Benefits of Co-processed High-Functionality Excipients in a Continuous Direct Compression Process

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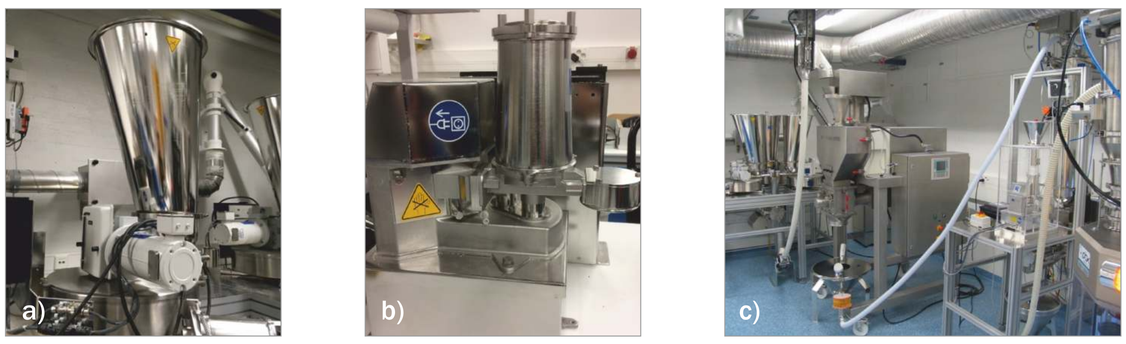
Introduction

Continuous manufacturing offers significant advantages over conventional batch processing such as smaller equipment, less footprint and no need for upscaling experiments. With these benefits, come challenges as well. In a fully continuous process, the excipients must be added through individual feeders, possibly resulting in many sources of variability. Co-processed excipient composites are thought to be perfectly suited for such processes due to their outstanding physicochemical characteristics and the reduction of the number of feeders. The aim of this study was to proof the superior performance of co-processed excipients in a continuous manufacturing setup.

Materials and Methods

The first trials on the feeding performance of different excipients were conducted with different loss-in-weight feeders. These feeders comprised a standard feeder and a microfeeder.
Depending on their type they were run with different speeds. The all-in-one excipient PROSOLV® EASYtab SP as well as its single components microcrystalline cellulose (VIVAPUR®, MCC), colloidal silicon dioxide (CSD), sodium starch glycolate (EXPLOTAB®, SSG) and sodium stearyl fumarate (PRUV®, SSF) were used for these trials.

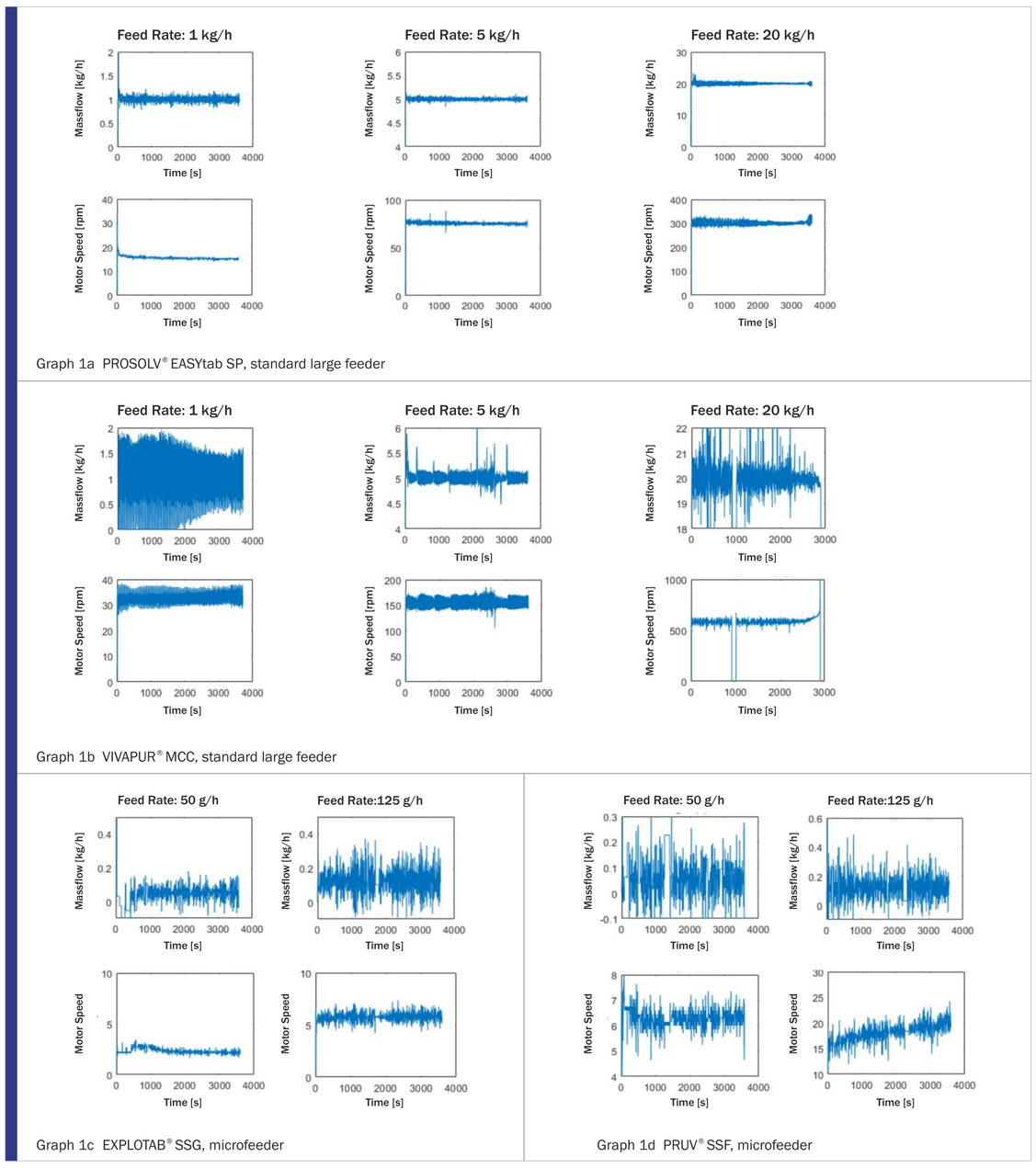


Pic 1 Equipment Used in this Study
a) Standard Feeder (Load Capacity ≈ 20kg); b) Microfeeder (Load Capacity 200-300 g); c) Continuous Manufacturing Line

The second part of the trials dealt with continuous tablet manufacturing. The continuous process set-up comprised a Coperion K-Tron loss-in-weight feeder, a Modulomix continuous mixer and a PTK-PR1000 tablet press. Either PROSOLV® EASYtab SP or the single components were continuously blended with 5 % of a model API and compressed afterwards.

Results and Discussion

In order to prove the hypothesis of superior performance of co-processed excipients feeding studies with different feed rates were performed. The major constituents (i.e. PROSOLV® EASYtab SP and VIVAPUR® MCC) were fed in the larger feeders with either 1 kg/h, 5 kg/h or 20 kg/h. The smaller constituents such as EXPLOTAB® SSG and PRUV® SSF were fed with microfeeders at lower speeds (i.e. 50 g/h and 125 g/h). Furthermore, trials with CSD were also undertaken.
The all-in-one composite PROSOLV® EASYtab SP could be fed homogenously at all tested feed rates. Irrespective of the feed rate, the motor speed was always constant indicating homogenous flow. In contrast, the flow of MCC was much less homogenous. A higher motor speed was needed for the same flow rate which is indicative of poorer flowability compared to PROSOLV® EASYtab SP. On top of that the mass flow curve exhibited much more noise and, thus, the powder was transported less constantly. Furthermore, the feeding behavior of MCC was influenced by the feed rate, while there was no influence of feed rate on the feeding performance of PROSOLV® EASYtab SP.
The minor excipients were fed with dedicated smaller feeders. Even though this special equipment was used, both, the mass flow as well as the motor speed curve were much noisier than the ones for the major components. Thus, it was much more complicated to dose these excipients accurately. CSD could not be fed at all due to its cohesivity and its low bulk density which made it stick to the walls of the feeder.
In the next step a formulation comprising a model active ingredient was tested in a continuous direct compression line. Since pure CSD was impossible to feed, a preblend made from MCC and CSD was used for this experiment. Consequently, four feeders were needed for the formulation made from the single components, while only two feeders were needed in case of the use of the excipient composite PROSOLV® EASYtab SP.



Graph 1a PROSOLV® EASYtab SP, standard large feeder

Graph 1b VIVAPUR® MCC, standard large feeder

Graph 1c EXPLOTAB® SSG, microfeeder

Graph 1d PRUV® SSF, microfeeder

Graph 1 Feeding Behavior of a) PROSOLV® EASYtab SP and b) VIVAPUR® MCC in the Large Feeder as well the Behavior of c) EXPLOTAB® and d) PRUV® in the Microfeeder.

Mass variation was good for both formulations, while the hardness of tablets made from the excipients composite was a bit higher compared to the one from the single components. Furthermore, the formulation using the single components needed the pre-blending and was, consequently, only semi-continuous.

	PROSOLV® EASYtab SP + Active		Single components + Active	
	Average	Standard deviation	Average	Standard deviation
Crushing Strength	137.54 N	5.33 N	125.79 N	6.65 N
Tablet Weight	200.76 mg	1.42 mg	201.48 mg	1.27 mg
API content after 20 min.	10.0 mg	0.10 mg	10.1 mg	0.12 mg

Tab. 1 Tablet Characteristics of Tablets Made from either the All-in-One Excipient or the Single Components.

Conclusion

The co-processed high-functionality excipient PROSOLV® EASYtab SP exhibited better feeding performance in a continuous tableting set-up. It could be fed homogenously at various feeding speeds and needed only one feeder in contrast to the single components which were either harder to feed or – in case of CSD – could not be fed at all. Furthermore, a smaller set-up could be used in case of PROSOLV® EASYtab SP since it needed only one feeder. Continuous manufacturing with a binary mixture containing PROSOLV® EASYtab SP and the active was easier to set-up, run, monitor and clean compared to the individual ingredients. At the same time a slightly better tablet hardness and weight uniformity was observed. In practice, using such an excipient instead of the individual excipients makes it likely that far fewer in-process feedback and feed forward controls will be needed, along with a reduction in PAT. Since the end-product might also be more amenable to real-time release, this, both simplifies and accelerates production.

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