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In-line dynamic torque measurement in twin-screw extrusion process

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ABSTRACT

Extrusion technology has been a focus of pharmaceutical research for many years. Extrusion processes are used for improvement of drug bioavailability, for bead manufacturing as well as for continuous granulation. Besides these, there are also several research efforts regarding the use of process understanding as a tool in quality management. Several initiatives of the Food and Drug Administration (FDA) about this issue such as Process Analytical Technology (PAT) and Quality by Design (QbD) are becoming more and more accepted.

In the present study, a corotating twin-screw extruder was equipped with a torque gauge as a tool for process monitoring. The experimental setup was qualified in accordance with the ICH guidelines. The torque of extrusion correlated linearly with the water content in a wet extrusion process. Moreover, a pelletisation process was performed using different formulations in wet extrusion/spheronisation. A relationship between the torque on the screws and the shape of the pellets was found. In conclusion, the torque was found to be a suitable extrusion parameter for monitoring wet extrusion processes.

1. Introduction

The extrusion process has gained increasingly more attention in pharmaceutical development during the last few years. These scientific efforts have focused on three main processes – Hot Melt Extrusion, Extrusion/Spheronisation and Continuous Granulation. *Hot Melt Extrusion* is a suitable tool for improvement of the bioavailability or manipulation of the solid state properties of the drug [1]. *Extrusion/Spheronisation* is excepted for manufacturing spherical beads based on high drug loading capabilities, high yields and reproducibility [2]. The third well-known process is *Continuous Granulation* using extrusion for improvement of the efficiency [3]. There are several types of extruders used for these applications, but the corotating twin-screw extruder has become the standard based on its universal use and reproducibility [4]. Therefore, this extruder type was chosen for this study.

In the last few years, there has been a paradigm shift from empiric process development to process understanding using various tools for process monitoring. Based on this trend, the Food and Drug Administration introduced the phrase “Process Analytical Technology” (PAT) in their guidelines [5]. PAT is a set of tools for implementing the “Quality by Design” (QbD) concept wherein the product properties are controlled by predefined process limits. The goal of these initiatives is the improvement of product quality by identifying, monitoring and controlling the crucial process and product parameters – i.e., process understanding and control.

The mechanical power consumption of an extruder is the most crucial process parameter in extrusion because it correlates with several other important parameters which can not be easily monitored during the manufacturing process. Such parameters include the rheological behaviour of the material, grinding processes during extrusion and the velocity of material through the extruder. The aim of this study was to establish an experimental setup to make in-line power consumption measurements as a PAT tool.

Most extruders measure the electric current of the motor during the extrusion process to detect an overload of the system. This is a safety measure and is not really useful as a PAT tool, because the resolution of the signal is too low for most applications. Nevertheless, it is often reported in the literature [6], because it is easy to calculate the power consumption from the electric current and voltage. Some single screw extruders use a torque gauge at the screw to measure the power consumption [7]. However, this setup is difficult using the common twin-screw extruders because the screws are close to each other. Based on this, there is not enough space to install two torque gauges directly at the screws. Therefore, one torque gauge for both screws was installed between the transmission box and the motor (Fig. 1) in this study. This setup is adequate if the yield of transmission is constant.

The power consumption (P) can be easily calculated from the torque (M) and either the angular velocity (ω) or the screw speed (n) by Eq. (1) [8]. However, these preliminary investigations dealt solely with the torque because the raw signal was the focus in this

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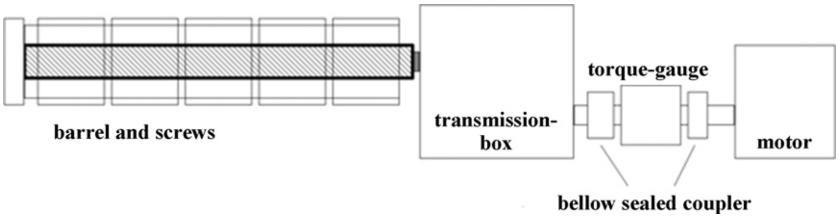

Fig. 1. Torque-gauge in the Leistritz Micro 27GL-28D.

study.

$$P = \omega M = 2\pi n M \quad (1)$$

The torque gauge was tested by a wet extrusion/spheronization process because the power consumption in this process is low compared to melt extrusion processes [6]. Therefore, this process adequately challenged the gauge while yielding results that should be applicable to processes with high power consumption such as melt extrusion and granulation.

In the extrusion/spheronization process, the powder material and water were constantly fed into an extruder, mixed and extruded through an 1 mm diameter die. Afterwards, these extrudates were transferred to a spheroniser and transformed from a cylindrical to a spherical shape. The pellet shape is highly affected by the extrusion process – particularly by the water content during extrusion [9]. Finally, the torque during extrusion was investigated with respect to the water content as well as the shape of the resulting pellets.

Similar studies were provided from Leuenberger et al. [10] in high shear granulation and Linder in extrusion/spheronisation [11]. The novelty of the study is the qualification of the experimental setup as well as the much higher resolution response signals.

2. Experimental

2.1. Experimental setup

The lab scale extruder Micro 27GL-28D (Leistritz, Nuremberg, Germany) was equipped with a torque gauge (T22/50, HBM Messtechnik, Darmstadt, Germany) between the motor and the transmission system. Two bellow sealed couplers were used to minimize the effects of tilts between the sensor, motor and transmission (Fig. 1). The signal was processed by an analogue/digital-transformer-card (PCI-6031-E, National Instruments, Los Angeles, USA) within a personal computer. The system was calibrated with a lever-mass-system with 9 different masses up to 2.5 kg (resulting in approx. 0–25 Nm) (Fig. 2). A 1.00 m lever was mounted to the coupling of the screw, and the motor was mechanically blocked. The calibration was done though the transmission.

2.2. Pelletisation process

The dry powders were weighed and blended for 15 min in a laboratory scale blender (LM40, Bohle, Ennigerloh, Germany) and then transferred into the gravimetric powder feeder (KT 20, K-Tron Soder, Niederlenz, Switzerland) of the extruder. The twin-screw extruder (Mikro 27GL-28D, Leistritz, Nuremberg, Germany) was equipped with an axial screen with dies of 1 mm diameter and 2.5 mm length. The extrusion took place at a constant powder feed rate of 30 g/min and a suitable liquid feed rate. De-ionised water was used as the granulation liquid supplied by a membrane pump (Cerex EP-31, Bran and Luebbe, Norderstedt, Germany) with a flow through metering device (Corimass MFC-081/K, Krohne, Duisburg, Germany). Batches of 300 g wet extrudate were collected and spheronised for 5 min in a spheronizer (RM 300, Schlueter, Neustadt/Ruebenberge, Germany) fitted with a 300 mm diameter, cross/hatched rotor. The drying step was carried out in a fluid bed apparatus (GPCG 1.1, Glatt, Dresden, Germany) for 10 min with an inlet air temperature of 65 °C.

The following materials were used as received: κ-Carrageenan (Gelcarin® GP 911 NF, FMC, Philadelphia, PA, USA), Lactose (Granulac 200, Meggle, Wasserburg, Germany) and MCC 102 (Pharmatrans Sanaq, Basel, Switzerland).

2.3. Loss on drying

Three samples of extrudates were taken from each batch during extrusion for the determination of the extrudate water content. The samples were dried at 70 °C for 14 d in a vacuum oven (Heraeus VT 6060M, Kendo, Hanau, Germany). The water content of the extrudates was calculated in % (w/w) based on dry mass.

2.4. Image analysis

Each batch was sieved with sieves of 2.0 mm and 0.63 mm apertures respectively. The fraction retained between 0.63 and 2.0 mm is denoted as the yield. Statistically representative samples were obtained from the yield fraction using a rotary cone sample divider (Retschmuele PT, Retsch, Haan, Germany).

Image analysis software (Qwin, Leica, Cambridge, UK) was used to analyze images obtained using a system consisting of a stereo microscope (Leica MZ 75, Cambridge, UK), a ringlight with cold light source (Leica KL 1500, Cambridge, UK) and a digital camera (Leica CS 300 F, Cambridge, UK). Images of at least 500 pellets from each sample were recorded at a suitable magnification (1 pixel ≅ 17.5 μm) and converted into binary images. Contacting pellets were separated by a software algorithm. If the automatic separation failed, pellets were deleted manually. For each pellet, 36 Feret diameters and the projected area were determined. The ratio of the maximum Feret diameter and the Feret diameter perpendicular to the maximum Feret diameter was used as the aspect ratio.

3. Results and discussion

3.1. Installation and calibration

The motor of the extruder has a maximum power consumption of 9.4 kW at 2350 rpm. The corresponding maximum torque

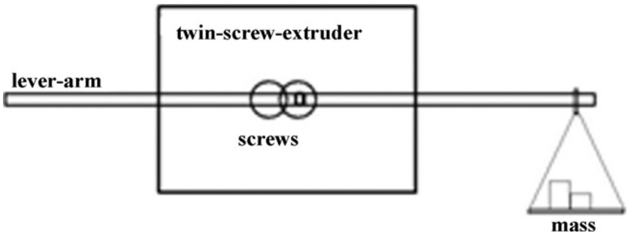

Fig. 2. Lever-Mass-System schematic drawing.

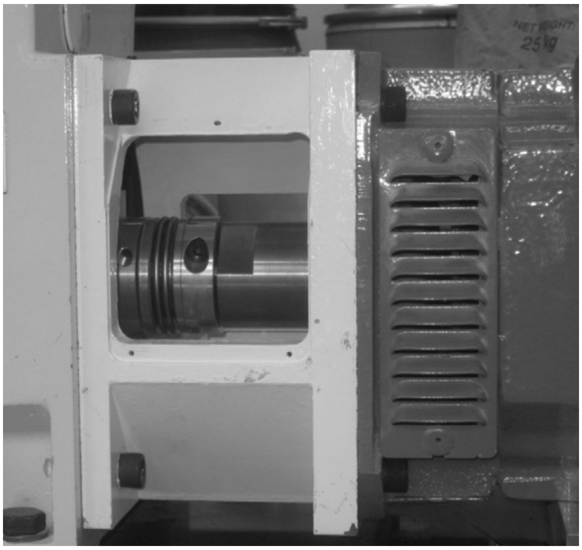

Fig. 3. Experimental setup, Transmission - Torque Gauge Housing – Motor.

of 38 Nm was calculated from Eq. (1) in order to select a torque gauge with a suitable range. The gauge (T22/50) used had an upper torque limit of 50 Nm which was considered to be adequate for this extruder [12]. The bellow sealed couplings were fitted to the shaft of the motor and the transmission. Additionally, a spacer was placed between the motor and transmission in order to create housing for the torque gauge (Fig. 3). The signal from the gauge was a voltage between −5 and +5 V.

The reproducibility of the signal was investigated first. This was done by recording the torque while running the machine for several minutes at different screw speeds without the screws. Air bubbles in the transmission oil changed the torque resulting in an irreproducible signal. This problem was overcome by increasing the filling level of the oil in the transmission box. Furthermore, an effect of the gear temperature on the torque signal was observed, which was attributed to a viscosity change of the oil. This effect became negligible by equilibrating the extruder for 1 h at 100 rpm before starting experiments.

The measuring system was qualified in accordance with the Q2(R1) guideline of the ICH [13]. The *Specificity* of the signal is intrinsic to the experimental setup. The torque at the screws could be correlated with the torque between the motor and transmission because the yield of the transmission was constant. Special conditions were mentioned previously. The *Accuracy* was demonstrated by placing weights at specified distances using the calibration lever described previously. The *Intermediate Precision* was established by calculating the coefficient of variation of three replicate measurements for nine different weights. The coefficients of variation ranged from 0.29 to 0.54%. The *Limit of Quantification* was defined as 10 times the baseline noise [13] at 0.23 Nm. The *Linearity* of the signal was investigated twice using the lever and 9 different weights generating torques from 3 to 23 Nm. The lever was loaded with increasing weights and afterwards stepwise unloaded by weight decreases. The small difference in the intercept of both calibrations was attributed to friction in the gear box. The coefficients of determination were $R^2 = 0.9999$ for the loading and $R^2 = 0.9994$ for the unloading (Fig. 4).

The scope of the torque gauge calibration model should be suitable for monitoring torque changes during a wet extrusion/spheronisation process.

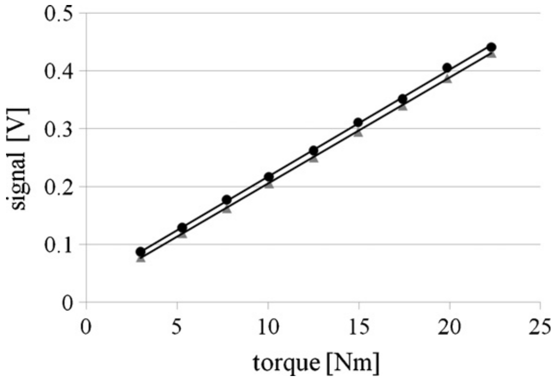

Fig. 4. Calibration of the torque gauge, (▲) loading and (●) unloading.

3.2. Extrusion process

Further evaluations dealt with the torque measurements during the extrusion process. For these investigations, mixtures of microcrystalline cellulose (MCC) and lactose without any drug were used (Table 1). MCC is a well established pelletisation aid and is often used in extrusion/spheronisation. It gives the extrudate a particular rheological behaviour which is necessary for the process. Lactose is a common water soluble filler used in pharmaceuticals. In these formulations, lactose was used to vary the amount of MCC.

The extrusion process was done using a constant screw speed (50 rpm) and a constant powder feed rate (33 g/min). The liquid feed rate was varied at defined levels. The water content of the extrudate was quantified by loss on drying. Linear correlation of the water content and the extrusion torque were observed for all formulations (Fig. 5).

Small changes in the liquid feed rate changed the torque signal, because the rheological behaviour of the material was different. Low water contents resulted in high torques whereas high water contents resulted in low torque signals. Based on this, the torque seems to be a suitable parameter for in-line monitoring of the water content in wet extrusion processes. Small fluctuation in powder or liquid feed rate can be recognized by torque changes.

Table 1
Powder formulations using MCC as pelletisation aid.

	MCC25	MCC50	MCC100
MCC 101	25	50	100
Lactose	75	50	

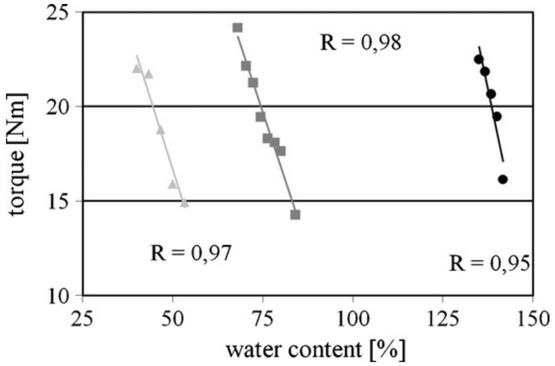

Fig. 5. Relationship of water content and torque in wet extrusion, (▲) MCC25, (■) MCC50, (●) MCC100.

Table 2
Powder formulations using κ-Carrageenan as pelletisation aid.

	Car25	Car50	Car100
κ-Carrageenan	25	50	100
Lactose	75	50	

3.3. Extrusion/spheronisation process

In this part of the study, six different placebo formulations (Tables 1 and 2) were pelletized by extrusion/spheronisation and the extrusion torque was correlated with the pellet shape. Besides microcrystalline cellulose, carrageenan was used as pelletisation aid. Lactose served as a filler in the formulations.

Each formulation was pelletised using different water contents. The water content is shown as a function of the pellet shape in Fig. 6a and b. This type of diagram is commonly used for evaluating the effect of the water content on the pellet shape [14].

The different formulations required different water contents in order to obtain spherical pellets (AR < 1.1, [15]). An increase of pelletisation aid (MCC and Carrageenan) increased the water binding capacity of the material thereby requiring higher amounts of water than for lower pelletisation aid concentrations. Carrageenan pellets needed more water than MCC pellets for the same amount of lactose [14]. The aspect ratio for each formulation decreased with an increase of the water content because the plastic properties of the extrudate increased too. Very high amounts of water however, cause a secondary agglomeration of MCC pellets causing the aspect ratio to increase above a certain water content [14].

This conventional approach to data evaluation was used to evaluate the aspect ratio of the same formulations with respect to the torque during the extrusion (Fig. 7a and b).

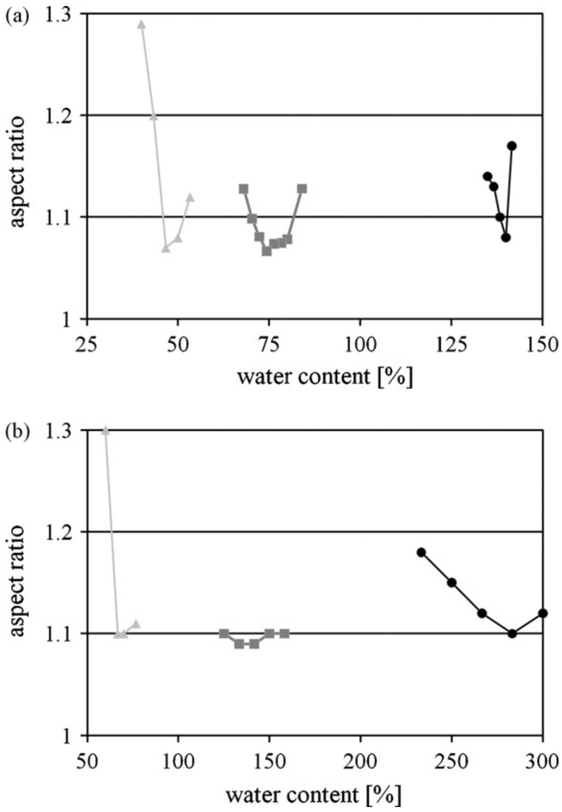

Fig. 6. (a) Pellet shape as a function of water content, (▲) MCC25, (■) MCC50, (●) MCC100. (b) Pellet shape as a function of water content, (▲) Car25, (■) Car50, (●) Car100.

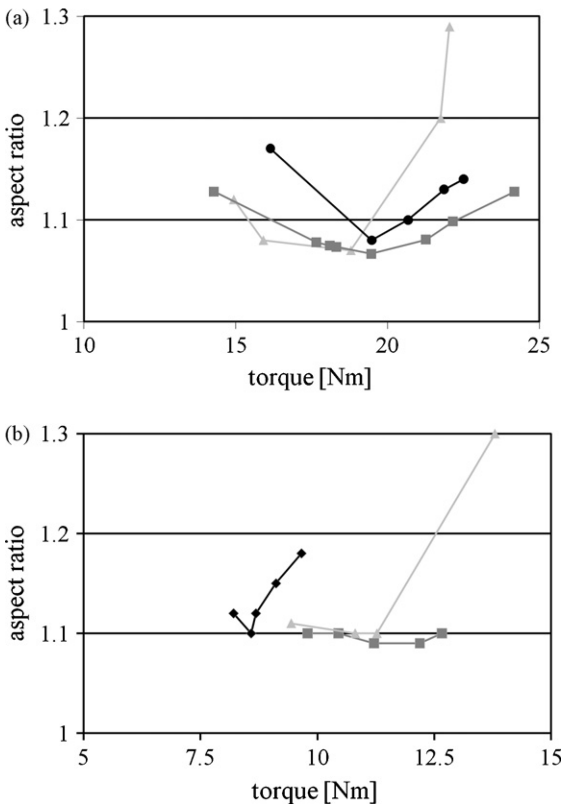

Fig. 7. (a) Pellet shape as function of extrusion torque, (▲) MCC25, (■) MCC50, (●) MCC100. (b) Pellet shape as function of extrusion torque, (▲) Car25, (■) Car50, (●) Car100.

All MCC formulations yielded spherical pellets (AR < 1.1) at similar torques of about 19 Nm (Fig. 7a). This can be explained by the rheological behaviour of the material. The torque correlates with the rheological properties of the material in the extruder whereas the rheological properties of the extrudates affect the pellet shape. Therefore, similar formulations yield spherical pellets at similar torques. The following hypothesis can then be posed about the shape of pellets produced from extrusion processes: The liquid feed rate can be adjusted on demand to achieve a torque which has a high probability of yielding spherical pellets.

This hypothesis is further supported by the carrageenan formulations (Fig. 7b). The formulations Car25 and Car50 also yielded spherical pellets at the same torque of about 10 Nm. However, Car100 had a much lower torque than the other formulations because it was produced using a lower powder feed rate of 15 g/min. This was necessary because it was impossible to obtain the demanded water content at the default powder feed of 30 g/min. Therefore, the powder feed rate was reduced. It is concluded from these investigations that the torque measurement during wet extrusion/spheronisation is a suitable tool for determining the necessary water content for producing spherical pellets.

4. Conclusion

In summary, a lab scale extruder was equipped with a torque gauge for measuring the mechanical energy uptake during extrusion. The measuring system was qualified in accordance with the ICH Q2(R1) and an adequate accuracy, precision, limit of quantification and linearity was found.

Small changes in the liquid feed rate resulted in differed torque signals in the wet extrusion process. Therefore, the torque sensor can be used for in-line monitoring of the water content in the continuous extrusion process. Initial experiments indicate a correlation between torque in wet extrusion and pelletisation behaviour of different formulations. This could be very beneficial for formulation development because costs and time can me saved.

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