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The influence of moisture content on the consolidation and compaction properties of paracetamol

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Summary

The influence of moisture content on the consolidation and compaction characteristics of paracetamol has been studied. Compression speed, mean yield pressure, relative powder density (D_0), tablet crushing strength and capping pressure were used as the basis of the investigation. At all speeds of compression, mean yield pressure decreased with increasing moisture content especially up to 6% w/w, due to the plasticizing effect of moisture on the paracetamol powder. The relative density of the paracetamol tablets increased with moisture content due to interparticulate and die wall lubrication effects of the moisture forming surface films on the paracetamol particles, which smooth surface microirregularities and so reduce frictional forces and promote particle rearrangement and slippage. Increasing percentages of moisture up to 6% w/w increased tablet crushing strength, whilst higher moisture contents of 8% w/w significantly reduced compact strength. The initial increase in compact strength was likely to be due to the hydrodynamic lubrication effect of moisture, which promotes compaction force transmission and formation of strong hydrogen bonds. The subsequent decrease in tablet strength with moisture content above 6% w/w can be ascribed to hydrostatic resistance of excessive moisture in the void spaces, which reduces particle-particle contact area, surface energy and corresponding adhesive forces. The capping pressure of the paracetamol compacts increased with moisture content up to 6% w/w, probably due to the formation of strong interparticulate hydrogen bonding, which reduces particle-particle separation. The subsequent decrease in capping pressure at 8% w/w moisture content can be attributed to bond weakening as a result of the disruption of particle-particle bonds by an excess of moisture.

Introduction

The presence of moisture in pharmaceutical powders can play a significant role in the consolidation properties and often produces changes in flow properties particularly after storage. Occasionally moisture is added deliberately in order to produce a cohesive mass suitable for further processing. Moisture can be present in powders in different physical forms; as adsorbed monolayers or multilayers on the particle surfaces, as condensed water on the surface, as physically absorbed water within the particles or as strongly bound chemisorbed water. The presence and distribution of moisture in the above forms will depend considerably on the chemical nature of

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the particulate material, its physical properties such as particle size and porosity, and on the ambient relative humidity which determines the equilibrium moisture content (York, 1981; Khan and Pilpel, 1987; Malamataris et al., 1991).

In 1971, Rees and Shotton reported the effects of moisture on the compaction of particulate material using sodium chloride and three liquids; water, decahydronaphthalene and light liquid paraffin. Differences in the behaviour of the three liquids were partly ascribed to the viscosity differences; water was found to exert a boundary lubricant effect in addition to having hydrodynamic properties. Despite its lower viscosity, water was a more effective lubricant than light liquid paraffin, whilst decahydronaphthalene adversely affected the compaction process.

Eaves and Jones (1972) studied the effects of surface tension on the tensile strength of beds of moist bulk solid and observed that increasing liquid content of a bed of non-porous bulk solid at a fixed state of packing resulted in an increase in tensile strength which either remained constant or decreased depending on whether the material possessed inherent tensile strength when dry. Lowering the surface tension of the liquid caused a reduction in tensile strength due to a weakening of the pendular bond strength. For a porous, cohesive material, the tensile strength was found to be independent of the liquid content and of the surface tension, ascribed to the liquid becoming located within the intraparticulate pores where it was unable to influence any interparticulate activity.

In a study of the strength of compacts containing moisture, Rees and Hersey (1972) showed that for compacts containing light liquid paraffin or decahydronaphthalene, the strength was determined primarily by the state of consolidation of the compact and this depended on the interrelated effects of die wall lubrication facilitating compaction, interparticulate lubrication opposing consolidation and hydrodynamic resistance to consolidation when the proportion of liquid in the voids exceeded a critical level. An increase in strength due to a surface tension effect of interparticulate liquid bridges was apparent during the initial stages of compaction; moisture decreased compact strength by reducing the strength of interparticulate bonds.

In 1976, Obiorah and Shotton studied the effect of waxes, hydrolysed gelatin and moisture on the compression characteristics of paracetamol and phenacetin. The behaviour of paracetamol or phenacetin and their mixtures with gelatin hydrolysate or water or both exhibited a similarity to a Mohr body. Maximum die wall pressure appeared to be affected by the particle size of the material compressed and also by the additives present.

In 1981, Khan et al. examined the influence of moisture content of microcrystalline cellulose on the compressional properties of some formulations and found that a decrease in moisture content of microcrystalline cellulose reduced its compressibility. It was suggested that the presence of an optimum amount of moisture will prevent elastic recovery by lowering the yield point and formation of bonds through hydrogen bond bridges.

Armstrong and Patel (1986) evaluated the relationship between moisture content and both tablet tensile strength and tablet toughness. An increase in the moisture content of anhydrous dextrose produced a corresponding increase in both strength parameters up to 8.9% moisture, due to a recrystallising effect and increased lubrication. A further increase in moisture content beyond this point produced a marked reduction in both tablet tensile strength and tablet toughness.

Pilpel and Ingham (1988) studied the effect of moisture on the density, compaction and tensile strength of microcrystalline cellulose and related the changes in mechanical properties of microcrystalline cellulose and the tensile strength of its compacts to the way in which water is sorbed into the cellulose structure. The yield pressure was observed to decrease with increasing addition of water, due to the disruption caused by the water of the hydrogen bonds cross-linking the hydroxyl groups on the cellulose chains causing the cellulose to become plasticized.

Li and Peck (1990) studied the effect of moisture content on compression properties of maltodextrin powders obtained at different degrees of hydrolysis of corn starch. An increase in the moisture content of the powder reduced the yield pressure and improved the densification for all five maltodextrins evaluated. Compacts produced by maltodextrins with a lower degree of polymerisation exhibited a greater tensile strength for a given pressure at a moisture content below 8.0%. Further increase in moisture content resulted in a decrease in compact tensile strength.

Giordano et al. (1990) investigated the binding capacities of β-cyclodextrin samples containing different amounts of water employing crushing strength of tablets obtained using a single punch machine as a measure of the cohesive properties of powders. The results clearly indicated a determinant role of adsorbed water on powder compactability.

Malamataris et al. (1991) reported the relationship between moisture sorption and tensile strength of some direct compression excipients using the Young-Nelson and GAB equations, which distinguish different physical forms of moisture. Tensile strength was observed to reach a maximum value and then decrease when moisture content was about double that corresponding to a tightly bound monomolecular layer. The changes in the mechanical characteristics were explained by the combined effect of moisture on the interparticle and intermolecular forces.

It would appear therefore that moisture has a very significant role to play in the consolidation mechanism. The present study aimed to investigate further the influence of moisture on the consolidation and compaction of the poorly compressible drug paracetamol, which is readily prone to capping. The effects of compression speed and moisture content on the mean yield pressure, relative powder density (D_0), crushing strength and capping pressure were evaluated.

Materials and Methods

Materials

Paracetamol B.P powder grade was obtained from Sterling Organics, Northumberland, U.K., apyrogenic water was from Pharma Hameln (GmbH), Germany, whilst magnesium stearate was obtained from BDH Chemicals, Poole, U.K.

Particle size fractions

45–125 μm sieve fractions of paracetamol powder were obtained by sieving the materials through test sieves on a mechanical vibrator (Endecott Ltd, London). The sieved fractions were dried in an oven to constant weight at 110°C.

Addition of moisture

Calculated weights of apyrogenic water from a microsprayer were uniformly distributed throughout the paracetamol samples to yield 0, 2, 6 and 8% w/w moisture content by stirring in a glass bottle attached to an electric motor rotating at 40 rpm for 20 min. The containers were then shaken manually three-dimensionally with simultaneous rotation about the axis and were subsequently sealed in air-tight polyethylene bags, placed in a dry desiccator and compressions were completed with a minimum of delay.

Compression

Compression was carried out using The Liverpool School of Pharmacy Modified High Speed Compaction Simulator (ESH Testing Ltd, Brierly Hill, West Midlands, U.K.), fitted with 12.5 mm flat-faced punches. A sawtooth time-displacement profile was used to control both upper and lower punches. Four tablets were produced at compression speeds from 24 to 150 mm/s. 500 mg constant weight was maintained for all the samples, and each tablet was compressed to a maximum compaction force of 20 kN. The die wall was cleansed with acetone and prelubricated with 4% w/v magnesium stearate in carbon tetrachloride before each compression.

During compression, upper punch load and punch separation were monitored to an accuracy of ± 0.05 kN and ± 12 μm, respectively (Bateman, 1988a,b). The compression data were manipulated in a manner identical to that described earlier (Garr and Rubinstein, 1991b).

Tablet crushing strength

Tablet crushing strength was determined from the force required to fracture the compacts on a motorised tablet hardness tester (Schleuniger, Model 2E, Switzerland). Crushing strength was employed instead of tensile strength because it was not possible to obtain idealised diametral tablet fracture as result of the fragile nature of the compacts. Tests were carried out 2 h after ejection.

Determination of capping pressures

Paracetamol tablets with varying moisture contents were made at a constant speed of 43 mm/s at varying compression pressures. The capping pressure at each moisture content was determined by close visual examination of the compacts on ejection for horizontal striations.

Results and Discussion

The presence and distribution of moisture will depend on the chemical nature of the particulate material, its physical properties such as particle size and porosity and on the ambient relative humidity. Fig. 1 illustrates schematically the interaction between paracetamol and moisture at a neutral pH. The addition of moisture to paracetamol will be expected to result in the formation of strong hydrogen bonds from the hydroxyl group and weak hydrogen bonds from the amino component. The chemical structure, however, will remain unchanged, because spontaneous hydrolysis is extremely negligible. Paracetamol is known to manifest maximum stability at an approximate pH of 5–7 and is highly stable in aqueous solution. Its pH-rate profile reveals specific acid and specific base catalysis with the maximum stability in the pH range 5–7 (Koshy and Lach, 1961; Connors et al., 1979; Malamataris et al., 1991).

At all compression speeds, an increase in moisture content resulted in a marked reduction in the mean yield pressure of paracetamol (Fig. 2). This indicates that the presence of moisture

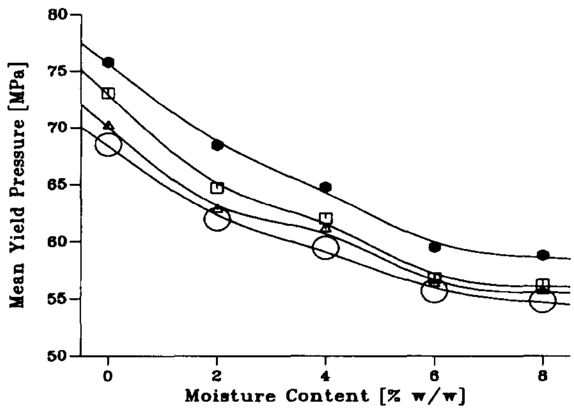

Fig. 2. Influence of moisture content on the mean yield pressure of paracetamol compacts at varying speeds of compression; (○) 24.0, (△) 43.0, (□) 60.0, (●) 150 mm/s.

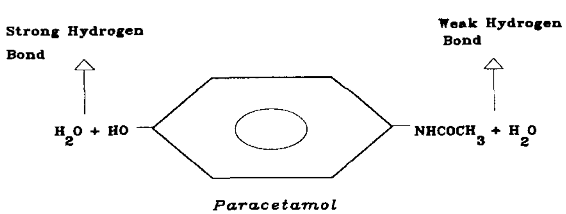

Fig. 1. Paracetamol/moisture interaction at neutral pH.

especially up to 6% w/w enhanced the plastic deformation of the powder under compression by acting as an internal lubricant. There was no significant difference in the mean yield pressure values at 6 and 8% w/w moisture content, indicating that 6% w/w moisture content may be adequate for optimum plasticizing influence of moisture on paracetamol powder. As found in earlier work (Garr and Rubinstein, 1991a), increasing compression speed increases mean yield pressure.

The relative density (D_0) values obtained from the Heckel analysis give an indication of the extent of particle rearrangement during compaction. The relative density at all compression speeds increases with moisture content (Fig. 3). This presumably is due to interparticulate and die wall lubrication effects as a result of the formation of a moisture film on paracetamol particle surfaces, which smooth surface microirregularities and so reduce frictional forces and promote particle rearrangement and slippage during the densification phase of compaction (Heckel, 1961; Pilpel and Ingham, 1988; Malamataris et al., 1991).

Fig. 4 summarises the relationship between moisture content and crushing strength of paracetamol compacts at compression speeds in the range 24–60 mm/s. Increasing moisture content up to 6% w/w, increased compact strength, whilst a higher moisture content of 8% w/w resulted in

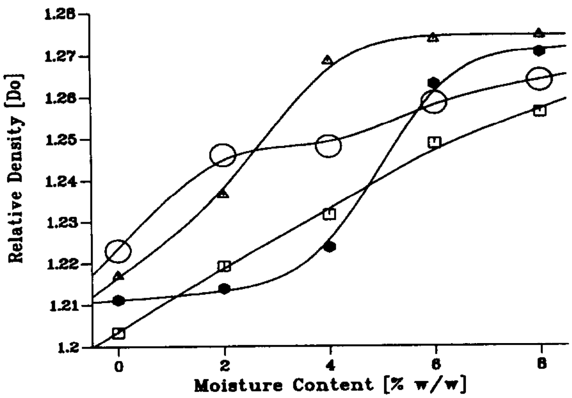

Fig. 3. Effect of moisture content on the relative density (D_0) of paracetamol compacts at varying speeds of compression: (○) 24.0, (△) 43.0, (□) 60.0, (●) 150 mm/s.

a marked reduction in tablet strength. The initial increase in tablet strength with increasing moisture content up to 6% w/w is believed to be due to the hydrodynamic lubrication effect of moisture which increases force transmission from the upper to the lower punch, facilitating greater powder consolidation. In addition, it is thought that the improved plastic deformation resulting from increased moisture content promotes interparticle contact and produces hydrogen bonding.

The subsequent decrease in crushing strength with moisture content above 6% w/w may be ascribed to hydrostatic resistance of excessive moisture in the void spaces. This reduces the particle-particle contact area, particle surface irregularities and particle surface energy and hence reduces the forces of adhesion, leading to bonds disruption. The observed decrease in compact strength at higher moisture contents can also be associated with the high relative density of paracetamol compacts as shown in Fig. 3. Further compaction might have exceeded the limiting density, causing elastic rebound. High moisture contents may also lead to a significant moisture squeeze out onto the particle surface, so reducing interparticle bonding and thereby increasing elastic recovery (Khan et al., 1981; Li and Peck, 1991; Malamataris et al., 1991).

In a previous work, Garr and Rubinstein (1991a) observed that the capping pressures of paracetamol decreased with increasing speed of compression, with the corresponding hardness being less than 1.50 kp, showing that paracetamol is inherently poorly compressible. In the present study, the incorporation of up to 6% w/w moisture at a compression speed of 24 mm/s was found to improve tablet strength to 3.30 kp, double the strength of compacts with no moisture present.

The capping pressure increased with moisture contents up to 6% w/w and there then followed a decrease at 8% w/w moisture content (Fig. 5). This appears to correlate with the relationship between moisture content, yield pressure and compact strength. Paracetamol compacts with up

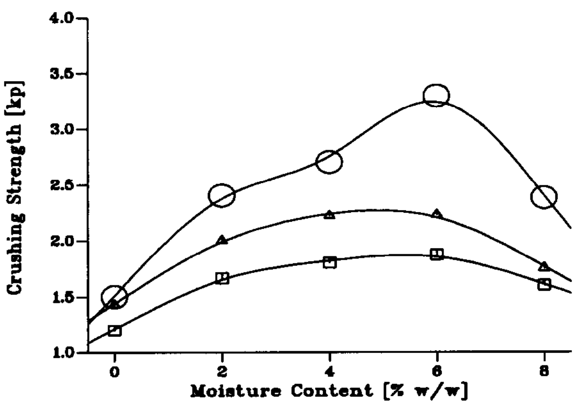

Fig. 4. Relationship between moisture content and crushing strength of paracetamol compacts at varying speeds of compression: (○) 24.0, (△) 43.0, (□) 60.0 mm/s.

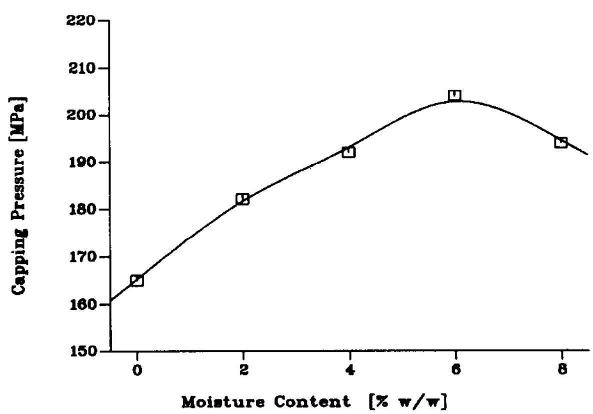

Fig. 5. Capping pressure and moisture content of paracetamol compacts at a compression speed of 24.0 mm/s.

to 6% w/w moisture content were found to have a higher capping pressure due to the presence of the moisture facilitating the formation of strong interparticulate hydrogen bonding. The subsequent decrease in capping pressure at 8% w/w moisture content may be due to the weakening of the intraparticle bonds as a result of the disruption of molecular forces and greater separation of the paracetamol particles by excess moisture.

Conclusion

A study of the influence of moisture content on the consolidation and compaction properties of paracetamol has been performed. The mean yield pressure was observed to decrease with increasing moisture content due to the overall plasticizing effect of moisture, whilst relative powder density increased due to the lubrication effects of moisture smoothing surface microirregularities and so reducing frictional forces.

Increasing moisture contents up to 6% w/w progressively increased compact strength due to the hydrodynamic lubrication effects of moisture promoting optimum transmission and utilisation of compaction force and the formation of strong hydrogen bonds. A higher moisture content of 8% w/w decreased tablet strength due to the hydrostatic resistance of the excess moisture in the void spaces which reduces particle-particle contact areas, surface energy and adhesive forces. The capping pressure similarly increases with moisture content up to 6% w/w as the surface molecular role of moisture promotes strong hydrogen bonding.

It seems from this study that the compressibility of paracetamol powder is strongly determined by the level of moisture present during consolidation and that a moisture content of 6% w/w produces tablets with optimal crushing strength, relative density and capping pressure. The study further demonstrates how moisture must be optimised in a formulation to achieve good powder compressibility.

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