Impact of excipient and blend properties on feeding consistency for continuous manufacturing

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aaps PharmSci 360
ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

Purpose

Continuous manufacturing (CM) gains more and more interest in the pharmaceutical industry, which is guided by the FDA in Pharma 4.0. With CM gaining ever so importance, understanding of physical properties of powders to predict behavior in different process units is crucial. Raw material feeding is usually one of the first units of operation in a continuous manufacturing line. Handling a high number of feeders, however can be challenging and costly. Especially clustering more than six feeders around a single transition is difficult and expensive (1). Pre-blending of excipients may be a logical process choice when the number of feeders in a continuous manufacturing system is limited.

The ability to feed powder consistently and continuously is regarded as one of the critical requirements for finished product quality and therefore stringent control on feeding is required (2). The accuracy of powder feeding can be impacted by intrinsic material attributes, such as particle size, electrostatic charging, flow, bulk density, or wall friction. These properties are usually known for pure materials, but properties of powder mixtures are often unknown and hard to predict due to strongly non-linear interactions.

The goal of this study is to understand the feeding variability of different types of excipients and binary excipient mixtures in a volumetric feeding system. 20 pure excipients are tested, varying from milled to sieved, granulated to spray dried and round to fibrous. Furthermore, a spray dried, granulated, anhydrous and milled lactose grade are mixed with MCC to evaluate the changes in feeding accuracy upon mixing.

Methods

Feeding consistency of excipients is evaluated by a volumetric force feeder. The feeder used in this study is a stainless-steel Force Feeder FF1 from Thermo Haake and contains a single feeding screw with a diameter of 15mm and a pitch of 15mm. The rotational speed of the feeder and agitator was set at 40%, corresponding to 24 rpm. The feedrate was monitored every second with BalanceLink Software of Mettler Toledo. Subsequently the output per second is calculated, and the feeding variability is calculated as the relative standard deviation over the output per second. Blends of lactose and MCC are prepared by blending lactose with 25%, 50% and 75% Pharmacel® 101 (%w/w) for 10 minutes in a Turbula blender at 96rpm. Lactose grades tested are Pharmatose® 200M, SuperTab® 11SD, SuperTab®30GR, and SuperTab® 21AN.

Result(s)

The feedrate and feeding variability of excipients is shown to be highly dependent on the type and shape of the particles. Granular and spherical lactose particles have feed rates between 1.3 and 2.3 g/s, while smaller tomahawks have feed rates below 0.5 g/s. Feeding variability of pure excipients is higher than observed in literature, which is explained by the lower timescale for calculation of the RSD (3,4). In general, materials with low feed rate show a high variability in feed rate. Anhydrous lactose is the exception on this, as for this material both a low feed rate and a low variability is observed. The difference in feed rates and feeding variability is shown to be dependent on a full set of excipient physical-chemical properties; size and flow alone are not enough to fully understand performance in a feeder system.

Powder feeding behavior becomes even more complicated when blends of different materials are evaluated. None of the four different excipient compositions evaluated here show a fully linear relationship for the feeding behavior as a function of mixture composition. For blends of modified lactose monohydrate grades (SuperTab® 30GR and SuperTab® 11SD) with MCC, the feed rate of the blend is dominated by the feed rate of MCC. Furthermore, blends of milled lactose (Pharmatose® 200M) with MCC show non-linear behavior for feeding variability with maximum variability in a 50:50 blend. This may be the result of chunk formation or segregation during feeding, due to differences in physical-chemical powder properties between the products.

Conclusions

The feeding behavior of excipients is shown to be dependent on the physical-chemical properties like size, shape, density, flow, internal friction and wall friction. Selection of the right excipient grade for consistent feeding is necessary. Caution should also be taken when pre-blends are used in a continuous manufacturing line, as binary powder mixtures do show strongly non-linear feeding behavior. In DFE Pharma's view it is key that users communicate openly with their suppliers to understand the full set of physical chemical properties of excipients to minimize feeder variation in continuous manufacturing systems.

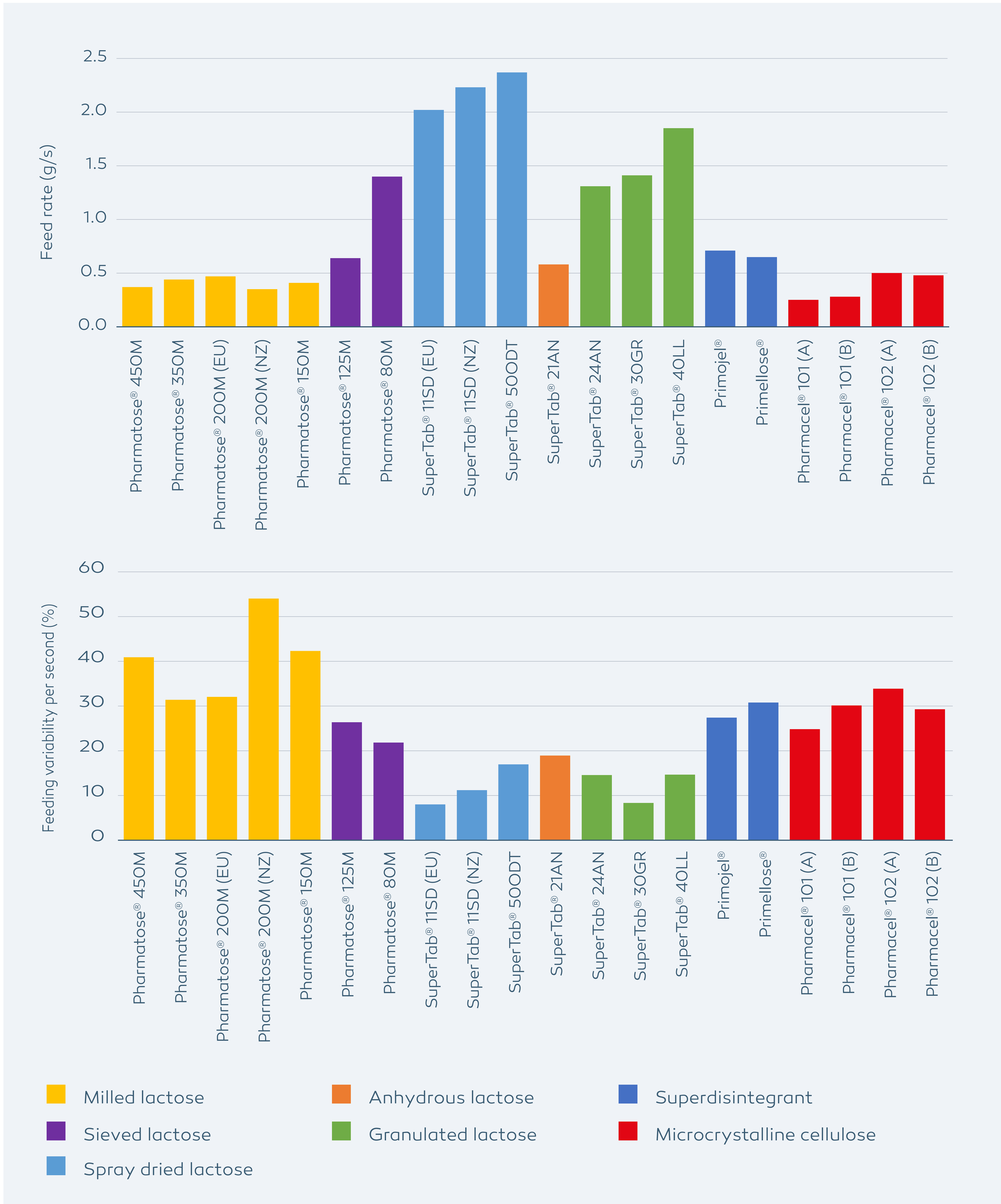

Figure 1: Feed rates and feeding variability of pure excipients.

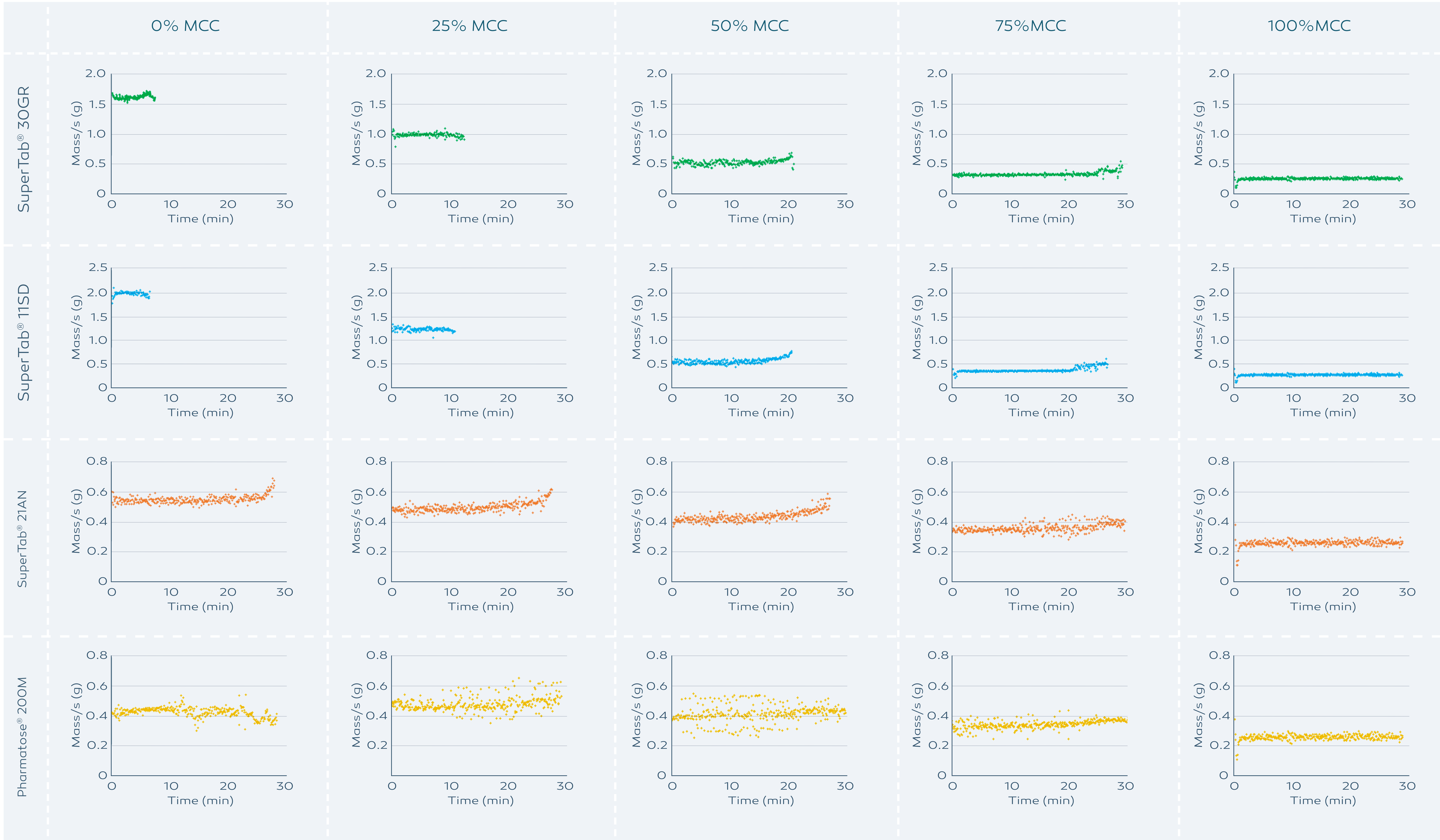

Figure 2: Non-linear feeding behavior is observed for lactose-MCC blends with varying ratios.

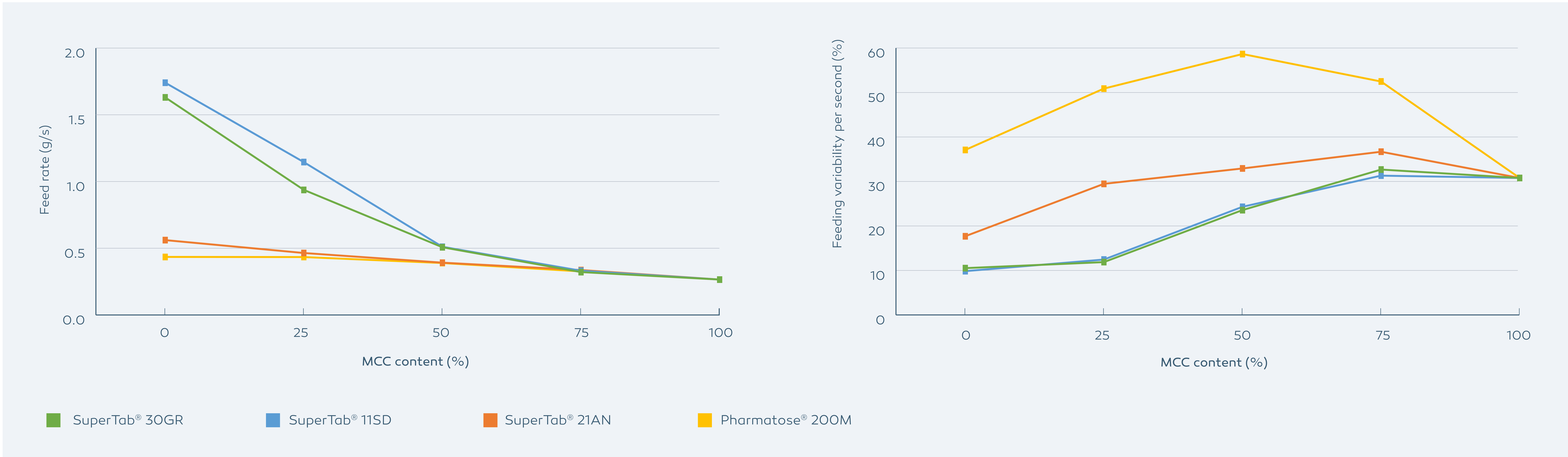

Figure 3: Feed rates and feeding variability of lactose-MCC blends with varying ratios.

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