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Melt granulation using a twin-screw extruder: A case study

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Abstract

The purpose of this study was to use a twin-screw extruder for melt granulation. Polyethylene glycols (PEG 400 and 4000) were used as binders for the development of a drinking water formulation with immediate drug release. The effect of drug content, PEG 400/4000-ratio, surfactant (type and concentration) and granulation temperature on granule properties and dissolution characteristics was determined. The granulation temperature had an important influence on the granule formation. High yield (95% of the granules <1400 μm) was obtained only at a temperature near the melting point of PEG 4000. During granulation the drug of BCS class II was finely dispersed in the PEGs, creating a micro-environment around the drug particles enhancing the dissolution rate. To obtain complete drug release within 10 min for a formulation containing 10% drug, the addition of 2% (w/w) surfactant (polysorbate 80 or Cremophor® RH40) was required. At a higher drug content (20%), the PEG 4000 concentration had to be increased to 20% to improve granule properties and 4% polysorbate 80 was required to obtain 100% drug release. X-ray diffractograms showed distinct peaks of crystalline drug, the crystallinity of the drug did not change after 50 days, independent of the storage conditions.

Keywords: Continuous granulation; Extruder; Melt agglomeration; Polyethylene glycol

1. Introduction

Melt granulation is an agglomeration technique where granules are obtained due to softening or melting of binders that are heated to near or above their melting point. Hydrophobic binders such as microcrystalline waxes, paraffin and glycerol monostearate are used for sustained release formulations, while hydrophilic binders such as polyethylene glycols are well suited for immediate release formulations. Melt granulation is most commonly performed in high shear mixers. Schaefer et al. (1992, 1993a; Schaefer, 1996) studied the effect of process and formulation (Schaefer et al., 1990; Schaefer and Mathiesen, 1996b, 1996c) variables on melt granulation with low molecular weight polyethylene glycols, while Zhou et al. (1996, 1997) described a production process of matrix pellets in a high shear mixer using microcrystalline waxes as binders. In high shear mixers the melting or softening temperature of the binder is reached by external heating and/or heat generated by friction. The latter makes it difficult to control the product temperature during granulation. Product temperatures as high as 100 °C have been recorded at a jacket temperature of the mixing bowl of 50 °C (Schaefer and Mathiesen, 1996a), which can result in uncontrolled granule growth and thermal decomposition of materials. Other disadvantages are long massing times and a difficult endpoint determination. Recently, fluidised bed granulators (Abberger et al., 2002; Seo et al., 2002) were used for melt agglomeration. Fluidised bed granulators have the advantage that the product temperature can be better controlled. However, endpoint determination remains difficult.

High shear mixers and fluidised bed granulators both produce granules in a batchwise manner. The main problem of batch production is scale-up from laboratory to industrial production capacity, as the granulator type and bowl dimensions are critical for the production process and the product characteristics (Schaefer et al., 1993b; Zhou et al., 1997). Scale-up problems can be avoided with a continuous granulation process, where the only parameter that needs to be changed is production time. In literature several continuous wet granulation techniques are described: a combination of a high shear granulator and a multicell fluidised bed dryer (semi-continuous granulation) (Leuenberger, 2001), rotary screw extrusion (Schroeder and Steffens, 2002), twin-screw extrusion. Twin-screw extrusion was introduced by Gamlen and Eardley (1986) using a Baker Perkins MP50 extruder to produce paracetamol extrudates.

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Lindberg et al. (1987, 1988) used a twin-screw extruder for the continuous granulation of an effervescent paracetamol preparation. However, milling was required to remove oversized agglomerates. Keleb et al. (2004) recently demonstrated that modifying the extrusion screw profile resulted in a granulation process yielding no oversized granules, eliminating the need of (wet or dry) milling. Based on these papers the application of twin-screw extrusion as a continuous melt granulation process for the development of a veterinary drinking water formulation with immediate drug release was investigated using polyethylene glycols as binders.

2. Materials

Polyethylene glycol 400 (PEG 400) and 4000 (PEG 4000) (BUFA, Uitgeest, The Netherlands) were used as binders. Sodium laurylsulphate (SLS) (Federa, Brussels, Belgium), Lutrol® F127 (poloxamer 407) (BASF, Ludwigshafen, Germany), Cremophor® RH40 (PEG-40 hydrogenated castor oil) (BASF, Ludwigshafen, Germany) and polysorbate 80 (BUFA, Uitgeest, The Netherlands) were used as surfactants. Spray-dried maltodextrin with a dextrose equivalent of 19 (MD) (Cerestar, Sas van Gent, Holland) was used as a filler. A drug of BCS class II (solubility: 1.3 mg/ml) was used in the formulations.

3. Methods

3.1. Preparation of granules

Granulation was performed using a MP 19 TC 25 laboratory-scale co-rotating twin-screw extruder (APV Baker, Newcastle-under-Lyme, UK) having a length-to-diameter ratio of 25/1. The geometry of the screws is illustrated in Fig. 1. Two kneading blocks are present, the first kneading block is placed at 26.6 cm of the dicharge end and consists of 10 paddles (4.75 mm thick). The first four paddles have a forwarding angle of 30°, the next six paddles a forwarding angle of 60° and the last paddle is placed at 90°. The second kneading block (at 15.2 cm of the discharge end) consists of six paddles (4.75 mm thick) with a forwarding angle of 60°. The conveying sections have a double helix and a pitch of 9.5 mm. The end of the screw consists out of a conveying screw element, allowing the formation of granules without any sizing step (Keleb et al., 2004). Powder and liquid feed rates were determined prior to each experiment by repeatedly weighing the powder and liquid amount delivered over a period of 5 min. PEG 400 was pumped into the extruder barrel by means of a peristaltic pump (Watson Marlow, Cornwall, UK) at 38.5 cm of the barrel end.

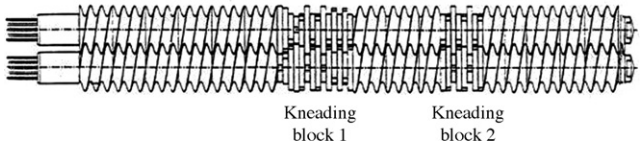

Fig. 1. Configuration of screw profile.

Prior to granulation PEG 4000, maltodextrin and drug were blended for 15 min at 60 rpm in a planetary mixer (Kenwood Major, Hampshire, UK) using a batch size of 1 kg. The composition of the different formulations can be found in Table 1, expressed as % (w/w). When a surfactant was required in the formulation, it was previously dissolved in the liquid PEG 400-fraction. All granulation experiments were performed with a screw speed of 250 rpm and a total input rate of 2 kg/h. Granules were collected 10 min after the process was started in order

Table 1
Formulations used and properties of resulting granules

Formulation							Granule properties				
No.	Drug (%)	PEG (%)		MD (%)	Granulation temperature (°C)	Surfactant	Friability (%)	$F_{<250\,\mu m}$ (%)	$F_{250–1000\,\mu m}$ (%)	$F_{1000–1400\,\mu m}$ (%)	Yield[a] (%)
		400	4000								
1a	10	18.75	5.25	66	30		ND	0	21	17	38
1b	10	18.75	5.25	66	50		32	0	80	15	95
2	10	12	12	66	50		3	1	80	13	94
3	10	5.25	18.75	66	65		3	1	45	31	77
4a	10	0	24	66	50		ND	ND	ND	ND	ND
4b	10	0	24	66	65		15	0	11	22	33
5	10	12	12	65	60	1% SLS[b]	4	0	31	43	74
6	10	12	12	64	60	2% SLS[b]	4	0	18	32	50
7	10	12	12	63	55	3% SLS[b]	9	0	26	27	53
8	10	12	12	62	50	4% SLS[b]	4	0	15	16	31
9	10	12	12	64	50	2% polysorbate 80	64	0	78	17	95
10	10	12	12	64	50	2% Lutrol® F127	21	0	76	17	93
11	10	12	12	64	50	2% Cremophor® RH40	84	1	77	17	95
12	20	12	12	54	50	2% polysorbate 80	4	1	42	27	70
13	20	12	12	53	50	3% polysorbate 80	6	0	22	16	38
14	20	12	12	52	50	4% polysorbate 80	54	0	11	14	25
15	20	5	20	51	50	4% polysorbate 80	4	0	48	36	84
16	20	0	25	51	55	4% polysorbate 80	13	4	38	27	69

[a] Yield defined as the fraction below 1400 μm, ND: not determinable.
[b] Sodium laurylsulphate.

to allow the system to equilibrate. The granules were cooled to ambient temperature before further processing. The influence of drug content, PEG 400/4000-ratio, surfactant (type and concentration) and granulation temperature on granule properties and dissolution characteristics was determined.

3.2. Evaluation

3.2.1. Differential scanning calorimetry

Differential scanning calorimetry (TA 2920, T.A. Instruments) was used to determine the melting range and melting peak temperature of PEG 4000. A sample of about 10 mg was sealed in a hermetic aluminum pan and scanned between −30 and 180 °C at a heating rate of 2 °C/min.

3.2.2. Drug crystallinity and stability

The crystalline drug fraction within the granules was investigated using X-ray diffraction. The X-ray patterns of drug, PEG 4000, maltodextrin and granules (formulation 16, Table 1) were determined using a D5000 Cu Kα Diffractor ($\lambda = 1.54$ Å) (Siemens, Germany) with a voltage of 40 mA in the angular range of $4° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 0.8 s/step). Drug crystallinity in the granules during storage (room temperature, exposed to light and protected from light) was evaluated using the Renishaw System-1000 Raman spectrophotometer (Wotton-under-Edge, United Kingdom) equipped with a 785 nm diode laser (50 mW at the source). The laser beam was focused on the sample by means of an Olympus BH-2 microscope. The spectrophotometer consisted of a 1200 grooves/mm grating and a Peltier-cooled CCD detector. Samples (formulation 16, Table 1) were analyzed using a laser wavelength ranging from 200 to 1800 cm^{-1} (analysis time: 30 s) immediately after preparation and after 50 days of storage protected from or exposed to light.

3.2.3. Particle size distribution

The particle size distribution was determined using a series of sieves (250, 1000 and 1400 μm). The sieves were placed on a sieve shaker (Retsch VE 1000, Haan, Germany) during 10 min at an amplitude of 2 mm. The amount of granules retained on each sieve was determined and the yield was defined as the fraction below 1400 μm.

3.2.4. Friability

The friability was determined in a friabilator (PTF E Pharma Test, Hainburg, Germany) set at a speed of 25 rpm for 10 min, by subjecting 10 g (I_{wt}) of granules ($F_{250–1000\,\mu m}$) together with 200 glass beads (mean diameter 4 mm) to falling shocks. Afterwards the glass beads were removed and the weight of the granules retained on a 250 μm sieve (F_{wt}) was determined after vibrating for 5 min at an amplitude of 2 mm. The friability was calculated as $[(I_{wt} - F_{wt})/I_{wt}] \times 100$.

3.2.5. Dissolution tests

Dissolution tests were performed using the paddle method at a rotational speed of 100 rpm (VK 7010, Vankel, Cary, NC, USA). An amount of granules ($F_{250–1000\,\mu m}$) containing 900 mg of drug was used. Additionally, the dissolution profile of 900 mg pure drug was measured. Demineralised water was used as dissolution medium. The temperature of the dissolution medium was maintained at room temperature. Five milliliters samples were withdrawn at 0, 5, 10, 15, 20, 30, 45 and 60 min after starting dissolution. The drug content was determined at 245 nm using a Perkin-Elmer UV–vis spectrophotometer (Lambda 12, Perkin-Elmer, Norwalk, USA). Within 10 min 100% of the drug should be dissolved in the dissolution medium, according to the EMEA guidelines for drinking water medication (European Medicines Agency, 2005).

4. Results and discussion

Continuous melt granulation has the advantage over batch granulation in terms of ease of processing and reduction of production times. A mixture of drug, PEG 400, PEG 4000 and spray-dried maltodextrin was processed via melt granulation in a twin-screw extruder in order to obtain an immediate release drinking water formulation for chickens and pigs.

The granulation temperature had an important influence on the agglomeration process. Processing of formulation 1 at 30 °C produced soft and sticky granules. In contrast increasing the temperature to 50 °C increased the yield from 38 to 95% and resulted in stronger granules, although the friability still exceeded 30% (formulation 1a and b, Table 1). As a granulation temperature of 50 °C approached the melting point of PEG 4000 (melting range: 45.2–67.2 °C; melting point: 61.3 °C, determined by differential scanning calorimetry), the molten fraction of PEG 4000 was mixed with PEG 400 during granulation and hardened during cooling of the granules, thus producing stronger granules (formulation 4a). The processing temperature also depended on the PEG 400/4000-ratio as without PEG 400 the PEG 4000 fraction molten at 50 °C was insufficient to produce granules. At 65 °C the melting point of PEG 4000 was reached, increasing the amount of molten material and enhancing the binding properties between particles after cooling (formulation 4b, Table 1).

A PEG-fraction of 24% (w/w) was used in the formulations. Changing the PEG 400/4000-ratio had an influence on the particle size distribution as a higher PEG 4000 content resulted in a decrease of the yield. A low friability was obtained for all formulations, except at a PEG 400/4000-ratio of 18.75/5.25 as the liquid fraction in the granules was too high (formulation 1b, Table 1). Fig. 2 shows the dissolution profiles of the different formulations. The presence of PEG 400 and 4000 had a clear influence on the drug dissolution rate: using PEGs about 70% of drug was dissolved within 10 min, compared to 20% for the pure drug. However, even after 1 h of dissolution testing drug release from the formulations was incomplete due to insufficient wetting of the drug particles, resulting in flotation of the formulation during dissolution. In order to solve this problem, a surfactant (SLS) was added to the formulation in a concentration range from 1 to 4% (w/w). All formulations could be granulated, but at least 3% SLS was required to obtain 100% drug release (Fig. 3). Although the addition of SLS resulted in the required dissolution profile, there were some disadvantages associated with the use of SLS: a negative effect on the granule yield (94

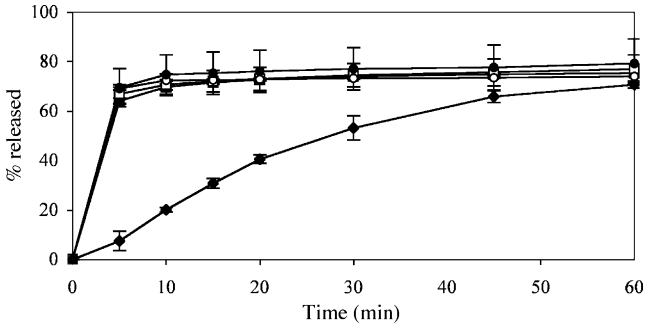

Fig. 2. Influence of PEG 400/4000-ratio on dissolution profiles: (■) 18.75/5.25; (□) 12/12; (◯) 5.25/18.75; (●) 0/24; (♦) pure drug (1 mg/ml).

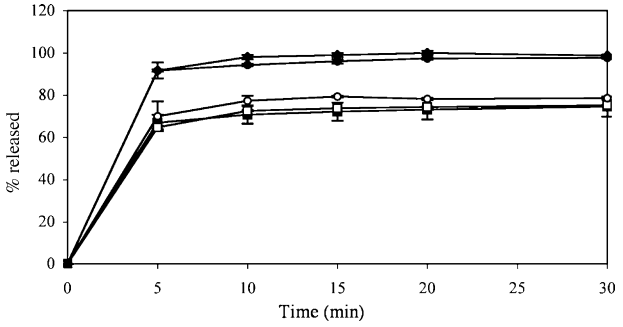

Fig. 3. Influence of sodium laurylsulphate on dissolution profiles: (■) 0%; (□) 1%; (◯) 2%; (●) 3%; (♦) 4%.

and 53% for granules containing 0 and 3% SLS, respectively) (Table 1), foaming during dissolution testing and the wetting properties which depend on water hardness (Rowe et al., 2005). Substituting SLS for non-ionic tensioactive agents improved the yield: 95, 93 and 95% for formulations containing polysorbate 80, Lutrol® F127 and Cremophor® RH40, respectively. Incorporation of polysorbate 80 and Cremophor® RH40 yielded soft granules, resulting in a high granule friability (Table 1). Granules containing Lutrol® F127 had a dissolution profile similar to SLS, while drug release was nearly complete within 10 min for the formulations containing polysorbate 80 and Cremophor® RH40 (Fig. 4).

The influence of drug content on granule properties and dissolution characteristics was investigated by increasing the drug concentration to 20%. At a PEG 400/4000-ratio of 12/12 in combination with polysorbate 80 as surfactant (formulations 12–14, Table 1) a higher drug concentration (20%) had a negative influence on the granule yield: 70% at 20% drug loading versus 95% at 10% drug loading. Moreover, increasing the polysorbate 80 concentration decreased the yield even further to 38 and 25% respectively (formulations 13 and 14, Table 1). Similar to the formulations at 10% drug loading an increase of the PEG 4000 concentration improved the yield and friability. For all formulations containing 20% drug, release was fast as within 10 min at least 95% of drug was released. Distinct peaks of crystalline drug were identified in X-ray diffractograms of the granules next to peaks of PEG 4000 (Fig. 5a–c). These peaks illustrate that the granules exist out of three discrete phases: maltodextrin, crystalline drug and the binding agent. During granulation the drug is finely dispersed in the PEG 400 and 4000, this creates a micro-environment for the drug, increasing the dissolution rate. Additional experiments showed that only 13% drug could dissolve in the molten PEG fraction. However, most of the drug had recrystallized after cooling as X-ray diffractograms showed that only at 1% drug concentration a solid solution was formed.

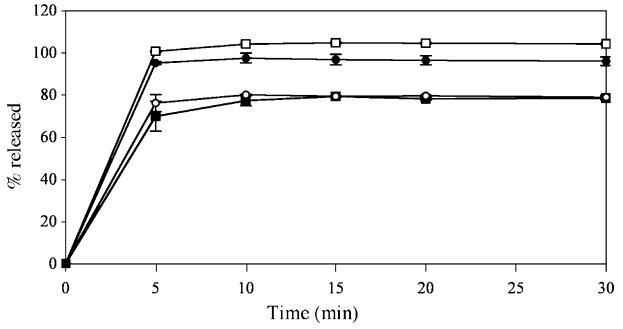

Fig. 4. Influence of different surfactants (2%) on dissolution profiles: (■) sodium laurylsulphate; (□) polysorbate 80; (◯) Lutrol® F127; (●) Cremophor® RH40.

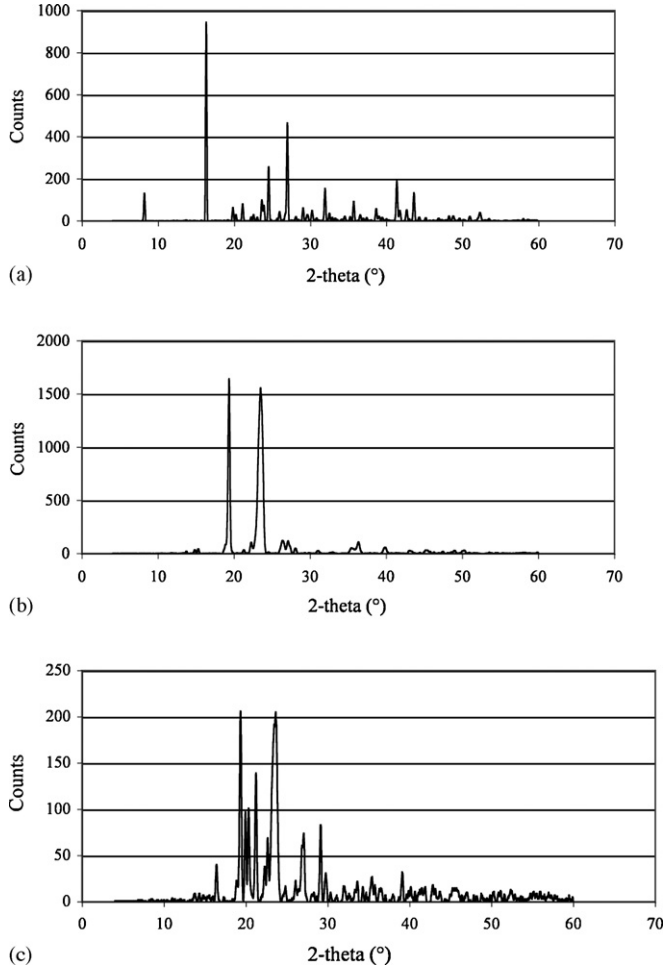

Fig. 5. (a) X-ray diffractogram of drug. (b) X-ray diffractogram of PEG 4000. (c) X-ray diffractogram of granules containing 20% drug, 25% PEG 4000, 4% polysorbate 80 and maltodextrin.

5. Conclusion

This paper showed that melt granulation was possible using a twin-screw extruder and that a veterinary drinking water formulation with immediate drug release could be manufactured using this process. During granulation the drug particles were finely dispersed in the molten mixture, whereby PEG 400 and 4000 created a micro-environment around the drug particles enhancing the dissolution rate.

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