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:

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

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:

$$\rho_H = \frac{W_3 - W_1}{V} \, \textbf{gm}\big/\textbf{cm}^3$$

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)

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

then

$$(\rho) = \frac{4}{Y} \, \textbf{g}\big/\textbf{cm}^3$$

where ρ is pellets apparent density.

Intraparticle porosity ($\varepsilon_{intraparticle}$) 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:

$$\varepsilon_{\text{intraparticle}}(\%)\frac{\rho_g}{\rho}\cdot 100$$

where

ρ_g is the pellets apparent density and
ρ is the true density of the materials.

3.7. Pellet shape analysis

The sphericity of pellets was determined using pellet parameters measured by an image analysis system (Quantimet 520 Version V4.00, Cambridge Instruments Ltd., UK) (QIA), which calculates the roundness factor using the magnified image of pellets from a microscope (Ergolux, Germany). A random sample of approximately 10 pellets was taken from the batch, mounted onto a glass slide and selected using the QIA system on a computer screen. This procedure was repeated 20 times to measure approximately 200 pellets.

3.8. Dissolution of pellets

The rotating basket method was used with 6-station dissolution apparatus (Erweka DT6, Germany). The basket rotation speed was 100 rpm and temperature maintained at 37 °C. A weigh of pellets equivalent to 100-mg ketoprofen was added to each basket and immersed in the dissolution medium. The experiments were carried out in 0.1 N HCl of pH 1.2 and in McIlvaine buffer solution of pH 6.8. Samples of 5-ml were withdrawn and replaced by equivalent volumes of pre-heated dissolution media at specific time intervals. The samples were assayed spectrophotometrically at 260 nm (Shimadzu UV-160, Japan), and the data was plotted as time vs. percentage drug released. Pellets subjected to this test were prepared under the conditions of 1250 rpm spheronizer speed and 10 −min spheronization time using the radial and the cross-hatch designs. The dissolution profiles were compared using the USP's similarity factor (f_2 -function) where values above 50 indicate similar dissolution profiles, while values below 50 imply different dissolution profiles. If the value equals 100, this will describe identical release rates [11].

3.9. Factorial design of experiments

Based on the results from non-factorial experiments, a **3x2** factorial experiment was designed to evaluate the factors of spheronization speed (1000, 1250, 1500 rpm) and spheronization time (5, 10, 15 min) using a cross-hatch and radial design friction plates on an optimized mix. The number of experiments required (**N**) is determined by the following formula: $\mathbf{N} = \mathbf{L^k}$, where **L** is the number of levels and **K** is the number of factors [12].

3.10. Analysis of variance (ANOVA)

The analysis of variance (ANOVA) is a good tool for the identification of the significance of factors and their levels in any factorially designed experiment, and the characterization and prediction of interactions in spheronization process. The comparisons between more than two-sample means were performed using two-way ANOVA test [13].

4. Results

4.1. Non-factorial experiments

The initial experiments were 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 in excess of 80%. Table 1 shows both the composition of these formulations and the yield of large pellets, pellets and fines. These formulations suggest that a high yield of pellets (> 80%) can be obtained if MCC content was increased, and this observation was accompanied with a decrease in large pellets formation. Production of fines was less than 13% in all batches, and this yield can be controlled by altering water content in the formulations. The initial experiments showed that water content had little effect on pellets yield. MCC content was the more significant factor in this set of experiments.

A summary of pellet apparent density and sphericity determinations is shown in Table 2. The density of pellets is a function of density of its ingredients and the operational conditions. Because of the limited number of initial experiments no specific pattern was observed for density of pellets. The effects of preparation conditions on pellet density will be fully investigated in the factorial experiments section. Sphericity measurements showed that all of the formulations produced pellets with a satisfactory sphericity score. The highest sphericity factor measured was 1.164. Pellets with a roundness score of 1.20 or greater were reported to have observable defects or distortions, whilst pellets with roundness scores less than 1.20 appeared increasingly smooth [14–16].

Based on the initial experiments it was decided to investigate the operational and formulation factors, employing two designs of friction plate, on mixes of ketoprofen (60%) and MCC (40%) using a full factorial design.

4.2. Factorial experiments

The results obtained from the factorial experiment are summarized in Table 3 for the yield of pellets, large pellets and fines.

4.2.1. Yield of pellets

The yield of pellets was generally high from both friction plate designs, ranging from 68 to 94%. The yield of pellets from formulations spheronized using the radial design was higher than yields obtained from mixes processed using the cross-hatch design, and these high yields were observed at all levels of spheronization time/ speed (Table 3). Based on the processing conditions, the yield of pellets was in the range of 68−90% and 84−94% for the cross-hatch and radial designs respectively. The results indicate that using either design of friction plate, the mixes demonstrate a "controlled" spheronization at all spheronization speeds tested, by maintaining

Table 2
Apparent density and sphericity factor of pellets produced in the initial experiments.

Batch #	Apparent density (g/cm³)	Sphericity (± SD[a])
1	1.107	1.139 ± 0.01
2	1.098	1.149 ± 0.02
3	1.086	1.164 ± 0.02
4	1.090	1.151 ± 0.02
5	1.073	1.154 ± 0.03
6	1.079	1.141 ± 0.01
7	1.057	1.146 ± 0.02
8	1.051	1.154 ± 0.04
9	1.031	1.154 ± 0.02
10	1.041	1.140 ± 0.05

[a] SD = standard deviation.

Table 3
The yield of pellets from 3^2 factorial design experiment using cross-hatch and radial friction plates.

Friction plate design	Sph[a] Time (min)	Spheronization Speed (rpm)								
		1000			1250			1500		
		F	P	LP	F	P	LP	F	P	LP
Cross-hatch										
	5	5.66	90.51	3.81	6.66	83.91	9.42	9.42	73.82	16.74
	10	6.59	89.72	3.67	9.31	82.30	8.92	9.31	71.70	18.99
	15	8.02	88.34	3.62	7.97	81.01	11.1	9.65	69.70	20.64
Radial										
	5	5	94	0.60	7.05	90.45	2.5	8.06	87.40	4.54
	10	4.93	94	0.66	6.7	89.45	3.0	9.18	85.3	5.58
	15	4.21	94	1.51	5.83	90.78	3.37	7.9	84.25	7.72

[a] **Sph** = Spheronization; **F** = Fines; **P** = Pellets; **LP** = Large Pellets.

pellet yield relatively unchanged.

The relative significance of the two factors of spheronization time/speed was calculated by analysis of variance (ANOVA). It was revealed that spheronization time appeared to have significant effect on pellet production only when the cross-hatch design was employed (P = 0.004). On the other hand, spheronization speed effect was highly significant for both designs of friction plate (P = 4.72E-06 and P = 0.001 for C–H & Radial respectively).

4.2.2. Yield of large pellets

The production of large pellets (LP) was considered an unwelcomed development during spheronizer as it represents a loss of yield from the desirable pellet size range and should be viewed in conjunction with the results obtained for the yield of pellets. The yield of LP ranged from 0.6 to 7.7%. The increase in spheronizer speed was always accompanied by increased L-Pellets production while spheronizer time had little effect on LP yield.

ANOVA results for the production of large pellets using both designs of friction plate indicated that spheronizer speed was the only significant factor affecting L-P production with either plate design, which is similar to results obtained for pellets production. The value of P-statistic was more significant for the cross-hatch design (P = 0.0002 and P = 0.002 for C–H & radial respectively).

4.2.3. Yield of fines

The yield of fines in all the formulations was relatively low, and was ranged from 4.2 to 9.6%. An examination of the data revealed that as the spheronizer speed was increased, the yield of fines was increased. Spheronization time appeared to have little effect on the production of fines. ANOVA results showed that spheronization speed was the only significant factor (p < 0.001) when a radial design plate was used, while both factors were insignificant when the cross hatch design was employed.

4.2.4. Pellets apparent density and porosity

A general trend of increasing pellet density as time progressed was observed at all speeds used (Table 4). Higher density scores were achieved at the highest speed and longest residence time using either plate design. This could be attributed to the high speed at which the pellets are thrown against the spheronizer wall, which enhances the association between ingredients, and such effect is likely to be more profound at longer spheronization times. The ANOVA results indicated that with either plate design, the main factors studied had no statistical significance on pellets apparent density.

The results shown in Table 5 imply that the pellets obtained by the radial design during spheronization have lower porosity than those pellets produced with the cross-hatch design. This means the

Table 4
Apparent density measurements (g/cm^3) for pellets prepared using cross-hatch and radial friction plates.

Friction plate design	Sph[a] Time (min)	Spheronization Speed (rpm)		
		1000	1250	1500
Cross-hatch				
	5	1.081	1.0335	1.0825
	10	1.03	1.0573	1.0973
	15	1.087	1.086	1.104
Radial				
	5	1.087	1.006	1.077
	10	1.090	1.113	1.135
	15	1.094	1.135	1.140

[a] Sph = spheronization.

Table 5
Intraparticle porosity calculations (%) for pellets prepared using design cross-hatch and radial friction plates.

Friction plate design	Sph[a] Time (min)	Spheronization Speed (rpm)		
		1000	1250	1500
Cross-hatch				
	5	8.77	12.8	8.65
	10	13.1	10.7	7.4
	15	8.2	8.35	6.8
Radial				
	5	8.3	10	9.1
	10	8	6.1	4.22
	15	7.7	4.22	3.4

[a] Sph = spheronization.

pellets produced by the radial design possess smoother surface. Statistically, there were no significant differences between the porosity values obtained with each design of friction plate.

4.3. Dissolution rate

The rate of drug release from pellets, as a function of spheronizer plate design, is shown in Fig. 1. The dissolution profiles appear to be identical in both media. The similarity factor (f_2) between the dissolution profiles was found to be above 97 for both formulations which indicate a highly similar drug release rates [10].

5. Discussion

The non-factorial experiments were useful in determining the range of levels which could be applied to the various factors and
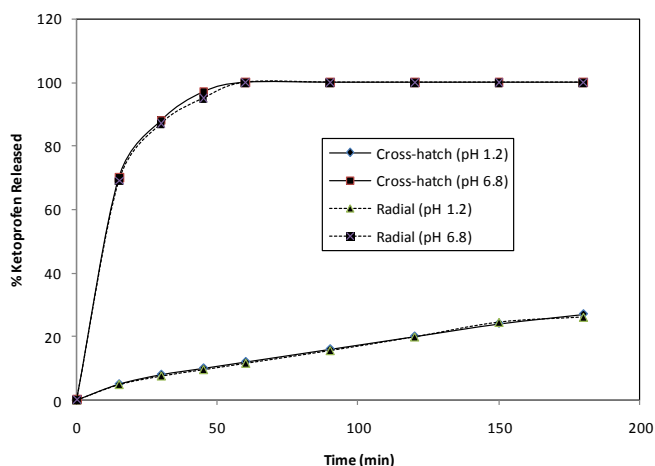
Fig. 1. Dissolution profiles of ketoprofen from pellets prepared by cross-hatch and radial design spheronizer plate as a function of pH (production conditions of pellets: water level: 52.5%, spheronizer speed/time = 1250-rpm/10-min). The results are the mean of 6 experiments.

indicated the relative importance of the factors in terms of the spheronized product characteristics. The formulations were initially composed of ketoprofen, MCC and lactose. The results indicated that a high level of MCC was required in order to produce satisfactory yields. Lactose was then excluded from the formulations and the pellets were composed solely of the drug and MCC. The yield of pellets was 82% up to 60% drug content, while lower yields were obtained when drug content was increased above that level. Apparent density determinations showed no significant changes between the different formulations which was attributed to the similar densities of the materials used. The sphericity factor score for all the preparations was below the threshold value of 1.2, which implied that the pellets were very spherical and possibly without any major surface defects. And according to literature, the only physical property of the pellets that did not respond to the various changes in the manufacturing process of the pellets is pellet shape [5].

A 3^2 factorial experiment was conducted to evaluate the effect of spheronizer plate design on the yield of pellets. Two-designs were used: the cross-hatch and the radial friction plates. The results revealed that the use of the radial design friction plate in the spheronizer can lead to a reasonable increase in the yield of pellets. At all the variables investigated, the yield of pellets was significantly higher when extrudates were spheronized using the radial design. The pellet yield was optimized up to 94% when using the radial design. Statistical analysis revealed that spheronization time had no significance on pellet production at the water level employed, while spheronization speed was significant for the yield of pellets, large pellets and fines. A desirable finding was observed in the ability of the formulations to maintain the yield of pellets without loss of yield to the larger fraction as spheronization time increases, which is termed "controlled spheronization" [17]. The increase in LP production as the spheronizer speed was increased probably was a consequence of the greater emotional energy of the pellets in the spheronizer chamber. The coalescence of forming pellets is more likely to occur as particles are forced together in the pellet bed at higher speeds [17,18].

No significant changes in density, porosity and dissolution rate between pellets produced by either design of friction plates. Also, the pellets showed slow drug release in the used dissolution media.

It was theorized that dissolution through MCC matrix is not affected by pH of the surrounding medium, which implies that the results of pH-dependency observed can be attributed to the variable ketoprofen solubility [10,19,20]. The MCC pellets do not disintegrate and drug release occurs via diffusion through an insoluble inert matrix [21]. The findings in dissolution testing are in agreement with other works in which the dissolution rate appears marginally affected by changes in the spheronization process [6].

6. Conclusion

It was clear from these results that the radial design of spheronizer friction plate is more suitable than the cross-hatch design for the spheronization of ketoprofen by providing a higher yield of pellets of the desired size without any significant changes in density, porosity or dissolution rate.

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