International Journal of Pharmaceutics 487 (2015) 72–80

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Continuous twin screw melt granulation of glyceryl behenate: Development of controlled release tramadol hydrochloride tablets for improved safety

Justin M. Keen [a,b,*], Connor J. Foley [a], Justin R. Hughey [a], Ryan C. Bennett [a], Vincent Jannin [c], Yvonne Rosiaux [c], Delphine Marchaud [c], James W. McGinity [a]

[a] The University of Texas at Austin, 1 University Station, Austin, TX 78712, USA
[b] DisperSol Technologies, 111 W. Cooperative Way, Suite 200, Georgetown, TX 78626, USA
[c] GATTEFOSSE SAS, 36, Chemin de GENGAS, Sain-Priest 69804, France

ARTICLE INFO

Article history:
Received 31 October 2014
Received in revised form 6 March 2015
Accepted 27 March 2015
Available online 31 March 2015

Keywords:
Melt granulation
Twin screw granulation
Dose dumping
Controlled release

ABSTRACT

Interest in granulation processes using twin screw extrusion machines is rapidly growing. The primary objectives of this study were to develop a continuous granulation process for direct production of granules using this technique with glyceryl behenate as a binder, evaluate the properties of the resulting granules and develop controlled release tablets containing tramadol HCl. In addition, the granulation mechanism was probed and the polymorphic form of the lipid and drug release rate were evaluated on stability. Granules were prepared using a Leistritz NANO16 twin screw extruder operated without a constricting die. The solid state of the granules were characterized by differential scanning calorimetry and X-ray diffraction. Formulated tablets were studied in 0.1 N HCl containing 0–40% ethanol to investigate propensity for alcohol induced dose dumping. The extrusion barrel temperature profile and feed rate were determined to be the primary factors influencing the particle size distribution. Granules were formed by a combination immersion/distribution mechanism, did not require subsequent milling, and were observed to contain desirable polymorphic forms of glyceryl behenate. Drug release from tablets was complete and controlled over 16 h and the tablets were determined to be resistant to alcohol induced dose dumping. The drug release rate from the tablets was found to be stable at 40 °C and 75% relative humidity for the duration of a 3 month study.

1. Introduction

Historically, pharmaceutical processes have been developed as batch unit operations, requiring batch specific release. A current industrial trend is to adapt or replace these batch processes with continuous processes, which corresponds to a changing regulatory environment (Plumb, 2005). The Food and Drug Administration's (FDA) question based review (QbR) is a shift in quality assessment focusing on critical quality attributes (CQAs) and quality by design (QbD) (Yu, 2008), which requires development and understanding of the formulation and process design space (Lionberger et al., 2008). This shift de-emphasizes the application of pharmaceutical batch operations and post-processing characterization and emphasizes the development of process analytical technologies (PAT) amenable to continuous processing and real-time release testing (Read et al., 2010). In addition to compliance with regulatory approaches and improved quality understanding, continuous processes have been demonstrated as a cost effective alternative to batch processing (Schaber et al., 2011).

Granulation, most broadly defined as a powder agglomeration, is applied in numerous pharmaceutical products for a variety of reasons, e.g., to facilitate compression (Lakshman et al., 2011), improve flow (Danish and Parrott, 1971), uniformity (Wan et al., 1992), and to enhance (Yang et al., 2007) or control (Ochoa et al., 2010) dissolution. Batch granulation processes may require complex modeling to scale up (Faure et al., 2001), suffer from variability (Sochon et al., 2010) and may require large capital investments in equipment relative to continuous processes

* Corresponding author. Present address: DisperSol Technologies, 111 W. Cooperative Way, Suite 200, Georgetown, TX 78626, USA. Tel.: +1 512 686 4740; fax: +1 512 686 4651.
E-mail address: jmkeen@utexas.edu (J.M. Keen).

http://dx.doi.org/10.1016/j.ijpharm.2015.03.058
0378-5173/

(Schaber et al., 2011). Continuous granulation processes are already known (Vervaet and Remon, 2005) with more recent reports applying the twin-screw extruder operating without a die h (Dhenge et al., 2011; Djuric and Kleinebudde, 2010; Lakshman et al., 2011; Mu and Thompson, 2012; Vasanthavada et al., 2011). It is notable that the majority of these reports focus on the use of thermoplastic binders.

Commonly, continuous granulation binders are polymeric, which are suitable for wet or melt granulation. Recent continuous melt granulation reports have employed polyethylene glycol (Mu and Thompson, 2012; Van Melkebeke et al., 2006; Weatherley et al., 2013) or the cellulosics hydroxypropyl methylcellulose and hydroxypropyl cellulose (Vasanthavada et al., 2011). Tan et al. (2014) evaluated polyethylene oxide and hydroxypropyl methylcellulose in combination with lipid binders. Polymeric binders may be undesirable if the granulation process is developed for modified or controlled release applications due to solubility in ethanol and susceptibility to dose dumping in hydroalcoholic media (Fadda et al., 2008). Lipids, which are insoluble in ethanol, can be employed for modified and controlled release applications as a safer alternative. Continuous melt processes have been previously demonstrated to produce controlled release matrices. However, they require either downstream grinding (Liu et al., 2001) or specialized equipment for handling of liquid extrudate (Lo et al., 2009). The continuous production of granules, suitable for continuous blending/compression and for sustained release from a lipid matrix has not previously been demonstrated. At the binder concentrations required for sustained release, these low melting point binders tend to form a paste or a liquid.

The objective of this study was to develop a continuous granulation process for tramadol hydrochloride and glyceryl behenate (C888), which directly results in granules suitable for blending and compression. Tramadol hydrochloride is an analgesic that is currently marketed as an oral controlled release dosage form. The FDA has issued a draft guidance requiring any new controlled release tramadol hydrochloride products be tested for propensity of dose dumping (FDA, 2007). C888 is a lipid excipient suitable for the controlled release of water soluble drugs (Patere et al., 2013). C888 is a mixture of mono-, di and tribehenate of glycerin that has a melting range between 65 °C and 74 °C (Brubach et al., 2007) and is supplied as a fine powder. In addition to conversion of the prepared granules into tablets having a safe hydroalcoholic dissolution profile, the granulation and drug release mechanisms were investigated. Finally, the stability of the polymorphic form was evaluated along with drug release following 3 months of storage at 40 °C, 75% relative humidity conditions.

2. Materials and methods

2.1. Materials

Glyceryl behenate, Compritol® 888 ATO (C888), was kindly donated by Gattefossé (Saint Priest, France). Tramadol hydrochloride was purchased from Letco Medical (Decatur, AL). Microcrystalline cellulose (Avicel® PH-102) donated by FMC BioPolymer (Philadelphia, PA). Magnesium stearate, USP/NF was purchased from Spectrum Chemicals Corporation (Gardena, CA). Spray dried lactose (Fast Flow® 316) was donated by Foremost Farms (Baraboo, WI). Dicalcium phosphate (Emcompress®) was donated by JRS Pharma (Rosenberg, Germany). 40 cc high density polyethylene (HDPE) packer white, Boston round bottles and 33-400 P/P closures with Hs035 induction sealable liners were purchased from Tricorbraun (St. Louis, MO). Analytical reagents of ACS grade or higher were purchased from Fisher Scientific (Pittsburgh, PA).

2.2. Methods

2.2.1. Milling

The tramadol hydrochloride as received contained a substantial fraction of particles greater than 250 μm. Prior to granulation, tramadol hydrochloride was milled using a Fitzmill Laboratory L1A (Fitzpatrick Inc., Elmhust, IN) operating at 9000 rpm, knives forward, using a 0.020 in. screen. The fraction less than 100 μm was collected for further processing and analysis.

2.2.2. Continuous twin screw granulation

Continuous granulation was performed using a NANO16 20:1 L:D 16 mm twin screw extruder (Liestritz, Somerville, NJ) operating at 200 rpm. The feeding zone was maintained at approximately 25 °C using recirculating ambient water. The subsequent control zones (Zone-1, Zone-2, Zone-3 and endplate) and feed rate were adjusted to control the granulation process. The screw design was fixed for all experiments, which included two kneading block sections. The first kneading block section (30° offset) extends from 11 diameters to 13 diameters of the screw length. The second kneading block section (60° offset) extends from 16.5 diameters to 18.5 diameters of the screw length. Materials were manually pre-blended in polyethylene bags for 1 min and charged to a Model 102M screw feeder (Schenck AccuRate Inc., Whitewater, WI). To mitigate bridging, the material was manually agitated in the hopper of the feeder to maintain a constant and repeatable flow rate. For all experiments, the extruder was operated without a die or transfer plate.

2.2.3. Melt mixing granulation

C888 was added to a beaker and melted at 80 °C on a hot plate with the aid of a stir bar. Once the C888 had completely melted, tramadol hydrochloride powder was slowly added to disperse. The mixture was then poured onto a glass plate to cool and solidify. The solidified dispersion was then manually ground through a No. 20 mesh sieve for further processing and analysis.

2.2.4. Blending and compression

Tramadol hydrochloride granules and various excipients intended to act as a pore former were blended for 15 min in a P-K Blend Master V-Shell blender (Patterson–Kelley Co., East Stroudsburg, PA) operating at 25 rpm followed by an additional 5 min of blending with the tableting lubricant, magnesium stearate. The batch size for the tablet blends was 100 g. Individual portions of the blend were weighed and compressed into 11 mm flat faced round tablets at 20 kN compression force using a tablet press, (Manual Tablet Compaction Machine, model MTCM-1, Globe Pharma, Inc., New Brunswick, NJ).

2.2.5. Particle size characterization

The granulation particle size distributions were determined by sieve analysis using a RX-24 Ro-Tap (W.S. Tyler Industrial Group, Mentor, OH). 25 g samples were agitated for 15 min using the following sieve mesh no.: 20, 30, 40, 60, 100, 230, Pan (850 μm, 600 μm, 425 μm, 250 μm, 150 μm, 63 μm, respectively). Each sieve was tared prior to addition of the sample and the amount retained on each sieve was determined following agitation.

2.2.6. Scanning electron microscopy

Granules were imaged using a Quanta 650 FEG scanning electron microscope (FEI company, Inc., Hillsboro, OR). Samples were analyzed under vacuum with the electron beam operating at 20 kV. Samples were distributed onto adhesive carbon tape affixed to an aluminum stage. Samples were sputter coated with a 60/40 mixture of palladium/gold under argon for 30 s prior to imaging.