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The effect of moisture on the properties of ibuprofen tablets

A. Nokhodchi [a], M.H. Rubinstein [a,*], H. Larhrib [b], J.C. Guyot [b]

[a] *School of Pharmacy, Liverpool John Moores University, Liverpool L3 3AF, UK*
[b] *Faculte de Pharmacie, Lille, France*

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Abstract

The crushing strengths of ibuprofen tablets produced at compression speeds ranging from 15 to 240 mm/s with varying moisture contents 24 h after ejection have been investigated. Increasing moisture content up to about 2.5% progressively increased compact strength probably due to the hydrodynamic lubrication effects of moisture promoting optimum transmission and utilisation of compaction force and the formation of a moisture film around the drug. This moisture film, which was tightly bound, could be regarded as a part of the surface molecular structure of the particles and facilitated the formation of inter particle hydrogen bonding. This bonding produced an increase in the van der Waals forces and so smoothed out the surface microirregularities and reduced interparticle separation. At higher moisture contents beyond 3.5% w/w, a decrease in tablet strength was observed attributed to hydrostatic resistance of the excess moisture in the void spaces producing force transmission which in turn reduces particle-particle contact areas, surface energy and adhesive forces. It was found that compressibility of ibuprofen powder was strongly determined by the level of moisture present during consolidation and that a moisture content of 1–3.5% w/w at the slowest compression speed of 15 mm/s and a compression force of 10 kN produced tablets with optimal crushing strength and minimum capping.

Keywords: Ibuprofen; Compression force; Moisture content; Compression speed; Capping tendency; Crushing strength

1. Introduction

Many parameters have been shown to exert an effect on the compaction process. The identification and quantification of these compaction parameters is of great importance during manufacture where the production of a uniform product is essential. One of the most important parameters is moisture. The presence of moisture in pharmaceutical powders can play a significant role in their consolidation properties (Shotton and Rees, 1966; Chowan and Palagyi, 1978; Chowan, 1980). The capping pressure of paracetamol has been observed to decrease with increasing speed of compaction, with the corresponding hardness being less than 1.5 Kp. This indicated that paracetamol is inherently poorly compressible (Garr and Rubinstein, 1991). The incorporation of up to 6% w/w moisture at a compression speed of 24 mm/s was found to

* Corresponding author.

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improve tablet strength to 3.3 Kp, double the strength of compacts with no moisture present. The capping pressure progressively increased with moisture contents up to 6% w/w and there then followed a decrease beyond 8% w/w moisture content (Garr and Rubinstein, 1992). An increase in compact density and a corresponding reduction in tablet porosity have been shown to increase the tensile strength for porous, non-porous, cohesive and non-cohesive powders (Eaves and Jones, 1972a,b,c). The characteristics of the material and its particle size are also important factors that influence the tensile strength of a powder. Khan and Pilpel (1987) examined the effect of moisture concentration on the compression properties of Avicel. The first 3% of moisture was found to be internally chemisorbed by the particles. This water was strongly bound by hydrogen bonds to the hydroxyl groups in the cellulose structure and consequently the water was not available on the particle surfaces, so preventing it from contributing to the bonding forces and hence to the strength of the bed. Higher moisture concentrations resulted in the formation of pendular bonds on the particle surfaces which would be expected to contribute to the compact strength.

Armstrong and Patel (1986) found that an increase in the moisture content of anhydrous dextrose produced a corresponding increase in strength parameters up to 8.9% moisture, due to a recrystallising effect. Pilpel and Ingham (1988) reported that the yield pressure of Avicel was decreased with increasing addition of water, due to the disruption of hydrogen bonds cross-linking the hydroxyl groups on the cellulose structure. Li and Peck (1990) found out that an increase in the moisture content of the maltodextrins reduced the yield pressure and improved the densification for all five maltodextrins evaluated.

Malamataris et al. (1991) examined the possible correlation between moisture distribution and the mechanical characteristics, such as tensile strength, brittle fracture propensity and yield pressure of compacts produced from some direct compression excipients after storage at various environmental relative humidities. They found that the tensile strength reaches a maximum value and then begins to decrease when the moisture content is about double that corresponding to a tightly bound monomolecular layer. Shukla and Price (1991) evaluated the effect of moisture content on compression properties of a directly compressible high beta-content anhydrous lactose. An increase in moisture content of the lactose resulted in a reduction in hardness of the tablets and increased pressure was required to achieve a specified hardness value. Heckel plots obtained from the compression data of the diluent were linear for all moisture contents. Yield pressure calculated from the Heckel plots increased at moisture contents greater than that of the original diluent. Differential scanning calorimetry performed on the diluent with 5.13% moisture showed that the added water was bound as the crystalline hydrate. Garr and Rubinstein (1992) reported that the mean yield pressure of paracetamol decreased 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.

Moisture has thus previously been shown to play a significant role in the compaction process, but conflicting evidence is reported as to both the optimum amount of moisture to include in a tablet formulation and how this moisture affects tablet strength. The aim of the present investigation was to examine the effect of moisture content on the consolidation of the poorly compressible and non-porous drug ibuprofen, which is readily prone to capping. The effect of compression speed, compression force and moisture content on the capping and crushing strength were evaluated.

2. Materials and methods

2.1. Materials

Ibuprofen B.P powder grade was obtained from the Boots Co. Ltd (Beeston, Nottingham, UK). Apyrogen water was purchased from Pharma Halmen (GmbH), Germany.

Particle size fractions 45–125 μm of ibuprofen powder were obtained by sieving the materials through test sieves on a mechanical vibrator (Pascal Engineering, UK). The sieved fractions were dried in an oven to constant weight at 50°C (ibuprofen melts at 76°C).

2.2. Addition of moisture

Dried samples of ibuprofen were stored in tared 5 cm diameter petri dishes and exposed to different relative humidities from 5 to 98%. The petri dishes containing the powder were periodically taken out of the humidity chambers and accurately weighed, to determine any moisture pick up. It was found that essentially no moisture increase occurred at relative humidities below 90%. Furthermore, the increase in moisture content after storage for 1 week above 90% R.H. was less than 0.5%. Therefore, for obtaining various moisture contents, calculated weights of apyrogenic water from a microsprayer were uniformly distributed throughout the ibuprofen samples to yield 0, 1, 2.5, 3.5, 5, 7.5 and 10% w/w moisture content. The moist powders were thoroughly mixed in a glass bottle attached to an electric motor rotating at 40 rpm for 10 min. The containers were then shaken manually three-dimensionally with simultaneous rotation about the axis and were subsequently sealed and placed in a dry chamber. Compressions were completed with a minimum of delay.

2.3. Compression

Compressions were carried out using the Liverpool School of Pharmacy Modified High Speed Compaction Simulator (ESH Testing Ltd, Brierley Hill, West Midlands, UK), fitted with 12.5 mm flat-faced punches. The simulator consists of a load frame, hydraulic power pack and electronic control unit. A sawtooth time-displacement profile was used to control both upper and lower punches. The data points of the profile are output at a pre-determined rate via a digital/analogue converter to the servo controller in the main control unit and onto the control valves situated on the load frame. The signal supplied to the valves determines the flow of hydraulic fluid from the power pack through the valves to the actuators. It is this flow of fluid which causes movement of the actuators according to the intended profile. The output rate of the profile may be set to produce compaction rates up to 3000 mm/s and to a maximum compaction force of 50 kN. Four tablets were produced at compression speeds from 15 to 240 mm/s. 400 mg constant weight was maintained for all the samples, and each tablet was compressed to a maximum compaction force of 40 kN. The die wall was cleaned with acetone and prelubricated with 4% w/w magnesium stearate in acetone 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, 1988; Bateman et al., 1989).

2.4. 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 a result of the fragile nature of the compacts. Tests were carried out 24 h after ejection.

2.5. Compression force / crushing strength relationship

The compaction force is likely to affect other characteristics of the tablets. The sensitivity of ibuprofen to changes in compression force and compression speed was determined at five compression speeds (15, 25, 66, 140 and 240 mm/s), by subjecting 400 mg of the ibuprofen to an applied compaction force in the range 5–40 kN and the corresponding crushing strengths of the compressed tablets were determined 24 h after ejection.

2.6. Determination of capping

Ibuprofen tablets were made at various speeds ranging from 15 to 240 mm/s at varying compres-

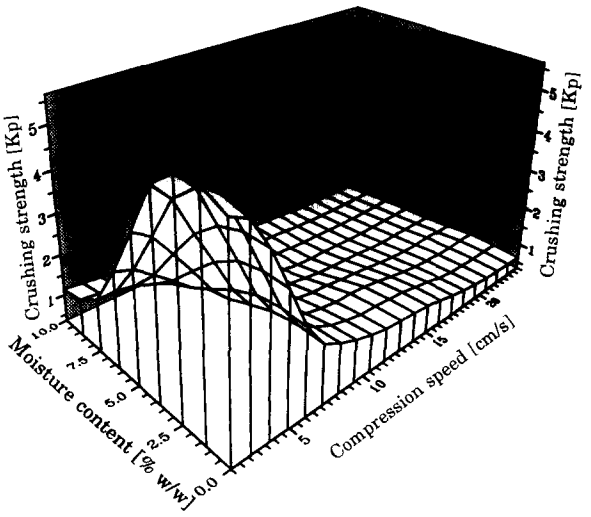

Fig. 1. Relationship between moisture content, compression speed and crushing strength (compression force 10 kN), for 400 mg ibuprofen tablets.

sion pressures and moisture contents as mentioned above. The intensity of capping was assessed visually and the tablets divided into four groups: no capping, low capping, high capping and very high capping. Capping assessment was conducted by observing the finished tablets for horizontal striations.

3. Results and discussion

Ibuprofen was found to consolidate mainly by plastic deformation. The relationship and response surface between moisture content, compression speed and crushing strength is shown in Fig. 1. At all moisture contents an increase in compression speed resulted in a marked reduction in the crushing strength of the ibuprofen tablets. This tends to indicate that time dependant bonding mechanisms contribute to the consolidation of ibuprofen and that ibuprofen is sensitive to the rate of application of the compression pressure. The extent of plastic flow exhibited by ibuprofen during compression was found to decrease as the compression speed increased.

Fig. 2 summarises the response surface between crushing strength, moisture content and compression force at a compression speed of 15 mm/s. Increasing moisture content up to about 2.5% w/w (Fig. 1 and 2), increased compact strength, whereas at higher moisture contents (5–10% w/w) a dramatic reduction in tablet strength occurs. The initial increase in crushing strength of ibuprofen compacts with increasing moisture content up to 2.5% w/w is believed to be due to the hydrodynamic lubrication effect of moisture, which allows a greater fraction of the applied force to be transmitted through the compact on to the lower punch. Since ibuprofen is a non-porous material, an initial increase in moisture content increased its crushing strength, due to increased particle-particle interaction. Consequently the moisture probably improved plastic deformation.

The tensile strength of tablets is mainly determined by the range and magnitude of the van der Waals' forces between the particles and the development of additional bonds formed by plastic deformation, melting of the powder particles or the binder films developed during granulation

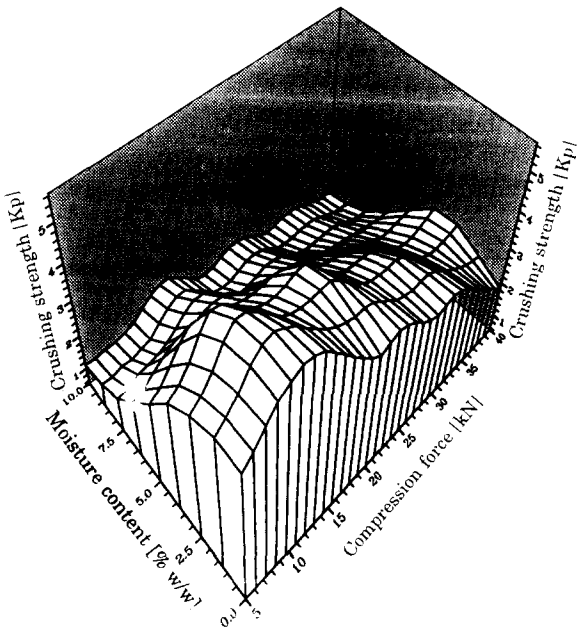

Fig. 2. Relationship between moisture content, compression force and crushing strength (compression speed 15 mm/s), of 400 mg ibuprofen tablets.

(Malamataris and Pilpel, 1983). The above-mentioned observations may constitute evidence that the increase in crushing strength due to moisture content is due to the water forming a 'monomolecular' layer around the ibuprofen particles. This tightly bound water can be regarded as a part of the surface molecular structure of the particles, which facilitates the formation of interparticle hydrogen bonding and/or increases the van der waals' forces, so smoothing out the surface microirregularities and reducing interparticle separation.

The presence of excessive moisture at moderate to high compression forces decreases the compact strength, by decreasing the hydrodynamic resistance and so increasing elastic recovery after ejection (Khan et al., 1981; Li and Peck, 1990; Malamataris et al., 1991). Excessive moisture also produces the capillary state of powder aggregation and therefore the surface tension effect becomes less significant in bringing the particles together in resulting improve bonding.

Ibuprofen exhibited significant sensitivity to changes in compression force at varying moisture contents (Fig. 2). As the force is increased, the crushing strength increases almost linearity up to 10 kN at speeds of 15–240 mm/s (1.5–24 cm/s). A high compaction force and high moisture content may also lead to a significant moisture squeeze out onto the particle surface, so reducing interparticle bonding and thereby increasing elastic recovery and reducing crushing strength. This behaviour is similar to that reported by Rees and Hersey (1972). Khan et al. (1981) also found that sodium chloride compacts containing higher moisture contents had lower strength when compacted at higher pressures.

Another possible explanation for an decrease in crushing strength at high moisture contents is the formation of multilayers of water at the particle surfaces. These layers may disturb or reduce inter molecular attraction forces and thereby reduce tablet strength (Kristensen et al., 1985; Ahlneck and Alderborn, 1989).

The response surface between crushing strength, compression speed and compression force is shown in Fig. 3. As the compression force is increased, the crushing strength increases or remains approximately the same up to 10 kN at speeds of 15–240 mm/s (1.5–24 cm/s). Further increases in compaction force with moisture content (Table 1) resulted in a decreases in tablet crushing strength. This can be ascribed to the possibility that the work associated with compaction above 10 kN is being recovered during elastic relaxation which results in a weakening of the tablet structure. It is interesting to note that tablets prepared at very high pressures which experienced particle fusion due to melting, were in fact weaker than compacts prepared under much lower pressure (Table 1).

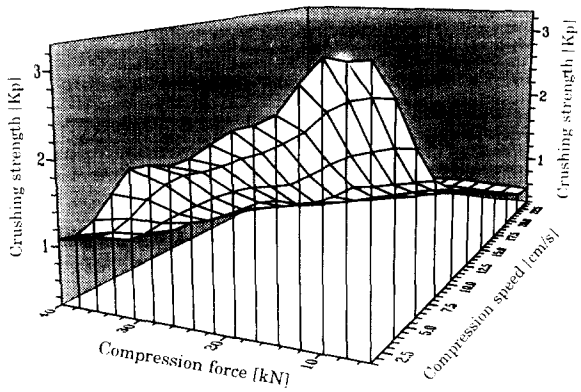

Fig. 3. Relationship between compression speed, compression force and crushing strength (moisture content 0%), of 400 mg ibuprofen tablets.

Table 1
The crushing strength (Kp) of ibuprofen tablets at low pressure (5 kN) and high pressure (40 kN) at varying moisture contents

Moisture content (%)	Crushing strength (Kp) at compression force of	
	5 kN	40 kN
0.0	4.22	1.40
1.0	4.30	2.15
2.5	4.58	3.20
3.5	3.20	2.55
5.0	3.10	2.30
7.5	1.30	1.10
10.0	1.15	0.75

The intensity of capping of ibuprofen tablets appears to increase with an increase in compression speed, and compression force (Table 2). At a high compression speed of 240 mm/s significant capping occurred within the die, particularly at high pressure and high moisture contents. These compression speed related effects are probably due to a combination of factors. Firstly, the reduction of the time available for escape of air from the powder bed may have caused increasing quantities of air to be entrapped within the compacts as the compression speed increased. During decompression the air expands rupturing the compact. The increased compression and decompression rate would effect the stress relaxation and stain recovery of the compact. As the dwell times become shorter the stress relaxation will be reduced and less particle-particle bonds will be formed. Consequently, the compact will be less able to withstand the stresses imposed during strain recovery.

Compacts prepared using high pressures, 40 kN, were of poor quality even at the slowest compression speed with varying moisture content. Compacts showed signs of lamination and sticking. A white flaky film was observed around the upper and lower punch tips after compression. The melting of asperities may be extended in the case of ibuprofen due to its relatively low melting point of 76°C. If the pressure further increases, molten material may be forced to the surface of the tablet and stick to the surfaces of the punches during compression.

The capping tendency of each set of samples (four tablets per set) was visually estimated according to the following scale: 0 = non, 1 = low, 2 = high, and 3 = very high. A mean value was then calculated for the set.

The best tablets were obtained at the slowest compression speed, moisture content between 0 and 3.5% w/w and compression force of 10 kN (Table 2). The capping tendency of ibuprofen tablets was observed to decrease up to 3.5% at the slowest compression speed, but at high moisture content (between 5 to 10% w/w) the intensity of capping of ibuprofen tablets increased (Table 2). Overall, compression speed was the one factor that influenced capping tendency most. Compression speed had a more marked effect on capping than compression force and moisture content. At moisture contents greater than about 3.5% w/w the tendency to cap increased probably due to the weakening of the interparticle bonds as a result of the disruption of molecular forces and greater separation of the ibuprofen particles by excess moisture. In conclusion this study shows that ibuprofen is very sensitive to compression speed, compression force and moisture content. In particular, moisture significantly affects the consolidation characteristics of ibuprofen powder and must be carefully controlled. The extent of consolidation and the bond-

Table 2
Visual assessment of capping tendency of ibuprofen tablets

Experiment 1 [a]		Experiment 2 [b]		Experiment 3 [c]	
Compression force (kN)	Capping tendency	Compression speed (mm/s)	Capping tendency	Moisture content (%)	Capping tendency
5	0.50	15	0.50	0.0	0.50
10	0.25	25	0.75	1.0	0.25
20	0.50	66	1.50	2.5	0.25
30	0.50	140	3.00	3.5	0.25
40	0.75	240	3.00	5.0	0.50
				7.5	1.00
				10.0	1.25

[a] Compression force variable; compression speed, 15 mm/s; moisture content, 0% w/w.
[b] Compression speed, variable; compression force, 5 kN; moisture content, 0% w/w.
[c] Moisture content, variable; compression speed, 15 mm/s; compression force, 5 kN.

ing of particles depends not solely on moisture content but also on the speed of compression and compression force. By careful control of these parameters tablet quality can be optimized.

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