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Continuous twin screw granulation of controlled release formulations with various HPMC grades

V. Vanhoorne[a], L. Janssens[a], J. Vercruysse[a], T. De Beer[b], J.P. Remon[a], C. Vervaet[a,*]

[a] Laboratory of Pharmaceutical Technology, Ghent University Belgium
[b] Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Belgium

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ABSTRACT

HPMC is a popular matrix former to formulate tablets with extended drug release. Tablets with HPMC are preferentially produced by direct compression. However, granulation is often required prior to tableting to overcome poor flowability of the formulation. While continuous twin screw granulation has been extensively evaluated for granulation of immediate release formulations, twin screw granulation of controlled release formulations including the dissolution behavior of the formulations received little attention. Therefore, the influence of the HPMC grade (viscosity and substitution degree) and the particle size of theophylline on critical quality attributes of granules (continuously produced via twin screw granulation) and tablets was investigated in the current study. Formulations with 20 or 40% HPMC, 20% theophylline and lactose were granulated with water at fixed process parameters via twin screw granulation. The torque was influenced by the viscosity and substitution degree of HPMC, but was not a limiting factor for the granulation process. An optimal L/S ratio was selected for each formulation based on the granule size distribution. The granule size distributions were influenced by the substitution degree and concentration of HPMC and the particle size of theophylline. Raman and UV spectroscopic analysis on 8 sieve fractions of granules indicated an inhomogeneous distribution of theophylline over the size fractions. However, this phenomenon was not correlated with the hydration rate or viscosity of HPMC. Controlled release of theophylline could be obtained over 24 h with release profiles close to zero-order. The release of theophylline could be tailored via selection of the substitution degree and viscosity of HPMC.

1. Introduction

Hydroxypropylmethylcellulose (HPMC) is widely applied in oral, ophtalmic and topical pharmaceutical formulations. In oral products, HPMC is applied as binder, film coating and hydrophilic matrix former. As matrix former, it sustains drug release resulting in a prolonged therapeutic effect, minimization of side effects, reduced administration frequency and improved patient compliance. Hydrogen bonding between HPMC and water forms a gel layer at the surface of a wetted tablet, controlling the drug release via diffusion through and erosion of the highly viscous polymer matrix. The matrix forming and drug release mechanisms have been thoroughly studied by several research groups (Ford et al., 1987; Colombo, 1993; Lapidus and Lordi, 1968). HPMC has a polymeric backbone of cellulose substituted with hydroxypropyl and methyl groups. The ratio of hydroxypropyl and methyl substitutions is referred to as the degree of substitution and will determine the characteristics of the polymer (e.g. solubility, hydration rate). Additionally commercially available HPMC grades differ with regard to molecular weight and therefore viscosity.

HPMC is the most popular hydrophilic matrix former for production of controlled release tablets as it is non-ionic, stable over a broad pH range, enzyme resistant, odourless and tasteless, extensively studied and understood, non-toxic and cost-effective (Li et al., 2005; Cao et al., 2013; Savaser et al., 2013; Ferrero et al., 2013; Rajabi-Siahboomi and Tiwari, 2008). Moreover the available variety of HPMC grades with different substitution degrees and viscosities make it a versatile matrix former for controlled release

Abbreviations: C%, Compressibility index; d_{50}, Median particle size; ffc, Flowability index; L/S, Liquid-to-solid; LOD, Loss on drying; PCA, Principal component analysis; PVP, Polyvinylpyrrolidone; V_0, Bulk volume; V_{1250}, Tapped volume; HPMC, hydroxypropylmethylcellulose; a_{50}, median aspect ratio; d_{50}, median particle size; GSD, granule size distribution; PCA, principal component analysis; PC, principal component.

* Corresponding author at: Ghent University, Laboratory of Pharmaceutical Technology, Ottergemsesteenweg 460 9000 Ghent, Belgium.
E-mail address: chris.vervaet@ugent.be (C. Vervaet).

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of a wide range of drugs with varying solubilities and doses (Rajabi-Siahboomi and Tiwari, 2008). Tablets with HPMC can be produced by direct compression but often granulation is necessary (Li et al., 2005; Herder et al., 2006). High shear and fluid bed granulation were successfully applied to improve the flowability of formulations with HPMC (Li et al., 2005; Cao et al., 2013; Herder et al., 2006; Kiortsis et al., 2005; Larsson et al., 2008; Nellore et al., 1998; Xu et al., 1997; Yu et al., 2014; Campos-Aldrete and Villafuerte-Robles, 1997; Huang et al., 2003; Rekhi et al., 1999), often requiring hydro-alcoholic granulation liquids as granulation with water yielded lumps as well as fines due to the irregular wetting of the formulation.

Twin screw granulation is an emerging continuous granulation technique that can be implemented in a fully continuous from-powder-to-tablet manufacturing line. This concept offers economic advantages, improved product quality and a lower environmental impact (Lee et al., 2013; Vervaet and Remon, 2005; Hurter et al., 2013; De Soete et al., 2013). However, up to now only two studies addressed continuous granulation of formulations with HPMC (Thompson and O'Donnell, 2016; Vanhoorne et al., 2016). Whereas these studies used the same HPMC grade and investigated the influence of process parameters, in current study the impact of formulation variables on critical quality attributes of granules and tablets was studied. Three HPMC grades (in two concentrations), varying in substitution degree and viscosity, and two theophylline grades, varying in particle size, were included in the formulations.

2. Materials and methods

2.1. Materials

Anhydrous theophylline, in a micronized and powdered grade, was used as model drug and was kindly donated by BASF (Ludwigshafen, Germany). Three HPMC grades (90SH-4000-SR, 90SH-100000-SR and 60SH-4000) were kindly donated by ShinEtsu (Tokyo, Japan). The substitution types (according to the USP and Ph. Eur.) and viscosities of these HPMC grades are included in Table 1. Magnesium stearate (Fagron, Waregem, Belgium) and α-lactose monohydrate (Pharmatose 200 M, DMV-Fronterra, Veghel, The Netherlands) were used as lubricant and filler, respectively.

2.2. Methods

2.2.1. Preparation granules

Theophylline (20% w/w), HPMC (20 or 40% w/w) and lactose were preblended in a tumbling mixer (Inversina Bioengineering, Wald, Switzerland) for 10 minutes at 25 rpm. An overview of the formulations is shown in Table 2. Subsequently they were transferred to the loss-in-weight feeder (DDW-MD2-DDSR20, Brabender, Duisburg, Germany) of the ConsiGma™-1 (GEA Pharma Systems, GEA Pharma Systems, Wommelgem, Belgium) system. This system is a laboratory-scale continuous granulator with an integrated fluid bed dryer intended for early R&D work. 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. A PT-100 temperature sensor was integrated in the work segment of the barrel and linked to a feedback control system which regulates the temperature in the barrel jacket and compensates for temperature increase during the process due to friction. Torque was monitored by a built-in torque gauge at 1-second intervals. All torque values were smoothed by application of moving average (over a period of 5 measurements). Water as granulation liquid was pumped into the barrel just before the first kneading element via a double liquid addition port (internal diameter 0.8 mm), injecting granulation liquid on top of each screw. For all experiments the distance between liquid addition and the first kneading element was kept constant. Granulation of the formulations was performed at constant process parameters (screw speed 900 rpm, throughput 10 kg/h, barrel temperature 25 °C) using a fixed screw configuration consisting of two kneading blocks with each 6 kneading elements at an angle of 60°. This screw configuration was schematically presented by Vanhoorne et al. (Vanhoorne et al., 2016). The liquid-to-solid (L/S) ratio was varied between 0.08 and 0.18 with intervals of 0.02. After stabilization of torque at least 100 g granules were collected at the outlet of the granulator at each L/S ratio, while 1000 g granules was collected at an L/S ratio considered optimal for each formulation. The optimal L/S ratio (listed in Table 2) was dependent on the HPMC grade and percentage HPMC included in the formulation. The granules were tray dried in an oven at 40 °C for 24 h. After drying, the granules processed with an optimal L/S ratio were milled through a 1000 μm grater screen with square impeller at 900 rpm using the Quadro comil (U10, Quadro, Ontario, Canada) incorporated in the ConsiGma™-25 line.

2.2.2. Preparation of tablets

The milled granules were blended with 0.5% magnesium stearate in a tumbling blender for 2 minutes at 49 rpm (T2F, W. A. Bachofen, Basel, Switzerland) before tableting. Tablets were prepared in manual mode at a speed of 230 tablets per minute on the Modul™ P tablet press (GEA Pharma Systems Courtoy™, Halle, Belgium). The press was equipped with 10 pairs of round flat-faced bevel-edged Euro B punches (GEA Pharma Systems, Halle, Belgium) (diameter 12 mm) and an overfill cam of 16 mm. The paddles in the feed frame were rotating at 15 and 20 rpm. Filling depths between 5.75 and 7.50 mm were used, dependent on the density of the samples. Tablets were compressed at 7 different main compression pressures in order to assess the tabletability of the granules: 60, 110, 150, 190, 260, 330, 410 MPa after precompression at 15 MPa. Tablets compressed at 190 and 330 MPa were selected for friability and dissolution testing.

Table 1
Overview and characterization of the starting materials.

Product	Substi-tution type[a]	Viscosity (mPa*s)	d_{10} ('m)	d_{50} ('m)	d_{90} ('m)	span	True density (g/cm^3)
HPMC Metolose 90SH-4000-SR	2208	4000	18.8	80.4	208.5	2.4	1.32
HPMC Metolose 90SH-100000-SR	2208	100000	14.5	49.7	287.6	5.5	1.32
HPMC Metolose 60SH-4000	2910	4000	16.6	42.6	253.2	5.6	1.29
™-lactose monohydrate	*	*	6.6	41.4	113.8	2.6	1.46
Micronized theophylline	*	*	0.52	8.6	25.6	2.9	1.49
Powdered theophylline	*	*	4.5	41.7	95.0	2.2	1.48

[a] Substitution type according to the USP and Ph. Eu.