Powder Technology 270 (2015) 476–483

Contents lists available at ScienceDirect

Powder Technology

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

Impact of needle-like crystals on wet and solid-lipid extrusion processes

G. Di Pretoro [a,b], L. Zema [a], A. Gazzaniga [a], P. Kleinebudde [b,*]

[a] Sez. di Tecnologia e Leg. Farmaceutiche "Maria Edvige Sangalli", Dipartimento di Scienze Farmaceutiche, Via G. Colombo 71, 20133 Milano, Italy
[b] Heinrich-Heine-University, Institute of Pharmaceutics and Biopharmaceutics, 40225 Duesseldorf, Germany

ARTICLE INFO

Available online 6 August 2014

Keywords:
Needle-like particles
Wet extrusion
Solid-lipid extrusion
Particle shape
Milling
Die diameter

ABSTRACT

The aim of the current work was to investigate systematically the impact of needle-like drug crystals on both wet and solid-lipid extrusion processes. Co-rotating twin-screw extrusion, through 0.5, 0.7 and 1.0 mm multi-holed capillary dies, was therefore used to assess the processability of formulations containing up to 80 wt.% of three needle-like, poorly soluble active ingredients, i.e. mesalamine, nimesulide and praziquantel. Their impact on both wet and solid-lipid extrusions was evaluated prior to and after an appropriate micronisation step aimed at reducing their particle size, and obtaining more isometric particles. Occlusion of die holes and a steady increase in extrusion pressure, whose extent was found to be dependent on both the drug loading and the morphology of the drug's crystal, was observed with all the active ingredients tested. A change in particle morphology, combined to a reduction in particle size, allowed the occlusion of die holes to be considerably reduced and/or prevented, and smooth and robust extrusion processes to be achieved.

1. Introduction

Extrusion is a well-known processing technology in which materials are mixed intimately under controlled conditions of temperature, shear, and pressure to generate a variety of in-process or finished products. In the last few years, the application of extrusion in the pharmaceutical field for the manufacture of multi-particulates and the development of controlled-release dosage forms has becoming increasingly important.

Success of a given extrusion process depends, among other factors (e.g. extruder type and process parameters), on the formulation [1,2]. Extrusion formulations represent, in fact, complex materials whose rheological behaviour is not fully predictable, being determined both by particle–particle interactions and liquid phase phenomena. The liquid phase represents, in particular, a critical aspect for solid–liquid pastes intended for wet extrusion processing: it provides inter-particle cohesion, promotes wall slip and also bears some of the stresses during the forming process. However, sometimes the pressure exerted on the liquid phase during extrusion might cause it to move faster with respect to the particulate network, giving rise to variation in the liquid content of the paste, hence of the extrudates. This redistribution of liquid phase within the solid matrix, also known as liquid phase migration [3], has been found to be strongly affected, other than by process parameters (e.g. extrusion velocity), by the amount and the viscosity of the liquid phase, the physico-chemical characteristics of the active ingredient and the extrusion aid used [4]. Another crucial formulation aspect to be considered in the wet extrusion is, in fact, the selection of an appropriate extrusion aid, namely an excipient able to provide the API, which does not have generally either lubricating or plasticising properties, with mechanical structure and rheological stability [5,6].

A relatively new extrusion approach is solid-lipid extrusion, in which APIs and powdered lipids are co-processed below their melting point, maintaining the crystallinity of the substances [7,8]. Applications of solid-lipid extrusion vary from controlled-release [9,10] to taste-masking [11] and enhancement of oral bioavailability of poorly soluble drugs [12,13]. The impact of the liquid phase, selection of an appropriate extrusion–spheronisation aid, or lipid, as well as the set-up of process parameters (e.g. temperature, extrusion velocity and selection of an appropriate mould/screen) are critical aspects to be considered.

The majority of research work on wet and solid-lipid extrusions focusses on the effect of the liquid phase (wet extrusion), extrusion aids, lipids and/or process parameters, while the importance of the physical characteristics of the active ingredient has been only occasionally taken into consideration. Nonetheless, particle size, morphology, packing behaviour and other related properties of solid components may strongly affect the paste rheology and extrusion performance. Physico-chemical characteristics of the active ingredient, the solubility of the API in the liquid phase [14,15], its particle size characteristics [16], particle morphology and hence packing behaviour [17] may become particularly important, depending on the drug strength.

In particular, the drug particle size was found to have a key influence on the extrusion characteristic of the wet powder mass [18] as well on the size [19,20] and roundness [21,22] of pellets prepared by extrusion–spheronisation. Fielden et al. [23] investigated the influence of lactose size distribution on extrusion behaviour of lactose/MCC water-based pastes. They reported that the redistribution of water

* Corresponding author. Tel.: +49 211 81 14220; fax: +49 211 81 14251.
E-mail address: kleinebudde@hhu.de (P. Kleinebudde).

http://dx.doi.org/10.1016/j.powtec.2014.07.047
0032-5910/

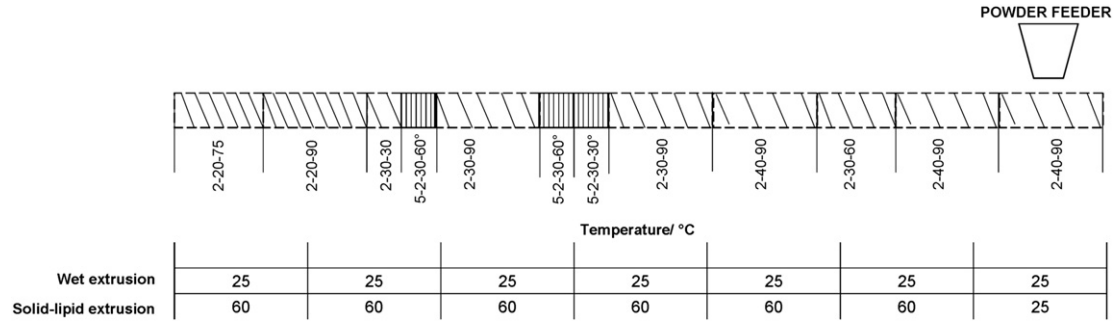

Fig. 1. Screw setup and extruder's module temperature as used in the study. In case of feeding and mixing elements '2–40–90' encodes 'double thread–pitch–length', in case of kneading blocks '5–2–30–60°' encodes 'no. of elements–double thread–length–angle'.

within the solid matrix increased with increasing lactose particle size. This was attributed to the lower porosity of pellets, leading to liquid phase migration phenomena hence sticking and agglomeration.

Particle shape may also have a key impact on extrusion processing as it determines the porosity and pore size distribution in the wet mass, as well as the rheological behaviour of suspension. In the Krieger–Dougherty equation, intrinsic viscosity of particles is in fact known to increase with the particles becoming less spherical [24].

Needle-like morphology, in particular, has been reported to be notably crucial both in wet and solid-lipid extrusions, as well as in different pharmaceutical processes [25–27].

Recently, the needle-like shape of 5-aminosalicylic acid (5-ASA, mesalamine) has been identified as a critical parameter in the processability of microcrystalline cellulose (MCC)-based pastes both by ram and basket extrusion [28,29]. A critical impact of needle-like APIs on solid-lipid extrusion, through a twin-screw extruder apparatus, has also been described [30,31].

This paper addresses a systematic investigation of needle-like drug crystals on both wet and solid-lipid extrusion processes. Co-rotating twin-screw extrusion through multi-holed capillary dies was therefore used to assess the processability of three prolate (needle-like), sparingly soluble APIs: i) mesalamine (5-ASA), ii) nimesulide and iii) praziquantel. An appropriate micronisation step was performed aiming at reducing the particle size, while changing the morphology of drug particles from acicular into isometrical. Particle shape and size were found to be dependent. Circularity of rod-like un-milled crystals increased with particle size decreasing. However, Witzleb et al. [30] have shown that the shape of the particles has a higher impact on the extrusion process than the size. Small needles were more problematic than larger isometric particles.

The impact of un-milled needle-like and circular milled drug crystals on the rheological performances of wet and solid-lipid masses undergoing both wet and solid-lipid extrusions was therefore assessed and compared.

2. Materials and methods

2.1. Materials

5-Aminosalicylic acid (5-ASA, mesalamine), nimesulide and praziquantel were provided by IMS Micronizzazioni SpA. (Milano, Italy), Helsinn Healthcare SA (Pambio-Noranco, Lugano, Switzerland), and Bayer Healthcare AG (Leverkusen, Germany), respectively. Sanaq® 101 grade of microcrystalline cellulose (Pharmatrans Sanaq AG, Basel, Switzerland) and glyceryl dibehenate (Compritol® ATO 888) (Gattefossé, Cedex, France) were used as the extrusion–spheronisation aids for wet and solid-lipid extrusion processes, respectively.

Table 1
Multi-holed die plates used in the study.

	Die plate		
Die land internal diameter/mm	0.5	0.7	1.0
Die land length/mm	1.35	1.75	2.5
Number of holes	91	45	23
Cross-section area/mm^2	0.196	0.385	0.785
Total area of holes/mm^2	17.9	17.3	18.1

2.2. Methods

2.2.1. Micronisation

The un-milled, commercial batches of 5-ASA and nimesulide were micronised using an air-jet-mill apparatus (Chrispro® Jet-Mill, Micro-Macinazione SA, Molinazzo di Monteggio, Switzerland), with a spiral chamber of 300 mm diameter. Dry air, injected through 8 nozzles at 8 bar, was used as the milling gas. As for praziquantel, a 200 mm diameter air-jet mill (Bayer CropScience, Leverkusen, Germany) was used; the milling gas (air) was injected at a pressure of 5.5 bar absolute.

2.2.2. Powder characterisation

2.2.2.1. Particle size and shape measurements. Particle size and shape characterisation was performed using an automated particle imaging apparatus (Morphologi® G3, Malvern Instruments Ltd, Worcestershire, UK). The machine featured a Nikon CFI 60 optical system and a 1/1.8″ global shutter progressive scan CCD camera. Powder samples (3 μm^3) were dispersed via an instantaneous pulse of compressed air at 2.5 bar. Image analyses were performed at 20× and 50× magnification.

Particle dimensions were quantified in terms of volume-based relative size distribution. Particle shape was quantified in terms of circularity (calculated as $4\pi A/p^2$, where A is the projected area and p the projected perimeter of the particle), elongation (defined as 1 − [width / length]), and aspect ratio (defined as minor axis/major axis). At least 60,000 particles were analysed.

Images of particles of un-milled and micronised APIs were taken by an optical microscope (DMLB, Leica Microsystems, Wetzlar, Germany), equipped with a CCD camera (Nikon D300, Tokyo, Japan), under polarised light. Morphology of drug crystals which had undergone solid-lipid extrusion was also investigated, via hot stage microscopy. Solid-lipid extrudates were melted on a Linkam THMS 600 heating system, equipped with a TMS 94 temperature control device (Linkam Scientific Instruments, Tadworth Surrey, United Kingdom). The melted mass was further dispersed using liquid paraffin.

2.2.2.2. Thermal analysis. Differential scanning calorimetry (DSC) was performed on a DSC 1 calorimeter (Mettler-Toledo, Giessen, Germany). DSC runs were performed on 3–5 mg samples in pierced aluminium pans (40 μL) at a scanning rate of 10 K min^{-1}, under nitrogen purging at 70 mL min^{-1}. The temperature ranges were 0–170 °C for Compritol® ATO 888, nimesulide and praziquantel, and