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Liquid phase migration in the extrusion and squeezing of microcrystalline cellulose pastes

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ARTICLE INFO

Article history:
Received 21 February 2006
Received in revised form 4 April 2006
Accepted 6 April 2006
Published on line 4 May 2006

Keywords:
Extrusion
Conical-entry die
Square-entry die
Squeeze flow
Dilation
Dewatering
Microcrystalline cellulose

Abbreviations:
CED, conical-entry die, ram extrusion; LPM, liquid phase migration; MCC, microcrystalline cellulose; SED, square-entry die, ram extrusion; SF, squeeze flow

ABSTRACT

Extensive movement of the liquid phase relative to the solids in solid–liquid pastes during extrusion forming is an undesirable process phenomenon. The impact of formulation and flow pattern on liquid phase migration (LPM) during extrusion of model pharmaceutical pastes (40–50 wt% microcrystalline cellulose/water) has been investigated by ram extrusion through square-entry and 45° conical-entry dies, and by lubricated squeeze flow (extensional flow). Threshold velocities for LPM were observed in both configurations. Squeeze flow testing showed that dilation during extension can cause LPM, while ram extrusion featured both dilation effects and drainage due to compaction. The threshold velocities observed in the two configurations agreed when presented as characteristic shear rates. The threshold velocity increased with paste solids content.

1. Introduction

The extrusion of highly filled granular suspensions (also termed 'pastes') is a key stage in the manufacture of solid dosage forms by extrusion–spheronisation and related technologies. In many instances the active agent is a minor component and the cohesive wet mass consists principally of a bulk excipient such as powdered lactose or microcrystalline cellulose (MCC) and a liquid binder, typically an aqueous solution. The solids volume fraction is high, giving rise to rheological phenomena such as yield stress behaviour and wall slip which make standard rheological testing of these materials difficult. Newton and co-workers (e.g. Harrison et al., 1987) have used the Benbow and Bridgwater (1993) characterization method to quantify the rheological behaviour and assess the impact of formulation of a range of paste systems. This

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0928-0987/$ – see front matter
doi:10.1016/j.ejps.2006.04.011

method employs a pseudo-plastic description which allows analogies to be drawn with concepts in soil mechanics, where granular properties and liquid behaviour also determine the rheology of the paste.

Liquid content is a particularly important feature of both pharmaceutical pastes and soils as this parameter determines the local strength of these multi-phase materials. During extrusion, the pressure exerted on the liquid phase can cause it to move faster relative to the particulate network, giving rise to variation in liquid content and consequently problems in processing. Regions of low water content are stiffer and therefore require higher stresses to extrude, and extrudate composition can deviate from the desired content. The phenomenon of liquid phase migration (LPM) in pharmaceutical pastes has been studied by Tomer et al. (1999a,b) using a range of techniques including magnetic resonance imaging (MRI) to track liquid phase distribution. The impact of LPM on the ram extrusion of MCC pastes, which can be related to extrusion–spheronisation processes, has been studied experimentally by Rough et al. (2000), who reported the existence of a velocity threshold above which LPM did not occur. This phenomenon has been observed in other paste materials (Bayfield et al., 1998; Chen et al., 2000; Poitou and Racineux, 2001; Roussel and Lanos, 2004) and can be related to a ratio of characteristic timescales, namely the time taken for the material to undergo extrusion, and the characteristic time taken for a material to dewater when subjected to a pore pressure gradient, or consolidation time (Wroth and Houlsby, 1984). The former is a process parameter whereas the latter is a material parameter which is directly related to the permeability of the solids network. LPM can therefore be avoided in principle by selecting appropriate processing speeds/strain rates, increasing liquid viscosity (i.e. reducing liquid mobility), or developing formulations which have a low permeability. However the latter, being microstructure dependent, is related to product properties and performance. Moreover, the scaling relationships for the threshold velocity to different equipment sizes and geometries needs to be established and requires quantitative modelling.

Rough et al. (2002b) modelled LPM in ram extrusion of MCC pastes using a Darcy's law approach to predict liquid phase permeation rates. The key parameters in calculating liquid permeation were the excess pore pressure (hydrostatic pressure exerted on the liquid phase, calculated from initial experimental data) and the permeability of the solids network, which was measured separately in a cell featuring controlled solids volume and stress rather than a standard compressive, drained test (Rough et al., 2002a). They reported reasonable agreement between their model and experimental results, and noted where further work was required. They could not predict the onset of LPM a priori, partly because they did not include the effects of dilation in their model. Soils and other high solids volume fraction systems have to increase in volume in order to undergo extensional shear as occurs in the die entry region of the extruder: this creates a local suction effect in the pore pressure. Their model was based primarily on drainage of the liquid through the solids matrix promoted by compaction of the paste. Similar approaches based on drainage have been used to describe LPM in pastes undergoing capillary extrusion by Yaras et al. (1994) and undergoing squeeze flow (SF) by Roussel and Lanos (2004) and Poitou and Racineux (2001). The latter work is noteworthy as it presented good agreement between experimental and modelling results for concentrated suspensions of TiO_2 particles with an initial volume fraction of ca. 31%. Small sample heights were used so the deformation in the diverging flow was dominated by simple shear, and suction effects were neglected. None of these studies have sought to link observations of LPM between different geometries, as is considered here.

This paper reports an experimental study of LPM on a model pharmaceutical paste and seeks to relate the onset of LPM observed in two different configurations, namely lubricated squeeze flow and ram extrusion. Lessons for scale up and implementation in process equipment can be extracted from comparing the two configurations in terms of characteristic processing times or strain rates rather than velocity. Lubricated SF is employed as this allows the phenomenon to be studied in an almost purely extensional mode, so that the effects of suction are expected to be relatively free of simple shear effects, and extensional strain rates can be calculated readily. Meeten's (2004a,b) contributions on the difficulty in achieving pure extension in squeeze flow are acknowledged, so we attempt to keep the simple shear contributions small by using tall samples. The extensional rheology of the MCC paste can be quantified using this approach and this will be reported in a separate paper. Ram extrusion is performed using square-entry and conical-entry dies: the latter offer a consistent flow pattern which can be approximated as a radial flow as described by Basterfield et al. (2005). Square-entry dies, however, give rise to complex flow configurations for plastic materials, as demonstrated experimentally for pastes using positron emission particle tomography (Wildman et al., 1999) and MRI (Barnes et al., 2006), and simulated by Horrobin and Nedderman (1998). Comparing the two die configurations allows the impact of die geometry to be assessed.

2. Theoretical

2.1. *Squeeze flow (SF)*

A full description of squeeze flow can be found in the work by Meeten (2004a,b). In this study well-lubricated plate surfaces (of radius R) and billets of aspect ratios ~0.5 (sample height $h_0 \sim R$) were used in order to study extensional flow and minimize the impact of shear in the material. Fig. 1(a) illustrates the geometry. For a uniform and incompressible material, the velocity field between the plates generated by a (vertical) plate approach speed of V_{sq} is

$$v_x = \frac{1}{2}\frac{x}{h}V_{sq} \tag{1}$$

$$v_y = \frac{y}{h}V_{sq} \tag{2}$$

where x and y are the radial and axial co-ordinates measured from the bottom of the sample, with x always being positive for this radially symmetric geometry. The extensional strain