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AN OVERVIEW OF THE EFFECTS OF SOME PHYSICO-CHEMICAL AND MECHANICAL CHARACTERISTICS OF PARTICULATES ON THE COMPACTION AND POST-COMPACTION PROPERTIES OF COMPACTS

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INTRODUCTION

The physico-chemical and mechanical properties of pharmaceutical powders can have a profound effect on the quality of tablet processing. Physico-chemical particulate properties, such as particle density, particle size, particle shape and size distribution, solid state properties, such as crystal density, crystal habit, crystal order/disorder state, crystal hardness, and hygroscopicity, and the mechanical properties such as elasticity, plasticity, and brittleness of the excipients and drugs dictate how formulations will behave during tablet processing and ultimately perform as a drug delivery system. It is, therefore, of critical importance to understand the potential influence of these parameters on the properties of the products during and after compaction. In this review article, the deformation of the solid systems and the methods of measuring the strength of their compacts will be briefly discussed and an emphasis will be given to the effects of the physico-chemical properties of the particulates on their compaction and post-compaction properties.

DEFORMATION OF THE SOLIDS:

It is important to give a brief overview of the deformation of particulate matter during compaction before dealing with the literature review.

The deformation of a solid system features either one or a combination of the following: elastic, plastic, and/or fragmentation. The type of deformation depends upon the rate and magnitude of the applied force as well as the duration of the locally induced stress and physical properties of the material.

If the applied load is released before the stress reaches a yield value, then the particles deform elastically, i.e., they regain their original form, and return to the closely-packed rearrangement state. The yield value is referred as the 'elastic limit' above which deformation of the particles becomes irreversible. The slope of the linear portion of stress/strain plots is termed the 'modulus of elasticity' (i.e., Young's modulus).

As the volume of the powder bed is reduced progressively with further load application, either plastic deformation or fragmentation becomes the dominant mechanism of compaction. Plastic deformation usually occurs with powders in which the shear strength is less than the tensile strength, whereas fragmentation becomes dominant with hard, brittle materials in which the shear strength is greater than the tensile strength. If the latter deformation occurs, the surface area of the powder and the potential 'bonding' area between the particles increase with the introduction of new, clean surfaces due to the formation of fragmented particles.

There is no pharmaceutical powder that exhibits only one of the above mentioned deformation mechanisms, although there is a spectrum of ranges from highly elastically deforming to highly plastically deforming or highly brittle materials. Even for materials that are known to be brittle, smaller particles of these materials may deform plastically.

Attraction between particles is inversely proportional to the distance between them and when the particles are in sufficiently close proximity they can become permanently

attached to each other. This is called 'bonding' and there are several mechanisms that will contribute to the strength of the bond, although they never act independently.

When a compact has been formed in the die, a further increase in the applied pressure, or application of a constant stress during dwell time, may cause further deformation of a time-dependant material as the compact consolidates by viscoelastic and plastic flow. When the applied pressure is removed during decompression, which is the final stage of the compaction event, the compact undergoes a sudden elastic expansion followed by a much slower viscoelastic recovery as the compact is ejected.

MEASUREMENTS OF THE STRENGTH OF THE TABLETS:

The need to quantify the strength of tablets has long been recognized both in compaction research and in industrial practice as a quality control parameter. The mechanical strength of the tablets has been described by several means including: the crushing strength (1,2); the axial (3-5) or radial tensile strength (6-8); hardness (9-12); and the work required to cause tablet failure (13).

A common method of assessing the strength of tablets involves the measurement of the force required to break a tablet in a diametral compression test. The Radial Tensile Strength (T_s) of tablets can be calculated from the following equation:

$$T_s = 2F_c / \pi D H_e \quad (1)$$

where F_c is the force needed to break the tablet, and D and H_e are the diameter and the thickness of the ejected tablet, respectively. Some authors (3-5) suggested the determination of axial tensile strength because of the sensitivity of radial tensile strength measurements to crack propagation variations. The Axial Tensile Strength (T_{sx}) can be calculated from the following relationship:

$$T_{sx} = 4F_c / \pi D^2 \quad (2)$$

The measurements of tablet strength in the axial direction were found to be valuable for the assessment of capping and/or lamination tendencies of materials (14).

Crushing strength is often imprecisely termed as hardness which is, in fact, a surface property measured by the resistance of a solid to local permanent deformation. Hardness can be determined by either static methods (e.g., the Brinell, Vickers, and Rockwell hardness tests) or dynamic methods (15). The static indentation methods involve the formation of a permanent indentation on the surface of the material tested and the hardness is then determined by means of the load applied and size of the indentation formed (16,9,11). In the dynamic indentation tests, either a pendulum is allowed to strike from a known distance or an indenter is allowed to fall under gravity onto the surface of the test material. The hardness is then determined from the rebound height of the pendulum or the volume of the resulting indentation. Using an apparatus consisting of a steel sphere pendulum acting as an indenter, Hiestand et al.(10) estimated the hardness (i.e., the mean deformation pressure) of compacted materials by dividing the energy consumed during impact by the volume of the indentation.

Hiestand and Smith (17) used the indentation hardness and the tensile strength measurements to formulate the following three dimensionless indices to characterize the relative tabletability of single components and mixtures:

- Bonding Index (BI) is defined as the ratio of the tensile strength to the dynamic indentation hardness and is claimed to be the indicator of the survival success of areas of contact.

- Brittle Fracture Index (BFI) is a measure of brittleness which is the principal cause of capping and lamination.

- Strain Index (SI) is obtained during the determination of dynamic indentation hardness and is indirectly related to the proximity of the surfaces that remain in contact after decompression.

Most of the above mentioned methods are destructive tests that examine the mechanical failure properties of compacts. These tests result in irreversible damage to the mechanical structure of the compact. Radebaugh et al. (18) proposed a nondestructive

technique capable of measuring the viscoelastic properties of the compacted powders without fracture or permanent deformation of the compact. The technique uses small strain sinusoidal oscillatory torsion of rectangularly shaped compacts. Using this method, the workers were able to determine the fundamental parameters of elastic modulus and viscous modulus of microcrystalline cellulose, a model powder, as a function of strain, rate of strain, formula composition, method of manufacture, and water content of the compact.

The 'observed' elastic limit for a crystalline material is dramatically smaller than the 'theoretical' values based on the calculation for a perfect crystal lattice of that material. This is due to the fact that actual crystals contain dislocations which facilitate the movement of the planes of molecules in the crystal lattice thereby lowering the elastic limit. Dislocations may be produced by any irregularity during the growth of a crystal. They occur at junctions between crystals which do not fit perfectly because there is an angle between sets of crystallographic planes.

Several methods of measuring the Young's modulus values for solids have been developed (19), however, these methods have practical and theoretical limitations when applied to powder or compressed powder specimens (20). In the field of pharmaceutical powders, elasticity has been generally studied by the use of elastic and viscoelastic expansion of the compacts (21,22).

Church and Kennerley (23) determined the Young's modulus values by the flexure testing of compacted rectangular beams. Paddon and Wilson (24) described a method for measuring the elasticity modulus of cylindrical specimens. Kerridge and Newton (25) determined the Young's modulus values of aspirin, microcrystalline cellulose and potassium chloride from the slope of the stress/strain curves.

Bassam et al. (20) measured the Young's modulus of numerous tableting excipients from their rectangular beam specimens over a range of porosities using a four-point beam bending technique. They observed a decrease in Young's modulus with increasing porosity for all materials tested. They also reported that Young's modulus was independent of the beam thickness within the range used. These workers applied their

data to the range of published equations which describe the relationship between Young's modulus and porosity and suggested that the best overall relationship was that proposed by Spinner et al. (26).

PHYSICO-CHEMICAL PROPERTIES:

Solid state properties, such as crystal density, crystal habit, crystal order/disorder state, crystal hardness, and hygroscopicity, and other physico-chemical particulate properties, such as particle density, particle size, particle shape and size distribution of the excipients and drugs play an important role on the quality of tablet processing and ultimately on the performance of the drug delivery system.

Solid State Properties:

The subject of solid-state properties of pharmaceutical powders is of particular importance since most drugs and excipients are crystalline materials or possess some degree of crystallinity. As suggested by York in a review article (27), these properties include: crystal structure; crystal habit; crystal hardness; polymorphism and solvate forms; wettability; surface polarity and moisture sorption.

Mitchell and Down (28) observed extensive surface recrystallization and changes in the matrix of the compacts of aspirin, anhydrous calcium gluceptate, and methenamine after storage at two different relative humidity conditions. They also reported complete reorganization of the surface of methoclopramide hydrochloride and methenamine compacts. The surfaces of the compacts of the latter were claimed to be dependent on the presence or absence of lubrication. The surfaces of the lubricated compacts of methenamine were found to be initially smooth whereas the unlubricated compacts possessed disordered surfaces with a characteristic granular appearance. However, after about 8 days and considerable surface growth, no significant differences remained between the compacts prepared with or without lubricant. From the findings in this study, the authors suggested that compression creates a less stable disordered state at crystal-die wall and punch interfaces and the interfaces between plastically deformed crystals. This process is the basis of the 'activation theory' of compact formation proposed by Huttenrauch (29). Friesen et al. (30) have also shown that mechanical stress

on single crystals in a punch and die can be expected to produce an increase in the number of defects, particularly at crystal surfaces.

Many drugs are produced by crystallization from solution. The solid state properties of the crystals, such as the crystal habit, can be altered by the use of different crystallization solvents. A change in the properties of the crystals can also affect the compaction behavior of that crystal. Marshall and York (31) observed differences in the compaction properties of samples of nitrofurantoin which were crystallized from formic acid or formic acid/water. Utilizing yield pressure values, which were calculated from 'in-die' and 'out-of-die' Heckel plots, the workers demonstrated that nitrofurantoin crystallized from formic acid exhibited plastic deformation. The higher total axial recovery of the compacts of the nitrofurantoin crystals from formic acid/water, as compared to the other sample, was suggested to be evidence for increased elastic deformation. The differing degrees of elastic and plastic deformation of these samples were attributed to their different solid-state properties. However, the authors could not distinguish between the effects of the different solvents and the additional drying time needed for the crystal samples from formic acid/water.

Chan and Grant (32), studying the intrinsic dissolution rates of the crystal forms and compacted disk forms of acetaminophen and adipic acid samples, showed the importance of crystal habit in controlling the dissolution rate of acetaminophen, and crystal defects in controlling the dissolution rate of adipic acid. They suggested that, during the preparation of a disk or tablet, compaction of the solid drug particles would destroy their habit and might also alter the densities of the various crystal defects, hence, the disk-intrinsic dissolution rate might be very different from the crystal-intrinsic dissolution rate due to the effects of compaction. The authors also pointed out the possible role of crystal engineering in modifying the dissolution rate of pharmaceuticals.

Polymorphism, the ability of any element or compound to crystallize as more than one distinct crystal species, has been the subject of many publications in the literature (33-38) because the physical state of pharmaceutical powders may have considerable effects on the bioavailability of a drug substance and control its dissolution rate as well as stability.

Kopp et al. (37) developed a melted disc technology in order to evaluate the role of polymorphism in the mechanical strength of compressed tablets and minimize the influence of such factors as compaction force, porosity, and particle size. They observed that both crystal size and crystal habit significantly affected the physical properties of the test materials.

Matsumoto et al (38) reported that the polymorphic transformation of chlorpropamide was affected by the temperature during compression and the mechanical strength of the tablets of this material depended on both the polymorphic form and the compaction temperature.

Crystal hardness can be defined as a measure of the resistance to local deformation (39) and can be measured by micro-indentation methods (40). Ridgway et al. (41) measured the crystal hardness of several pharmaceutical materials and the radial pressure transmission for these crystals, and Aulton (40) observed that larger radial force transmission for crystals with lower surface hardness values could be linked with the ability of such materials to form good tablets.

Ichikawa and others (42), using a Vickers hardness tester, measured the crystal hardness of a number of pharmaceutical materials and correlated the reciprocal of the crystal hardness values to the slope of the linear portion of the Heckel plots. However, they did not observe any relationship between the hardness of the crystals and tensile strength of the resulting compacts.

Duncan-Hewitt and Weatherly (43) investigated the flow and fracture behavior of small crystals using a microindentation technique. Later, utilizing the Vickers microindentation hardness of single crystals of sodium chloride, they developed a model to predict the densification behavior of this material during uniaxial compaction (44). Using this model, they were able to predict the densification of sodium chloride at a very low punch velocity (1 mm/min).

Moisture Content:

It is well known that moisture can affect both compaction and post-compaction properties of materials. Powder, packing volume, and density as well as tablet weight, crushing

strength, and tensile strength may be altered due to changes in the moisture content of a formulation. Powders or granulations with 'too low' or 'too high' water content may result in unsatisfactory tablets. In general, three thermodynamic states of water can be described as: i) tightly bound water; ii) relatively free water; and iii) water in intermediate states. Just as materials differ in physical structure and chemical composition, they will also differ in the manner by which they sorb water. Solids are basically of two types when comparing the manner in which water is held: a. granular or crystalline-type solids and b. amorphous-type solids. Crystalline solids have a lattice structure as well as surface pores that are capable of holding water. Water loss from crystalline solids is met with minimal resistance and, therefore, these substances are usually not temperature sensitive unless the temperature is high enough to remove the water of hydration. Amorphous solids are more complex structures, i.e.: polymers or gelatinous materials, with water being an integral part of the structure. Due to their complex nature, amorphous solids are capable of entrapping water in small interior capillaries or pores that would cause water removal to be slower than from the crystalline-type solids. For this reason, amorphous solids are sensitive to high temperatures (45).

Numerous studies have been conducted in order to determine the effect of moisture on the compaction and post-compaction properties of various substances. The factors to be considered include: the properties of the active substance, excipient properties, temperature and relative humidity of the storage area as well as that of the production area, and the pressure applied during compaction.

Shotton and Rees (46) looked at the effect of moisture on the compaction properties of sodium chloride (NaCl), a crystalline-type solid, by measuring both compaction and ejection forces. It was observed that water formed a saturated solution at the surfaces of the crystals which caused a decrease in the interparticulate friction as well as a decrease in the friction between the particles and the die wall. However, in all cases, except at low pressures, the dry material formed stronger compacts than the wet material. Upon drying of compacts prepared using NaCl with sorbed moisture, an increase in tablet strength was observed. This was attributed to interparticulate recrystallization as the water was removed during drying.

Shotton and Harb (47) studied the effects of humidity and temperature on powder cohesion, which could ultimately alter the compaction properties of a powder. Nine different powders were studied and their cohesion determined at different relative humidities (RH's) and temperatures. It was found that maize, wheat, and potato starch reached a maximum cohesion at intermediate relative humidities and temperatures while acacia, tragacanth, and alginic acid cohesion was independent of moisture content. Lactose, dextrose, and sucrose were free flowing at all except high relative humidities. Cohesion in a powder can also be affected by particle size, shape, and surface properties, which will be discussed later. The cohesion of the starch materials reached a maximum at intermediate temperature and relative humidity values because at high moisture contents the starch began to form granules. Tragacanth, alginic acid, and acacia had equal cohesion at all relative humidities and temperatures until deliquescence occurred for tragacanth and acacia due to absorption of water. At high relative humidities dextrose and sucrose absorbed water and formed a cake or a solution.

Microcrystalline cellulose (MCC) is commonly used in tablet formulations and, therefore, the effect of moisture content is of considerable interest. As early as 1968, Shah and Wilson (48) studied the effects of heat and humidity on MCC formulations. Comparing MCC which was "fresh", i.e. unexposed to the atmosphere, to MCC which had been subject to an uncontrolled atmosphere where conditions varied from 10-28°C and 50-80% RH over a 3 week period, significant differences were observed. MCC formulations made with the exposed MCC did not flow well from the hopper. In order to correct for this "exposure", three strategies were employed in order to improve the flow of the exposed MCC: i) heating the exposed material; ii) adding magnesium stearate as a lubricant; and iii) both heating and addition of magnesium stearate. Their results indicate that heating of the exposed MCC improved tablet weight and crushing force while adding magnesium stearate alone improved tablet weight, but decreased crushing force. Applying heat with magnesium stearate addition gave an average increase in weight, but still showed a decrease in crushing force.

Rees and Shotton (49) studied the effects of moisture on particulate material by studying the effects of three liquids (water, decahydronaphthalene, and light liquid paraffin) on the

compaction properties of NaCl. The authors suggested that the differences between the three liquids might have been partly due to differences in their viscosities, but water was also found to have boundary lubrication and hydrodynamic effects. They reported that it was possible to decrease the friction that occurred during the compaction process by use of water which was acting as a hydrodynamic lubricant or a boundary lubricant.

In later studies of the strength of NaCl compacts containing moisture, Rees and Hersey (50) observed that moisture decreased die wall friction and that this effect was increased at high pressures and high moisture content. They reported that the strength of the NaCl compacts decreased as the increased moisture content reduced the strength of interparticulate bonds.

Cole et al. (51) looked at the effect of moisture content on the physical properties of a granulation containing 69% maize starch, 29% lactose, and 1% of each glycerin and paraffin oil. The authors found that with increasing granule moisture content, the flow rate through circular orifices increased as did the poured bulk density. The effect of moisture on tablet properties varied with compaction pressure. At lower compaction pressures, the breaking strength of tablets followed a somewhat linear increase with increases in moisture. However, at higher compaction pressures, a maximum breaking strength was achieved at approximately 6% moisture content, above and below this there was a decrease in the breaking strength.

The relationship between moisture, crushing force, disintegration, and dissolution of compressed tablets prepared by wet granulation was studied by Chowhan (52). It was found that tablets allowed to equilibrate at high relative humidities had a decrease in crushing force values which depended linearly upon the initial tablet crushing force values upon compaction. After overnight exposure to ambient conditions, crushing force values increased, but the magnitude of the increase also depended upon the initial values of the tablets upon compaction. Increases in crushing force values resulted in increased disintegration times, but did not affect in vitro dissolution times. After exposure to high RH conditions, tablets compressed from granulations with high moisture contents had an increase in crushing force after storage. Tablets compacted from low moisture content

granulations did not show an increase in crushing force with storage, but in vitro dissolution was strongly dependent on the initial tablet crushing force upon compaction.

Khan et al. (53) investigated the effect of moisture content of three formulations, containing microcrystalline cellulose (MCC) as the additive, on the compressional properties of some formulations. Moisture content of the MCC varied from 0.6 to 7.3%. As the moisture content increased the compressibility of MCC, the strength of the compacts of the formulations, and their disintegration and dissolution times also increased. However, capping was observed for all the compacts of the formulations at high pressures. The authors suggested that this problem might occur due to expression of the condensed water from the pores at high pressures.

Bangudu and Pilpel (54) studied the effects of composition, moisture, and stearic acid on the plasto-elasticity and tableting properties of paracetamol-MCC mixtures. Tensile strength is proportional to the inverse of the ratio of elastic recovery (ER) to stress relaxation (SR). Addition of 2 to 4% W/W of water increased the tensile strength of tablets provided that they contained less than 75% W/W of MCC, but increasing the water content above this, decreased the tensile strength. Paracetamol has very little tendency to absorb water while MCC slowly absorbs up to 14% W/W at 20°C and 85%RH over 5 days. Studies showed that desorption of water from the MCC was relatively easy and, therefore, is a reversible process. This accounts for the softening seen with tablets at high RH's containing greater than 25% W/W MCC. It is, however, possible to dry these tablets. For all mixtures adding less than 4% W/W of water, there was a decrease in ER/SR, but at higher levels of water, there was an increase in ER/SR. With MCC alone, only an increase in ER/SR was seen. Initial decreases are due to the development of surface tension and pendular bonds that hold the particles together. The optimum range of water in paracetamol-MCC tablets will be strongest at 2 to 4%. The authors suggested that ER/SR increased with increased water and tensile strength then decreased because at these levels the water is probably beginning to form multilayers on the surface of the particles acting as a lubricant and, therefore, decreasing frictional forces responsible for particle attraction.

Ahlneck and Alderborn (55-57) conducted a three part study involving the affects of moisture adsorption on tableting. In part I (55), six substances were compressed at a range of relative humidities. Volume reduction and tablet strength were measured and it was found that water adsorbed at particle surfaces had a limited effect on the volume reduction behavior of the solid except when a fairly large amount of 'condensed' water was present in the mass. This 'condensed' water would facilitate volume reduction probably due to decreased friction between particles and between particles and the die wall. At mid- to low relative humidities, there was an increase in tensile strength, but at high relative humidities there was weakened tensile strength due to the 'condensed' water vapor. At low relative humidities there was monolayer adsorption of water which was tightly bound, non-movable water. At high relative humidities multilayer adsorption occurred involving the movable 'condensed' water which was 'solvent-like'. Yield pressure values were found to be higher for unlubricated materials, therefore, yield pressure was markedly affected by die wall friction. In general, tensile strength was found to increase with increasing relative humidities. In part II (56), the effects of moisture adsorption on the mechanical strength and air permeability of tablets during storage were studied. Three crystalline substances were used, saccharose and sodium chloride (two particle size fractions), both water-soluble, and calcium hydrogen phosphate which is practically water-insoluble. When stored at increased relative humidities, tensile strength for saccharose tablets increased and tablet surface area decreased. The authors suggested that this might be due to rearrangement of molecules at the particle surfaces by the action of adsorbed water leading to formation of solid bridges. This effect was much less for the fine fraction of sodium chloride and no effect was observed for the more coarse fraction of sodium chloride and for calcium hydrogen phosphate. In part III (57), these workers investigated the effects of relative humidity on the tensile strength of the compacts of saccharose, NaCl, and dicalcium hydrogen phosphate dihydrate for up to 168 hours. Tablet strength generally increased during storage for NaCl and saccharose. Increases in relative humidity caused an increase in the rate and degree of strength increase. At greater than the critical relative humidity, the tablet strength decreased after a few hours of storage. Dicalcium hydrogen phosphate dihydrate showed no change in tablet strength with time or storage conditions. NaCl and saccharose surface areas decreased with storage time and the effect was more at increased relative

humidity, therefore, tablet strength is inversely proportional to surface area. Changes in strength were attributed to rearrangement of solid within the tablet which was facilitated by sorbed water.

Li and Peck (58) studied the effect of moisture content on the compression properties of maltodextrins. They found that moisture appeared to act as an internal lubricant and facilitated consolidation. Increasing moisture content produced a decrease in yield pressure values, indicating that moisture enhanced plastic deformation. Increasing moisture also caused a decrease in tensile strength of the maltodextrin compacts which was attributed to the lubricant effect of water which improved force transmission from the upper to the lower punch, allowing for increased consolidation.

Uzunarslan and Akbuga (59) studied the effect of moisture on an active substance, ranitidine HCl. They found that bulk volume decreased (therefore, cohesion increased) with increasing moisture content, therefore, any parameters influenced by volume might be affected. Moisture adsorbed powders were more easily packed and porosity decreased with increases in moisture content. The authors suggested that moisture might be acting as a binder. Increased moisture caused the crushing strength of the ranitidine HCl tablets to decrease. No change in density was observed up to 1% moisture content, but above this, there was a significant decrease in density.

Ando et al. (60) wet granulated anhydrous theophylline with several different pharmaceutical excipients. It was observed that when granulated with hygroscopic materials, needle-like crystals formed on the surfaces of the compressed tablets after storage at 37°C and relative humidities ranging from 75 to 95%. Crystal formation increased as moisture uptake by the hygroscopic materials increased at the higher relative humidity conditions.

Heidemann et al. (61) studied the rates of moisture sorption and its effect on the stability of a drug which is sensitive to moisture. Materials that were found to have a high capacity to bind water (and, therefore, less unbound/free water) were found to achieve high levels of free water very slowly, therefore, materials with a low capacity to bind

water had increased amounts of water which was free to interact and increased the degradation of a moisture sensitive drug. Hygroscopic materials might preferentially bind water and subsequently leave less available to interact with the drug.

Malamataris et al. (62) measured the moisture sorption and desorption of some directly compressible excipients in order to correlate moisture distribution with some mechanical properties of compacts after storage at various relative humidities. They observed that the presence of tightly bound 'monomolecular' water increased the plasticity and weakened the interparticle bonds. The tensile strength reached a plateau and then began to decrease when the moisture content was about double that corresponding to a tightly bound monomolecular layer.

Shukla and Price (63) using Emdex and Sweetrex, two dextrose-based directly compressible diluents, studied the effects of moisture sorption on the tablets of these materials. Both materials were found to sorb moisture rapidly when relative humidities were greater than 60%. The pressure required to compress tablets to a given relative density decreased as the moisture content increased. Yield pressures decreased with increasing moisture content. Sweetrex was found to be more hygroscopic than Emdex, but crushing force for both materials increased with increasing moisture content and decreasing compaction pressure. Sweetrex's crushing force was found to reach a maximum crushing force at 7% moisture content and then decrease at 8.3% moisture content.

Other Particle Properties:

Hersey et al. (64), in their study of the effect of particle size on the strength of NaCl tablets, observed a linear relationship between compaction pressure and crushing strength for all particle size fractions studied except at higher pressures. Increases in tablet strength were seen with increasing particle size and compaction pressure.

Marks and Sciarra (65) investigated the effect of particle size on other physical properties of granules and their corresponding tablets using 3 different formulations containing sulfadiazine, sodium saccharin, or placebo, in combination with dicalcium phosphate

dihydrate, lactose USP, starch USP, and methylcellulose. No direct relationship was found between granule size and granule volume. It was found that the degree of granule friability and flowability increased as the size of the granule decreased. It was suggested that when the size of the granules to became smaller, there was a greater loss of weight due to the friability of the granules. In addition, it was observed that as granule size decreased the weight variation of the tablets decreased probably because the weight of the die fill increases as the granule size decreases.

Hersey and Rees (66) studied the effect of particle size on the consolidation of NaCl and lactose powder during compaction. Particle size and particle size distribution were found to effect particle slippage and deformation and, therefore, consolidation. The ratio of the particle size of the powder being considered to the diameter of the die effects the amount of void spaces during tablet compaction. It was observed that contact points between particles and, therefore, the number and total area of these contact points depends on particle size and particle size distribution as well as the arrangement of the powders. Using the plots obtained from the Ludde and Kawakita equation (67) and the Heckel equation (68), these workers observed a linear increase as a function of pressure for NaCl at all particle sizes. On the other hand, the plots for the crystalline lactose and spray dried lactose exhibited a linear increase only at high pressures for the particle size ranges studied and a linear decrease was found for larger particle sizes of these material at lower pressures.

Fell and Newton (69) also studied the effects of particle size of crystalline and spray dried lactose on the density changes in tablets of these materials and observed that, when the measurements of the relative volumes were made under pressure, the values for the compacts made from smaller particles at slow speeds were less than those made from larger particles. However, the relationship was reversed when the compacts were made at high speeds. The differences in the relative volumes of the compacts made from different particle size fractions at different speeds no longer existed when the measurements were obtained from the ejected compacts.

Hunter and Ganderton (70) studied lactose as well, by looking at the effect of particle size on the granulation of lactose by massing and screening. The authors found that

increases in the mean initial particle size, decreased the amount of binder necessary to form granules and also decreased the strength, porosity, flow, and packing of the granules. Having a narrow particle size distribution increased the porosity of granules, but decreased the strength of the granules even further. However, increases in the concentration of binder produced granules of increased strength, but decreased porosity. When using intermediate binder concentrations, the granules produced had the poorest flow and packing properties.

Shotton and Obiorah (71) investigated the effect of particle shape and crystal habit (dendritic and cubic) on the properties of NaCl. They observed that the bulk and tapped density of the cubic crystals were greater than those of the dendritic crystals while the angle of repose and the strength of the resulting compacts of the former were less than those of the latter.

Nyström et al. (72) studied the influence of the particle size of a dry binder on the mechanical strength of tablets using lactose, paracetamol, ascorbic acid, and NaCl where 5 different particle size fractions of methycellulose were used as binders. Upon direct compression, the authors observed increasing strength of all materials as the amount of methylcellulose was increased, but small additions of the larger particle size fraction of the binder decreased the strength of the NaCl tablets. It was concluded that the particle size of the binder has a very important effect especially when dealing with the finer particle size fractions. Of the materials tested, the authors found that lactose was affected least by changes in the particle size of the binder probably due to the fact that it fragments upon compaction, while NaCl, which is a plastically deforming material, was most significantly affected by changes in the particle size of the binder. The strength of the paracetamol and ascorbic acid tablets seemed to be directly related to the degree of surface coating by the binder.

McKenna and McCafferty (73) studied the effect of particle size on the compaction mechanism and tensile strength of tablets of spray-dried lactose, Sta-Rx 1500, and Avicel PH101. Decreasing the particle size of spray-dried lactose and Sta-Rx 1500 produced stronger compacts while Avicel compacts were unaffected by changes in particle size.

The compaction mechanism was found to be independent of size fraction for all 3 materials. Examination of the angle of repose and the Hausner ratio indicated that a correlation existed between the internal forces of friction and cohesion of the powders and the tensile strength of their compacts.

Alderborn and Nyström (74) investigated the effect on tablet strength of particle shape and texture before and after milling of NaCl, saccharose, and sodium citrate. Two different fractions, from both unmilled and milled, were characterized based upon shape for each of the three materials. The milled particles were found to have a much rougher texture, a greater surface area, and more irregular particles. The compressibility of saccharose and sodium citrate was found to be independent of the shape of the original particles, while that of the NaCl was significantly effected by changes in particle shape. Milled NaCl particles produced stronger tablets and this increase in strength was most significant at higher compaction loads. The fraction of milled particles resulted in tablets with greater strength. No significant difference in the strength of sodium citrate and saccharose tablets was observed when comparing the different shape fractions of particles for these two materials.

Roberts and Rowe (75) investigated the effect of the relationship between punch velocity and particle size on compaction behavior of materials with different deformation mechanisms, i.e. lactose (fragmenting), microcrystalline cellulose (plastically deforming), and a drug which is a phthalazine derivative. Heckel plots and the strain rate sensitivity (SRS) index were used to describe the relationship between punch velocity and particle size. The yield pressure and SRS index values for microcrystalline cellulose were found to be independent of changes in particle size, however, yield pressure was inversely proportional and the SRS index was directly proportional to changes in particle size for lactose. The phthalazine derivative that was studied also had an increase in yield pressure with decreasing particle size, but the SRS index dropped to zero. The authors suggested that this was indicative of a change in the deformation mechanism, i.e. from plastic to brittle fragmentation as particle size decreased.

Kaneniwa et al. (76) studied the effect of particle size on the compaction properties and compaction mechanism of sulfadimethoxine (SD) and sulfaphenazole (SP). A plot of

compaction pressure vs the thickness of the powder of the two materials revealed that there were two different stages of compaction for SD and SP except for the large particle size fraction (42/48 mesh) of SD. SD compacts were found to be more significantly affected by changes in particle size than SP. Evaluation by use of the Janssen equation suggested that a cyclical structure formation and fracture process during compaction was occurring. Compacts of SP were found to have higher tensile strength values than compacts of SD. Compacts produced from SP all had similar structures regardless of the particle size fraction compacted. However,compacts of SD produced from larger particle size fractions had higher tensile strength values than those compacts produced from smaller particle size fractions possibly because binding between the larger particles was more effective. The authors suggested that these results indicated that SD deformed by a fragmentary mechanism while SP deformed by a plastic mechanism.

Wong et al. (77) investigated the effect of particle shape on the compaction of a number of model powders including the plastically deforming NaCl and Sta-Rx 1500 as well as the brittle fracturing lactose and Emcompress. NaCl and Sta-Rx 1500 exhibited an increase in plastic deformation and a decrease in elastic recovery and yield pressure when changing from regular to irregular shaped particles. Therefore, an increase in tensile strength was attributed to an increase in the contact area between particles. Shape had no effect on tensile strength, elastic recovery, or yield pressure for lactose and Emcompress.

Riepma et al. (78) studied four types of crystalline lactose, i.e. α-monohydrate, anhydrous α-, roller dried ß-, and crystalline ß-lactose, and their behavior when mixed as same particle size fraction binary mixtures and then compacted into tablets. The authors found that both crushing strength and internal specific surface area correlated linearly with the blend composition when compressing the binary mixtures of the same particle size fraction. Changes in the particle size fraction or the applied force did not alter this linear relationship. As specific surface area increased, the crushing strength of the tablets was found to increase for any binary mixture.

Nilsson et al. (79) reported that the tablets of the ordered mixture of griseofulvin and oxazepam showed higher dissolution rates than the ordered mixtures alone. The authors

suggested that the increases in dissolution rates due to compaction might have been attributed to a breakage of the carrier particles and the possible 'film' of primary particles around these former. As a result of both, the total external surface area of carrier material exposed to the dissolution media would have been increased, subsequently resulting in a faster release of discrete drug particles to the dissolution media (80).
El Gindy and Samaha (81) observed a quantitative correlation between the tensile strength values of the compacts of numerous pharmaceutical powders and the surface free energy of the materials studied. These authors reported that high surface free energies were associated with high strength parameters because both depend on the bonding strength.

Karehill et al. (82), measuring the axial tensile strength of double layer compacts from a precompressed layer with varying surface roughness and a layer of material in powdered form, concluded that materials consolidating mainly by plastic deformation were all very sensitive to a decrease in the surface roughness of the precompressed layer of the double-layer tablet. The brittle materials, lactose, sucrose and Emcompress, were found to be relatively unaffected by pretreatment of the first layer. They also suggested that high fragmentation of tableting compounds and excipients would facilitate the formation of mechanically strong multilayer tablets.

REFERENCES

1. D.B. Brook and K. Marshall, J. Pharm. Sci., 57, 482 (1968).
2. J.E. Rees, J.A. Hersey and E.T. Cole, J. Pharm. Pharmacol., 22, suppl. 64S (1970).
3. S.D. David and L.L. Augsburger, J. Pharm. Sci., 63, 933 (1974).
4. B.W. Muller, K.J. Stephens and P.H. List, Acta Pharm. Technol., 22, 91 (1976).
5. P.L. Jarosz and E.L. Parrott, J. Pharm. Sci., 71, 607 (1982).
6. J.T. Fell and J.M. Newton, J. Pharm. Pharmacol., 20, 657 (1968).
7. J.T. Fell and J.M. Newton, J. Pharm. Sci., 59, 688 (1970).
8. K.G. Pitt, J.M. Newton and P. Stanley, J. Pharm. Pharmacol., 42, 219 (1990).
9. K. Ridgway, M.E. Aulton and P.H. Rosser, J. Pharm. Pharmacol., 22, suppl. 70S (1970).

10. E.N. Hiestand, J.M. Bane and E.P. Strzelinski, J. Pharm. Sci., 60, 758 (1971).
11. M.E. Aulton, H.G. Tebby and P.J. White, J. Pharm. Pharmacol., 26, suppl. 59P (1974).
12. M.E. Aulton, Acta Pharm. Helv., 56, 133 (1981).
13. J.E. Rees and P.J. Rue, Drug Dev. & Ind. Pharm., 4, 131 (1978).
14. G. Alderborn and C. Nyström, Acta Pharm. Suec., 21, 1 (1984).
15. H. Leuenberger and B. Rohera, Pharm. Research, 3, 12 (1986).
16. M. Çelik, Ph.D. Thesis(CNAA), Leicester Polytechnic (1984).
17. E.N. Hiestand and D.P. Smith, Powder Technol., 38, 145 (1984).
18. G.W. Radebaugh, S.R. Babu and J.N. Bondi, Int. J. Pharmaceutics, 57, 95 (1989).
19. R.J. Roberts and R.C. Rowe, Chem. Eng. Sci., 42, 903 (1987).
20. F. Bassam, P. York, R.C. Rowe and R.J. Roberts, Int. J. Pharm., 64, 55 (1990).
21. I. Krycer, D.G. Pope and J.A. Hersey, Int. J. Pharmaceutics, 12, 113 (1982).
22. M. Çelik, Drug Dev. & Ind. Pharm., 18, 767 (1992).
23. M.S. Church and J.W. Kennerley, J. Pharm. Pharmacol., 35, suppl. 43P (1983).
24. J.M. Paddon and A.D. Wilson, J. Dent., 4, 183 (1976).
25. J.C. Kerridge and J.M. Newton, J. Pharm. Pharmacol., 38, suppl. 79P (1986).
26. S. Spinner, F.P. Knodson and L. Stone, J. Res. Nat. Bur. Stand. Eng. Instr., 1, 39 (1963).
27. P. York, Int. J. Pharmaceutics, 14, 1 (1983).
28. A.G. Mitchell and G.R.B. Down, Int. J. Pharmaceutics, 22, 337 (1984).
29. R. Huttenrauch, Acta Pharm. Technol., suppl. 6, 55 (1978).
30. M. Friesen, H.M. Burt and A.G. Mitchell, J. Pharm. Pharmacol., 33, suppl. 22P (1981).
31. P.V. Marshall and P. York, Int. J. Pharmaceutics, 67, 59 (1991).
32. H. Chan and D.J.W. Grant, Int. J. Pharmaceutics, 57, 117 (1989).
33. M.P. Summers, R.P. Enever and J.E. Carless, J. Pharm. Pharmacol., 28, 89 (1976).
34. M.P. Summers, R.P. Enever and J.E. Carless, J. Pharm. Sci., 66, 1172 (1977).
35. N. Kaneniva, K. Imagawa and M. Otsuka, Powder Technol., 33, 802 (1985).

36. T. Matsumoto, J. Ichikawa, N. Kaneniva and M. Otsuka, Chem. Pharm. Bull., 36, 1074 (1985).

37. S. Kopp, C. Beyer, E. Graf, F. Kubel and E. Doelker, J. Pharm. Pharmacol., 41, 79 (1989).

38. T. Matsumoto, N. Kaneniwa, S. Higuchi and M. Otsuka, J. Pharm. Pharmacol., 43, 74 (1991).

39. F.B. Bowden and D. Tabor, The Friction and Lubrication of Solids, Part II, 2nd Edn., Oxford University Press, London, 1964.

40. M.E. Aulton, Manuf. Chem., 48(5), 28 (1977).

41. K. Ridgway, J. Glasby and P.W. Rosser, J. Pharm. Pharmacol., 23, suppl. 24S (1969).

42. J. Ichikawa, K. Imagawa and N. Kaneniwa, Chem. Pharm. Bull., 36, 2699 (1988).

43. W.C. Duncan-Hewitt and G.C. Weatherly, Pharm. Research, 6, 373 (1989).

44. W.C. Duncan-Hewitt and G.C. Weatherly, J. Pharm. Sci., 79, 147 (1990).

45. K. Marshall, in "Theory and Practice of Industrial Pharmacy", Edited by L. Lachman, H. Lieberman and J. Kanig, 3rd Ed., Lea and Febiger, Philadelphia, p.66 (1986).

46. E. Shotton and J.E. Rees, J. Pharm. Pharmacol., 18, suppl. 160S (1966).

47. E. Shotton and N. Harb, J. Pharm. Pharmacol., 18, 175 (1966).

48. M.A. Shah and R.G. Wilson, J. Pharm. Sci., 57, 181 (1968).

49. J.E. Rees and E. Shotton, J. Pharm. Sci., 60, 1704 (1971).

50. J.E. Rees and J.A. Hersey, Pharm. Acta Helv., 47, 235 (1972).

51. E.T. Cole, P.H. Elworthy and H. Sucker, J. Pharm. Pharmacol., 27, suppl. 1P (1975).

52. Z.T. Chowhan, Drug Dev. & Ind. Pharm., 5, 41 (1979).

53. K.A. Khan, P. Musikabhumma and J.P. Warr, Drug Dev. & Ind. Pharm., 7, 525 (1981).

54. A.B.Bangudu and N. Pilpel, J. Pharm. Pharmacol., 37, 289 (1985).

55. C. Ahlneck and G. Alderborn, Int. J. Pharmaceutics, 54, 131 (1989).

56. C. Ahlneck and G. Alderborn, Int. J. Pharmaceutics, 56, 143 (1989).

57. C. Ahlneck and G. Alderborn, Int. J. Pharmaceutics, 73, 249 (1991).

58. L.C. Li and G.A. Peck, J. Pharm. Pharmacol., 42, 272 (1990).

59. K. Uzunarslan and J. Akbuga, Pharmazie, 46, 273 (1991).
60. H. Ando, M. Ishii, M. Kayano, and H. Ozawa, Drug Dev. & Ind. Pharm., 18, 453 (1992).
61. D.R. Heidemann and P.J. Jarosz, Pharm. Research, 8, 292 (1991).
62. S. Malamataris, P. Goidas, and A. Dimitriou, Int. J. Pharmaceutics, 68, 51 (1991).
63. A.J. Shukla and J.C. Price, Pharm. Research, 8, 336 (1991).
64. J.A. Hersey, G. Bayraktar, and E. Shotton, J. Pharm. Pharmacol., 19, suppl. 24S (1967).
65. A. Marks and J. Sciarra, J. Pharm. Sci., 57, 497 (1968).
66. J.A. Hersey and J. E. Rees, Proceedings of the 2nd Particle Size Analysis Conference, Society for Anal. Chem., Bradford, p.33 (1970).
67. K. Kawakita, Science, Japan 26(3), 149 (1956).
68. R.W. Heckel, Trans. Met. Soc. AIME, 221, 671 (1961).
69. J.T. Fell and J.M. Newton, J. Pharm. Sci., 60, 1866 (1971).
70. B.M. Hunter and D. Ganderton, J. Pharm. Pharmacol., 24, 17P (1972).
71. E. Shotton and B.A. Obiorah, J. Pharm. Pharmacol., 25, suppl. 37P (1973).
72. C. Nyström, J. Mazur, and J. Sjogren, Int. J. Pharmaceutics, 10, 209 (1982).
73. A.M. McKenna and D.F. McCafferty, J. Pharm. Pharmacol., 34, 347 (1982).
74. G. Alderborn and C. Nyström, Acta Pharm. Suec., 19, 147 (1982).
75. R.J. Roberts and R.C. Rowe, J. Pharm. Pharmacol., 38, 567 (1986).
76. N. Kaneniwa, K. Imagawa, and J. Ichikawa, Chem. Pharm. Bull., 36, 2531 (1988).
77. L.W. Wong, N. Pilpel, and S. Ingham, J. Pharm. Pharmacol., 40, suppl. 69P (1988).
78. K.A. Riepma, C.F. Lerk, A.H. deBoer, G.K. Bulhius, and K.D. Kussendrager, Int. J. Pharmaceutics, 66, 47 (1990).
79. P. Nilsson, M, Westerberg and C. Nyström, Int. J. Pharmaceutics, 45, 111 (1988).
80. M. Westerberg, B. Jonsson and C. Nyström, Int. J. Pharmaceutics, 28, 23 (1986).
81. N. A. El Gindy and Magda W. Samaha, Int. J. Pharmaceutics, 13, 35 (1983).
82. P.G. Karehill, M. Glazer and C. Nyström, Int. J. Pharmaceutics, 64, 35 (1990).