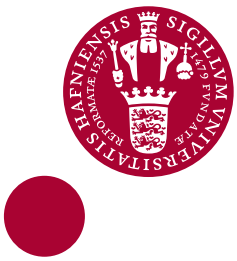

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Rapid Communication

Rapid prototyping of miniaturized powder mixing geometries

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ABSTRACT

Continuous manufacturing is an important element of future manufacturing solutions enabling for both high product quality and streamlined development process. The increasing possibilities with computer simulations allow for innovating novel mixing principles applicable for continuous manufacturing. However, these innovative ideas based on simulations need experimental validation. The use of rapid prototyping based on additive manufacturing opens a possibility to evaluate these ideas at a low cost. In this study, a novel powder mixing geometry was prototyped using additive manufacturing and further, interfaced with an in-line near-IR spectrometer allowing for investigating the residence time distribution (RTD) in this geometry.

Introduction

Continuous manufacturing has recently gained more interest as an alternative to conventional batch manufacturing due to, e.g., the ability to perform straightforward scale up, to achieve a more constant quality product and a possibility for reducing the cost of production.[1-4] In addition, this approach is supported by regulatory initiatives including a risk-based approach with implementation of Quality by Design (QbD) and Process Analytical Technologies (PAT),[5-7] as well as an initiative for a guideline from The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, ICH (ICH Q13 Continuous Manufacturing for Drug Substances and Drug Products).

The mixing of powders is a ubiquitous step in manufacturing of pharmaceuticals and has traditionally been carried out as a batch process. The performance of continuous powder mixing is of major importance when developing a continuous manufacturing line.[8,9] The performance of a continuous mixer can be evaluated by the residence time distribution (RTD), which is a well-established practice in many areas of chemical engineering.[10-12] The RTD will describe the behavior of powder within the mixing unit and thus, address the challenge of material traceability within continuous manufacturing lines.[13,14] RTD was originally used for describing flow in liquid-phase processes, but is also used to describe the flow of particles in solid-phase processes.[9] A common approach for investigating RTD is based on an empirical model, which includes three considerations; material (tracer) added to the system, mean residence time (MRT), and the number of continuously stirred tank reactors (CSTR) in series. The number of CSTR provides a model for defining the statistical moments of the RTD.[13,15]

For the detection and measurement of powder within a mixing unit, in-line process interfacing would be ideal for continuous manufacturing processes.[4] A well-established in-line process analytical method is near infrared spectroscopy (NIR) that is suitable for continuous manufacturing due to the speed of analysis and size of the analytical equipment.[16-18] Moreover, NIR is suitable for in-line measurements as the method is non-destructive and the accessibility of specifically optic fiber probes for diffuse reflectance measurements creates the possibility of cheap implementation in continuous manufacturing lines.[19]

Additive manufacturing (AM) or "3D printing" has gained interest broadly within the pharmaceutical area, as it serves as a platform for rapid prototyping at low cost. Examples cover, e.g., analytical method development,[20] production in microfluidics-based geometries[21] and design of innovative drug delivery systems.[22] AM coupled with in-line analysis is suitable for producing prototypes of pharmaceutical powder handling processes to assist in process development.[23,24] At the same time, there is a growing interest to use process modeling and simulation to support pharmaceutical product and process design. This has been demonstrated with several examples with pharmaceuticals allowing for, e.g., *in silico* optimization of operating conditions[25] and virtual 'design of experiments'.[26] However, it is necessary to experimentally validate the *in silico* work, and the use of

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AM for rapid prototyping of the optimized processing geometries is an attractive alternative testing innovative process solutions.

The aim of this study was to demonstrate the use of 3D printing for rapid prototyping of continuous manufacturing equipment. A miniaturized powder blending unit coupled with an NIR spectroscopy was used as a model of a continuous process and the estimation of RTD in this geometry.

Material and methods

Materials

Three common excipients and one active compound were used in the model powder mixture system: lactose monohydrate (FlowLac 100 SD, Maggie Pharma; Wasserburg, Germany) was used as carrier and mannitol (Pearlitol 100 SD, Roquette; Lestrem, France), isomalt (Isomalt DC 101, Beneo; Mannheim, Germany), calcium carbonate (Scora SA; Caffiers, France) and paracetamol (Fagron; Barcelona, Spain) were used as tracers.

3D Printing of mixing geometries

For the printing of experimental setup, two different filament materials were used. Polylactic acid (PLA, Innofil 3D, Emmen, Netherlands) for the 3D printed structure and polyvinyl alcohol (PVA, Ultimaker, Geldermalsen, Netherlands) for structural support during printing.

Two different 3D-printers were used: An Ultimaker 3 Extended (Ultimaker, Geldermalsen, Netherlands) and a Makerbot 2 Replicator (Makerbot, New York, USA).

All the 3D printed designs are available as supplementary material. The geometries were designed with the software program FreeCAD 0.16, Juergen Riegel, Werner Mayer, Yorik van Havre 2001-2015. The final mixing geometry is presented in Fig. 1.

Powder characterization

Flowrate was tested in triplicate by timing the flow of 100 g powder through the hopper designed for the mixing experiment.

The bulk density was measured in triplicate using a graduated cylinder readable to 1 ml, with an amount equal or more than 60 percent of the total volume of the graduated cylinder.

Mixing experiments

The experiments were performed by feeding the carrier, lactose monohydrate, until the mixing unit volume was filled. A pulse of 15 g tracer material was then loaded instantly into the pulse inlet (Fig. 1). The in-line measurements were initiated simultaneously with the tracer pulse. The offline sampling was collected with a 20-second frequency for a 5-second period at the powder outlet. All experiments were performed with a screw rotation speed of 14 rpm.

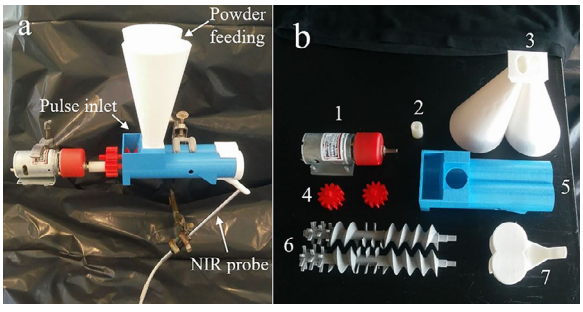

Fig. 1. a) The assembled experimental setup b) The experimental setup disassembled (1: Motor for rotating the twin screws, 2: Connection part between motor and sprocket, 3: Hopper with two feeding funnels, 4: Sprockets connecting active and passive screw, 5: Twin screw chamber, 6: Screw design, 7: Powder outlet).

Estimation of RTD based on the in-line NIR measurement

The in-line data was measured with an NIR probe (Control development, South Bend, USA) placed under the powder outlet (Fig. 1). Each spectrum was an average of 32 spectra recorded within an interval of approximately 4 s at the spectral range of 1090-2223 nm. The off-line samples were subsequently measured at a stationary NIR instrument (ABB, Zürich, Switzerland) at the spectral range of 833-2703 nm.

The spectral data were processed using SIMCA 14.1 (Sartorius Stedim Biotech; Malmö, Sweden). The NIR data were analyzed using principal component analysis (PCA). After exploratory investigation of the spectral data and comparison with the loading vector of the PCA analysis, it was assumed that PCA score values correlated directly with the concentration of the tracer material. Based on this, the PCA scores were referred to as the 'concentration profile' for the purposes of this study. The NIR spectral data were preprocessed with standard normal variate (SNV) and mean centering applied for all datasets.

The residence time distribution (RTD) and subsequently the mean residence time (MRT) of the tracer materials was estimated using the continuous stirred tank reactor (CSTR) in series model, $C(t)$, given below:[27]

$$C(t) = C_0 E(t) = C_0 \frac{t^{n-1}}{(n-1)!\left(\frac{\tau}{n}\right)^n} e^{\left(\frac{-nt}{\tau}\right)} \quad (1)$$

where C_0 is the normalized concentration of the pulse tracer, t is time, n is the number of tanks used in the CSTRs in series model and τ is the MRT of the distribution. It should be noted that the normalized concentration factor C_0 is a unit less factor dependent on the method of analysis used to measure the concentration profile.

The concentration profiles based on PCA models were fitted with the CSTRs in series model applying the least square curve fit function (*lsqcurvefit*) in MATLAB® 2015a (MathWorks, Massachusetts, USA).

Results and discussion

Pulse tracer experiments were conducted in the 3D printed mixing geometry (Fig. 1) for the four investigated tracers using pure lactose monohydrate as a carrier. An example of a pulse tracer experiment with mannitol is presented below (Fig. 2). The mean

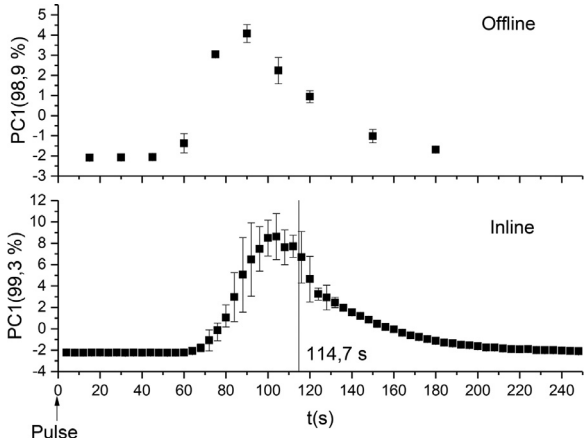

Fig. 2. An illustration of RTD profile for pulse experiment using mannitol as tracer. The offline data consists of 1 sample tested in triplicate at the different timestamps for the first experimental run. The inline data is an average of three consecutive experimental runs. The error bars indicate 95 % confidence interval.

Table 1
Flowrate and bulk densities of the materials used in the conducted experiment.

Materials	Flowrate ($\bar{X} \pm SD, n = 3$)	Bulk density ($\bar{X} \pm SD, n = 3$)	MRT ($\bar{X} \pm SD, n = 3$)
lactose monohydrate	11.6 g/s ± 0.8	0.6 g/ml ± 0.010	-
mannitol	7.5 g/s ± 0.12	0.4 g/ml ± 0.003	114.7 s ± 1.3
isomalt	17.5 g/s ± 0.14	0.5 g/ml ± 0.003	114.8 s ± 1.0
calcium carbonate	-	1.0 g/ml ± 0.015	113.1 s ± 1.8
paracetamol	31.0 g/s ± 1.18	0.8 g/ml ± 0.010	112.7 s ± 2.1

residence time (MRT) is indicated with a vertical line. The offline results were comparable with the inline data.

The CSTRs in series model was applied to the RTD profiles of all the pulse tracer experiments to derive the MRT (Table 1). For every tracer material, a low standard deviation of the MRT was derived which indicate a high repeatability of experiments in this geometry.

It is an important aspect to have an efficient data analytical solution for the in-line process measurements used for estimating the RTD. All the materials in the current study exhibited spectral features in the NIR region (Fig. 3) that were different from those of the carrier material (lactose monohydrate). This is essential to investigate when building the analytical method to generate a robust model with distinct results. The streamlined NIR method development based on using the first principal component score value allows for exploring the behavior of a broad range of tracer materials in a continuous production line (Table 1).

The material properties of the tracer materials were quite diverse, especially calcium carbonate was a very cohesive material with poor flowability as this did not flow in the hopper (Fig. 1) and had a high bulk density (1,0 g/ml). Despite of these different powder properties, none of the MRTs was significantly different (Table 1), which indicates that for this system, the powder characteristics of the tracer had a minimal effect on the mean residence time. This observation was contrary to the expected, as current practice of pulse tracer experiments is to choose tracer material with comparable material properties with the mixture system to eliminate tracer influence on the mechanism of powder mixing.[13,15,28]

However, the smaller physical scale of the current mixing geometry cannot be directly compared to previous studies, where similar pulse experiments were conducted by adding a pulse at the inlet of the feeding funnel.[9,13,14] As such, the RTD of the system is commonly measured for both the feeding funnel and the mixing unit. In this study, the mixing unit is designed with a separate inlet for pulse feeding (Fig. 1). The pulse is "injected" directly into the mixing unit and thus, tracer pulse will bypass the feeding funnel. In the current mixing unit, the low shear environment in the conveying elements of the screw design will ensure a uniform movement of the tracer pulse. In turn, no significant difference in the MRT was observed, which could be attributed to "injecting" the powder directly into the mixing unit and having the twin screws move the powder at a constant rate with minimal impact of the powder characteristics of the pulse material which for more cohesive tracer materials would be expected to be held up in the feeding funnel. For the mixing system itself this indicates that the materials chosen in this study all are suitable for determining the RTD in this geometry. Additionally, observing similar MRT for all tracer materials could be an indication of plug flow behavior of the tracer material commonly observed in low shear systems such as this geometry. However, given the broad residence time distributions presented in this study, some degree of axial mixing must occur during the process, suggesting that RTD measurements are representative for this specific geometry.

One typical feature for development of pharmaceuticals is a high number of product development projects in relatively small-scale processing systems. While moving to continuous manufacturing, the need for even smaller production equipment is obvious.[29] Process intensification using, e.g., microreactors, microwave radiation, and ultrasound, will allow for development of totally new processing principles for primary manufacturing of pharmaceuticals,[30] typically with small-scale production solutions. The capacity of production lines should be aligned for end-to-end manufacturing, which is further highlighting the importance of small-scale solutions for secondary manufacturing.

Additionally, one key challenge in the implementation of manufacturing innovation is related to education of pharmacist: the pharmaceutical curriculum is covering broadly several disciplines ranging from chemistry and biology towards social sciences, but is not having enough elements of mathematics and engineering.[31] We envision small scale processing equipment, such as the continuous powder mixing geometry reported here, being an ideal solution for

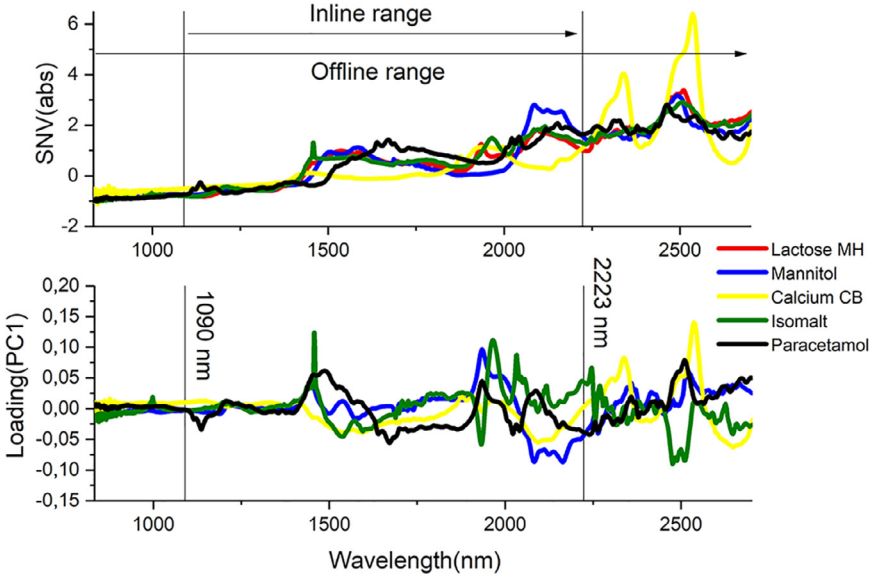

Fig. 3. The spectral difference of materials. Above: the SNV treated spectra of each material. Below: The spectral difference between each tracer and the carrier (lactose monohydrate) illustrated by loadings.

introducing the basic principles of complex engineering aspects. This type of teaching approach would allow for hands-on introduction to continuous manufacturing, process measurements and mathematics related to complex concepts, such as the residence time distribution.

More innovation is needed in the field of powder handling processes, and rapid prototyping of powder handling equipment is an efficient approach for exploring this.[23] The current work is illustrating how even very simple powder handling geometries can be interfaced with PAT tools and used for exploring RTD and MRT at low cost and time efficiently.

Conclusion

In this study, 3D printing was utilized for rapid prototyping of continuous powder mixing element. Interfacing with NIR spectroscopy allowed for exploring important aspects related to continuous processing, such as RTD and MRT. This example demonstrated an efficient approach for intensification of powder handling processes.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xphs.2021.03.019.

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