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Power consumption measurement and temperature recording during granulation

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Abstract

This study was performed to elucidate the influences of process and formulation design using power consumption and temperature measurements during granulation. Power consumption was recorded "in process" using a previously introduced computer program for optimal end-point detection at an early stage. The temperature increase (ΔT) during granulation was recorded using a temperature sensor. The temperature increase in the wet powder bed expresses the friction forces at interparticle contacts occurring during granulation. The maxima of temperature profile occurred at 130% saturation, whereas the maxima of power consumption were determined at 100% saturation. The ratio of temperature and power consumption (TPR factor) is introduced as a signature of formulation design. TPR factor was found to be dependent on particle size, particle surface, water absorption capacity and solubility of the excipient and model drug, respectively. However, TPR factor was found to be independent of process design, such as the filling level of the mixer.

Understanding and controlling the granulation process is a key factor in robust dosage form design. The "in process" control fits ideally the prerequisites of a drug quality system for the 21st century and FDA's Process Analytical Technology (PAT) initiative. The results of previous and present works of our research group will be used in a following step to develop an artificial neural network for granulation "in process" control.

Keywords: Granulation; Power consumption; Temperature control; In process control; Formulation design

1. Introduction

The pharmaceutical industry commonly applies wet granulation to powder mixtures in order to improve powder characteristics, such as flow and compressibility. Granulation is the process of agglomerating particles together into larger, semi-permanent granules in which the original particles can still be distinguished (Ennis and Lister, 1997). The granulating liquid binds the particles together by a combination of capillary and viscous forces until more permanent bonds are formed by subsequent drying or sintering. Granulation is an example of particle design and the control of the process is a key factor in robust dosage form design and should assure a constant quality of the granulate. The desired properties of the granulate are controlled by a combination of formulation design (choosing the starting material and liquid according to its properties) and process design (choosing the type of granulator and the operating parameters).

The process control is often linked to torque of the mixer shaft in the granulating equipment (Lindberg et al., 1974, 1977) or by power consumption of the mixer motor (Bier and Leuenberger, 1979;

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Leuenberger, 1982, 1983; Werani, 1988). The power consumption measurement of the mixer motor as a function of the granulating liquid added per unit time was published in the work (Bier and Leuenberger, 1979) to control the granulation process efficiently. In a previous paper (Betz et al., 2003a), the relationship between tensile strength and power consumption of the wet powder mass was investigated. It was proven that the power consumption measurement is an alternative, simple and inexpensive method to determine the cohesion of powder particles. Therefore, an "in process" computer calculation program was developed to record the power consumption profile during granulation. The reference point of the profile, the turning point, was introduced as a signature of the process taking into account the properties of the starting material without preliminary experiments.

The tensile strength of wet granular material is a strong function of the packing density. When smaller particles are used the number of interparticle contacts is increased and the average interparticulate pore size is decreased leading to an increase of capillary and viscous forces. Tensile strength of the wet granular material decreases as granulating liquid surface tension is lowered (Betz et al., 2003a; Kristensen et al., 1985; Usteri, 1988) due to capillary suction pressure and surface tension forces which are both proportional to liquid surface tension (Iveson et al., 2001). Capillary forces increase with increasing granulating liquid content up to the capillary state. However, granulating liquid can also lubricate interparticle contacts, thus reducing frictional forces (Usteri, 1988). Hence, the effect of liquid content depends on which force is dominant.

Tensile strength of granulates is controlled by three forces—capillary and viscous forces in the liquid phase and frictional forces at interparticle contacts. These forces are interrelated in a complex way. Capillary forces control the rate of granule consolidation by acting on the effective contact surfaces and therefore modifying the interparticle friction forces. For low saturation levels, friction forces increase as the interparticle contact area increases and for high saturation levels capillary forces act as lubricant of the interparticle contact. Due to interparticle friction forces occurring during granulation the temperature is increasing within a wet powder bed. Heat transfer through a particulate system is not entirely due to conduction, as in a homogeneous solid, but to a combination of different modes of heat transfer, such as conduction through the solid particles and liquids, radiation at the particle surfaces, and conduction and convection through the gaseous and liquid space (Widenfeld et al., 2003).

The objective of the present study was to evaluate temperature recording during granulation as an "in process" control in a high shear mixer. Furthermore, to compare temperature and power consumption profiles during wet granulation. Finally, the comparison will lead to the conclusion, whether the power consumption measurements correlate with the temperature profile of the wet granular material. Moreover, a temperature-power consumption-ratio (TPR) factor is introduced to compare various compositions in order to predict the effect of formulation properties. Finally, the process of scale-up was considered at different filling levels by the determination of power consumption and temperature profile. The results are contributing to the development of an artificial neural network for granulation "in process" control.

2. Materials and methods

2.1. Materials

Paracetamol and Phenazon were a gift from Sandoz AG, Basel, Switzerland. Corn starch (Cerestar Gruppo Feruzzi, Gent, The Netherlands), polyvinylpyrrolidone (PVP) (ISP Technologies, Wayne, New Jersey) and α-lactose (200 mesh) monohydrate (Pharmatose, type 200M, 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.

Further lactose 35/40 mesh (De Melkindustrie, Veghel, The Netherlands), lactose 140 mesh (Granulac, type 140M, Meggle GmbH, Wasserburg, Germany),

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

lactose 400 mesh (Sorbolac, type 400M, Meggle GmbH, Wasserburg, Germany) and Aerosil 200/R972 (Degussa AG, Hanau, Germany) were used. The physical properties of the various types of lactose are compiled in Table 2.

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

2.2. Equipment

A Loedige M5 high-shear mixer (Loedige, Paderborn, Germany) with a volume of 5 l, and constant impeller speed kept at 278 rpm during the experiments was used. The power consumption of the mixer motor is determined by the electric current consumption of the motor taking into account the actual value of voltage U of the electric power source according to the equation $P = U \times I$, where P = power (W), U = electric voltage (V), and I = 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, Laptop Type AST 950N, Pentium P54c and displayed graphically.

Table 2
Physical properties of the used types of lactose

	Lactose		
	35/40	140	400
Bulk density (g/cm^3)	0.75	0.69	0.49
Tapped density (g/cm^3)	0.82	0.86	0.59
True density (g/cm^3)	1.28	1.42	1.73
Mean diameter (μm)	534	68	43

2.3. Methods

2.3.1. Power consumption profile recording and analysis

In order to analyse the power consumption profile "in process" a computer program was developed in a previous work (Betz et al., 2003a; Junker, 1998) to calculate the characteristical points and to save the obtained data digitally. These works have shown that the granulation process can be controlled by power consumption measurement using the "in process" (real time) 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 turning point of stage II is calculated using a polynomial approximation third order and the simplex method. Details of the program are described in Betz et al. (2003a).

2.3.1.1. 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 polynomial 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. Temperature recording during granulation

A problem in temperature recording during granulation is, that the temperature in the powder bed of the high-shear mixer at the beginning of the experiment is not constant. In succession, with each experiment the temperature is increasing and therefore the starting temperature of the powder bed of the following experiment. In order to eliminate this influence on further experiments the temperature difference between the start of granulating liquid addition and the temperature maximum was determined with a temperature sensor (Jumo, Switzerland). This parameter describes the temperature increase in function of the granulating liquid addition. A further parameter was the amount

of granulating liquid required to reach the temperature maximum.

2.3.2.1. Reproducibility of temperature increase during granulation. The temperature difference between the start of granulating liquid addition and the temperature maximum was determined six times.

2.3.2.2. Reproducibility of the required amount of granulating liquid. The amount of granulating liquid required to reach the temperature maximum was determined six times.

2.3.3. Introduction of the temperature-power consumption-ratio factor

The temperature and the power consumption profile are recorded in parallel. In order to compare various compositions of powder mixtures a specific dimensionless ratio $W(T/P)R$ between the amount of water used to obtain the maximum temperature and the amount of water to reach the maximum of power consumption is introduced:

$$\mathrm{TPR} = \frac{W(T_{\mathrm{Max}})}{W(P_{\mathrm{Max}})} \quad (1)$$

where $W(T_{\mathrm{Max}})$: amount of water to reach the maximum of temperature (g), $W(P_{\mathrm{Max}})$: amount of water to reach the maximum of power consumption (g).

2.3.4. Granulation procedure

2.3.4.1. Moist granulation. Powders were weighed and added to the bowl of the mixer. The powder mixture was premixed for 5 min prior to granulation liquid addition. After premixing the powders, purified water 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 granulation liquid addition was adjusted to result in a supplying rate of 1/75 cm^3/min/g. The temperature and power consumption measurements were started at the same time as the granulation liquid addition and stopped at the same time for sample drawing.

2.3.4.2. Drying. In order to reduce the possible effects of friability during the drying process in dish dryers, on the granule size distribution as a function of the amount π of granulation liquid added, the granules were dried for 2 min in a fluidised 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).

2.3.5. Granulate characterization

2.3.5.1. Particle size analysis. The dried granules were analysed 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 series with increasing particle size, in order to avoid obstruction of the upper sieve (Imanidis, 1986).

2.3.6. Influence of formulation design on the power consumption and temperature profile

2.3.6.1. Influence of model substances. The influence of increasing amounts of Paracetamol and Phenazon on the temperature and power consumption profile as well as the amount of required granulating liquid was investigated in a Loedige M5 high shear mixer. For that purpose the granulation procedure, see Section 2.3.4, was performed at five different mixing ratios (10–50%, m/m), respectively. The filling level of the Loedige M5 high shear mixer was kept at 52% (v/v).

2.3.6.2. Influence of corn starch. The influence of increasing amounts of corn starch on the temperature and power consumption profile as well as the amount of required granulating liquid was investigated in a Loedige M5 high shear mixer. For that purpose the granulation procedure, see Section 2.3.4, was performed with six different mixing ratios (0–96%, m/m), respectively. The filling level of the Loedige M5 high shear mixer was kept at 52% (v/v).

2.3.6.3. Influence of Aerosil. The influence of increasing amounts of Aerosil 200 (hydrophilic) and R972 (hydrophobic) on the temperature and power consumption profile as well as the amount of required

granulating liquid was investigated in a Loedige M5 high shear mixer. For that purpose the granulation procedure, see Section 2.3.4, was performed with four different amounts of Aerosil (0.1, 1.0, 3.0, and 10%, m/m). The concentration of corn starch (10%) and PVP (4%) was kept constant, see standard mixture. Increasing amounts of Aerosil were compensated with decreasing amounts of lactose. The filling level of the Loedige M5 high shear mixer was kept at 52% (v/v).

2.3.6.4. Influence of lactose quality. The influence of four lactose qualities (35/40, 140, 200, 400 mesh) on the temperature and power consumption profile as well as the amount of required granulating liquid was investigated in a Loedige M5 high shear mixer. For that purpose the granulation procedure, see Section 2.3.4, was performed with 4% (m/m) PVP addition to each lactose quality. The filling level of the Loedige M5 high shear mixer was kept at 52% (v/v).

2.3.7. Consideration of the energy processes in the powder bed

2.3.7.1. Calibration of the weighing method to determine the area under the curve (AUC). The AUC was determined by weighing. The mass of the weight can be converted into kW h.

2.3.7.2. Calibration curve to determine the volume reduction with increasing granulating liquid requirement. The volume of a powder bed is dependent on the water content. In order to consider energy/volume a calibration curve with increasing amounts of water (4, 7, 11, 15, 19%, w/w) in the powder bed is established. Seven percent corresponds to the water content at the turning point TP of the power consumption profile and 19% to the maximum saturation.

Five beakers were filled with 100.0 g dry standard mixture. Using diameter of the beaker (d) and height of the powder bed (h), the dry powder volume (V) was calculated according to

$$V = \pi r^2 \times h \quad (2)$$

The powder was stirred and water was added with a constant rate of 10 g/min up to the predetermined calibration point. Finally, the volume of the wet powder bed was calculated according to Eq. (2). The volume reduction of the wet powder bed compared to the volume of the dry state was plotted against the water content.

2.3.8. Scale-up precision

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 followed to quickly obtain optimisation and control of the process (Faure et al., 2001).

2.3.8.1. Influence of the filling level on the temperature and power consumption profile. The influence of the filling level of the Loedige M5 high shear mixer on the temperature profile and the amount of required granulating liquid was investigated. For that purpose the granulation procedure, see Section 2.3.4, was performed at eight different filling levels (26, 32.5, 39, 43.3, 47.7, 52, 58.5, 65%, v/v).

2.3.8.2. Area under the curve at various filling levels of the mixer. The energy consumption of the high shear mixer to reach each characteristic point, TP and MAX, was determined at eight different filling levels (26, 32.5, 39, 43.3, 47.7, 52, 58.5, 65%, v/v).

3. Results and discussion

3.1. Temperature recording

3.1.1. Reproducibility of temperature increase during granulation and the required amount of granulating liquid

The temperature increase during granulation (ΔT) and the required amount of granulating liquid was determined to be 20.6 °C and 462.3 g, respectively. The parameters for temperature recording are reproducible, see Table 3.

Table 3
Parameters for temperature recording

	ΔT (°C)	Amount of granulating liquid (g)
Mean	20.6	462.3
±S.D. ($n = 6$)	0.91	9.8
S.D. relative (%)	4.4	2.1

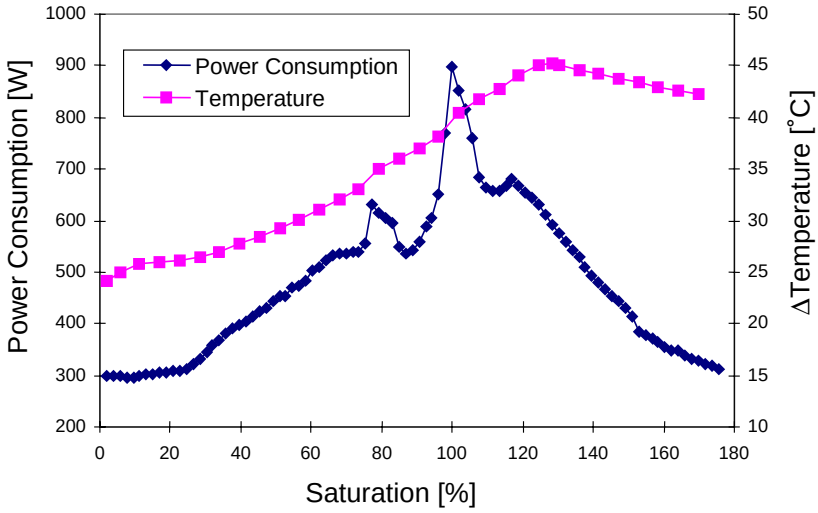

Fig. 1. Power consumption and temperature profile during wet granulation.

3.2. Comparison of the power consumption profile and the temperature profile

In Fig. 1, the temperature and power consumption profile is shown in function of the water saturation (%) during granulation. The maximum of each profile appeared at different saturation levels. The maximum of the power consumption profile appeared at 100% saturation and the maximum of the temperature profile at 130% saturation using Loedige M5 high-shear mixer and the standard mixture at a filling level of 52% (v/v). 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. The same was observed for the temperature curve, where the temperature was constant within the range of 2 °C up to a saturation level of 25%. In phase II, power consumption increased, due to the start of formation of liquid bridges between the primary particles, corresponding to the pendular state. In phase III, the plateau phase, the granulates are growing in size and the inter-particulate void space is filled up with the granulating liquid (transition from the pendular to the funicular state). The liquid bridges are mobile (low viscosity of the granulating liquid, Newtonian liquid).

The temperature curve increased about 3.5 °C during phase II and about 7 °C during phase III. In the work of Tardos (2003), a method to measure stresses on actual granulates moving in the powder bed during granulation by adding test particles with defined yield stresses was introduced. Shear stresses transmitted from the high shear mixer to the powder bed were found to increase with increasing granulating liquid content. In the equilibrium of shear stress and tensile stress the particles do not grow. In phase III the tensile strength is exceeding the shear stress, particles are growing in size and friction forces are increasing and therefore the temperature in the powder bed. Tensile strength of granulates is controlled by three forces—capillary and viscous forces in the liquid phase and frictional forces at interparticle contacts. Capillary forces are acting on the effective contact surfaces and therefore modifying the interparticle frictional forces (Widenfeld et al., 2003). In phase III, the saturation levels were still low, friction forces were increasing and heat transfer is transmitted through the powder bed by conduction and convection due to the presence of granulating liquid. At higher saturation levels granulating liquid can also lubricate interparticle contacts. Thus, the effect of granulating liquid content depends on which force is dominant.

A marked increase in the power consumption was observed at approximately 80% saturation and the maximum was reached at 100% saturation. The temperature curve rose 3 °C in phase IV and reached its maximum at 130% saturation. Usable granulates can

be produced in a conventional way within the plateau region phases III and IV, corresponding to the funicular state. The temperature curve showed the highest increase during phases III and IV and is therefore promising for granulation process control. In a previous work (Betz et al., 2003a), a simple apparatus for tensile strength measurements was introduced and the influence of the amount of liquid present in the granular material (% saturation) was investigated. The maxima of tensile strength measurements occurred at 90% saturation, named entry suction (Rumpf, 1958). The tensile strength expresses the cohesiveness between the powder particles, which is dependent on saturation and capillary pressure.

3.3. Influence of the formulation design on the power consumption and temperature profile

The temperature and the power consumption profile are recorded in parallel. In order to compare various compositions of powder mixtures a TPR is introduced and the influence of formulation design on the TPR factor is investigated.

3.3.1. Influence of model drugs

Two active drugs with different water solubilities were compared on their influence on TPR factor, see Fig. 2. Phenazon representing a highly water-soluble active drug and Paracetamol a low water-soluble one. With increasing amounts of Paracetamol in the formulation the TPR factor is increasing. Paracetamol, representing a low water-soluble drug, contributed to a faster saturation of the interparticular void space and therefore to less granulating liquid requirement to reach the power consumption maximum (100% saturation). The opposite behaviour was found with Phenazon representing a highly water-soluble active drug, where the TPR factor is decreasing with increasing amounts of Phenazon in the formulation. If the active substance is soluble in the granulating liquid more liquid is required to fill up the interparticular void space. All TPR factors are greater than one, which means that the maximum of the temperature curve was always occurring after the maximum of the power consumption profile.

The presented results showed that two model drugs with different water solubility could be distinguished with the TPR factor. This is a promising result in order to predict the influence of material properties on process control.

3.3.2. Influence of corn starch

Increasing amounts of corn starch in the standard formulation prolonged the duration of phase I and phase II in power consumption analysis and therefore the amount of granulating liquid requirement increased to reach the characteristic point MAX, which corresponds to 100% saturation of the powder bed, see Fig. 3. Therefore, increasing amounts of corn starch showed increasing amounts of granulating liquid requirement. This is due to the high water absorption capacity of corn starch. Liquid bridges are formed delayed due to absorption, depending on the amount of corn starch in the mixture.

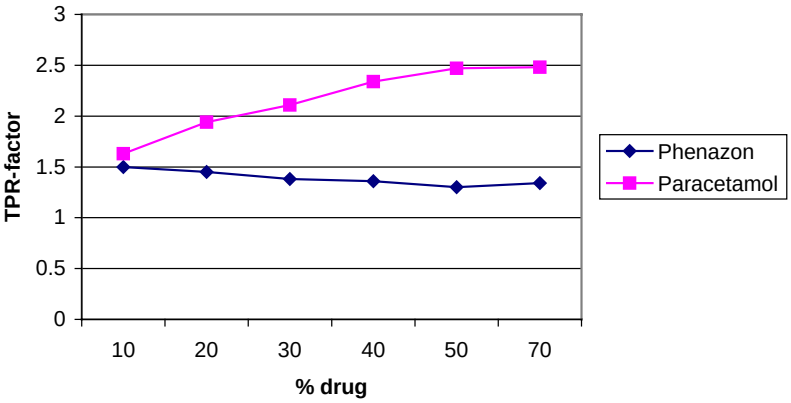

Fig. 2. Comparison of the influence of two active drugs on the TPR-factor.

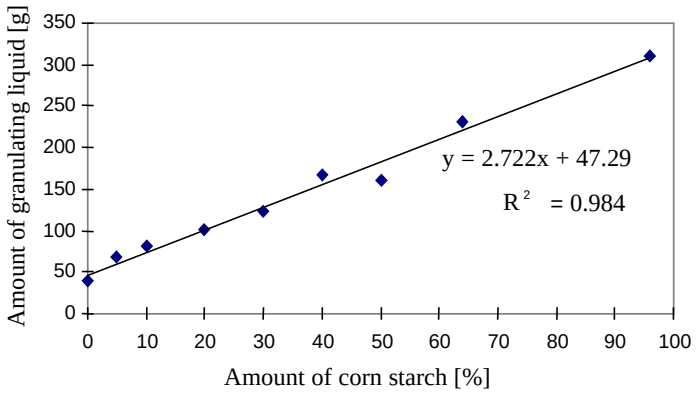

Fig. 3. Influence of increasing amounts of corn starch on the amount of granulating liquid requirement in (g) during phase II.

The temperature increase ΔT between starting point and end of granulation was also observed to increase with increasing amounts of corn starch and never exceeded the gelatinisation temperature of 75–80 °C. The wet powder bed containing corn starch and water forms a gel structure, which contributed to the increase of cohesiveness. Power consumption of the high shear mixer motor and the temperature in the wet powder bed was rising. With increasing amounts of corn starch, increasing amounts of granulating liquid were required and therefore heat transfer is enhanced with water as a heat conductor.

Introducing the TPR factor showed that all factors are greater than 1, meaning in all investigated granulation processes the temperature maximum occurred after the power consumption maximum. The composition of the formulation was observed to have great influence on the TPR factor, taking into account the gelatinisation temperature of corn starch of 75–80 °C was not exceeded.

With increasing amounts of corn starch, taking into account the TPR factor is decreasing. This is explained by the fact that the power consumption maximum is occurring at higher amounts of granulating liquid requirements with increasing amounts of corn starch due to the high absorption capacity. Especially, phases I and II are prolonged.

3.3.3. *Influence of Aerosil*

With increasing amounts of Aerosil in the formulation, the granulating liquid requirement is decreasing to reach the characteristic points of the power consumption profile, this was found to be true for both, Aerosil 200 and R972. Aerosil is insoluble in water and forms a colloidal dispersion. Therefore, less granulating liquid is required with increasing amounts of Aerosil, see also Section 3.3.1 model drug Paracetamol. Aerosil 200, with its hydrophilic properties on the particle surface required more granulating liquid than Aerosil R972, due to free silanol groups, which adsorb water over silica surface.

Besides the water adsorption capacity, Aerosil is able to enwrap and to attach to the surface of other particles, which leads to a lubricating effect due to ball bearing behaviour. Therefore, increasing amounts of Aerosil decreased the cohesiveness of the wet powder mass and therefore the absolute power consumption values of the profile.

Studies of wetting thermodynamics have focused on two aspects: the contact angle between the solid and the granulating liquid, and the spreading coefficients of the liquid phase over the solid phase and vice versa (Ennis and Lister, 1997). The solid–liquid contact angle of the system directly affects the characteristics of the granulated product. In the work of Aulton and Banks increasing amounts of a hydrophobic powder (salicylic acid with a contact angle of $\theta = 103^\circ$) were mixed with a hydrophilic powder (lactose with a contact angle of $\theta = 30^\circ$). As the contact angle of powder mixture increased, the mean granule size decreased (Aulton and Banks, 1979). In the present work, increasing amounts of Aerosil R972 (wettability of the powder mixture decreased with a contact angle of $\theta \approx 140^\circ$, Ohta et al., 2003) required decreasing amounts of granulating liquid to reach the characteristic points

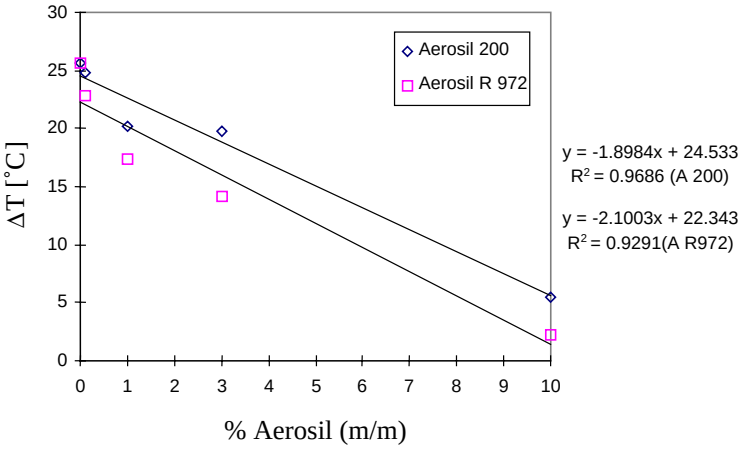

Fig. 4. Influence of Aerosil addition on ΔT during granulation.

of the power consumption profile. The results indicated the same trend.

These results were consistent with the temperature profile. Due to decreasing friction forces within the powder bed, ΔT was decreasing with increasing amounts of Aerosil addition, see Fig. 4. This result was more pronounced for Aerosil R972 due to lower water content.

The important point is that the structural difference of the model substances Aerosil 200 and R972 could be detected using power consumption and temperature process control.

3.3.4. Influence of lactose

In order to investigate the influence of particle size on the power consumption profile and the temperature in the powder bed, four different lactose qualities were used in the formulation (35/40, 140, 200 and 400 mesh corresponding to a median particle size of 534, 93, 68 and 43 μm, respectively).

With decreasing particle size the granulating liquid requirement increased to reach the characteristic points TP and MAX of the power consumption profile, see Fig. 5. Parallel to that observation, the absolute value of power consumption increased as well with decreasing particle size.

Comparing the standard mixtures containing corn starch with the different lactose qualities containing just PVP 4% (m/m), it is obvious that the high absorption capacity of corn starch is causing higher granulating liquid requirement, see also Section 3.3.2. The power consumption of the mixer motor was not influenced, due to prolongation of phase I, where no liquid bridges are present.

The same relationship was observed for the temperature profile. With decreasing particle size of lactose ΔT was increasing during granulation. A linear relationship was observed between the volume-specific surface (cm^2/ml) and ΔT.

3.4. Consideration of the energy processes in the powder bed

3.4.1. Calibration of the weighing method to determine the area under the curve (AUC)

0.01943 g (relative standard deviation 5.11%, $n = 9$) of the paper were determined to correspond to 5.87 10^{-3} kW h.

3.4.2. Volume reduction with increasing granulating liquid content

In order to consider energy per volume wet powder bed a calibration curve was performed with increasing water content, see Fig. 6. The volume reduction at 19% water content was found to be about 30% and equals to the saturation at the characteristic point MAX.

3.5. Scale-up of the granulation process

3.5.1. Influence of the filling level of the mixer

3.5.1.1. Temperature increase during the granulation process. A linear relationship was found between

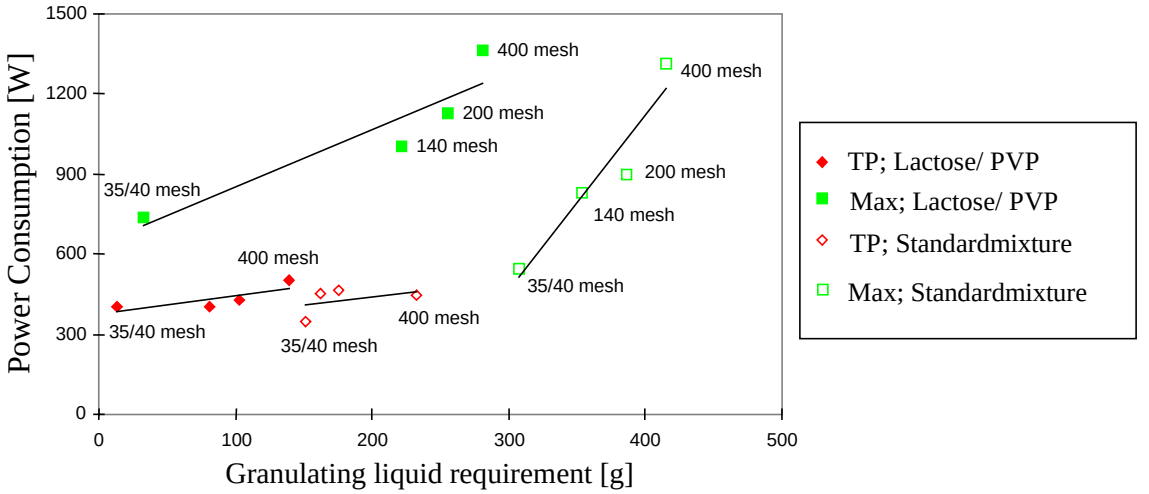

Fig. 5. Influence of particle size on power consumption profile.

the temperature increase ΔT (starting point and end of granulation) and the filling level of the mixer, see Fig. 7. The friction forces are increasing with increasing filling levels and decreasing space in the mixer. Furthermore, the probability of collision of powder particles is increasing and led to energy transformation into heat.

3.5.1.2. Granulating liquid requirement to reach power consumption and temperature maximum. The granulating liquid requirement to reach the temperature and power consumption maximum was found to be linearly increasing with the filling level of the mixer, see Fig. 8. Friction processes are accumulating and the collision of powder particles is increasing. The temperature maximum always occurred after the power consumption maximum irrespective of the filling level. The TPR factor was found to be constant at 1.31 (relative standard deviation 1.64%, $n = 8$) in the filling range of 26–65%. Therefore, the TPR factor is independent of the filling level, which is important for the scale-up of the granulation process in the same mixer. Whereas the TPR factor was found to be dependent on the composition of the formulation. Friction forces occurring in a powder bed are dependent on the properties of the powder, such as particle size, particle form, particle surface, and solubility and therefore the TPR factor is influenced by formulation design.

3.5.1.3. Area under the curve at various filling levels of the mixer. The energy consumption (kW h) increased linearly up to the characteristic points of the

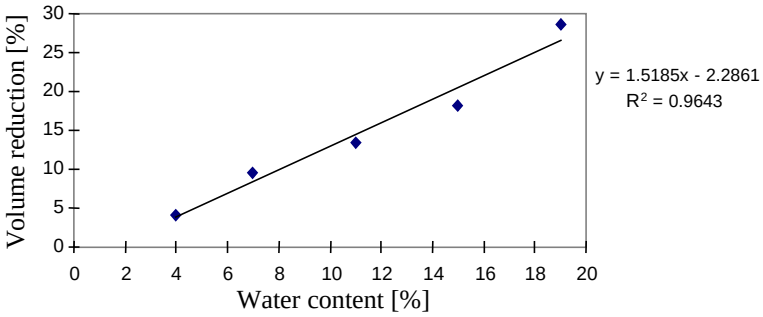

Fig. 6. Calibration curve.

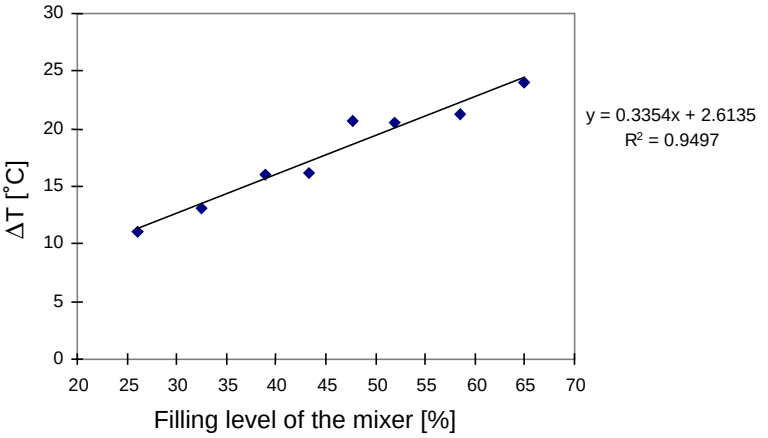

Fig. 7. Influence of the filling level of the mixer on ΔT between start and stop of the granulation procedure.

power consumption profile with increasing filling level of the high shear mixer, see Fig. 9.

This is an important result and a prerequisite in scale-up of the granulation process using power consumption measurements for "in process" control.

Power consumption (W) divided by the wet powder volume (ml) (see Fig. 10) was found to be independent of the relative filling level at both characteristic points of the profile. This is an important prerequisite in scale-up and allows calculations to estimate the power consumption of larger scales before the process is started.

In previous works of the research group in Basel was already reported that the ratio of granulating liquid requirement and amount of powder mixture is constant (Bier and Leuenberger, 1979). The power consumption profile as defined by the parameters S3, S4, S5 (Leuenberger, 1983) or TP and MAX (Betz et al., 2003a) is independent of the batch size.

Furthermore, the temperature recording was found to be independent of the filling level in this work, when ΔT was divided by the amount of required granulating liquid to reach temperature maximum. This means that temperature recording is applicable for "in process" granulation control, if the temperature is known at which the optimal granulate is obtained.

From these previous and present findings one can conclude that the correct quantity of granulating

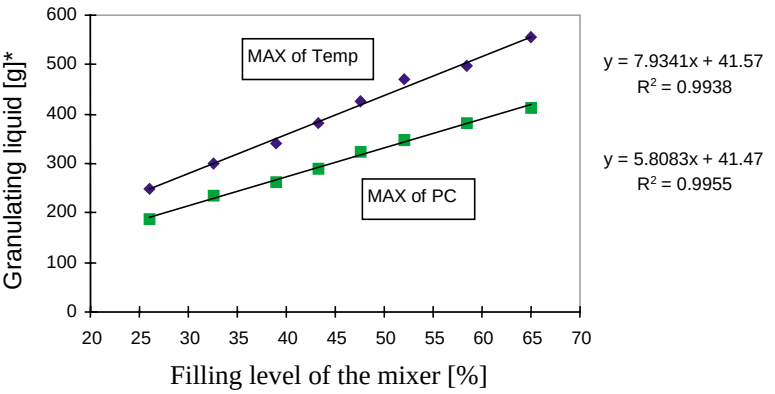

Fig. 8. Granulating liquid requirement to reach temperature and power consumption maximum. (*) Granulating liquid requirement (g) to reach the maxima of the temperature and power consumption profile; MAX of Temp: maximum of the temperature profile; MAX of PC: maximum of the power consumption profile.

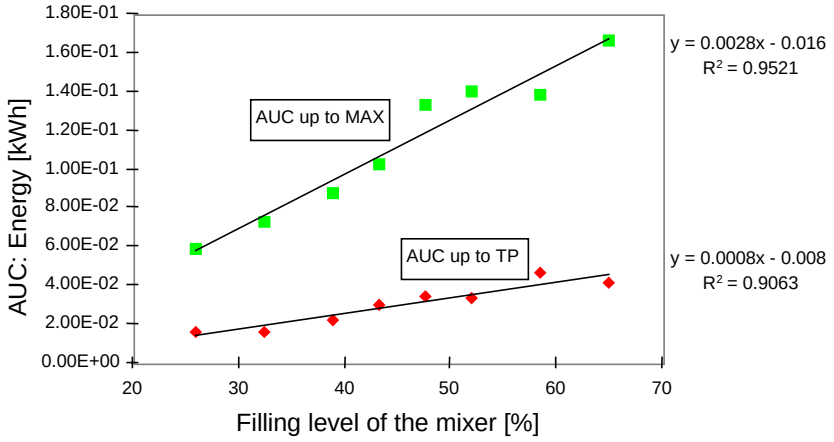

Fig. 9. AUC with increasing filling levels of the mixer at the characteristic points of the power consumption profile.

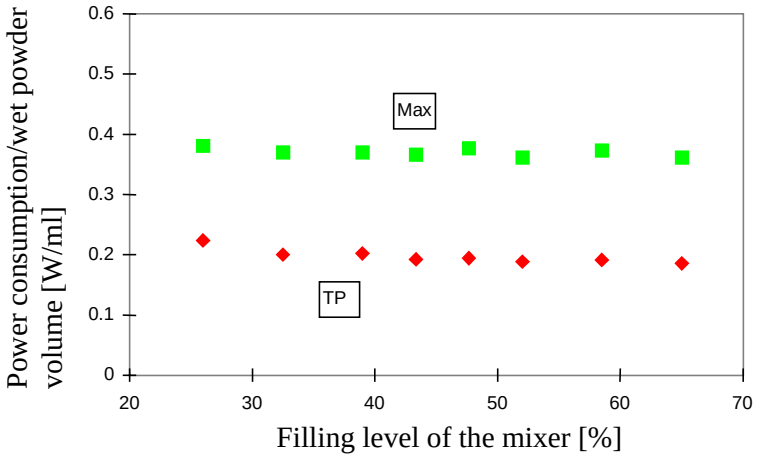

Fig. 10. Volume-specific power consumption.

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 in a quasi-continuous process, where no scale up is involved (Leuenberger, 2001a,b). Consistent and reproducible granule quality is a key factor in robust dosage form design and fits ideally the prerequisites of a drug quality system for the 21st century and FDA's PAT initiative (Betz et al., 2003b).

4. Conclusion

This work has introduced power consumption measurements and temperature recording during granulation as an "in process" control. Furthermore, the ratio of power consumption measurement and temperature recording (TPR factor) was introduced as a signature of formulation design. The influence of changing the formulation can be predicted by considering particle size, particle surface, water absorption capacity and solubility of the starting material. TPR factor was determined to be dependent on formulation design,

however not on process design, such as the filling level of the mixer. The filling volume-specific power consumption was also detected to be independent of the relative filling level. This is an important result for granulation process scale-up and allows calculations to estimate the power consumption of larger scales before the process is started. The results have given valuable information about the granulation process.

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