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The Effect of Moisture on Powder Flow and on Compaction and Physical Stability of Tablets.

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Introduction

Water vapor pressure in the atmosphere is quantified by the percent relative humidity. The moisture content at which a solid material produces a water vapour pressure equal to that of the surrounding environment is defined to be the equilibrium moisture content (EMC). The resultant weight gain of the solid is expressed as a percentage of its initial dry weight at a specified temperature and percent relative humidity.

The magnitude of the EMC depends on the percent relative humidity, temperature, binding site

energy, surface area and the nature of the material. Certain materials have a low EMC such as non-porous talc, and kaolin. Conversely, organic sugars, hydrogen bonding polymers and crystal hydrates have high a EMC. The EMC of starch, alginic acid, and tragacanth was reported to increase with increased percent relative humidity, but remained unaffected by increases in temperature (1). In contrast, increases in temperatures allowed the formation and deliquescence of hydrates to occur at lower percent relative humidity (1). However, lactose did not show deliquescence and its EMC increased only slightly even at 50°C and 100 % relative humidity (1).

The surface area of material also affects its EMC. Fine particle sizes of both sucrose and sodium chloride had higher EMC values compared to the coarse particles of these materials (2). Most of the 4.8% of the moisture content usually present in microcrystalline cellulose is within the porous structure of its particles. The internal surface area represents 95% of the surface area of the microcrystalline cellulose particle that interacts with water vapor in the atmosphere (3).

Moisture in solids exists in several states. The adsorbed water vapor can become bound in the form

of water of crystallization, for example, in the crystal hydrates of inorganic salts such as dibasic calcium phosphate dihydrate, and in organic sugars (lactose monohydrate). When the moisture is present in excess, as in the hygroscopic and deliquescent states, the water is said to exist in the unbound state.

In amorphous solids, and in polymers such as starch and acacia, sorption of water proceeds beyond that required to satisfy all external particle surface area. Sorption of moisture also occurs within the amorphous solid, with the result that the mobility of moisture increases from tightly bound state to solvent like state. This is due to the lowering of the glass transition temperature by the moisture with the consequent increase in the free volume of individual molecules.

Effect Of Moisture On The Flow Of Powders.

The two fundamental forces that can affect the flow of powders are cohesion and friction. Cohesion is the mutual attraction, and resistance to seperation of contacting powder particles of a indentical material. Friction is the resistance exerted by one particle against the motion of another

particle at the points of contact. The frictional forces act at a tangent to the contact point surface. The frictional force increases as the true (microscopic) contact area and as the average stress required to shear cold-welded junctions that form between contacting asperities of particles increases. The adsorbed moisture film lubricates the particles, and possibly prevents to some degree the cold welding of asperities, and thereby reduces the frictional force that opposes the relative motion of the particles.

Cohesion in dry powder is a function of van der Waals forces, electrostatic forces and mechanical interlocking. The van der Waals forces increase as the particle diameter decreases. The electrostatic forces are influenced by the particulate nature, shape and the particle size distribution. Mechanical interlocking is a macroscopic phenomenon. It is more pronounced with particles of smaller size, which have a more irregular surface relative to diameter. Cohesion in moist powder involves liquid bridges and may also involve solid bridges, between particles. The liquid bridges connections depends on the percent of water and its distribution. The contributing factors are interfacial tension and capillary

pressure. If the number of solid bridges increases it can result in increased cohesion and aggregation, and ultimately formation of a hard cake. Caking is the state in which the powder cannot be moved by vigorously shaking or tapping of the container.

A parameter known as tensile strength of a powder bed, is obtained from measurements of the shear strength of a packed powder bed, with a shear cell. The influence of moisture content on the flow properties of powders has also been quantified by tensile strength values. Factors that influence tensile strength of powder bed include the nature of the material, percent moisture, particle size and the material packing density. Moisture significantly influenced the tensile strength of powders by formation of liquid bridges (4-6). At higher moisture content and at higher packing densities liquid bridges may progress from pendular to funicular bonds (4-6). Although the packing density of fine powder is less than that of coarse powder, the tensile strength of dry fine powder is greater than that of dry coarse powder. This is because of the greater number of contact points of fine powder particles (greater surface irregularity relative to diameter). This makes the particle-particle interaction forces greater

than the mobilizing gravitational force. For coarse particles gravitational force exceeds interaction forces, leading to greater mobility (5,6).

Increased packing density has been shown to increase the tensile strength for porous and non-porous, and also for cohesive and non-cohesive, powders (4-6). The nature of material and its particle size were important factors that influenced the tensile strength of powders. For a porous and cohesive powder (calcium phosphate), tensile strength was not changed because the moisture entered the intraparticulate voids and was therefore unable to accumulate on external surface to influence interparticulate forces by formation of liquid bridges (4). A non-porous and non-cohesive powder, the coarse fraction (32-75 um) of sodium chloride (5,6), showed an increase in tensile strength with increase in moisture content up to about 4% because of the increase in the number of liquid bridges initially at points of actual contact (lower percent moisture) and eventually at points of near contact (at 4 percent moisture). Beyond a certain moisture content, the number of liquid bridges of both types remain constant. The forces of attraction of the liquid bridges at actual contact points are more powerful

than at near contact points. However, with further increase in moisture content, the tensile strength reached a plateau because of the balance between increased net attractive forces at points of near contact and decreased attractive forces at points of actual contact, as the dimension of liquid bridges at points of actual contact increased (4,5). Therefore, an increase in moisture content can be expected to decrease the powder flow of both non-porous and non-cohesive materials.

With non-porous and cohesive powder such as fine sodium chloride particles there are more potential sites of contact compared to coarse particles (5,6). A small initial increase in moisture content raised its tensile strength even further, due to increased particle-particle interactions. The combined effects of the number and attractive forces of the liquid bridges are similar as with coarse sodium chloride particles. However, with further increase in moisture content the particle-particle interaction decreased and became insignificant. As a result, the tensile strength exponentially decreased to a low level plateau value (5,6). Therefore, increase in moisture cannot be expected to help improve the flow properties of already cohesive

powder. Excessive moisture will further increase the tensile strength and may lead to caking of the powder. Caking has been observed at high percent relative humidity with several commonly used powder excipients including starch (2,7,8). The occurrance of caking was suppressed by the addition of 0.25 to 0.5% magnesium oxide to starch, or by 1.0% of magnesium oxide to sugars and salts (2,5). It was suggested that the fine plate shaped magnesium oxide particles adhered to the surfaces of caking material by van der Waals and electrostatic forces and that their presence reduced interparticulate cohesion by decreasing the number liquid bridges within caking material (2,8).

Effect of Moisture on Compaction of Powders.

Compaction is a process by which powder particles are brought sufficiently close together so that the bonding forces between them are large enough to produce a strong compact. The necessity for the presence of moisture in formation of strong tablets was indicated by the fact that the crystal hydrates that inherently compressed well did not do so when their water of crystallization was removed e.g. ferrous sulphate heptahydrate (9). Moisture increases the compact strength by increasing the tensile

strength of the powder bed, by increasing the contact area among the particles for bonding, by decreasing the variation of density within the tablet and by the recrystallization effect.

The reduced variation of density within the tablet was mainly attributed to the lubrication of the die walls (which allows a greater fraction of the applied force to be transmitted through the compact onto the lower punch, this is also known as the R value) and only slightly attributed to the lubrication of powder particle surface (which facilitates rearrangement and repacking of particles) (10-12). The adsorbed water film decreases the particle surface energy and thus decreases the adhesion of the tablet to the die wall. In addition, the expressed water film on the die wall during compaction functioned as a low viscosity lubricant (10-12). The increase in lubrication was indicated by the increase in the R values, decrease in the ejection forces and decrease in the forces lost to the die wall (10-12).

Repacking and rearrangement of anhydrous dextrose and dextrose monohydrate increased with increasing percent moisture content as indicated by decrease of <u>in situ</u> porosity and decrease of yield force and by increased compact density (13). This

presumably was due to interparticulate and die wall lubrication effects, and due to plasticizing effect of water, as the moisture content increased (13). With substances like microcrystalline cellulose, the moisture within its pores acts as an internal lubricant and facilitates the slippage and flow within individual microcrystals during compaction (3,14). The moisture facilitates plastic deformation of microcrystals to allow close contact and hydrogen bonding between particles (3,14). The moisture acted as a plasticizer, and thereby reduced the yield point and the elastic recovery during compaction (3,14). Microcrystalline cellulose (14) and also soy protein (15) tablets, when directly compressed, showed increase in hardness as the percent moisture content increased and as the compression force increased until the true density of the material was reached. Either lack of moisture or insufficient moisture is one of the factors responsible for lamination of tablets since the yield force becomes high and the elastic recovery is increased.

With crystalline, water soluble substances such as sodium chloride, the thin adsorbed layers of moisture increase the effective surface area for intimate contact (10-12). The phenomenon of

recrystallization during compression will increase compact strength, when water is present as vapor in the pores of the particles. For anhydrous dextrose, with up to 8.9% moisture content the percent relative humidity is below the critical value of less than 81.3% (RHo), and therefore the moisture is present as vapor in the pores. The water vapor condenses on application of compression force and promotes the formation of a saturated solution which moves to the flaws within the particles or to the particle crystal contact points, mobilized in part by surface tension forces (13). Recrystallization upon decompression in these areas of weakness results in an increase in tensile strength (13).

The presence of "excessive" moisture at moderate to high compression force decreases the compact strength, by decreasing the tensile strength of the powder bed, decreasing the microirregularities of the particles, by hydrodynamic resistance and by increased elastic recovery after ejection when compressed beyond true density.

The tensile strength of dextrose monohydrate tablets decreased with any increase of moisture content (13,16), and the microcrystalline cellulose tablets capped in the presence of excessive moisture

at high compression force (14), because of hydrodynamic resistance, together with increased elastic recovery after ejection. The tensile strength of anhydrous dextrose tablets decreased when made at moderate to high compression force in presence of excessive moisture due to hydrodynamic resistance of the liquid present in the voids of the compact (13).

Excessive moisture also produces the cappillary state of the powder aggregation and thereby the surface tension effect becomes insignificant in maintaining the high tensile strength of the powder bed. The moisture has a solvent effect of eliminating the surface cracks and irregularities in the crystals. This increases the crystals' resistance to fragmentation, and decreases the crystal surface energy, which therefore decreases adhesion between particles. The electrostatic charges of attraction also become dispersed (10-12). The hardness of lactose tablets containing naproxen at low and high compression force decreased as the moisture content increased beyond two percent (17).

Effect of Moisture on Physical Stability.

Physical stability is the study of in vitro changes in a dosage form properties when subjected to

physical stress and time. These in vitro changes may alter bioavailibility and therapeutic efficacy, even though the drug potency and purity appear unaltered.

Major changes in the physical stability of a compact can result from moisture gain and/or moisture loss at different points in time. The sorption of moisture by ingredients of tablets can result in formation of their solution for water soluble substances, with consequent crystal change and/or growth of crystalline substances or can manifest as swelling of polymeric materials.

Moisture Gain.

Changes in tablet appearance (18,19) and increase in tablet volume (14,18,20-23) as a result of moisture sorption was observed with several direct compression excipients. Amorphous or spray dried lactose tablet volume increased monotonously due to hygroscopic swelling at 35% relative humidity and 30°C (21,23). No crystallization of lactose was detected because the amount of water sorbed was not sufficient for making super saturated solution of lactose (21,23). At high percent relative humidity, the amorphous lactose tablet volume expansion was more rapid and extensive and, corresponded to rapid increase in crystallinity as the moisture content

stabilized to a plateau level (21,23). It was suggested that the water liberated from super-saturated amorphous lactose solution was due to decrease in surface area. This liberated water further promoted the formation of supersaturated amorphous lactose solution, and accelerated the autocatalytic crystallization into α-monohydrate and β-anhydrous lactose (21,23). Tablets containing hygroscopic materials such as docusate sodium, magnesium chloride, or potassium acetate and made up of crystalline water soluble excipients e.g. lactose or mannitol, showed crystal growth of these excipients when stored at high percent relative humidity at 37° C for 4 months. The identity of these crystal growths was confirmed by DSC and TLC (18).

The crushing strength of tablets, made from crystalline substances or polymers, which are either water soluble or insoluble, will decrease when exposed to high percent relative humidity. Lactose tablets the with highest initial crushing strength underwent the greatest decrease in hardness, and vice versa, in a linear fashion (24,26). With dibasic calcium phosphate dihydrate, the tablet hardness decrease was greater for tablets with lower initial moisture content compared to tablets with higher initial

moisture content (25). Dibasic calcium phosphate dihydrate tablets made at an initial moisture content of 2.8% showed the least decrease in tablet hardness (25). The decrease in crushing strength of microcrystalline cellulose tablets was directly related to the amount of water sorbed (22).

The effect of moisture sorption on disintegration time depends on whether the tablet material is crystalline or polymeric. The disintegration time of microcrystalline cellulose tablets decreased more rapidly as the amount of sorbed moisture increased and as the exposure period to the high percent relative humidity increased (22). These tablets when evaluated after 202 days had the same hardness, thickness, and percent moisture content but shorter disintegration times, than those tablets evaluated after the 9 days. The change in the tablet internal structure was indicated by the abscence of fragments which disintegrated slowly from the tablets stored for 202 days (22). For tablets that contained lactose only and lactose plus naproxen there was a tendency for the disintegration time to slightly increase (25). For dibasic calcium phosphate dihydrate tablets prepared with an initial moisture content of 1.5 to 3.2% the disintegration time

increased as the period of exposure to high humidity increased (25). For shorter periods of exposure the tablets with initial moisture content of 2.5 to 2.8% seemed to be least affected. However, with a prolonged period of exposure the disintegration time increased regardless of the initial moisture content (25).

After exposure to four humidity levels, the physical stability of the tablets were ranked using the criteria of minimum moisture uptake, minimum increase in volume of tablets and the retention of the maximum hardness and the minimum disintegration times. The excipients dibasic calcium phosphate dihydrate, and both hydrous and anhydrous lactose resulted in more physically stable tablets than did mannitol or monobasic calcium phosphate monohydrate. Sorbitol, dextrose and sucrose gave the least physically stable tablets (20).

The T50% values for dissolution of naproxen from dibasic calcium phosphate increased as the period of exposure to high humidity increased (25). The T50% values of naproxen from dibasic calcium phosphate dihydrate did not increase more significantly in the tablets with higher initial moisture content as compared to lower initial moisture content tablets for

any given period of exposure to the high percent humidity (25). However, only a slight trend towards the decrease in dissolution rate of naproxen at 5 and 15 minutes from lactose tablets exposed to high percent relative humidity occurred (24). The dissolution rate of sodium naproxen at 5 and 10 minutes, from microcrystalline cellulose tablets made with increasing initial moisture content from 3 to 7 % did not significantly change (17).

Moisture Loss.

Moisture loss from tablets containing high initial moisture content will cause recrystallization. The effect of this phenomenon will be discussed in the section below. The crushing strength of microcrystalline cellulose tablets showed only a slight decrease or no change, especially in the abscence of water soluble components (3,14). With dibasic calcium phosphate dihydrate tablets, moisture loss is accompanied by general hardening in the bulk of the tablets (25).

Moisture loss also shortened the disintegration times of the tablets containing microcrystalline cellulose (3,14). The disintegration time of dibasic calcium phosphate

dihydrate tablets remained unchanged for short period of exposure to low relative humidity (25). Prolonged exposure to low percent relative humidity slightly shortened the disintegration time (25).

Moisture Gain Followed by Moisture Loss.

Partial moisture loss from moisture rich tablets results in formation of solid bridges in the form of recrystallized and/or material hardening of polymeric binding materials. The partial moisture loss generally results in an increase in the crushing strength of the tablets (16,24,25,27). As the percent lactose was increased the tablet hardness increased because the lactose recrystallization effect became more pronounced (17). Dibasic calcium phosphate dihydrate tablets softened by exposure to high percent relative humidity were able to regain some of their loss in hardness after storage at low percent relative humidity (25). Almost complete restoration to original tablet hardness was possible when the initial moisture content was 2.8% (25). The strength of crystalline bridges formed is dependent on the recrystallization rate. The recrystallization rate affects the tablet hardness by modifying the size and the numbers of the crystalline bridges formed in the

void spaces. The recrystallization rate is affected by formulation changes that modifies the formulation moisture sorption properties.

The magnitude of hardness increase in lactose containing tablets at a given moisture content depended on the concentration and the type of binder used (17). When the various binders were compared, the celluloses types gave greater increases in hardness compared to either gelatin or povidone. Acacia produced a minimal increase, and starch produced the least increase, in tablet hardness (17). As the amount of the binder was increased, a higher initial moisture concentration in the granulation could be incorporated without getting the severe hardness increases following partial moisture loss. This suggested that the higher binder concentration slowed recrystallization rate of water soluble drug and/or excipients which in turn resulted in formation of fewer crystalline bonds, and hence, the minimal increase in the tablet hardness with partial moisture loss (17,24,27). The greater effectiveness of higher binder concentration in reducing the recrystallization rate is possibly due to increased viscosity which would slow down the rate of diffusion of the dissolved substances to the growing crystal surfaces.

It has been shown that the strength of the crystalline bridges are not dependent on the tablet hardness immediately following compression (24). The lactose based tablets that had been softened by exposure to high percent relative humidity, when exposed overnight to ambient conditions, showed that the hardness increase did not depend on the initial post compression hardness (24). With polymeric materials such as microcrystalline cellulose, recrystallization of water soluble substances may lead to increases in the tablet hardness (17).

The disintegration times of the microcrystalline cellulose tablets did not increase to their original values after partial moisture loss, indicating that the hydrogen bonds were not regenerated (22). For dibasic calcium phosphate dihydrate tablets, previously conditioned at high relative humidity, a single overnight room condition exposure further prolonged the disintegration times, especially if the tablets had very low or very high moisture content at the time of compression (25). For pure lactose tablets, and also for lactose tablets containing naproxen, the recrystallization effect tended to slightly prolong disintegration times (24,28).

The recrystallization effect did not significantly change the dissolution rate of naproxen from lactose tablets with high initial moisture concentration at the time of compression, or which had been exposed to high percent relative humidity, followed by an overnight exposure to ambient conditions (17,24,27), or by change of percent lactose in the formulation (17). Compared to the lactose tablets with an initial moisture content of under 2.3%, the tablets after partial moisture loss, had somewhat lower percent of naproxen dissolved at 5 minutes compared to their initial value, indicating a lag time (17). The dissolution rate of sodium naproxen and the sodium benzoate from the microcrystalline cellulose tablets remained rapid and unchanged (17). Modification of recrystallization rate by the presence of different binders had no effect on salicylic acid T50% dissolution from lactose containing tablets (27). The dissolution rate of naproxen from dibasic calcium phosphate dihydrate tablets after partial moisture loss remained close to their elevated T50% values as obtained after exposure to high percent relative humidity (24,25). In summary, the effect of moisture gain is similar to partial moisture loss in slowing the dissolution rate

of naproxen from dibasic calcium phosphate dihydrate tablets.

Conclusions.

Powder flow properties are affected by numerous factors. In general, the presence of moisture tends to decrease the flow of the powders by increasing their tensile strength. The adsorbed moisture film acts as a low viscosity lubricant during compaction, thereby promoting uniform density within the tablets and decreasing the adhesion of the tablets to the die wall. In addition, the plasticizing effect of moisture on amorphous and polymeric materials, and the recrystallization effect with some crystalline materials contributes to formation of a strong tablet. Conversely, excessive moisture decreases the tablet strength by decreasing the powder tensile strength, increasing both elastic recovery and hydrodynamic resistance. Physical stability of the tablets is significantly altered by moisture gain, moisture loss and partial moisture loss. The effects observed are largely dependent upon the formulation.

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