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Effect of spheronizer plate design on the spheronization of ketoprofen

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ABSTRACT

Spheronization is a rapid process for production of microspheres. The process involves the dry mixing of drug with microcrystalline cellulose (MCC), which on subsequent wetting with water forms a plastic mass suitable for extrusion and spheronization. As in any pharmaceutical operation, large number of factors may affect the production of pellets, which can be related to formulation or processing machinery. Among the factors related to spheronizers is the spheronization plate design. This work is aimed at evaluation of the effect of using the radial design and the cross-hatch design on product quality through a factorial experiment using ketoprofen as a model drug. The factors studied were MCC level, spheronizer speed and spheronization time. The evaluation methods included sieving analysis, density and porosity measurements, shape analysis, and dissolution testing. Preliminary experiments revealed that MCC level is of great significance on pellets yield. Also, all the produced pellets were of acceptable sphericity score. The factorial experiments showed that an increase of pellets yield of desired size can be obtained when using the radial design of friction plate, while no significant changes were found regarding density, porosity and dissolution rate.

1. Introduction

Extrusion – spheronization is well established technique for the production of pellets or microspheres. There are many factors which affect the production of pellets by this technique related to formulation and processing variables. Among the factors related to the spheronization stage is the design of spheronizer plate [1]. The design of the friction plate is very important and it has been claimed to be among the most important components of a spheronizer [2–4]. A grooved pattern is cut into the upper surface of the plate which can have a variety of designs. The groove size is usually matched with the desired size of the pellets. A 500 μm pellet would be processed on a friction plate with a groove opening that is 50–100% larger, allowing the extrudate to fall into the wider opening where the extrudate fracture into relatively uniform lengths as it is cut by the leading edge of the peak. The two most common patterns used are the cross-hatch and radial designs. The cross-hatch pattern has grooves which intersect with each other at 90° angles all over the surface of the plate. In the radial design, the grooves radiate from the center of the plate and may intersect with concentric grooves radiating from the centre of the plate. It was suggested that the dimension of the teardrop studs on the rotating frictional base plate affected spheroid quality [5]. Some reported that the pattern of the friction plate used in the spheronization of diclofenac sodium (i.e. cross-hatch, radial, striated edge pattern) affected the properties of the pellets, and the yield values varied by up to 20%, and for an otherwise optimised formulation the use of a striated edge plate appeared advantageous in this respect [6].

In other works it was found that the radial design could be more efficient as there are more cutting edges (grooves) perpendicular to the direction of rotation resulting in greater transfer of the energy to the spheronizing pellets. However as the grooves move outward from the centre, their effectiveness is reduced due to the increasing distance between the cutting edges. The cross-hatch plate is recommended for general use, but some products spheronize better on a radially cut plate [7,8].

The aim of this work is to evaluate the effect of friction plate design (cross-hatch *vs* radial) on the spheronization of ketoprofen extrudate. The evaluation criteria will involve the use of factorial and non-factorial experiments with subsequent size analysis, density measurements, shape analysis and dissolution testing.

2. Materials

The materials used in this work were of analytical grade. The

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following materials were obtained from the indicated sources: MCC (Avicel® PH101, FMC, Belgium), lactose (Granulac®200, Meggle, Germany), and ketoprofen (S.I.M.S, Italy).

3. Methods

3.1. Non-factorial experiments

These were initial experiments designed to establish the minimum level of MCC and water level required for successful spheronization to produce pellets with high drug load and a yield of pellets in excess of 80%. Usually such experiments are done randomly but the factor of previous experience with such technique is a helping factor. The extrudates were spheronized at 1250 rpm with a residence time of 10 min using cross-hatch friction plate. A summary to the formulations prepared is given in Table 1.

3.2. Mixing

100 g of powder mix containing ketoprofen, MCC and lactose were loaded into planetary mixer (Kenwood chef Excel, UK). Powders were mixed at speed 1.0 using a "K" shaped mixing arm. The powders were pre-blended for 10 min and mixing was continued for a further 4 min after slowly adding the required amount of water. The mixer was stopped after every 2 min to scrape any powders from the wall with a spatula. The wet mass was placed into airtight container and allowed to stand overnight for 24 h to allow the powders and added water to reach equilibrium.

3.3. Extrusion

The wet mass was extruded using a rotary gravity-fed cylinder-type extruder (*Alexanderwerk Type GA65, Germany*) fitted with a 7.0 cm diameter, 14.8 cm long perforated cylinder. The perforations were 1 mm in diameter and the cylinder wall was 4 mm thick. The perforated cylinder was placed against a solid cylinder in the extruder and was capable of rotating from 20 to 100 rpm.

3.4. Spheronization

The extrudate was spheronized on a 5 inch (120 mm) pre-calibrated spheronizer *(Caleva model-120, UK)*, using either a cross-hatch friction plate or a radial design friction plate for 5–15 min at various speeds 1000–1500 rpm. The resulted spheres were allowed to dry at room temperature, followed by drying at 45 °C for 48 h in a forced air circulation oven *(Memmert type UL40, Germany)*, after which they were removed and evaluated.

Table 1
Formulations used in the initial experiments and the yield of large pellets, pellets and fines.

Batch #	K (%)	A (%)	L (%)	H (%)	% Yield		
					L Pellets	Pellets	Fines
1	50	25	25	37	50	46	4
2	50	25	25	35	37	57	6
3	50	40	10	45	15	77	8
4	50	45	5	50	8	83	9
5	50	50	0	50	6	82	12
6	50	50	0	55	8	82	10
7	60	40	0	52.5	9	82	9
8	65	35	0	45	24	65	11
9	70	30	0	50	37	53	10
10	70	30	0	40	34	55	11

NB: K = ketoprofen; A = MCC; L = lactose; H = hydration level; L pellets = large pellets.

3.5. Sieve analysis

Sieve analysis was performed using a nest of standard sieves. These sieves were placed on top of each other, the largest aperture sieve at the top with the decreasing apertures as the sieve nest approached the base plate. The sieve apertures used were 1680, 1180, 850, and 300 μm. A batch of pellets was placed onto the nest of the stainless-steel sieves *(Endecott-Germany)*, which was securely mounted on an Endecott test-sieve shaker *(1 MK11, UK)*. The sieve shaker was sit to agitate the nest for 15-min. The sieves were subsequently separated and their retained fractions weighed. The weight of each sieve function was expressed as percentage of the weight of dry solids added to the sieves. In this work, the desirable size range of pellets was taken to be between the 1180 and 850 μm and any spheronized product occurring within this size range is referred to as "**pellets**". Pellets occurring above this size are described as "**large pellets**" and fractions below the desired size are referred to as "**fines**". The terms pellets, beads, beadlets, microspheres or millispheres are used to describe solid particles or agglomerates of particles with a high degree of sphericity having a diameter of around 1 mm.

3.6. Pellet apparent density

Pellets apparent density was calculated using the classical method of solvent-displacement method [9–11]. A-25 ml density bottle *(BS733, Tay Tec, UK)* was washed, dried and weighed **(W_1)**. The bottle was filled with distilled water and placed in a water-bath maintained at 25 °C until no water emerged from the stopper. After drying the outside of the bottle it was again weighed **(W_2)** and its volume **(V)** calculated from the formula:

$$\textbf{Volume of bottle } (\mathbf{V}) = \frac{W_2 - W_1}{0.9971}\mathbf{cm^3}$$

where 0.9971 g/cm^3 is the density of water at 25 °C. The bottle was then emptied, cleaned and filled with hexane. Hexane was chosen as none of the pellets components were soluble in it. The above procedure was repeated and weight of bottle filled with hexane was noted **(W_3)**. The density of hexane (ρ_H) at 25 °C was then determined as follows:

$$\boldsymbol{\rho_H} = \frac{W_3 - W_1}{V}\mathbf{gm}\Big/\mathbf{cm^3}$$

4 g of pellets were placed in the pycnometer, filled with hexane and left at 25 °C until hexane ceased to emerge through the capillary stopper, at which time the outside of the bottle was dried and its weight noted **(W_4)**. The above procedure was repeated and an average of three readings was taken. An apparent density was calculated as follows:

Volume of hexane displaced by 4 g of pellets **(Y)**

$$(\mathbf{Y}) = \frac{W_3 - W_1}{p_H} - \frac{W_4 - W_1 - 4}{p_H}\mathbf{cm^3}$$

then

$$(\boldsymbol{\rho}) = \frac{4}{Y}\mathbf{g}\Big/\mathbf{cm^3}$$

where ρ is pellets apparent density.

Intraparticle porosity ($\varepsilon_{\text{intraparticle}}$) of the pellets may then be computed from knowledge of the true density of the materials and pellet density. The porosity is given by the equation:

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