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*Research Paper*

# The Relation Between Granule Size, Granule Stickiness, and Torque in the High-Shear Granulation Process

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***Purpose.*** To investigate the background of the observed relationship between measured torque and granule size in high-shear granulation processes.
***Methods.*** Torque was measured during the granulation process; the behavior of individual wet granules during compaction was investigated using micromanipulation. Surface properties of wet granules were manipulated by coating them with talc.
***Results.*** The torque-granule size relationship could not be explained by the rise in mass of the individual granules; it occurs rather through an increase in stickiness of the granules when the moisture content is increased. Obviously, the increased stickiness that causes the granules to grow also increases the torque. Increased stickiness was shown to be the result of an increased deformability of the granules at higher moisture contents, in combination with a change in surface properties. The elastic-plastic behavior (ratio of elastic to plastic deformation) was found to change at increasing moisture contents.
***Conclusions.*** Our results imply that changes in the stickiness of the granular material that may be caused by changes in composition shift the torque-size relationship. This may be of particular importance when, for example, granulation results from placebo batches are used to predict the granule size of drug-containing batches.

**KEY WORDS:** elastic-plastic deformation; granule size; stickiness; torque; wet granulation.

## INTRODUCTION

In high-shear granulation, powder particles are swept through the bowl due to impacts of a fast-rotating impeller. Liquid is added and will be distributed over the powder particles. Particles stick together to form nuclei, which will be consolidated by the impacts with the impeller and the wall. This densification of the nuclei pushes water to the outer surface of the granule, which can result in growth. Next to the impeller, a chopper may be present to chop large lumps into smaller pieces. Granule growth stops when the equilibrium between growth and breakage (caused by impacts of particles, impeller, or wall) is reached (1).

The granulation process can be monitored by torque or power consumption measurement. Torque is a measure of the amount of energy needed to rotate the impeller. Therefore, torque depends on the resistance of the mass against rotation of the impeller (2–4). In the wet mixing process, changes in torque occur as the result of a change in the cohesive force of the granules in the wet powder bed. Leuenberger (5) described five stages in the wet granulation process on the basis of power consumption, shown in Fig. 1. In stage I, the powder is moistened. However, an increase in torque is not observed and no noticeable agglomeration has occurred. In stage II, a rapid increase in torque is observed, caused by agglomeration. The agglomerates formed in this stage are very weak and break upon drying. In stage III, a plateau region is reached, where the volumes of liquid bridges are increased without significant changes in the cohesive force. Stage IV is reached when pore spaces begin to fill completely with liquid. This results in a fluctuating torque value. Finally in stage V, when too much liquid is added, a slurry is formed, which leads to a decrease in torque.

However, during a normal granulation process, the above described procedure is not fully completed; in general the aim is to add such an amount of liquid that the process stops in stage III. This provides the most robust and reproducible process. A torque curve obtained from such a normal granulation process is shown in Fig. 2. During the first 30 s liquid is added, which gives a sharp rise in torque. When all particles are moving, torque drops a little bit, to rise again when growth occurs. Finally, a steady-state torque is reached, during which particle size was found not to change anymore. We refer to torque at this stage as equilibrium torque. The value of the equilibrium torque changes when process parameters are changed. During the past decades, many people tried to identify the parameters by which torque was changed.

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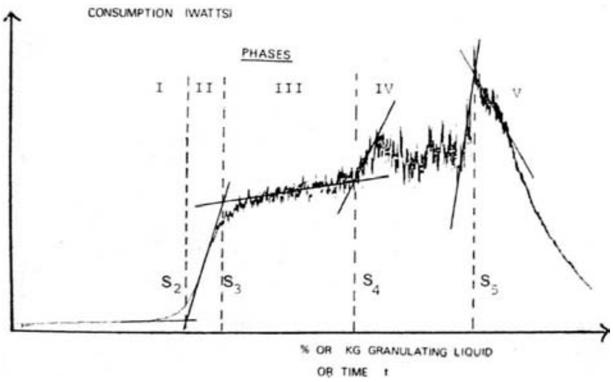


**Fig. 1.** Torque graph, showing five stages due to continuous liquid addition as described by Leuenberger (5).

Knight *et al.* (6) claim that an increase in (equilibrium) torque is found at increasing surface wetness of the granules. Increased wetness may be the result of increased impaction forces on the granules (e.g., a higher impeller speed) resulting in higher granule density or from an increase in the liquid content. Holm *et al.* (7,8) suggest that torque depends on the properties of the wet agglomerates, like brittleness, plasticity, and granule strength. These properties are controlled by the porosity and liquid saturation of the agglomerates. Holm *et al.* (7,8) and Parker *et al.* (9) show a dependency of torque on liquid addition as a second-degree polynomial function. According to them, in the funicular phase (stage III) a linear relationship is found. The above-described investigations all point at the effect of liquid related parameters. On the other hand, Kristensen *et al.* (10) measured a close correlation between torque during stage III and granule size as long as process variables, like powder mixture; liquid addition rate; and granulator equipment, are kept constant. We also observed a relationship between torque and particle size.

From the above, it is clear that a relation between torque during high shear granulation and particle size of the final granule exists. However, the background of this relation is not clear. The question whether the increase found in torque is caused by the simple fact that the particle size of the granules is increased or by the fact that one or more granule properties are changed that both affect the torque and cause the granule size to increase is not answered yet. In this paper, we try to answer this question by linking results from granulation experiments with results from measurements on individual granule properties performed with a micromanipulation technique.

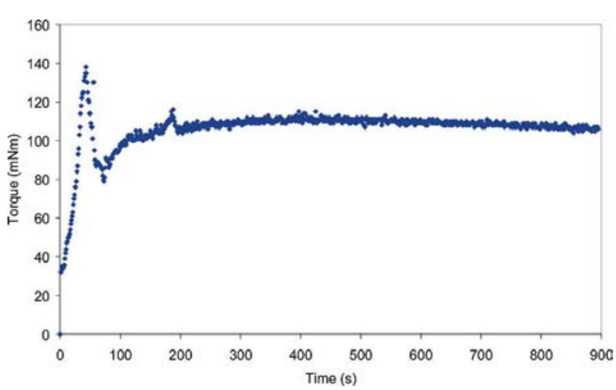


**Fig. 2.** Torque graph found for a common high shear granulation process. The first 30 s liquid is added, which gives a rise in torque. The moment all powder particles are moving, torque drops again. Another torque increase is seen when growth starts, leading to a steady-state during which growth and breakage are in equilibrium.

## MATERIALS AND METHODS

### Materials

Granulation was performed with Microcrystalline Cellulose (MCC) Pharmacel 101 ($d_{50}$ = 58 μm) (DMV-International, Veghel, The Netherlands). The binder liquid used was tap water.

### Equipment

Granulation was performed in a high-shear mixer. Two different setups were used; in Groningen, a small-scale granulator MiPro 250 (ProCepT, Zelzate, Belgium) with a 250 ml glass bowl; and in Birmingham, a homemade large-scale granulator (University of Birmingham, UK) with a stainless steel 10 L bowl. The small-scale equipment was equipped with both an impeller and a chopper, whereas the large-scale granulator only had an impeller. The small-scale setup measures absolute mixer torque, which means that torque is measured in the impeller shaft. In the large-scale setup, torque is measured on the side wall of the vessel, as described by Knight *et al.* (6).

### Granulation

In the small-scale equipment 24 g MCC (Pharmacel 101, lot 60841) was granulated with amounts of water varying from 18 up to 30 ml. Liquid was added at 48 ml/min. Impeller speed was 1000 rpm (tip speed 3.14 m/s) and chopper speed was 1500 rpm (tip speed 1.6 m/s). Total granulation time was 900 s. These settings were chosen to provide in the most spherical granules.

Stickiness was manipulated by carefully rotating freshly formed wet granules in 8 g talc. The coated granules were put back in the granulator, impeller and chopper were started and torque was measured again.

In the large-scale setup 1400 g MCC (Pharmacel 101, lot 21153) was granulated with amounts of water varying from 1050 to 1750 ml. Liquid was poured on all at once. Impeller speed was 400 rpm (tip speed 3.14 m/s), a chopper was not present. Total granulation time was 900 s.

According to Horsthuis *et al.* (11), scaling up needs to be performed by keeping the Froude number constant, as this results in comparable temperatures and size distributions, whereas a constant relative swept volume and a constant impeller tip speed do not. Our own measurements confirm this statement. The Froude number (Fr) is shown in Eq. 1, in which $N$ means impeller speed ($s^{-1}$), $D_{\text{impeller}}$ means the diameter of the impeller (m), and $g$ the gravitational constant ($m/s^2$).

$$\text{Fr} = \frac{N^2 D_{\text{impeller}}}{g} \quad (1)$$

### Granule Size Measurement

Granules prepared in the small-scale equipment were dried in an oven at 40°C overnight. The whole batch was sieved and the $d_{43}$ (the moment mean diameter based on weight) of the batch was calculated according to Eq. 2, in which $d_i$ means the mean diameter in class $i$ (m) and $n_i$ the amount of particles in that class.

$$d_{43} = \frac{\sum_i n_i d_i^4}{\sum_i n_i d_i^3} \quad (2)$$

Following general practices in pharmaceutical industries, the $d_{43}$ was considered to be the most suitable size parameter.

The amount of water used for granulation was referred to as the mass of water relative to the mass of powder used (e.g., 24 g water used to granulate 24 g powder is referred to as 100% w/w granules). From every batch produced at large scale, 100 g wet material was dried in an oven at 40°C overnight. From this material the $d_{43}$ was measured. One hundred fifty grams of the wet granules were transferred from the granulator bowl into a plastic bag, which was sealed. These granules were used for micromanipulation measurements.

### Micromanipulation Measurements

A micromanipulation rig (shown in Fig. 3) has been used to characterize the granules (12,13). Single granules were compressed with a glass probe of 2.5 mm, which is significantly greater than their diameter. The probe was connected to a force transducer with a compliance of 1.054 $\mu m \cdot g^{-1}$ and a sensitivity of -8.510 $g \cdot V^{-1}$ (model 407A; Aurora Scientific Inc., Ontario, Canada). The force transducer was mounted on a three-dimentional fine micromanipulator (MicroInstruments Ltd., Oxon, UK) that was programmed to travel a given distance at a given speed. The force being imposed on the compressed granule was measured simultaneously by sampling the voltage signal from the force transducer and transferred into a computer via a data acquisition board (Amplicon Liveline, Brighton, UK). The deformation processes were monitored with a side view COHU high-performance CCD camera, which was connected to a screen and a video recorder. Deformation was expressed as the ratio of granule displacement to its original diameter.

Wet granules with a size between 1.00 mm and 1.18 mm were taken for micromanipulation measurements. The somewhat larger size of the granules was chosen because the chance of measuring powder properties, instead of granule properties, is lower in the larger granules than in smaller granules. Also, small-sized particles possess a relatively large surface area relative to their volume and drying of the granule will take place more rapidly, which largely affects the measurement. Therefore, a relatively small size fraction was used to perform the measurements on, to be sure that differences were not caused by size differences of the granules.

Micromanipulation measurements were only possible with granules with liquid contents between 100% w/w and 125% w/w. Using only 75% w/w of water results in granules that were too small to be measured. Addition of more than 125% w/w water does not result in granules anymore; large lumps are formed, or, upon even further addition of water, a slurry is obtained.

Measurements were conducted 45 s (±3s) after the wet granules were taken out of their container, to prevent them from drying. The prevention of drying was crucial in these measurements, as dried granules required much higher forces to produce a given deformation. Compression and release tests were performed to calculate Emschermanns index. This index is the ratio of elastic deformation and plastic deformation (14).

## RESULTS AND DISCUSSION

In Figs. 4 and 5, the relation between torque and particle size is shown. Particle size is defined as the $d_{43}$ of the distribution measured after drying; equilibrium torque is measured on the wet granules. The linear relation between torque and particle size was found both for the small-scale and for the large-scale equipment. This finding shows that the relationship was independent of the way the torque was measured, as torque is measured in the impeller of the small-scale equipment and on the side of the bowl of the large scale. Various reasons may explain the increased torque found at increasing particle size.

One explanation for the increased torque could be the simple fact that larger particles have a higher mass. Impacts of larger granules (higher mass) may result in a larger resistance (torque). To investigate the relevance of this aspect, granules were dried and put back in the granulator. The torque measured on the dried granules is given in Fig. 5 (closed symbols). Indeed, this figure shows a minor increase of torque at increasing particle size. However, the effect is really small considering the fact that the mass increases by a factor 250 over the given size range. Moreover, the changes in torque are much smaller as those found for the wet granules (both in an absolute as well as in a relative sense). Therefore, it can be concluded that size (mass) of the granules as such is not the determining parameter for torque. Obviously there must be

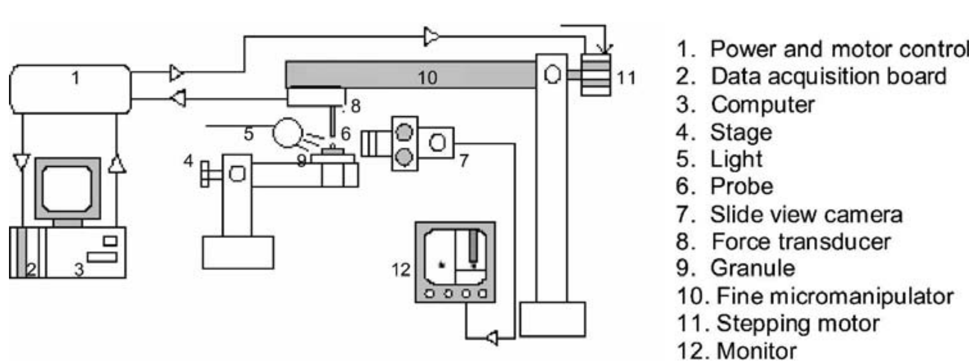


**Fig. 3.** Schematic diagram of the micromanipulation rig.

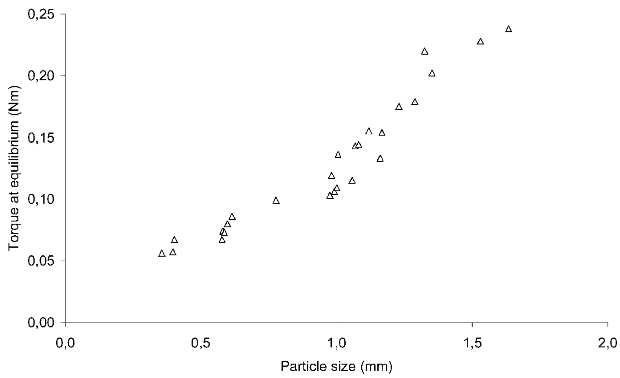


**Fig. 4.** Equilibrium torque as a function of particle size ($d_{43}$) measured in the small-scale equipment.

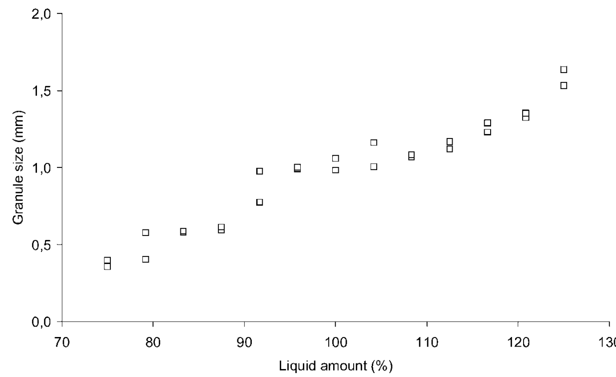


**Fig. 6.** The effect of an increase in liquid content on granule size ($d_{43}$).

another parameter that causes both an increase in torque and in particle size.

Parameters of the granules to consider in this respect are those that are affected by the liquid content of the granules, because the only possibility to increase particles size (when using the same compound and the same experimental setup) is by increasing the liquid content. Figure 6 shows that the particle size increases with liquid content, as expected. Liquid content is expressed as the mass of water relative to the mass of powder. If torque is dependent on granule size, and granule size is dependent on liquid content, a relation between torque and liquid is expected. Figure 7 confirms this relation. The figure clearly indicates that liquid changes the character of the granules in such a way that torque increases.

The relation between torque and liquid content has also been demonstrated by several others (9,10). However, only hypotheses have been launched concerning the granule property that causes the change in torque and the growth of granules. Parker (9) explains this by the increased cohesiveness of the wet mass, comparable to Leuenbergers torque graph (5), whereas Kristensen (4,10) uses change in rheology to explain the same effect by saying that the plasticity is increased by increasing the flexibility in the fibers of the powder. However, experimental evidence is not presented till now. We would like to reinforce the ideas of Parker and Kristensen by supposing that an increased plasticity leads to an increased stickiness of the wet material (15) and providing experimental data showing changes in stickiness.

A major reason to follow this approach was the fact that this increase in stickiness was observed in the glass vessel of the small scale setup. At low liquid content (e.g., 100% w/w), particles sticking to the wall were released by impacts of other granules. However, at high liquid content (e.g., 125% w/w) particles immobilized on the wall were not released; on the contrary, the impact of new granules led to a thick layer of granules sticking to the wall. This highly increased the resistance for the impeller, thereby increasing impeller torque. When measuring torque on the wall, torque is computed from the measured load (6). This means that the increased mass on the wall results in an increased torque as well. In Fig. 8, the mutual relationship between granule size, granule stickiness, and torque is shown. The amount of liquid determines granule size and granule deformability. Deformability and surface properties of the wet granule determine stickiness. Finally, stickiness influences torque, as explained above.

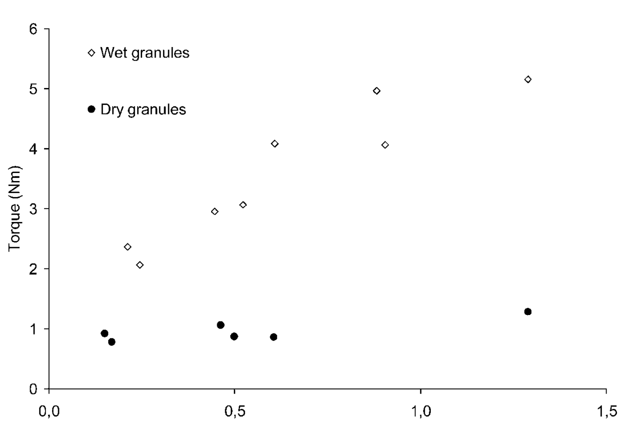


**Fig. 5.** Torque of wet and dry granules of different size ($d_{43}$) measured in the large-scale equipment.

## Stickiness

Stickiness is a concept hard to understand. Gay and Leibner (15) describe that a material is not sticky in itself; the mechanical and surface properties of the test probe determine its stickiness. A material is sticky (tacky) if an applicable force is needed to separate it from a certain surface immediately after contact. The wet mass in the granulation bowl satisfies all requirements for being a sticky material. It consists of a soft, solid material that can resist shear, deforms under pressure, and shows elastic-plastic behavior. The water present at

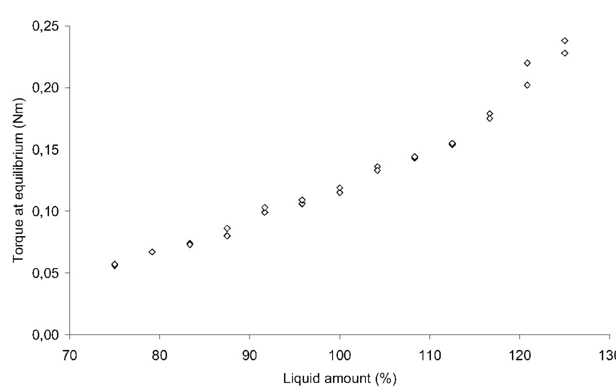


**Fig. 7.** The effect of an increase of granulation liquid on torque.

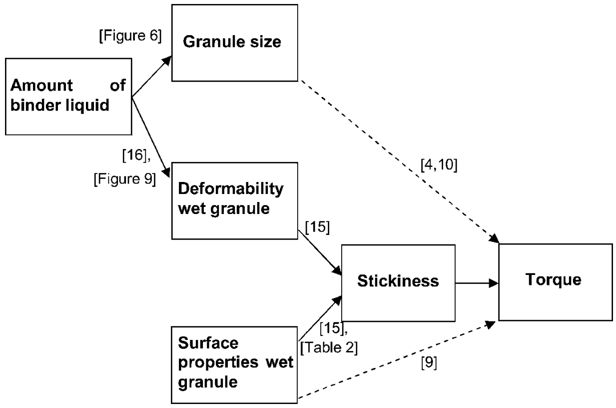


**Fig. 8.** The mutual relationship between granule size, granule stickiness, and torque. The solid lines show the ideas presented in this manuscript, the dashed lines indicate the explanations given in previous papers. References to other papers or parts of this paper are given between brackets.

the surface provides in a capillary force between the granule and the wall or between the granule and another granule.

The resistance against shear is the principle of high shear granulation. If granules would not be able to resist shear, the wet mass would be dispersed throughout the bowl as single particles, and granules would simply not exist. The ability to deform under pressure is a second characteristic of sticky materials. If a material deforms more easily, impaction will result in a larger contact area resulting in higher adhesion forces. Deformation under pressure is shown by compression tests. We tested single wet granules on their reaction to imposed deformation, for which the micromanipulation setup as described by Zhang *et al.* (12) was used. The measurements were performed on single granules originating from batches that were produced using 100% or 125% of water (relative to the powder mass). The results of the compression tests in Fig. 9 show that the increase of liquid content from 100% to 125% leads to a higher deformability. The deformation of the wetter granules requires a lower pseudo stress (defined by the ratio of force to their original cross-section area) than the same deformation of the 100% moisture containing granules. Newitt and Conway-Jones (16) were the first to assume that an increase in liquid saturation leads to increasing capillary cohesive forces and increasing granule deformability; our results

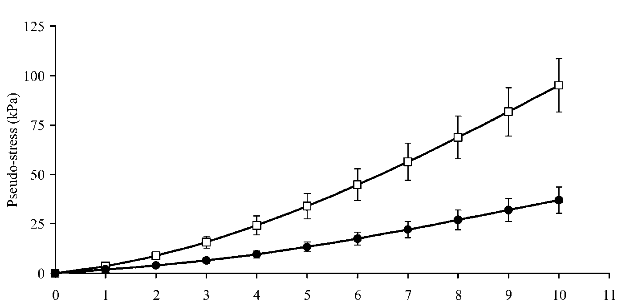


**Fig. 9.** Graph showing the resistance of individual granules against deformation ("compress and hold" test): □: 100%-moisture-containing granules (n = 19), ●: 125%-moisture-containing granules (n = 22). All measurements were performed at a probe speed of 47.6 μm/s, with a wet granule size between 1.0 and 1.18 mm. Error bars represent standard error of the mean.

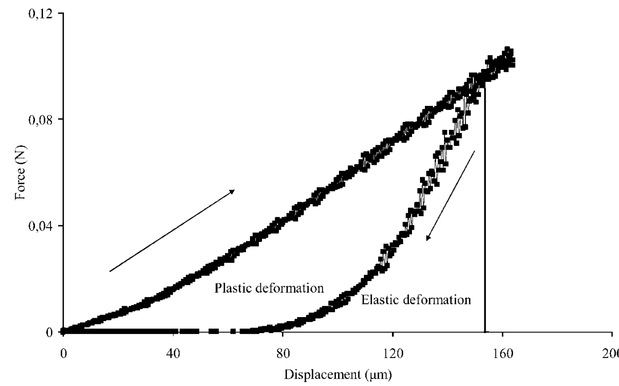


**Fig. 10.** Force-displacement of a single 100%-moisture-containing granule with a wet granule size of 1 mm.

provide experimental evidence for this hypothesis. Higher deformability leads to an increased stickiness due to the fact that the better deformable 125% granules create a larger contact surface area upon impaction with wall impeller or other granules.

Furthermore, the elastic-plastic behavior is shown by force displacement curves corresponding to compression and release. Granules were compressed to a preset displacement after which the force was released by upward movement of the probe. In both directions, the force exerted on the probe was measured, which is shown in Fig. 10. As can been seen, when a granule was compressed, the force imposed on it increased with the displacement, as expected. However, when the granule was released, the force dropped to zero before the displacement returned to zero. This indicates the granule had undergone plastic deformation. The area between the compression and release curves roughly indicates the plastic deformation and that under the release curve represents elastic deformation. The ratio of the elastic part and the plastic part is called Emschermanns ratio (14). A complete plastic material would result in a value of zero, whereas a complete elastic material would result in an infinite value. The values of Emschermanns ratio for two liquid contents are shown in Table I. It shows that indeed a higher liquid content increases plasticity.

The three changed characteristics (surface properties, plasticity, and resistance against deformation) of the wet granules indeed provide experimental evidence that wet material containing 125% water is stickier than the material containing 100% water. To investigate whether stickiness indeed causes a higher torque or not, granules were made and torque was measured. The wet granules were coated by rolling them in bowl with talc, and immediately put back in the granulator. Again torque was measured. Torque decreased dramatically, as shown in Table II. It proves that reducing stickiness of wet

**Table I.** Emschermanns Index at Different Liquid Contents After 16% Deformation of the Granule

| Water conent | Emschermanns index[a] (elasticity/plasticity) |
|---|---|
| 100% | 0.86 |
| 125% | 0.71 |

[a] Standard deviation of each individual measurement was below 7%.

**Table II.** Torque Values at Equilibrium at Different Water Contents[a]

| Water content | Torque at equilibrium (mNm) | Torque after coating with talc (mNm) |
|---|---|---|
| 75% | 72 | 59 |
| 100% | 125 | 59 |
| 125% | 206 | 80 |

[a] At $t$ = 900 s, granules were taken out of the bowl, coated with talc, and put back in the granulator to measure torque again.

granules indeed results in a lower torque, thus linking stickiness to torque.

The reduction in torque when using talc-coated wet granules (deformable, nonsticking surface properties) varied between 18% and 61%, depending on the initial surface properties of the granules. The reduction in torque was larger for the wet (125% water content) granules, whereas it was smaller for the less-water-containing granules. The lower initial surface stickiness of the latter granules is due to the lower contribution of the capillary forces. When dry granules (nonsticking surface properties, nondeformable) were used, torque decreased once more with approximately the same percentage, indicating that the contribution of surface properties to stickiness is of approximately the same magnitude as the contribution of deformability.

## CONCLUSIONS

We have shown that the increased torque found when granule size increases is not caused by the higher mass of the individual granules. The major granule property determining torque is stickiness. Obviously, stickiness links the granule size to torque. This implies that changes in composition or surface properties of the granules that affect stickiness will change the granule size-torque relationship. The relevance of this finding may for example be found when pharmaceutical granulation processes are developed. Many experiments in the development phase are performed with placebo formulations, and these experiments are used to establish the torque-granule size relationship. If now the drug is added to the formulation, the stickiness of the granule may change, resulting in a change in the torque-granule size relationship. Therefore, the relationship as established with the placebo formulations may not be valid anymore to predict the final size of the drug containing granules.

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