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Research Article

Miniaturization in Pharmaceutical Extrusion Technology: Feeding as a Challenge of Downscaling

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Abstract. In recent years, extrusion technology has shifted the focus of pharmaceutical research due to versatile applications like pelletization, bioavailability improvement or manipulation of solid-state properties of drugs, continuous granulation, and the development of novel solid dosage forms. Meanwhile, a major effort has been devoted to the miniaturization of equipment in pharmaceutical extrusion technology, particularly with regard to the requirements of the development of new chemical entities and formulations. In the present study, a lab-scale twin-screw extruder was investigated in order to determine the limitations imposed by the feeding systems. The wet extrusion process was considered as challenging because both a powder and a liquid feeder have to be considered. Initially, the accuracy and uniformity of the powder and liquid feeder were tested independently of the extrusion process. After modification of the powder feeder, both feeders were investigated in conjunction with extrusion. Based on this, an optimization of the liquid feeder was required and completed. Both feeder modifications reduced the variability of the moisture content in the extrudates 10-fold. This led to a reliable small-scale extrusion process.

KEY WORDS: excipients; extrusion; feeding; granulation; MCC; processing; scaling; unit operations.

INTRODUCTION

Extrusion is a well-known process technology that has been established for more than 70 years. Several types of extruders have been used for a number of applications, but twin-screw extruders have some advantages due to their inherent design and operating characteristics. The modular setup of most twin-screw extruders gives the opportunity to combine several unit operations in one machine. The feeding, mixing, and extrusion are realized simultaneously in every twin-screw extruder, due to the continuous process (1).

In recent years, twin-screw extruders have been applied successfully to pharmaceutical applications by downsizing machines from the plastics and food industries (1). In the field of solid dosage forms, twin-screw extrusion has become an efficient and flexible technique because of advantages such as cost reduction, improvement of process efficiency, and flexibility in production capacity (2). Twin-screw extruders are used for various manufacturing processes like pelletization (3,4), bioavailability improvement, or manipulation of solid-state properties of drugs (5,6). Extrusion is also applicable for continuous granulation (7–9) and the development of novel solid dosage forms for personalized medicine (10).

The high material throughput required by the continuous extrusion process is an advantage in production but is disadvantageous in the development of new formulations. Especially in the early development, new chemical entities are not available or are too expensive in high quantities. Therefore, the extrusion technology is frequently restricted to special applications where other technologies fail, even if extrusion processes would be useful in many other pharmaceutical processes. Because of this, there is a need for extruders with low throughput for pharmaceutical development. However, even in pharmaceutical production, small extruders are sometimes useful because they are more reliable when using small quantities, and the batch size can be easily adjusted by changing the process time (11).

A major effort has been devoted to the miniaturization of components in pharmaceutical extrusion technology. There are different types of miniaturized extruders, which differ in screw diameter or length but also in the process sectional design. The small-scale extruders can be divided in two different groups: The first group of machines, like DSM Xplore, the MiniLab from Haake, Nano 16 from Leistritz, the MP&R ME7.5, Rondol Microlab 10, or the Three-Tec ZE 5, is designed for early development because they can be run with only a few grams of material (Table I). The disadvantage of these machines is their particular screw and barrel geometry, which does not allow a direct scale-up to larger machines. However, these machines are useful for performing first rheological investigations of the melt and to screen for decomposition based on heat and shear stress. The second group contains downsized extruders of well-established larger models, like Brabender KETSE 12, Coperion ZSK 18, Leistritz ZSE 18, Steer Omicron 12P, ThermoScientific

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Table I. Different Types of Miniature Extruder

Machine type	Screw diameter (mm)	Screw length (mm)	Throughput	Ref.
Brabender KETSE 12	12	432	0.1–5 kg/h	(12)
Coperion ZSK 18 MEGALab	18	720	up to 40 kg/h	(13)
DSM Xplore 15 ml	<22	170	10 g/batch	(14,15)
Leistritz Nano-16	16	400	20–100 g/batch	(16)
Leistritz ZSE 18	18	720	Up to 40 kg/h	(17,18)
MP&R ME7.5 Mini-Extruder	7.5	112.5	50–200 g/h	(19,20)
Rondol Microlab 10	10	200–400	25–400 g/h	
Steer Omicron 12P	12	288–744	0.2–2 kg/h	
ThermoScientific HAAKE MiniLab	5.3–14	109	10 g/batch	(21–24)
ThermoScientific Pharma TSG 16	16	400	Up to 5 kg/h	(25,26)
Three-Tec ZE 5	5	100	0.5–5 g/batch	
Three-Tec ZE 16	16	512	1–250 l/h	

Pharma TSG 16, and Three-Tec ZE 16 (Table I). Based on the concept of geometrical similarity, an up-scaling of the extrusion process should be possible.

One dominant hurdle for the development of miniaturized extruders is the optimization of crucial parts of the equipment when downsizing. It is difficult to scale down the equipment such that it is effective for general use due to the variables between products. Factors that affect scale-up or scale-down include volume, heat transfer, and mass transfer (11) and are affected by both the feeding equipment and the process sectional design. The feed rate must be reduced to the lower throughput of the extruders, which is frequently a challenge with respect to feeding uniformity. Cohesive powder materials, in particular, cause fluctuations of the feed rate resulting in a non-reproducible loading of the extruder. This affects the residence time of the material in the extruder and sometimes the properties of the final product.

The scale-down of the process section, consisting of the barrel, screw, and die, is difficult because general concepts of scaling used for large extruders fail. The concept of geometrical similarity, for example, has a scope that becomes invalid when using tiny extruders. One major issue is the disproportion of the surface-to-volume ratio of components that affect friction and heat transfer. Another problem when downscaling is that the substance properties, like particle size and viscosity, stay constant, while the machine gets smaller. This could also affect the process (27).

It is true that many investigations have been done with regard to downsizing of twin-screw extrusion equipment, as mentioned before, but the limitations imposed by the feeders have not been given adequate consideration. Therefore, a definite need exists to investigate feeding systems for the twin-screw extrusion process. In this study, one of the listed extruders (Leistritz ZSE 18) was investigated in order to determine the limitations of downscaling. The focus in this study was the material feeding which was identified as crucial, as discussed before (28). The wet extrusion process was chosen for this investigation because a powder feeder as well as a liquid feeder had to be taken in account. This was considered as particularly discriminative because small differences in the powder or liquid feed rate affect the moisture content of the material and the properties of the final product (29–32). Mixtures of microcrystalline cellulose and lactose, with water used as the granulation liquid, are frequently used in granulation experiments performed by extrusion (29,33–35). Therefore, this system was considered to be adequate for this study. However, similar results should be obtained for the hot melt extrusion process, if the process is sensitive to fluctuations of the feeders. This becomes particularly important when using more than one feeder (split feeding).

EXPERIMENTAL

Experimental Setup

Materials

The formulation consisted of 50% (*w*/*w*) microcrystalline cellulose (MCC M101, Pharmatrans Sanaq, Basel, Switzerland) in α-lactose monohydrat (Granulac 200, Meggle, Wasserburg, Germany). Deionized water was used as the granulation liquid.

Blending

The powder was blended for 15 min in a laboratory scale blender (LM 40, Bohle, Ennigerloh, Germany) at 25 rpm and afterward transferred to the gravimetric powder feeder of the twin-screw extruder.

Extrusion

The 18-mm-diameter corotating twin-screw extruder (ZSE 18GL-40D) was equipped with a gravimetric powder feeder (K-PH-Cl-24-KT20, K-Tron Soder, Lenzard, Switzerland) and a liquid feeder (Goehler Tankanlagen, Hoesbach, Germany: D-series gear pump, Tuthill, Ilkeston, Derbyshire, England; MFM Coriolis flowmeter, Krohne Messtechnik, Duisburg, Germany; PID-Controller Imago 500, Jumo, Fulda, Germany) as well. An electronic proportional integral controller was used to control both feeders. The experiments were done using various powder and liquid feed rates, which are given in the "RESULTS AND DISCUSSION" section. The used die contained 22 holes of 2 mm diameter and 5 mm length, and the extrusion was done at a screw speed of 150 rpm.

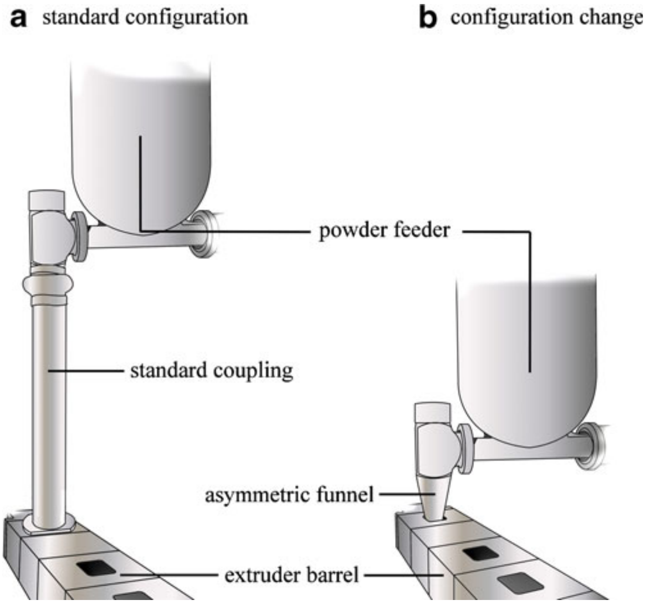

Fig. 1. Standard configuration **a** and configuration change **b** of the powder feeding

Uniformity of Dosing Units

The powder and the liquid feeder were characterized with respect to their precision and accuracy (36). Since the feeding is a continuous process, the precision (ICH) of the feed rate is a function of the sampling rate. In order to avoid confusion, the term "uniformity" will be used herein for purposes of discussion, rather than "precision," as given in the guideline. Uniformity means the absence of fluctuations in the feed rate.

The accuracy and uniformity of the powder feed rate was determined by an external scale (BP 2100S, Sartorius AG, Goettingen, Germany) using a sampling rate of 1 Hz. The accuracy of the liquid feeder was investigated with an external scale (BP 2100S, Sartorius AG, Goettingen, Germany), while the uniformity was quantified using a calibrated inline flow through metering device at a sampling rate of 1 Hz. In order to compare different feed rates, the weight change (x_i) was normalized to the median weight change (x_{50}) of the distribution. The resulting parameter is the dimensionless weight change (DWC):

$$\mathrm{DWC} = \frac{x_i}{x_{50}} \tag{1}$$

The width of the distribution was quantified by the interquartile range (IQR) based on the quartiles (x_{25}, x_{75}) and the median (x_{50}):

$$\mathrm{IQR} = \frac{x_{75} - x_{25}}{x_{50}} \tag{2}$$

The IQR is a common statistic parameter to describe the width of the distribution of non-normal distributed data. An IQR of 0 means a monodisperse distribution and a uniform feed rate. This applies to feeders that deliver a constant quantity of material per time unit. Theoretically, the IQR is defined from 0 to positive infinity, while high values characterize a wide distribution. However, since an IQR of 1 means the fluctuations in the feed rate are in the same order of magnitude as the median of the feed rate, that is rather high from a practical point of view.

Loss on Drying

The moisture content of the extrudates was determined during extrusion once per minute. To do this, samples of about 1 g were collected and dried at 105°C for 24 h in a drying oven (Heraeus UT-6060, Kendo, Hanau, Germany). The moisture content of the extrudates was calculated in percent (*w*/*w*) based on dry mass.

RESULTS AND DISCUSSION

Powder Feeder

The accuracy and the uniformity of the powder feeder were characterized without connecting the extrusion barrel. Thus, a scale was placed below the powder feeder, and the weight change was measured. The accuracy of the powder feeder was calculated for 1 min six times. The difference between the set and the measured value was smaller than

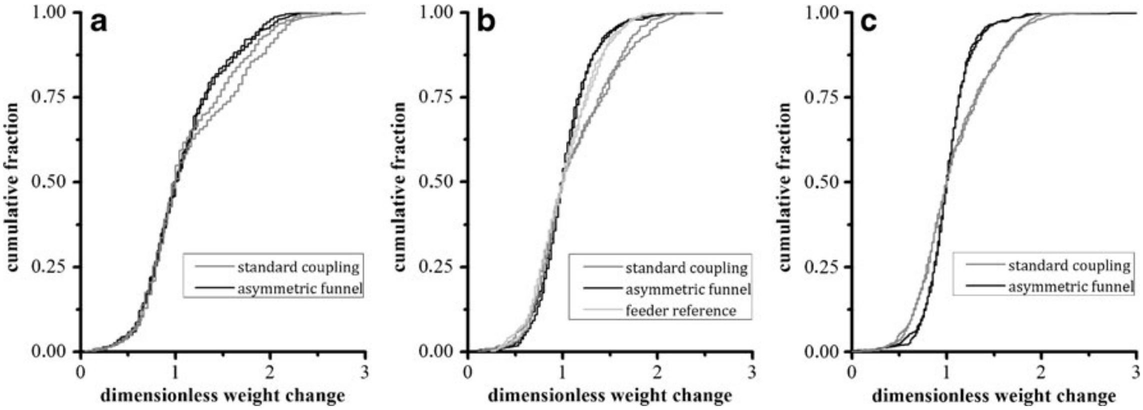

Fig. 2. Differences in the behavior of the powder case when comparing different feeder configurations at different feeding rates: 1.0 kg/h **a**; 1.5 kg/h **b**; 2.0 kg/h **c**; (n=2)

Table II. Uniformity of the Powder Feed Rate

	1.0 kg/h	1.5 kg/h	2.0 kg/h
Standard coupling	0.75	0.61	0.51
Asymmetric funnel	0.54	0.34	0.26

Table III. Uniformity of the Liquid Feed Rate

	0.5 kg/h	1.0 kg/h	1.5 kg/h	2.0 kg/h	2.5 kg/h
IQR	0.0040	0.0012	0.0005	0.0002	0.0005

0.003 kg/h, for all three feed rates (1.0, 1.5, and 2.0 kg/h). Based on these results, the accuracy was considered as sufficient and disregarded in further investigations.

The uniformity of the powder feed rate was tested using the feeder with the coupling to the extrusion barrel (Fig. 1 A). In these experiments, an accumulation of powder inside the coupling was observed visually. That led to powder lumps slipping off randomly from the inside wall of the coupling, resulting in a feeding that was not uniform. In order to overcome this problem, a shorter coupling was designed with an asymmetric funnel shape (Fig. 1 B). The conical shape was required to connect the large outlet of the powder feeder with the smaller inlet of the extruder. An asymmetric shape was considered as more promising with respect to a symmetrical funnel because a more homogenous flow can be expected (37). However, it should be mentioned that the standard coupling also had a conical shape in order to connect the large outlet of the feeder with the small inlet of the extruder. Based on the higher length, the angle and the inner surface are different. Therefore, different powder flows were expected from both couplings.

The comparisons of the two feeder configurations (standard coupling and asymmetric funnel) were performed for three different powder feed rates (1.0, 1.5, and 2.0 kg/h). Figure 2 shows the distribution of the weight change on the scale in 1 s measured over a period of 10 min for each feed rate. The narrow distribution indicates a uniform feed rate. The feeder with the standard coupling had a wider distribution than the feeder with the modified coupling for all three feed rates. This effect was attributed to an attraction of powder particles to the standard coupling as discussed earlier. The shape of the weight distribution also confirms this mechanism, showing that a high deviation at higher weights was observed. That was attributed to powder lumps that slipped off randomly, increasing the weight changes. To rule out any effect of the funnel itself on the uniformity of the feed rate, the powder feeder without coupling or funnel served as reference (for 1.5 kg/h). Figure 2b indicated no effect of the asymmetric funnel on the uniformity of the powder feed rate.

In order to quantify that the uniformity of the feed rate depends on both couplings as well as the feed rate, the IQR was used (Table II). The uniformity of the feed rate was increased with increasing feed rate, consistent with the fact that small amounts of powder are difficult to dispense reproducibly. The asymmetric funnel showed a narrow distribution of the weight change. Applying the IQR, the asymmetric funnel was twice as good as the standard coupling for feed rates of 1.5 and 2.0 kg/h. Using a feed rate of 1.0 kg/h, the asymmetric funnel was still better than the standard coupling, but the difference was narrower. Probably, this feed rate is close to the lower limit of uniform feeding using this feeder and this powder formulation.

Therefore, 1.0 kg/h was considered as insufficient feed rate for further investigations. Due to a low throughput having been requested, 1.5 kg/h was used.

Liquid Feeder

The accuracy and uniformity of the liquid feeder were also investigated outside of the extrusion barrel using five different feed rates (0.5, 1.0, 1.5, 2, and 2.5 kg/h). The differences of the liquid feed rate from the set value were smaller than 0.05% (Fig. 3). The evaluation of the uniformity of the feed rate was performed similarly to that done with the powder feeder. The liquid feeder showed a more uniform feed rate than the powder feeder at all feed rates (Tables II and III).

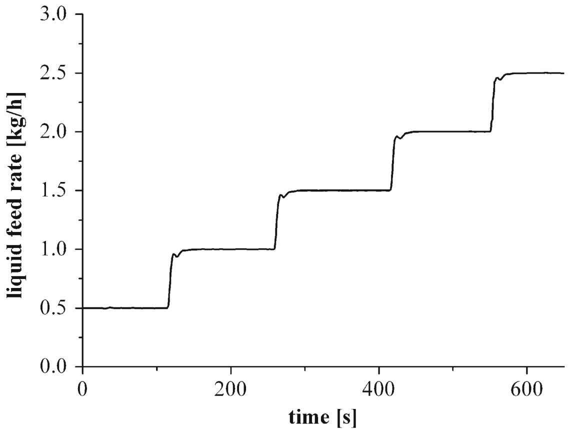

Fig. 3. Uniformity of liquid feeding without concurrent extrusion process

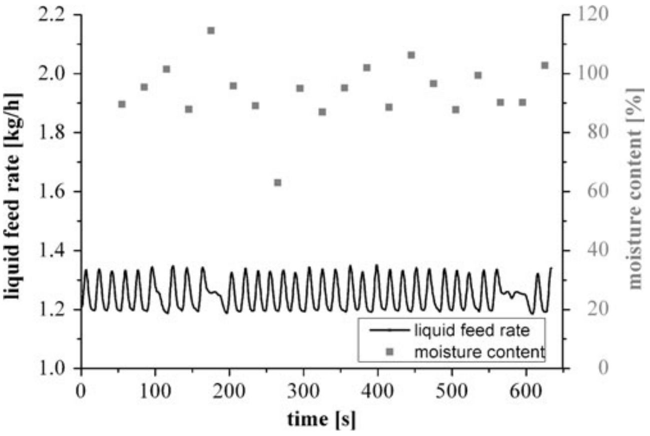

Fig. 4. Uniformity of liquid feeding during a representative extrusion process (using 1.25 kg/h as set value, *black*) and resulting moisture content of the extrudates (*gray*)

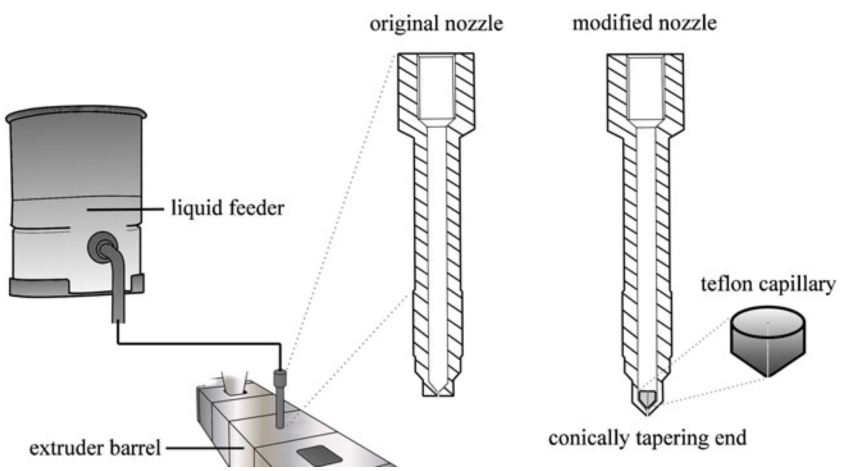

Fig. 5. Original and modified liquid feeding setup

Therefore, the powder feeder was considered as more discriminative than the liquid feeder with respect to the moisture content of the extrudates.

Wet Granulation Process

Since the powder and the liquid feeder were validated independently of the extrusion system, further investigations in extrusion were required. It was unlikely that the extrusion process was affecting the powder feed rate because there was no mechanical connection between the powder feeder and the extrusion barrel. Therefore, the investigations focused on the liquid feeder, which was considered as more relevant for inline investigations. The impact of the powder feed rate was monitored by the moisture content of the extrudates.

The powder was granulated with water in the extruder, without a die, in order to avoid a blockage resulting from material with low moisture content. Therefore, the liquid feed rate was set to 1.25 kg/h. The measured liquid feed rate is given in Fig. 4, as well as the moisture content of the granulate. High fluctuations in the liquid feed rate caused fluctuations in the moisture content. First thoughts dealt with an unsuitable alignment or air in the feeder as a possible reason for this effect. However, the feeder showed a very uniform flow rate outside of the extruder, but never when the extrusion process was running, which was tested multiple times. In order to analyze this phenomenon, the extrusion process was interrupted when these fluctuations occurred, and the liquid nozzle was removed from the system and inspected visually. In so doing, a sticky paste clogging the liquid nozzle was observed. In further experiments, the fluctuations in the feed rate were correlated with pressure fluctuations in the nozzle.

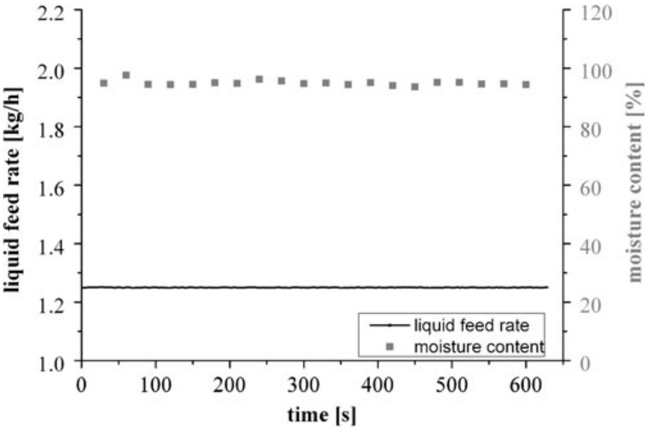

Fig. 6. Uniformity of liquid feeding with the modified nozzle during a representative extrusion process (*black*) and resulting moisture content of the extrudates (*gray*)

These fluctuations of up to 12% in feed rate result in varying moisture content in the extrudates. The standard deviation of samples taken during the extrusion process is 10%. Due to the liquid feeding, fluctuations in the moisture content occur which cannot be rectified by further mixing processes in the extruder.

The fluctuations in the liquid feed rate were attributed to an inadequate design of the liquid nozzle. Therefore, the geometry of the nozzle was optimized by two modifications. The original nozzle, which had a blunt tip, was replaced by a tapered tip nozzle (Fig. 5). This modification reduced the dead volume and the amount of material in front of the nozzle. Additionally, a Teflon capillary of 4 mm length and 0.3 mm diameter width was inserted that reduced the diameter of the nozzle, resulting in an increased pressure from 0.4 to 1.0 bar. It was expected that the higher pressure would reduce the clogging of the nozzle that might be one reason for the fluctuations.

The two modifications to the nozzle improved the uniformity of the liquid feed rate (Fig. 6) as well as the moisture of the extrudate to less than 1%. Compared to previous investigations, the uniformity is reduced by one order of magnitude. The tapered tip nozzle without the capillary caused fluctuations in the liquid feed rate (data not shown), while a blunt tip nozzle with a Teflon capillary was impossible to produce for steric reasons.

Table IV. Uniformity of the Moisture Content

	Original nozzle	Modified nozzle
Standard coupling	0.0616	0.0107
Asymmetric funnel	0.1215	0.0074

Wet Extrusion Process

The proof of concept was done by wet extrusion process for 10 min at steady state where samples were taken every 0.5 min in order to determine the variation of the extrudate moisture. The variability was quantified by the IQR as given in Table IV. In this manner, the standard coupling and the asymmetric funnel, as well as the original and modified nozzle, were considered. Using the original nozzle, different fluctuations in the liquid feed rate occurred randomly, preventing a comparison of the powder feeder (data not shown). The difference in the IQR between the standard coupling and asymmetric funnel is mainly attributed to the insufficient nozzle. Using the modified nozzle, a much lower IQR was observed, resulting in more homogeneous moisture content. The modification of the powder feeder had less effect on extrudate moisture than the modification of the liquid feeder.

These results were verified using multiple ratios of lactose in MCC (0%, 50%, 60%, 70%, and 80%) as a formulation. Pure MCC showed an excellent extrusion behavior even without modification of the feeders. That was attributed to the robustness of the formulation due to the high water binding capacity of the MCC (38). Therefore, high water contents, between 166.7% and 200% (calculated in percent (*w*/*w*) based on dry mass), were required to obtain an extrudate of cylindrical shape. However, high amounts of MCC are not suitable for practical reasons. Therefore, the amount of MCC should be reduced by using lactose as a filler. Formulations with 50% lactose required a modification of both feeders as discussed before. The needed water content of 63.3% to 90% that led to a cylindrical extrudate was lower compared to pure MCC because the water binding capacity of lactose is lower than that of MCC. Based on this, the formulation was less resistive to moisture fluctuations. Further increase of lactose in the formulation to 60% and 70% confirmed this trend. Seventy percent lactose in MCC for example required 56.6% to 70% water content in order to obtain cylindrical extrudates. Lower amounts of MCC required lower water content; moreover, the moisture range leading to extrudates became narrower too (39). Based on this, the robustness of the formulation is decreasing while fluctuations in the powder feeder become important.

CONCLUSION

The powder and the liquid feed rate were identified as crucial parameters in small-scale extrusion. The wet extrusion process was used to evaluate these effects. Even if the feeders showed a reliable feed rate after connecting to the extruder, the uniformity of the feed rate changed dramatically. A modification of the coupling between powder feeder and extruder improved the uniformity of the feed rate. The liquid feed rate was improved by a modification of the nozzle. Consequently, the pressure in the liquid feeder was increased, and the dead volume at the nozzle was reduced. The modifications of both feeders led to a more uniform moisture content in the final extrudates that is particularly relevant for small-scale extrusion.

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