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Development of a controlled release formulation by continuous twin screw granulation: Influence of process and formulation parameters

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ABSTRACT

The aim of this study was to evaluate the potential of twin screw granulation for the continuous production of controlled release formulations with hydroxypropylmethylcellulose as hydrophilic matrix former. Metoprolol tartrate was included in the formulation as very water soluble model drug. A premix of metoprolol tartrate, hydroxypropylmethylcellulose and filler (ratio 20/20/60, w/w) was granulated with demineralized water via twin screw granulation. After oven drying and milling, tablets were produced on a rotary Modul^{TM} P tablet press. A D-optimal design (29 experiments) was used to assess the influence of process (screw speed, throughput, barrel temperature and screw design) and formulation parameters (starch content of the filler) on the process (torque), granule (size distribution, shape, friability, density) and tablet (hardness, friability and dissolution) critical quality attributes. The torque was dominated by the number of kneading elements and throughput, whereas screw speed and filling degree only showed a minor influence on torque. Addition of screw mixing elements after a block of kneading elements improved the yield of the process before milling as it resulted in less oversized granules and also after milling as less fines were present. Temperature was also an important parameter to optimize as a higher temperature yielded less fines and positively influenced the aspect ratio. The shape of hydroxypropylmethylcellulose granules was comparable to that of immediate release formulations. Tensile strength and friability of tablets were not dependent on the process parameters. The use of starch as filler was not beneficial with regard to granule and tablet properties. Complete drug release was obtained after 16–20 h and was independent of the design's parameters.

1. Introduction

Twin screw granulation (Keleb et al., 2002; Lee et al., 2013) has received much attention in recent years as this continuous manufacturing concept can be implemented by the pharmaceutical industry to make the switch from batch to continuous processing in order to improve time and cost efficiency, flexibility, quality and environmental impact during manufacturing of oral solid dosage forms (Vervaet and Remon, 2005; Hurter et al., 2016; De Soete et al., 2013). Additionally, regulatory authorities also encouraged the pharmaceutical industry to adopt continuous processing (Hurter et al., 2016).

Up to now most studies on twin screw granulation focused on the influence of process parameters on granule quality (Vercruysse et al., 2012, 2015; Dhenge et al., 2010, 2011; Djuric and Kleinebudde, 2008, 2010; Thompson and Sun, 2010; Keleb et al., 2004; Shah, 2005; Van Melkebeke et al., 2008) while only a limited number of papers addressed formulation parameters (Rocca et al., 2015; Fonteyne et al., 2014; Tan et al., 2011; Thompson et al., 2012; El Hagrasy et al., 2013; Yu et al., 2014). In most studies excipients intended for immediate release formulations were used such as lactose, microcrystalline cellulose (MCC), dicalciumphosphate and blends thereof. Occasionally formulation parameters were investigated such as different lactose isomers (Keleb et al., 2004), lactose grades with different size characteristics (Keleb et al., 2004; El Hagrasy et al., 2013) and the

Abbreviations: C%, compressibility index; d, tablet diameter; d_{50}, median granule size; F, diametral crushing force; F_{wt}, weight of granules retained on a 250 μm sieve after friability testing; HPMC, hydroxypropylmethylcellulose; I_{wt}, weight of granules subjected to friability testing; L/S, liquid-to-solid; MCC, microcrystalline cellulose; MPT, metoprolol tartrate; SME, screw mixing elements; t, tablet thickness; TS, tensile strength; V_0, bulk volume; V_{1250}, tapped volume.

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hydrophobicity and solubility of excipients (Lee et al., 2013; Djuric et al., 2009). More complex formulations however require special attention.

Continuous granulation of controlled release formulations was up to now exclusively examined by Thompson and O'Donnell (2014). They studied the granulation behavior of two placebo formulations with hydroxypropylmethylcellulose (HPMC) or polyvinylacetate/povidone (5–20% w/w) as matrix formers and a mixture of MCC and lactose as filler (MCC/lactose ratio 20/80, w/w) on a 27 mm Leistritz extruder. This process yielded large granules with a twisted morphology, especially using HPMC as matrix former. The poor shape of the granules (the aspect ratio of the individual granules was as low as 0.25) could not be eliminated by changing the liquid-to-solid ratio (L/S), screw speed, throughput or polymer concentration. It was observed that these twisted granules were formed immediately after a non-conveying zone. Screw configurations with a kneading block or comb mixing elements at the end were the only effective means of eliminating the formation of these aberrant granules.

It was the aim of this study to investigate the potential of continuous twin screw granulation with water as granulation liquid, for the production of a controlled release formulation with HPMC as hydrophilic matrix former and metoprolol tartrate (MPT) as very water soluble model drug. Therefore the influence of process (throughput, screw speed, temperature and screw design) and formulation (starch content of the filler) parameters on critical quality attributes of the process, granules and tablets were investigated using an experimental design.

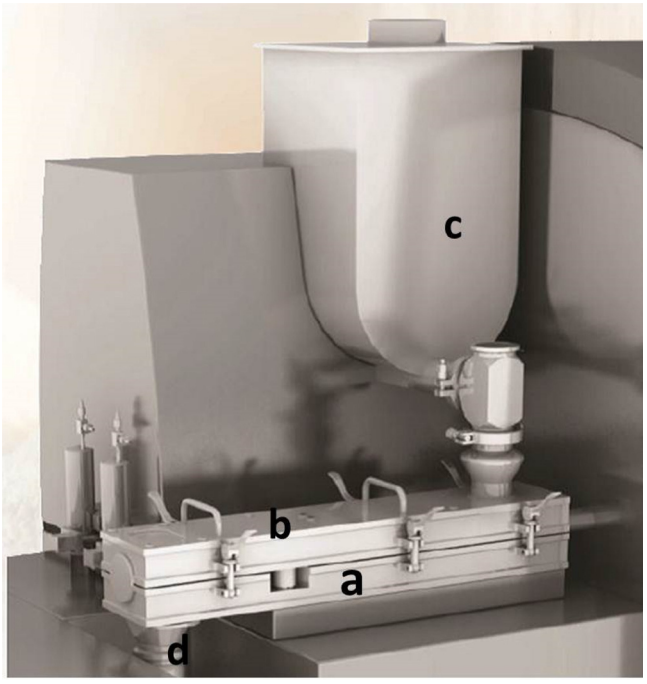

Fig. 1. ConsiGma™-1 system with (a) high-shear granulator barrel, (b) liquid addition on both screws, (c) gravimetric feeder and (d) granulator exit to be optionally coupled to a fluid bed dryer.

2. Materials and methods

2.1. Materials

MPT was used as model drug and was purchased from Utag (Almere, The Netherlands). HPMC grade 90SH-4000 (substitution type 2208 according to the USP and Ph. Eur.) was kindly donated by ShinEtsu (Tokyo, Japan). Native maize starch (C*Gel™, Cargill, Mechelen, Belgium), MCC (Avicel PH101, FMC Health and Nutrition, Cork, Ireland) and α-lactose monohydrate (Pharmatose 200M, DMV-Fronterra, Veghel, The Netherlands) were used as fillers. Distilled water was used as granulation liquid. Magnesium stearate (Fagron, Waregem, Belgium) was used as lubricant during tableting.

2.2. Methods

2.2.1. Preparation of granules

MPT (20% w/w), HPMC (20% w/w) and filler (lactose or 1/1-mixture of lactose/starch) were preblended in a tumbling mixer (Inversina Bioengineering, Wald, Switzerland) for 10 min at 25 rpm and transferred to the loss-in-weight feeder (DDW-MD2-DDSR20, Brabender, Duisburg, Germany) of the ConsiGma™-1 (GEA Pharma Systems, Collette™, Wommelgem, Belgium) system. This system is a laboratory-scale continuous granulator with an integrated fluid bed dryer intended for early R&D work (Fig. 1). The granulation unit consists of a co-rotating twin screw granulator without a die plate and has a length-to-diameter ratio of 20/1. The barrel can be divided in a feed segment with conveying elements and a work segment where the powder is intensively mixed with the granulation liquid by kneading elements. Water as granulation liquid was pumped into the barrel just before the first kneading element via a double liquid addition port, dripping granulation liquid on top of each screw. For all experiments the distance between liquid addition and the first kneading element was kept constant. The L/S ratio was kept constant at 0.08 and 0.10 in MPT/HPMC mixtures using lactose and a lactose/starch (1/1-ratio) mixture as filler, respectively. The barrel jacket was equipped with an active cooling system in order to maintain the set temperature during processing, and torque was monitored by a built-in torque gauge at 1-second intervals. For each run, 1000 g of granules were collected at the outlet of the granulator and tray dried in an oven at 40 °C for 24 h. After drying, 750 g of the granules were milled through a 1000 μm grater screen with square impeller at 900 rpm using the Quadro comil (U10, Quadro, Ontario, Canada).

In addition a formulation used by Thompson and O'Donnell (2014), consisting of 20% HPMC, 16% MCC and 64% lactose was granulated using the granulation unit of the ConsiGma™-25 system (GEA Pharma Systems, Collette™, Wommelgem Belgium) in order to evaluate the tendency of this formulation to form noodle-like granules on the ConsiGma™-25 system (Thompson and O'Donnell, 2014). The HPMC type used in current study was identical to the HPMC type used by Thompson et al. (2012) according to classification of the USP and Ph. Eur. with regard to substitution degree and viscosity. Screw speed, temperature and throughput were fixed at 900 rpm, 25 °C, 25 kg/h, respectively, and a screw configuration with one block of six kneading elements was used. The L/S ratio was varied between 0.10 and 0.30.

2.2.2. Preparation of tablets

The milled granules were blended with 0.5% w/w magnesium stearate in a tumbling blender (T2F, W.A. Bachofen, Basel, Switzerland) before tableting. Tablets were prepared using a Modul™ P tablet press (GEA Pharma Systems, Courtoy™, Halle, Belgium) in manual mode at a speed of 230 tablets per minute. The press was equipped with 10 round flat-faced bevel-edged Euro B punches (SPC, Rillieux-la-Pape, France) of 13 mm diameter and an overfill cam of 16 mm. The paddles in the feed frame were rotating at a speed of 15 and 20 rpm. Filling depths between 9.8 and 10.5 mm were used, in function of the density of the samples. Tablets were compressed at 7 different main compression forces: 6.8 (±1.8), 15.9 (±3.5), 29.0 (±5.8), 44.3 (±2.3) and 65.7 (±7.4) kN after precompression at 2 kN in order to assess the tabletability of