ELSEVIER

International Journal of Pharmaceutics 232 (2002) 91–106

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Factors influencing the physical characteristics of pellets obtained by extrusion-spheronization

J.J. Sousa [a,*], A. Sousa [a], F. Podczeck [b], J.M. Newton [b]

[a] *Laboratório de Galénica e Tecnologia Farmacêutica, Faculdade de Farmácia, Rua do Norte, 3000 Coimbra, Portugal*
[b] *Department of Pharmaceutics, School of Pharmacy, University of London, 29–39 Brunswick Square, London WC 1N 1AX, UK*

Received 9 April 2001; received in revised form 1 October 2001; accepted 3 October 2001

Abstract

The objective of this work was to analyse the influence of the solubility of the drug and the filler on the physical characteristics of pellets prepared by extrusion/spheronization. Different formulations were prepared according to a statistical plan, using five different drugs and five different fillers selected according to their water solubility. The pellets were then obtained by a standardized extrusion/spheronization process and evaluated in terms of their physical characteristics by measuring the pellet size, density, porosity, mechanical strength, residual moisture after drying and shape. The results were first analysed by the analysis of variance to identify the main factors involved. The results were further assessed by canonical analysis and the significant influence factors were quantified in terms of regression equations. It can be concluded that the solubility of materials used (both drugs and fillers) plays an important role in the quantity of water required to form satisfactory pellets and on the physical characteristics of pellets. Quantitative relationships were identified between (a) the extrusion force required to provide extrudate, which would form pellets and the natural log of the filler solubility; (b) the quantity of the pellets in the size range 1–1.4 and the solubility of both the filler and the drug; (c) the apparent pellet density and both the level of drug and filler plus the solubility of the filler; (d) the pellet porosity and the quantity of drug and the inverse function of the filler solubility; and (e) the mechanical strength of the pellets and the square root of the quantity of drug.

Keywords: Extrusion/spheronization; Extrusion force; Formulation variables (type and level of drugs and fillers); Pellet properties (density, porosity, mechanical strength, size and shape); Statistical analysis

1. Introduction

The extrusion/spheronization process is an accepted method of producing pellets. This process consists of five unit operations—blending, wet massing, extrusion, spheronization and drying—resulting in the formation of spherical pellets showing a homogeneous surface (Otsuka et al., 1994). Since these phases are strongly related to each other (Newton, 1994) the quality of the end product—pellets—is also strongly dependent on the process factors (Woodruff and Nuessle, 1972;

* Corresponding author. Tel.: +351-239837902; fax: +351-239837731.
E-mail address: jjsousa@pop.ci.uc.pt (J.J. Sousa).

0378-5173/02/$ - see front matter
PII: S0378-5173(01)00908-5

Noche et al., 1994). Hence, in any study it is important to know what was the actual procedure at each stage. Furthermore, formulation parameters, such as the presence of soluble or insoluble fillers (Vecchio et al., 1994), surface active agents (Vervaet et al., 1994), pH adjusters (Bianchini, 1992), drug load (Bianchini and Vecchio, 1988) and ratio of filler/drug (Rekki et al., 1995), have also been identified as factors, which can influence the drug release profiles. An important factor is the solubility of the drug, especially in terms of the amount of water to provide a satisfactory product (Lustig-Gustafsson et al., 1999).

A problem of identifying the influence of formulation factors in the preparation of pellets by the process of extrusion/spheronization is the scale of the process available to carry out the investigation. Manufacturing size equipment requires large quantities of materials, making multiple experiments expensive. Small scale screen extruders are available but thin screen extruders do not densify the wet powder mass and usually produce extrudate, which is at best rough and more likely 'shark skinned'. Such extrudate responds in a very different way to the spheronization process to extrudates produced by long dies. Much more reliable information on the influence of formulation variables can be obtained by using long dies to produce the extrudate. The ram extruder has been shown to correlate to the performance with commercial long die gravity feed extruders (Chapman, 1985; Fielden et al., 1992; Baert et al., 1992; Newton et al., 1995a,b) and experiments can be carried out with relatively small quantities of materials. In general, formulations, which will form pellets from extrudate produced by extrusion through a long die will produce pellets from extrudate produced by a screen extruder. The converse, however, is usually not the case. A further advantage of the ram extruder is that it does also provide some measure of the consistancy of the wet powder mass by providing a measurement of the extrusion force used to produce the extrudate. It also allows a standardized process to be used and provides a record of the process. Therefore, for this study the ram extruder will be used to form the extudate prior to spheronizaion.

1.1. Experimental design

The objective of this study was to analyse the influence of drug and filler solubility on the physical characteristics of pellets obtained by the extrusion/spheronization process.

The experiments were drawn up to investigate the effect of these formulation variables on the physical characteristics of pellets. The reference preparation contained the model drug (propranolol hydrochloride P), the model filler (α-lactose monohydrate L) and microcrystalline cellulose (Avicel PH 101 A) as a palletising enhancer, in the proportion of 2:3:5 (PLA 2:3:5) calculated on a dry weight basis. One of the problems with the application of statistical design to formulation experiments is the need to obtain a product whose characteristics can be measured. Failure to provide a product to measure can lead to difficulties of analysis. Extrusion/spheronization is a process, which is subject to failure when slight changes in formulation are made. Hence in the current design, the level of microcrystalline cellulose was maintained at a level of 50%, a value at which most drugs will form pellets. An entirely different approach would be required if the objective were to identify the extreme values of drug content, which could be formulated into pellets.

One of the sub-groups into which the study can be divided-the effect of drug solubility-was analysed by changing the drug type but not its relative level within the formulation, or the other components.

The second sub-group consists of the analysis of the ratio of drug to filler. Maintaining the model formulation as the central design, the relative proportions of the model drug (P) and model filler (L) were changed but their total amount remained constant (50% of the pellet weight).

The third and fourth sub-groups analysed the influence of different fillers at two levels 30 and 45%. The fillers involved in the study were also chosen according to their relative solubility to the model filler (L), with mannitol (M) and glucose (G) being more soluble, while calcium phosphate(C) and barium sulphate (B) were included as insoluble fillers.

2. Materials and methods

2.1. Materials

Propranolol hydrochloride, (P) (Lusochimica, Milano, Italy), ephedrine hydrochloride (E) (S & D Chemicals Ltd, Harrow, UK), paracetemol (Pa) (Rhone Poulenc, Roussillon, France), ibuprofen (I) (Boots Pharmaceuticals, Nottingham, UK) and sodium salicylate (S) (BDH Lab Supplies, Poole, UK), microcrystalline cellulose (A) (Avicel PH 101) (FMC Ltd, Cork, Ireland), α-lactose monohydrate (L) (Sheffield Products, Norwich, USA), glucose anhydrous (G) (BDH Lab Supplies, Poole, UK) and mannitol (M) (BDH Lab Supplies, Poole, UK), calcium phosphate (C) (Fisons Sci. Equip., Loughborough, UK) and barium sulphate (B) (BDH Lab Supplies, Poole, UK) were of EP standard and were used as received. Water freshly demineralised was used as a liquid binder.

The particle size of the materials was determined by laser light diffraction (Malvern Laser Sizer 2600C, Malvern Instruments, Malvern, UK) after dispersion by ultra-sonication in an appropriate solvent. The values are presented in Table 1 together with the experimental values for the apparent particle density (determined by the same method as for the pellet apparent density) and the values for the aqueous solubility taken from the literature (Martindale Extrapharmacopoeia 31st edition).

2.2. Extrusion/spheronization process

The powder components of the various formulations were premixed in a small-scale planetary mixer (Kenwood Chef, Kenwood Products Ltd, London, UK) for 5 min. The required amount of water was added and the wet mass processed for a further 10 min, with occasional pauses to allow scrapping of the bowl and the blade. The wet mass was allowed to equilibrate for at least 12 h before extrusion. Extrudates were obtained by using a ram extruder attached to a physical testing instrument (Lloyd MX 50, Lloyds Instruments) fitted with a 50 kN load cell, extruding at a constant ram speed of 250 mm/min, through a die 1 mm in diameter and 4 mm in length. A spheronizer (Caleva, Dorset, UK) equipped with a radial plate 203.2 mm in diameter was used for the spheronization stage. Five hundred g of extrudates were processed for 10 min at a speed of 1000 rpm. Pellets were dried at 60 °C for 30 min in a fluid bed drier (PRC Engineering, Wrexham, UK). A suitable level of water required to prepare

Table 1
The characteristics of the model drugs, fillers and microcrystalline cellulose used in the preparation of pellets

Materials	Particle size (μm)			Density (kg/m^3)	Solubility (g/l)
	Mean	<10%	>90%		
Ibuprofen[a]	40.1	24.9	52.8	1120	0.0025
Paracetamol[a]	88.0	63.8	111.9	1300	14.48
Propranolol[a]	80.6	33.8	110.2	1200	50.00
Ephedrine[c]	20.8	6.9	53.3	1200	250.00
Sodium salicylate[c]	88.7	11.7	219.6	1570	1000.00
Microcrystalline cellulose[b]	51.5	18.8	100.2	1560	0.0
Glucose[b]	13.8	6.3	20.4	1520	1000.0
Mannitol[b]	20.1	6.7	42.9	1210	166.67
Lactose[b]	33.2	5.9	74.2	1550	166.67
Calcium phosphate[a]	8.1	3.2	13.6	3200	0.01
Barium sulphate[a]	8.7	4.8	12.7	4360	0.0025

[a] Suspending medium, water.
[b] Suspending medium, ethanol.
[c] Suspending medium, chloroform.

a good preparation, was assessed in terms of the quantity of water, which gave the largest proportion of pellets in the size fraction 1.0–1.40 mm. The starting point for these experiments was the water requirement that would be predicted by the relationship between the solubility of the components of the formulation and water obtained by Lustig-Gustafsson et al. (1999). For all the formulations, the water level was increased and/or decreased by approximately 10%, providing at least three water levels for each formulation. From these experiments the appropriate water level was chosen. Once the level of water had been identified, each of the formulations was prepared on three separate occasions, to confirm the reproducibility of the process. The values for the water levels, required for each formulation and the mean and standard deviation of the percentage of pellets in the 1.0–1.40 size fraction, are presented in Table 2.

2.3. Characterisation of the pellets

2.3.1. Apparent pellet density

Samples were weighed (Oertling YP4 balance) and placed in the air pycnometer (air comparison pycnometer, model Beckman 930, Beckman LTD, Irvine, CA, USA) using ambient air as a gaseous medium, and their apparent density was determined in triplicate.

2.3.2. Porosity

The porosity of the pellets was calculated from the ratio between the apparent pellet density as determined by air pycnometer and the apparent particle density of the powder mixtures (also determined by the air pycnometer), according to the following relationship, Porosity $= 1 -$ (apparent pellet density/apparent powder density). The apparent powder density of the powder blends was calculated from the value of the individual powders, allowing for their proportion in the mixture. Both Harrison (1983), Chapman (1985) established that this ratio was equivalent to the value of the porosity obtained by measuring the density of the pellets by a mercury intrusion pycnometer and far safer.

2.3.3. Mechanical crushing force

At least 20 pellets in the size range 1–1.4 mm of each formulation were evaluated for their diametral crushing force using a tablet strength tester (CT 40 Engineering Systems, Nottingham, UK), at a crosshead speed of 1 mm/min.

2.3.4. Water content

The residual water content present in the pellets after drying was determined by thermogravimetric analysis (TGA Hi-Res TGA 2950 thermogravimetric analyser) connected to a sample analyser (Thermal analyst 2000, TA Instruments Leatherhead, UK).

2.3.5. Sieve analysis

The size of the pellets was analysed by using mechanical sieving (Test sieve shaker, Endicott Ltd, London, UK). One hundred grams of each preparation were shaken for 10 min. The mesh diameter of the British Standard no. BS 410 sieves followed a $\sqrt{2}$ progression between 500 and 2000 μm.

2.3.6. Shape

The shape factor e_r reported by Podczeck and Newton (1994) was used to evaluate the pellet shape. Measurements were carried out using a Seescan Image Analyser (Solitaire 512, Seescan, Cambridge, UK) attached to a black and white camera (CCD-4 miniature video camera, Toyhashi, Japan) connected to a zoom lens (18–108/2–5, Olympus, Hamburg, Germany) and analysed for shape. To perform this analysis, 40 spheres were mounted on a surface previously painted with non-reflective black ink. The pellets were illuminated from above using a twin cold light source placed at 180° to the surface (Olympus, Hamburg, Germany) under conditions, which satisfied the requirements set by Podczeck et al. (1999).

2.3.7. Statistical methods

Results were analysed using different software available. Analyses of variance and of simultaneous pair comparisons were undertaken using an-house software (Podczeck, unpublished). The median pellet size was calculated using the pack-

Table 2
The influence of water content on the extrusion force, total yield, % of pellets in the 1.00–1.40 mm size fractions for the range of formulations

Formulation	Water level (parts weight)	Extrusion (kN)	Total yield %	%1.00–1.40 mm	Pellet median diameter (mm)
PLA (2:3:5)	5.33	9.19	71.74	75.40	1.10
	5.41	9.07	74.71	80.42	1.12
	5.50	7.82	83.05	82.79	1.18
ILA (2:3:5)	5.41	15.80	90.79	78.20	1.10
	5.50	14.34	91.19	77.52	1.10
	5.58	13.09	86.45	86.43	1.11
PaLA (2:3:5)	5.16	13.87	23.24	83.93	1.09
	5.50	10.06	86.11	82.49	1.09
	5.66	9.66	89.72	59.71	1.10
ELA (2:3:5)	4.66	10.81	80.21	67.38	1.05
	4.83	9.74	83.16	84.20	1.17
	5.00	8.27	85.74	80.11	1.21
SLA (2:3:5)	3.00	15.29	24.60	30.88	1.37
	3.16	13.28	26.01	23.92	1.58
	3.33	11.83	34.89	24.18	1.57
	3.41	10.53	82.70	53.40	1.31
	3.50	10.81	58.67	0.00	1.54
PLA (0.5:4.5:5)	5.50	9.90	38.27	61.15	1.06
	5.58	8.60	93.95	71.42	1.08
	5.66	8.25	81.66	86.60	1.16
PLA (1:4:5)	5.50	9.31	83.85	69.65	1.08
	5.58	8.37	94.58	83.36	1.11
	5.66	7.93	94.38	87.54	1.16
PLA (3:2:5)	5.33	8.25	96.13	96.22	1.15
	5.41	7.74	94.16	92.26	1.18
	5.50	7.74	92.89	62.80	1.33
PLA (4:1:5)	5.53	8.09	96.47	94.18	1.18
	5.41	7.42	96.24	57.70	1.35
	5.50	7.31	93.29	25.37	1.54
PLA (5:0:5)	5.00	16.70	89.56	78.56	1.17
	5.12	14.24	93.21	82.40	1.21
	5.33	15.80	94.56	72.54	1.43
PGA (2:3:5)	3.66	15.56	92.76	72.80	1.21
	4.00	12.34	94.98	74.86	1.15
	4.16	9.98	95.53	58.96	1.35
PMA (2:3:5)	4.83	11.36	96.85	93.96	1.15
	4.91	10.85	96.24	93.87	1.15
	5.00	10.65	95.82	93.32	1.16
PCA (2:3:5)	5.66	12.22	32.13	*	1.10
	6.00	8.56	77.89	92.78	1.15
	6.33	6.99	92.91	92.33	1.18
PBA (2:3:5)	5.53	9.45	85.00	75.31	1.05
	5.41	7.46	92.80	63.08	1.11
	5.50	6.60	81.25	78.31	1.11
PGA (0.5:4.5:5)	3.83	18.83	95.38	78.35	1.22
	3.91	15.80	90.54	72.99	1.18
	4.00	7.31	95.52	*	1.13
PMA (0.5:4.5:5)	5.00	14.58	94.27	85.80	1.13
	5.16	12.34	94.98	91.71	1.13
	5.33	9.27	93.27	90.28	1.14
PCA (0.5:4.5:5)	6.33	10.25	90.76	93.43	1.09
	6.50	8.41	93.91	96.09	1.12
	6.66	7.23	93.21	93.20	1.15
PBA (0.5:4.5:5)	5.41	6.99	78.41	39.46	0.96
	5.50	6.68	91.04	41.86	0.98
	5.58	5.26	83.45	83.57	1.06

*Pellets irregular in shape. The water levels in bold are those used in further experiments.

age SPSS for WINDOWS (version 6.0, 1995 SPSS Inc, Woking, UK). A canonical analysis was also performed, which allowed the identification of the significant influence factors (SPSS, as above).

3. Results and discussion

3.1. Preliminary experiments

Due to the influence of the amount of water on the processability of the wet mass, several water levels were tried to achieve the ideal proportion. This was judged in terms of a high batch yield (calculated as the amount of pellets that was possible to be obtained from the amount of extrudate placed on the spheronizer plate) and a high percentage of pellets obtained within the 1.0–1.4 mm size fraction. The results for these experiments are set out in Table 2.

Within a given set of formulations as the water level increased the extrusion force decreased, confirming previous observations by for example, Fielden et al. (1989), Bains et al. (1991), Tomer et al. (2001). For drugs with low water solubility e.g. ibuprofen and paracetamol, the water in the quantities studied did not have a great influence, with the pellet size being almost the same for changes in water level of approximately 10%. For the more soluble drugs, the pellet size increases considerably for an equivalent increase in water level. It was also observed that the amount of water required decreases when the drug solubility decreases, as drug dissolves during the process, removing solids from the system confirming the results of Lustig-Gustafsson et al. (1999). Overall however, there is no simple relationship between the quantity of water and the extrusion force and the quantity of water present in the formulation. Generally, the high extrusion forces are found when water level is low, but the highest force (18.33 kN) is found at a water level of 3.83 (PGA 0.5:4.5: 5) and not the lowest water level of 3.00, while the lowest force (5.26 kN) is obtained with a water level of 5.50 (PBA 0.5:4.5:5), not at the highest water level of 6.33 parts by weight. Also, for the same water content, 5.50 parts, it is possible to obtain an extrusion force of 6.68 kN (PBA 0.5:4.5:5) and 16.70 kN (PLA 5:0:5). Clearly the nature of the solids present and the solution produced by dissolution of the solids, have an important part to play in the determination of the consistency of the wet powder mass.

From these preliminary studies, the amount of water that gave the best yield of high quality pellets was chosen for each formulation and the reproducibility of the process assessed by preparing three batches for each formulation. As can be seen from the results in Table 3, for the levels of water chosen, the process was highly reproducible, in terms of the small values for the standard deviation and highly effective in terms of the large proportion of pellets in the one sieve fraction. Those formulations containing a drug or filler with a high solubility were the least reproducible and provided the lowest quantity of pellets in the desired size fraction.

3.2. Residual moisture

The various materials used in addition to the drugs, have different solubilities and capacity to retain water. For this reason the amount of water required was also different for different formulations. For the standard drying conditions it was found that, the differences in the residual moisture of pellets were very small, indicating that in spite of the different initial water contents of the pellets, the drying process removed the free water added during the initial wet massing stage.

3.3. Extrusion force

The extrusion force required to obtain the extrudate is related to the rheological properties of the wet mass. For the preparations containing the 'best' level of water, the extrusion force was found to be related to the solubility of the drug included in the formulation as can be seen in the ANOVA results in Table 4. Compared with the reference formulation, when the drug changes, the extrusion force also changes but not to provide a statistical significant difference. The value of the extrusion force does not seem to be influenced by modification in the ratio drug/filler, as all the preparations of this sub-group gave statistically equivalent results. The exception is the formulation PLA 5:0:5, which is surprising as these two ingredients have approxi-

mately the same water solubility. The influence of the filler solubility is only statistically significant for the most soluble filler (glucose) at its higher level, although when this material is used in is lower level, no significant changes were recorded.

3.4. Geometric shape of the pellets

3.4.1. Shape factor e_r

The value of the shape factor e_r considers both the geometrical shape and the surface texture of spherical pellets.

The ANOVA analysis (Table 5) shows that the variable, the shape factor, e_r, is not influenced by the solubility of the drug for the formulation assessed. However, different fillers have clear influence on the e_r value. This cannot be attributed solely to their solubility because a very soluble filler (glucose) and a practically insoluble (barium sulphate) gave results, which were not significantly different when compared with the reference formulation. The difference appears to be more related to another feature of the filler. This hypothesis can be supported for the lowest filler level and can be confirmed when the higher level was applied. The behaviour of mannitol and calcium phosphate tends to provide a different value of e_r when used in their lower level, which was confirmed with statistical significance when the higher level was tested. The lower value of e_r observed with the preparation PLA 5:0:5 seems to be more related to the absence of the filler (lactose). This composition had the highest extrusion force (see Table 2) for this series of mixtures and in general the higher the extrusion force, the more difficult is pellet rounding.

3.5. Apparent pellet density

The density of pellets should be taken into consideration not only for technological purposes, but also because the majority of them are usually encapsulated in two-piece hard shell capsules and thus for these fixed volume dosage forms the density will determine the fill weight. In addition, this physical property could have an influence on the gastric emptying times if it exceeds a limiting value above 2400 kg/m^3 (Clarke et al., 1995).

Table 3
The best water levels and the reproducibility of the process as the % of pellets in the size fraction 1.0–1.40 mm (mean and standard deviation of three batches)

Variable	Formulation	Water level (parts by weight)	% Pellets in1.00–1.40 fraction	
			Mean	S.D.
Drug type	PLA 2:3:5	5.50	82.9	2.36
	ILA 2:3:5	5.58	85.0	1.42
	PaLA 2:3:5	5.50	85.3	2.45
	ELA 2:3:5	4.83	77.3	3.60
	SLA 2:3:5	3.41	58.7	4.70
Drug level	PLA 0.5:4.5:5	5.66	85.9	0.71
	PLA 1:4:5	5.66	87.3	0.86
	PLA 3:2:5	5.41	90.3	1.94
	PLA 4:1:5	5.33	93.2	0.95
	PLA 5:0:5	5.12	81.9	0.51
Filler level (−)	PGA 2:3:5	4.00	77.5	2.82
	PMA 2:3:5	4.83	93.6	1.88
	PCA 2:3:5	6.33	92.2	0.42
	PBA 2:3:5	5.50	80.0	1.08
Filler level (+)	PGA 0.5:4.5:5	3.83	79.6	1.13
	PMA 0.5:4.5:5	5.16	92.5	0.92
	PCA 0.5:4.5:5	6.50	95.1	1.51
	PBA 0.5:4.5:5	5.58	84.6	1.06

Table 4
Analysis of variance of the force (EF) values (kN) recorded when the best formulation in each sub-group of the formulations were obtained

Variable	Formulation	EF mean[a]	S.D.[b]	*F*-value
Drug type	PLA 2:3:5	9.21	1.50	
	ILA 2:3:5	13.15	0.07	7.65
	PaLA 2:3:5	12.79	2.81	6.30
	ELA 2:3:5	9.14	0.52	1.00
	SLA 2:3:5	10.98	0.40	1.55
Drug level	PLA 0.5:4.5:5	10.19	1.52	1.00
	PLA 1:4:5	9.30	1.19	1.00
	PLA 3:2:5	8.78	0.90	1.00
	PLA 4:1:5	9.33	1.15	1.00
	PLA 5:0:5	15.58	1.24	19.97*
Filler level (−)	PGA 2:3:5	12.18	0.23	4.35
	PMA 2:3:5	11.24	1.12	2.04
	PCA 2:3:5	7.79	0.72	1.00
	PBA 2:3:5	7.71	1.10	1.00
Filler type (+)	PGA 0.5:4.5:5	15.12	1.51	17.19*
	PMA 0.5:4.5:5	9.89	0.54	1.00
	PCA 0.5:4.5:5	8.84	1.40	1.00
	PBA 0.5:4.5:5	6.50	1.07	3.61

[a] Mean value of extrusion force EF ($n = 3$).
[b] Standard deviation S.D. ($n = 3$).
(−) Lower filler level; (+) higher filler level, variance between classes, 20.36; variance within classes, 3.04; 1st degree of freedom, 17; 2nd degree of freedom, 51; $*P < 0.05$.

The results of powder density and resultant pellet density are summarised in Table 6. All the preparations have density values that are statistically different when compared with the reference formulation, in particular, preparations containing the two dense inorganic fillers calcium phosphate and barium sulphate. The pellet density is very sensitive to small alterations in the composition. For instances, all the preparations in the second subgroup, where only the relative proportion between one model drug and one filler varied, gave results which are statistically different.

The results presented in Fig. 1 illustrate that the apparent pellet density changes with the drug solubility in a different way to that of the powder density indicating that the drug solubility influences the structure of the pellets. The increase in the pellet density as the drug solubility increases, could be due to the dissolution of drug in the water during processing, followed by its recrystallisation in the pores on drying. This effect however, is not just a simple function of solubility. The density of pellets containing the most soluble drug, sodium salicylate, does not increase to the same extent as the next two in the series, ephedrine and propranolol. The latter are weak salts of weak bases, whereas, sodium salicylate is the salt of a relatively strong acid. This illustrates that acidic and basic compounds interact with cellulose in a different manner. There is a residual acidity in MCC left from its method of preparation. The apparent densities of pellets obtained when the concentration of the model drug is changed (Fig. 2), decreased as the amount of the model filler increased, and again the resultant pellets are less dense than the correspondent powder. However, the preparation without lactose (PLA, 5:0:5) shows a lower than expected decrease in the pellet density. This is somewhat surprising as this particular drug and filler have very similar solubilities and densities.

Pellets obtained with different fillers, in the higher and lower proportions are less dense than the corresponding powder mixtures. This differ-

ence is more marked for pellets obtained with insoluble inorganic fillers, which can be explained by the lack of dissolution and recrystallisation of the water insoluble fillers.

3.6. Porosity

The porosity of the pellets is an important characteristic, which might influence the drug release profile in different ways. The porosity also has the potential to change the ability of a film to adhere to the surface of the pellets. The value of the porosity is derived from the apparent powder and pellet densities.

The porosity of the pellets cannot be directly related to the drug solubility. Although the values obtained with the median soluble drugs (paracetamol, propranolol and ephedrine) seem to decrease as the solubility increases (Table 6), pellets produced with the two extremes of solubility, the highly insoluble ibuprofen and the highly soluble sodium salicylate appear to depart from this order. The ibuprofen pellets are less porous than expected, while the sodium salicylate formulation is more porous than expected. This is not related to the amount of water used during the processing stage as the formulation SLA 2:3:5 which required the lowest level of water produces the higher porosity while preparation ILA 2:3:5, which required the highest level of water produces a lower porosity than the sodium salicylate formulation.

Table 5
The effect of formulation on the shape of the pellets, as measured by the shape factor e_r

Variable	Formulation	e_r	S.D.	F-value
Drug type	PLA 2:3:5	0.62	0.095	
	ILA 2:3:5	0.63	0.083	1.00
	PaLA 2:3:5	0.63	0.085	1.00
	ELA 2:3:5	0.60	0.089	1.00
	SLA 2:3:5	0.63	0.097	1.00
Drug level	PLA 0.5:4.5:5	0.57	0.138	2.97
	PLA 1:4:5	0.62	0.101	1.00
	PLA 3:2:5	0.61	0.104	1.00
	PLA 4:1:5	0.63	0.124	1.00
	PLA 5:0:5	0.46	0.116	38.54***
Filler level (−)	PGA 2:3:5	0.62	0.101	1.00
	PMA 2:3:5	0.57	0.102	2.56
	PCA 2:3:5	0.58	0.099	2.17
	PBA 2:3:5	0.62	0.109	1.00
Filler level (+)	PGA 0.5:4.5:5	0.60	0.100	1.00
	PMA 0.5:4.5:5	0.55	0.115	6.99**
	PCA 0.5:4.5:5	0.48	0.162	26.55***
	PBA 0.5:4.5:5	0.64	0.083	1.00

Variance between classes, 0.08; variance within classes, 0.011;1st degree of freedom, 17; 2nd degree of freedom, 663; **, $P<0.01$; ***, $P<0.001$; S.D. = standard deviation ($n=40$).

3.7. Pellet mechanical strength

The values of the mechanical strength, expressed as crushing force of the pellets, obtained with the different formulations, are shown in Table 7. As the strength was determined on pellets in the same size fraction, 1–1.4 mm, values are comparable and, therefore, the calculation of a derived value of the tensile strength has not been undertaken. The value of the strength of the pellets obtained with the different preparations varied considerably and in a complex way. However, a relationship between this physical characteristic and the values of porosity can be observed. For pellets obtained with the full range of drugs but the same filler, it can be seen in Fig. 3 that, the mechanical strength changed in the same manner as the porosity.

The mechanical strength variations for the pellets produced with the same model drug but with different ratios of filler are presented in Fig. 4. Here, the same trend of decreasing strength with decreasing pellet density was found.

3.8. Canonical analysis

ANOVA was performed using the results from the characterisation of the pellets and showed that there are statistical differences between preparations within the four sub-groups. However, the approach only identifies the significance of the differences between each preparation and the reference formulation. It would be useful if all the results of all the formulations could be considered in a single analysis. To expand the design to provide a full factorial design would have required a considerable increase in the number of experiments required. To quantify each effect, a

Table 6
Analysis of variance of the influence of formulation on the apparent density of pellets plus values of the pellet porosity

Variable	Formulation	Apparent density (kg/m^3)		S.D.	*F*-value	Porosity (%)
		Powder	Pellet			
Drug type	PLA 2:3:5	1489	1450	20	2.6	
	ILA 2:3:5	1469	1420	20	127.4***	3.3
	PaLA 2:3:5	1505	1420	20	127.4***	5.1
	ELA 2:3:5	1485	1460	10	14.2*	1.6
	SLA 2:3:5	1559	1450	20	1.0	6.9
Drug level	PLA 0.5:4.5:5	1533	1530	70	906.0***	0.5
	PLA 1:4:5	1552	1550	20	353.9***	1.4
	PLA 3:2:5	1456	1430	10	56.6***	1.7
	PLA 4:1:5	1423	1390	20	509.6***	2.3
	PLA 5:0:5	1380	1330	20	2038.4***	4.2
Filler level (−)	PGA 2:3:5	1480	1390	20	509.6***	6.0
	PMA 2:3:5	1387	1360	40	1146.6***	1.5
	PCA 2:3:5	1984	1750	50	12 774.2***	11.7
	PBA 2:3:5	2332	1800	10	17 340.8***	22.8
Filler level (+)	PGA 0.5:4.5:5	1525	1490	20	226.5***	2.2
	PMA 0.5:4.5:5	1375	1350	30	1415.6***	2.2
	PCA 0.5:4.5:5	2281	2000	60	42 821.2***	12.3
	PBA 0.5:4.5:5	2800	2150	40	69 363.3***	23.2

S.D., standard deviation of pellet density; variance between classes, 0.1624; variance within classes 1.059×10^{-5}; 1st degree of freedom, 17; 2nd degree of freedom, 36; *, $P < 0.05$; ***, $P < 0.001$; S.D., standard deviation ($n = 3$).

statistical test procedure is required, which is able to detect single and cross effects in a multivariate data analysis. Such a method is described by Podczeck et al. (1993) in the form of canonical analysis, which can be used to explain the relationship between two sets of variables, one representing the influencing factors or the independent variables, X and the other being the results or the dependent variables, Y.

Although these variables are supposed to be independent of each other, it is impossible to use a simple determination procedure to establish to which degree there is significance due to the complexity and number of the results. Using canonical analysis, the significance of the relationship between X and Y can be calculated using the Wilks test Λ (multivariate test of significance). The Λ-value indicates a global interdependence between the influencing (X) and the dependent (Y) variables. Commonly, Λ will be approximated onto the F distribution through which it is possible to identify a first and second degree of freedom (f_1 and f_2), as well as the probability (P) for the test criterion.

The independent variables considered here are the drug solubility, its level, the filler solubility, and its level. The dependent variables considered were the extrusion force (kN), the reproducibility of the pellet size, perimeter, shape factor e_r, density, porosity and mechanical strength (dependent variables). The Wilks test value obtained was

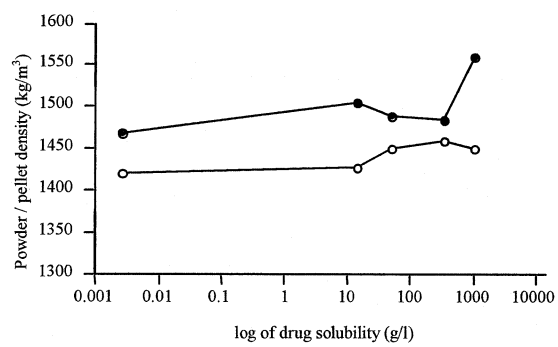

Fig. 1. Comparative apparent densities of the powder mixtures (●) and corresponding pellets (○); (a) different drugs (from left to right, ibuprofen, paracetamol, propranolol, ephedrine and sodium salicylate).

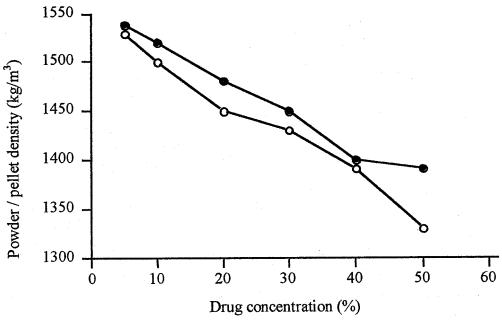

Fig. 2. Comparative apparent densities of the powder mixtures (●) and corresponding pellets (○) for different ratios propranolol:lactose.

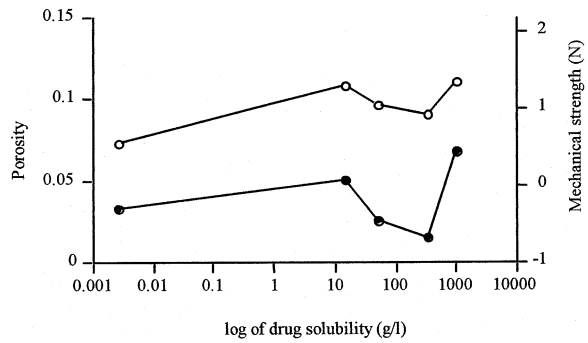

Fig. 3. Porosity (●) and mechanical strength (○) of pellets obtained with different drugs, according to their solubility.

0.0011 (F(ca.) = 4.00, $f_1 = 32$; $f_1 = 24$; $P < 0.001$), which confirms a significant interdependence.

3.8.1. Measures of redundancy g

These values can explain which part of the whole variance of one range can be explained by the canonical variables of the other set of variables. It means that they indicate to what extent the one set of variables can be predicted by the second set of variables. The g-values described here for the systems studied indicate that a prediction is possible only with limitations:

$g^2_{Y/U}$, 46.32%; $g^2_{X/V}$, 34.61%

The lower level obtained (34.61%) can signify that the dependent variables must have been influenced by some other factors, which were not measured. While it is a low value, it does indicate that there may be the possibility of obtaining some relationships between the input variables and the response.

Table 7
Analysis of variance of the effect of formulation on the mechanical strength of pellets

Variable	Formulation	Mean crushing force (N)[a]	S.D.	F-values
Drug type	PLA 2:3:5	1.06	0.14	
	PIA 2:3:5	0.55	0.09	105.5***
	PaLA 2:3:5	1.31	0.18	25.4***
	ELA 2:3:5	0.93	0.10	6.5*
	SLA 2:3:5	1.36	0.19	37.7**
Drug level	PLA 0.5:4.5:5	1.27	0.18	18.7***
	PLA 1:4:5	1.27	0.23	2.81
	PLA 3:2:5	0.98	0.16	18.9***
	PLA 4:1:5	0.93	0.19	6.64*
	PLA 5:0:5	0.91	0.16	9.05
Filler type (−)	PGA 2:3:5	0.70	0.12	54.1***
	PMA 2:3:5	0.80	0.12	28.4***
	PCA 2:3:5	0.75	0.09	36.7***
	PBA 2:3:5	0.68	0.17	60.4***
Filler type (+)	PGA 0.5:4.5:5	0.94	0.13	6.0*
	PMA 0.5:4.5:5	1.12	0.17	1.5
	PCA 0.5:4.5:5	0.63	0.18	76.7***
	PBA 0.5:4.5:5	0.80	0.12	28.4***

[a] Mean ($n = 20$); S.D. = standard deviation ($n = 20$).
Variance between classes, 1.21; variance within classes, 0.024; 1st degree of freedom, 17; 2nd degree of freedom, 342; *, $P < 0.05$; **, $P < 0.01$, ***, $P < 0.001$.

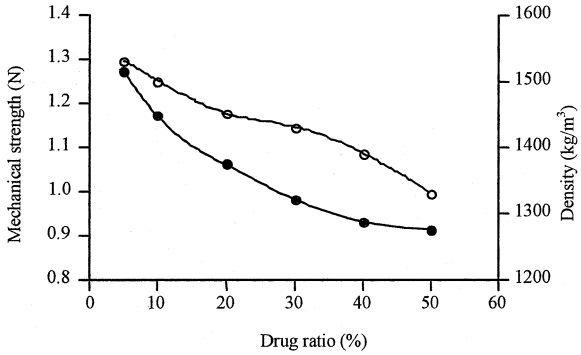

Fig. 4. The pellet apparent density (○) and mechanical strength (●) for preparations obtained with different ratios of propranolol to lactose.

3.8.2. Inter-ranging communalities d

These values (Table 8) describe the variance of one variable, which can be explained, by the variance of the other range of variables.

The *d*-values indicate that for pellet size, density and in a limited way for porosity a relationship with the influence variables exist, whereas the other pellet properties do not depend on the influence factors employed.

3.8.3. Significant influence factors

In the final step, the canonical analysis provides a list of significant influence factors for each dependent variable. These results should, however, be discussed in relation to the *d*-values listed in Table 8.

3.8.3.1. Extrusion force (values from Table 4). Canonical analysis indicated that the filler solubility is the only influence factor for this variable ($P = 0.009$). The small *d*-value is a sign that other variables should be considered which are currently unknown. Actually the behaviour of the different fillers during the extrusion process varied according to their water solubility. Preparations with glucose, either in the lower or upper level tended to stick to the internal barrel wall, making it difficult for the wet mass to flow easily. This is not related only to the solubility but also perhaps to the way the water is distributed inside the powder mass. On the other hand, with insoluble fillers, the wet mass becomes smooth and the extrudate flows easily through the die. With these fillers small variations in the water content do not have the drastic effect as observed with very soluble fillers, and the behaviour of the wet mass is more constant. For median soluble fillers (lactose) the way the water is held inside the mass is different from the former two groups. The movement of the water was evident and part of the lactose could be dissolved during the extrusion. The dissolution of the soluble components leads to different liquid phases within the extrudate. While the first portion is wet, the later extrudate is dry. The graphs of extrusion force obtained with these preparations showed irregular portions of the curve, as well as a sudden increase in the pressure towards the end of the process, representing force flow.

Table 8
d-Values and their significance levels for the range of variables assessed by canonical analysis

Variables	*d*-value	Significance level
d^2_{force}	0.460	n.s.
d^2_{size}	0.791	$P<0.001$
$d^2_{\text{perimeter}}$	0.233	n.s.
d^2_{shape}	0.193	n.s.
d^2_{AR}	0.177	n.s.
d^2_{density}	0.572	$P = 0.019$
d^2_{porosity}	0.480	$P = 0.059$ (n.s.)
d^2_{strength}	0.419	n.s.

3.8.3.2. Yield of the selected fraction size (values from Table 2). The reproducibility in obtaining the optimal size of spheres was influenced by the drug solubility ($P < 0.001$) and the filler solubility ($P = 0.015$). This is probably due to the critical level of water required to obtain the wet mass when highly soluble drugs or fillers are present. For these, small differences in the total amount of water can signify a good yield or the loss of the batch. The difference between the amount of water required when insoluble and soluble materials (drugs or fillers) are present, is not only important in absolute terms but also in the correct calculation.

3.8.3.3. Shape factor (values in Table 5). The value of the shape factor was not influenced by any of

the independent variables studied, but as the process attempts to prepare spherical pellets, this is perhaps not surprising.

3.8.3.4. Density of pellets (values in Table 6). The influence of drug level ($P = 0.034$) and filler level ($P = 0.013$) on this variable can be explained by the differences, which exist in the density of the raw materials. As shown in Table 6, for a given diluent (lactose), when the level of propranolol increased, the density of resultant pellets decreased significantly. The results obtained with high-density fillers when used in a lower or higher level explained the statistical differences observed. Furthermore, it is interesting that a statistical significance can be observed for the filler solubility as an independent variable ($P = 0.017$). One possible explanation lies in the compact structure obtained with pellets made with mannitol. Although the apparent density of pellets followed the density of the corresponding powders, the values are closer for low-density fillers (glucose, mannitol and lactose) than those with high density (calcium phosphate and barium sulphate).

3.8.3.5. Porosity (values in Table 6). The results showed that there was a statistical difference that was caused by the drug level ($P = 0.013$) and filler solubility ($P = 0.046$), otherwise no significant relationship can be established (compare *d*-values).

3.8.3.6. Mechanical strength (values in Table 7). The drug level was identified as the independent variable, which had a statistical influence ($P = 0.037$) on the strength of pellets. This could be due to the corresponding change in the quantity of MCC in the pellets. MCC is a strong binder and as its proportion increase, so does the mechanical strength of the pellets.

3.9. Multiple regression analysis

From the quantitative analysis of the degree of influence of each independent variable, it could be possible to predict their behaviour when processed in these types of preparations if relationships can be established between in input variables and the responses. To achieve this, a multiple regression analysis was performed based on the suggestions of the canonical analysis. As the groups of variables are independent of each other, it is possible to calculate the best equation, which relates them. This is only possible in the cases where a statistically significant relationship was observed. Various relationships were tried beginning with a simple multiple-linear one, and the equation, which provided the lowest value of both P and root mean square of the fit (R.M.S.) was chosen.

3.9.1. Calculation of the regression equations

3.9.1.1. Extrusion force. The influence of the filler solubility on this variable can be described by a logarithmic equation as follows:

$$\text{Extrusion force} = 0.350 \times \ln(\text{filler solubility}) + 9.384$$

which is characterised by $F = 11.58$, $P = 0.004$ and R.M.S. = 18.28%. From this equation it can be seen that, because there is a logarithmic relationship, a small increase in the filler solubility can produce a large increase in the extrusion force for very soluble fillers, while for practically insoluble fillers only small differences are found, which are not significant.

3.9.1.2. Pellets in required fraction size. The best equation obtained corresponds to a linear relationship between filler and drug solubility:

$$\text{Pellets in size fraction } 0.7\text{–}1.7 = -0.0099 \times \text{filler solubility} - 0.0303 \times \text{drug solubility} + 90.8671$$

with $F = 21.48$, $P = 0.001$ and R.M.S. = 5.22%. From this equation it is obvious that an increase in both the filler and the drug solubility leads to a reduction in the yield obtained for the selected pellet fraction size. The low value of RMS obtained indicates a good fit between the theoretical and the experimental values.

3.9.1.3. Pellet density. The multiple regression equation obtained for this variable is:

$$\text{Pellet density} = 0.0095 \times \text{filler level} - 0.0004 \times \text{filler solubility} + 0.0063 \times \text{drug level} + 1.109$$

where $F = 6.23$, $P = 0.007$ and R.M.S. = 9.91%. This provides a significant linear relationship and shows that if the filler or drug level increases an increase in pellet density can be expected. On the other hand, the pellet density will decrease if the filler solubility decreases, no doubt due to the high density of the insoluble fillers used in these experiments.

3.9.1.4. Pellet porosity. The equation, which relates the independent factors with this variable is:

$$\text{Porosity} = 0.0005 \times (\text{filler solubility})^{-1} + 0.0004 \times \text{drug level} + 0.0204$$

where $F = 81.95$, $P < 0.001$ and R.M.S. = 32.58%. Although there is a significant slope, the high R.M.S. obtained provides a poor fit between theoretical and experimental data, indicating some degree of uncertainty in this relationship even if it is still significant. The assumption that an increase in the drug level leads to an increase in the porosity value, while an increase on the filler solubility has the opposite effect, provides conflicting information on the way in which soluble materials influences the porosity of the pellets. That the drugs have a pharmacological effect is of no significance in terms of pellet formation. Some factor must differentiate between the behaviour of the drugs and the fillers, other than their solubility.

3.9.1.5. Pellet strength. The prediction of the pellets strength can be provided by the relationship:

$$\text{Strength} = -0.0937 \times (\text{drug level})^{1/2} + 1.4804$$

where $F = 9.00$, $P = 0.008$ and R.M.S. = 21.34%. From the equation shown it can be assumed that an increase in the drug level signifies a decrease in the resultant strength of pellets. The effect is less pronounced for low drug loading (square root relationship). The fit is not too good but nevertheless the relationship is significant.

3.10. Discussion

The production of pellets with good physical characteristics depends on the properties of the materials used and the success of the process can be classified as formulation dependent. One of the most critical variables is the identification of the most appropriate amount of water incorporated into the formulation. It not only interacts with the particle size but can also imply structural modifications. The appropriate amount depends largely on the solubility of both fillers and drugs. However, it seems to be more critical when the solubility of those components increases. The extrusion force recorded during the extrusion process gives an important estimation of whether the formulation will or will not be successful. However, when a correct formulation was established the extrusion force, which represents both the resistance of the material to enter the die and the resistance of the material to flow through the die, was found to be similar for all the preparations analysed. Whatever the solubility of the components and consequently the amount of water used, statistical difference between the extrusion force values only occurred when the formulation tends to be problematic. The residual moisture in the pellets after the drying process was consistent with the removal of the free water added to be able to provide the consistency to extrude and spheronize the formulation and provided an indication that the drying process was effective.

The sphericity of the pellets, judged in terms of their shape factor values also depends on the solubility of the materials used. In some extreme cases it was not possible to produce extrudate which could be formed into pellets. Such systems were not included in the statistical analysis. When the correct proportions of the different components was achieved these values seem to be constant, at least within narrow ranges. The results obtained suggested that ideal proportions of drug/filler exist which should be calculated for each different case.

The density of the pellets produced by extrusion/spheronization, using a ram extruder, was mainly

related to the density of the materials used in the formulation. The calculated porosity also seems to be related to the amount of water used and the solubility of the filler and drug. However, the drugs with the highest and lowest solubility did not fit into this pattern.

As the porosity is an indication of the structure of the pellets, it was also expected that similar interference occurred in the mechanical strength. This assumption was valid for some formulations but surprisingly some batches gave higher porosities and simultaneously higher mechanical strength values. This can be associated with the type and amount of filler used rather than its solubility. Pellets produced either with insoluble (barium sulphate) or soluble (mannitol) fillers have mechanical strength significantly different from the pellets obtained with the most soluble filler (glucose). This can be explained by the structure established between the filler particles (glucose) and drug (sodium salicylate) after their partial dissolution and recrystallization on drying.

For the first time, quantitative relationships were obtained between formulation parameters and pellet characteristics. There is however, some way to go before formulations can be predicted from drug and filler properties.

4. Conclusions

The extrusion force required to produce extrudate suitable for spheronization was found to be influenced by the absence of lactose and the presence of a high level of glucose. All other formulations required a similar extrusion force.

The absence of lactose was again the only factor, which had a significant influence on the shape of the pellets. All formulations produced pellets, which had an acceptable level of sphericity.

The apparent pellet density was strongly influenced by the composition. The porosity of the pellets increased as the proportion of water insoluble material in the formulation increased.

The mechanical properties of the pellets were related to the porosity. Pellets with a low porosity were stronger than those with a high porosity. The higher the proportion of MCC in the pellets the greater was their mechanical strength.

Quantitative relationships have been identified, which allow prediction of the extrusion force, the quantity of pellets in the required size fraction, the pellet density, porosity and mechanical strength from the quantities of the various components of the formulations.

References

Baert, L., Remon, J.P., Knight, P., Newton, J.M., 1992. A comparison between the extrusion forces and sphere quality of a gravity feed extruder and a ram extruder. Int. J. Pharm. 86, 187–192.

Bains, D., Boutelle, S.L., Newton, J.M., 1991. The influence of moisture content on the preparation of spherical granules of barium sulphate and microcrsytalline cellulose. Int. J. Pharm. 69, 233–237.

Bianchini, R., 1992. Influence of extrusion-spheronization processing on the physical properties of d-indobufen pellets containing pH adjusters. Drug Dev. Ind. Pharm. 18, 1485–1503.

Bianchini, R., Vecchio, C., 1988. Modified release beads coated with cellulose derivatives by pan technique. Boll. Chim. Farm. 126, 441–448.

Chapman, S.R., 1985. Influence of process variables on the production of spherical granules, Ph.D. Thesis, University of London.

Clarke, G.M., Newton, J.M., Short, M.B., 1995. Comparative gastrointestinal transit of pellet systems of varying density. Int. J. Pharm. 114, 1–11.

Fielden, K.E., Newton, J.M., Rowe, R.C., 1989. The effect of lactose particle size on the extrusion properties of microcrystalline cellulose-lactose mixtures. J. Pharm. Pharma. 41, 217–221.

Fielden, K.E., Newton, J.M., Rowe, R.C., 1992. A comparison of the extrusion and spheronization behaviour of wet powder masses processed by a ram extruder and a cylinder extruder. Int. J. Pharm. 81, 225–233.

Harrison, P., 1983. The evaluation of wet powder masses used in the process of extrusion/spheronization, Ph.D. Thesis, University of London.

Lustig-Gustafsson, C., Kaur Johal, H., Podczeck, F., Newton, J.M., 1999. The influence of water content and drug solubility on the formulation of pellets by extrusion and spheronization. Eur. J. Pharm. Sci. 8, 147–152.

Newton, J.M., 1994. In: Chulia, D., Deleuil, M., Pourcelot, Y. (Eds.), Extrusion/spheronization, in Powder Technology and Pharmaceutical Processes. Elsevier, Amsterdam.

Newton, J.M., Chapman, S.R., Rowe, R.C., 1995a. The assessment of the scale up performance of the extrusion/spheronization process. Int. J. Pharm. 120, 95–99.

Newton, J.M., Chapman, S.R., Rowe, R.C., 1995b. The influence of process variables on the preparation and properties

of spherical granules by the process of extrusion/spheronization. Int. J. Pharm. 120, 101–109.

Noche, C., Barochez, B.H., Brossard, C., Horvath, S., Cuiné, A., 1994. Optimising the manufacturing process for controlled release pellets. Pharm. Techn. Eur. 4, 39–46.

Otsuka, M., Gao, J., Matsuda, Y., 1994. Effect of amount of added water during extrusion-spheronization process on pharmaceutical properties of granules. Drug Dev. Ind. Pharm. 20, 2977–2992.

Podczeck, F., Newton, J.M., 1994. A shape factor to characterize the quality of spheroids. J. Pharm. Pharmacol. 46, 82–85.

Podczeck, F., Merkel, G., Revesz, P., 1993. The application of canonical analysis to the evaluation of the influence of changes in the components of standard direct compression tablet formulations. Int. J. Pharm. 97, 15–28.

Podczeck, F., Rahman, S.R., Newton, J.M., 1999. Evaluation of a standardised procedure to assess the shape of pellets using image analysis. Int. J. Pharm. 192, 123–138.

Rekki, G.S., Porter, S.C., Jambhekar, S.S., 1995. Factors affecting the release of Propranolol hydrochloride from beads coated with aqueous polymeric dispersions. Drug Dev. Ind. Pharm. 21, 709–729.

Tomer, G., Podczeck, F.and, Newton, J.M., 2001. The influence of the type and quantity of model drug on the extrusion/spheronization of mixtures with micocrystalline cellulose 1 extrusion parameters. Int. J. Pharm. 217, 237–248.

Vecchio, C., Bruni, G., Gazzaniga, A., 1994. Preparation of indobufen pellets by using centrifugal rotary fluidized bed equipment without starting seeds. Drug Dev. Ind. Pharm. 20, 1943–1956.

Vervaet, C., Baert, L., Remon, J.P., 1994. Enhancement of in vitro drug release by using polyethyleneglycol 400 and PEG-40 hydrogenated castor oil in pellets made by extrusion/spheronization. Int. J. Pharm. 108, 207–212.

Woodruff, C.W., Nuessle, N.O., 1972. Effect of processing variables on particles obtained by extrusion-spheronization processing. J. Pharm. Sci. 61, 787–790.