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The influence of plate design on the properties of pellets produced by extrusion and spheronization

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ABSTRACT

The aim of this work was to produce pellets using a standard formulation by means of extrusion and spheronization. Three different spheroniser friction plate patterns (i.e. cross-hatch, radial, striated edge pattern) have been used in order to investigate whether the plate pattern affects physical properties of the pellets such as pellet size distribution, yield, shape, mechanical strength, density and drug dissolution. Extrusion was performed with a screen extruder and the screen size was varied to determine whether the extrudate produced could affect the physical properties of pellets. The plate load was also varied. Diclofenac sodium was chosen as a model drug. The pattern of the friction plate used in the spheronization of extrudates affected the properties of the pellets. 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. However, these pellets had a reduced mechanical strength despite their lower porosity, which might be disadvantageous. In addition, other factors such as the amount of extrudate loaded into the spheroniser, the maintenance of a constant moisture content within the spheroniser and the size of the extruder screen influenced these findings significantly. The only physical property of the pellets that did not respond to the various changes in the manufacturing process of the pellets is the pellet shape, which remained spherical. The dissolution of the drug appeared to be related to the median pellet size and was only marginally affected by changes in the spheronization process.

1. Introduction

Pellets as oral pharmaceutical dosage forms are of great interest to the pharmaceutical industry because they are convenient, safe and easy to administer, even though they are generally only intermediates in the manufacture of modified release capsule and tablet formulations. Pellets are spherical units with a smooth surface, ideally between 0.7 and 1.4 mm in size (Ghebre-Sellassie, 1989). One of the main advantages of pellets is that they have a "minimum surface to volume ratio" (Fekete et al., 1998) making them ideal units for subsequent coating processes.

Pellets produced by extrusion–spheronization have been the subject of extensive research including manufacturing steps, the influence of process variables and the physical properties of pellets (Newton et al., 1995a). The desirable properties of pellets include uniform spherical shape and size, good flow properties, high mechanical strength, low friability, low dust and smooth surface (Summers and Aulton, 2002). The final properties of pellets produced by extrusion–spheronization vary with different process variables, and both the formulation and the process conditions are important factors to consider. For example, the speed of the spheroniser plate influences the pellet properties; it is adequate to produce a reasonable quality product if extrudates are spheronised for 10 min at a rotational speed of 800–1500 rpm using a 21.2 cm diameter spheroniser plate (Newton et al., 1995a,b). As the diameter of the plate increased, Newton et al. (1995b) found that the speed of the plate had to be reduced so that the peripheral velocity of the plate remained the same; about 420 cm s^{-1}. They also considered the effects of plate loads and found that for a plate speed of 800 rpm and a spheroniser plate size of 21.2 cm, the optimum load is approximately 300 g of wet mass. If the load on the plate is too low then there are insufficient particle–particle interactions, which results in larger pellets with low densities and non-spherical shapes. If the plate load is too high the particles cannot interact with the spheroniser plate, which means that it takes longer to produce spherical particles (Newton et al., 1995b). Similar effects of loads were observed for the large diameter plates of the same design (Newton et al., 1995b). The plate must therefore "chop" the extrudate after which the fragments move in a characteristic toroidal

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motion due to friction between the particles and the plate to the outside edge of the plate due to the centrifugal force generated. Chapman (1985) was able to demonstrate that the extrudate was chopped into lengths of about 1.5–2 times their diameter, which are then compressed along their lengths until they eventually formed spherical particles of increasing density.

Different manufacturers produce different types of plates. Most spheroniser plates have grooved surfaces, which are designed to increase the frictional forces (Vervaet et al., 1995). The rounding of the extrudates into the final spherical shape depends on the frictional forces, i.e. on the generated particle–particle and particle–equipment interactions. Newton et al. (1995a) considered two different plate patterns, cross-hatched and radial surface and found that plate design did not have much effect on the ability of the extrudates to spheronise. They used a long-die extruder, and when the force of extrusion was varied, the plates produced pellets, which varied in their physical properties. Therefore the influence of the plate design may depend on the type and quality of the extrudate. However the plate designs may have the potential to influence less robust formulations (Newton et al., 1995a), yet to date this has not yet been further evaluated and the optimum characteristics of the friction plate have as yet to be established.

The preferred choice of friction plate seems to be the so-called "cross-hatch" plate (Fig. 1a). This is simply a matter of manufacture, as independent of spheroniser plate diameter the pattern remains the same in terms of grove size and spacing. In comparison, plates with a radial pattern (Fig. 1b) or plates with striated edges (Fig. 1c) change grove size and spacing with increasing plate diameter, which is more difficult to manufacture, and the frictional effects that result are also different resulting in variable scale-up properties.

The aim of this work was to produce pellets using a standard formulation by means of extrusion and spheronization. Three different spheroniser friction plate patterns have been used (Fig. 1) in order to investigate whether the plate pattern affects physical properties of the pellets such as pellet size distribution, yield, shape, mechanical strength, density and drug dissolution. Extrusion was performed with a screen extruder and the screen size was varied to determine whether the extrudate produced could affect the physical properties of pellets. The plate load was also varied. Diclofenac sodium was chosen as a model drug. It is a white crystalline powder, which is sparingly soluble in water but soluble in alcohol.

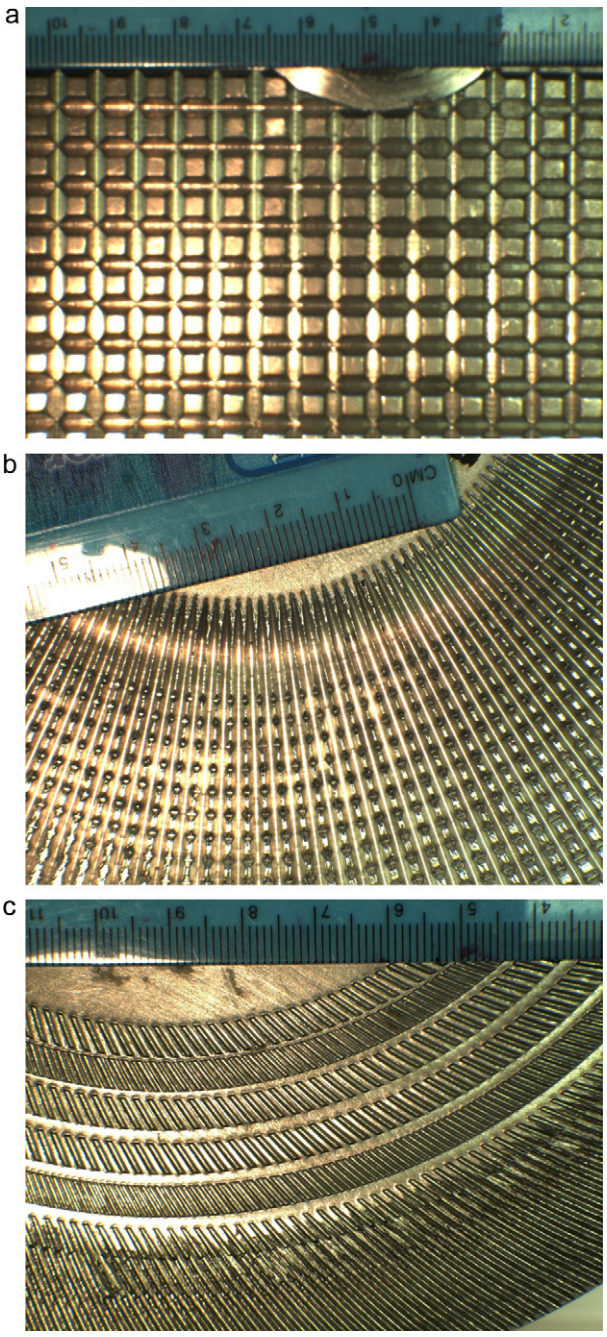

Fig. 1. Friction plate design. (a) Cross-hatch pattern; (b) radial pattern; (c) striated edge pattern.

2. Materials and methods

2.1. Materials

Diclofenac sodium of European Pharmacopoeial quality, mean particle size of 12.05 μm, determined by Malvern Master Sizer (Malvern Instruments Ltd., Worcester, UK) was obtained from Heumann Pharma GmbH, Feucht, Germany (batch 0112785); lactose monohydrate, mean particle size of 65.71 μm was obtained from Borculo Whey Products (Saltney UK, batch 749035), and microcrystalline cellulose N. F. (MCC), mean particle size of 69.71 μm was obtained from FMC international (Avicel® PH101, batch 6842C; Little Island, Cork, Ireland). Freshly demineralised water was used as granulating fluid.

2.2. Production of pellets

A robust standard formulation, which had a ratio of MCC to water of 1:0.9, was used in all main experiments. For an optimum spheroniser loading, the pellet formulation contained 10 g diclofenac sodium, 40 g lactose monohydrate, 150 g MCC and135 g distilled water. To achieve different plate loadings, this formulation was varied by ±50% i.e. for low loading conditions the above stated quantities were reduced to 5 g drug, 20 g lactose monohydrate, 75 g MCC and 67.5 g distilled water, whereas for a high plate loading the quantities were increased to 15 g drug, 60 g lactose monohydrate, 225 g MCC and 202.5 g distilled water.

The drug and lactose monohydrate were mixed in a planetary mixer (Kenwood Chef, Kenwood products Ltd, London, UK) at the lowest speed for 5 min. MCC was then added to the mixer and mixed for a further 5 min. Distilled water was added and the mixture was mixed for 15 min, interrupting every 3 min to scrape the sides of the vessel and the mixer blade. The wet mass was placed into a polythene bag and left for 1 h to equilibrate.

Extrusion–spheronization was used to prepare the pellets. A screen extruder (Caleva model 10, Dorset, England) was employed.

Screen sizes of 1 mm and 1.5 mm aperture were investigated with the rotation speed of the extruder kept constant at "low". The extrudates were collected and placed into a spheroniser (Caleva model 250, Dorset, UK), which was equipped with various friction plates with different plate patterns, all having a diameter of 22.5 cm. The different plate patterns that were investigated were the "cross-hatch", "radial" and "striated edges" plates (Fig. 1). The pellets were produced using a rotation speed of 1000 rpm for 12 min.

The pellets were collected and dried for 1 week at environmental conditions (18–20 °C; 35–40% RH) on a large sieve, having established previously that this resulted in equilibrium moisture content of the pellets, before assessing their physical properties.

2.3. Pellet size distribution

The total amount of pellets produced was recorded prior to characterisation. The pellet size distribution was determined with a set of British Standard brass sieves following a $\sqrt{2}$ progression from 250 μm to 1400 μm mesh diameter (Endecotts Ltd., London, UK). The sieves were subjected to vibration (Retsch, Stanmore, England) whereby one-third of the batch was placed on the top sieve and shaken for 10 min. This process was repeated twice. The percentage of weight of the pellets in each size fraction was determined. From the cumulative undersize and oversize distribution the median and interquartile range were obtained using 2-cycle log-probability paper (Chartwell, UK). The modal fraction was determined as the pellet sieve fraction with the highest percentage of pellets, and the yield was defined as the percentage of pellets in the size range between 0.7 and 1.4 mm.

2.4. Pellet shape

An image analysis system was used to determine the shape of the pellets (Seescan Solitaire 512, Seescan, Cambridge, UK) connected to a black and white camera (CCD-4 miniature video camera module, Rengo Co. Ltd., Toyohashi, Japan), zoom lens (18–108/2.5, Olympus Co., Hamburg, Germany) and top position cold light source (Cold light 2000, Olympus Co., Hamburg, Germany).

Fifty pellets taken at random from the 1.0 to 1.4 mm sieve size fraction were inspected and the projected area diameter (Allen, 1997), Aspect Ratio (Schneiderhöhn, 1954) and shape factor (Podczeck et al., 1999) were determined for each batch of pellets. The pellets were placed onto a black holder and lit from above so that they appeared as white pellets on a black background without shadows affecting the image. The magnification was set so that the pixel size was between 10 and 15 μm.

2.5. Pellet surface tensile strength

Thirty pellets taken at random from the 1 to 1.4 mm sieve size fraction were assessed using a physical testing instrument equipped with a 5 kg load cell (CT-5, Engineering Systems, Nottingham, UK). The pellets were subjected to constant strain (strain rate 1 mm/min) and the failure load was noted when the pellets split into two equal halves. The surface tensile strength was calculated applying Eq. (1) (Shipway and Hutchings, 1993; Salako et al., 1998):

$$\sigma_{t(s)} = \frac{0.4P}{\pi R^2} \quad (1)$$

where $\sigma_{t(s)}$ is the surface tensile stress, P is the failure load and R is the radius of the pellet, which was determined from the mean projected area diameter.

2.6. Pellet density and porosity

Samples of 1.5–2.5 g of pellets were weighed to ±0.001 g (Analytical balance, Precisa 125 A, Switzerland) into the sample cell and transferred to the gas pycnometer (Multipycnometer, Quantachrome Co., New York) using helium as the displacement fluid. All pellet batches and powders were analysed in triplicate.

Eq. (2) was used to calculate the porosity ε of the pellets:

$$\varepsilon = 1 - \frac{\rho_p}{\rho_m} \quad (2)$$

where ρ_p is the density of the pellets and ρ_m is the density of the powder mixture (1484 kg m^{-3}).

2.7. Drug dissolution

Dissolution studies were performed in 900 ml phosphate buffer pH 7.2 in a BP Paddle Apparatus (Copley Instruments, Nottingham, UK) at 37 ± 1 °C using a paddle speed of 50 rpm. Six samples of 250 mg of pellets were used in each experiment. Ten-ml samples were taken at 5, 10, 15, 20, 30, 40, 50 and 60 min, filtered through a 0.4 μm ceramic filter (Copley Instruments, Nottingham, UK) and analysed at 275 nm using a UV spectrophotometer (CE 272, Cecil Instruments Ltd., Cambridge, UK).

2.8. Statistical analysis

One-way and two-way Analysis of Variance was undertaken using SPSS 14.0 (SPSS Inc., Woking, UK). This was complemented with post hoc analysis using the Scheffé test (Berry and Lindgren, 1996).

3. Results and discussion

3.1. Experimental design

The quantitative composition of the formulation in terms of solid powder components was kept constant in this study i.e. 75% MCC, 20% lactose monohydrate and 5% model drug (diclofenac sodium). In preliminary experiments, the amount of water added during the wet massing step was varied in a ratio of MCC to water of 1:0.8; 1:0.85; 1:0.9; 1:0.95 and 1:1. The MCC to water ratio of 1:0.9 was found to produce pellets with a narrow size distribution in the required size range of 0.7–1.4 mm, smooth appearance and satisfactory pellet shape (Aspect Ratio approximately 1.1). This MCC to water ratio was hence used in all main experiments. To ensure that the pellet properties were reproducible, initially three batches using this MCC to water ratio and standard production parameters (cross-hatch plate, extruder screen size of 1 mm, spheroniser lid closed, 335 g wet mass) were produced and compared. During the main experimental design, a further batch was then produced using the same production parameters and also compared with the initially produced three replicate batches. All main experiments were performed in random order using random number tables (Weber, 1980). The random numbers are indicated with "R" in tables and figures.

3.2. Pellet production parameters

In most cases, pellets act as intermediates for the manufacture of modified release dosage forms, whereby they are typically filled into hard capsules, or they might be compressed into tablets. To ensure uniformity of dose requires in both instances a narrow particle size distribution, and the amount of particles outside the target size of 0.7–1.4 mm should be very small. Therefore, production parameters that are typically assessed are the modal pellet

Table 1
Batch description, modal fraction ("mode"), percentage in modal fraction ("mode %"), yield, median pellet size ("MPS"), interquartile range ("IQR") and area under the dissolution curve ("AUC").

Code	Plate pattern	Screen (mm)	Load (%)	Mode (mm)	Mode %	Yield (%)	MPS (mm)	IQR (mm)	AUC (% min)
Repeatability									
N/A	Cross-hatch	1	100	1–1.4	59.6	77.1	1.18	0.25	4732.1 ± 8.4
N/A	Cross-hatch	1	100	1–1.4	56.9	79.1	1.15	0.35	4714.6 ± 6.7
N/A	Cross-hatch	1	100	1–1.4	60.7	75.5	1.16	0.25	4726.6 ± 6.1
Plate pattern									
R10	Cross-hatch	1	100	1–1.4	61.7	75.5	1.22	0.25	4725.4 ± 9.6
R4	Radial	1	100	1–1.4	72.0	83.5	1.18	0.15	4741.7 ± 7.9
R2	Striated edge	1	100	1–1.4	76.4	93.9	1.08	0.20	4750.0 ± 0.0
Lid off									
R3	Cross-hatch	1	100	1–1.4	60.2	89.8	1.10	0.25	4748.6 ± 6.7
R6	Radial	1	100	1–1.4	62.5	70.8	1.25	0.20	4736.7 ± 9.3
R9	Striated edge	1	100	1–1.4	63.2	84.8	1.12	0.20	4750.0 ± 0.0
Plate loading									
R5	Cross-hatch	1	50	1–1.4	54.9	78.9	1.15	0.31	4750.0 ± 0.0
R7	Radial	1	50	0.7–1	62.4	88.5	0.90	0.22	4750.0 ± 0.0
R12	Striated edge	1	50	0.7–1	62.1	84.8	0.86	0.24	4750.0 ± 0.0
R13	Cross-hatch	1	150	1–1.4	50.5	61.0	1.32	0.30	4750.0 ± 0.2
R15	Radial	1	150	1–1.4	67.8	88.2	1.15	0.25	4748.4 ± 6.4
R11	Striated edge	1	150	1–1.4	67.6	90.4	1.10	0.25	4748.8 ± 4.9
Extruder screen size									
R8	Cross-hatch	1.5	100	1–1.4	45.2	57.9	1.30	0.45	4750.0 ± 0.0
R1	Radial	1.5	100	1–1.4	55.1	69.5	1.22	0.40	4745.3 ± 3.1
R14	Striated edge	1.5	100	>1.4	53.1	36.9	1.45	1.14	4732.7 ± 9.3

fraction i.e. sieve fraction containing most pellets of the batch, the yield, which is defined as the percentage of pellets in the target size range (0.7–1.4 mm), the median pellet size and the interquartile range, obtained from the total pellet batch. The results for the replicate batches and the batches of the experimental design are listed in Table 1.

The results from the 3 replicate batches were pooled into arithmetic mean and standard deviation values (% in modal fraction 59.1 ± 2.0; yield 77.2 ± 1.8%; median pellet size 1.16 ± 0.02 mm; interquartile range 0.28 ± 0.06 mm). These values were then compared with those obtained from batch R10, which is similar in all manufacturing parameters, but was manufactured several weeks later, using a *t*-test in order to establish the final reproducibility of the experiments. No statistically significant differences were found.

When comparing the different friction plate patterns (batches R10, R4 and R2), it can be seen that although the modal fraction as such is the same (1–1.4 mm), there is an increase in the percentage of pellets in the modal fraction from cross-hatch over radial to striated edge pattern. The yield increases in a similar fashion, with the striated edge plate producing 18.4% more pellets in the desired size range than the typically used cross-hatch plate. At the same time there is a decrease in median pellet size from cross-hatch over radial to striated edge pattern, whereas the width of the pellet size distributions remained similar. For this formulation a larger yield is therefore combined with a slight decrease in median pellet size, and it would appear as though the use of the striated edge friction plate would be advantageous.

When the experiments were repeated leaving the spheroniser lid open (batches R3, R6 and R9), the percentage of pellets in the modal size fraction was very similar and fairly low for all three friction plate patterns. Using the cross-hatch plate an increase in the yield by about 15% was found, whereas for either remaining plate pattern design a decrease in yield value occurred. This might indicate that radial and striated edge friction plates require an increased plasticity, compared to the cross-hatch plate. When the lid remained open, moisture could have evaporated and as a result the plasticity of the wet mass might have been reduced. On the other hand, the loss in moisture resulted in smaller pellets when using the cross-hatch plate (median pellet size dropped by 10%), indicating that although the change in plasticity did not negatively affect the yield value, it resulted in more brittleness and hence smaller pellets.

Both a decrease in spheroniser loading from 335 g of wet mass to 167.5 g and an increase to 502.5 g of wet mass resulted in a decrease of the amount of pellets found in the modal sieve fraction, plus for the radial and the striated edge pattern the modal sieve fraction decreased from 1–1.4 mm to 0.7–1 mm when lowering the spheroniser load. The increase in the spheroniser load also resulted in slightly larger median pellet size values, especially when using the cross-hatch plate, and in general the increase in load resulted in slightly wider pellet size distributions, reflected in increased values for the interquartile range. Using cross-hatch frictions plates, also Hasznos et al. (1992) and Newton et al. (1995a,b) reported an increase in pellet size with increased spheroniser load. When the loading is increased then there is less space for each individual extrudate particle and they will move slower. As a result, the impact with the spheroniser walls results in larger fragments, which then round into pellets of larger diameter.

The use of a larger screen during the extrusion step resulted in larger pellets, especially when using the striated edge plate. For this formulation, the percentage of pellets in the modal sieve fraction and the yield are drastically reduced, indicating that the water content, which was optimised using the 1 mm extruder screen, is critical for the performance and not transferrable to the larger extrusion screen. The process is clearly out of control, as indicated by the very large values for the interquartile range, whereby in particular the striated edge plate seems no longer suitable to produce good quality pellets. When using the 1 mm extruder screen, the extrudate was smooth and shiny, but when using the 1.5 mm screen, the extrudate appeared "shark-skinned" i.e. showed regular, sharp circumferential ridges with deep cracks that penetrated the core of the extrudate. Shark-skinned extrudate breaks more randomly, resulting in wider pellet size distributions (Fielden and Newton, 1992).

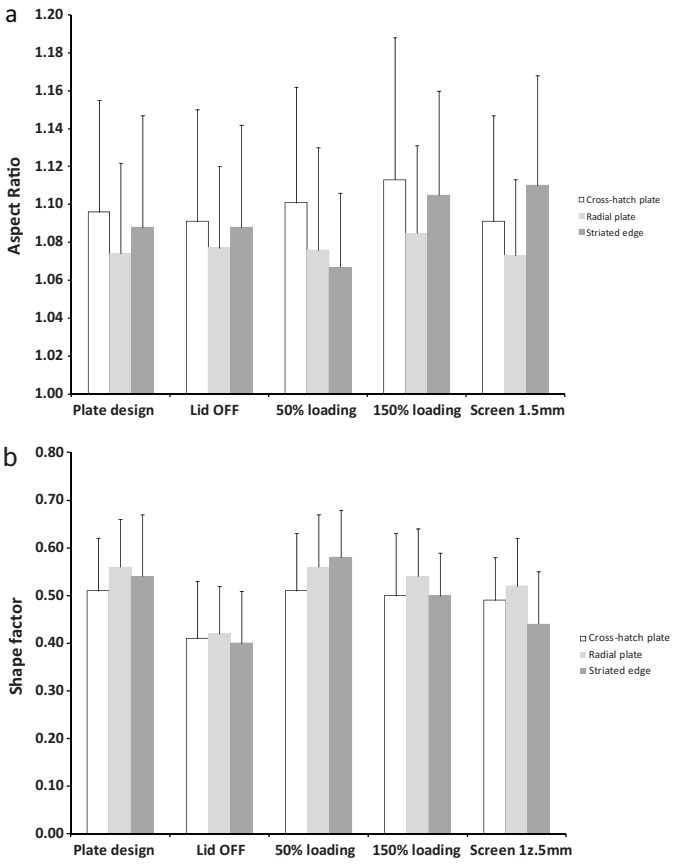

Fig. 2. Shape of pellet batches produced with varying production parameters (see Table 1). (a) Aspect Ratio; (b) shape factor as defined by Podczeck et al. (1999).

3.3. Pellet shape

The pellet shape was assessed using both the Aspect Ratio (Schneiderhöhn, 1954) in order to determine deviations from spherical shape in terms of elongation towards ellipticity, and the shape factor (Podczeck and Newton, 1994, 1995; Podczeck et al., 1999), which is mainly reflecting surface irregularities, macro surface roughness, bumps, holes, etc. Podczeck et al. (1999) defined smooth-surfaced spherical pellets as those characterised by an Aspect Ratio of $\leq$1.1 and a shape factor of $\geq$0.6. In terms of downstream processing by encapsulation an Aspect Ratio of $\leq$1.2 and a shape factor of $\geq$0.4 were identified as essential (Chopra et al., 2002).

As before, the reproducibility of the process was evaluated using the three test batches plus batch R10. For the Aspect Ratio, values of 1.103 ± 0.076, 1.125 ± 0.097, 1.107 ± 0.070 and 1.096 ± 0.059 were found, respectively, and one-way ANOVA confirmed the differences as being insignificant at an error probability of $p = 0.05$. For the shape factor, the experimental results were 0.51 ± 0.12, 0.53 ± 0.15, 0.49 ± 0.13 and 0.51 ± 0.11, respectively. Again, one-way ANOVA confirmed the reproducibility of the shape of the pellet batches. These pellet batches can be classed as spherical (Aspect Ratio $\approx$ 1.1) with moderate surface irregularities (shape factor $\approx$ 0.5), which would pose no problems during downstream processes such as capsule filling.

Fig. 2a compares the Aspect Ratio for batches R1–R15. All batches can be classed as spherical, and ANOVA did not identify any significant differences between the batches. Fig. 2b shows the results for the shape factor. All pellet batches show moderate surface irregularities, but due to their spherical shape they would not cause problems during capsule filling. Again, two-way ANOVA could not detect any statistically significant differences between the mean values except when comparing batches R10, R4 and R2 (spheroniser lid closed) with batches R3, R6 and R9 (spheroniser lid removed). The shape factor is significantly lower ($F = 4.04$; $p = 0.05$) for the batches where the spheroniser lid remained open, permitting evaporation of moisture during the spheronization process. The plate pattern did not affect this, nor was there any statistically significant interaction between the factors plate pattern and lid closure. As discussed earlier, the evaporation of moisture might have reduced the plasticity of the wet mass, resulting in spherical pellets with a larger degree of surface irregularities. There is also a small trend that the increase in the extruder screen width from 1 to 1.5 mm caused more irregular surface structures, but this trend is statistically not significant.

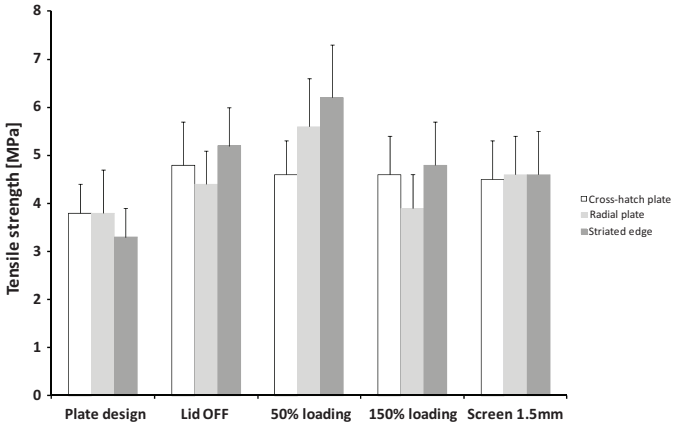

Fig. 3. Surface tensile strength of pellet batches produced with varying production parameters (see Table 1).

3.4. Pellet surface tensile strength

As before, the reproducibility of the pellet manufacture was assessed using the three test batches plus batch R10, and the surface tensile strength values were 3.8 ± 0.5, 3.5 ± 0.5, 4.1 ± 0.6 and 3.8 ± 0.6, respectively. One-way ANOVA could not detect any significant differences between these values.

Fig. 3 compares the surface tensile strength values between the 15 batches of the experimental design (Table 1). Comparing the effect of friction plate pattern (batches R10, R4 and R2) with one-way ANOVA resulted in an overall significant difference ($F = 4.49$; $p = 0.01$). Post hoc assessment using the Scheffé test identified pellet batch R2 (striated edge plate) as a batch with significantly lower surface tensile strength ($F = 7.35$; $p = 0.01$). The striated edge pattern is comparatively "smooth" and hence less able to compact and densify pellets, which here resulted in a decrease in the mechanical strength of the pellets.

Using two-way ANOVA, the combined effect of plate design (batches R10, R4, R2) and spheroniser lid closed or removed (batches R3, R6, R9) was computed, and the analysis showed an overall statistically significant effect ($F = 24.69$; $p < 0.001$). However, the main factor "plate pattern" was found not to influence the results significantly, whereas the main factor "lid on/off" ($F = 101.76$; $p < 0.001$) and the interaction between both factors ($F = 10.17$; $p < 0.001$) were identified as statistically significant. Comparing the mean values of the surface tensile strength using SPSS embedded graphical techniques (Edwards, 1979) revealed that the interaction between plate pattern and closure of the spheroniser is "ordinal" i.e. despite the fact that the difference between the two effects is not the same for each factor level, the rank order of the effects is similar. There is an increase in surface tensile strength when the spheroniser lid was left off, but

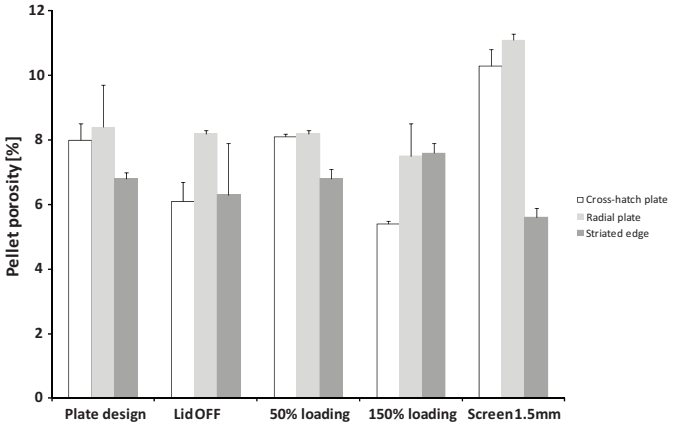

Fig. 4. Porosity of pellet batches produced with varying production parameters (see Table 1).

this increase is least for the radial plate pattern and largest for the striated friction plate.

The plate loading also affected the surface tensile strength significantly, as shown by two-way ANOVA comparing batches R10, R4 and R2 (335 g extrudate) with batches R5, R7, R12 (167.5 g extrudate) and R13, R15, R11 (502.5 g extrudate). The overall effect ($F = 38.81$; $p < 0.001$) was accompanied by significant main effects ($F = 110.34$ for plate loading and $F = 8.18$ for plate pattern; $p < 0.001$) and a significant interaction term ($F = 18.36$; $p < 0.001$). A post hoc Scheffé test revealed that in terms of surface tensile strength cross-hatch and radial plate resulted in similar values, but pellets prepared with the striated edge plate were significantly stronger. The interaction was again of ordinal character. Both under (167.5 g extrudate) and especially overloading (502.5 g extrudate) resulted in mechanically stronger pellets than using the optimum spheroniser load of 335 g extrudate. The increase in pellet surface tensile strength at decreased spheroniser load was more pronounced for the striated edge plate, followed by the radial plate, and was least yet still statistically significant for the cross-hatch plate design. The increase in pellet surface tensile strength at increased spheroniser load was slightly larger for the striated edge plate than for the cross-hatch plate. However, for the radial plate the effect was not significant. Barrau et al. (1993) reported an increase in the mechanical strength of pellets when the spheroniser load was increased, using a cross-hatch plate. It has to be borne in mind that the surface tensile strength of pellets is related to pellet porosity. As discussed below, the pellets produced with the striated edge plate are less porous when using the lowest and the standard spheroniser load, which could account for their larger surface tensile strength.

The effect of the extruder screen size was also evaluated using two-way ANOVA, comparing batches R10, R4 and R2 with batches R8, R1 and R14. The results are overall significantly different ($F = 13.88$; $p < 0.001$), but only due to the effect of the extruder screen size ($F = 61.17$; $p < 0.001$). Pellet prepared with the 1.5 mm extruder screen are all mechanically stronger, despite their larger porosity.

3.5. Pellet porosity

As before, the reproducibility of the pelletization process was assessed using the three test batches plus batch R10, and the porosity values obtained were 0.078 ± 0.005, 0.076 ± 0.005, 0.084 ± 0.005 and 0.080 ± 0.005, respectively. One-way ANOVA could not detect any significant differences between these values.

Fig. 4 illustrates the findings for all main batches of the experimental design. One-way ANOVA demonstrated that there is no significant effect of plate design on porosity (batches R10, R4 and R2). However, when the plate design results (batches R10, R4, R2) were combined with the results from the open spheroniser (batches R3, R6, R9), two-way ANOVA revealed an overall significant difference between all mean values ($F = 3.91$; $p = 0.003$), both main factors i.e. plate design ($F = 4.07$; $p = 0.047$) and spheroniser open or closed ($F = 6.19$; $p = 0.003$) were statistically significant. The interaction between both factors was statistically insignificant. The post hoc Scheffé test clarified that with the spheroniser lid closed pellets produced using the striated edge plate were significantly less porous, whereas with the lid left open pellets made with the radial plate were more porous than those made with the other two plates.

The plate loading affected the porosity of the pellets significantly, as shown by two-way ANOVA comparing batches R10, R4 and R2 (335 g extrudate) with batches R5, R7, R12 (167.5 g extrudate) and R13, R15, R11 (502.5 g extrudate). The overall effect ($F = 11.15$; $p < 0.001$) was accompanied by significant main effects ($F = 9.79$ for plate loading and $F = 10.23$ for plate pattern; $p < 0.001$) and a significant interaction term ($F = 12.28$; $p < 0.001$). The interactions were found to be disordinal. Comparing the results for the cross-hatch and the radial plate, the porosities between plates were similar at all loading levels and also similar for underloading and normal loading. However, they were significantly smaller when the spheroniser was overloaded by 50%. On the other hand, for the striated edge plate a significantly higher porosity was observed at the highest spheroniser load, whereas the porosity was similarly low at the two other loading levels. The striated edge plate is not as powerful in densifying pellets due to lack of grooves, and at an increased spheroniser load frictional forces are further reduced, resulting in more porous pellets. The increased friction combined with the increased weight of a larger load, however, results in larger densification, when cross-hatch or radial plate patterns are employed.

The effect of the extruder screen size was also evaluated, again using two-way ANOVA, comparing batches R10, R4 and R2 with batches R8, R1 and R14. The results are overall significantly different ($F = 38.66$; $p < 0.001$), and both plate pattern ($F = 65.48$; $p < 0.001$), extruder screen size ($F = 21.38$; $p < 0.001$) and a disordinal interaction between them ($F = 20.49$; $p < 0.001$) were determined as being significant. Pellets produced using the striated edge plate were significantly less porous than those produced with the other plates, and their porosity decreased further with an increase in extruder screen size from 1 to 1.5 mm. However, for cross-hatch and radial plate the pellet porosity increased when the extruder screen size increased.

3.6. Adhesion to the plate

The processing of some formulations can result in adherence of the wet mass to the plate as demonstrated for a range of formulations spheronised with a radial plate (Podczeck et al., 2008). Heng et al. (2002) evaluated the influence of the "teardrop" stud dimensions of the frictional base plate of a rotary processor. This system produces spheroids from powder formulations by the addition of spraying fluid onto the bed of powder that is moving on a rotating base plate. The final stage of this process resembles that of the spheronization stage of the processing of extrudate in that the agglomerated wet powder mass is formed into spheroids, which maintain their size and shape for a period of time sufficient to provide a reproducible pellet product. Heng et al. (2002) clearly found that the design of the rotary plate influenced the characteristics of the pellets. It might hence be expected that the design of the plate in an extrusion/spheronization system could also influence the pellets produced. Heng et al. (2002) noted that the greatest extent of adhesion of the wet powder mass to the plate occurred with the plate that had the smallest size of teardrop studs. With the formulation and conditions used in the current study, there was no adherence

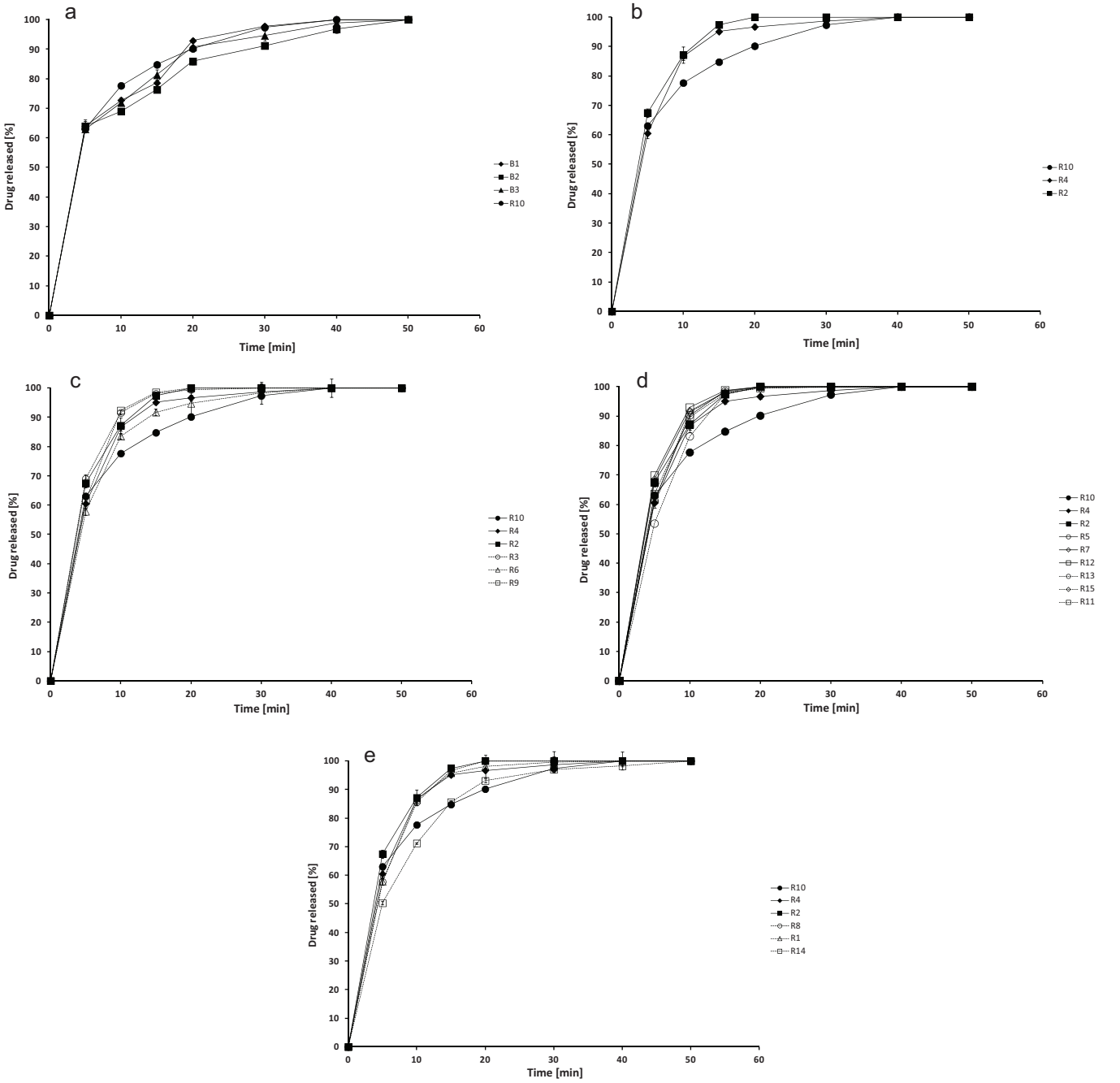

Fig. 5. Drug dissolution profiles for pellet batches produced with varying production parameters (see Table 1). (a) Test of reproducibility; (b) spheroniser plate pattern; (c) spheroniser lid closed or open; (d) spheroniser loading; (e) extruder screen size.

to the plate. As adhesion could occur with formulations used in the process of extrusion and spheronization, this factor should be considered in the choice of the plate design.

3.7. Drug dissolution

All pellet batches released the drug completely within 50 min, and in most instances 75% of the drug was released in less than 10 min. As a result the dissolution profiles are very similar. They are shown in Fig. 5 and the values for the Area under the dissolutions curves (AUC) are reported in Table 1. The values for the Mean Dissolution Time were all between 5 and 6 min and are hence of little value. Statistical comparison is hence based on the AUC values only.

As can be seen from Fig. 5a, the diclofenac sodium dissolution was reproducible for the three test batches and batch R10 of the main experimental design. ANOVA did not detect a significant difference between the AUC values. The dissolution of the drug from pellets produced using the cross-hatch plate (batch R10) is significantly slower ($F = 18.24$; $p < 0.001$) than that from pellet batches R4 (radial plate) and R2 (striated edge plate; Fig. 5b). When the spheroniser lid remained open, the drug release from the cross-hatch pellet batch (R3) became similar to the drug release from the other batches (Fig. 5c). Plate loading did also only affect pellets produced with the cross-hatch plate (Fig. 5d) i.e. under and overloading of the spheroniser by 50% resulted in more rapid drug dissolution similar to that found for pellets produced with the radial or striated edge plate. Using a 1 mm extruder screen the AUC values increased

in the order cross-hatch < radial < striated edge plate. When the extrudates were prepared using the 1.5 mm screen, this trend was reversed (Table 1). As can be seen from Fig. 5e, the drug dissolution profiles of pellet batch R10 (cross-hatch, 1 mm screen) and batch R14 (striated edge, 1.5 mm screen) are similar but distinctively different from those obtained from the other pellet batches. When comparing the AUC values with the values for the median pellet size (Table 1) it was found that pellets with a smaller median pellet diameter up to 1.12 mm released the drug more rapidly than those with larger median pellet diameters, indicating that the effects seen are mainly related to the surface area of the pellets, in line with Noyes–Whitney's law (1897).

4. Conclusions

The pattern of the friction plate used in the spheronization of extrudates affects the properties of the pellets. Yield values can vary by up to 20%, and for an otherwise optimised formulation the use of a striated edge plate appears advantageous in this respect. However, these pellets have a reduced mechanical strength despite their lower porosity, which might be disadvantageous. In addition, other factors such as the amount of extrudate loaded into the spheroniser, the maintenance of a constant moisture content within the spheroniser and the size of the extruder screen influence these findings significantly. The only physical property of the pellets that seems not to respond to the various changes in the manufacturing process of the pellets is the pellet shape, which remained spherical. The dissolution of the drug appears to be related to the median pellet size and is only marginally affected by changes in the spheronization process.

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