Advanced Powder Technology 25 (2014) 659–665

Contents lists available at ScienceDirect

Advanced Powder Technology

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

Influence of the standing time of the extrudate and speed of rotation of the spheroniser plate on the properties of pellets produced by extrusion and spheronization

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ARTICLE INFO

Article history:
Received 26 April 2013
Received in revised form 15 October 2013
Accepted 21 October 2013
Available online 4 November 2013

Keywords:
Extrusion
Extrudate standing time
Linear peripheral velocity
Pellet properties
Spheronization

ABSTRACT

The aim of the investigation was to study the influence of the standing time of the extrudate prior to spheronization and the speed of rotation expressed as linear peripheral velocity of the spheroniser plate on the properties of pellets using a 5^2 factorial experiment. Pellets composed of diclofenac sodium (5%), lactose monohydrate (20%) and microcrystalline cellulose (75%), prepared with water as the liquid binder (total solids to liquid ratio 1:0.675) using a screen extruder were produced after various standing times of the extrudate (ranging from immediate spheronization to 2 h) and at different rotational speeds ranging from 770 to 2900 rpm, which translates into a linear peripheral velocity of the friction plate from 4.84 to 18.22 m/s. The relative yield in the practically used pellet size fraction of 0.71–1.44 mm depended significantly on the standing time of the extrudate. Pellets produced at the lowest linear peripheral velocity were not round, and this was not affected by the standing time of the extrudate. Both the surface tensile strength and the density of the pellets were related to the extrudate standing time and the linear peripheral velocity, whereby the two factors were found to interact. However, neither of the process parameters nor the pellet properties themselves appeared to have an influence on the dissolution of the drug.

1. Introduction

Pellets are dense spherical agglomerates comprising a smooth surface. Their diameter can range between 100 μm and 2 mm, whereby pellets in a size range between 700 μm and 1.4 mm are typically used as intermediates for capsule or tablet type solid oral dosage forms. Pellets are increasingly used in the preparation of modified-release dosage forms. One method of preparing pellets is that of extrusion and spheronization, first described in the pharmaceutical literature in Europe by Reynolds [1] and in the USA literature by Conine and Hadley [2]. The process includes an extrusion stage, which has technologically advanced and can be used as a continuous process, but the spheronization step still remains a batch process. As a result, extrudate produced might be subjected to differing standing times before it is finally spheronised. This aspect has, however, not received much attention in the literature, and it is not known how the standing time of the extrudate will influence the properties of the pellets. When establishing a protocol for the evaluation of the rheological properties of microcrystalline cellulose/water mixtures used in the extrusion/spheronization process, Raines [3] found that in the ram extruder the steady state extrusion force fell, as the time of storage of the wet mass prior to extrusion increased. The rate of decline decreased with time, until after about two hours, when it remained relatively constant. Thus, simply by standing, the structure of the wet mass was changed sufficiently to alter its rheological properties. Zografi et al. [4] claimed that in water—microcrystalline cellulose systems, water existed in three states: (i) "tightly bound to an anhydroglucose unit"; (ii) "less tightly bound"; and (iii) "as bulk water". Luukkonen et al. [5] proposed four distinct states of water in microcrystalline cellulose wet masses: (i) "non-freezing"; (ii) "freezing bound"; (iii) "free" and (iv) "bulk water". Neither of these papers identified the rates of establishment of these different states. However, Blair et al. [6], performing microcalorimetry studies, found that the process proposed by Zografi et al. [4] followed a first-order rate process in all three stages, namely (i) an initial rapid sorption process" followed by a (ii) "very slow stage" and then a (iii) "final more rapid region moving towards equilibrium". These observations were made on single measurements limiting their robustness, but clearly show that water—microcrystalline cellulose association changes with time. Several authors therefore prefer to extrude after the wet mass has been stored over night [7–12]. While these authors were able to relate the rheological characteristics of a range of formulations to the quality of the extrudate, attempts to relate the influence these changes in the rheological

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http://dx.doi.org/10.1016/j.apt.2013.10.011

characteristics had on the ability to prepare pellets were not however, undertaken. Studies, which have attempted to relate the rheological characteristics of wet powder masses to the ability to prepare spherical pellets, have met with limited success. MacRitchie et al. [10] found that shear stress/shear rate curves were not helpful but there appeared to be limiting values for storage and loss modulus of the wet powder mass determined by low strain rate methods, which gave an indication of the ability to produce good quality pellets. They used long dies to produce the extrudate for spheronization, which could be very different to extrudate produced by screen extruders. Thus simple rheological studies do not as yet provide a satisfactory method for the characterisation of the ability to prepare good quality spherical pellets. The plasticity is an important property during the spheronization stage for pellets to form, whereby here the plasticity of the extrudate is of concern [13,14]. While the influence of the standing time of the wet mass on extrudability has been clearly established, there are no studies relating the standing time of the extrudate prior to spheronization to the properties of the pellets, despite the potential of changes in the plasticity of the extrudate and hence, variability of the final pellet product.

The speed of rotation of the spheroniser has been a popular factor used in experimental designs to study the spheronization process for a long time [15]. However, the important factor in scale up is not simply the spheroniser speed, but the linear peripheral velocity of the friction plate [16], which depends on the rotational speed of the spheroniser and the diameter of the friction plate. By adjusting the speed of the spheroniser during scale up from small friction plate diameters used in development to larger diameters used in production, so that the linear peripheral velocity of the plate of the spheroniser remains the same, it is possible to scale up the spheronization process without major problems [16]. Unfortunately this parameter cannot always be identified in publications. Some papers, which report rotational speeds, fail to identify the dimension of the friction plate, e.g. [17,18]. Equally when this information is available, the process is complex and it is not always possible to identify just how this factor influences the quality of the final product, as it is both formulation and process dependent. This results in the presence of interactions between speed and other factors when statistical experimental designs are employed, e.g. [19–21]. As pointed out by Newton [14], because spheronisers differ in size, it is not just the rotational speed that is the controlling factor, but the combination of speed and plate dimensions resulting in the peripheral velocity at the tip of the friction plate. Using the tip speed rather than just rotational velocity for a given plate dimension it was shown that scale up of the process for a formulation from the laboratory to the industrial production scale was possible [16]. Some formulations are clearly very sensitive to the setting of the linear peripheral velocity of the friction plate in terms of producing pellets and there are cases, where the linear peripheral velocity has to be adjusted to lower values than normally employed in order to account for extremely low densities of the extrudate, for example, when larger amounts of disintegrants [22] or low density spheronization aids [23] are used. Formulations prepared by screen extrusion are also less dense than those produced with long die extruders, and hence might also require optimisation of the linear peripheral velocity of the friction plate.

The aim of the paper is to study the influence of the standing time of the extrudate and the speed of rotation of the spheroniser plate, expressed as linear peripheral velocity, on the properties of pellets made using microcrystalline cellulose as spheronization aid. As pointed out above, microcrystalline cellulose wet masses used in extrusion/spheronization respond to standing times in sealed containers with changes in the water movement through the wet mass and in changes in their rheological properties. One objective of this research is to investigate whether also the standing time of the extrudate influences the properties of the pellets. In order to elucidate any interaction between the standing time of the extrudate and the speed of rotation of the spheroniser plate and to be able to detect potential non-linear relationships adequately, a 5^2 factorial experiment was performed. An optimised standard formulation [24] in terms of percentage of microcrystalline cellulose and binder concentration was chosen over a random selection of formulations, because the objective of the work is to demonstrate that process parameters have to be tightly controlled in the manufacture of pellets in order to maintain product yield and quality of an otherwise optimum formulation. Again this is achieved by the use of the experimental design as is common practice in Quality by Design assessment of optimum formulations in the industrial manufacture of dosage forms.

2. Materials and methods

2.1. Materials

All materials were of BP grade and used as supplied. Diclofenac sodium was used as a model drug (batch 0112985, Heumann Pharma GmbH, Feucht, Germany), lactose monohydrate as filler (batch TG 206, Lactochem, Borculo Whey, Netherlands), and microcrystalline cellulose as spheronization aid (PH 101, batch 6440C, FMC, Cork, Ireland). The particle size distribution of these powders was determined using laser light diffraction (Malvern Mastersizer, Malvern Instruments Ltd., UK). The mean particle sizes were 12.05 μm, 65.71 μm and 69.71 μm for the drug, lactose monohydrate and microcrystalline cellulose, respectively. Freshly distilled water was used as liquid binder. For dissolution studies, phosphate buffer pH 7.2 was prepared from disodium hydrogen orthophosphate (batch k.36061480, VWR International Ltd., Poole, UK) and potassium dihydrogen orthophosphate (batch 9944387 449, Fisher Scientific UK Ltd., Loughborough, UK), using freshly distilled water.

2.2. Methods

2.2.1. Preparation of the wet mass

Twelve g of drug, 48 g of lactose monohydrate and 180 g of microcrystalline cellulose were accurately weighed and transferred into the bowl of a planetary mixer (Kenwood Chef, Kenwood Products Ltd., London, UK). The powder was mixed at the lowest available speed for 2 min. Distilled water (162 g) was added gradually over a time span of 3 min using a pump (Glatt FM—VG—01, Glatt/Powrex Corporation, Osaka, Japan) while continuing to mix. The mixing speed was then increased and the wet mass was mixed for a further 5 min. The process was stopped to scrape down the sides and the bottom of the bowl, and then the mixing was continued for a further 5 min. This resulted in a total mixing time of 15 min. It is important to keep the mixing process consistent as Suzuki et al. [25] found that mixing times of water and microcrystalline cellulose in a high speed granulator influenced the interaction between them.

2.2.2. Extrusion of the wet mass

The wet mass was extruded using a Caleva Model 10 radial screen extruder (GB Caleva, Sturminster Newton, Dorset, UK; Fig. 1), equipped with a screen diameter of 15 cm, a die diameter of 1 mm and a mesh thickness of 1 mm. The extrusion speed was kept to 10 rev/min. The amount of extrudate produced was collected in a plastic box and the lid was tightly closed immediately after the process had finished.