystals which exhibit a greater moisture loss at the higher temperature.

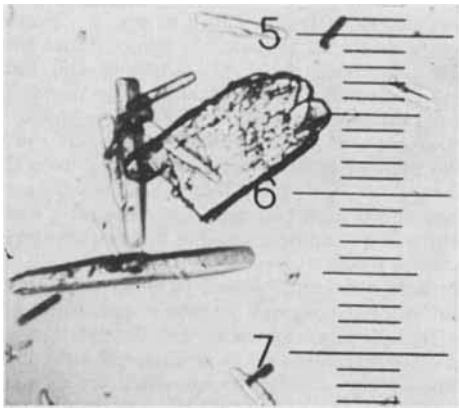

Fig. 10.—Hydrochlorothiazide crystals.

Although batch A crystals had a larger average particle size than B or C and more closely approximated in particle size range the directly compressible crystals, they did not directly compress. This can be attributed to the fact that batch A crystals were compacted on a Chilsonator[1] to attain a larger average particle, and the amount of occluded moisture was low as seen from the data in Table III. The photomicrograph of these crystals (Fig. 7) shows them to be rounded and somewhat opaque with few natural transparent aggregates, unlike the crystals formed by evaporation of solvent and not further subjected to any mechanical compaction process. Since moisture is apparently an important factor in compaction, the crystals should not be subjected to any treatment which will cause excessive loss of moisture.

Lubricant Effect.—The addition of different lubricants was studied in conjunction with the compressibility of the potassium chloride crystals. Stearic acid, magnesium stearate, and calcium stearate were each added in varying amounts to potassium chloride crystals. The magnesium and calcium stearates produced good lubrication, but decreased the bonding characteristics of the salt excessively as seen from the data presented in Table V.

Drug Effect.—The addition of hydrochlorothiazide to the mixture containing potassium chloride and stearic acid reduced tablet hardness and the resistance of the tablets to splitting in the friabilator as evidenced by the data in Table VI. The good bonding properties of the directly compressible potassium chloride crystals were adversely affected as evidenced by the data in this table. The hydrochlorothiazide crystals were essentially needle-like in shape with an occasional flat-platelet and which could be readily fractured and is shown in Fig. 10.

Directly Compressible Formulas.—To overcome the adverse effect of hydrochlorothiazide on the

[1] Manufactured by the Fitzpatrick Co., Chicago, Ill.

TABLE VII.—COMPARISON OF TWO PRODUCTION METHODS

Lots	Tablet Wt. Mean ± S. D.	Tablet Wt. Coeff. of Var., %	Drug Content, mg. Mean ± S. D.	Drug Content, mg. Coeff. of Var., %
Direct Compression				
D	1.0752 ± .0050	.47	48.59 ± .60	1.23
F	1.0704 ± .0052	.49	48.28 ± 1.65	3.42
H	1.0739 ± .0044	.41	47.66 ± .93	1.95
Wet Granulation				
K_4	1.0647 ± .0066	.62	48.67 ± 1.68	3.46
K_6	1.0664 ± .0063	.59	48.60 ± 1.33	2.74
K_8	1.0649 ± .0068	.64	49.00 ± 1.24	2.53

directly compressible properties of potassium chloride, additives were incorporated in the formulation. The rationale for the use of the various raw materials in the formulation will now be presented.

The polyethylene glycol 6000 powder was used as a water-soluble binder, and the small amount of moisture which is atomized into the mixture most likely activates its binding properties. Since the potassium chloride crystal is well balanced ionically, it does not have ideal surfaces for attracting poorly soluble additives, such as a hydrochlorothiazide. The polyethylene glycol 6000 may act as a bridge to provide the necessary bonding between these two crystals.

The moisture may also act to leak-off electrostatic charges induced by mixing the dry powders in the presence of hydrochlorothiazide. The surface of the potassium chloride crystals may be altered by the addition of moisture through surface dissolution of the salt followed by recrystallization on drying.

The colloidal silica improved the flow of the mixture by its adsorbent properties, particularly when the distribution of the small quantity of moisture added was not absolutely homogeneous. In the presence of the water, the colloidal silica may modify the surface of the potassium chloride by forming a surface film.

In order to overcome picking of the tablets at the monogram, it was found necessary to add talc. Such picking did not occur on nonmonogrammed, smooth-faced punches.

Inter-Unit Tablet Variation.—The directly compressible method (method *2*) required less manufacturing and material handling time than the wet granulation procedure (method *1*). At least 12 material handling steps are involved in method *1* as compared to four for method *2*. The manufacturing time for method *1* is approximately 3.5 manhours, not including the delay for drying time. There is no delay for drying in method *2*, and the manufacturing time is about 1.25 manhours.

The purpose of the statistical analysis was to determine the variation in inter-unit tablet weight and drug content existing in the tablets prepared by method *2* and to compare these results with similar data reported for method *1* (5).

The mean, standard deviation, and coefficient of variation for tablet weight and drug content were estimated for each lot. The contribution to heterogeneity introduced by sampling from two sides of the compressing machine and the different times of sampling were disregarded. The data are presented in Table VII.

The tablets from method *1* show a tendency for larger inter-unit tablet weight variability than do the tablets from method *2* as judged from the values for the coefficients of variation. A stronger tendency for larger variability of drug content exists also in method *1*. In view of these results, one can conclude that the directly compressible formulation is at least as good, if not better, than the wet granulated formula.

SUMMARY

Several factors were found to influence the direct compression of potassium chloride crystals into nonconventional shaped tablets. These were particle size distribution, crystal shape, apparent bulk density, moisture, additives, and punch shape.

A larger particle size distribution was observed for the potassium chloride crystals which could be directly compressed into modified ball-shaped tablets. These crystals had many straight edges, were generally cubic or oblong in shape, or formed clusters from these shapes. Rounded surfaces and smaller particle size distribution were characteristic of the potassium chloride crystals which could not be directly compressed into modified ball-shaped tablets. The larger irregular crystals had an expected lower apparent bulk density and exhibited more occluded moisture. As lubricants, calcium and magnesium stearate tended to produce weaker tablets than stearic acid. Hydrochlorothiazide had a similar effect as the stearates. The development of a directly compressible formulation for hydrochlorothiazide-potassium chloride tablets is described. The inter-unit tablet weight and drug content variability for the tablets prepared from the directly compressible formulation and those prepared by the wet granulation technique were found to be comparable.

REFERENCES

(1) "Remington's Pharmaceutical Sciences," 13th ed., Mack Publishing Co., Easton, Pa., 1965.

(2) Seth, P. L., "The Influence of Physical and Mechanical Factors in Tablet Making," Tent House, Calcutta, India, 1956.

(3) Shafer, E. G. E., Wollish, E. G., and Engel, C. E., *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 114(1956).

(4) Smith, G. F., Stubblefield, F. M., and Middleton, E. B., *Ind. Eng. Chem. (Anal Ed.)*, **6**, 314(1934).

(5) Lachman, L., and Sylwestrowicz, H. D., *J. Pharm. Sci.*, **53**, 1234(1964).