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Predicting optimal wet granulation parameters for extrusion-spheronisation of pharmaceutical pellets using a mixer torque rheometer

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ABSTRACT

Mixer torque rheometry (MTR) was evaluated as a pre-production (pre-formulation and optimization) tool for predicting ideal liquid-to-solid ratios (*L/S*) for extrusion-spheronisation of a wide range of APIs using 10 g formulations. APIs of low, medium and high solubility were formulated at low and high loadings (15 and 40% w/w, respectively) with PVP as binder (5%) and MCC as the major excipient. *L/S* corresponding to the maximum torque produced during wet massing in the MTR, $L/S_{(\max T)}$, was 0.8 for the low solubility APIs, which decreased to 0.6 for some of the more soluble APIs, especially at high loadings. Formulations extruded-spheronised at $L/S_{\max T)}$ produced pellets of acceptable size (between 900 and 1400 um) for all formulations, but mostly of unacceptable shape (dumb-bells of aspect ratio 1.2). Increasing *L/S* by 25% successfully produced spherical or near-spherical (aspect ratio 1.1) pellets for all formulations except one of the highly soluble APIs (piracetam) at high loading. Overall, MTR was demonstrated to be a useful pre-formulation and optimization tool in extrusion-spheronisation.

1. Introduction

Extrusion-spheronisation is one of the most popular techniques for producing pharmaceutical pellets. In this process, the formulation is first agglomerated by mixing with a liquid (usually water), following which the wet mass is extruded and then spheronised. This first step, wet granulation, is critical in influencing many of the characteristics of the final pellets such as sphericity, porosity, dissolution and disintegration. A mixer-torque rheometer (MTR), first investigated by Rowe and colleagues, (Rowe and Sadeghnejad, 1987) can be used to characterise the rheological properties of the wet mass, and is gaining popularity (Sakr et al., 2012; Zhang and Lamberto, 2014) in determining the "end point" of wet granulation, defined as the maximum torque required to mix the mass. The torque describes the mass resistance to mixing, and the maximum is assumed to correspond to the strongest particle–particle binding (capillary state). The influence of mixing parameters on the measured torque has been studied in detail by Rowe et al. (Hancock et al., 1991) MTR and its application was reviewed several years ago (Sakr et al., 2012).

In terms of applications, several companies have begun using MTR to reduce pre-formulation work for agitated filter dryers by successfully predicting the maximum wet massing possible without causing agglomeration in the subsequent drying step (am Ende et al., 2013; Birch and Marziano, 2013; Zhang and Lamberto, 2014). The ability of MTR to predict ideal wet granulation conditions for achieving optimum quality of pellets produced by extrusion-spheronisation of the wet mass has received probably the most attention. Several studies examined the impact of different grades of microcrystalline cellulose (MCC) on the final extruded-spheronised pellets (Alvarez et al., 2002; Soh et al., 2006). In the latest of these studies, the authors found the torque values measured during wet massing of eleven grades of MCC strongly correlated with final pellet properties such as friability, flow and density, concluding that MTR can be used to reduce preformulation work related to changes in MCC grades (Soh et al., 2006). Alternatively, a texture analyser has recently been demonstrated to predict pellet qualities of a range of 120 pharmaceutical formulations from the wet mass characteristics

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(Gao et al., 2013). The only studies involving APIs relating MTR to extrusion-spheronisation performance have been focussed on demonstrating correlation of MTR values with dissolution rates of sustained release pellets (Ibrahim, 2013; Mahrous et al., 2010). There is to date no published study investigating the ability of MTR to predict the effect of different APIs at different liquid-to-solid (*L/S*) ratios on the subsequent extrusion-spheronisation performance.

We examine here the ability of MTR to predict ideal wet granulation parameters for producing optimum pellets of a wide range of active pharmaceutical ingredients (APIs). Each API was formulated at a low and high loading (15 and 40%), respectively, with polyvinylpyrrolidone (PVP, 5%, a popular binder) and MCC (80 and 55%, respectively; one of the most common excipients in extrusion-spheronisation). For each formulation, MTR was used to measure the relationship between torque and *L/S*. Pellets were extruded-spheronised corresponding to the maximum torque conditions, as well as several other conditions for comparison. The sphericity and particle size distribution of the resultant pellets were measured, and correlated to the rheological behaviour of the wet mass as measured by MTR.

2. Materials and methods

2.1. Formulations

2.1.1. Mixer torque rheometer

Using a Mixer Torque Rheometer (Mixer Torque Rheometer 3, Caleva, UK), the relationship between torque of wet massing and liquid-solid ratio (*L/S*) was measured for each formulation using a multiple addition method at 50 rpm. For each of the following periods the torque was measured for 20s, and the mean line torque relative to the first measurement reported for that period: in the first period, the torque of the empty bowl was measured and set as the baseline (i.e. 0 torque); in the second period, 10 g of formulation were added and mixed for 40s, following which the torque was measured for the dry powder in the third. Then water was added by a computer-controlled syringe pump in 2 mL (i.e. *L/S* of 0.2) steps (except for the blank, which had 4 mL steps), mixing for 40 s after each addition before measuring the torque and then adding the next 2 mL. This was repeated until at least 12 mL were added.

The *L/S* corresponding to the maximum torque measured, was subsequently wet massed in the MTR using a variable mix time method at 50 rpm, with the torque for each section again calculated as the mean torque measured over 20s. First, the torque baseline was measured with an empty mixing bowl, followed by addition of 10 g formulation which was mixed for 50 s before measuring the torque. Then the total amount (as determined by *L/S*) of liquid binder was added in a single 20 s step and the torque measured again. This was followed by three more mixing sessions of 20s, for each of which the torque was again measured. Thus the total mixing time is 5 $^{1}/_{2}$ min. In comparison, the torque values measured for *L/S* of 0.8 (the most common $L/S_{(\max T)}$) in the multiple addition method is for 5 min of mixing, which is almost equivalent.

As most formulations did not yield spherical pellets at $L/S_{(\max T)}$, these formulations were wet granulated again, usually at $1.2 \times L/S_{(\max T)}$, using the same method as described in the previous paragraph.

2.1.2. Extrusion-spheronisation

The wet mass was then extruded in a Mini Single Screw Extruder (Caleva, UK) running at 100 rpm with a circular die diameter 0.8 mm and depth 4 mm (prior to extrusion large clumps were broken up using a mortar and pestle to prevent clogging of the extruder feed port). The entire batch of extrudate was then spheronised in a Mini Bowl Spheroniser (Caleva, UK) of diameter 12 cm and height 6.5 cm for 15 min at 2000 rpm and the resultant pellets left to dry overnight at ambient conditions prior to analysis.

2.1.3. Characterisation

A particle image analyser (Eyecon, Innopharma Labs, Ireland, software v. 0.6.3) was used to measure the sphericity and size distribution of the pellets. Its mechanism of operation is outlined elsewhere (Silva et al., 2013); in short, it fits an ellipse to the measured outline of each detected particle and records the maximum and minimum diameter of each fitted ellipse, the ratio of which is taken as the aspect ratio. The averages of the 3 parameters are then calculated for each sample, along with the coefficient of variation (CV) of the aspect ratio. Compared to other particle sizing methods, the Eyecon generally gives comparable results in its nominal range of 50–3000 um, though it tends to overestimate the presence of over-sized particles especially when care to separate particles during analysis is not taken (Hagrasy et al., 2013; Kumar et al., 2015; McAuliffe et al., 2014; Silva et al., 2013).

In our case, the Eyecon was used in batch mode, in which a subsample of pellets is analysed by the Eyecon. As the Eyecon analyses only a small portion of the sample presented to it at a time, the position of the sample relative to the Eyecon is varied to capture most of the subsample. Depending on the pellet size, around 20–50 pellets are visible to the Eyecon in a single snapshot. For every subsample, 15–20 snapshots were measured by the Eyecon to give an average, representative result. Care was taken to ensure that pellets formed a monolayer.

3. Results & discussion

3.1. Torque measurements

The general trend of the torque profiles for *L/S* produced by MTR (see example in Fig. 1) always followed the expected pattern corresponding to the different wetting phases. With increasing *L/S*, an initial increase in torque is observed (usually interpreted as corresponding to pendular and funicular wetting phases) reaching a maximum (capillary phase), followed by a relatively steep decline (droplet phase) (Sakr et al., 2012). The peak represents the *L/S* with the strongest resistance to mixing ($L/S_{(\max T)}$) as evidenced by the highest measured torque value. This is usually considered to be a

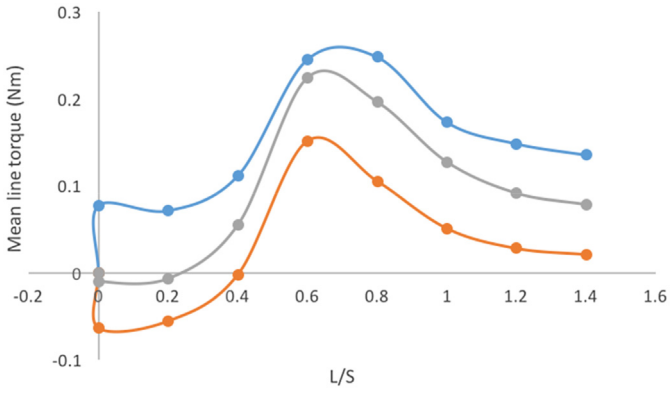

Fig. 1. Rheological profile of wet massing of theophylline 15% formulation as measured by MTR, repeated three times. There are two points at *L/S* = 0; the first is the torque measured before powder addition, i.e. for the empty mixing bowl, which is taken as the baseline; the second is after powder addition but before liquid addition. The somewhat low reproducibility is discussed below. Points are actual data; curves are guides for the eyes only.