

(6) who stored Fluidextracts of *Krameria* for 12 months in air-tight containers and compared the loss of tannin with the loss observed in the same samples which had not been sealed. It was found that the tannin loss in unsealed samples was much greater than that in sealed samples. This further indicates that oxidation plays a part in the decomposition of tannic acid solutions.

SUMMARY AND CONCLUSIONS

1. Results obtained from this study seem to indicate that most of the well-known chemical antioxidants are ineffective in the stabilization of tannic acid solutions.

2. Sodium sulfite and other sulfite salts are effective in preventing discoloration and loss of tannin in aqueous solutions of tannic acid, at least for a period of four months.

3. In aqueous tannic acid solutions decrease in the tannic acid content is not only immediate but accompanied by marked discoloration of the solutions.

4. There is evidence that the presence of atmospheric oxygen contributes to the decomposition of tannic acid solutions.

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Homogeneity of Tablet Mixtures Before Granulating*

By E. C. Beeler and E. N. Gathercoal†

Tablet forms have been recognized for many years as one of the most convenient methods of administering medicines with uniform and exact dosage. There have been many phases of tablet making reported in the literature, but few of them have considered the homogeneity of tablet mixtures. The fabrication of compressed tablets consisting of multi-component substances can be divided into four factors wherein uni-

formity is either consummated or modified; named in the order of processing tablets, they are (1) mixing before granulating, (2) granulating, (3) mixing after granulating prior to compression and (4) compression. The first three factors involve the mixing of relatively small solid particles to uniformity, while the fourth, compression, involves the effect of mechanical vibrations of the tablet machine; any mechanical disturbance in the latter could break the homogeneity established in the granulation.

Any type of mixture, *i. e.*, liquid solution, solid solution, gases, mechanical mixtures, etc., is homogeneous when each component substance possesses a constant proportional relationship to every other component substance in any fractional part of the mixture. An ideal mixture is one in which intermingling of particles of the component substances down to molecular magnitude can be accomplished. A solid substance reduced to powder form by mechanical means could never be made to reach such a minute size; therefore, medical powder mixtures are classified as mechanical mixtures in which homogeneity can never be completely realized. Snow and Fantus (1) advanced the theory on tablet making that the material to be compressed must be heterogeneous with respect to the electrical potential set up by mechanical friction of the particles being compressed.

Homogeneity will be used in this paper to indicate the uniformity of composition to which a tablet mixture can be prepared under specific physical conditions of the component substances. Experimental evidence of homogeneity is obtained from the results of several analyses on at least one of the component substances. Consequently, the term homogeneity as applied to a powder mixture is a general description of the uniformity of composition in a fractional part of the mixture convenient for ordinary analysis.

Conditions entering into the problem of mixing solids with solids are of a mechanical or physical nature. Physical, or inherent, characteristics of the component substances comprise the factors which cannot be controlled while mechanical factors can be

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regulated to a reasonable extent. Some of the physical characteristics are density, electrostatic dynamics, segregation and characteristic surface. Mechanical conditions include particle size and shape, bulkiness (partially controlled by particle size), proportional relationship of ingredients, methods of mixing and rate of mixing.

EXPERIMENTAL

Magnesium pyrophosphate, barium sulfate, sodium carbonate and corn starch were selected for the study of the effects of particle size and particle density of component substances on the homogeneity of powder mixtures. Simple binary mixtures of magnesium pyrophosphate-starch and of barium sulfate-starch were first studied. N. B. S. sieves were used in grading the particle sizes with the exception of starch, used as received, the particle size of which was microscopically determined to range between 5 and 35 microns. Forty-mesh particles refer to all material passing through No. 40 sieve and retained on No. 60. Two-hundred mesh

Forty-mesh starch was prepared from oven dried starch paste. The density of packaged starch was determined to be 1.5 Gm. per cc. at 25° C.

The component substances were mixed together by the principle of tumbling by rotation on a diagonal axis of a cylinder. The components to be mixed were placed in a wide-mouth, cylindrical bottle, 7 inches long by 3 1/2 inches in diameter, made of clear glass. The bottle was tied in the holders of a horizontal ball mill one quart size, at such an angle that the axis of rotation was approximately on a diagonal of the cylinder. An arrangement was made to tap the bottle at the shoulder at each revolution of the bottle. The bottle was rotated for a period of 12 to 15 hours at a rate of about 40 r. p. m.

After the mixing period, six samples were taken from the top of the mixture without removing the bottle from the ball mill. Sample number 1 in the table of results was taken next to the mouth of the container while number 6 was taken at the rear; samples numbered 2, 3, 4 and 5 were taken in consecutive points between numbers 1 and 6. Approximately 2-Gm. samples were taken, which represented about one-three-hundredth of the total

Table I.—Per Cent of Inorganic Salt in the Mixture

Sample Number	Decld.	No. 1 No. 200 BaSO ₄ 5-35 μ Starch		Decld.	No. 2 No. 40 BaSO ₄ 5-35 μ Starch		Decld.	No. 3 No. 200 BaSO ₄ No. 40 μ Starch	
		Found	Effy.		Found	Effy.		Found	Effy.
1	19.85	19.72	99.35	20.00	19.88	99.40	20.17	16.72	82.90
2	19.85	19.73	99.45	20.00	20.07	100.35	20.17	16.81	83.34
3	19.85	19.69	99.19	20.00	19.99	99.95	20.17	16.62	82.40
4	19.85	19.44	97.93	20.00	19.96	99.80	20.17	16.90	83.79
5	19.85	19.68	99.14	20.00	19.98	99.90	20.17	16.81	83.34
6	19.85	20.20	101.76	20.00	19.98	99.90	20.17	16.80	83.29
Average			99.47			99.88			83.17
Range of efficiency			3.83			0.95			1.39

Sample Number	Decld.	No. 4 No. 200 Mg ₂ P ₂ O ₇ 5-35 μ Starch		Decld.	No. 5 No. 40 Mg ₂ P ₂ O ₇ 5-35 μ Starch		Decld.	No. 6 No. 200 Mg ₂ P ₂ O ₇ No. 40 μ Starch	
		Found	Effy.		Found	Effy.		Found	Effy.
1	21.39	22.18	103.69	20.31	20.99	103.35	16.03	15.77	98.38
2	21.39	22.15	103.55	20.31	20.68	101.82	16.03	15.08	94.07
3	21.39	22.15	103.55	20.31	20.41	100.49	16.03	14.91	93.01
4	21.39	22.04	103.04	20.31	18.28	90.00	16.03	14.46	90.21
5	21.39	21.83	102.06	20.31	20.72	102.02	16.03	14.51	90.52
6	21.39	21.84	102.11	20.31	20.73	102.06	16.03	14.87	92.76
Average			103.00			99.95			93.16
Range of efficiency			1.63			13.35			8.17

particles refer to those which passed through No. 200 sieve.

Forty-mesh barium sulfate was prepared by completely moistening the finely powdered material with water, drying, igniting and grinding the hard mass to the desired particle size. Its density was determined to be 4.2 Gm. per cc. at 25° C. Two hundred-mesh barium sulfate was sieved from the fine powder before moistening.

Magnesium pyrophosphate was prepared by ignition of ammonium magnesium pyrophosphate, precipitated from magnesium sulfate solution with ammoniacal sodium phosphate solution. The hardened mass was ground to the desired particle size. Forty-mesh magnesium pyrophosphate was found to have a density of 2.3 Gm. per cc. at 25°.

mixture. Inorganic salts in the samples were determined by ignition of the starch. Results of the binary mixtures were as follows:

A ternary powder mixture was prepared using the method described above for mixing the ingredients. The mixture contained the following component substances:

	Weight, Gm.	Per Cent
Corn starch (5-35)	125.13	80.31
Barium sulfate (40-mesh)	24.68	15.84
Reagent sodium carbonate (40-mesh)	6.00	3.85
Total	155.81	100.00

The carbonate was screened from the reagent bottle as received which was almost all 40-mesh.

It was heated to 270° C. for one hour before entering with the other ingredients. The method of mixing and sampling the mixed components were the same as described for the binary mixture.

The assay process was as follows: The weighed sample was placed in a 250-cc. beaker with about 50 cc. of distilled water and stirred to dissolve the carbonate. Insoluble substance was filtered through a Gooch crucible previously ignited and tared, the beaker and residue being washed with several portions of distilled water to complete the transfer. The filtrate was titrated with twentieth-normal sulfuric acid using methyl orange T.S. as indicator; each cc. of the acid was equivalent to 0.0265 Gm. of Na₂CO₃. The residue in the Gooch was ignited and weighed after one hour at 970° C.; the weight of the ignited residue was taken as barium sulfate. Starch was determined by the difference between the total weight of the sample and the sum of the carbonate and sulfate. Each filtrate after titration gave a negative test for starch with iodine T.S. Results of the assays of the ternary mixture were as follows:

particles and in some places were trapped in the air spaces. Had the amount of inorganic salt been such that it would have filled all the air spaces between the starch particles the mixture might have analyzed closer to theoretical, for there could be no settling of small particles down through the mixture. On the other hand, the packaged starch, being of smaller particle size, fills the air space between particles of 200-mesh or 40-mesh size. The number of small starch particles being greatly in excess of the amount necessary to fill in the spaces between the larger particles, the latter were separated from contact with each other.

Mixture No. 3 was a distinct exception to all the other mixtures. There was a decided tendency by the barium sulfate to adhere to the front and rear of the mixing container during rotation; the particles continued to adhere despite the fact that 0.5% of packaged starch was added to prevent it. This accounts for the deviation of 17 per cent from theoretical in mixture No. 3.

Sample 4 of mixture No. 5 requires some consideration since it is about 10 per cent below theoretical.

Table II.—Results of Assay of Ternary Mixture

Sample No.	Na ₂ CO ₃ , 3.85% Found	Effcy.	BaSO ₄ , 15.84% Found	Effcy.	Total Inorg., 19.69% Found	Effcy.	Starch, 81.31% Found	Effcy.
1	3.71	96.36	15.26	96.34	18.97	96.35	81.03	100.90
2	3.78	98.44	15.71	99.18	19.49	98.98	80.01	99.63
3	3.63	94.29	15.04	94.95	18.67	94.82	81.33	101.27
4	3.84	99.74	15.96	100.76	19.80	100.56	80.20	99.00
5	3.81	98.96	15.77	99.56	19.58	99.44	80.42	100.14
6	3.86	100.26	15.80	99.75	19.66	99.85	80.34	100.04
Average		98.00		98.42		98.33		100.13
Range of efficiency		5.97		5.81		5.74		1.64

DISCUSSION OF RESULTS

Mixture No. 2 was found to be closest to theoretical as well as the most uniform of the six binary mixtures, while No. 5 was less uniform and not so close to theoretical. This might be attributed to the difference in physical characteristics of barium sulfate and magnesium pyrophosphate. Magnesium pyrophosphate gave results of efficiency which were higher than with barium sulfate in mixtures with the same particle size of component substances. This fact further substantiates the possibility that the uniformity of a solid-solid mixture depends upon the characteristic surface and density of the component substances.

Forty-mesh barium sulfate mixed uniformly with packaged starch, mixture No. 2, while 200-mesh magnesium pyrophosphate was required to obtain a uniform mixture with starch, mixture No. 4. Forty-mesh starch did not mix well with either of the inorganic salts probably by reason that, being present in the largest amount, it has a considerable volume of air space between particles for the component substance of lesser particle sizes and present in smaller amounts to settle between. All of the samples for analysis were taken from the top of the mixture. It is conceivable that the small particles of inorganic salt were sticking to the larger starch

particles and in some places were trapped in the air spaces. Had the amount of inorganic salt been such that it would have filled all the air spaces between the starch particles the mixture might have analyzed closer to theoretical, for there could be no settling of small particles down through the mixture. On the other hand, the packaged starch, being of smaller particle size, fills the air space between particles of 200-mesh or 40-mesh size. The number of small starch particles being greatly in excess of the amount necessary to fill in the spaces between the larger particles, the latter were separated from contact with each other.

Results on the ternary mixture, Table II, indicate about 6 per cent range of efficiency in the series of analyses taken at various positions after mixing. A more uniform mixture was expected on the basis of binary mixture No. 2 in Table I and, assuming that the physical characteristics of sodium carbonate simulated those of barium sulfate. The results do stress the importance of physical characteristics of component substance in obtaining the homogeneity of powder mixtures. It is worthy of noting that the minimum of inorganic salts was found between samples 3 and 5 with a maximum in starch content at that point; this is a problem of mixing methods which has not been investigated.

From the results in Tables I and II there is no indication that density of the component substances had any influence upon the homogeneity of the mixtures.

THEORETICAL DISCUSSION

Particle Size, Shape and Density.—Heywood (2) attempts to numerically define particle size and shape, confining the definition to irregular particles, based on a projected image. He was dealing with materials of pebble size so that the projected image was microscopic. However, with small particles the projected image can be obtained with the microscope.

There is evidence (4) that particulate materials obey a normal law of distribution of particle sizes and shapes. Not only does a homogeneous powder mixture (3) conform to a normal distribution law, but its physical state is characterized by surface area per unit volume and particles per unit weight, a quality known as fineness. Roller (4) has shown that size distribution may be determined from the relation between weight per cent and particle size.

Bulkiness is a common expression in referring to a powdered material. It is measured by the amount of air space (voids) contained in a given weight of the material when in packing. Various methods have been given for measuring void content (5, 6), the simplest being to fill a graduated cylinder with a given weight of material and tap it on the bottom until no change in volume is noted.

Void content of a powder mixture is very important in determining the extent of uniform distribution in a mixture of varying particle sizes. There are three essentials necessary in predicting the expected accuracy of dosage and extent of uniformity of a particulate material neglecting surface characteristics (1) the void content, (2) particle size (3) proportion by weight of the active ingredient. Roller (7) has given a simple method for calculating void content in relation to density and specific volume. Circumstance decidedly alters the conditions. In the case of a tablet mixture containing a large amount of excipient material and a small amount of active ingredient the total volume of voids between particles of the excipient should not exceed the volume of the active ingredient, assuming that the ideal condition for homogeneity is that particles of active ingredient are just small enough to fit into the free space surrounded by larger particles of excipient. Therefore, the amount of excipient and the most desirable particle size for the active ingredient that can be used are limited entirely by the particle sizes of the excipient or vice versa. In the case where large amounts of active ingredients contain little excipient, homogeneity would depend entirely upon the extent of uniformity in size of particles of the active ingredient and the amount of excipient that could be used without destroying uniformity would be determined by the void content as in the case above. In the case in between the cases mentioned, *i. e.*, there is about as much ingredient as excipient, the principle of mixing becomes one in which the component substances are put in such a condition that each particle of the active ingredient lies adjacent to a particle of the excipient.

G. F. Smith (8) has shown that, when materials of different density are mixed together followed by grinding to pass a 200-mesh sieve, there is no indication of segregation due to vibrational disturbances. Density is very closely allied to particle size in determining the amounts of excipients necessary for obtaining ideal conditions of mixing the active ingredients. It would seem, therefore, that when component substances are properly mixed there could be no direct variation in accuracy of a tablet mixture due to density of the ingredients.

SUMMARY

From the experimental investigation of powder mixtures carried out in the A. Ph. A. Laboratory up to the writing of this report the following have been deduced concerning a tablet mixture before granulating:

1. Physical characteristics of component substances affect the homogeneity of powder mixing.

2. Agglomeration in powder mixtures is intensified as the particle size is reduced. Materials which tend to pack to very small volumes when in very fine powder form show a definite tendency toward agglomeration when mixed with other materials of larger particle size.

3. Particle size and weight per cent is of great importance in determining the amount of excipient to be used.

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Sir Ernest Rutherford (1871-1937) was was the recipient of the Nobel Prize for Chemistry in 1908 for his investigations of the decay of elements and the chemistry of radio-active substances.