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The influence of four selected processing and formulation factors on the production of spheres by extrusion and spheronisation

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Summary

A factorial designed experiment has been used to investigate the effect of formulation and extrudate production variables on the properties of spheroids produced by extrusion and spheronisation. The variables were the Avicel and water content of the formulation (which also contained lactose, and indomethacin as a model drug), extrusion speed and die length. The effects that were investigated were the force required for steady-state extrusion (ram extruder), the shape and size distribution of the spheroids, and the drug release profile from the products. The most important variable was found to be the water content, in particular the water content at the die wall during extrusion (and presumably at the surface during subsequent spheronisation) was found to be important. Factors which may be expected to decrease water availability at the die wall (decreased water and Avicel contents, increased extrusion speed and die length) were found to have detrimental effects on the product (in terms of size distribution and shape). All the variables had some effect on the dissolution performance of the spheroids, but those due to die length and extrusion speed were only significant when the Avicel content was low and the water content high.

Introduction

The processes of extrusion and spheronisation allow the production of aggregates which have a high degree of sphericity. From a defined formulation and process it is possible to produce spheres of a uniform narrow size distribution, smooth surface and reproducible density. Such properties offer advantages for the production of multi-particulate oral drug delivery systems, and are also potentially useful as a well controlled granulation for tabletting.

The production of a sphere with desirable properties (e.g., optimised shape and size) is highly dependent on the formation of a good extrudate, however, not all good extrudates will produce a good sphere. Selection of the formulation and processing conditions that will produce good extrudate and good spheres of desirable properties is by no means straightforward, as in some cases increasing one factor may, for example, improve the quality of the extrudate, but may have a detrimental effect on spheronisation. It has been shown that a balance between plasticity and brittleness must be achieved in the formula-

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tion (Harrison, 1982; Chapman, 1985). The plasticity of the mass is usually achieved by use of certain proportions of microcrystalline cellulose (MCC) (routinely Avicel PH-101) and water. A mass consisting of only MCC and water will extrude, however, even though it spheronises, the presence of a third component in the formulation can be beneficial. Previous workers (Harrison, 1982; Chapman, 1985; Fielden, 1987) have used lactose for this purpose, but other excipients, or excipient/drug mixtures, may be acceptable.

Chariot et al. (1987) have utilised a factorial designed experiment to investigate the variation in yield of spheroids as a consequence of processing variables in both the extrusion and spheronisation stages, resulting in the ability to define limits for formulation variables which in combination would result in a good yield of spheroids. Processing variables also have significant influences on the properties of the extrudate and the spheres, for example, Malinowski and Smith (1974) noted that certain changes in processing resulted in differences in the hardness and dissolution properties of tablets that were compressed from spheroids.

The aim of this study is to consider a combination of changes in formulation and processing on the properties of the final spheroid. To limit the processing variables, the spheronisation stage has been standardised and only variables in the extrusion process are considered. The factors that have been investigated are: (1) Avicel PH-101 content, (2) water content (formulation factors), (3) die length (with fixed radius) and (4) extruder speed (processing factors). Indomethacin was selected as a model drug.

Materials and Methods

Materials

The model drug (indomethacin; Bechpharm) was found to have a median particle size of 57.0 ± 1.86 μm ($n = 3$) as measured by a Malvern Master Sizer. Its melting range was 154.3–155.8°C (Mettler hot stage mounted on an Olympus microscope) which means that the drug is in polymorphic form II (O'Brien et al., 1984). Lactose EP (Meggle-Wasseburg, Germany) had a particle size of 16.8 ± 0.35 μm (Malvern) ($n = 3$). The microcrystalline cellulose was Avicel PH-101 (FMC Corp., U.S.A.), which had a median particle size of 53.8 ± 0.54 μm ($n = 3$). All water used was freshly distilled, and pH control was achieved by use of phosphate buffers BP.

Methods

Production of the spheres

Avicel, lactose, and indomethacin were mixed for 20 min (Turbula mixer T2C): this time was selected as it was found to give the most uniform distribution (assessed by sampling from different positions in the container at different times, dissolving the sample and assaying for indomethacin at a UV wavelength of 264 nm (Perkin Elmer spectrophotometer)). The dry mixture was then transferred to a planetary mixer (Kenwood Chef) and the wet mass was produced by adding the water and stirring at 90 rpm for 10 min. The formed wet mass was allowed to stand for 12 h in a sealed plastic bag to ensure good water distribution.

The mass was extruded using a ram extruder mounted in a mechanical press (Lloyd Instruments, MX 50) which was fitted with a 50 kN load cell. The ram extruder consisted of a stainless-steel barrel of 2.54 cm internal diameter and 20 cm length, with a centrally mounted die (radius 1 mm) in the base plate. The press was used to press a piston into the barrel (at a defined constant rate), and thus to extrude the wet mass through the die. The force exerted to move the piston at a constant rate was recorded, via the load cell, using an IBM compatible PC.

High and low values for the four variables (Avicel and water content, die length and extrusion speed) were selected (see Table 1), and a factorial design was prepared for the experiment. These variables can only be adjusted within very narrow limits, beyond which it becomes impossible to extrude and/or spheronise the mass. Work by Harrison (1982) has demonstrated that there is a linear relationship between the required pressure for extrusion (at steady state) and the

TABLE 1

Outline and experimental conditions for the factorial design [a]

Factor	Value	
	Low level (−)	High level (+)
A (avicel)	3 [b]	5 [b]
W (water)	1:1 [c]	1:1.12 [c]
L (die length; mm)	2	8
S (extrusion speed; mm/min)	200	400

[a] Lactose and Indomethacin contents were kept constant at 4 and 1 parts in the formulations, respectively.
[b] Number of parts of microcrystalline cellulose in the formulations.
[c] Relationship between microcrystalline cellulose and water in the formulations.

length-to-diameter ratio of the die (in the length-to-diameter ratio range from 1 to 16). The lengths of dies were selected to keep within this range. The extrusion speeds of 200 and 400 mm/min reflect the approximate extremes for which it is possible to achieve a steady-state flow of extrudate. At present, the upper and lower limits for Avicel content in the formulation are unknown; the proportions used do not necessarily reflect extreme values. Equally, the water content values, which are added as a ratio to Avicel content (not total weight of the formulation), are not necessarily extreme limits for the formulation.

The extrudate was spheronised on a 27.5 cm diameter spheroniser (Caleva), for 20 min at 1000 rpm using a radial plate. The spheroniser was only partially covered to allow water vapour to escape. The processing parameters relating to spheronisation were not varied. The spheres were dried, at 60°C in a laboratory fluid bed drier (PRL Engineering).

Characterisation of the process and products

The extrusion was monitored by measuring the force exerted during, and the duration of, the steady-state phase (extrusion has been classified as an initial phase during which consolidation occurs, then steady-state flow and finally forced flow; see Harrison et al. (1985)).

TABLE 2

Calculation matrix for a 2^4 factorial design

Factor [a]	Level [b]				Level of interactions [c]										
	A	*W*	*L*	*S*	*AW*	*AL*	*WL*	*AS*	*WS*	*LS*	*AWL*	*AWS*	*ALS*	*WLS*	*AWLS*
awls	−	−	−	−	+	+	+	+	+	+	−	−	−	−	+
Awls	+	−	−	−	−	−	+	−	+	+	+	+	+	−	−
aWls	−	+	−	−	−	+	−	+	−	+	+	+	−	+	−
AWls	+	+	−	−	+	−	−	−	−	+	−	−	+	−	+
awLs	−	−	+	−	+	−	−	+	+	−	+	−	+	+	−
AwLs	+	−	+	−	−	+	−	−	+	−	−	+	−	+	+
aWLs	−	+	+	−	−	−	+	+	−	−	−	+	+	−	+
AWLs	+	+	+	−	+	+	+	−	−	−	+	−	−	−	−
awlS	−	−	−	+	+	+	+	−	−	−	−	+	+	+	−
AwlS	+	−	−	+	−	−	+	+	−	−	+	−	−	+	+
aWlS	−	+	−	+	−	+	−	−	+	−	+	−	+	−	+
awLS	−	−	+	+	+	−	−	−	−	+	+	+	−	−	+
AWlS	+	+	−	+	+	−	−	+	+	−	−	+	−	−	−
AwLS	+	−	+	+	−	+	−	+	−	+	−	−	+	−	−
aWLS	−	+	+	+	−	−	+	−	+	+	−	−	−	+	−
AWLS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

[a] *a/A*, *w/W*, *l/L* and *s/S* represent MCC content, water content, die length and extrusion speed at low and high levels, respectively.
[b] −, factor at low level; +, factor at high level.
[c] To obtain signs for interaction terms in combination multiply signs of factors.

The products were assessed in terms of their particle size distribution (Endecott analytical sieves, after shaking for 10 min) and their shape. The shape, in terms of sphericity of the spheroids, was quantified using the one plane critical stability (OPCS) model (Chapman et al., 1988). According to Chapman (1985) the OPCS method is the most appropriate indicator of sphericity. Essentially, this is the smallest angle from horizontal that would be required in order to force the spheroid to roll. Products with a low OPCS tend towards perfect spheres, and are thus good formulations (in that they produce uniform product in terms of shape, and usually size).

Drug release from the spheres was investigated in a USP paddle apparatus (Pharmatest), under sink conditions, stirring at 100 rpm with a phosphate buffer (BP, pH 7.4) at 37°C.

Results and Discussion

The results have been analysed using the ANOVA approach of Yates (1937). The interactions of effects associated with the factorial design experiments are indicated in Table 2.

Extrusion force at steady state

The effects of changes in Avicel and water contents, die length and extrusion speed on the force required at steady-state flow during extrusion are listed in Table 3. An increase in MCC

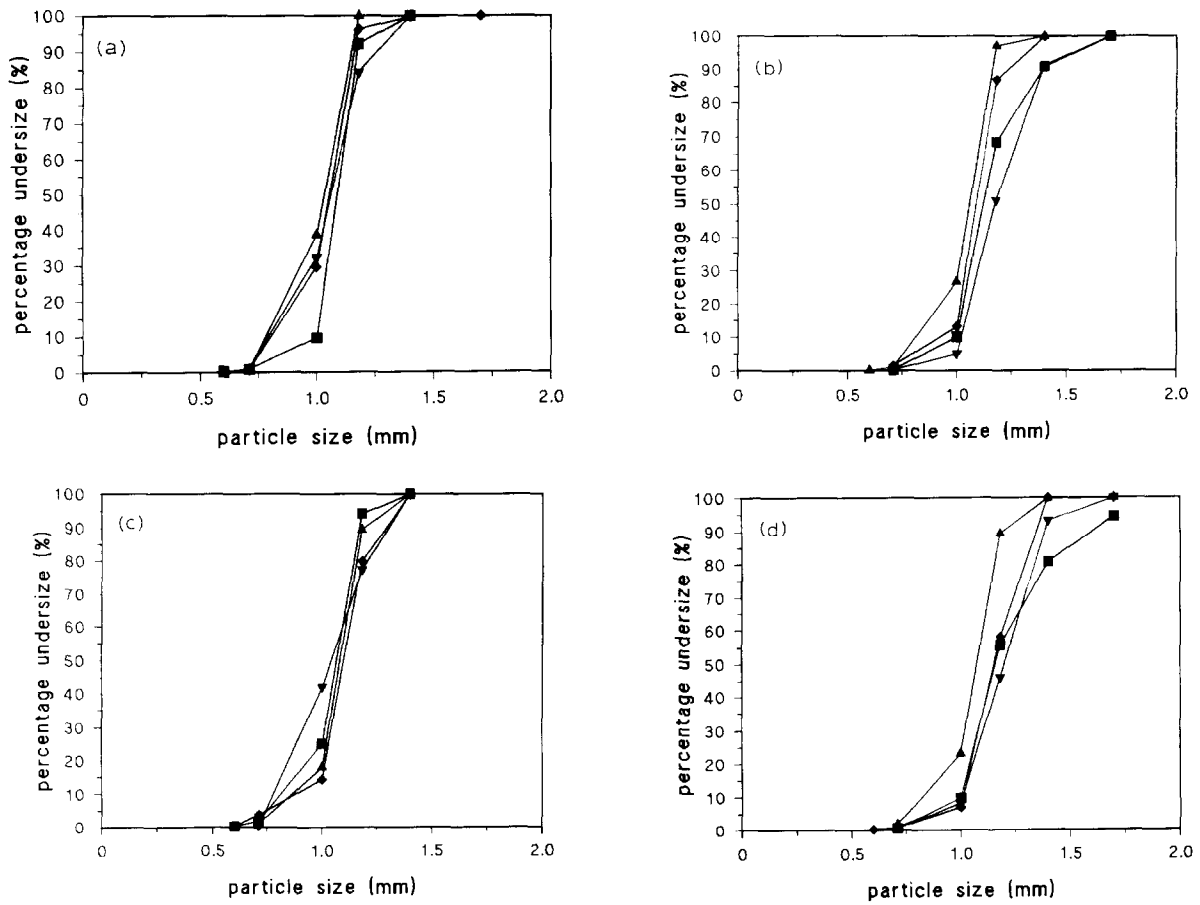

Fig. 1. Particle size distributions for the spheres. Percentage undersize of the spheres as a function of particle size (mm). Panel a: (■) *awls*, (▲) *awlS*, (▼) *awLs*, (◆) *awLS*; panel b: (■) *aWls*, (▲) *aWlS*, (▼) *aWLs*, (◆) *aWLS*; panel c: (■) *Awls*, (▲) *AwlS*, (▼) *AwLs*, (◆) *AwLS*; panel d: (■) *AWls*, (▲) *AWlS*, (▼) *AWLs*, (◆) *AWLS*.

TABLE 3

Results and ANOVA for the 2^4 factorial design (the effects of Avicel content (a / A), water content (w / W), die length (l / L) and extrusion speed (s / S) over the extrusion force at steady state)

Factor	Extrusion force (kN)	df	Effect	Mean sq.	F [a]
awls	9.9	1	19.11		
Awls	7.4	1	−0.438	0.766	17.95 [c]
aWls	6.4	1	−0.338	0.456	10.69 [c]
AWls	4.3	1	1.263	6.376	149.44 [b]
awLs	13.8	1	0.038	0.006	
AwLs	10.9	1	−0.163	0.106	
aWLs	7.9	1	0.563	1.266	29.67 [c]
AWLs	5.8	1	−2.813	31.64	741.56 [b]
awlS	13.3	1	2.513	25.25	182.98 [b]
AwlS	7.1	1	1.963	15.41	111.64 [b]
aWlS	9.1	1	4.063	66.02	1547.3 [b]
awLS	18.8	1	0.963	3.706	86.86 [b]
AWlS	5.3	1	−2.563	26.27	190.33 [b]
AwLS	10.1	1	−0.063	0.016	
aWLS	12.5	1	0.538	1.156	27.09 [c]
AWLS	10.3	1	−2.913	33.93	795.23 [b]

[a] EMS (error mean square) based on *awLs*, *AwLs* and *AwLS* interactions; 3 degrees of freedom (df).
[b] $p < 0.01$.
[c] $p < 0.05$.

content (designated *a* to *A*), or the water content (*w* to *W*) results in a decrease in the required extrusion force. These effects are found to be almost additive, as an increase in both MCC and water content shows a large reduction in required force. However, increases in die length or extrusion speed resulted in increased force requirements especially when these were both raised simultaneously. The combined effect of the four variables showed a significant interaction ($p < 0.01$), not surprisingly, indicating that the effects of water and MCC are not equal and opposite to those of die length and extrusion speed.

No significant interaction ($p < 0.05$) was detected between MCC content and die length, which is as expected as these have opposite effects and there is no obvious reason for the two effects to be dependent upon each other, but there was an interaction between water content and extruder speed. During the extrusion process, the water acts as a die wall lubricant, and thus it is possible that when the speed is increased water is unable to move through the mass rapidly enough to provide effective lubrication; i.e., at high speeds of extrusion, water remains evenly distributed throughout the mass, whilst at slower speeds it can migrate to the edge of the mass to effect lubrication.

Sphere size

The extrusion-spheronisation process is capable of producing spheres of uniform shape and of very narrow particle size distribution (Reynolds, 1970), thus any minor changes in median particle size can be regarded as significantly different. The particle size distributions of the 16 formulations are presented in Fig. 1 (a–d).

The formulations with higher water content were found to have the most significant variation in size (Fig. 1a–d). This observation is confirmed in the ANOVA table (Table 4), i.e., as water content increases, the median sphere size, and the size distribution increase. Indeed, the water content used in this study is strictly limited by the ability to extrude and spheronise; too much water will result in aggregation during spheronisation and too little water will result in unsuccessful extrusion (Bains et al., 1991). It is reasonable to postulate that the differences in size are a consequence of both water content and the effectiveness of the water distribution in the extrudate (and by extension the spheres). It has been reported above that increases in extruder speed result in higher extrusion forces due to poor die wall lubrication (i.e., poor water distribution to the die wall). From Table 4, it can be seen that increased extrusion speed results in smaller spheres, reflecting the reduced water distribution, to the surface of the extrudate. Furthermore, these 'drier' extrudates resulted in spheroids with a higher percentage of fine particles, indicating that the extrudate breakage was not optimum.

The effects of MCC content and die length on sphere size were minimal (Table 4), but notably, the effect of MCC was greater in formulations which were prepared with high water content (e.g., the median sizes for (*awLs*) and (*AwLs*) were both 1.08 mm, but for (*aWls*) and (*AWls*) they were 1.18 and 1.25 mm, respectively). It can

TABLE 4

Results and ANOVA for the 2^4 factorial design (the effect of Avicel content (a / A), water content (w / W), die length (l / L) and extrusion speed (s / S) over the spheres' median size)

Factor	Size (mm) (IQR)	df	Effect ($\times 10^3$)	Mean sq. ($\times 10^3$)	F [a]
awls	1.09 (1.02–1.15)	1	2226.0		
Awls	1.07 (0.99–1.12)	1	26.3	2.76	67.71 [b]
aWls	1.18 (1.05–1.25)	1	68.8	18.91	450.24 [b]
AWls	1.25 (1.06–1.35)	1	13.8	0.76	18.10 [c]
awLs	1.08 (0.92–1.15)	1	18.8	1.41	33.57 [c]
AwLs	1.08 (0.88–1.17)	1	3.8	0.06	
aWLs	1.18 (1.08–1.32)	1	1.3	0.006	
AWLs	1.20 (1.08–1.31)	1	1.3	0.06	
awlS	1.04 (0.89–1.11)	1	−56.3	12.7	302.38 [b]
AwlS	1.08 (1.01–1.14)	1	8.8	0.31	7.38
aWlS	1.06 (0.99–1.12)	1	−53.8	11.6	276.19 [b]
awLS	1.06 (0.94–1.12)	1	−13.8	0.76	18.10 [c]
AWlS	1.08 (1.01–1.14)	1	31.3	3.9	92.86 [b]
AwLS	1.11 (1.02–1.17)	1	11.3	0.51	12.14 [c]
aWLS	1.09 (1.04–1.15)	1	13.8	0.76	18.10 [c]
AWLS	1.16 (1.06–1.27)	1	18.8	1.41	33.57 [c]

[a] EMS based on *AwLs*, *aWLs* and *AWLs* interactions; 3 df.
[b] $p < 0.01$.
[c] $p < 0.05$.
IQR, inter-quartile range.

TABLE 5

Results and ANOVA for the 2^4 factorial design (the effect of Avicel content (a / A), water content (w / W), die length (l / L) and extrusion speed (s / S) over the roll of the spheres)

Factor	Roll	df	Effect	Mean sq.	F [a]
awls	18.7	1	37.06		
Awls	14.6	1	−0.0125	0.0006	
aWls	13.4	1	−0.863	2.98	32.84 [c]
AWls	16.9	1	5.213	108.7	1199.4 [b]
awLs	24.6	1	−2.213	19.58	216.1 [b]
AwLs	18.7	1	−2.638	27.83	307.1 [b]
aWLs	14.0	1	−2.938	34.52	381.0 [b]
AWLs	13.7	1	−4.613	85.10	939.2 [b]
awlS	25.7	1	3.423	46.58	514.1 [b]
AwlS	15.4	1	1.688	11.39	125.7 [b]
aWlS	15.5	1	3.788	57.38	633.3 [b]
awLS	36.9	1	1.913	14.63	161.5 [b]
AWlS	17.3	1	−4.063	66.02	728.6 [b]
AwLS	16.7	1	−1.238	6.126	67.61 [b]
aWLS	19.1	1	0.213	0.1806	
AWLS	15.3	1	−4.113	67.65	746.6 [b]

[a] EMS based on *Awls* and *aWLS* interactions; 2 df.
[b] $p < 0.05$.
[c] $p < 0.1$.

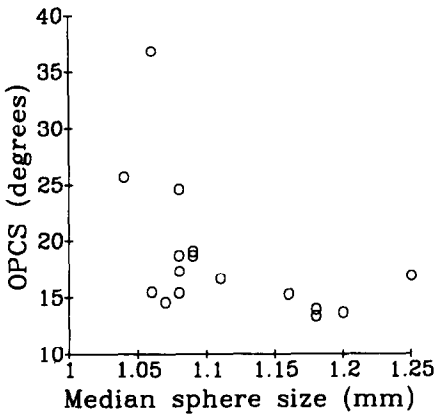

Fig. 2. OPCS as a function of median sphere size.

be concluded that the water content, and its associated distribution to the extrudate surface, is the critical factor in determining size, thus the factors which cause the die wall to be wetter result in spheres of increased size (i.e., primarily increased water content, but also slower speed, and the increased content of the 'molecular sponge' MCC).

Sphere shape

The value obtained for OPCS was found to decrease following increases in MCC content, water content and die length (although the MCC content was seen to have the smallest effect of the three). The most spherical products were obtained from formulations in which the conditions may be expected to encourage the extrudate to be wet at the surface. The ANOVA analysis is presented in Table 5.

Generally, it was observed that low OPCS values were found for formulations which had a narrow size distribution (see interquartile ranges in Table 4) (there is only a general trend between median size and OPCS, as indicated in Fig. 2), thus the factors discussed above under sphere size are also relevant to the discussion on sphere shape.

Dissolution

As all the factors that have been investigated (i.e., MCC and water content, die length and extruder speed) have been shown to influence the product that is produced (to a greater or lesser extent), in terms of size and shape, then it is not unreasonable to assume that changes in formulation and production variables may influence dissolution performance (and consequently possibly cause changes in biological response).

When plotted on a semi-logarithmic scale, all formulations approximated to first-order release kinetics over the first 80% of release. The apparent first-order rate constants are presented in Table 6. It is clear from the apparent first-order rate constants that the formulations can be divided into four distinct groups. The slowest release of drug was obtained from formulations which had a high Avicel content and were made using a low water content; for these formulations the rate constants were in the range $4.9–5.5 \times 10^{-5}$ s^{-1} (equating to 70% drug release in just under 3 h). Of very similar release rate were the formulations with high Avicel content which were prepared with the high level of water; these also had dissolution profiles which resulted in 70% release in just under 3 h (apparent first-order release rates were in the range $6.1–6.7 \times 10^{-5}$

TABLE 6

Apparent first-order rate constants for drug release from the different formulations, and the gradient of double-logarithmic plots of release as a function of time (after Korsmeyer et al., 1983)

Factor	First-order plot		Korsmeyer plot	
	k ($\times 10^5$) (s^{-1})	r	Gradient	r
awls	8.0	0.968	0.42	0.999
Awls	5.4	0.930	0.44	0.999
aWls	7.2	0.935	0.49	0.995
AWls	6.4	0.934	0.52	0.999
awLs	7.9	0.939	0.42	0.992
AwLs	5.4	0.939	0.42	0.999
aWLs	11.0	0.919	0.40	0.973
AWLs	6.3	0.924	0.52	0.996
awlS	7.9	0.965	0.42	0.999
AwlS	4.9	0.965	0.36	0.999
aWlS	7.8	0.962	0.41	0.999
awLS	7.7	0.988	0.39	0.997
AWlS	6.7	0.949	0.44	0.999
AwLS	5.5	0.946	0.43	0.999
aWLS	6.7	0.952	0.43	0.996
AWLS	6.1	0.961	0.39	0.999

s^{-1}). It is not surprising that the formulations with high Avicel content had the slowest release profiles, as the MCC causes the formation of a hydrophilic matrix sustained release delivery system. When the Avicel content was high, there was little effect of other variables (i.e., die length and extrusion speed) on the release profiles (the differences being indistinguishable within experimental error). The major differences in release rate are observed for formulations which have low Avicel content. These can also be divided into two groups, one which was prepared with low water content (70% release in just under 2 h, apparent release rate constants in the range 7.7–8.0×10^{-5} s^{-1}), and those which were prepared with high water content for which there was the greatest variation in apparent release rates (i.e., the greatest influence of die length and extrusion speed). The fastest release was from formulation aWLs: 70% release in just over 1 h, apparent release rate constant 11.0×10^{-5} s^{-1}; whilst the apparently minor change from slow to fast extrusion rate resulted in an apparent release rate constant of 6.7×10^{-5} s^{-1}. The release profiles for the formulations prepared with low Avicel

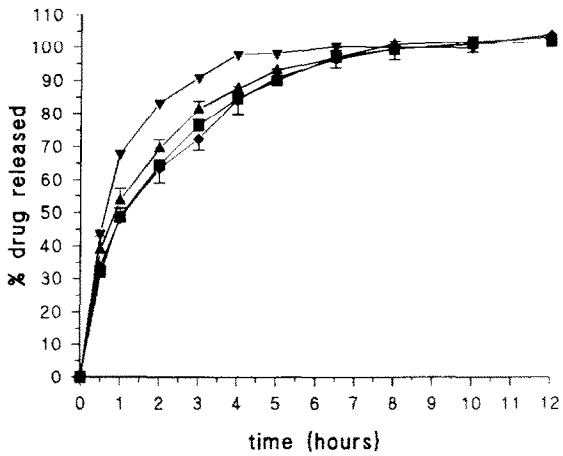

Fig. 3. Release profiles of drug from formulations with low Avicel and high water content. (■) *aWls*, (▲) *aWlS*, (▼) *aWLs*, (◆) *aWLS*.

TABLE 7

Results and ANOVA for the 2^4 factorial design (the effect of Avicel content (a / A), water content (w / W), die length (l / L) and extrusion speed (s / S) over the release constant of the drug from the spheres)

Factor	k ($\times 10^5$) (s^{-1})	df	Effect ($\times 10^5$)	Mean sq. ($\times 10^5$)	F [a]
awls	8.0	1	13.8		
Awls	5.4	1	−1.94	15.02	534.09 [b]
aWls	7.2	1	0.94	3.516	125.06 [b]
AWls	6.4	1	0.39	0.194	6.90
awLs	7.9	1	0.04	0.0056	
AwLs	5.4	1	−0.31	0.391	13.91 [d]
aWLs	11.0	1	0.21	0.181	6.44
AWLs	6.3	1	−0.79	2.481	88.24 [c]
awlS	7.9	1	−0.54	1.156	41.12 [c]
AwlS	4.9	1	0.71	2.031	72.24 [c]
aWlS	7.8	1	−0.11	0.0506	
awLS	7.7	1	0.49	0.951	33.83 [c]
AWlS	6.7	1	−0.86	2.976	105.85 [b]
AwLS	5.5	1	0.64	1.626	57.83 [c]
aWLS	6.7	1	−0.74	2.176	77.40 [c]
AWLS	6.1	1	0.21	0.106	3.77

[a] EMS based on *awLs* and *aWlS* interactions; 2 df.
[b] $p < 0.01$.
[c] $p < 0.05$.
[d] $p < 0.1$.

and high water content are presented in Fig. 3, which includes an indication of error (expressed as ± the standard deviation). The dissolution profiles demonstrate that in certain cases the processing effects can have an influence on the drug release rate. This is particularly true when the release is rapid, but becomes far less significant if the release is slow (i.e., when Avicel content is high). Considering that formulation and processing variables can alter the size and shape of the particles, it is perhaps to be expected that the dissolution will be altered. However, if the apparent first-order release rates are plotted as a function of either median size, or OPCS there is no obvious correlation (not shown), thus demonstrating that the changes in dissolution are not simply a consequence of minor changes in size.

Malinowski and Smith (1974) have also reported that processing variables can influence the properties of the formed product (in that case a tablet produced from spheroids that were prepared by extrusion and spheronisation), however, the current study demonstrates that the effect of processing variables may only be significant when certain formulation variables are selected.

The fit to a double-logarithmic plot of % released as a function of time (Table 6) was, however, much better than the first-order plots with correlation coefficients in the order of 0.999. The gradients of the double-logarithmic plot allow some details of the release mechanism to be described. A number of the formulations have a gradient tolerably close to that which is indicative of a Fickian diffusion release process (i.e., a gradient of 0.43; see Ritger and Peppas (1987)), whilst others have gradients in the range 0.43–1.00 which is described as anomalous (non-Fickian) diffusion (Ritger and Peppas, 1987). There is no obvious correlation between the formulation content and/or preparation method and the presence or absence of a Fickian diffusion mechanism. The presence of a diffusional release mechanism was expected as all the formulations remained as spherical ghosts on completion of drug release. Scanning electron microscopy clearly revealed that during dissolution, the soluble matter had been removed from the MCC ghosts producing large pores in the sphere surface.

Conclusion

The factors that have been investigated (Avicel and water content, extrusion speed and die length) can all influence the properties of the product that is formed. All the variables were held within limits that would allow the formation of spheres, and indeed major changes in any of these variables would prevent either extrusion or spheronisation from occurring.

The major factor in producing spherical particles is the presence of water at the surface of the extrudate. Factors which may be expected to decrease water at the die wall (decreased water and Avicel content, increased extrusion speed, increased die length) all had detrimental effects.

All of the variables were shown to have the potential to influence dissolution, but the effects of die length and extrusion speed were only significant when the Avicel content was low and the water content high. The water content that was present during processing remains significant even though it is removed by drying during the process, as the structure of the sphere has already been determined.

Although previous studies (e.g., Malinowski and Smith (1974)) have demonstrated the potential for processing effects to influence product performance, it is important to realise that the composition of the formulation can significantly influence the susceptibility to such effects.

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