Continuous Manufacturing – how to overcome feeding challenge of Magnesium stearate

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Purpose

The implementation of continuous manufacturing tech-nology for solid applications brings up benefits as easy scale-up, consistent products, lower manufacturing costs and smaller footprint. However, dosing accuracy of minor components or badly flowing components – either API or excipients – is technically a key challenge. To overcome this hurdle, the pragmatic approach is evaluated using a excipient system of mannitol and magnesium stearate for continuous direct compression. In the current study, the powder properties of the pre-mix are analyzed with respect to flowability and feeding. The tableting per-formance of this excipient system and in presence of model drugs is then evaluated and compared to the standard mixture with magnesium stearate added last. Finally, the suitability of the excipient system approach is tested on a continuous line.

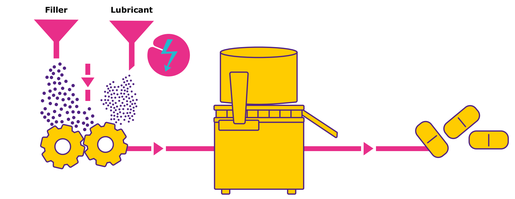

Figure 1: Schematic illustration of a continuous tableting process using a combined Excipient system to overcome the feeding challenge.

Methods

A spray-granulated mannitol grade (Merck KGaA, Darmstadt, Germany) was used as binder, magnesium stearate (MST) (Merck KGaA, Darmstadt, Germany) as lubricant and Propranolol*HCl (Selectchemie, Jiangsu, China) was one model drug. The mixtures were prepared by mixing mannitol and MST (2% w/w) or API (10% w/w) for 5 min at 47 rpm using a Turbula® (T2A, (Willy A. Bachofen AG-Maschinenfabrik, Muttenz, Schweiz). The third component (API or MST) was added and mixed again for 5 min, 47 rpm. The whole in one mixture was prepared by weighing the components and mixing for 5 min, 47 rpm. MST was always sieved using a 250 µm sieve. The mixtures were compressed with a single punch press (EKO, Korsch, Berlin, Germany) equipped with strain gauges to detect the ejection force. For tablet characterization a Mul-ticheck (Erweka, Langen, Germany) was used. Dissolution tests were run using a Sotax AT Extend (Sotax, Aesch, Switzerland) with Phosphate buffer pH 6.8 as medium (wavelength 214 nm, 0.5 mm cuvette).

Results

PERFORMANCE in batch mode comparison

The analysis of the powder properties demonstrates a comparably good flowability of the excipient system to the pure mannitol filler (data not shown). The good flow behavior correlates with adequate feeding of the excipient system in the continuous line.

The performance of the excipient system in a tableting process is shown in presence of Propranolol (Figure 2). Overall, the detected ejection forces are acceptable. The ejection force for the excipient system where Propranolol is added last is slightly higher for 5 and 10 kN compaction force and higher at 20 kN. The suitability of the excipient system is also demonstrated with other model drugs (Ibuprofen, Ascorbic acid) showing comparable or even lower ejection forces for the excipient system (data not shown).

For all tested model formulations, the tablet hardness is comparable and not affected by the mixing order (Figure 2).

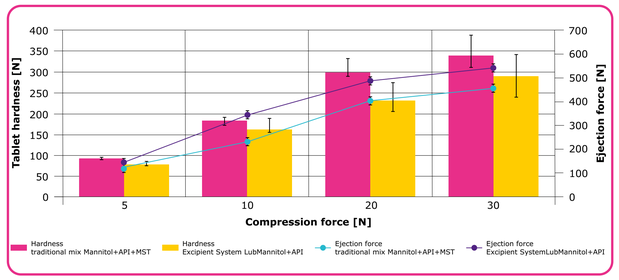

Figure 2: Ejection force and tablet hard-ness of mixtures prepared by different mixing sequence with Propranolol as model drug.

Furthermore, the dissolution performance is similar for all tablets produced with the different mixtures, the mixing sequence does not impact the API release (Figure 3).

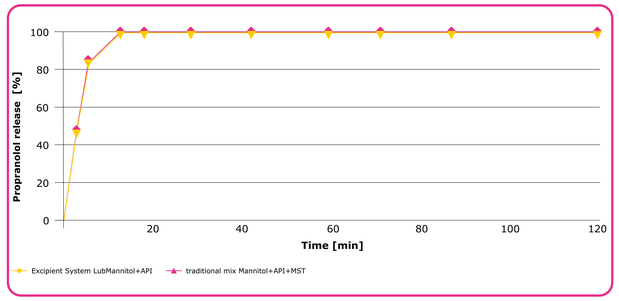

Figure 3: Dissolution results of tablets with Propranolol as model drug (n=3).

PERFORMANCE in continuous mode comparison

Comparing the perfor-mance of a combined excipient system with the classical separate dosing and mixing ap-proach using a state of the art continuous in line Mixing and com-pression unit Sytegon TPR 200 was used.

Figure 4: Continuous in line mixing and compression line Syntegon TPR 200.

In this configuration also the ejection forces could be shown to be constant for both operation modes (Figure 5).

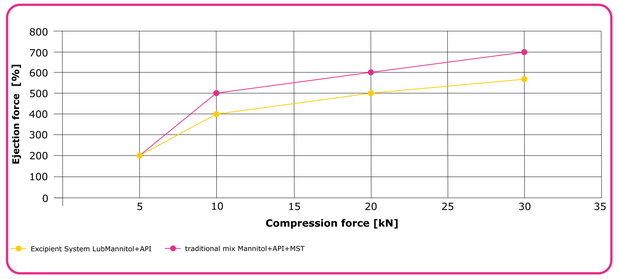

Figure 5: Ejection forces vs. compaction forces for excipient system + API vs. traditional mixing operation.

Also the performance with regards to hardness was found to be constant for both operation modes (Figure 6).

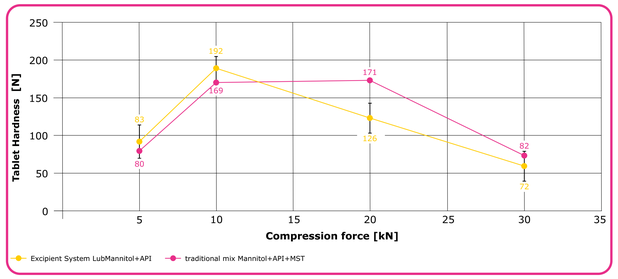

Figure 6: Tablet hardness vs. compaction forces for excipient system + API vs. traditional mixing operation.

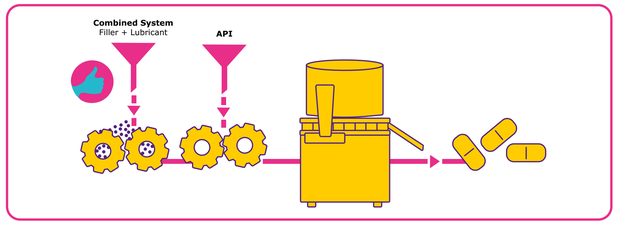

Figure 7: Schematic view of the 3-axis laser measurement device used as an in process control.

Lessons Learned

The use of a combined excipient system of mannitol and magnesium stearate is a promising solution to overcome the feeding challenge in continuous manufacturing.

References

[1] Merck KGaA, Darmstadt, Germany

[2] Syntegon Technology GmbH, Waiblingen, Germany