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The influence of model drugs on the preparation of pellets by extrusion/spheronization: II spheronization parameters

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Abstract

Five drug-models, 4-parahydroxybenzoic acid (4HBA), methyl (MBA), propyl (PBA) and butyl (BBA) paraben and propyl gallate (PG), all of similar chemical nature, were mixed in different proportions (50–73.7%) with microcrystalline cellulose (MCC) (26.3–50%) plus various levels of water (26.9–50.0%). The wet powder mass was extruded and spheronized under standard conditions. The pellets produced were evaluated in terms of their median diameter, their modal size range, the % within a given size range (0.7–1.7 mm) and their shape factor. For the majority of formulations, all drug models, except 4HBA, produced pellets. This material only had two combinations of excipients that produced acceptable pellets. For all the model drugs, two combinations of formulations could be identified; (1) a combination, which produced pellets from all the model drugs and (2) a combination, which was too wet to produce pellets with any of the model drugs. Between these two extremes, whether pellets could be made and their quality varied with the model drug. Cluster analysis was able to divide the formulations into 4 clusters. In cluster 1 all the model drugs produced pellets except 4HBA; in cluster 2 all drugs produced pellets except MBA; in cluster3, pellets were produced with PBA, BBA and PG while MBA produced agglomerates and 4HBA was too dry; in cluster 4, MBA and BBA produced pellets, PBA produced agglomerates while 4HBA was too dry to pelletise and PG too dry to extrude. The five drug models showed different relationships between the median pellet size and drug-load and initial water content in the formulation. Cluster analysis indicated that, the level of water and type of model drug were the most significant factors in determining the pellet size. Three clusters could be identified, but the response to water content was drug dependent. It was not possible to identify a relationship between the force required to extrude the wet mass and the ability to produce good pellets nor their median size. All the products, which could be classified as good pellets, when produced, had a shape factor that can be considered to be indicative of a spherical shape. The most consistent material, in terms of spheronization, as represented by median diameter, size range and roundness, was propyl gallate (PG), which throughout all the formulations produced an almost constant value for shape factor and median pellet size, which in the majority of cases fell within a limited pellet size. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Cluster analysis; Model drugs (parabens); Spheronization; Water/microcrystalline cellulose ratio

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1. Introduction

Extrusion is the process of forcing a material through a narrow orifice. This process is used in many industries, among which is the pharmaceutical industry. Here, the extrudates manufactured from a paste by this process are subjected to a spheronization phase during which they are chopped and rounded to the final desired shape of a round pellet. After drying, the pellets, either coated or uncoated are then pressed to a form of a tablet or filled into capsules. The way in which extrusion and spheronization is carried out will affect the quality and uniformity of the pellets making interpretation of the literature to identify formulation rules rather difficult. There is the general concept that water solubility is a factor involved in predicting the quantity of water required when extrusion is carried out with long dies (Jover et al., 1996; Hileman et al., 1997; Lustig-Gustafsson et al., 1999) but the prediction of the processability from chemical structure remains elusive.

In a previous paper (Tomer et al., 2001), the extrusion properties of a series of model drugs of similar chemical structure established that there was a difference in behaviour of similar compounds. Even when extrudable, there are several factors that are involved to ensure that an extrudate is capable of being spheronized: (1) The extrudate must be uniform in its consistency. (2) The wet extrudate must be mechanically strong enough to survive the handling and collection, yet it must be brittle enough to be broken to short lengths in the spheronizer. (3) The extrudate must be plastic enough to enable the cylindrical rods to change shape to spheres while rolling on the spheronizer plate, yet rigid enough to retain its shape under normal handling conditions. (4) The extrudate must be non-adhesive to itself; otherwise an agglomeration will occur creating large sized pellets. (5) The extrudates should not stick to the spheronizer's plate or wall—an important feature if a continuous process is to be achieved.

To date there are no quantified measurements of these properties in relation to the way formulations function on the spheronizer plate. Hence even if a formulation can be extruded, it may not be possible to spheronizer the extrudate.

The spheronization process can take from 5 to 30 min, depending on the different variables (elasticity, plasticity, brittleness of material, plate speed, plate geometry, load, water content etc.). In an attempt to investigate the influence of inclusion of different drug to microcrystalline cellulose (MCC) and different solids to water ratios, a set of model drugs with similar chemical structure used in the previous study, were mixed with microcrystalline cellulose (MCC) in various ratios and blended with water and extruded under standard conditions. The extrudates from the wet masses, were spheronized under standard conditions, and the properties of the pellets produced evaluated. The choice of these particular model drugs was because the physico-chemical properties of solubility parameters had been derived previously (Tomer and Newton, 1999) and hence it might be possible to relate the performance in the process of extrusion/spheronization to their chemical structure. The level of drug incorporation is associated with the performance of the process. At drug levels lower than 50%, layering of non-pareil seeds might be considered to be a more economical process. It is at the higher drug loadings that extrusion/spheronization becomes competitive as a process, yet more difficult to undertake hence the level of drugs added commenced at 50% and increased to in excess of 70%.

2. Materials and methods

The five following materials of similar chemical structure were chosen as drug models: (1) *p*-hydroxybenzoic acid lot: 401251 (4HBA), (2) methyl paraben lot: M20225 (MBA), (3) propyl paraben lot: P7822 (PBA), (4) butyl paraben lot: N433 (BBA) and (5) propyl gallate lot: 4491 (PG), all manufactured by Nipa laboratories (Pontypridd, Mid Glamorgan, UK). The particle size of the model drugs was determined by image analysis (Seescan solitaire 512, Seescan, Cambridge, UK). The value as a number average of Feret diameter (an average of 32 values) was determined from 512 particles from each material. The following values were obtained (4HBA): 27.9 ± 14.0 μm, (MBA): 26.6 ± 19.7 μm, (PBA): 24.8 ± 14.3 μm,

(BBA): 44.1 ± 30.0 μm, (PG): 31.7 ± 13.1 μm. Values for the solubility parameters of the model drugs can be found in the paper by Tomer and Newton (1999).

The combinations of model drug, MCC (Avicel PH 101 lot 6521, FMC Corporation Cork Ireland) and water and the mixing of materials and the extrusion procedure is described by Tomer et al., 2001. A 1 mm diameter die, which was 4 mm in length, with a ram speed of 200 mm/min was used to produce the extrudate. After extrusion, the extrudates (approximately 100 g) were placed onto the plate of a spheronizer model: 120 (GB Caleva, Dorset, UK) fitted with a 12.00 cm plate of a cross-hatch geometry rotating at 1880 rpm. The spheronization time was 15 min, chosen to allow 'dry' formulations to round and provide 'wet' formulations with the opportunity to agglomerate. 'Good' formulations would round in a shorter time than this but would not agglomerate on extended spheronization. Formulations, which do not provide pellets under these conditions, are not satisfactory and it is extremely unlikely that any alterations in the spheronizing conditions would produce a satisfactory product. After 15 min the pellets were collected through the collection tube and were dried in a fluidised bed dryer (P.R.L. Engineering Ltd, Flintshire, UK) for 30 min at 60 °C, conditions, which ensured that added water had been removed.

2.1. Pellet size

The pellets were sieved through a nested set of sieves (BS410), arranged in a $\sqrt{2}$ progression from 0.5 to 2.8 mm, plus an additional sieve at 1.70, for 10 min using a mechanical sieve shaker (Endecots, London, UK). The pellets retained on each sieve fraction were collected and weighed. The method of sieving measures the minimum width of the particle, which may not be its actual diameter, e.g. in a case of an ellipse or dumbbells, the measured diameter would be their smallest diameter, i.e. their width. In the case of round pellets the sieving measurement would be the diameter. This method of size assessment is sufficient for this evaluation as the aim is to obtain a rough idea of the size of the pellets and most of the particles are nearly-rounded pellets. From the weight collected in each size fraction the median particle size from a cumulative % average graph and the % of pellets in the size range 0.71–1.70 mm was derived as representative of a size fraction of pellets, which could be used in practice.

2.2. Pellet shape

The shape of the pellets was measured using an Image Analyser (Seescan Sonata 512, Seescan, Cambridge, UK) fitted with a black and white camera (CCD-4 miniature video camera, Rengo Co Ltd, Toyohashi, Japan) and a zoom lens (18–108/2.5, Olympus Europe, Hamburg, Germany). A cold light source was used (Olympus Co, Hamburg, Germany) to illuminate the pellets from above against the black surface of a painted glass plate. The conditions employed complied with those recommended by Podczeck et al., 1999.

The image analyser will calculate the value of the shape factor e_r, which is a shape factor that takes into consideration both deviation of shape from sphericity and surface irregularities. This factor theoretically should equal 1.0 for a complete smooth and round particle, though in practice the projection of the three dimensional particle onto a two dimensional plane results in some deviations from the ideal value. It was found that the shape factor, which describes the perfect sphere, in the form of a 1 mm ball bearing, is 0.7. A value for the shape factor below 0.7 describes a deviation from a perfect circular shape or surface irregularity (Podczeck and Newton, 1994) but values above 0.6 can be considered to be satisfactory. The shape of 100 pellets from the modal size was measured.

3. Results and discussion

The overall evaluation of the effectiveness of the process in producing pellets from the range of formulations, is reported in Fig. 1, which presents the type of product produced for the different model drugs in four distinct categories of increasing water content:

1. unable to produce extrudate,

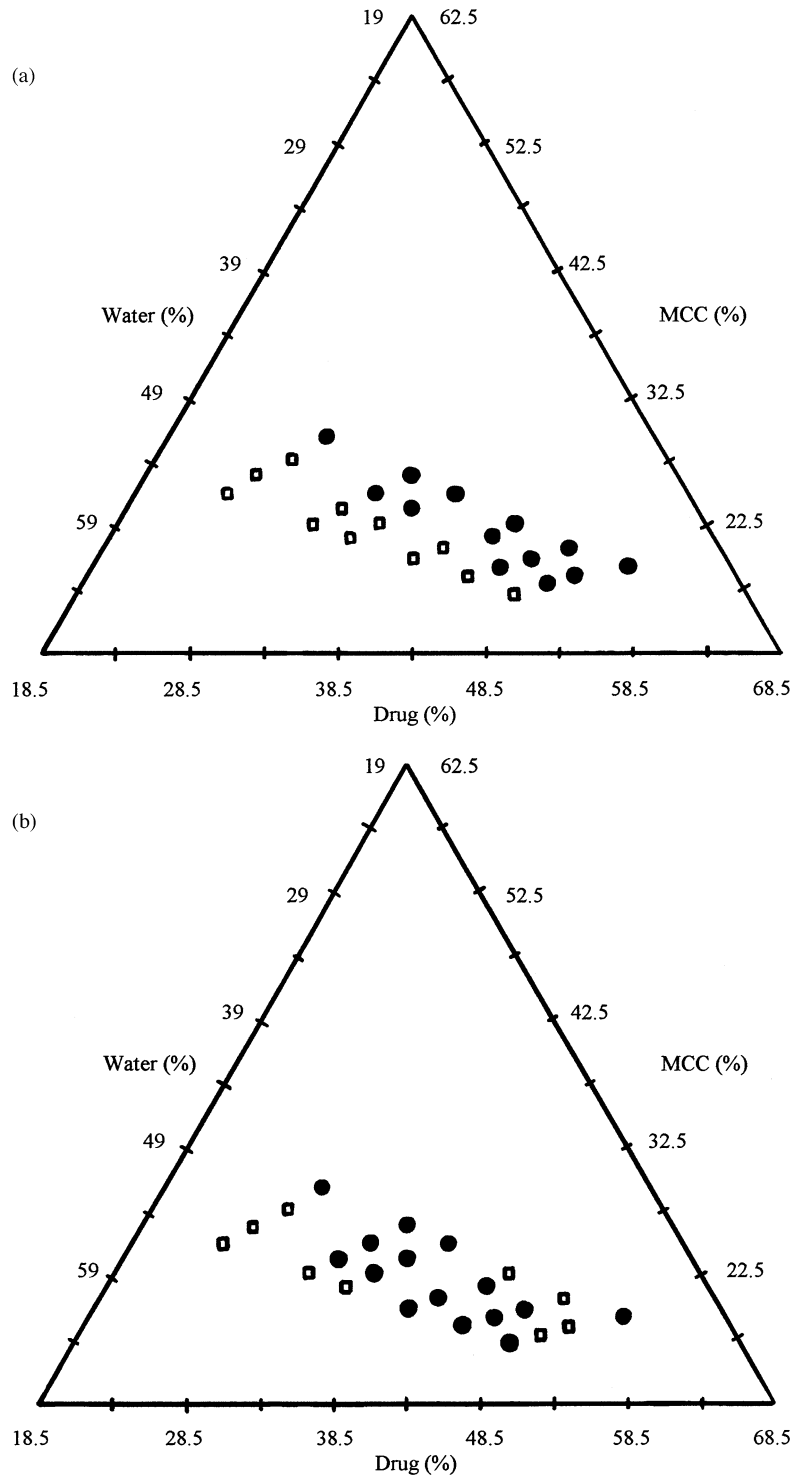
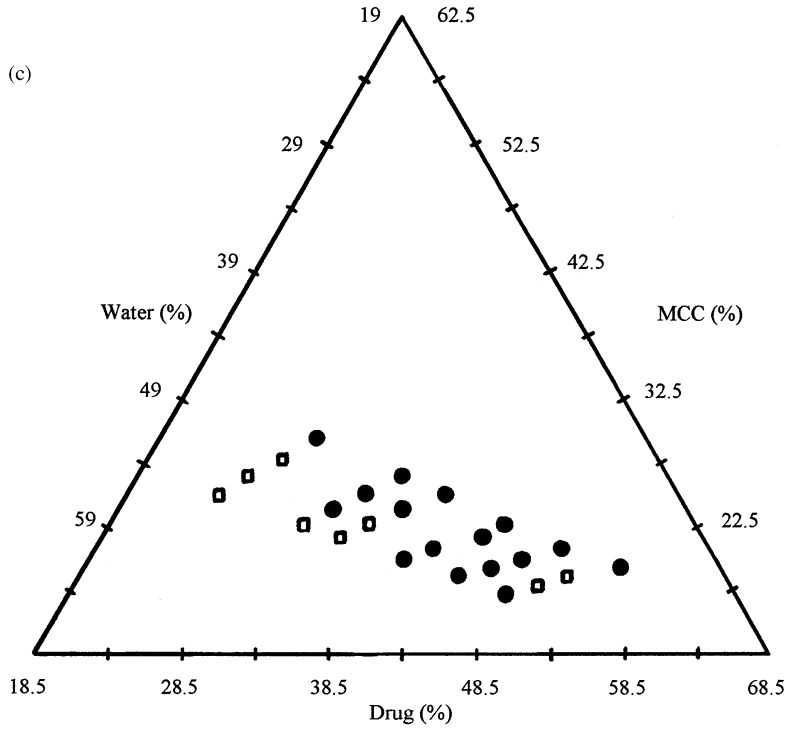


Fig. 1. The influence of water combinations on the products of combinations of model drugs and MCC for (a) MBA, (b) PBA, (c) BBA, (d) 4HBA and (e) PG. The grades of the process/products are; (1) unable to extrude +; (2) extrudable but the extrudate is too dry to spheronize □; (3) extrudable and produces pellets ●; (4) extrudable but forms agglomerates ○.



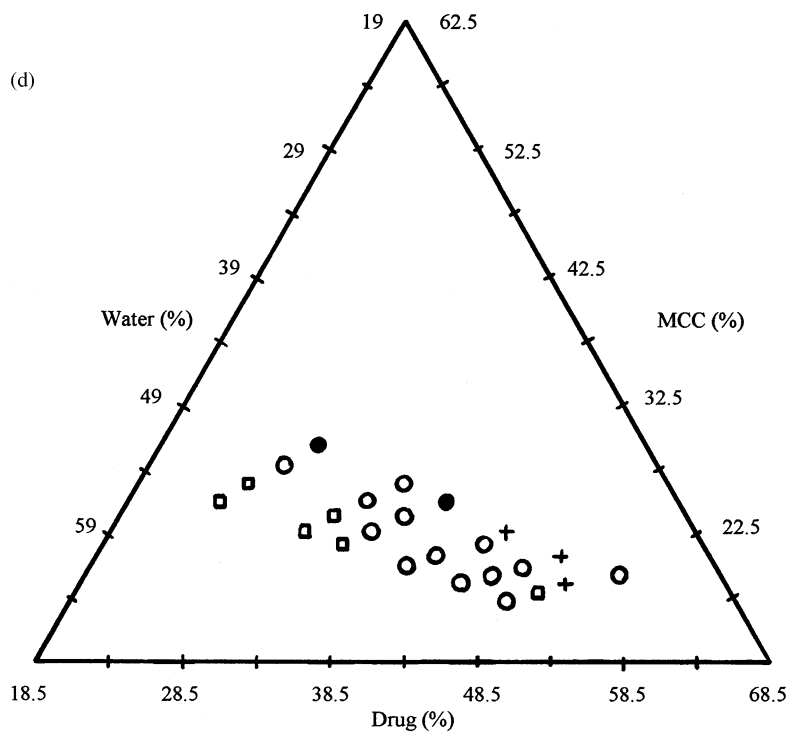


Fig. 1. (*Continued*)

2. extrusion possible but extrudate too dry to spheronize providing pellets with an aspect ratio of greater 2 or lost from the spheronizer plate,
3. pellets with a median size in the range 0.7–2.00 mm,
4. extrudate too wet to spheronize, resulting in agglomeration to give pellets with a median diameter greater than 2 mm.

The results clearly show the difference in behaviour of the model drugs, in terms of ease of processability. As described previously (Tomer et al., 2001), 4HBA and PG provide combinations, which will not extrude. 4HBA is unusual in that it is the only model drug which provides extrudate that is too dry to process. All the model drugs have combinations, which are too wet allowing agglomeration to occur. PG is different in that only 2 combinations are too wet while the other systems have more than a third of the combinations that are too wet. 4HBA is again unusual in that there are only two combinations, which provide satisfactory pellets. When the combination of variables, in terms of percentage of MCC plus model drug in ascending order of water content, with the same four categories are considered, at low water contents, below 30%, two of the model drugs, 4HBA and PG, fail to extrude at all. These two drugs showed the highest sensitivity to water levels in terms of extrusion force (Tomer et al., 2001). At the other end of the water level scale, i.e. above 40%, only PG formulations could be relied upon to produce pellets but even for this material once a water content of 46% had been exceeded, the extrudate was too 'wet' to prevent agglomeration. Calculation of the molar surface free energy for the drug molecules as described by Newton et al., 1993, 4HBA and PG provide the two extreme values of 4.02 and 5.98 kJ/mol, respectively. MBA, PBA and BBA have intermediate values (4.27, 4.80 and 5.11 kJ/mol, respectively). The molar surface free energy is smaller the more hydrophobic the drug. Hence, difficulty in extruding the 4HBA may be due to

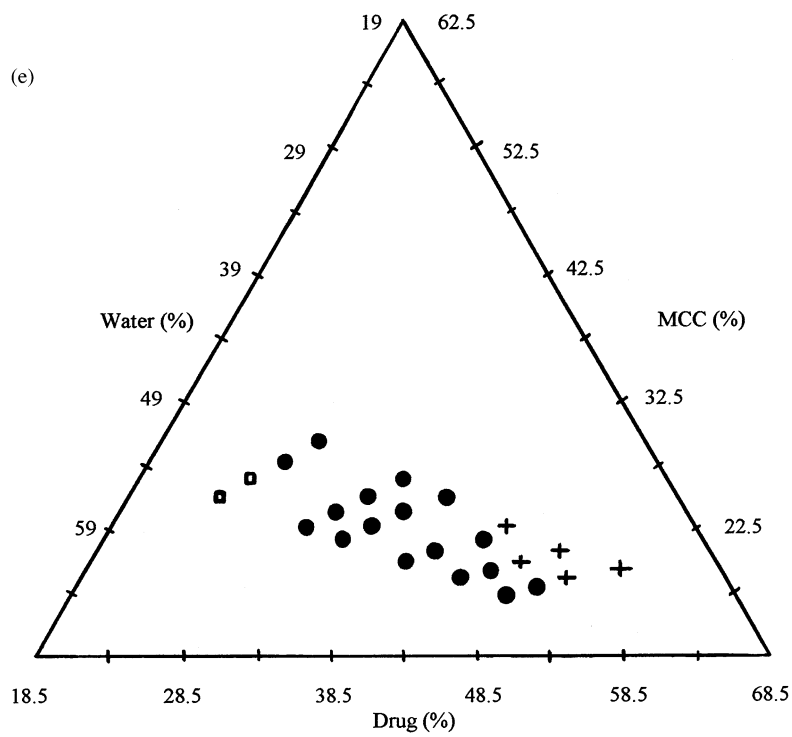


Fig. 1. (*Continued*)

the fact that the powder mass is not wetted homogeneously, especially at higher drug levels (see Fig. 1d). At lower water levels, MCC could be capable of holding the water with in its structure, leaving the powder mass without the liquid film necessary for lubrication of the extrusion process, whereas at intermediate and higher water levels, excess water would not wet the drug particles and hence be freely available to form liquid bridges to initiate pellet agglomeration on the spheronizer plate. At the other extreme, PG containing uniform wet masses might always provide homogeneously wetted powder with a thin film of water surrounding the drug particles. For the higher drug contents, the MCC could become starved of water required to plasticise the wet mass to allow extrusion.

Looking at the overall performance of the materials, in spite of the similar chemical nature of the model drugs, there are considerable differences in processability. Of all the combinations, only two successful products could be produced with 4HBA. One of the combinations did produce a successful product for all the model drugs (61.5% drug, 38.5% MCC and 35% water), the other (50% drug, 50% MCC and 41.2% water) was able to produce pellets for all the model drugs except MBA. At the other end of the range of behaviour, PG formed successful pellets in 17 of the 24 combinations. Two extremes, which limited the performance of this material were readily recognisable; a lower limit of the % of water, where extrusion could not be achieved($< 32.0\%$) and the upper end, a water level ($> 45.5\%$) which induced agglomeration.

In an attempt to rationalise the combinations of ingredients, which produced successful products, it was possible to identify a group of combinations in Fig. 1 which were successful for most of the model drugs. Between total water contents in the range 32.1 and 45.5% all combinations of PG produced satisfactory products. This involved formulations ranging from 50–73.7% PG ie. all ranges tested. Between the 34.5 and 41.2, all formulations containing 50–73.7% PBA and BBA (except 61.5% BBA) produced pellets. For MBA only 3 formulations produced pellets in this range of water contents, two products containing 58.3% and one containing 61.5% MBA. This particular model drug produced pellets at lower water contents (26.9–32.0%) with MBA contents ranging from 66.7 to 73.7%. For lower MBA contents, all formulations were too wet. The two formulations of 4HBA lie in the range (32.1–45.5%) of water contents, namely 35 and 41.2% water. Depending on 4HBA:MCC ratio, there were formulations that were both too wet and too dry within their overall water contents.

To clarify these effects, cluster analysis (SPSS version 10, SPSS Ltd Woking,UK) was performed on the data. The factors of drug, MCC, water and type of drug were all significant at 5% level. Four clusters were identified, which can be summarised in Table 1. Cluster 1 has the lowest drug content and an equivalent content of MCC and the highest water content. In this cluster, only 4HBA forms pellets while all the other drugs produce pellets, which have agglomerated. In cluster 2, which has a higher content of drug than MCC and a lower water content than cluster 1, all the drugs except MBA, which forms agglomerates, form pellets. In cluster 3, which has an even higher drug content and lower water content, PBA, BBA and PG form pellets, MBA forms agglomerates while HBA is too dry to produce spherical pellets. In the final cluster 4, which has the highest drug content and the lowest water content, MBA and BBA form pellets, while PBA produces agglomerates, for 4HBA the extrudate will not spheronize while PG systems will not even extrude. An attempt to relate the grade of performance to the steady state extrusion force, applying statistical procedures, failed. For the same extrusion force, it was possible to obtain different performances. For example, with an extrusion force of 8 kN, one combination of BBA/MCC/water agglomerated, while another combination produced good pellets and the same ratio of ingredients prepared with MBA was too dry. Certainly no pellets were prepared from extrudate, which was produced with an extrusion force below about 3 kN, but at the other end of the scale, with PG formulations, pellets could be produced with extrudate, which required 18 kN to extrude. Thus simple extrusion force measurements are insufficient to characterise the ability of extrudate to spheronize.

Table 1
Average spheronization performance of formulations in clusters of different drug, MCC and water for the 5 model drugs

Cluster	1	2	3	4
Factor	Average value			
Drug%	26.4	34.4	43.7	50.8
MCC%	26.4	24.4	20.6	19.3
Water%	47.3	41.1	35.7	30.0
	Grade of spheronization performance			
MBA	4	4	4	3
PBA	4	3	3	4
BBA	4	3	3	3
4HBA	3	3	2	2
PG	4	3	3	1
Number of cases in cluster	3	8	5	8

Spheronization performance grades: 1. not extrudable; 2. extrudable but will not produce pellets with an aspect ratio greater than 2; 3. pellets within the size range 0.71–2.00 mm; 4. pellets with a size above 2.00 mm.

The observations associated with Table 1 and Fig. 1, relate to the ability to prepare pellets over a relatively wide size range (0.7–2.0 mm). The question arises, whether there is further information to be gained by a more detailed consideration of the size and shape analysis. The results for the modal size fractions are presented in Table 2. Those formulations with acceptable pellets are identified as predominantly in the size fraction 1.40–1.70 mm, especially those produced successfully with PG, BBA and PBA. This implies that the extrudate 'chopped' into lengths longer than their diameter before rounding. The modal fraction is also often of this size range, but there are several products where this modal fraction is the next range down ie. 1.0–1.4 mm. MBA produces several successful pellets that have modal sizes less than 1.0 mm. Fluctuations in median size occur with MBA, PBA and BBA formulations, the size generally increasing as the total water content present increases. For PG however, the median size is quite consistent until agglomeration commences at higher water levels. Applying cluster analysis to the results in Table 3, indicated that best grouping of the median size results was obtained by considering only the water content rather than the solids components as a factor. The clusters grouped the results into three average water contents, see Table 3. The way the different model drugs were influenced by these three water levels differed. For MBA, there was a maximum size at the middle water level with smaller sizes at the other two levels. For 4HBA, PBA and BBA, the middle water level indicated the smallest average median size, with higher values at either side. For PG, there was a slight and consistent decrease in median size as the water level increased. In general one would think that this latter effect was the likely response as higher water levels tend to produce agglomeration. Dry extrudate can produce agglomeration when there is water migration during the extrusion resulting in extrudate, which is variable in water content. The three model drugs (MBA, PBA and BBA), which produced the same response, also provided similar extrusion force/composition relationships (Tomer et al., 2001). Formulations containing 4HBA and PG produced similar composition/extrusion force response, but very different spheronization response. Attempts to establish relationships between extrusion force and the median pellet size proved unsuccessful. The results are presented as scatter plots in Fig. 2 and illustrate why this is the case. The results show that 4HBA is very sensitive to extrusion force, the size increasing rapidly as the force decreases. For PG the median size does not appear to be influenced by the extrusion force. For the other three model drugs, there is no clear pattern.

A factor, which is of practical significance in addition to their size, is the range of the size produced. A good product will have a relatively narrow size range. To evaluate the quality of the pellets produced by the various formulation, the percentage of pellets in the size range 0.71–1.70 mm are presented in Table 4. In most cases, where pellets are produced, the quantity in the designated range was very high, indicating that the products were highly satisfactory.

A further indication of the quality of the pellets is their shape, values for which as represented by

Table 2
The modal fraction range in mm for pellets produced from the range of formulations

Formulation							
Drug	MCC	Water	MBA	PBA	BBA	4HBA	PG
5	5	7	1.70–2.00	1.40–1.70	1.00–1.40	1.00–1.40	1.40–1.70
7	5	7	1.00–1.40	1.00–1.40	1.40–1.70	NP	1.40–1.70
8	5	7	1.00–1.40	1.00–1.40	1.40–1.70	1.40–1.70	1.40–1.70
10	5	7	0.50–0.71	2.36–2.80	1.40–1.70	NP	NE
12	5	7	0.50–0.71	2.36–2.80	1.40–1.70	NE	NE
14	5	7	1.00–1.40	1.70–2.00	1.40–1.70	NE	NE
5	5	8	>2.80	2.36–2.80	2.00–2.36	>2.80	1.40–1.70
7	5	8	1.00–1.40	1.40–1.70	1.40–1.70	NP	1.40–1.70
8	5	8	1.00–1.40	1.40–1.70	1.40–1.70	NP	1.40–1.70
10	5	8	1.70–2.00	1.00–1.40	1.40–1.70	NP	1.40–1.70
12	5	8	1.00–1.40	1.40–1.70	1.40–1.70	2.00–2.36	NE
14	5	8	0.71–1.00	2.36–2.80	2.36–2.80	NE	NE
5	5	9	>2.80	>2.80	>2.80	>2.80	2.00–2.36
7	5	9	>2.80	1.70–2.00	1.70–2.00	1.70–2.00	1.40–1.70
8	5	9	>2.80	1.00–1.40	1.00–1.40	NP	1.40–1.70
10	5	9	1.70–2.00	1.40–1.70	1.00–1.40	NP	1.40–1.70
12	5	9	1.70–2.00	1.40–1.70	1.00–1.40	NP	1.40–1.70
14	5	9	1.40–1.70	2.00–2.36	2.36–2.80	1.70–2.00	1.00–1.40
5	5	10	>2.80	>2.80	>2.80	>2.80	>2.80
7	5	10	>2.80	>2.80	>2.80	1.70–2.00	1.40–1.70
8	5	10	>2.80	>2.80	2.00–2.36	>2.80	1.40–1.70
10	5	10	>2.80	1.40–1.70	1.40–1.70	2.36–2.80	1.40–1.70
12	5	10	>2.80	1.40–1.70	1.40–1.70	>2.80	1.40–1.70
14	5	10	2.36–2.80	1.00–1.40	1.00–1.40	NP	1.40–1.70.

NE: not extruded; NP: no product.

Table 3
Cluster group values for the analysis of relationships between extrusion force and pellet size

Cluster number	1	2	3
Water %	43.6	36.1	30.3
Drug	Average median diameter in cluster in mm		
MBA	1.89	2.13	1.34
PBA	2.04	1.70	2.64
BBA	2.11	1.67	2.19
4HBA	2.23	2.02	2.52
PG	1.87	1.80	1.69
Number of cases in cluster	10	8	6

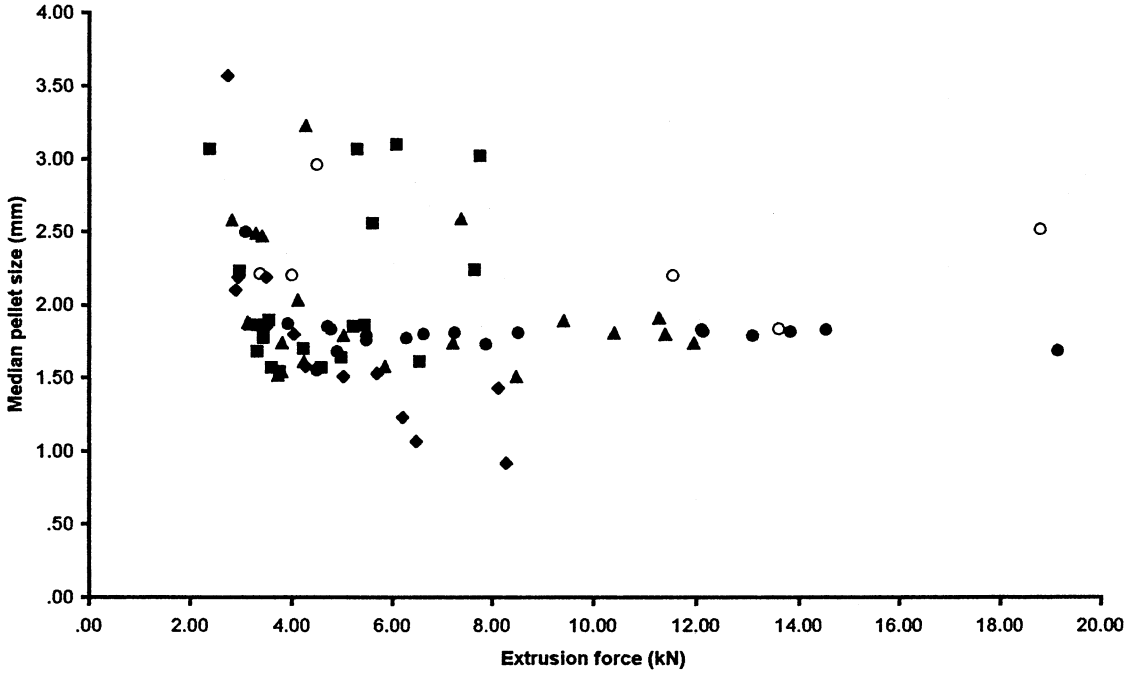


Fig. 2. The median pellet diameter as a function of the extrusion force for MBA (◆), PBA (■), BBA (▲), 4HBA (O) and PG (●).

the shape factor e_r, are presented for the model drugs in Table 5. The majority of pellets had shape factors greater than 0.6, which can be considered to be acceptably round (Podczeck et al., 1999). Some pellets had values equivalent to those for steel ball bearings. There is some variation in shape with water content present in the formulation. There is a slight tendency for pellets to become less round at higher water contents, presumably due to agglomeration of pellets due to free water at the pellet surface. The best results in terms of shape are those produced with formulations containing PG. This factor coupled with the wide range of combinations of PG, MCC and water and the consistent median diameter, clearly make this the best material to process.

The source of the differences in behaviour between these similar drug models is difficult to isolate. Certainly there are difficulties with extruding 4HBA (Tomer et al., 2001) as there was with PG, yet the latter was the best material in forming pellets whereas the former is the worst. These two materials had the highest water retention capacity, as assessed by a centrifuge technique (Tomer and Newton 1999) and differed from the three other materials. The particle size ranged from 24.8 μm for PBA to 44.1 μm for BBA, yet these were the drugs with a similar performance. The two materials with the closest size were 4HBA and MBA with values of 27.9 and 26.6 m, respectively, yet they had a very different performance. The solubility does range over a wide set of values but even the highest solubility material 4HBA (at 1 in 125 g) is of insufficient level to cause gross loss of material as reported by Lustig-Gustafsson et al., 1999. Less than 2% of the 4HBA, the most soluble of the model drugs, would dissolve in the formulation containing the highest water content, hence the loss of solid from the mixture by dissolution into the water could not account for the gross difference in response. For all the other model drugs, the loss of the solid component due to dissolution would be even less than that for 4HBA. What we do not know is whether the presence of 4HBA in solution has an effect on the interaction between MCC and water. Tomer and Newton (1999) identified a positive correlation between the moisture retention capacity (MRC)

and the hydrogen bonding energy. Such a simple correlation does not appear to exist here, which is perhaps not surprising considering the complexity of the process involved with the preparation of pellets by extrusion/spheronization.

4. Conclusions

In spite of the similarity of chemical structure, the 5 model materials, 4HBA, MBA, PBA, BBA and PG, produced very different responses to the process of extrusion/spheronization when combined in a range of preparations with MCC (50–73.7% of model drug) and water (MCC:water ratios from 1:1.4 to 1:2.0). Materials, which were difficult to extrude, either failing to extrude or producing water separation, produced poor pellets (here particularly 4HBA). While PG failed to extrude in some instances, due to insufficient water, formulations, which did extrude were insensitive to water content and produced reproducible pellets with a limited size distribution and a high level of sphericity. Combinations of 4HBA only produced two specific combinations suitable as pellets. Most other formulations of the compound agglomerated in the spheronizer. Agglomeration was the most significant feature, which resulted in the failure of extrudates to spheronize. Such formulations contained water, which was mobile and could allow water to transfer to the surface of the pellet, resulting in the joining of pellets to produce agglomerates. Combination of formulations, which produced a similar response, could be identified by cluster analysis. As yet, no physico-chemical property that would provide productive indications of processability has been identified even for compounds of very similar chemical structure. It appears that numerous as yet unidentified factors are involved and the ability to pre-

Table 4
The percentage of pellets in the size fraction 0.71–1.70 mm

Formulation			Percentage				
Drug	MCC	Water	MBA	PBA	BBA	4HBA	PG
5	5	7	21.5	100.0	100.0	100.0	100.0
7	5	7	96.4	100.0	100.0	0.0	99.3
8	5	7	100.0	100.0	91.2	100.0	97.0
10	5	7	96.2	0.0	96.7	0.0	0.0
12	5	7	73.3	0.0	82.1	0.0	0.0
14	5	7	100.0	0.0	73.0	0.0	0.0
5	5	8	0.0	0.0	0.0	0.0	100.0
7	5	8	84.2	100.0	100.0	0.0	100.0
8	5	8	0.0	100.0	100.0	0.0	100.0
10	5	8	24.1	92.0	99.5	0.0	100.0
12	5	8	97.5	97.6	78.6	0.0	0.0
14	5	8	96.1	0.0	0.0	0.0	0.0
5	5	9	0.0	0.0	0.0	0.0	0.0
7	5	9	0.0	0.0	46.1	0.0	100.0
8	5	9	0.0	100.0	0.0	0.0	100.0
10	5	9	0.0	100.0	100.0	0.0	100.0
12	5	9	0.0	97.6	97.1	0.0	100.0
14	5	9	2.6	0.0	0.0	0.0	100.0
5	5	10	0.0	0.0	0.0	0.0	0.0
7	5	10	0.0	0.0	0.0	0.5	88.5
8	5	10	0.0	0.0	0.0	0.0	96.8
10	5	10	0.0	80.8	88.8	0.0	100.0
12	5	10	0.0	93.6	81.5	0.0	98.8
14	5	10	0.0	100.0	100.0	0.0	100.0

Table 5
Shape factor e_r for pellets in the modal size range for the pellet formulations

Formulation							
Drug	MCC	Water	MBA	BBA	PBA	4HBA	PG
5	5	7	0.65	0.65	0.62	0.67	0.68
7	5	7	0.65	0.64	0.60	NP	0.46
8	5	7	0.66	0.62	0.58	0.69	0.60
10	5	7	0.63	0.63	0.63	NP	NE
12	5	7	0.60	0.63	0.54	NE	NE
14	5	7	0.64	0.68	0.47	NE	NE
5	5	8	0.60	0.64	0.63	0.56	0.71
7	5	8	0.65	0.63	0.65	NP	0.69
8	5	8	0.62	0.61	0.65	NP	0.69
10	5	8	0.61	0.62	0.64	0.68	0.71
12	5	8	0.62	0.63	0.66	0.70	NE
14	5	8	0.64	0.63	0.64	NE	NE
5	5	9	0.51	0.53	0.58	0.52	0.66
7	5	9	0.60	0.64	0.63	0.62	0.69
8	5	9	0.59	0.60	0.63	NP	0.72
10	5	9	0.65	0.62	0.60	NP	0.69
12	5	9	0.65	0.64	0.65	NP	0.70
14	5	9	0.64	0.64	0.62	0.60	0.70
5	5	10	0.44	0.50	0.62	0.61	0.60
7	5	10	0.45	0.58	0.59	0.61	0.69
8	5	10	0.54	0.58	0.63	NP	0.66
10	5	10	0.59	0.63	0.63	0.60	0.71
12	5	10	0.56	0.64	0.63	0.57	0.68
14	5	10	0.63	0.63	0.63	NP	0.73

NE: no extrusion; NP: no product.

dict whether a drug will produce a satisfactory product form the chemical structure is not possible.

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