International Journal of Pharmaceutics 381 (2009) 192–198

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Optimization of melt pelletization in a high shear mixer

P. Bukovec[a,*], V. Krošelj[a], S. Turk[a], F. Vrečer[a,b]

[a] KRKA d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
[b] University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, 1000 Ljubljana, Slovenia

ARTICLE INFO

Article history:
Received 30 November 2008
Received in revised form 27 March 2009
Accepted 23 June 2009
Available online 4 July 2009

Keywords:
High shear mixer
Melt pelletization
Lutrol® F68
Gelucire® 50/13
Lansoprazole
Process parameters

ABSTRACT

The effects of process conditions and binder content on the process yield and pellet characteristics of two formulations prepared by melt pelletization in a laboratory-type high shear mixer were investigated. The formulations were prepared using Gelucire® 50/13 and Lutrol® F68 as meltable binders. The factors under investigation were impeller speed, mixing time, mixer load, binder concentration, and their reciprocal interactions. Analysis of variance (ANOVA) was used in order to study the significance of above mentioned process variables on the useful yield. Twenty-seven experiments were required for the response surface methodology based on Box–Behnken experimental design (24 combinations with three replications of the centre point) for each formulation.

The control over the process and the quality of the resulting pellets were found to depend on the rheological properties of the binders used. In the case of a low viscosity binder (Gelucire® 50/13), the process was easily controllable whereas in the case of a high viscosity binder (Lutrol® F68), the process was more difficult to control.

The useful yield of the formulation in the case of the low viscosity binder was found to be mostly influenced by the concentration of the binder. On the other hand, different binder concentrations did not affect the useful yield of the formulation prepared by use of the high viscosity binder. In the latter case, mixing time was identified as the variable that mostly influenced the pelletization process.

Finally response surface methodology was applied to find the optimum values of the process variables.

1. Introduction

Thermoplastic pelletization in a high shear mixer belongs to the group of hot-melt technologies which represent an alternative to the classical solvent-mediated technological processes of agglomeration. The main advantage of the hot-melt processes, including the thermoplastic pelletization, is the absence of solvents, which enables simple and fast formulation of moisture-sensitive active ingredients (Schaefer et al., 1990). Moreover, the drying phase is eliminated and, consequently, the process is more economical and environmentally friendly. Furthermore, the availability of the chemically and physically versatile group of meltable binders ensures flexibility in the design of the pharmaceutical dosage forms.

The main limitation of the hot-melt technologies is the required high temperature which can cause chemical degradation of the ingredients, especially of the active substance. Another disadvantage is their high sensitivity to process variables and changes in the formulation (Schaefer et al., 1990, 1992b, 1993; Voinovich et al., 1999; Heng et al., 2000).

The influence of process variables and formulation changes on the process yield of pelletization has been studied by many authors. The most investigated parameters are mixer load, impeller speed, mixing time (Schaefer et al., 1992b, 1993; Campisi et al., 1999; Voinovich et al., 1999; Heng et al., 2000), temperature of the heating jacket (Schaefer, 1996; Voinovich et al., 1999), chopper action (Schaefer et al., 1992b; Voinovich et al., 1999), binder concentration (Schaefer et al., 1992b; Voinovich et al., 1999), binder particle size (Schaefer et al., 1992b; Schaefer and Mathiesen, 1996b; Voinovich et al., 1999), binder viscosity (Schaefer and Mathiesen, 1996a; Eliasen et al., 1998), apparatus variables (Schaefer et al., 1993; Voinovich et al., 1999), and physical properties of the materials (Schaefer et al., 1992a; Voinovich et al., 1999). The mentioned parameters were studied simultaneously by use of factorial experimental designs (Campisi et al., 1999; Voinovich et al., 1999; Heng et al., 2000).

In our previous studies (Krošelj et al., 2008) it was proven that pellets with very fast release of a low soluble model drug (lansoprazole) can be prepared by thermoplastic pelletization with surface-active low melting point binders.

The aim of the present study was to investigate the influence of individual variables onto the process yield of the thermoplastic pelletization in a high shear mixer using molten surface-active binders.

* Corresponding author. Tel.: +386 7 331 38 12; fax: +386 7 331 32 70.
E-mail address: polona.bukovec@krka.biz (P. Bukovec).

0378-5173/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2009.06.036

The two formulations were prepared using the stearyl polyoxyglyceride binder Gelucire® 50/13 and the poloxamer binder Lutrol® F68, which differ in their particle size, melting point, and in the viscosity in their molten phase.

Using statistical methods, the influences of the binder concentration, impeller speed, mixing times and mixer load on the process yield, and the physical properties of the produced pellets were studied.

Within the studied intervals, an optimum quantity of binder was identified as well as optimum process parameters. The aim was to minimize the quantity of residual powder and the formation of lumps while maximizing the amount of pellets of appropriate size.

2. Materials and methods

2.1. Materials

Lansoprazole (Krka, Novo mesto, Slovenia) was used as a poorly soluble active ingredient, magnesium carbonate (Cognis, Düsseldorf, Germany) as a stabilizer, lactose 450 mesh (α-lactose monohydrate; DMV, Veghel, The Netherlands) as a diluent, and Gelucire® 50/13 (Gattefosse, Saint Priest, France) and Lutrol® F68 (BASF, Burgbernheim, Germany) as binders.

Gelucire® 50/13 consists of a mixture of mono-, di- and triesters of glycerol and of mono- and diesters of macrogol with stearic (octadecanoic) acid and has an HLB value of 13. Lutrol® F68 is a hydrophilic block copolymer of ethylene oxide and propylene oxide with an HLB value of 29. While the former was provided in the form of solid beads, Lutrol® F68 was used in the form of small prills.

2.2. Methods

2.2.1. Characterization of starting materials

The melting behavior of the binders was evaluated by a Mettler STAR^e SW 8.01, differential scanning calorimeter (Mettler, Schwarzenbach, Switzerland). Samples of about 4 mg were sealed in 40 μL aluminum pans and scanned between 10 °C and 70 °C at a heating rate of 5 K/min.

The viscosities of the molten binders were measured with a Physica Rheolab MC 100 UM (Germany) at different shear rates and different temperatures.

2.2.2. Pellet preparation

The matrix pellets were prepared by hot-melt pelletization in a ProCept Mi-Pro high shear mixer equipped with a double jacket for heating/cooling and a three-bladed impeller with a mixing vessel capacity of 200–300 g.

The pelletization process and the formulation were optimized on the basis of preliminary trials with placebo mixtures. Amounts of binders, mixing times and temperatures were varied (based on trial and error principle). After approximate composition was determined, a part of the filler was replaced with lansoprazole (10%) and magnesium carbonate (10%), the latter used as an alkaline stabilizer.

All ingredients were mixed manually in a plastic bag and transferred into the mixing vessel of the high shear mixer preheated to 45 °C. The heat required for the softening and melting of the binder came from the mixer wall (the double-jacket wall was heated by a heating liquid to 50 °C in the case of Gelucire® 50/13 and to 55 °C in the case of Lutrol® F68) as well as from the friction as a consequence of particle movement during the process.

The concentration of the two binders, mixing times, impeller speed and mixer load were varied according to the Box–Behnken design with factor levels as shown in Tables 1 and 2 randomly. At the end of the pelletization process, the pellets were cooled down at room temperature on metal plates and sieved through a 2.4 mm sieve to determine the amount of lumps.

2.2.3. Characterization of the prepared pellets

The total yield of the process was measured as the amount of pellets passing through the 2.4 mm sieve, divided by the total mass of starting material. Pellets in the range of 0.500–1.400 mm were selected as the useful fraction.

The size distribution of the so obtained pellets was determined by the vibrating sieve analysis, using seven sieves in the range of 0.250–2.00 mm (Prufsieb Jel 200, Hosokawa, Augsburg, Germany). The shape and surface properties of selected pellet samples were investigated using an optical microscope (Stereomicroscope Olympus SZH10, Tokyo, Japan), equipped with a Sony DXC-107AP camera.

Microphotographs of the pellets were made using a field emission scanning electron microscope, FE-SEM SUPRA 35 VP (Carl Zeiss, Oberkochen, Germany), equipped with energy dispersive spectroscopy Inca 400 (Oxford Instruments, Oxford, UK).

The Box–Behnken experimental design and the response surface methodology were used to determine the influence of particular process parameters and binder concentration on the process yield, the amount of by-products and the size of the final product. A second-order polynomial model obtained by multiple regression analysis for four factors was used to describe the response surface.

Furthermore, optimum values of the selected factors were calculated in order to obtain the maximum product yield by use of the SAS system (version 9.1.3).

3. Results and discussion

3.1. Characterization of starting materials

Molten Gelucire® 50/13 has lower viscosity than Lutrol® F68 at a given temperature (Figs. 1 and 2). As expected, the viscosity of both molten binders is inversely proportional to the temperature. The viscosity is also influenced by mechanical stress which is more pronounced at lower shear forces whereas at higher shear forces the viscosity is less influenced. At temperatures higher than 55 °C in the case of Gelucire® 50/13 and above 60 °C in the case of Lutrol® F68, the effect of the mechanical stress on the viscosity is not substantial any more.

The DSC measurements demonstrate that the two binders also differ in their melting behavior (Fig. 3). While Lutrol® F68 has a relatively narrow melting range at 55 °C (T_{onset} = 53 °C), Gelucire® 50/13 has a wider peak at approximately 43 °C (T_{onset} = 37 °C) as it is not a simple single-component excipient but is composed of mono-, di-, tri-glycerol esters and macrogol esters with stearinic acid, which cause widening of the melting peaks and, sometimes, even a two-peak melting range (Sutananta et al., 1994).

Table 1
Selected process variables and levels for pellets with Gelucire® 50/13 and Lutrol® F68.

Level	Factor x_1: binder concentration (%)		Factor x_2: impeller speed (rpm)		Factor x_3: mixing time (min)		Factor x_4: mixer load (g)	
	Gelucire® 50/13	Lutrol® F68	Gelucire® 50/13	Lutrol® F68	Gelucire® 50/13	Lutrol® F68	Gelucire® 50/13	Lutrol® F68
−1	15	18	900	1300	6	3	200	200
0	16	19	1200	1500	9	6	250	250
1	17	20	1500	1700	12	9	300	300