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The use of rheology to elucidate the granulation mechanisms of a miscible and immiscible system during continuous twin-screw melt granulation

Tinne Monteyne[a,*], Liza Heeze[a], Séverine Thérèse F.C. Mortier[a,c], Klaus Oldörp[d], Ingmar Nopens[c], Jean-Paul Remon[a], Chris Vervaet[b], Thomas De Beer[b]

[a] Laboratory of Pharmaceutical Process Analytical Technology, Department of Pharmaceutical Analysis, Faculty of Pharmaceutical Sciences, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium
[b] Laboratory of Pharmaceutical Technology, Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium
[c] BIOMATH, Department of Mathematical Modelling, Statistics and Bioinformatics, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, 9000 Ghent, Belgium
[d] Center for Material Characterization of Products, Thermofisher, Dieselstrasse 4, 76227 Karlsruhe, Germany

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ABSTRACT

Twin-screw hot melt granulation (TS HMG) is a valuable, but still unexplored alternative to granulate temperature and moisture sensitive drugs in a continuous way. Recently, the material behavior of an immiscible drug–binder blend during TS HMG was unraveled by using a rheometer and differential scanning calorimetry (DSC). Additionally, vibrational spectroscopic techniques proved the link between TS HMG and rheology since equal interactions at molecular level did occur in both processes. This allowed to use a rheometer to gain knowledge of the material behavior during hot melt processing of an immiscible drug–binder blend. However, miscibility of a drug–binder formulation and drug–binder interactions appear to influence the rheological properties and, hence conceivably also the granulation mechanism. The aim of this research was to examine if the TS HMG process of a miscible formulation system is comparable with the mechanism of an immiscible system and to evaluate whether rheology still serves as a useful tool to understand and optimize the hot melt granulation (HMG) process. The executed research (thermal analysis, rheological parameters and spectroscopic data) demonstrated the occurrence of a high and broad tan(δ) curve without a loss peak during the rheological temperature ramp which implies a higher material deformability without movement of the softened single polymer chains. Spectroscopic analysis revealed drug–polymer interactions which constrain the polymer to flow independently. As a result, the binder distribution step, which generally follows the immersion step, was hindered. This insight assisted the understanding of the granule properties. Inhomogeneous granules were produced due to large initial nuclei or adhesion of multiple smaller nuclei. Consequently, a higher granulation temperature was required in order to get the binder more homogeneously distributed within the granules.

1. Introduction

The pharmaceutical industry has traditionally relied on batch processing to manufacture their drug products. Within the scope and need of increased process efficiency and reduced manufacturing costs, there is a growing interest in alternative manufacturing models having the possibility of automation and continuous production. Implementing a switch from batch to continuous processing, however, could be perceived as a challenge since this requires overall process understanding. As a benefit, this in-depth process understanding will reduce the numerous development runs and limit the amount of material required during development (Vervaet and Remon, 2005; Plumb, 2004). Twin-screw wet granulation is examined already extensively and seems a promising continuous granulation technology, allowing fully continuous from-powder-to-tablet manufacturing (Keleb et al., 2004; Van Melkebeke et al., 2008; Vercruysse et al., 2012).

* Corresponding author.
E-mail addresses: Tinne.Monteyne@UGent.be (T. Monteyne), Liza.Heeze@UGent.be (L. Heeze), Severine.Mortier@UGent.be (S.T.F.C. Mortier), Klaus.Oldoerp@Thermofisher.com (K. Oldörp), Ingmar.Nopens@UGent.be (I. Nopens), JeanPaul.Remon@UGent.be (J.-P. Remon), Chris.Vervaet@UGent.be (C. Vervaet), Thomas.Debeer@Ugent.be (T. De Beer).

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Granulation is an important process step to improve processability, flowability, compactability and content uniformity of the raw materials to be formulated into a final solid dosage form (e.g., tablets). This particle size enlargement process is commonly done via wet granulation using a granulation liquid (mostly water) to initiate binding between powder particles, followed by a drying step. However, some pharmaceutical actives are not suitable for wet processing and drying because of stability and degradation problems. Studies proved HMG or thermoplastic granulation using a twin-screw granulator to be a valuable alternative for continuous wet granulation (Kowalski et al., 2009; Lakshman et al., 2011). Continuous HMG uses a molten binder instead of a granulation liquid to agglomerate the pharmaceutical powder particles. Since no liquids or solvents are used, no drying step is needed, reducing the process time and energy consumption. HMG using the twin-screw granulation technology is even more unexplored than twin-screw wet granulation (Mu and Thompson, 2012).

Understanding the agglomeration mechanism during melt granulation is very important for formulation and process optimization, process control and troubleshooting. The major research is done on batch melt granulation processes (high shear and fluidized bed melt granulation) and only little research has been performed to elucidate the agglomeration mechanisms during continuous twin-screw melt granulation (Kidokoro et al., 2002; Schæfer, 2001; Mu and Thompson, 2012). Due to the temperature-controlling barrel surrounding the screws in TS HMG, the material temperature is more localized and controlled compared to batch melt granulation processes. Through the design of the equipment, the shear forces are acting differently on the material compared to melt granulation batch processes. As a consequence, material residence time inside the equipment is reduced from minutes/hours for batch processing to several seconds for continuous twin-screw melt granulation. Hence, the melt granulation mechanism is likely to be different in continuous hot melt granulation compared to batch melt granulation. Mu et al. described a correlation between the original binder particle size and the final granule size and therefore, they considered the immersion mechanism to be the nucleation mechanism in continuous melt granulation using a twin-screw granulator. The final granules appeared to have a homogeneous binder distribution indicating that the temperature and the intensive mechanical mixing during the process induced a mechanism shift from the immersion (at nucleation) to the distribution mechanism, allowing besides layering also coalescence as a growth mechanism. Mu et al. used polyethylene glycol (PEG) as a binder to agglomerate lactose particles which is an immiscible formulation without drug–binder interactions (Mu and Thompson, 2012).

In our previous work, the agglomeration mechanism of the immiscible blend caffeine anhydrous-Soluplus® was examined. Thermal analysis of the granules revealed two glass transition temperatures. One glass transition temperature (T_g) exceeded the T_g of pure Soluplus® (i.e. 70 °C), whereas the other T_g was lower. In addition, the rheological properties of the blend showed a clear peak in the rheological tan(δ) curve owing to friction between the polymer chains and/or drug particles which became more explicit when using a higher binder content. Both results headed toward the hypothesis that the binder is distributed over the surface of the drug particles during granulation with the formation of a thin layer with restricted mobility (T_g > 70 °C). This fraction is limited and the remaining binder fraction is supposed to form a second layer with improved mobility over the initial low mobility layer (T_g < 70 °C). This high mobility layer was established when granulation was performed using 15% (w/w) Soluplus®. For a more detailed description of the mechanism, the reader is referred to our publication (Monteyne et al., 2016a). The knowledge of the granulation mechanism was useful to understand the granule properties. When the Soluplus® concentration added up to 20% (w/w) or more, the high mobility layer became thicker which generated smaller and more spherical granules in function of temperature. A lower binder concentration, on the other hand, produced larger and more needle-shaped granules in function of temperature (Monteyne et al., 2016a). For these immiscible systems, it was proven that a rheometer in combination with DSC can be used as a fast screening tool to unravel the material flow behavior of the drug–binder blend as a function of binder concentration and granulation temperature which can be extended to the continuous melt granulation process.

Since the binder distribution is influenced by the chemical interactions of the material, not only the physical properties (rheology) but also the chemical properties are of a great importance. Therefore, spectroscopy was executed during the rheological characterizations. If existing, drug–binder interactions seem to influence the microstructure, dissolution rate, stability and ease of processing. The research group of Kidokoro et al. performed high shear melt granulation using Eudragit® RS PO as binder to agglomerate ibuprofen and observed hydrogen bond formation between both. Ibuprofen has permeated in between the polymer chains inducing an enlargement of the free volume and hence lowering the T_g of the binder. This implies that ibuprofen had a plasticizing effect on the Eudragit® RS PO polymer, due to the miscibility of ibuprofen with the polymer (Kidokoro et al., 2001). In contrast, Wu et al. described the binder-active pharmaceutical ingredient (API) system Eudragit® RS 30D-theophylline as being immiscible which had have no influence on the T_g and viscosity of the binder (Wu and McGinity, 1999). Accordingly, binder-API interactions can influence binder viscosity through their plasticizing or anti-plasticizing effects and hence manipulating binder flow, binder distribution and, material deformability (Ueda et al., 2014; Evrard et al., 1999). Apparently, binder-API interactions can thus have an influence on the granulation mechanism. However, no previous work could be found to address the granulation mechanism of a miscible drug–binder formulation during continuous twin-screw melt granulation.

2. Objectives

The objective of this paper is to evaluate the use of rheology and vibrational spectroscopy to increase the understanding of the continuous melt granulation mechanism of a miscible formulation. These findings will be compared with the results obtained in our previous study, where the flow behavior of an immiscible system is thoroughly examined. This will highlight the importance of acquiring formulation insight prior to process understanding and optimization. Furthermore, the granulation mechanism will be used in order to understand the different granule properties.

3. Materials and methods

3.1. Materials

Soluplus® (SLP) (BASF, Ludwigshafen, Germany) (T_g = 70 °C) was used as binder to agglomerate the API. Soluplus® (X10 = 184 μm, X50 = 301 μm, X90 = 478 μm) is a graft copolymer consisting of three parts, being polyvinyl caprolactam (57%), polyvinyl acetate (PVA) (30%) and PEG 6000 (13%) (Cespi et al., 2014). Caffeine anhydrous (CAF) (BASF, Ludwigshafen, Germany), having a solubility of 0.03 g per g Soluplus®, was used as a non-miscible model drug for Soluplus®. Caffeine has a particle size below 150 μm (X10 = 1.4 μm, X50 = 11.1 μm, X90 = 106.6 μm) and appears in two polymorphs, namely Form I and Form II, the latter being the commercially available polymorph. Metoprolol tartrate (MPT) (UTAG, Almere, The Netherlands) (melting temperature T_m = 120 °C) was used as a model drug miscible in Soluplus® (solubility of 0.72 g per gram Soluplus®). MPT is a micronized powder having a particle