

**THE ROLE OF PARTICLE SIZE AND SHAPE IN THE
PREPARATION OF TABLETS**

by

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I. HISTORY

Tablets have been defined in a number of ways. Perhaps one of the better definitions, formulated by the Combined Contact Committee of the American Pharmaceutical Manufacturers' Association and the American Drug Manufacturers' Association, is the following: "Tablets are unit forms of medicinal substances prepared by compression or molding. They are most frequently of round or discoid form, but may be of a great variety of shapes. Compressed tablets may be plain or coated in various ways for protection of ingredients, masking of tastes, or for special therapeutic uses. Molded tablets are usually easily friable and quickly soluble or disintegrable. In all cases, medicinal tablets should exert their effect within a satisfactory period of time under normal conditions of use."*

In 1914, Kebler estimated that from one-fourth to one-third of all the medicinals in the United States were administered in the form of tablets (1). Tablets are probably employed in even a greater ratio today. It is also true that nearly every industry makes some use of a tablet machine (2). The main impetus for such an enormous development of the tablet industry has been the versatility of use of the tablet as a convenient form for the dispensing of medicines, for the preparation of chemical test solutions, for sterilizing agents, for food, for fuel, and in the munition and explosive industry (3). But chiefly and foremost the tablet is a convenient mode for the administration of therapeutic agents. When coated, the tablet renders nauseating or bitter medicinals tasteless, it prevents decomposition of active ingredients susceptible to the effects of light or moisture, or permits the combination of incompatible ingredients. The advantages of this type of pharmaceutical preparation are: accuracy of dosage, economy, concentration, stability, portability,

* Osol and Farrar, U.S.D., 24th Ed., p. 1177 (1947)

absence of alcohol, elegance, and convenience in dispensing and shipping (h).

Although tablets are considered a comparatively modern type of pharmaceutical preparation, dry remedies in the form of small discs, cylinders, or tablets have been known since time immemorial. Possibly the earliest reference to this type of remedy is contained in the Papyrus Ebers, written about the fifteenth century B.C. (5). Tablets were also a very popular form of medication during the Greco-Roman epoch of medicine and pharmacy. The Hippocratean Corpus (whose authorship is attributed to Hippocrates) includes a process for the preparation of such remedies (6). In the early literature they were described as "trochisci" from the Greek word trochos, meaning "round or circular"; or "pastils," from the Latin word pastillus, meaning "a little loaf of food." These two terms were used interchangeably. In the first century A.D., a Roman, Celsus, referring to important characteristics of pastils, stated that they were made from certain metallic substances rather than from vegetable materials. He gives the following description for the preparation of this group of remedies: "Dry medicaments which have been rubbed together are mixed by the aid of a liquid free from fat, such as wine or vinegar, and the mixture is dried again." (7) Celsus mentioned seven different formulas for troches, five of which were for external use. These troches could also be liquefied by the same liquid used in their preparation and administered as fluid remedies. Actually, the original process of tablet making, which consisted of cutting the plastic mass into the desired forms, is still employed at the present time for the preparation of throat remedies, namely, lozenges. Present practices,

however, replace the wine or vinegar by mullages, pastes, syrups, or alcohol, or may subject dry powders to direct compression.

It was during the time of Dioscorides (first century) and Galen (A.D. 131-201) that the troches prepared from various earth or clays became popular as remedial agents (8). These types of earth were natural forms of clays, exhibiting properties similar to kaolin and other clays still recognized in the pharmacopeias of today. The most famous of these clays was Terra Sigillata, obtained from the island of Lemnos. Terra Sigillata means "the earth whose authenticity was established by a seal," for these troches bore the imprint of the figure of Artemis or of her symbol, a stag. This imprint was a form of an early proprietary which may be regarded as one of the predecessors of our modern trade marks. The earth for the troches was carefully washed, dried and then molded into small blocks, each of which was imprinted with the seal of its origin. Another clay, Terra Mellitea, was obtained from Malta and bore the effigy of St. Paul, as St. Paul had landed upon Malta and blessed its soil; Terra Portugallica was stamped with the figure of a rose; Terra Germanica or Terra Strigensis, which was obtained from Hungary, bore a design of mountain peaks and crossed keys. Dioscorides, in his "De materia medica," mentions other earths as those of Samos, Chios, Eretria, etc. (9).

Famous troches containing viper's flesh were originated by Andromachus, physician to the Emperor Nero (first century A.D.). These troches were used for the preparation of theriaca, a kind of universal antidote against serpents' and animals' bites. The formula for viper's troches was followed for more than a thousand years and was reprinted in most of the

pharmacopeias of the Western world until the late eighteenth century (10). Another group of troches, also representative of empirical medicinal practice, employed astringent metallic compounds as eye remedies. Such "collyria" were prepared by liquefaction of troches containing usually alum, burnt lead, antimony trisulfide, zinc oxide, copper oxide, and similar metallic compounds in various combinations. Since eye diseases are very widespread in the Orient, Arabs paid much attention to this group of medicaments. They called such troches "siefs." The use of the clays by the ancients and by the medieval peoples was not founded entirely on superstition, but is a revelation of their empirical medicine. The results of recent scientific research have justified the use of clays as limited bactericides, because of their reported agglutinating effect on bacteria, which are attracted and absorbed into the clay itself. At the end of the seventeenth century there was a great variety of white, red, and yellow sealed earths on the market showing different impressions such as images of saints, ships, coats of arms, etc., but one hundred and fifty years later, they had fallen into disuse. C. J. Thompson notes that "probably the last appearance of Terra Sigilata" in any important work on pharmacy was in Grey's "supplement to the (London) Pharmacopeia," 1848 (11).

The term "tablet" probably was first used by Jean de Benou in 1615 in his Dispensatorium Medicum in which the Latin term "tabella" was applied to a special type of troche. In 1698 Nicholas Lemery in his Pharmacopée Univeselle differentiated between pastils, troches proper, and tablets. He reserved the term "pastils" for troches containing aromatics and intended for fumigating purposes. The term "troches" remained in use

for solid preparations containing very little or no sugar, and the modern term "tablets" was limited to troches containing sugar. Lemery's Pharmacopée Universelle lists sixty-three formulas for tablets.

However, it was not until the tablet machine was invented that the preparation of tablets by compression became possible. On December 6, 1813, William Brockedon was granted English patent No. 9977 under the title: "Shaping Pills, Lozenges and Black Lead by Pressure in Dies." (12) Thus was officially recognized the first tablet machine in which tablets were compressed in a hand die using a mallet (13,14). In pharmaceutical practice Brockedon's patent was first applied to "Condensing the carbonates of soda and potassa into the form of pills and lozenges." (15) At a later date the right and title to manufacture compressed tablets was purchased by Francis Newberry and Sons and finally it was acquired by Hurrells Wellcome and Co., in whose current price list the original "Brockedon Products" are still catalogued (16).

The mass production of tablets did not, however, immediately follow the invention. The technical skill and spirit of the twentieth century were required to perfect this comparatively simple device which has encouraged the development of tablets until they have become in our day a very commonly used form for the administration of medicines.

In the United States the initial manufacture of "compressed pills" is attributed to a Philadelphian, Jacob Dunton. He also constructed a tablet machine of his own invention in 1864; besides, he was the first to secure a patent for the preparation of materials to be used in the manufacture of compressed tablets. This patent "consisted of first drying the materials to be compressed in order to expel the natural moisture, thus increasing

the cohesion; and second, in lubricating the die or mold."(17) The first automatic "compressed pill" machine in the United States was invented by J. A. McFerran of Philadelphia in 1874, in the shop of R. Shoemaker, Jr., who was succeeded by the P. J. Stokes Machine Co. in 1895. In 1875 Joseph P. Remington, also of Philadelphia, devised an apparatus for the use of retail druggists to manufacture their own compressed tablets as called for on prescription. Thus Philadelphia became an early center of the tablet industry.

At about the same time triturate tablets or tablet triturates (T.T.) were prepared by molding fine powder which has been previously moistened. They are an American idea, having been introduced in 1878 by Dr. Robert Fuller (18). At present tablet triturates are also called molded tablets, dispensing tablets, or hypodermic tablets. Tablet triturates are usually made on a triturate machine or in a mold which gives them the shape of cut sections of a cylinder. Tablet triturates can be made by compression on a tablet machine, but the term "tablet triturate" is still used and may refer to an uncoated flat tablet, regardless of whether it is molded or compressed.

A further change in the tablet industry was introduced with the discovery of the disintegrating power of starch added "in proper quantities" to the insoluble matter to be compressed. Although the discoverer, an American, Charles Kilgore, was not granted a process patent, he made no attempt to keep his finding secret. "The discovery," says Kohler, "was a great triumph for the industry."(19) The subsequent growth of the industry was phenomenal.

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In 1885 the British Pharmacopeia listed a representative of this new medicinal mode of administration: "Tabellae Nitroglycerini or Tablets of Nitroglycerin." This tablet remained the only one official in the British Pharmacopeias of 1914 and 1932. The first edition of the British Pharmaceutical Codex of 1907 was more progressive and listed no less than fifty-four different tablets. The latest edition of the British Pharmacopeia of 1948 lists forty-nine tablets and the British Pharmaceutical Codex of 1949 lists eighty tablets.

Similarly in the United States tablets were not immediately included in the official compendia. It was only in the United States Pharmacopeia IX of 1916 that "Toxitabellae Hydrargyri Chloridi" appeared for the first time and no other tablet preparation was added to the United States Pharmacopeia X of 1926. However, the National Formulary V of 1926 introduced six different tablets. The United States Pharmacopeia XI of 1936 listed two more tablets: Glyceryl Trinitrate Tablets and Erythrityl Tetranitrate Tablets, while the National Formulary VI of 1936 included fifty-eight different tablets. The latest United States Pharmacopeia XIV of 1950 lists ninety-two tablets and the National Formulary IX of 1950 includes another forty-six tablet formulas.

II. INTRODUCTION

The importance of particle size of the substances used in the preparation of compressed products was realized very early in the manufacture of tablets. There is, however, practically no literature concerning this subject. On the other hand, there are accounts of numerous investigations referring to the importance of particle size in other sciences such as chemistry, physical chemistry and crystallography, and in industries such as the manufacture of cosmetics, dyes, cements and explosives. Recently, reports on clinical investigations conducted with powdered medicinal substances have emphasized the importance of materials in the subsieve range (finer than those corresponding to 325 mesh sieve), and of micronized products. At present some manufacturing houses advertise the virtues of sulfonamides and penicillin in micronized form. However, there is no report on compressed tablets prepared from microcrystalline drugs, concerning either their ease of compressibility or their therapeutic advantages. Very finely ground acetylsalicylic acid is claimed by the Bayer Company, Inc., in one of its more popular advertisements, to be the main factor for nearly instantaneous disintegration of "Bayer's Aspirin" tablets. Perhaps some of the dearth of literature on particle size is a result of the reluctance on the part of manufacturers to publish their trade secrets (1). Any attempt to secure technical information concerning particle size and shape studies must be made in fields other than pharmacy.

Many investigators think of the shape of a particle in terms of the crystal system to which it belongs. However, the general shape or physical outline of the particle does not always correspond to the particular crystal

system, especially in the case where material has been subjected to mechanical means of comminution. Many substances show by their physical properties no regularity of crystalline structure whatsoever. Such substances never exhibit characteristic polyhedral forms, and therefore are considered amorphous (2). The appearance of different characteristics in the same kind of crystals may vary considerably with conditions of crystallization such as temperature, concentration of solution etc., but the angles between corresponding faces (plane surfaces) remain constant. Accordingly the relative orientations of the crystal faces are characteristic properties while the external forms as such are not. Some substances exhibit the ability to crystallize in polymorphous forms. For instance, sulfathiazole when crystallized from water, acetone, or methyl or ethyl alcohol forms hexagonal prisms and plates; when crystallized from n-propyl alcohol prismatic rods are formed (3). Similarly phenobarbital can exist in the three crystal phases (4). According to Lehmann, sodium chloride may be obtained in octahedrons, instead of the usual cubes, when crystallized from a solution containing sodium hydroxide or urea; potassium and ammonium alum, which usually crystallize in octahedrons, can be produced in form of cubes from a solution containing potassium hydroxide or sodium borate (5). Although crystal faces may be accidentally or intentionally destroyed, yet the substance does not thereby cease to be a crystal (6). The potential ability of all crystals to develop faces under proper conditions of growth is, however, a characteristic and important property which played a decisive role in the establishment of the identification system for various compounds. The particular crystal structure that will be taken by a given element or compound depends partly on the type of:

1. Binding force (charge of the nucleus)
2. Atomic grouping
3. Relative size of different ions or atoms etc. (7)

There are six different fundamental systems of crystals: the regular or cubic system, e.g., alums, methenamine, alkali halides; hexagonal, e.g., iodoform, calcium carbonate, sodium nitrate; tetragonal, e.g., urea, potassium dihydrogen phosphate; orthorhombic, e.g., iodine, sulfur, barium sulfate; monoclinic, e.g., tartaric acid, most of the sugars, hydrated ferrous sulfate; and triclinic system, e.g., boric acid, potassium dichromate, hydrated copper sulfate. The units of crystal lattice are not necessarily atoms or monoatomic ions. They may be molecules, e.g., carbon dioxide. The forces holding these molecular crystals together are very weak. Many of the low melting organic compounds are of this molecular type. In the ionic lattice, e.g., sodium chloride, there is no union to form molecules in the crystal. There are two fundamentally different types of attractive forces which hold atoms together:

1. Ionic or electrostatic attraction giving rise to heteropolar bonds
2. Electron pair bonding or exchange energy giving rise to homopolar bonds

Different crystals have different so-called magnetic susceptibility and magnetic effect is considerably greater for ionic bonds with their transferred electrons than for covalent bonds. Most of the simple crystalline salts have ionic binding. Although the heteropolar and homopolar bonds account for many crystals and for the formation of chemical compounds from atoms, the presence of additional electrostatic attraction explains the attraction which exists between molecules. Thus many of the properties of crystals can be predicted from classification of the crystal lattice, type of binding and ionic size.

The nature of atoms and forces existing within the molecule pre-determines chemical and physical properties of the substance; among them the compressibility of the particular material. The experiments performed by Richards et al. indicate that the compressibility is closely related to the cohesive pressure of the substance, as shown by their boiling points, and is therefore periodic in the system of elements. Thus the compressibility seems to be not merely an isolated physical fact but rather a phenomenon of chemical significance immediately connected with the most important properties of the material. Evidently, compressibility is a property as definitely periodic as any other property of the elements. Further work by the same investigator indicates that the compressibility is large when the surface tension is small and vice versa. In every case it can be observed that the volatility, which may be ascribed to the lack of cohesive tendency, seems to be associated with increased compressibility. Besides, not all substances have the same compressibility when subjected to the same increase in pressure, even when they were at first under the same internal pressure. Moreover, the compressibility includes within its magnitude not only the change in volume of the molecule, but also the internal alteration of the molecule as well (8). Specific gravity is greater in compounds with great surface tension and small compressibility than in those with small surface tension and great compressibility. It should be mentioned also that the specific gravity is enormously affected by the nature of the elements which build up the molecule, and variations in composition may wholly conceal the effects due to surface tension (9). The preceding deductions were drawn on the basis of experiments performed upon pure elements. The properties of salts composed of two, three, four, etc. elements would become progressively more complicated.

Richards and Jones, studying the compressibility of chlorides, bromides and iodides of potassium, sodium, thallium and silver, concluded that the compressibility of a salt is smaller than the average compressibility of the two elements concerned. Likewise molecular compressibility is less than the sum of the atomic compressibilities of the elements constituting it. Chlorine is more volatile than bromine, which in turn is more volatile than iodine. The compressibility of those elements is in the order of: chlorine more compressible than bromine and both of these are more compressible than iodine. However, the compressibility of potassium salts is in the opposite order as potassium iodide is more compressible than potassium chloride. This phenomenon is attributed to the chemical and cohesive affinity of the elements, as chlorine has greater affinity and hence is under greater internal pressure than potassium iodide (10). The following table illustrates the compressibilities of these salts, expressed in kgs/cm².

Compressibilities x 10⁶ At 20°C.

	<u>Chloride</u>	<u>Bromide</u>	<u>Iodide</u>
Potassium	4.93	6.11	8.4
Sodium	4.03	4.98	6.8
Thallium	4.6	5.0	6.57
Silver	2.18	2.54	3.85

These values are based on 0.00000371 for the average compressibility of mercury between 100 and 500 kilograms per square centimeter. The numbers in the table must be multiplied by 10⁻⁶ to obtain the true value.

However, little has been published concerning the compressibility of materials used in the preparation of tablets. Pressure employed for compression of tablets is usually expressed in kgs/cm² or tons/sq. in. and may be as high as 10,000 kgs/cm² or 62.0 tons/sq. in. (11) The

magnitude of pressure employed for the compression depends on the type and the purpose for which the tablets are intended. In each case preliminary tests have to be performed before the "master formula" for the particular tablets is decided upon as well as the modus operandi. A general idea concerning the compressibility of the substance is reported by Mitchell. He believes that most materials have a 2:1 compressibility ratio; for such material a depth of one-half inch of material in the die would produce a finished tablet one-fourth inch in thickness (12).

A few words should be said about the method used for the production of microcrystalline materials, as lately such a form of medicinals is finding recognition in chemotherapy. There are chemical and mechanical means of producing these types of materials. A chemical method for preparing, for instance, microcrystalline sulfonamides, consists in neutralizing, at low temperature, a solution of the sodium salt of the drug, with the reacting mixture maintained in violent agitation by sonic vibration or by some suitable high speed mixing device. The size of the resulting crystals may be regulated within wide limits by controlling the speed of the admixture, the temperature of the reactants, or both. The microcrystals produced are fairly uniform in size. Water may be removed by filtration or centrifugation and the precipitate dried to a fine powder (13). Physical methods for producing microcrystalline powders utilize mechanical mills and fluid energy mills with intense centrifugal fields to effect classification in the fine size range (14). The Mikro-Atomizer (Pulverizing Machinery Company) and Raymond Vertical Mill (Combustion Engineering Company) are machines of the high speed rotor design; the Micronizer (International Pulverizing Corporation), the

Reductionizer (Reduction Engineering Corporation), and the Eagle Mill (Eagle Pencil Company) are of the fluid energy type using compressed gases or high pressure steam to effect the size reduction.

Much work has been done in the field of therapeutics concerning the particle size of medicinal substances. In general, the solubility and speed of action of a relatively insoluble material depends on surface area, which is a function of particle size and shape. The use of fine powders in compounding procedures results also in the more satisfactory pharmaceutical preparations. To increase the amount of surface area and to hasten solubility, some products were prepared and tested in micronized form. A number of investigators report "microcrystalline sulfonamides show differences from ordinary sulfonamides in both pharmacodynamic behavior and therapeutic activity" (15,16,17,18,19,20). In general, such differences suggest that in microcrystalline form the activity of a powder is enhanced. It is obvious that the saturation level of a drug in blood or tissue fluids will be the same regardless of the original crystal size, but the rate of attaining that level in the case of substances of low solubility is affected by the total surface area available. Microcrystalline preparations of sulfonamides give considerably higher blood levels, especially during the first six hours after administration, than the preparations of the macrocrystalline drug. This increased rate of activity is true equally in cases of aqueous suspensions injected hypodermically or of powders applied locally. In both cases it has been reported that the decreased tendency of the microcrystalline drug to lump or cake assures a much greater surface for solution into local tissue fluids. Microcrystalline drugs dispersed in hydrophilic and white ointment bases show likewise an

increased rate of absorption (21). The addition of a wetting agent such as sodium lauryl sulfate seems to produce even greater dispersing effect in suspensions of microcrystalline sulfadiazine (22) and an increased liberation of drug from ointment bases. In conclusion, one might add that the particles of the regular powder grades of the sulfonamides range widely in diameter, with a large proportion between twenty and twenty-five microns, and that it is not possible to reduce the particle size of macrocrystalline sulfonamides in suspension by passing them through a colloid mill (23). On the other hand, a large number of particles of microcrystalline sulfadiazine measure usually $1 \times 1 \times 3$ microns and are approximately $1/350$ of the mass of ordinary sulfadiazine crystals (24).

Similarly the efficiency of penicillin in oil and wax is influenced by the size and relative weight of the penicillin particles (25). However, in this case delayed rather than more rapid absorption was sought by the investigators. From the clinical experiments it was concluded that, with the solid preparations in oil and wax, the size and relative weight of penicillin particles were of little or no importance as far as the prolongation of the blood levels was concerned. With liquid preparations, however, it could be seen that the size and relative weight of the particles influenced the absorption from the intramuscular site of injection, and consequently the duration of the penicillin level in the blood. Apparently the larger particle is absorbed more slowly and the level in the blood thus prolonged. The standards for liquid depot type of preparations limit the subdivision of penicillin particles to fifty microns or larger in size. On the other hand, the presence of two per cent aluminum monostearate in preparation of small particles of procaine penicillin G in oil appears to prolong the penicillin action (26).

Particle size of the active material is of importance in estrogen therapy (27). It has been shown in experiments with estrone on rats that if most of the crystals in aqueous suspension are small (ten microns or less) the average duration (ten days) of estrogenic stimulation is less than half (twenty-four days) that produced when the same dose of a suspension contains large crystals (fifty per cent or more are fifty to hundred fifty microns). The lasting action of estrone in an aqueous suspension containing only small crystals is slightly greater in tests on rats than an oil solution of estrone.

As the fineness and uniform distribution of particles of the medicinals influence the quality of some liquid and solid pharmaceutical products, similarly the size and uniformity of powders plays an important role in the preparation of satisfactory tablets. Powder of uniform size is essential in order to assure even distribution of ingredients in case more than one substance enters into the composition of a tablet and in order to assure uniform weight of a tablet. Fineness and shape of the powder employed influence directly the disintegration time of a tablet. In many cases ground crystals are subjected to direct compression. Since all crystals (of different salts) fracture differently it is unavoidable that one powder will contain more fine particles than will another and that such combinations will not feed evenly into the die (28). Mottled tablets are produced by fine particles falling onto the surface of the lower punch while the coarser particles remain on the top, resulting in the lower side of the tablet being smoother. Consequently, the reduction of all ingredients to similar sizes and the use of good mixers is essential, particularly in the preparation of colored tablets.

Even distribution of the material is influenced by the density of the particles of the component ingredients. It has been reported that coarsely ground mixtures of two or more solid materials differing in density will separate upon the jarring which results from handling, transportation, or storage under conditions subject to vibration (29). The magnitude of vibration is considered as inversely proportional to the degree of subdivision and directly proportional to the differences in density of the mixed materials. From the experiments performed it was concluded that, when materials of different density are mixed to uniformity and then ground and passed through a 200-mesh sieve, they cannot be segregated by jarring or by influence of vibrational storage conditions regardless of the actual difference in density. Card, experimenting with mechanical blending of materials, states that it is difficult to obtain an intimate mixture if the powders have widely differing apparent specific gravity. The aim should be to have the several powders as nearly the same density as possible (30). On the other hand, Beeler et al., experimenting with tablet mixtures before granulating, believes that there is no indication that the density of the component substances has any significant influence upon the homogeneity of the mixed materials (31).

Much work has been done on the granulating processes employed in tablet manufacture since, in many cases, fine powders cannot be subjected to direct compression because they occlude air, compress unevenly and do not feed uniformly into the die. Granulation accomplishes three purposes: it assures uniform feeding of the material into the die; it provides accurate dosage (because a die will contain only a certain volume of granules and consequently a certain weight of material); it also provides uniform hardness because of the effect of a uniform pressure on a given

volume of material. The preferable size of dry granules is usually specified as that of 8-20 mesh (32), 12-20 mesh (33,34), or 20-40 mesh (35). The size of granules is determined by the size of tablets into which the particular granulation is to be compressed. Clarkson makes the following suggestions (36):

For	1/8"	to	3/16"	diameter tablets	-	#20	mesh	granulation
	7/32"	to	5/16"	"	"	#16	"	"
	11/32"	to	7/16"	"	"	#14	"	"
	for over		7/16"	"	"	#12	"	"

Brown from his experimental work has concluded that the size of the granule affects greatly the solubility of a tablet, but that the size and shape of the tablet has no influence on the length of time it remains in the stomach (37).

Uniformity in the size of the granule is also essential. It is believed that not more than fifteen per cent of the granules should pass through the second smaller sieve; otherwise the amount of medicament in the tablets will not be constant (38). Uniformity of granules also helps to prevent the occurrence of common difficulties during the process of compression. The presence or excess of "fines" is often a cause of "capping." Individual particles may be only a few microns in size and hence if the granulation contains too many "fines", they will sift down between the punch and die and cause sticking (39). Wolfe, examining the shape of granules prepared from different materials, stated that there is no correlation between the general structure of a granule (whether round, elongated, rectangular, or cubical) and its compressibility. He goes on to state that sucrose and sodium chloride both produce cubical granules yet sucrose is not compressible. At the same time granules with no definite shape are as compressible as those having a rectangular or

cubical structure. According to Wolfe, granules having smooth edges appear to be non-compressible (40).

Simultaneously with the production of powders in the fine size range and the recognition of the importance of their particle size in all different industries, new methods had to be developed for determining particle size distribution, especially in the subsieve range. The finest sieve available is that of only 325 mesh corresponding to particles of 44 microns. The limited scope of this discussion does not allow the detailed description of all the methods that have been devised or are in use for measuring particle size in the subsieve range. Following is a list of those methods as classified by Schweyer and Work (41):

- I. Sieve Analysis
- II. Microscopic Analysis
 - A. Conventional Microscopic Methods
 - B. Ultramicroscopic Methods
- III. Sedimentation Analysis
 - A. Increment Methods
 - 1. Pipette
 - 2. Hydrometer
 - 3. Pressure
 - 4. Photographic
 - B. Cumulative Methods
 - 1. Balance
 - 2. Pressure
- IV. Centrifugal Analysis
 - A. Ordinary Centrifuge Methods
 - B. Supercentrifuge Methods
 - C. Ultracentrifuge Methods
- V. Elutriation Analysis
 - A. Air Elutriation
 - B. Liquid Elutriation
- VI. Turbidimetric Analysis
 - A. Cross Methods
 - B. Size Distribution Methods
- VII. Miscellaneous Methods
 - A. Permeability
 - B. Adsorption

Many of these methods of particle evaluation use different criteria: for example, the sieve aperture, the Stoke's Law diameter, surface evaluation

by gas adsorption, etc. There have been many serious attempts of correlation, but the literature does not reveal the relation of values obtained by these methods (42). For instance, it has been shown that size distribution based on the sedimentation methods cannot be compared with microscopic counts unless a correlation factor is applied to one or the other diameter. Also there are several inherent factors in sedimentation technique that tend to give higher particle size values than those obtained, for instance, by the air permeability method. This higher particle size results from the failure to obtain efficient or thorough dispersion of the powder in the settling liquid which thus contains agglomerates. They would settle out faster and thereby give an apparent larger particle size than the material really has. Consequently, particle size values obtained by the sedimentation method are about twice the value obtained by the air permeability method, and the same holds true on the microscopic counts (43). Lately the air permeability method has gained some popularity on account of the remarkable reproducibility of results, especially when using the Fisher Sub-Sieve Sizer (Fisher Scientific Company) (44). Using this apparatus, the average particle size of a powdered material is determined by weighing an amount of it equal to its true density and compressing it in a sample tube between two perforated plugs covered with filter paper. The tube containing the sample is then inserted in an air stream and the air flow at a predetermined pressure through the packed column of material is measured on a flow meter. Since the air flow is dependent upon the specific surface of the powder which in turn is dependent on its particle size, the latter can be read from a calibrated chart after equilibrium in the flow system has been established.

A few words should be said about microscopic analysis since it is one of the simplest methods for certain size ranges, although this method consumes considerable time and is quite laborious. Observation of finely ground particles under the microscope shows the necessity of defining particle size by some arbitrary diametric dimensions, since very few materials are spherical in shape. There are numerous ways by which microscopic dimensions may be reported. Here again the results of different investigators cannot be compared unless the relation among the various diameters is known, and few are. According to Schweyer, the most simple microscopic diameters to determine are those of Ferrott and Kinney (in which the diameter, d_k , is the side of a square having the same area as the projected area of the particle) and of Work (who used a diameter, d_b , which is the intermediate dimension, being the shorter of the two visible dimensions at right angles to each other) (45). However, in most of the cases maximum or average particle size is observed by examination of one or more fields of the sample. Because contrast and visibility decrease rapidly with the decrease of the size of particle, great errors may occur in the estimating of sizes, and in judging the percentages of components in mixture (46). Recently a method was developed for measuring the size of penicillin particles in suspension of mineral oil using a hemacytometer microscope (47). In the subsieve range the electron microscope has opened new possibilities for photographic examination, with the result that the magnification resolutions are now manifold greater than with the conventional microscope.

Just as the size of the particles plays a paramount role in judging the suitability of material for particular industries, so is the shape of the particles of equal importance, especially in the paint and cement

industry (48). There have been many attempts to devise a system of classification of shape of particles, but so far no standard system has been agreed upon. Each investigator seems to use his own classification. Dunn et al., for instance, used the following classification of crystals (49):

1. Lamellar
2. Lamellar - acicular
3. Acicular
4. Lamellar or acicular with spheres
5. Spherical or roundish
6. Columnar or tabular

The classification used by Dalla Valle et al. seems to be easier to follow while trying to reproduce the numerical counts (50):

<u>Type</u>	<u>Form</u>
Regular	Cubical
Angular	Tetrahedron
Acicular	Bar, Cone
Plate-like	Plate, Disc

While there are many published articles on the measurement of the properties where the particles were assumed to be spheres, there are relatively few papers in which the authors have attempted to evaluate shape in absolute terms. Green has proposed considering the shape of the particle in relation to its volume and surface (51,52). Haywood, measuring the surface and volume of relatively large particles, has proposed shape factors based on the projected area of the particle and its thickness but those relations become exceedingly complex in defining surface and volume (53). Schweyer, who has made extensive studies on particle sizes, states that there is no reason to assume that the relation for macroscopic particles applies to microscopic ones. As the sub-division increases, the particles tend to lose the shape of the mass from which they were derived and may or may not become spheroidal (54). As with the measurements of particle size, there does not appear to be any correlation among the methods for evaluating shape of particles.

PERIODIC CLASSIFICATION OF ELEMENTS BASED ON CRYSTALLINE SYSTEMS

Elements of the periodic table were classified according to the pattern of their internal arrangement or so-called crystal system*. Comparison of such classification reveals that there is a definite relationship within practically each group of the periodic table concerning the pattern in which the corresponding elements tend to crystallize. Inert gases, i.e., neon, argon, krypton and xenon, crystallize in the cubic system. Similarly all alkali metals crystallize in the cubic system. Elements of group two of the periodic system show certain variability in that calcium, strontium, barium and radium (?) on crystallization assume cubic arrangement and beryllium, magnesium, zinc, cadmium and mercury crystallize in the hexagonal crystal system. Rhombohedral lattices of crystals of mercury (in the solid state) belong to the general type of the hexagonal system. Considerable variation in crystal structure is found among the elements of group three of the periodic table as it includes representatives of the cubic, hexagonal, tetragonal and monoclinic crystal systems. Group four is fairly uniform, and with the exception of hafnium, which belongs to the hexagonal crystal system, all elements on crystallization assume cubic arrangement of crystals. Elements of group five of the periodic table are somewhat variable in that nitrogen (when in the solid state), phosphorus, vanadium and tantalum belong to cubic crystal system; arsenic, antimony and bismuth to the hexagonal crystal system; and uranium was lately reported as having a rhombic pattern of inner arrangement. Similarly, considerable variations are found among

* According to the Handbook of Chemistry and Physics, by Ch. D. Hodgman, 31-ed., p. 2041, 1949.

the elements of group six-B. Oxygen can be crystallized in three forms: cubic, rhombic, or rhombohedral, depending on the degree of cooling; sulfur crystallizes in the rhombic form. Tellurium belongs to the hexagonal, and polonium to the monoclinic crystal system. Elements of the group six-A crystallize in the cubic crystal system. Halogen elements (when brought to the solid state) in group seven-B of the periodic table crystallize in the rhombic crystal system. Most of the elements in group eight crystallize in the cubic system; exceptions are rhutenium and osmium which crystallize in the hexagonal pattern. It is remarkable that none of the elements of the periodic table so far examined crystallizes in a triclinic crystal system. In spite of some irregularities, the pattern of the internal arrangement of crystals of the elements within practically each group of the periodic system seems, in most cases, to constitute one of the common properties of the elements of the same group.

TABLE I.

CRYSTAL SYSTEMS OF THE ELEMENTS

Period	Order	cub - cubic		tetr - tetragonal		rhom - orthorhombic		rhombr - rhombohedral		mon - monoclinic	
		Group I	Group II	Group III	Group IV	Group V	Group VI	Group VII	Group VIII		
		A	B	A	B	A	B	A	B	A	B
1			H hex								
2	1	He cub	Be hex	B mon	C cub hex	N cub	C cub rhom rhombr	F cub			
3	2	Ne cub	Mg hex	Al cub	Si cub	P cub hex rhombr rhom	S rhom	Cl rhom			
4	3	A cub	Ca cub	Sc cub	Ti cub hex	V cub	Cr cub hex	Mn cub hex	Fe cub hex hex	Co cub hex	Ni cub hex
5	4		Cu cub	Zn hex	Ga rhom tetr	Ge cub	As hex rhombr	Se hex mon			
6	5	Kr cub	Sr cub	Y hex	Zr hex	Nb cub	Sb hex rhombr	Mo cub	Ru hex cub	Rh hex cub	Pd hex cub
7	6	Xe cub	Ba cub	Lr hex	Ce cub hex	Pr cub tetr	La hex cub				
8	7										
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159	158										

EXPERIMENT NO. 1

An attempt was made to ascertain if there is any interdependence between the ease of compressibility and the fundamental pattern of the internal arrangement of different crystalline substances. In this instance the ease of compressibility referred to the absence of sticking of the tablets to the punches and dies. For this purpose the behavior upon direct compression of fifty-six compounds belonging to various crystal systems was tested. Substances for this experiment were selected at random and were compressed into tablets using Coltons' motor driven single punch tablet machine equipped with a 3/8 inch diameter punch*. No lubricant or disintegrator was used. The materials compressed were used in either granular or powder form; when a granular material had a particle size larger than that of the No. 20 mesh sieve, it was ground to correspond approximately to No. 20 powder and then subjected to direct compression. No attempt was made to reduce all the substances to the same particle size as preliminary tests have indicated that there is no evident relationship between the ease of compression (as defined above) and the particle size of the material. In each case where sticking to the punches was encountered upon preliminary compression, the substance was dried for two hours at 40°C. and then subjected again to compression. This precaution was taken to assure that sticking to the punches was not caused by the moisture acquired by the material while stored previous to the compression. In every instance pressure on the upper punch had to be adjusted, as

* Coltons' 2BT motor driven single punch tablet machine having 3/8 inch diameter punches was used for all the experiments.

different substances, regardless of their particle size, require different degrees of pressure in order to be compressed into a smooth firm tablet. The materials compressed were obtained from different chemical manufacturing firms.

The results of this experiment are tabulated; substances belonging to the cubic (isometric) crystal system are grouped separately (Table II). The main criterion for judging the ease and suitability of the substance for direct compression was the absence of sticking to both upper and lower punches of the tablet machine. Upon comparison of the results of this experiment it was concluded that the substances belonging to the cubic crystal system present no difficulty for direct compression. Tablets of this group of substances were satisfactory in appearance; although no lubricant was used these tablets had a glossy surface. Sticking to the upper and lower punch was encountered only with lithium bromide which is very deliquescent in nature. It is remarkable that practically all chlorides, bromides and iodides of sodium, potassium and silver crystallize in the cubic crystal system. An exception constitutes silver iodide which belongs to the hexagonal crystal system.

The results of the direct compression of the substances listed in Table III are quite variable as difficulty of sticking to the punches was encountered regardless of the type of crystal system of the material. Perhaps the number of substances tested is insufficient to draw any definite conclusions; however, the results so far obtained seem to indicate that the substances belonging to the monoclinic crystal system present most of the difficulties encountered during direct compression. Water of crystallization does not seem to play any particular role so far as the

behavior of the substance upon direct compression is concerned. Some substances having no water of crystallization show as much tendency to stick to the punches as those which do contain water of crystallization; ammonium and potassium alum, both crystallizing in the cubic crystal system and having twelve molecules of water of crystallization, present no difficulty upon direct compression. It is remarkable that there are comparatively only few metal-organic and organic compounds which do crystallize in the cubic crystal system. X-ray crystallographic data, as compiled by J. G. Albright*, show that of one thousand thirty-five inorganic compounds listed, 45% belong to the cubic crystal system. Of the metal-organic and organic compounds listed only 6.9% crystallize in the cubic form. Among organic compounds the most commonly encountered form seems to be that of the monoclinic crystal system.

However, the pattern of the internal arrangement of crystals cannot be, in most of the cases, identified with the actual shape of the particles of the material. The actual shape of the particles of the material is determined by the method and by the conditions of the preparation of the material. Since the compounds used in the foregoing experiment were, in most of the cases, subjected to grinding before being compressed, the eventual conformity of the shape of the particles to the particular crystal system was lost. The data obtained in this experiment thus would indicate that it is rather a chemical composition and not the shape of the particles of the substance that determines its behavior upon direct compression.

* Handbook of Chemistry and Physics, by Ch. D. Hodgman, 31-ed., p. 2041, 1949.

TABLE II

COMPARISON OF DIRECT COMPRESSION OF SUBSTANCES BELONGING TO THE
CUBIC (ISOMETRIC) CRYSTAL SYSTEM

+ smooth compression, no sticking encountered.

Name of Substance	Compressibility	Structural Formula	Remarks
Ammonium alum	+	$AlNH_4(SO_4)_2 \cdot 12H_2O$	
Ammonium bromide	+	NH_4Br	
Ammonium chloride	+	NH_4Cl	
Antimony trioxide	+	Sb_2O_3	
Arsenic trioxide	+	As_2O_3	
Barium nitrate	+	$Ba(NO_3)_2$	
Barium sulfide	+	BaS	
Lithium bromide	-	$LiBr$	Very deliquescent. Sticking
Methenamine	+	$C_6H_{12}NH_4$	
Potassium alum	+	$AlK(SO_4)_2 \cdot 12H_2O$	
Potassium bromide	+	KBr	
Potassium chlorate	+	$KClO_3$	
Potassium chloride	+	KCl	
Potassium iodide	+	KI	
Silver bromide *	+	$AgBr$	
Silver chloride *	+	$AgCl$	
Sodium bromate	+	$NaBrO_3$	
Sodium bromide	+	$NaBr$	
Sodium chlorate	+	$NaClO_3$	
Sodium chloride	+	$NaCl$	
Sodium iodide	+	NaI	

* prepared in the laboratory

TABLE III
COMPARISON OF DIRECT COMPRESSION OF SUBSTANCES BELONGING
TO VARIOUS CRYSTAL SYSTEMS

+ smooth compression, no sticking encountered.

Name of substance	Compressibility	Structural Formula	Crystal System*
Acetanilid	+	C_8H_9NO	rhomb
Acetophenetidin	+	$C_{16}H_{13}O_2N$	non
Barium chloride	sticking	$BaCl_2 \cdot 2H_2O$	rhomb
Barium sulfate	sticking	$BaSO_4$	rhomb
Benzole acid	+	$C_7H_6O_2$	non
Benzenaphthol	+	$C_{16}H_{10}O$	non
Boric acid	+	H_3BO_3	tric
Calcium carbonate	+	$CaCO_3$	hex
Copper sulfate	+	$CuSO_4 \cdot 5H_2O$	tric
Dextrose	sticking	$C_6H_{12}O_6 \cdot H_2O$	non
Ferric nitrate	sticking	$Fe(NO_3)_3 \cdot 9H_2O$	non
Ferric oxide	sticking	Fe_2O_3	hex
Ferrous sulfate	sticking	$FeSO_4 \cdot 7H_2O$	non
Lactose	sticking	$C_{12}H_{22}O_{11} \cdot H_2O$	non
Magnesium sulfate	sticking	$MgSO_4 \cdot 7H_2O$	rhomb
Potassium bicarbonate	+	$KHCO_3$	non
Potassium dihydrogen phosphate	sticking	KH_2PO_4	tetr

* Crystal systems: mon - monoclinic hex - hexagonal
rhomb - orthorhombic tetr - tetragonal
tric - triclinic

TABLE III (continued)

Name of substance	Compressibility	Structural Formula	Crystal System*
Potassium permanganate	+	$KMnO_4$	rhomb
Potassium sodium tartrate	sticking	$KNaC_4O_4O_6 \cdot 4H_2O$	rhomb
Silver iodide	+	AgI	hex
Sodium acetate	sticking	$NaC_2H_3O_2 \cdot 3H_2O$	mon
Sodium bicarbonate	+	$NaHCO_3$	mon
Sodium borate	sticking	$Na_2B_4O_7 \cdot 10H_2O$	mon
Sodium carbonate	+	$NaCO_3 \cdot H_2O$	rhomb
Sodium citrate	sticking	$Na_3C_6H_5O_7 \cdot 2H_2O$	mon
Sodium nitrate	+	$NaNO_3$	hex
Sodium sulfate	sticking	$Na_2SO_4 \cdot 10H_2O$	mon
Sodium sulfate	+	Na_2SO_4	mon
Strontium chloride	sticking	$SrCl_2 \cdot 6H_2O$	tric
Strontium nitrate	sticking	$Sr(NO_3)_2 \cdot 4H_2O$	mon
Sucrose	sticking	$C_{12}H_{22}O_{11}$	mon
Sulfadiazine	sticking	$C_{10}H_{10}N_4O_2S$	mon
Sulfur, precipitated	+	S	rhomb
Talc	+	hydrous magnesium silicate	mon
Tartaric acid	sticking	$C_4H_6O_6$	mon
Urea	+	CH_4N_2O	tetr

EXPERIMENT NO. 2

Substances representing different patterns of internal arrangement (crystal system) were selected for this experiment in order to determine whether the behavior of the material on direct compression parallels the behavior of the substance when it is prepared in the form of a granulation. In each instance the material was subjected to direct compression and its ease of compressibility (vide definition Exp. I) was compared with the compressibility of the same material prepared in the form of granules. The granules were prepared according to the following formula:

Active ingredient	88%
Corn starch (as disintegrator)	10%
Magnesium stearate (as lubricant)	2%
Starch paste 10% w/w (as a binding agent)	q.s.

The disintegrator was used in two portions: 3% of corn starch was mixed with the powdered material before granulating and the remaining 7% was added to the dried granules. The results of compression are given in Table IV.

The results of this experiment indicate that substances presenting no difficulty of sticking to the punches upon direct compression usually present no difficulty while being compressed in the form of a granulation. In most cases the sticking to the punches encountered upon direct compression is overcome by the addition of lubricant either directly to the granular form of the substance or to the prepared granulation. Severe capping in the case of barium sulfate and boric acid resulted from the inadequate binding power of 10% w/w of starch paste for barium sulfate having such high specific gravity (4.50) and small particle size (from one

to two microns), and for boric acid which has practically no adhesive property. When these two substances were granulated with 50% w/w liquid glucose solution as a binding agent and the prepared granules lubricated with 2% magnesium stearate, no difficulty was encountered compressing either barium sulfate or boric acid.

TABLE IV
COMPARISON OF THE COMPRESSIBILITY OF POWDER AND GRANULES OF
THE SAME MATERIALS

Active ingredient	Crystal system	Direct compression	No. 10 granules	No. 20 granules	Remarks
Potassium alum	cub	+	satis. tab	satis. tab	
Methenamine	cub	+	" "	" "	
Potassium chloride	cub	+	" "	" "	
Sodium chloride	cub	+	" "	" "	
Sodium nitrate	hex	+	" "	" "	
Calcium carbonate	hex	+	" "	" "	tablets fragile
Urea	tetr	+	" "	" "	
Potassium dihydrogen phosphate	tetr	-	" "	" "	
Sulfur, sublimed	rhomb	+	" "	" "	
Sulfur, precipitated	rhomb	+	" "	" "	
Barium sulfate	rhomb	-	capping	capping	
Ferrous sulfate	monoc	-	satis. tab	satis. tab	
Sucrose	monoc	-	" "	" "	
Tartaric acid	monoc	-	" "	" "	
Boric acid	tric	+	capping	stick. cap	
Copper sulfate	tric	+	satis. tab	satis. tab	

EXPERIMENT NO. 3

Unlike most crystalline substances, crystals of sodium chloride, upon cleavage, retain in general the geometric forms of the original material regardless of the degree of subdivision obtained by subjecting the salt to the simple method of grinding in a mortar. The possible explanation of this phenomenon may lie in the fact that under pressure the crystals of sodium chloride have a tendency to cleave along their crystal axes. Sodium chloride also does not present any difficulty upon direct compression and does not require lubrication. For these reasons sodium chloride was selected to study the effect of the degree of subdivision of the material on the compressibility of the material. A commercial brand of sodium chloride was ground in a mortar and sifted for 15 min. using the Ro-Tap Sieve Shaker*. The following portions of the powder were separated:

I.	passed through the sieve No. 10 but retained on No. 20
II.	" " " " No. 20 " " " No. 40
III.	" " " " No. 40 " " " No. 60
IV.	" " " " No. 60 " " " No. 80
V.	" " " " No. 80 " " " No. 100
VI.	" " " " No. 100

Microscopic examination of corresponding fractions revealed that grinding did not alter appreciably the identity of shape of the original crystalline material. The same generality of shapes of individual particles was observed in the six groups examined except that in each following group the size of individual particles was correspondingly smaller. Each of the

* U.S.P. XIV, p. 714

six particle size fractions of sodium chloride after drying for two hours at 40°C. was subjected to direct compression using Colton's ZBT motor driven single punch machine, with the size and depth of the die kept constant.

The results of compression are given in the following table:

TABLE V
PHYSICAL PROPERTIES OF TABLETS PREPARED FROM DIFFERENT
PARTICLE SIZE MATERIAL

No. of batch	Av. weight of tablet*	Av. thickness of tablet	Av. hardness of tablet **	Density of tablet ***
I	0.3260 Gm	3.5 mm	5.085 Kg	0.0931
II	0.3455 Gm	3.6 mm	11.525 Kg	0.0959
III	0.4503 Gm	4.5 mm	9.825 Kg	0.1000
IV	0.5092 Gm	4.6 mm	13.900 Kg	0.1106
V	0.5211 Gm	4.6 mm	13.900 Kg	0.1133
VI	0.4016 Gm	4.4 mm	3.830 Kg	0.0912

* Average of ten tablets

** The degree of hardness was measured by an instrument known as Hardness Tester for Tablets (Monsanto Chemical Company, St. Louis, Mo.) which determines the number of kilograms of pressure required to fracture a tablet.

*** Obtained by dividing the weight of the tablets by the thickness

The same pressure was used to compress batches I and II. However, to compress the succeeding four batches, a decidedly decreased pressure was necessary to prevent jamming the machine. The data obtained from the above experiment indicate that, in the first five batches, as the particle size of the material was progressively decreased, the weight, thickness and the density of tablets increased. In the case of Batch VI the degree of subdivision of sodium chloride decreased the "apparent density" or bulk density of the powder. During the compression of Batch VI, more air was trapped which caused the die of the tablet machine not to be filled as densely; consequently, the weight, thickness, hardness and density of these tablets decreased. The variation in the hardness of the tablets indicate that each of the subsequent batches of sodium chloride actually required less pressure for their compression. In the case where the same pressure was used to compress batches of different particle size (e.g., I and II; III and IV), the tablets of the second batch were considerably harder. It appears that the smaller the particle size of the material used the smaller the pressure required for its compression.

Comparison of the surface appearance of the tablets revealed that as the particle size of the material became smaller, the tablets became progressively whiter in color.

However, there is a certain range of fineness beyond which powdered material, as such cannot be subjected to direct compression. Where the degree of subdivision of the material causes the "apparent density" to be less than the actual density, such material loses its "free flowing" property and may feed uniformly into the die. To be compressed into satisfactory tablets, materials having an "apparent density" considerably

less than the actual density generally must be granulated before compression.

EXPERIMENT NO. 4

The following are the results of the microscopic examination of the macrocrystalline sulfadiazine (U.S.P. - Lederle) and of microcrystalline sulfadiazine (U.S.P.) * :

	Shape	Average size of particles	Crystal system **
Microcrystalline sulfadiazine	needle-like crystals	1.5 - 3 microns	monoclinic
Macrocrystalline sulfadiazine	needle-like crystals	20 - 25 microns	monoclinic

Direct compression of both macrocrystalline and microcrystalline sulfadiazine into tablets is not practical as the powder is much too fine to feed uniformly into the die of the tablet machine; when this material is forced with a spatula into the die and compressed, sticking to the punches occurs. Sticking can be prevented by lubricating the powder with 2% magnesium stearate; however, even then the powder does not feed uniformly into the die.

To determine whether microcrystalline sulfadiazine has any considerable electrostatic charge which possibly could be the cause of the sticking of the material to the punches of the tablet machine, the following determination was made: microcrystalline sulfadiazine, spread on a sheet of paper was held over a charged electroscope. Sulfadiazine on the sheet of paper

* Microcrystalline sulfadiazine used in all experiments was supplied by the Calco Chemical Division of the American Cyanamid Company.

** According to Castle, R. N., N. F. Wittand and C. F. Poe, J. Am. Chem. Soc. 71, 228-231, 1949.

discharged the electroscope in the same manner as did the plain sheet of paper.

Next the tablet machine was grounded by attaching one end of an insulated copper wire to the machine and the other end to a water pipe, and microcrystalline sulfadiazine subjected to direct compression. Sticking of the tablets to the punches continued while operating the grounded machine. Thus it was concluded that the electrical charge, if any, on the powder is of an insufficient degree to affect in any appreciable manner the compressibility of microcrystalline sulfadiazine.

EXPERIMENT NO. 5

Macrocrystalline and microcrystalline sulfadiazine, when granulated with 10% w/w starch paste, form very sticky masses difficult to force through the granulating sieve. An attempt was made to prepare the granulation using only water as a binding agent, which again resulted in a sticky mass. The following formula was used for both types of sulfadiazine:

Macrocrystalline or microcrystalline sulfadiazine	83%
Corn starch (as disintegrator)	15%
Magnesium stearate (as lubricant)	2%
Water q.s. to make suitable mass	

In both cases 5% corn starch was mixed with the original powders before granulating; the remaining 10% corn starch was added to the dry granules followed by 2% magnesium stearate as a lubricant. No. 10 and No. 20 mesh size granules were prepared. The results of compression are given in the following table:

TABLE VI
COMPARISON OF TABLETS PREPARED FROM GRANULES OF REGULAR AND
MICROCRYSTALLINE SULFADIAZINE

Name of substance	Compression of No. 10 mesh granules	Compression of No. 20 mesh granules
Macrocrystalline sulfadiazine	Unfirm granules, easily crushed into powder; persistent capping of the tablets	Unfirm granules, easily crushed into powder; persistent capping of the tablets
Microcrystalline sulfadiazine	Persistent capping of the tablets; not remedied by the addi- tion of 1% stearic acid to granules	Capping prevented by increasing pressure on the upper punch and by addition of 1% stearic acid. Tablets satisfactory. Disintegration time: * 35 seconds

* Using N.F. method, p. 706.

Although macrocrystalline and microcrystalline sulfadiazine formed very sticky masses when granulated with water alone as a binding agent, the resultant granules after being dried lost their firmness and crushed easily into a powder during the process of regranulation. Tablets prepared in such a manner were very fragile and persistent capping occurred during the process of compression due to the lack of firmness in the granules themselves. In the case of the microcrystalline sulfadiazine, No. 20 mesh granules were successfully compressed into tablets by adding 1% of stearic acid to prevent occasional capping. Tablets prepared in such a manner had a very short disintegration time when tested directly after compression and also after six months of storage under normal conditions

of storage. However, such a method of granulating sulfadiazine powders is not feasible for the preparation of tablets because of the capping encountered during the compression.

EXPERIMENT NO. 6

This experiment was intended as a study of the qualities of tablets prepared from the macrocrystalline and microcrystalline sulfadiazine. Veegum* was used as a disintegrating agent. It has been reported recently that approximately 2% Veegum can be employed as an efficient disintegrating agent for tablets. Veegum is derived from a naturally occurring mineral base, consisting chiefly of a colloidal magnesium aluminum silicate. It is a fine powder of a dull white color; individual particles are very irregular in shape and are approximately 115 x 75 microns in size. The ingredients were mixed in the following proportions:

Macrocrystalline or microcrystalline sulfadiazine, No. 10 mesh sieve granules, prepared with 10% w/w starch paste as a binding agent.....	96%
Magnesium stearate (as lubricant).....	2%
Veegum (as disintegrator).....	2%

During the compression of microcrystalline sulfadiazine the pressure had to be considerably reduced below that used to compress the macrocrystalline salt to prevent excessive hardness of tablets. The determinations made on the compressed tablets are given in the following table:

* Manufactured by R. T. Vanderbilt Co. Inc.

TABLE VII

COMPARISON OF REGULAR AND MICROCRYSTALLINE SULFADIAZINE
INCLUDING 2% VEEGUM AS DISINTEGRATOR

Name	Av. weight of tablet	Av. thick- ness of tablet	Av. hard- ness of tablet	Density	Disin- tegra- tion time
Macrocrystalline sulfadiazine	0.2401 Gm	4.0 mm	3.290 Kg	0.0600	Over 1 hour
Microcrystalline sulfadiazine	0.2724 Gm	4.5 mm	4.145 Kg	0.0605	Over 1 hour

Microcrystalline sulfadiazine tablets were heavier in weight than those prepared from the macrocrystalline salt although the depth of the die of the tablet machine was kept constant. They were also harder although compressed with reduced pressure; their thickness and density was greater. This increase in weight, thickness and hardness of tablets can be explained by the fact that microcrystalline sulfadiazine, because of the smaller size of its particles, apparently forms denser granules than those prepared from macrocrystalline sulfadiazine. Denser granules seem to require a smaller pressure for their compression since the die contains more mass of the material per unit volume. Besides, due to the smaller size of individual particles within the granules, smaller pressure was required for their compression. However, the density of the compressed tablets increased. The main factor responsible for the smaller pressure required for the compression of tablets from finer particle size materials may be the increased mass of the material per unit volume of the die, or the smaller resistance toward the compression offered by smaller particle size of the substance although it cannot be stated definitively on the

basis of the foregoing experiment, which of these two factors plays the more dominant role; they seem to be related to one another.

The disintegration time of tablets was determined by the method described in the National Formulary IX, p. 706 using six tablets for each determination. On the basis of this determination, Veegum proved to be a very unsatisfactory disintegrating agent, as it required over one hour for tablets to disintegrate and still in this time not all particles of the tablets passed the wire screen of the apparatus.

Additional experiments were performed to determine the qualities of sulfadiazine tablets prepared from No. 10 and No. 20 mesh sieve granules. In this case starch was used as a disintegrating agent. The granules were prepared according to the following formula:

Macro- or microcrystalline sulfadiazine.....	80%
Magnesium stearate (as lubricant).....	2%
Corn starch (as disintegrator).....	10%
Starch paste 10% w/w (as binder) q.s.	

The disintegrator was added to the dried granules. During the compression pressure was varied to obtain approximately the same hardness of tablets. The qualities of compressed tablets are summarized in the following table:

TABLE VIII
COMPARISON OF SULFADIAZINE TABLETS PREPARED WITH
DIFFERENT SIZE GRANULES

No. 10 mesh sieve granules	Av. weight of tablets	Av. hardness of tablets	Av. thickness of tablets	Density of tablets
Regular sulfadiazine	0.2375 Gm.	3.425 Kg	3.7 mm	0.0642
Microcrystalline sulfadiazine	0.2808 Gm.	3.965 Kg	4.4 mm	0.0638
No. 20 mesh sieve granules				
Regular sulfadiazine	0.2756 Gm.	3.260 Kg	4.3 mm	0.0641
Microcrystalline sulfadiazine	0.3009 Gm.	4.220 Kg	4.8 mm	0.0627

TABLE IX
DISINTEGRATION TIME OF SULFADIAZINE TABLETS

Tablets from	No. 10 mesh sieve granules	No. 20 mesh sieve granules
Regular sulfadiazine	Tablets disintegrated in half an hour; few particles from the tablets did not pass the screen after one hour	Tablets disintegrated in 23 min., 4 sec.; all particles passed the screen in 48 min., 25 sec.
Microcrystalline sulfadiazine	Tablets disintegrated in 3 min., 30 sec. All particles passed the screen in 27 min., 20 sec.	Tablets disintegrated in 1 min.; all particles passed the screen in 17 min., 9 sec.

The data obtained indicate that as the size of the granules is decreased, the weight and the thickness of the tablets is increased. No. 10 mesh sieve granules of microcrystalline sulfadiazine required less pressure for their compression than the corresponding granulation of regular sulfadiazine. Similarly No. 20 mesh sieve granules of microcrystalline sulfadiazine required less pressure for their compression than the corresponding granulation of regular sulfadiazine. However, the hardness of tablets increased in the reverse order. This would indicate that the smaller the particle size of the material, the smaller the size of the granules, and the smaller is the pressure required for compression. Further, microcrystalline sulfadiazine tablets, prepared with an efficient disintegrating agent, disintegrate more quickly than the similar tablets of the regular sulfadiazine. Also, the smaller the size of the granules, the shorter the disintegration time of the tablets.

EXPERIMENT NO. 7

The purpose of this experiment was twofold:

1. To determine the effect of negligible variation in size of the particles of a material on the qualities of compressed tablets
2. To compare the qualities of tablets prepared from a fine particle size amorphous material and a fine particle size crystalline material

As an amorphous material, Dried Aluminum Hydroxide Gel, U.S.P., having the following specifications was selected:

Type F-1000, 75% of which passed through 325 mesh sieve*

Type F-2000, 85% of which passed through 325 mesh sieve

In a gel form dried aluminium hydroxide is amorphous in nature, having particles that are flake like in shape. The two types of aluminium hydroxide gel were prepared in the form of No. 10 and No. 20 granules with 5% w/w starch paste as a binder; 15% corn starch was used as a disintegrator and 2% magnesium stearate was employed as a lubricant. Corn starch was used in two portions: 7.5% was added to the dry powders before granulation and the remaining 7.5% was added to the dry granules. Each batch of granules was compressed into tablets using minimal pressure, sufficient, however, to produce tablets with a smooth surface when examined through a magnifying lens. The properties of compressed tablets are summarized in the following table:

TABLE X
DRIED ALUMINIUM HYDROXIDE GEL TABLETS

Type of Dried Aluminium Hydroxide Gel and Size of Granules	Av. weight of tablets	Av. thickness of tablets	Av. hardness of tablets	Density of tablets
F-1000, No. 10 mesh granules	0.1882 Gm	4.2 mm	4.860 Kg	0.0448
F-2000, No. 10 mesh granules	0.2067 Gm	4.5 mm	4.895 Kg	0.0459
F-1000, No. 20 mesh granules	0.2200 Gm	4.7 mm	6.072 Kg	0.0468
F-2000, No. 20 mesh granules	0.2450 Gm	5.0 mm	6.135 Kg	0.0490

* Supplied through the courtesy of the Reheis Company, Inc.

No 10 mesh granules of the Dried Aluminum Hydroxide Gel type F-1000 required compression into the smallest volume for the tablets to have a smooth surface. During the compression of the subsequent batches (in the order given in the table) volume of the tablets was increased and still these tablets had perfectly smooth surfaces when examined under a hand lens. Although the pressure was progressively released as each of the batches of tablets was compressed, still the hardness as well as the thickness and density increased. Since in each case the depth of the die (volume of granules) was kept constant, the progressive increase in the weight of the tablets can be attributed to an increase in the density of the granules with a decrease in the size of the particles of Dried Aluminum Hydroxide Gel. The above data also indicate that the smaller the size of the granules (No. 20 versus No. 10 mesh), the more complete was the filling of the die of the tablet machine and thus smaller granules produced heavier tablets.

The above results obtained with amorphous material, having flake-like particles are parallel to those obtained during the compression of different grades of sulfadiazine, which is a crystalline material composed of needle-like particles. This would suggest that regardless of the type of substance (whether amorphous or crystalline), as the size of the particles of the material used for the preparation of granules for tablets is decreased, the weight, hardness and density of the tablets is increased, provided the depth of the die is kept constant. This experiment also suggests, that the smaller the size of the particles of the material employed in the form of the granules, the smaller is the amount of pressure required for their compression.

EXPERIMENT NO. 8

To determine and compare the properties of tablets prepared from materials differing in "apparent density," the heavy, medium, light and extra-light grades of bismuth subcarbonate, U.S.P.* were tested for direct compressibility. However, bismuth subcarbonate, regardless of whether heavy, medium, light or extra-light, cannot be subjected to direct compression as the powders do not have a "free flowing" property and thus do not feed uniformly into the die. Upon microscopic examination, using a stage micrometer and water as a dispersing medium, the following data were obtained concerning the shape and size of the particles of different grades of bismuth subcarbonate:

TABLE XI

THE SHAPE AND SIZE OF AVERAGE PARTICLES OF BISMUTH SUBCARBONATE

Grade	Shape of particles	Size of particles
Bismuth subcarbonate, heavy	round	3-4 microns
Bismuth subcarbonate, medium	round	2.5-3.5 microns
Bismuth subcarbonate, light	round	1.5-2.5 microns
Bismuth subcarbonate, extra-light	round	1-2 microns

All grades, and particularly the heavy bismuth subcarbonate included particles which were disproportionately large. The heavy bismuth subcarbonate had also the largest number of aggregates of small particles (balling up

* Bismuth Subcarbonate supplied through the courtesy of the J. T. Baker Chemical Company.

effect). The lighter the grade of bismuth subcarbonate the smaller was the number of aggregates and these aggregates were smaller in size.

Since bismuth subcarbonate could not be subjected to direct compression, No. 20 mesh sieve granules were prepared with 5% w/w starch paste as a binding agent. These granules were lubricated and the disintegrator added in the following proportions:

Bismuth subcarbonate granules.....	92%
Corn starch (as disintegrator).....	5%
Magnesium stearate (as lubricant).....	3%

All four grades of bismuth subcarbonate were compressed into tablets having the same volume. The properties of the compressed tablets are summarized in the following table:

TABLE XII
DATA ON BISMUTH SUBCARBONATE TABLETS

Name	Average weight of tablets	Average hardness of tablets	Average thickness of tablets	Density	Disintegration time
Bismuth subcarbonate, extra-light	0.1354 Gm	2.045 Kg	4.6 mm	0.0946	Over 1 hour
Bismuth subcarbonate, light	0.6579 Gm	2.720 Kg	4.7 mm	0.1399	Over 1 hour
Bismuth subcarbonate, medium	0.6721 Gm	2.810 Kg	4.7 mm	0.1430	Over 1 hour
Bismuth subcarbonate, heavy	0.8432 Gm	3.745 Kg	4.7 mm	0.1740	Over 1 hour

The above data indicate that weight, hardness and density of the compressed tablets increased with the increase of the size of the particles of bismuth subcarbonate. These results are contradictory to the data

obtained in the previous experiments concerning the qualities of tablets prepared from the different particle size ranges of sulfadiazine, dried aluminum hydroxide gel and sodium chloride (first five batches). With these compounds the smaller the particle size of the material produced the heavier tablets. In the case of bismuth subcarbonate, the extra-light grade having the smallest, from remaining grades, particle size, produced the tablets which were the lightest in weight. This would suggest that the weight and density of the compressed tablets is influenced primarily by the "apparent density" of the material and secondarily by its particle size. The difference in density between different grades of bismuth subcarbonate was best illustrated by the fact that the thickness of the tablets of heavy, medium and light bismuth subcarbonate remained the same while the weight and density of the tablets increased in the order of compression.

EXPERIMENT NO. 9

In the course of experimentation it was hoped that a study of the geometrical forms of the granules might suggest a clue which would assist in tablet making. For this purpose, different compounds were granulated with 10% w/w starch paste as the binding agent and passed through No. 10 or No. 20 mesh sieves. The dried granules were examined under a magnifying lens. The variation of shapes of granules is given in the following table:

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TABLE XIII

GEOMETRICAL FORMS OF GRANULES

Name of compound granulated	Shape of No. 10 mesh granules	Shape of No. 20 mesh granules
Dried Aluminum Hydroxide Gel, F-1000	tetrahedral	cubical
Dried Aluminum Hydroxide Gel, F-2000	tetrahedral	cubical
Bismuth subcarbonate, light	irregular	spherical
Bismuth subcarbonate, medium	irregular	spherical
Bismuth subcarbonate, heavy	irregular	spherical
Formic acid	spherical	spherical
Lactose	irregular	irregular
Macrocrystalline sulfadiazine	tetrahedral	spherical
Microcrystalline sulfadiazine	tetrahedral	spherical
Pethenamine	cubical	cubical
Sodium chloride	cubical	cubical

Granules prepared from the above compounds varied somewhat in external appearance but the geometrical distinctions were not definite. This lack of variation in shapes of granules is due to the fact that the sieve imparts to the granulated material the pattern of the openings in the screen. However, close examination of the above granulations under a magnifying lens allowed one to make certain generalizations by classifying the shapes of granules into spherical, cubical, tetrahedral or irregular. When examining any sample of granules it was noted that even though one particular geometric form may predominate it did not exclude other forms. Moreover, the process of regranulation further decreased geometrical variations. When the same compounds granulated with 5% acacia powder or 25% liquid glucose solution and passed through No. 10 and No. 20 mesh sieves were compared with those prepared with 10% starch paste as binding agent, no significant difference in the shape of granules was noted. Thus it was concluded that the type of binder does not

influence the shape of granules. However, the size and shape of particles of the material to be granulated affects the manner in which the mass will shread through the screening sieve. The smaller the particles of the material and the more flaky in shape, the more likely the granules will take the pattern of the screen. Other physical properties of the material seem to affect the manner in which the granules are shaped. If the ingredients are light and fluffy and possess considerable cohesive property, as dried aluminum hydroxide gel or sulfadiazine, first screening of the material produces long, very often, tetrahedral granules. On the other hand, saline substances, lacking any adhesiveness, when granulated even with strong binders, have a tendency to break into short cubical granules. The process of regranulation, usually through a smaller screen than that used for the primary granulation, further decreases the geometrical variations among the granules. Compression of No. 20 mesh granules produced tablets which had a somewhat finer texture and a more brittle fracture with a clean break and little crumbling than the tablets compressed from No. 10 mesh granules. Thus it seems that the actual shape of the granules has little if any effect on the appearance and properties of the tablet; however, the mesh of the powder and more particularly, the sizes of the particles of the powder used to prepare the granules and the size of the granules themselves, are of paramount importance so far as the properties and the texture of tablets are concerned.

CONCLUSION

Classification of the elements according to the pattern of their internal arrangement or so-called crystal system, indicates that there is a definite relationship within practically each group of the periodic

table. The systems in which the elements crystallize are: cubic, tetragonal, hexagonal, orthorhombic and monoclinic. However, none of the elements of the periodic table so far examined crystallizes in a triclinic crystal system. There are comparatively few metal-organic and organic compounds which crystallize in the cubic crystal system. Among organic compounds the most commonly encountered crystalline form seems to be the monoclinic crystal system. The actual shape of the particles of the material cannot, in most cases, be identified with the crystal system of a substance.

To determine the relation between the ease of compressibility (absence of sticking to the punches of the tablet machine) and the crystal system fifty-six compounds were subjected to direct compression. Substances belonging to the cubic crystal system presented no difficulty for direct compression. The direct compressibility of the compounds belonging to the tetragonal, hexagonal, orthorhombic, monoclinic and triclinic crystal systems was variable. The results obtained seem to indicate that usually the substances associated with the monoclinic crystal system present difficulties during direct compression. The substances presenting no difficulty upon direct compression usually present no difficulty while being compressed in the form of granules.

A comparison of physical properties of tablets prepared from different particle sizes of the examined materials (some of which were compressed directly and others in the form of granules) suggests that as the particle size is progressively decreased, the weight and density of granules, and the weight, thickness and density of the compressed tablets are increased. Bismuth subcarbonate appears to be an exception to this hypothesis. Texture of the tablets was progressively finer as the particle size decreased. When

a substance can be made into tablets either by direct compression or by the compression of granules, a decrease of the particle size generally facilitates the preparation of superior tablets.

However, there is a certain range of fineness beyond which powdered material as such cannot be subjected to direct compression. In the case where the degree of fineness of the material causes the "bulk density" to be considerably less than the actual density, such material loses its "free flowing" property and does not feed uniformly into the die of the tablet machine. To be compressed into satisfactory tablets, material having a "bulk density" considerably less than the actual density, has to be first processed into granules. In choosing a binder for a particular tablet, one has to consider not only the properties desired for the tablets but also the "bulk density," the size and the adhesive property of the particles of the material.

There was little variation in the shape of the granules prepared in the experiment since the sieve imparts to the granulated material the pattern of the openings in the screen. Generally, it was possible to classify the granules into: spherical, cubical, tetrahedral or irregular. However, the predominance of one geometric form did not exclude the presence of other forms. The process of regranulation further decreased the geometrical variations among granules. The type of binder (among those that were tried) did not significantly influence the shape of granules. However, the size and possibly the shape of the particles of the material granulated affected the manner in which the mass was shreaded through the screening sieve. The shape of the granules examined had little if any effect on the appearance the properties of the tablets that were prepared; however, the mesh of the granules and more particularly, the sizes of the particles in the powder, were of paramount importance so far as the properties and the texture of the tablets were concerned.

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