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The relationship between granule growth mechanism, amount of liquid binder added and properties of the wet powder mass determined using a split bed shear tester

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Abstract

The Peschl-split bed shear tester was utilised to study the formation of different liquid states during wet massing for granulation. Using lactose monohydrate as a model bulking agent the threshold between pendular and funicular state was found to be at about 6% (w/w) of liquid binder added to the wet mass, here a 5% colloidal solution of HPMC in water. The upper limit of the funicular state appeared to be at approximately 15% (w/w) of liquid binder. The threshold values obtained from the shear cell measurements did correlate with values obtained from dried granule characteristics such as granule density and compressive Young's modulus determined by Dynamic Mechanical Analysis. The compressive Young's modulus increased with an increasing density of the wet mass during the shear experiments and decreased with an increase in the angle of internal friction. The results suggest that stiffer granules were a result of densification, not the strength of liquid bridge bond formation.

Keywords: Split-bed shear tester; Granule growth mechanisms; Wet granulation

1. Introduction

The majority of prescriptions dispensed by pharmacists are for solid dosage forms such as tablets, capsules or sachets. These are manufactured on an industrial scale involving highly sophisticated machinery and processes. To ensure efficient manufacture fundamental understanding of the processes is essential. The preparation of agglomerates is a key stage, which is difficult to evaluate from a fundamental point of view.

Agglomeration is the formation of powder particle assemblies. Agglomeration can occur spontaneously, but for purposes of dosage form manufacture it is usually forced either by dry or by wet granulation. The formation of wet granules depends, for example, on the particle size of the powder, the viscosity of the liquid binder, the contact angle between binder liquid and solid, and the interfacial free energy (Keningley et al., 1997; Pierrat and Caram, 1997). Three (Newitt and Conway-Jones, 1958) or four (Barlow, 1968) stages of agglomerate growth can be distinguished in the wet granulation process. These are first the pendular state, in which only discrete contact points are formed between liquid and particles. The capillary forces are very small. The funicular state follows and is due to an increased amount of moisture. The network of liquid surrounding the particles is still incomplete, and air

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pockets are present. The capillary forces, however, are large and will reach their maximum value for a defined distance of separation between the particles and defined filling angle. The capillary state is characterised by complete filling of intragranular void spaces with liquid. A concave meniscus has formed connecting the particles at the outside of the agglomerates. The capillary force drops due to increasing disjoining pressure between the individual particles of the agglomerate. If more liquid binder is added, a conversion from the liquid-in-solid into the solid-in-liquid state occurs and an excessive disjoining pressure reduces the capillary forces close to zero. In wet granulation, the amount of binder liquid just below the quantity needed to initiate the capillary state (i.e. an upper limit for the funicular state) is regarded to be optimal (Leuenberger, 1994).

Under manufacturing conditions, the optimum amount of granulation liquid can be found using power consumption measurements (Leuenberger, 1994). On a laboratory scale, the use of a mixer-torque rheometer has been reported (Rowe and Sadeghnejad, 1987). The latter equipment, however, suffers from constructional faults and the torque measured does not readily reflect the formation process of agglomerates during wet granulation. Shear cells (Pilpel, 1971), split bed shear testers (Shah et al., 1995) and split plate tensile testers (Khan and Pilpel, 1986) have also been used to identify the different stages of agglomerate formation during wet massing. According to Pilpel (1971) the graph of the shear strength as a function of the moisture content, when measured on a soil, shows two peaks, separated by a deep trough. It was suggested that the first peak indicates that the granulation liquid has formed agglomerates in the pendular state. The following drop in shear strength to its minimum was attributed to the beginning of the funicular state. As the pores fill increasingly with water, the shear strength again increased first moderately and later steeply. Beyond the second peak all agglomerates were thought to be in the capillary state and further addition of liquid decreased the shear strength due to droplet formation. However, soils are porous materials and can take up large quantities of moisture. The droplet state occurs between 40 and 60% of liquid added. Pharmaceutical powders such as lactose monohydrate are smoothly surfaced and take up considerable less liquid binder. The droplet stage can be reached well below 25% of granulation liquid (Pettersson et al., 1996).

The aim of this work was to study the agglomerate growth of a typical pharmaceutical bulking agent in wet granulation: lactose monohydrate. A novel automated split bed shear tester was chosen to monitor the development of liquid bridges during wet massing. Hydroxypropyl methylcellulose (HPMC) was chosen as granulation liquid. The results were linked to typical granule properties, that is, granule density, granule size distribution and mechanical granule properties, as these are important characteristics to ensure successful processing.

2. Materials and methods

Lactose monohydrate (SorboLac 400, Meggle, Wasserburg, Germany, batch L8298Fr) and HPMC (Colorcon Ltd., Dartford, UK, batch MM8702111E) were used in this study.

A 5% colloidal solution of HPMC in demineralised water was used as granulation liquid. The amount of liquid added to the powder was determined as % w/w of the wet mass. Two hundred fifty grams of powder were placed in a high shear mixer granulator (Vertical granulator, model FM-VG-01, Glatt/Powrex Corporation, Osaka, Japan) and the amount of granulation liquid was added gradually via the pump at a rate of 5 ml/min. The mixer blade speed was set to 500 rev/min, and the cross screw to 800 rev/min.

The wet mass was filled into a 50 cm^3 standard cell body of the Peschl-split bed shear tester (IPT, Vaduz, Liechtenstein) using a standard operating procedure. The wet mass was pre-consolidated with an automatic pre-consolidation bench (IPT, Vaduz, Liechtenstein) for 10 min using a normal load of 50 g/cm^2. Afterwards the shear lid was assembled and the complete cell was transferred to the semi-automated shear tester. A standard operating procedure was used to obtain one yield locus. In addition, the equipment determines the bed density during the shearing process continuously via a displacement transducer attached to the top of the cell. It was found that the maximum bed density was reached during pre-consolidation of the wet mass and did not change during the shearing process. The calculation of the shear parameters was performed with the software provided by the equipment. The whole procedure was replicated three times. The yield loci were all non-linear with the degree of deviation from a straight line progressing with an increase in binder liquid added. Hence, non-linear regression (SPSS 10.0, Woking, UK) was employed to solve the following equation:

$$\tau = B(\sigma + c)^M \quad (1)$$

where τ and σ are the shear stress and the normal load, respectively, and B, c and M are constants. The value of B is the intercept of the non-linear yield locus with the ordinate and hence a measure of the cohesiveness of the wet mass ("cohesion coefficient"). The tangent of the value of M is the non-linear equivalent to the angle of internal friction.

The granules were oven-dried at 60 °C until the residual moisture content was between 4.3 and 4.7% (Sartorius Thermo Control YTC 01L, Sartorius, Göttingen, Germany). The dry granules were subjected to sieve analysis (Endecotts, London, UK) using a root-2 progression of sieves between 63 μm and 1 mm. The granule density was determined using a Helium pycnometer (Quanta Chrome, MVP-1, Quanta Chrome Corp., Syosset, NY, USA). Approximately 3 g were used per measurement. All results are the mean and standard deviation of three replicates.

The compressive Young's modulus for individual 1 mm granules was obtained using a dynamic mechanical analyser (DMA-7, Perkin Elmer, Norwalk, CT, USA) equipped with a 3 mm compression plate. Only static loading was used, and the Young's modulus was obtained from the linear portion of the stress–strain curves. All results are the mean and standard deviation of five replicates.

3. Results and discussion

A maximum of 19% (w/w) of 5% liquid HPMC binder solution could be added to lactose monohydrate without reaching the droplet state. A further increase in liquid binder added led to over-wetting of the powder mass and the wet mass formed one coherent wet

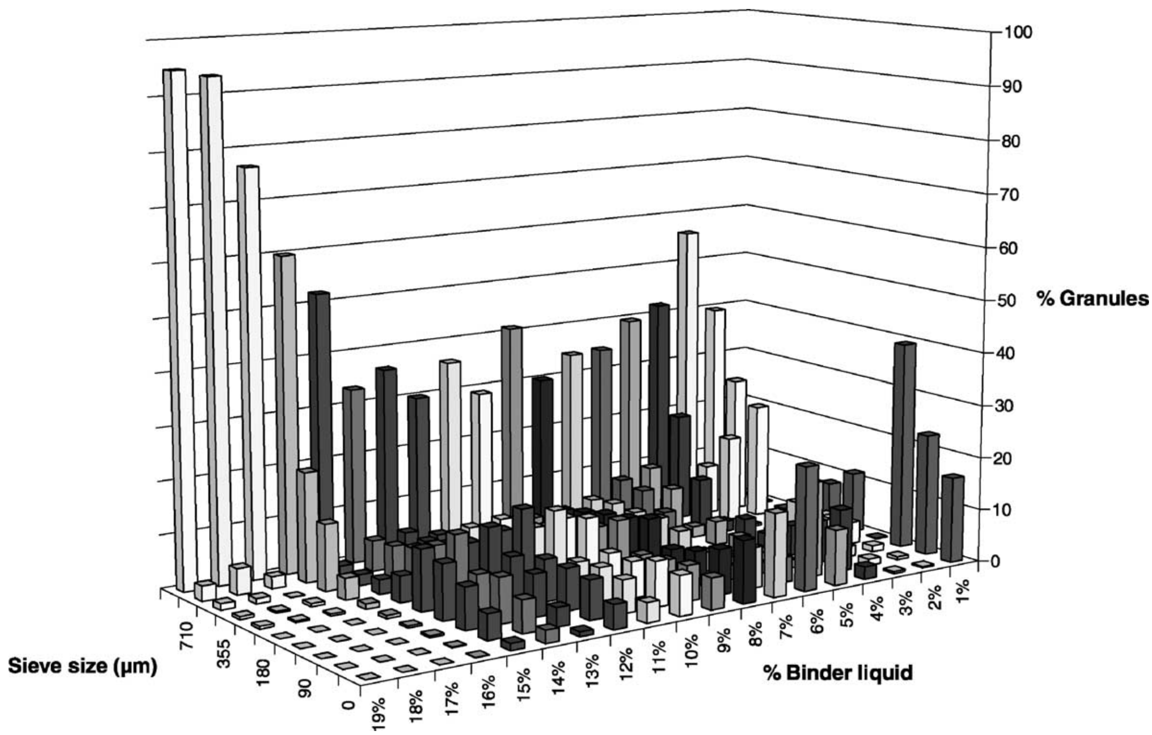

Fig. 1. Particle size distributions of dried granules prepared from lactose monohydrate and 5% HPMC colloidal solution in demineralised water.

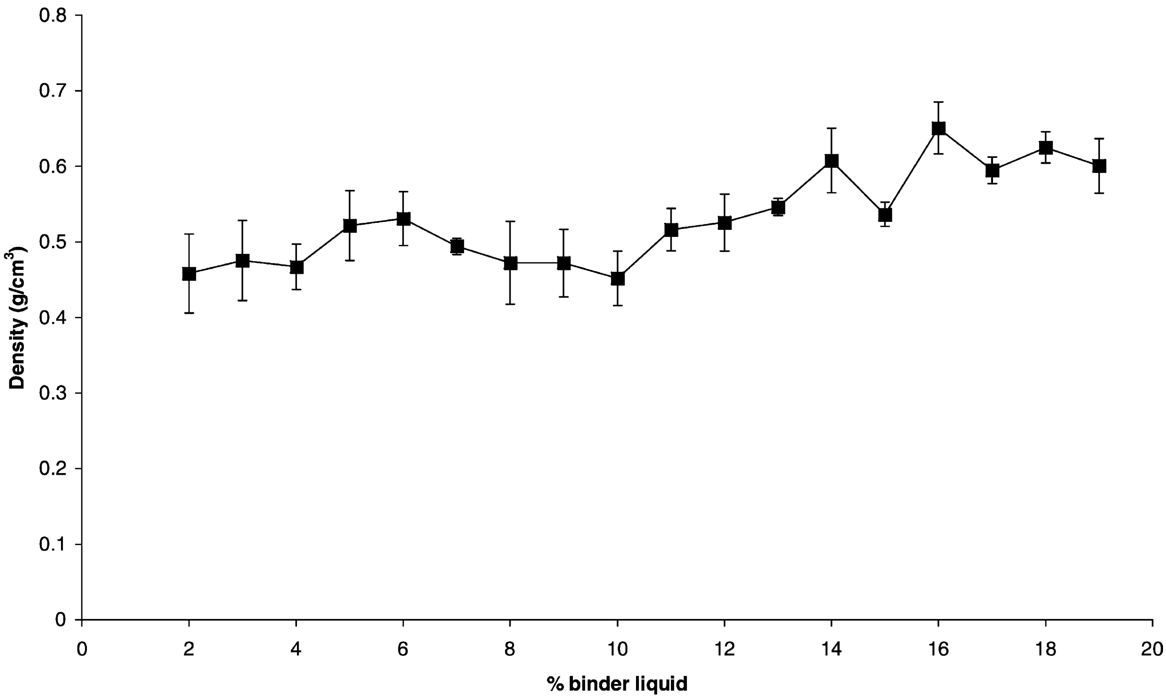

Fig. 2. Increase in dry granule density as a function of the amount of binder liquid added (calculated as % w/w of the wet mass using a 5% HPMC colloidal solution in demineralised water).

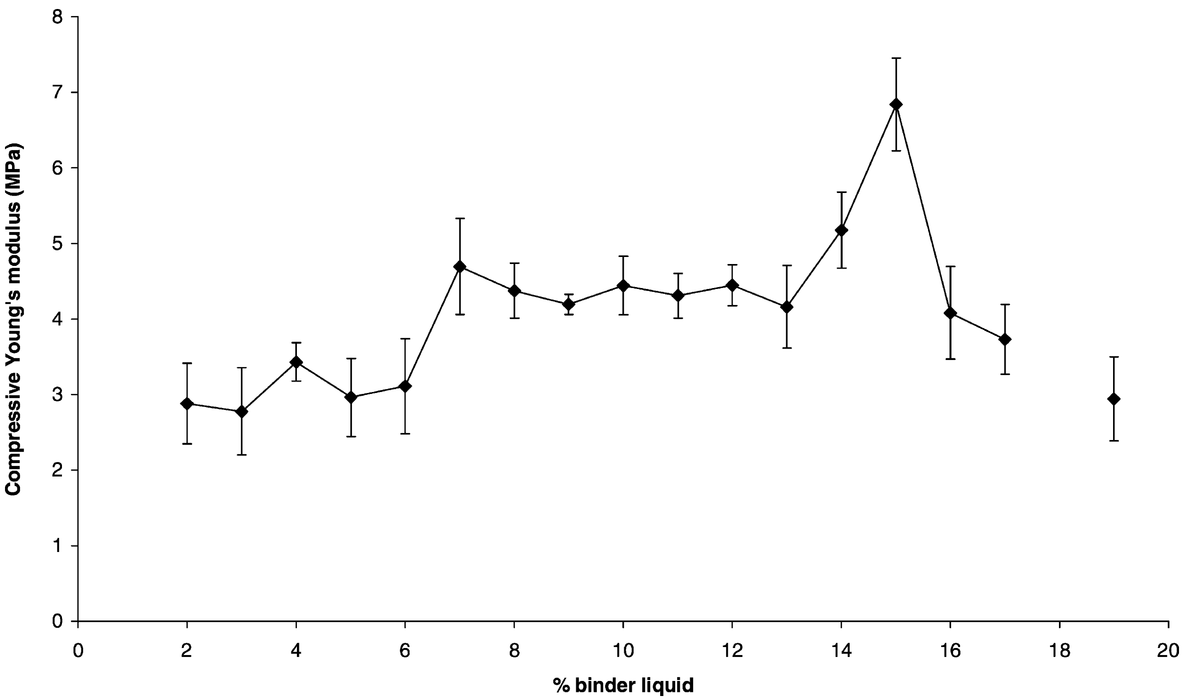

Fig. 3. Compressive Young's modulus as a function of the amount of binder liquid added (calculated as % w/w of the wet mass using a 5% HPMC colloidal solution in demineralised water).

ball inside the mixer. The lactose monohydrate powder employed consisted of particles below 50 μm with an average particle size of 14 ± 8 μm. The particle size increased already adding just 1% (w/w) of liquid binder shifting the mode from 10 to 90 μm. From 5% (w/w) up to 15% (w/w) of liquid binder addition, the mode of the granule size distributions was found at 250 μm. Further addition of liquid binder caused a shift in the modal granule fraction first to 500 μm (16% (w/w)) and then to 720 μm. A comparison of the full size distributions is shown in Fig. 1.

The density of the dried granules is compared in Fig. 2. The density of agglomerates should increase gradually with an increase in granulation liquid (Augsburger and Vuppala, 1997). Although there is an overall trend for an increase in particle density, there appears to be a first peak in density at 5–6% (w/w) of liquid binder, and the density of the granules starts to fluctuate largely above an amount of 14% (w/w) of liquid binder.

The compressive Young's modulus of the dried granules was determined from individual granules as a measure of the mechanical properties of the agglomerates. The smaller the Young's modulus the more elastic are the granules, and any deformation under load, for example, during tabletting, will be accompanied by elastic recovery unless the forces applied are strong enough to cause brittle fracture. In Fig. 3, the compressive Young's modulus is shown as a function of the % w/w of liquid binder added. Initially, the Young's modulus is comparatively small with values varying around 3 MPa. After addition of 7% (w/w) a sharp increase in Young's modulus was observed. Again, values remained fairly constant between 7 and 13% (w/w) approximating 4.5 MPa. The Young's modulus reached its maximum at 15% (w/w) liquid binder and above this quantity dropped down to reach its initial value of approximately 3 MPa at 18% (w/w) liquid binder concentration in the wet powder mass. These results could be indicative of the influence of the state of the wet mass on mechanical properties of granules. They would suggest that the transition between pendular state and funicular state occurs at 6% (w/w) liquid binder, and that the

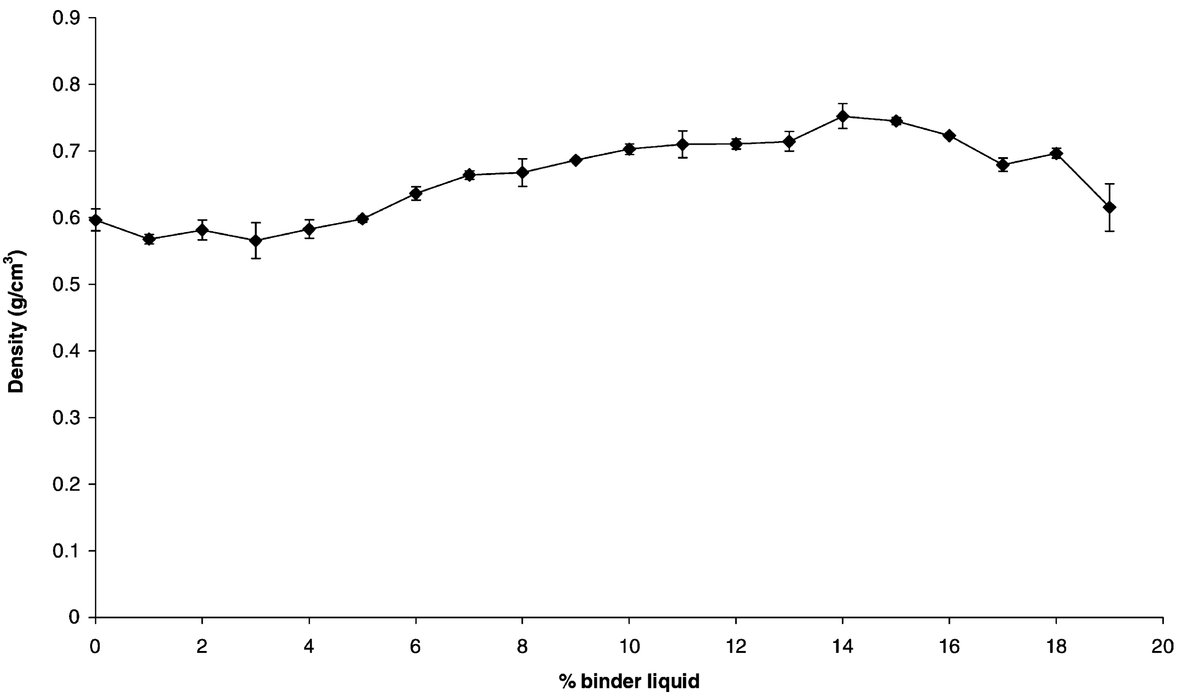

Fig. 4. Packing density of the wet mass in the shear cell during shear testing as a function of the amount of binder liquid added (calculated as % w/w of the wet mass using a 5% HPMC colloidal solution in demineralised water).

funicular state changes gradually into the capillary state between 13 and 15% (w/w) liquid binder in the wet powder mass. The Young's modulus apparently increases stepwise from pendular state to the funicular state. Granules obtained from a capillary state of the wet mass, however, appear to have a rather low compressive Young's modulus.

The split bed shear tester employed in this work permits the observation of the powder bed density during shear. Although all wet mass samples had been consolidated with the same normal load (50 g/cm^2), Fig. 4 shows that the bed density varied from experiment to experiment. From about 5% (w/w) liquid binder the bed density during shear increased gradually, until it reached a maximum value at about 14% (w/w) liquid binder in the wet powder mass. The increase observed could be an indication of the formation of capillary forces of increasing magnitude between the individual particles of the wet agglomerates. The reduction in packing density above 14% (w/w) of liquid binder would hence be a reflection of increasing disjoining forces developing.

The change in angle of internal friction, which is a measure of interparticulate friction during shear, as a function of the amount of liquid binder added is illustrated in Fig. 5. Initially, the values for the angle of internal friction decrease up to a liquid binder concentration of 8% (w/w). Between 8 and 15% (w/w) liquid binder the values of the angle of internal friction remain fairly constant, while above this binder concentration a rapid increase in this shear property occurs. The results imply that the transition from a pendular state to formation of funicular liquid occurs at 8% (w/w) of liquid binder, and the capillary state is reached just above 15% (w/w) of liquid binder in the wet powder mass, confirming the conclusions drawn from the values of Young's modulus (Fig. 3).

The cohesion coefficient, that is, the intercept of the yield locus with the axis of shear stress (ordinate) depends partly on the density of the powder bed in the shear cell. The yield locus is shifted parallel upward or downward with increasing or decreasing powder bed density. Hence, larger fluctuations in this value should be expected. To compare the influence of the packing state of the bed on the cohesion coefficient, Figs. 6 and 7 plot this quantity as a function of the % w/w liquid binder in the wet mass as calculated (Fig. 6)

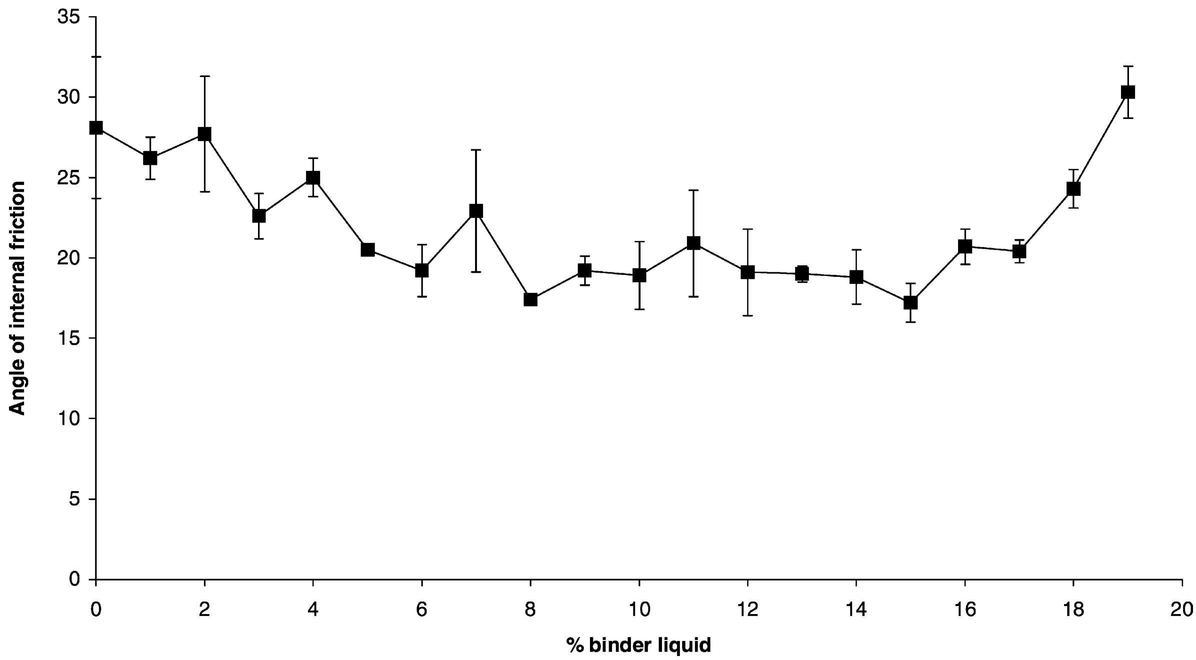

Fig. 5. Angle of internal friction of the wet mass as a function of the amount of binder liquid added (calculated as % w/w of the wet mass using a 5% HPMC colloidal solution in demineralised water).

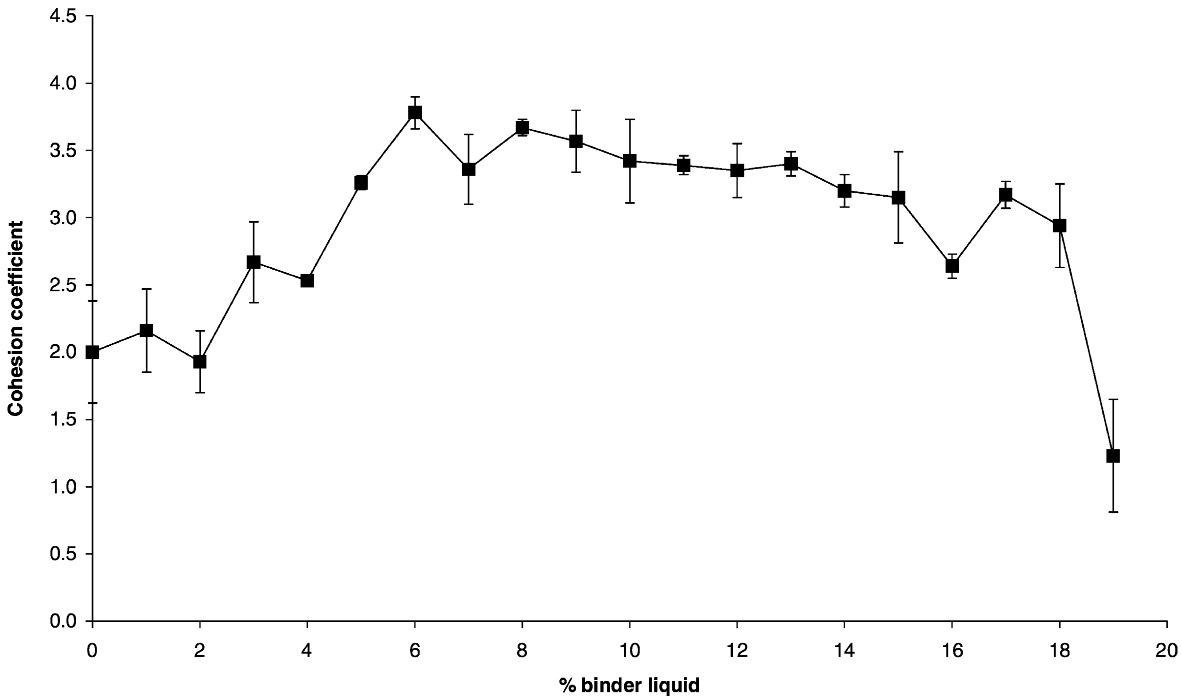

Fig. 6. Cohesion coefficient of the wet mass (original data obtained from non-linear yield locus) as a function of the amount of binder liquid added (calculated as % w/w of the wet mass using a 5% HPMC colloidal solution in demineralised water).

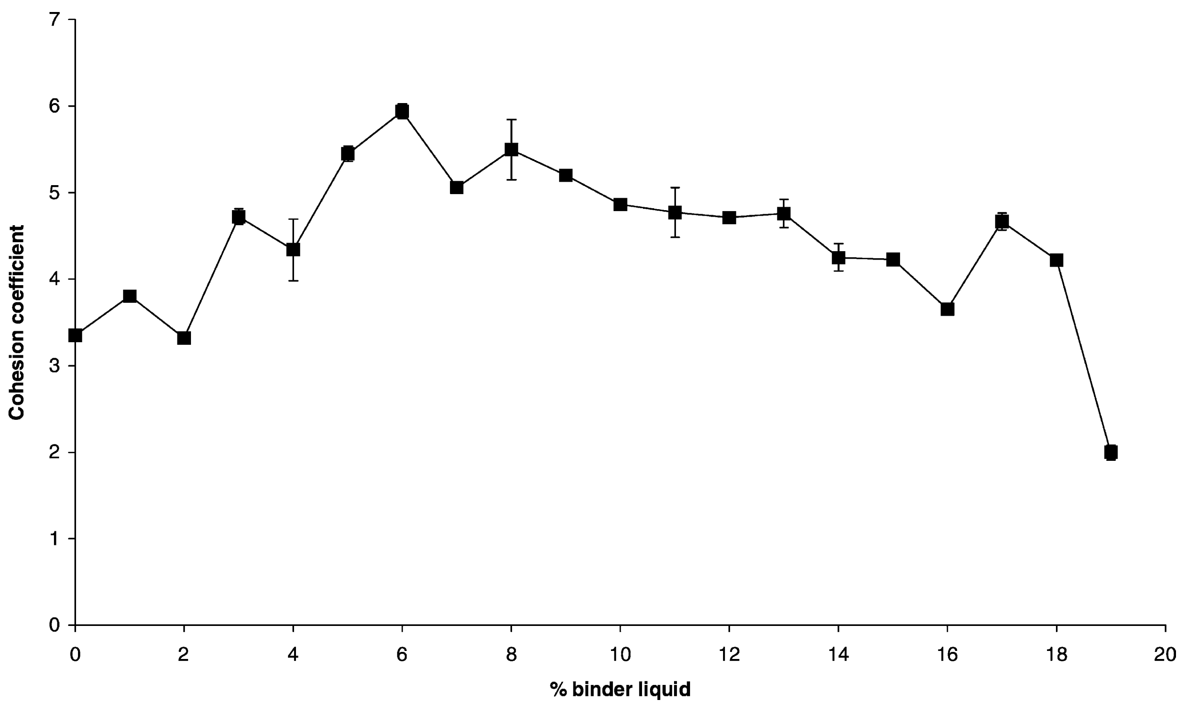

Fig. 7. Cohesion coefficient of the wet mass corrected for the influence of the packing density during shear, as a function of the amount of binder liquid added (calculated as % w/w of the wet mass using a 5% HPMC colloidal solution in demineralised water).

and corrected for density (corrected value = cohesion coefficient/bed density; Fig. 7).

Looking at the uncorrected data (Fig. 6) the values plotted resemble curves reported for data of mixing torque obtained using the mixer-torque rheometer (Rowe and Sadeghnejad, 1987), that is, after an initial small plateau the values show a steady increase up to a defined maximum, followed by a significant decrease. Initially, the addition of water leads to formation of pendular (≤6% (w/w) of liquid binder) and later funicular liquid bridges (≤15% (w/w)). These restrict the mobility of individual particles and hence should result in an increase in the cohesion coefficient. At the upper limit of the funicular state all pores become filled with water and a disjoining pressure starts to develop. Hence, agglomerates in the capillary state should be more deformable and the mobility of the wet mass should increase. In soil mechanics the cohesion coefficient is usually discussed as a measure proportional to the amount and strength of interparticulate forces formed between individual particles, although these two physical properties are strictly not the same (Podczeck, 1998). Thus, the results would indicate that the capillary state, which is equal to a decrease in interparticulate forces due to the developing disjoining pressure, is accompanied by a decrease in the cohesion coefficient. The threshold value appears to be the addition of about 15% (w/w) of liquid binder to the wet powder mass. When the values for the cohesion coefficient are corrected for the change in bed density in the shear experiment (Fig. 7), the threshold value between pendular and funicular state becomes more obvious. However, Fig. 7 also suggests that there is already a decrease of the cohesion coefficient between 6 and 15% (w/w). The cohesion coefficient, therefore, does not only reflect the magnitude of interparticulate forces, as earlier suggested. It appears to be a mirror of the mobility of aggregates during shear, which is larger at very low or very high liquid binder concentrations. At low levels of liquid binder this could be the result of water acting as a lubricant, whereas at high concentrations of liquid binder

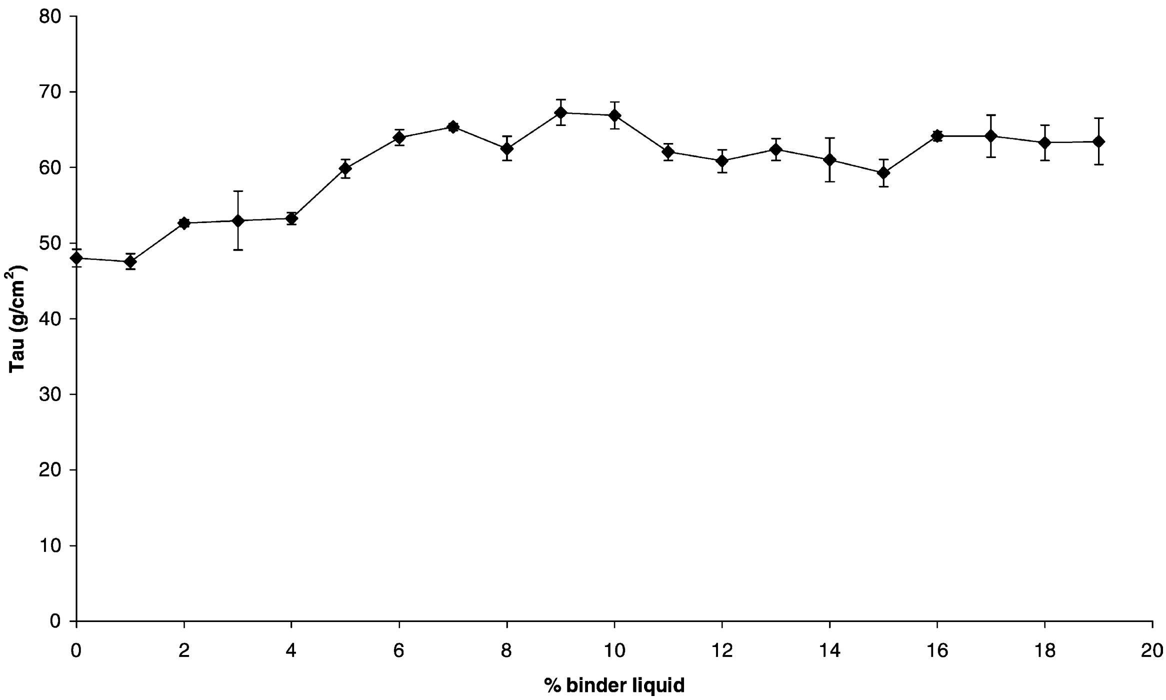

Fig. 8. Maximum shear stress τ (wet mass) as a function of the amount of binder liquid added (calculated as % w/w of the wet mass using a 5% HPMC colloidal solution in demineralised water).

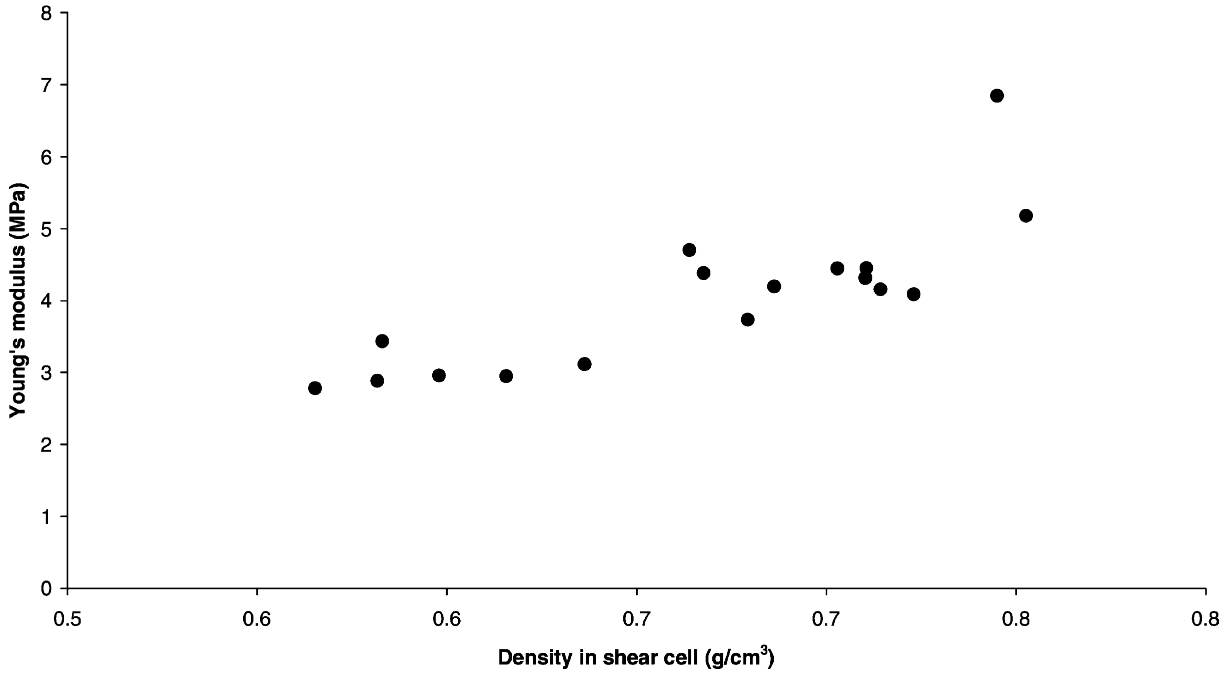

Fig. 9. Compressive Young's modulus of 1 mm dry granules as a function of the bed density of the wet mass during shear.

in the wet mass this might be the first sign of the change from the liquid-in-solid into the solid-in-liquid state.

The maximum shear stress as a function of the liquid binder added to the wet mass is depicted in Fig. 8. Theoretically, the curve should show some similarities to that reported by Pilpel (1971) which was described in Section 1. However, the values obtained in the experiments do not show two distinctive different peaks. The absence of the first peak might be a result of the fact that lactose monohydrate contains approximately 2–3% of water when used as powder. Hence, very minute pendular bridges might already be present in the material when handled as a bulk. Following this hypothesis the steady increase up to about 9–10% (w/w) of liquid binder might reflect the formation of funicular liquid bridges. However, the fact that the shear stress does not decrease significantly at higher concentrations of liquid binder cannot be explained in this way. From Pilpel's (1971) work it is not clear how the liquid was incorporated into the soil to form a wet mass of defined liquid concentration. The differences observed here hence might be simply a result of a different wet massing process.

In Fig. 9, the compressive Young's modulus of the dry granules is drawn as a function of the bed density of the wet mass during shear. As can be seen there is a tendency for the value of the compressive Young's modulus to increase with increasing density of the wet powder mass. As all wet masses were pre-consolidated with the same load (50 g/cm^2) this indicates that the granulation process, when producing denser granules, results in stiffer, less deformable granules due to densification, not due to liquid bridge bond formation.

The compressive Young's modulus of the dry granules as a function of the angle of internal friction of the wet mass is shown in Fig. 10. Here, a tendency for the value of compressive Young's modulus to decrease with increasing value of angle of internal friction can be observed, especially at lower values of the angle of internal friction. Larger values for the angle of internal friction were found at low ($\leq$8% (w/w)) and high concentrations ($\geq$15% (w/w)) of liquid binder added. A larger degree of friction hinders den-

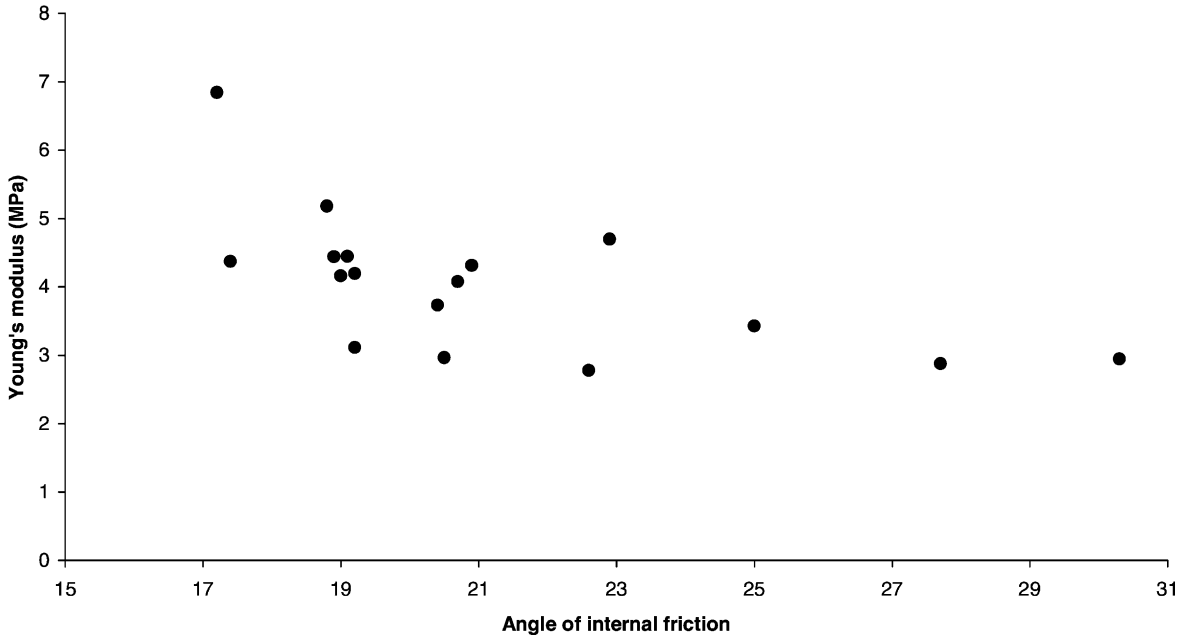

Fig. 10. Compressive Young's modulus of 1 mm dry granules as a function of the angle of internal friction of the wet mass during shear.

sification (reflected in lower bed densities of the wet mass in the shear cell) and hence the interparticulate void space in the granules remains larger, adding to the elastic behaviour and reduced strength of the dry granules.

No relationship between compressive Young's modulus and the uncorrected or corrected cohesion coefficient could be found, strengthening the above suggestion that stiffer granules are a result of densification, not strength of liquid bridge bond formation.

4. Conclusions

The Peschl-split bed shear tester can be utilised to study the formation of different liquid states during wet massing for granulation. Using lactose monohydrate as a model bulking agent the threshold between pendular and funicular state was found to be at about 6% (w/w) of liquid binder added to the wet mass, here a 5% colloidal solution of HPMC in water. The upper limit of the funicular state appeared to be at approximately 15% (w/w) of liquid binder. The threshold values obtained from the shear cell measurements did correlate with values obtained from the final dry granule characteristics such as granule density and compressive Young's modulus.

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