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Power consumption profile analysis and tensile strength measurements during moist agglomeration

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Abstract

This study was performed to elucidate the influences of process and formulation design on the granulation process using power consumption and tensile strength measurements. In order to record and analyze the power consumption profile "in process" a computer program was developed to be used for optimal end-point control in reproducible granule production. The program analyzes and calculates a characteristical point, the turning point of the S-shaped ascent of the profile.

The tensile strength expresses the cohesiveness between the powder particles, which is dependent on saturation and capillary pressure. In order to investigate the influence of the amount of liquid present in the granular material on tensile strength a device was developed. The maxima of tensile strength occurred at 90% saturation, whereas the maxima of power consumption were determined at 100% saturation. The measured tensile strength σ (N/m^2) equals to the volume specific cohesion (J/m^3). The present work proved that the power consumption measurement is an alternative, simple and inexpensive method to determine the cohesion of powder particles. The turning point is introduced as a signature of the starting material and furthermore as a parameter for the cohesiveness of the starting material and therefore for optimal end-point detection at an early stage.

Keywords: Moist agglomeration; End-point control; Power consumption; Tensile strength

1. Introduction

In the early beginning of granulation process technologies, objective criteria for process parameter adjustments during granulation were missing. Equipment was very basic, with little or no instrumentation for controlling the process. Granulation end-point was often determined by the intuition of the operator, who may apply additional water and/or continue mixing until the product had the "right feel". The subjective nature of this evaluation technique resulted in variability in product properties depending on which person developed the formulation. Instrumentation has improved over the years, and more recently, end-point is linked to torque of the mixer shaft in the granulating equipment (Lindberg, 1984; Lindberg et al., 1974, 1977) or by power consumption measurement of the mixer motor (Bier et al., 1979; Leuenberger, 1982, 1983; Leuenberger and Dürrenberger, 1979; Leuenberger and Imanidis, 1984; Werani, 1988). A constant quality of granules is a key factor in robust dosage form design. The power consumption measurement of the mixer motor as a function of the granulating liquid added per unit time has been used as an end-point control system in the industry and was first published to control the agglomeration process efficiently by Bier et al. (1979). The power consumption measurement is

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an inexpensive, simple and quick method to control the granulation process and to determine the end-point. However, its use in the industry is still not very common.

In granulation processes, many problems in choosing the ideal formulation and process conditions as well as difficulties in controlling the process arise because of variations in the physical properties of the starting materials. A comprehensive knowledge of the starting material properties should make it possible to predict the required amount of granulating liquid and the process conditions for granulation without performing preliminary experiments. Furthermore the physical properties of bulk solids are of great importance in the pharmaceutical development and production of robust solid dosage forms. The flow properties of the bulk is an important characterization and can be determined by the forces acting between the individual powder particles, like van der Waals, capillary and electrostatic forces. The most commonly used equipment in the field of powder technology for the determination of flow characteristics and cohesion of bulk solids is the Jenike shear cell (Jenike et al., 1960). A new approach was presented in the work of Sindel and Zimmermann (2001), where the interparticle forces were measured successfully using an atomic force microscope. Tensile strength measurement is also used as an important parameter in powder characterization. In the work of Schweiger and Zimmermann (1999) a new tensile strength tester, taking into account the correlation with the effective surface of the particles, is presented and compared with the Jenike shear cell. The tensile strength of wet granular material can be measured with a split cell tester developed by Hartley and Parfitt (1984). The interaction between the liquid and the solid in wet granular materials depends on the amount of liquid present. A small quantity of liquid causes the 'pendular state', by increasing the amount of liquid, the 'funicular state' is obtained where both liquid bridges and pores filled with liquid are present. The 'capillary state' is reached when all the pores are filled with the liquid and concave menisci developed at the surface of the agglomerate. The tensile strength of wet granular material is a strong function of the packing density. The correlation for the tensile strength requires knowledge of the particle diameter, the surface tension of the wetting liquid and the void fraction of the agglomerate (Pierrat and Caram, 1997).

The objective of the present study was to investigate the influence of formulation (using various granulating liquids) and process design on the power consumption profile during the moist agglomeration process and on the tensile strength in wet granular materials.

A simple apparatus to measure tensile strength of wet granular material is introduced in this work in order to compare the results with the power consumption measurements. Finally, the comparison will lead to the conclusion, whether the power consumption measurements correlate with the tensile strength of the wet granular material. Moreover a reference point of the power consumption profile is introduced as a parameter of the cohesiveness of the starting material.

2. Materials and methods

2.1. Materials

Corn starch (Cerestar Gruppo Feruzzi, Gent, The Netherlands), polyvinylpyrrolidone (PVP) (ISP Technologies, Wayne, NJ) and α-lactose (200 mesh) monohydrate (Pharmatose, type 200 M, Sugro AG, Basel, Switzerland) were used to prepare a standard mixture of the following composition:

α-Lactose 200 mesh monohydrate	86% (m/m)
Corn starch	10% (m/m)
PVP	4% (m/m)

The physical properties of the standard mixture are compiled in Table 1.

All other chemicals and reagents purchased from commercial sources were of analytical grade.

2.2. Granulation equipment

Three different granulation equipments were used in this work. A Loedige M5 high-shear mixer (Loedige,

Table 1
Physical properties of the standard mixture

	Corn starch	PVP	Lactose 200
Bulk density (g/cm^3)	0.59	0.40	0.60
Tapped density (g/cm^3)	0.66	0.45	0.74
True density (g/cm^3)	1.52	1.14	1.59
Mean diameter (μm)	35.9	147.6	92.7

Paderborn, Germany) with a volume of 5 l, and constant impeller speed kept at 278 rpm during the experiments, a Diosna P10 high-shear mixer (Dierks & Söhne, Osnabrück, Germany) with a volume of 10 l and constant impeller speed kept at 452 rpm and chopper speed at 3000 rpm during the experiments, and a Loepthien P5 planetary mixer (Loepthien, Belp, Switzerland) with a volume of 5 l and constant impeller speed kept at 60 rpm. The power consumption of the mixer motor is determined by the electric current consumption of the motor according to the equation $P = U \times I$, where P is the power (W), U the electric potential (V), and I is the electric current (A). The product of electric potential (V) times electric current (A) is measured by a measuring transducer (Sineax Type PQ 502, 0–2 kW, Camille Bauer AG, Wohlen, Switzerland). The power consumption is converted into an electric potential signal between 0 and 10 V, 10 V corresponding to 2 kW and sampled by an I/O card to a PC, Labtop Type AST 950N, Pentium P54c and displayed graphically.

2.3. Methods

2.3.1. Power consumption profile recording and analysis

The first power consumption measurements to control the granulation process were performed by Leuenberger and Dürrenberger (1979, 1982). In order to analyze the power consumption profile the tangent technique was applied. The typical profile (see Fig. 2) consists of five different phases, the characteristical points S2, S3, S4 and S5 are calculated using the tangent technique in order to determine the optimal amount of granulating liquid for the granulation process (Leuenberger et al., 1979). Usable granulates can be produced in a conventional way within the plateau region stage III and in the stage IV region. At point S5 the liquid saturation is equal to 100%. S5 is defined as the point at which maximum power is taken by the motor of the mixer. The main disadvantage of this technique is that the characteristic points of the profile can be calculated after having obtained the first profile. Therefore, a computer program was developed to calculate the characteristical points of the power consumption profile 'in process' and to save the obtained data digitally in order to be used for optimal end-point control in reproducible granule production. A computer program with the properties mentioned above was developed in co-operation with Pharmatronic AG, Pratteln, Switzerland.

In order to calculate the profile "in process" a new characteristic point, the turning point of the power consumption profile in stage II, is introduced. The turning point could be described by using either the Hill equation (Hill, 1913; Oti-Amoako, 1988) or the Simplex method (Sucker et al., 1978). The Hill equation (see Eq. (1))

$$W_t = W_0 + \frac{W_{PL} t^S}{k^S + t^S} \quad (1)$$

where W_0 is the power consumption at the beginning, W_{PL} the power consumption of the plateau, t the time, S the Hill coefficient, and k is the turning point was applied to the S-shaped ascent in stage II of the profile in order to calculate the turning point. Experimental data (Junker, 1998) were fitted into the Hill equation (Eq. (1)) using Systat 5.0, non-linear equation, resulting in a correlation coefficient of >0.999. The S-shaped ascent in stage II of the profile is well described with the Hill equation (Eq. (1)), but not applicable for an 'in process' calculation.

Using a polynome approximation and the Simplex method (see Eq. (2)), it became possible to calculate the turning point of stage II of the profile 'in process'.

$$y = ax^3 + bx^2 + cx + d \quad (2)$$

where y is the voltage (V), x the time and a, b, and c are constants.

Therefore, Eq. (2) was utilized to analyze the power consumption profile 'in process'.

2.3.1.1. Characterization of the new power consumption computer program. The power consumption is measured using a measuring transducer (Sineax PQ 502, 0–2 kW, Camille Bauer AG, Wohlen, Switzerland) with an initial voltage signal between 0 and 10 V. The program consists of two operation modi, DAT files and CSV files. DAT files contain the data binary and are not available for the user. CSV files can be read with Microsoft Excel and contain the time and the power consumption as well as the slope (V/s). Using the configuration panel the following settings can be made:

x-axis:	Time 0–120 min
y-axis:	Voltage 0–10 V, 1 V equals to 200 W
Offset:	Adjustable in the range of ±5 V, offset was kept constant at 0.1 V (20 W) during all experiments in order to determine the filtered power consumption profile
Acquisition rate:	Number of samples measured per second, adjustable in the range of 5–100 was kept at 10 during all experiments
Play speed:	Reproduction of data in the Play modus
Measuring transducer:	Range 0.5–20 kW, was kept constant at 2 kW during all experiments
Filter:	Number of samples (5–200) to calculate the filtered power consumption profile. The filter was kept at 15 during all experiments
Start of calculation:	The sample number (100–10,000) from which on the data are used for the calculation of the turning point
Percentage of slope (100–30,000 ppm):	Mean of slope to indicate the start of stage II of the profile
Granulation timer:	Time in seconds (0–300) to stop the granulating liquid addition after having reached the turning point

Using the settings "Start of calculation" (sample number) and "Percentage of slope" (ppm) stage II is selected in real time. The mean of the slope indicates the start of stage II of the profile and the setting avoids that fluctuations caused by the mixer are recognized as the start of stage II.

2.3.1.2. Characteristic points of the power consumption profile. In order to determine and compare the influences of formulation and process design on power consumption measurement the two characteristic points were used:

Turning point (TP) of the S-shaped ascent in stage II of the profile calculated by a polynome approximation and the simplex method.

Maximum point (Max) equals to 100% saturation of the particulate system and is defined as the point at which maximum power is taken by the motor of the mixer.

2.3.2. Calculation of the dimensionless amount of granulating liquid

The correct amount and type of granulating liquid are key factors in the production of granules and therefore in robust dosage form design. In developing a dosage form, it is often necessary to compare the performance of two different granule formulations. These two formulations differ in composition and as a consequence vary also in the amount of granulating liquid required.

A correct comparison between two formulations is important because the dissolution process of the active substance in the final granules or tablet can be affected both by the amount of granulating liquid and the qualitative change in the formulation. In order to calculate corresponding amounts of granulating liquid in different compositions, it is necessary to introduce a dimensionless amount of granulating liquid π. This amount π can be defined as degree of saturation of the interparticulate void space between the solid material (Imanidis, 1986):

$$\pi = \frac{S - S_2}{S_5 - S_2} \tag{3}$$

where S is the amount of granulating liquid (in liters), S_2 the amount of granulating liquid (in liters) necessary, which corresponds to a moisture equilibrium at approximately 100% relative humidity, and S_5 is the complete saturation of interparticulate void space before a slurry is formed (amount of liters).

Power consumption measurements are used as an analytical tool to define S values for different compositions. Thus, the granule formation and granule size distribution of a mixture of excipients are analyzed as a function of the dimensionless amount of granulating liquid π.

In the present work, the characteristic points calculated by the computer program for power consumption profile recording (see Section 2.3.1) such as the turning point (TP) in stage II and the maximal power consumption (MAX) of the profile were

used to determine the dimensionless amount of granulating liquid π. A modified equation is introduced (Junker, 1998):

$$\pi = \frac{S - \mathrm{TP}}{\mathrm{MAX} - \mathrm{TP}} \quad (4)$$

where S is the amount of granulating liquid (in liters), TP and Max the amount of granulating liquid (in liters) required to reach the "in process" calculated turning point of the S-shaped ascent in stage II and complete saturation of interparticulate void space, respectively.

2.3.3. Granulation procedure

2.3.3.1. Moist agglomeration. Powders were weighed and added to the bowl of the mixer. The powder mixture was premixed for 5 min prior to granulating liquid addition. PVP was added in a dry state to the powder mixture at a level of 4% (m/m). After premixing the powders, purified water, ethanol 96% or a mixture of both was pumped to the powder mixture using a pump (Kolpenpumpe, type B 06.012 S, CFG ProMinent electronic, Regensdorf, Switzerland) and a spray nozzle while blades were activated. The granulating liquid addition was adjusted to result in a supplying rate of 1/75 cm^3/min/g for each mixer. The temperature and power consumption measurements were started at the same time as the granulating liquid addition and stopped at the same time for sample drawing.

2.3.3.2. Drying. In order to reduce the possible effects of friability, or second agglomeration during the drying process in dish dryers, on the granule size distribution as a function of the amount π of granulating liquid added, the granules were dried for 2 min in a fluidized bed (Glatt, Binzen, Germany) and subsequently in a dish dryer at 50 °C to obtain moisture equilibrium corresponding to 45% relative humidity of the air ambient temperature (25 °C) (Leuenberger et al., 1981).

2.3.3.3. Scale-up precision. The influence of the filling level of the Loedige M5 high-shear mixer on the position of the characteristic points was investigated. For that purpose the granulation procedure (see Section 2.3.3) was performed at eight different filling levels of the mixer capacity.

2.3.4. Granule characterization

2.3.4.1. Granule size analysis. In order to determine the granule size growth during moist granulation the process was stopped after adding different amounts of granulating liquid (total five levels). The drawn samples were dried as described in Section 2.3.3. Granulation procedure and drying were analyzed using a particle sizing equipment (Retsch, Type Vibro) with ISO-norm sieve sizes (Leuenberger et al., 1981). Depending on the experiment a wide range of either 63–1400 or 90–2000 μm was used. The dried granules were premixed in a Turbula mixer (Type 2A, Bachofen, Basel, Switzerland) for 3 min and a sample of approximately 100 g was drawn and fractionated into four samples by hand sieving. The four fractions were sieved in serial with increasing particle size, in order to avoid obstruction of the upper sieve (Imanidis, 1986).

2.3.5. Tensile strength measurements

In order to measure the tensile strength of moist agglomerates a tensile strength measurement device was developed with the aim to compare various granules with different water contents and furthermore to compare the obtained results with the power consumption measurements. The constructed device is suitable to calculate the tensile strength by measuring the total weight (m_{tot}) which is necessary to break the bonding forces in the powder bed and inserting in Eq. (7). The following equations describe the forces occurring in the wet powder bed filled until bed height (h) into the device. After loading the string with weights, a tensile strength has effect on the powder bed. In the equilibrium Eq. (5) is valid:

$$F_{St} = \sigma \cdot A + F_R \quad (5)$$

where F_{St} is the force of the string tension (N), σ the tensile strength in the powder bed (N/m), A the fraction plane (m^2), and F_R is the force of frictional resistance (N), which is described by Eq. (6) (Orell, 1984):

$$F_R = \mu_0 \cdot N \quad (6)$$

where μ_0 is the frictional resistance and N is the normal force (N).

The force of the string tension consists of the product of total weight loaded on the string (m_{tot}) and the value of acceleration due to gravity (g). Whereas the normal force (N) consists of the sum of the tare weight of the movable part of the device (m_k) and half of

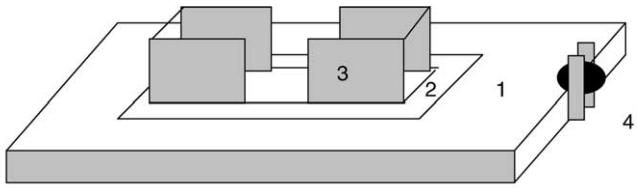

Fig. 1. Tensile strength measurement device. (1) Basic plate, (2) frame, (3) extended half-cells limited by a frame, which can be clamped together to fill in the wet granular material. The half-cell on the left hand side is fixed and on the right hand side is moveable, (4) roll for the string with can to load with weight and move the half-cell.

the weight of the powder filled in the device ($0.5m_f$). Substitution of these results into Eq. (5) yields:

$$\sigma = \frac{m_{tot} \cdot g - \mu_0 \, (0.5m_f + m_k) \, g}{A} \tag{7}$$

where σ is the tensile strength in the powder bed (N/m^2), m_{tot} the total weight loaded on the string (kg), μ_0 the frictional resistance, and A is the fraction plane (m^2).

2.3.5.1. Tensile strength measurement device and procedure. The developed device has a rectangular form with two halves from Plexiglas. The closed form has a size of 10 cm × 20.5 cm and the extended form of 10 cm × 26.5 cm, limited by a frame (see Fig. 1). The two halves of the device can be clamped together. The half in the front is the moveable part of the device and can be pulled by loading weights on the string, which is connected to the moveable part. The height of the device is 5.5 cm and the bed height can be adjusted with two Plexiglas plates. The device was built in order to perform tensile strength measurements on wet granular materials.

The testing procedure was performed as follows: the two halves of the device are clamped together. The wet granular material to be tested is filled into the device and the bed height is adjusted to approximately 5.0 cm with two Plexiglas plates. Once the cell is filled and the granular bed is consolidated that no air pockets are present in the material the clamps are removed. The force needed to fracture the sample is determined by measuring the total weight (m_{tot}) loaded on the string. The tensile strength is obtained by inserting the total weight into Eq. (7). The samples were tested at different moisture contents corresponding to different saturation levels using purified water, ethanol 96% or mixtures of both as granulating liquid.

2.3.5.2. Determination of the frictional resistance of the device. The frictional resistance (μ_0) of the device was determined using three different weights (m_v), 300, 500, and 800 g, respectively, to load the movable part of the device. The can fixed on the string was loaded with a set of weights in order to measure m_{tot}. Every 10 s a piece of weight was added until the equilibrium was reached (see Eq. (8)):

$$m_{tot} \cdot g = \mu_0 (m_v + m_k) g \tag{8}$$

where m_{tot} is the total weight loaded on the string (g), g the acceleration due to gravity: 9.81 m/s^2, m_v the weight in the movable part of the device (g), and m_k is the tare weight of the moveable part of the device (g).

The frictional resistance (μ_0) can be calculated for the system in equilibrium using Eq. (9):

$$\mu_0 = \frac{m_{tot}}{m_v + m_k} \tag{9}$$

2.3.5.3. Reproducibility of tensile strength measurements. The Loepthien P5 planetary mixer was filled with 1.5 kg standard mixture and water was pumped to the powder mixture with a constant rate of 20 g/min. The granulation procedure was stopped four times at different moisture contents corresponding to different saturation levels. Each time five samples were drawn and tensile strength was determined.

2.3.5.4. Effect of saturation on tensile strength. Granulation experiments were conducted with purified water as described in Section 2.3.3 and 13 samples were drawn at different saturation levels in the range of 10–131% saturation (see Table 5).

2.3.5.5. Effect of ethanol addition on tensile strength. Granulation experiments were conducted in the Loepthien P5 planetary mixer with purified water and various ethanol additions, as described Section 2.3.3, and seven samples were drawn at different saturation levels in the range of 10–131% saturation (see Table 5).

In order to investigate the proportionality of the results of tensile strength and power consumption measurements of the wet granular material to the surface tension of the used granulating liquid, the measured tensile strength and power consumption values obtained with various granulating liquids were divided by the value obtained with water. The results were compared with the ratio of the surface tension of the various granulating liquids, α_{GL}, to that of water, α_W (Pierrat and Caram, 1997). The values for the surface tension of alcohol–water mixtures were taken from the literature (Grunmach, 1913).

3. Results and discussion

3.1. Comparison of the power consumption profiles of three different mixers

The power consumption profiles generated with a Diosna P10 and Loedige M5 high-shear mixer and a Loepthien P5 planetary mixer using the standard mixture and purified water as granulating liquid are shown in Fig. 3. The granulation process in both high-shear mixers can be monitored by the determination of the power consumption profile. The typical power consumption profile consists of five different stages (see Fig. 2). All profiles shown in Fig. 3 indicate the maximum of power consumption at 100% saturation of the particulate system independent of the used mixer. Leuenberger et al. (1979) showed that changing the type of mixer has only a slight influence on the positions of the phases during granulation. However, the absolute power consumption of different types of mixers differs greatly for the tested standard mixture.

The classical power consumption profile, first described by Bier et al. (1979), was obtained with the Diosna P10 planetary mixer and is well described by the works of Leuenberger and Imanidis (1984), Imanidis (1986), and Usteri (1988). In phase I, an initial wetting of the powder occurs, and moisture becomes absorbed by the powder particles without the formation of any liquid bridges. In this phase the power consumption does not increase, indicating that the particle growth is insignificant. At a saturation of approximately 25%, the power consumption was observed to increase, because liquid bridges are formed between the powder particles and the first granules in phase II. At S3 the power consumption leveled off. The addition of granulating liquid results in a fill-up of the interparticulate voids and the formation of coarser granules. In phase III, the agglomerates are growing in size. A marked increase in the power consumption was observed at approximately 80% saturation. Large areas in the particulate system are completely filled with liquid. The power consumption rises and drops before reaching point S5. At this point the liquid saturation is equal to 100%. After an increase in power consumption which is due to an artifact, the power consumption drops. Due to the excess of liquid the system passes into a suspension.

The profile obtained with Loedige M5 is promising but not well described yet. The difference to the classical power consumption profile obtained with a Diosna lies particularly in stage II and III. Using Loedige M5, there is no sharp increase in power consumption during phase II, but a slow increase with a slight maximum at the end of phase III.

The differences of the obtained power consumption profiles using two types of high-shear mixers are due to construction design and working principle of the mixer. However, the computer program was able to determine the turning point in stage II and the maximum at 100% saturation, using both equipments.

The actual value of power consumption of the profile generated with a Loepthien P5 planetary mixer was about one-third of the value obtained with the high-shear mixers. The profile progression (see Fig. 4) was discontinuous in stage I to III and the calculation of the turning point is only possible within a narrow configuration setting. The actual value of the plateau region did not significantly increase compared to stage I. Therefore, in stage II only limited sample numbers are available for calculation of the turning point.

3.1.1. Granulating liquid requirement using different mixers

The granulating liquid requirement is dependent on the working principle of the used mixer. In the work of Johansen and Schaefer (2001) is shown that the pack-

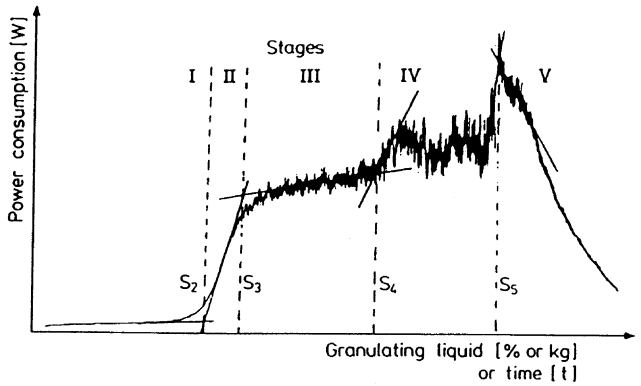

Fig. 2. Power consumption profile.

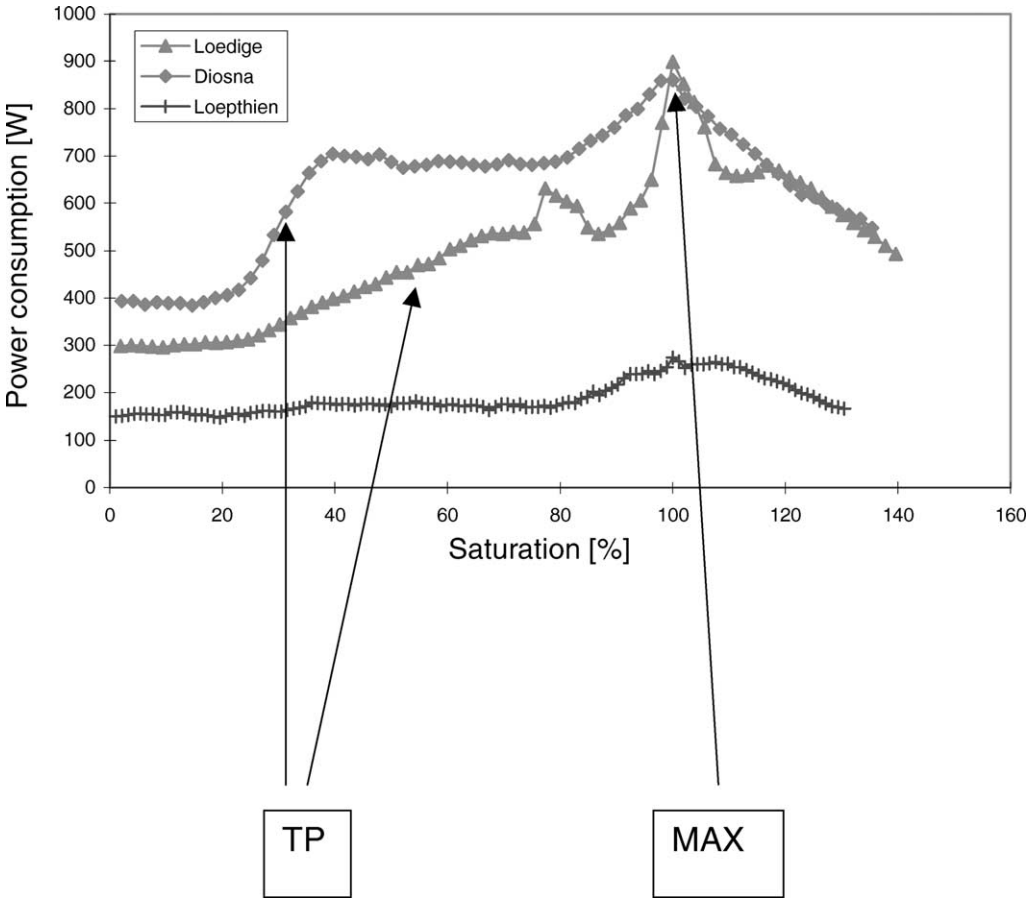

Fig. 3. Power consumption profiles of three different mixers.

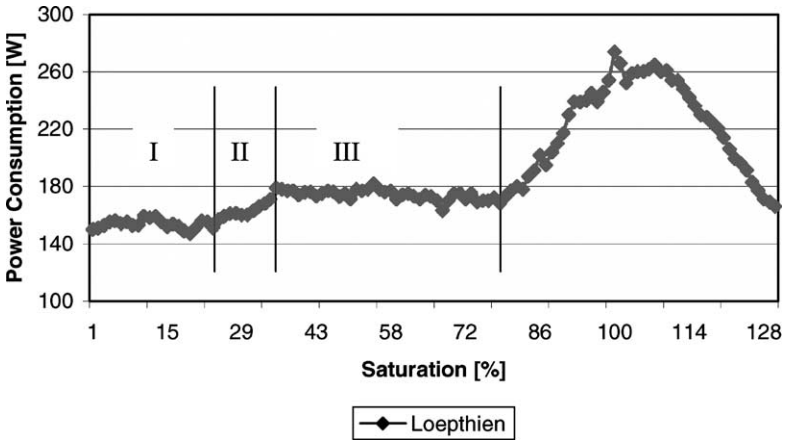

Fig. 4. Power consumption profile generated by a Loepthien planetary mixer.

ing properties of the particles are of great importance for granulating liquid requirement and suggested to use a compaction simulator as a method to predict the densification of powders and thus the granulating liquid requirement. The liquid requirement in the nucleation phase of the process is primarily dependent on the surface area of the initial particles. Further growth depends on the liquid saturation of the agglomerates and therefore the amount of liquid required is dependent on the packing properties of the granular material (Newitt and Conway-Jones, 1958). These findings are in agree with the results of the present work, where the lowest granulating liquid requirement to reach 100% saturation of the particulate system was observed for the Diosna P10 high-shear mixer (see Table 2). The mixing properties of the high-shear mixer are more intensive than of a planetary mixer (Loepthien P5) due to the working principle and therefore a more compact packing structure of the particles is obtained. Thus, less granulating liquid is required to fill the interparticulate void space to reach saturation. The comparison of the high-shear mixers showed that the Loedige M5 high-shear mixer required more granulating liquid than the Diosna P10. This result is due to the working principle of the blades.

3.1.2. Reproducibility of the characteristic points obtained with power consumption measurement

In the present work, new characteristic points are introduced in order to determine the granulation end-point at an early stage. Furthermore the characteristic points are used to calculate the dimensionless amount of granulating liquid π. Therefore, the reproducibility of the absolute value of power consumption and the granulating liquid requirement at the characteristic points was investigated.

The standard deviation (S.D.) of the absolute value of power consumption and the granulating liquid requirement (GLR) at the turning point is greater than at the maximum (see Table 3). This is due to the fact, that there is no sharp increase in stages II and III. Therefore, the settings for the "in process" calculation of the turning point are of great importance (see Section 2.3.1.1).

3.1.3. Scale-up precision of the characteristic points obtained with power consumption measurement

By definition, scale-up is the transfer of a controlled process from one scale to another. It implies that the process on the small scale is understood and controlled, and ideally that some basic rules can be

Table 2
Granulating liquid requirement using different mixers

	Loedige M5	Diosna P10	Loepthien P5
Required amount of granulating liquid to obtain 100% saturation (g)/standard mixture (g)	0.233	0.205	0.395

Table 3
Reproducibility of the characteristic points

Absolute value (W)	GLR (g)
Power consumption turning point, mean ± S.D. ($n = 6$), S.D. relative (%)	
432.0 ± 46.0 (10.7)	176.2 ± 23.7 (13.4)
Power consumption maximum (100% saturation), mean ± S.D. ($n = 6$), S.D. relative (%)	
870 ± 28.8 (3.3)	349.6 ± 8.3 (2.4)

followed to quickly obtain optimization and control of the process (Faure et al., 2001). The results published in the work Leuenberger (1983) proved that the power consumption profile as defined by the parameters S3, S4, S5 (Fig. 2) is independent of the batch size. From these findings one can conclude that the correct quantity of granulating liquid per amount of particles to be granulated is a scale-up invariable and can be used as an in process control and for fine tuning the amount of granulating liquid required. A new possibility for industrial manufacturing and galenical development of pharmaceutical solids is realized a quasi-continuous process, where no scale-up is involved (Leuenberger, 2001).

Power consumption is used as a monitoring parameter and relates back to the properties of the starting material and the wet granular material. The influence of eight different filling levels on the power consumption profile, as defined by the parameters TP and MAX, is demonstrated in Fig. 5. The amount of granulating liquid requirement, calculated using Eq. (4), is linearly dependent on the filling level of the mixer. However, the correlation coefficient for the MAX is greater than that for the TP. This is due to the error of the reproducibility of the TP (see Table 4).

3.2. Granule size analysis during moist agglomeration in a Loedige high-shear mixer

The correct amount and type of granulating liquid are key factors in the production of granules and therefore in the robust dosage form design. In a granulation process, the granule size distribution should not vary from batch to batch. Variation of the amount π resulted in a linear dependency of the median granule size diameter with the amount of granulating liquid π added per unit time, demonstrated in Fig. 6. The dimensionless amount of granulating liquid was calculated using the Eq. (3) (Fig. 6, DA 1) and Eq. (4) (Fig. 6, DA 2). The results of both equations show a linear dependency. Therefore, granule size design can be controlled by the amount of granulating liquid π in both cases DA 1 and DA 2. The results prove that the characteristical points introduced in this work are suitable to determine and calculate the dimensionless amount of granulating liquid π.

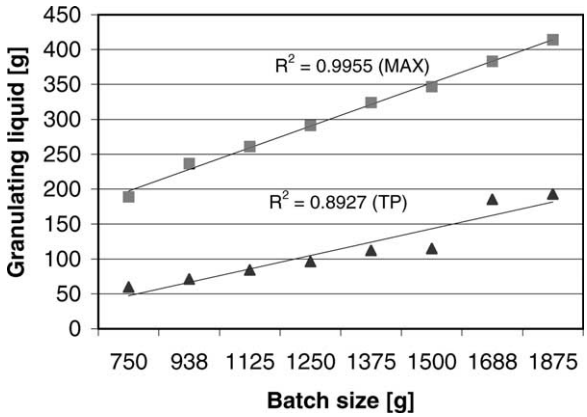

Fig. 5. Scale-up precision of the characteristic points obtained with power consumption measurement.

3.2.1. Tensile strength measurements

3.2.1.1. Determination of the frictional resistance of the device. The frictional resistance of the device was determined to be 0.46 ± 0.02.

Table 4
Reproducibility of tensile strength measurements

	Stop			
	1	2	3	4
Saturation (%)	20.1	40.0	64.8	85.0
Tensile strength (N/m^2), ±S.D., $n = 5$	451 ± 25.8	1169 ± 48.8	1201 ± 36.2	2534 ± 57.8
S.D. relative (%)	5.7	4.2	3.0	2.3

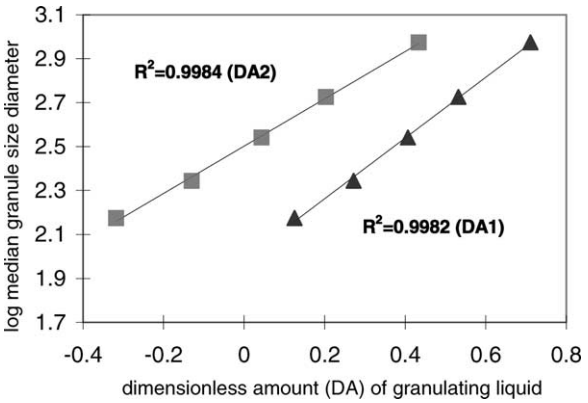

Fig. 6. Granule size analysis during moist agglomeration in a Loedige high-shear mixer. DA 1: calculated by using Eq. (3), DA 2: calculated by using Eq. (4).

3.2.1.2. Reproducibility of tensile strength measurements. The measured values of the tensile strength are shown in Fig. 7. Each point corresponds to the average value calculated from five measurements (see Table 4). The vertical bars represent the standard error. The relative S.D. at different saturation levels was found to be within 2 and 6%. The relative S.D. decreases with increasing water content.

The tensile strength measurements are considered as reproducible. However, the following limitations of the developed device were taken into consideration for the experiments performed in this work:

1. The dead weight of the can has already a force on the powder bed; therefore very low tensile strength measurements cannot be performed in this device. No measurements can be performed before granulating liquid addition. In this work the measurements were carried out not starting before point S2 (see Fig. 2).
2. The bed height was adjusted with a Plexiglas plate in order to avoid air pockets in the powder bed.
3. A saturation of more than 100% leads to a suspension and no clear fraction plane can be obtained. Therefore, the upper limit for tensile strength measurements in this work was point S4 (see Fig. 2).

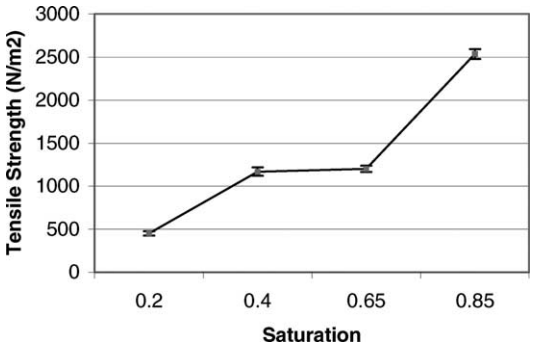

Fig. 7. Reproducibility of tensile strength measurements.

3.2.2. Comparison of power consumption and tensile strength measurements

The influence of the amount of liquid present in the granular material (% saturation) on power consumption and tensile strength measurements at different stops during the agglomeration process is shown in Fig. 8. The maxima of power consumption were determined at 100% saturation, whereas the maxima of

Table 5
Influence of various ethanol mixtures as granulating liquid on power consumption (PC) and tensile strength (TS) on wet granular material

Saturation (%)	20.1	40.0	65.1	85.0	100.0	115.0	129.8
PC water	0	28.2	38.4	91.8	258.6	106.8	13.2
TS water	462.5	1203	1138.5	2736	1110	616.5	238
Saturation (%)	14.3	28.9	62.2	90.6	100.0	116.5	130.5
PC ethanol 24%	0	25.8	43.8	112.8	165.0	136.8	38.4
TS ethanol 24%	378.5	904.5	1150.5	2483	1742.5	736.5	530.5
Saturation (%)	12.8	25.4	54.4	83.4	91.7	100.0	112.4
PC ethanol 48%	4.2	15.6	28.2	51.6	139.8	97.2	105.6
TS ethanol 48%	396.5	702.5	1144	2407	2031.5	1787	1312.5
Saturation (%)	10.3	26.0	47.9	87.5	100.0	112.8	124.4
PC ethanol 96%	0	17.7	24.0	44.1	104.4	78.3	30.9
TS ethanol 96%	301.5	764.5	950	1518	1442.5	1389	1047.5

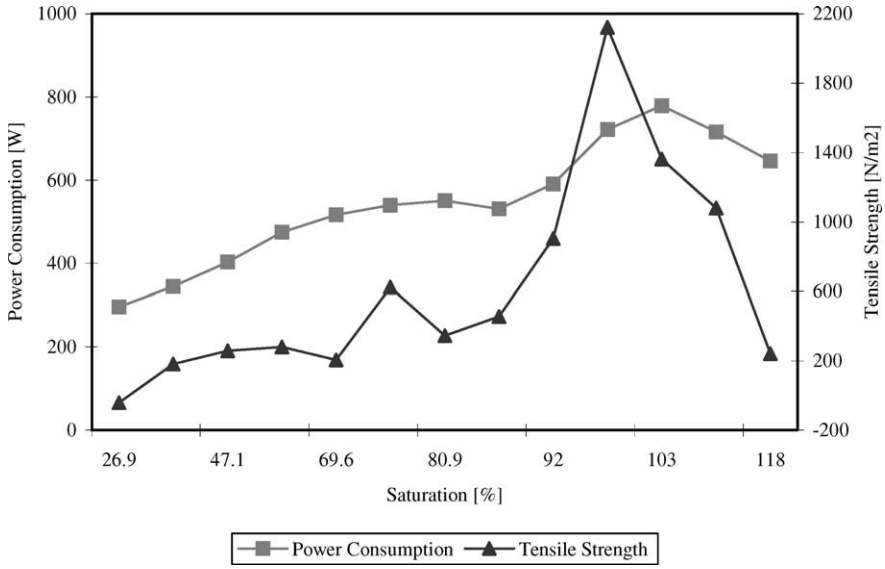

Fig. 8. Comparison of power consumption and tensile strength measurements.

tensile strength measurements occurred at 90% saturation, named entry suction by Rumpf (1958). The tensile strength expresses the cohesiveness between the powder particles, which is dependent on saturation and capillary pressure. The measured tensile strength σ (N/m^2) equals to the volume specific cohesion (J/m^3). The obtained results proved that the power consumption measurement is an alternative, simple and inexpensive method to determine the cohesion of powder particles.

3.2.3. *Effect of ethanol addition on the power consumption and tensile strength measurements*

The influence of the type of granulating liquid on tensile strength and power consumption was investigated using increasing amounts of ethanol addition to

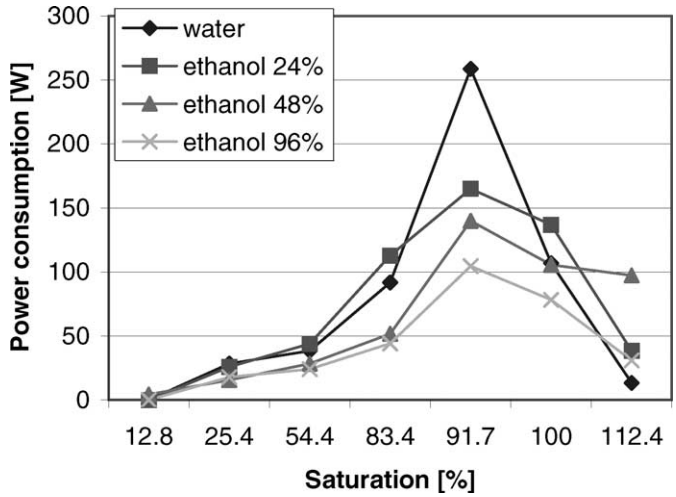

Fig. 9. Influence of various ethanol mixtures as granulating liquid on power consumption measurements.

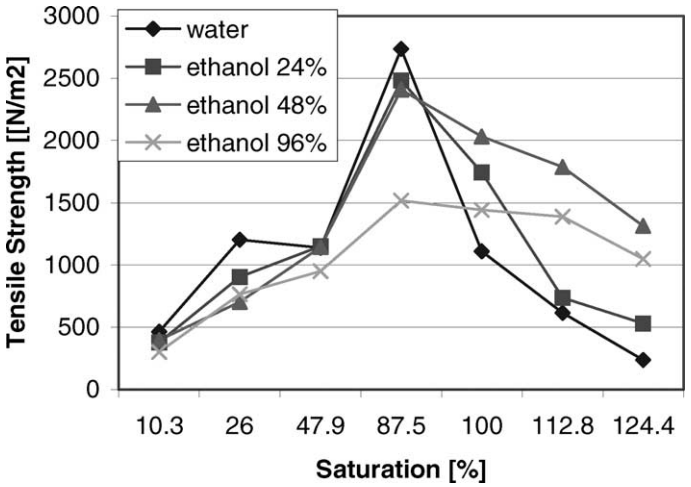

Fig. 10. Influence of various ethanol mixtures as granulating liquid on tensile strength measurements.

water and pure ethanol as granulating liquid, respectively. The results presented in Figs. 9 and 10 indicate that the values of tensile strength and power consumption declined with decreasing surface tension of the granulating liquid. The forces acting between the individual particles, like van der Waals, capillary and electrostatic forces, and tensile strength are dependent on the surface tension of the granulating liquid. The mentioned forces decline with decreasing surface tension of the granulating liquid (Pietsch and Rumpf, 1967; Schuber, 1972). This is in agree with the results obtained in this work. Whereas independent of the type of granulating liquid the maxima of the tensile strength was constantly determined at 90% saturation and the maxima of power consumption at 100% saturation.

In Fig. 9, the absolute value of the power consumption profile decreased with increasing ethanol additions to the granulating liquid, this is especially true for the values obtained at the maxima of power consumption (100%). In Figs. 9 and 10, the tensile strength profiles at 90% saturation showed highest tensile strength with pure water and lowest with ethanol 96%. The ethanol–water mixtures in between showed no significant difference in tensile strength of the powder bed.

3.2.3.1. Proportionality between tensile strength at 90% saturation, power consumption at 100% saturation and surface tension of the granulating liquid. The results, given in Table 6, proved the proportionality between power consumption and surface tension of the granulating liquid since the calculated ratios are about identical and the discrepancies within experimental error. Whereas, no clear proportionality could be observed with the ratios of tensile strength and surface tension to that of water, respectively. The use of ethanol 24 and 48% as granulating liquid had little effect on tensile strength reduction (9 and 12% reduction compared to water, respectively). Ethanol 96% reduced the tensile strength by 44% to that of water.

Table 6
Comparison of the ratios of tensile strength (σ), power consumption (PC) and surface tension (α) of the granulating liquid (GL) to that of water (W), respectively

	Water	Ethanol		
		24%	48%	96%
σ_{GL}/σ_W	1	0.91	0.88	0.56
PC_{GL}/PC_W	1	0.64	0.38	0.40
α_{GL}/α_W	1	0.48	0.39	0.31

This proportionality between power consumption and surface tension of the granulating liquid can be used to predict the influence of the granulating liquid on the power consumption profile by calculating the ratios of the surface tension of the granulating liquids.

4. Conclusions

This work has shown that the granulation process can be controlled by power consumption measurement

using an "in process" computer calculation program in order to determine the turning point of the profile as a parameter for the cohesiveness of the starting material and therefore for optimal end-point detection at an early stage. The influence of changing the granulating liquid on the power consumption profile can be predicted by calculating the ratios of the surface tension of the granulating liquids. Furthermore, the tensile strength measurements proved that the power consumption is an alternative and simple method to determine the cohesion of powder particles. Therefore, the turning point is introduced as a signature of the process taking into account the properties of the starting material "in process" without preliminary or further experiments.

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