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Research paper

Downstream processing from melt granulation towards tablets: In-depth analysis of a continuous twin-screw melt granulation process using polymeric binders

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ABSTRACT

The concept of twin-screw melt granulation (TSMG) has steadily (re)-gained interest in pharmaceutical formulation development as an intermediate step during tablet manufacturing. However, to be considered as a viable processing option for solid oral dosage forms there is a need to understand all critical sources of variability which could affect this granulation technique. The purpose of this study was to provide an in-depth analysis of the continuous TSMG process in order to expose the critical process parameters (CPP) and elucidate the impact of process and formulation parameters on the critical quality attributes (CQA) of granules and tablets during continuous TSMG. A first part of the study dealt with the screening of various amorphous polymers as binder for producing high-dosed melt granules of two model drug (i.e. acetaminophen and hydrochlorothiazide). The second part of this study described a quality-by-design (QbD) approach for melt granulation of hydrochlorothiazide in order to thoroughly evaluate TSMG, milling and tableting stage of the continuous TSMG line. Using amorphous polymeric binders resulted in melt granules with high milling efficiency due to their brittle behaviour without producing excessive amounts of fines, providing high granule yields with low friability. Therefore, it makes them extremely suitable for further downstream processing. One of the most important CPP during TSMG with polymeric binders was the granulation-torque, which - in case of polymers with high T_g - increased during longer granulation runs to critical levels endangering the continuous process flow. However, by optimizing both screw speed and throughput or changing to polymeric binders with lower T_g it was possible to significantly reduce this risk. This research paper highlighted that TSMG must be considered as a viable option during formulation development of solid oral dosage forms based on the robustness of the CQA of both melt granules and tablets.

1. Introduction

Downstream processing of a drug compound into tablets is often the preferred choice during formulation development as it combines a high economic efficiency with good patient compliance. This is clearly reflected in the number of oral solid dosage forms reaching the market, for which over 70% are tablets [28]. Direct compression (DC) of a formulation is intuitively the preferred tablet manufacturing route based on its simplicity and cost efficiency, however the powder mixture requires specific properties (e.g. high flowability, low segregation tendency and high compactibility) which are often lacking [28]. The addition of directly compressible excipients may overcome some of these problems and yield satisfactory tablets for such materials. However, these products are often relatively expensive. Moreover, in case of high-dose formulated DC-mixtures (e.g. acetaminophen) this may lead to very large tablets, hampering the patient compliance [9]. Regarding low-dose formulations, DC is challenging since poorly flowing and cohesive drugs need to be uniformly dispersed in a powder blend to guarantee an acceptable tablet content uniformity [2]. Considering the possible drawbacks of DC, pharmaceutical companies often implement granulation as a pre-treatment step in the tablet manufacturing route in order to reduce the risk of final product failure.

Granulation is a well-established pharmaceutical processing technique to agglomerate primary drug and excipient particles into larger secondary particles (granules) which meet the required properties (e.g. flowability, compactibility and content uniformity) for processing into a final dosage form [5, 21, 37, 41]. A variety of both wet- and dry granulation techniques are used in the pharmaceutical field and have

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Table 1
Overview of the raw materials used in the study and their powder characteristics.

Product	Abbreviation	Onset of degradation (°C)	T_g (°C)	T_m (°C)	δ[a] ($MPa^{0.5}$)	d_{50} (μm)	True density (g/ml)	Moisture content (%)
Soluplus®	SOL	289	64	–	19.4[b]	81.4 ± 0.9	1.163	2.10 ± 0.12
Eudragit® EPO	EPO	250	53	–	19.7[c]	8.81 ± 0.4	1.108	0.99 ± 0.02
Kollidon® VA64	VA64	270	108	–	19.7[b]	48.2 ± 0.3	1.213	3.98 ± 0.01
Affinisol™ 15LV	15LV	308	97	–	24.8[d]	102 ± 4.0	1.218	2.29 ± 0.31
Affinisol™ 4M	4M	318	96	–	24.7[d]	102 ± 3.9	1.210	2.93 ± 0.10
Acetaminophen	APAP	212	–	171	27.7[c]	16.6 ± 0.4	1.287	0.41 ± 0.02
Hydrochlorothiazide	HCT	303	–	272	36.7[d]	178 ± 4.5	1.512	0.27 ± 0.01

[a] δ representing the total Hansen's solubility parameter, as obtained from literature:
[b] (Kolter et al., 2012).
[c] (Albers and Kleinebudde, 2008).
[d] (Devalapalli et al., 2017).

been reviewed where twin-screw wet granulation is most prominently investigated during the last decade especially in the context of continuous granulation [7, 42]. However, some pharmaceuticals experience stability and degradation issues by wet processing and proper control of the drying-step is critical during continuous twin-screw wet granulation (TSWG) to avoid flow and compression issues [20].

Twin-screw melt granulation (TSMG) can counter some of the wet-granulation drawbacks since the agglomeration is initiated by a softened or molten binder instead of a granulation liquid, making TSMG extremely suitable for moisture-sensitive drugs [19]. Lakshman et al. evaluated various granulation techniques for the development of a robust manufacturing process for high-dose metformin HCL whereby TSMG was the most suitable technique. Enhanced tableting properties of the poorly compactible high-dosed drug were noticed whereas highly reproducible low moisture levels of the granules ensured end product stability and quality [20]. Moreover, the technology enabled to reduce both process time and energy consumption since no additional drying-step is needed after granulation compared to TSWG [25]. This makes TSMG extremely interesting in the context of continuous manufacturing and therefore the technique steadily regained interest of research groups and industry [1, 18, 26, 27]. Continuous processing is currently a main focus in pharmaceutical manufacturing to accelerate the transition towards more robust and efficient processes, reducing development and manufacturing costs and eventually increase the quality of the end product [31, 33].

The aim of this research paper was to establish a continuous TSMG concept using a twin-screw extruder and evaluate various critical stages in such continuous line using amorphous polymeric binders. Previous research successfully used amorphous polymers as carriers in solid dispersions prepared by continuous hot-melt extrusion for downstream processing towards tablets [11,13]. The high milling efficiency and excellent tableting properties of these polymers suggested their use as polymeric binder during TSMG. In a first part of the study, five amorphous polymers were screened with two model drugs for their potential as polymeric binder. Afterwards, a quality-by-design (QbD) approach was implemented to thoroughly understand the critical process parameters (CPP) during TSMG and to elucidate the impact of process and formulation parameters on the critical quality attributes (CQA) of granules and tablets during continuous manufacturing of high drug-loaded melt granules.

2. Materials

Three amorphous polymers were selected from a previously established polymer database for hot-melt extrusion/tableting [13]. Kollidon® VA64 (VA64) and Soluplus® (SOL) were kindly donated by BASF (Ludwigshafen, Germany), while Eudragit® EPO (EPO) was provided by Evonik (Darmstadt, Germany). Two HPMC-grades developed for hot-melt extrusion (HME) (Affinisol™) with varying molecular weight were donated by DOW (Bomlitz, Germany): 15 LV and 4 M having a low and high molecular weight, respectively. Acetaminophen (APAP, Mallinckrodt, St. Louis, USA) and hydrochlorothiazide (HCT, UTAG, Amsterdam, The Netherlands) were used as model drugs for melt granulation based on their different melting point (171 and 272 °C for APAP and HCT, respectively) which might reflect in their behaviour during melt granulation. All raw materials and their characteristics are listed in Table 1.

3. Methods

3.1. Continuous twin-screw melt granulation

This research paper intended to introduce a concept for implementation of TSMG into a continuous tablet manufacturing line by combining mixing, TSMG, milling and compression. Fig. 1 gives a schematic overview of the process-flow and the possible integration of the various stages in a continuous manufacturing line. The feeding and continuous mixing stage has been thoroughly investigated and evaluated at our department by Van Snick et al. for a continuous direct compression line [38, 39]. Therefore, this research paper mainly focused on the later stages of the continuous concept with TSMG being the first unit following the feeding/mixing stage.

3.1.1. Blending and gravimetric feeding

Before blending the active pharmaceutical ingredient (API) and polymer, the neat API was milled (Quadro® U5, Waterloo, Canada) using a round arm impeller at 900 rpm with a 1395 μm screen to break up possible powder lumps. Afterwards, blends were prepared for both model drugs with all amorphous polymers using a tumbling mixer (W.A. Bachofen, Basel, Switzerland) for 10 min at 15 rpm. These blends were gravimetrically fed to the granulation unit using a DD Flexwall® gravimetric feeder (Brabender Technology, Germany).

3.1.2. Twin-screw melt granulation

A co-rotating intermeshing twin-screw extruder (Prism Eurolab 16, ThermoFischer Scientific, Karlsruhe, Germany) was used as granulator with a barrel length of 25 L/D, where L is the axial screw length and D the inner bore diameter corresponding to one of the screws. The screw configuration was identical for all experiments, with 2 mixing zones in the third and fifth segment, each consisting of 6 kneading discs at 60° stagger angle in reversed direction and a screw-mixing element at the end of each screw intended for break-up of potentially large melt-granule lumps. The granulation barrel is divided into 6 segments ($T_{1\text{-}6}$) which can be heated/cooled separately. The temperature at the end of the barrel (T_6) was lowered to 40 °C during all runs in order to cool the granules below the glass transition temperature (T_g) of the polymers, enabling break up of very large agglomerates by the screw-mixing elements and avoiding sticking of the granules when leaving the barrel. All other segments in the granulator ($T_{1\text{-}5}$) were kept constant at the same temperature, except for mixtures with EPO for which the