ELSEVIER

International Journal of Pharmaceutics 144 (1996) 159–169

international journal of pharmaceutics

Influence of process conditions on drug release from pellets

J.J. Sousa[a,b,*], 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, 29–39 Brunswick Square, London, WC 1N 1AX, UK*

Received 19 July 1996; accepted 10 September 1996

Abstract

The preparation of pellets by the extrusion/spheronization process is widely used. Although a body of work already exists which identifies the most important factors involved, there are areas of uncertainty still remaining. One of them is the role of water. In addition to the effect water has on the physical characteristics of the pellets, some authors have also noted that the amount of water required for extrusion can influence the dissolution profiles achieved with this dosage form. The objective of this work was to study the different ways in which water can be considered an active excipient in terms of the amount used to obtain the wet mass, the dispersion within the mass and the drying process. To achieve this goal, a statistical design was performed, considering three levels for the first variable (water content) and two for both the second (pre-extruser storage time) and third (drying process). Physical characteristics of the pellets were analysed for pellets within the same fraction size of 1–1.4 mm diameter. The analysis indicated that the amount of water and the extrusion and drying processes are of great importance and influenced the physical characteristics of the resultant pellets. As the analysis of variance procedure indicates, the influence of the independent variables on the dissolution characteristics of AUC, MDT, RDC and cumulative drug release after 12 h are related in a complex manner to the different pellet performances. Hence, water should be considered as an 'active' excipient rather than an inert component of the extrusion masses. Copyright © 1996 Elsevier Science B.V.

Keywords: Drug release; Extrusion/spheronization; Pellets; Pellet structure

1. Introduction

Sustained release preparations have become a suitable way of solving some problems connected with classical oral pharmaceutical dosage forms. Certain drugs—principally those with a short half-life—are of more benefit when administered daily in a form which maintains the drug blood

* Corresponding author. Tel.: +44 171 7535800; fax: +44 171 7535942; e-mail: jjssou@pharm.lon.ac.uk

PII S0378-5173(96)04745-X

level over the 'minimum effective level' (Ligarski et al., 1991).

Among the various methods that have been proposed, pellets, due to their particular properties seem an attractive method in the design and development of these kind of preparations. In fact, pellets or beads, have the minimum surface/volume ratio and are an ideal shape for coating. These properties offer a practical method to control the site and rate of drug dissolution in the gastro-intestinal tract. Moreover, the lower level of gastric irritation, the fewer dose dumping accidents and the possibility of building up different barriers for different drugs are a few of the advantages which confirm the success of this particular dosage form (Follonier and Doelker, 1992).

One of the most successful processes to obtain pellets is extrusion/spheronization, which came increasingly into use during the late 1970s (Newton, 1990). Since then, various works have been published pointing out the interacting factors of the whole process: the formulation factors (Hasznos et al., 1992), the extrusion conditions (Bataille et al., 1993) and the relationship with the quality of the spheres (Noché et al., 1994; Vervaet et al., 1994) are some of these studies.

Among the formulation factors, the role of water as a binding agent has been seen of great importance with respect to the physical performance of the end product (Bains et al., 1991). Because it acts as a binder during wet massing, a lubricant during extrusion and a plasticizer during spheronization, it can be considered as a critical variable in the extrusion (Hileman et al., 1993).

Furthermore, as concluded by Dyer et al. (1994) and Kleinebudde (1994a,b) the drying process has a great influence in the pellets structure and can be closely related to the drug release pattern.

The objective of this work was to study the behaviour of water in three stages of the extrusion/spheronization process: the wetting phase, the water distribution within the powder mix and the drying process.

2. Materials and methods

2.1. Materials

Propranolol hydrochloride, BP (Lusochimica, Milano, Italy), Barium sulphate, EP (Sachtleben Chemie GmbH, Hamburg, Germany) and cellulose microcrystalline (Avicel PH101) (FMC, Cork, Ireland) were used as received. Water freshly demineralised, was used as a liquid binder. Freshly distilled water was used as a medium in the dissolution tests.

2.2. Formulation

The same formulation was used, based in a model drug propranolol hydrochloride (P), barium sulphate (B) and Avicel PH101 (A) in the ratio 1:9:10. Water, as will be explained below, was used in terms of 10.8; 11.2; 11.6 and added to the solid mixture.

2.3. Preliminary studies

In the extrusion/spheronization process, particles are formed from extrudate during the spheronization step. As a consequence the extrudate must break down in small pieces and form round pellets due to the force in the spheronizer, so the mass has to fulfill several requirements. It must be brittle enough to break down in small cylinders but it must be sufficiently cohesive not to be deaggregated in the spheronizer (Lindner and Kleinebudde, 1994).

Preliminary studies had shown by trial and error, that using these materials, the ratio of water between 9 and 11 parts of the dry mixture was necessary to provide appropriate consistency. This allows a wet mass to be obtained with appropriate rheological characteristics that can give a high yield of spheres in the chosen fraction size.

Initial experiments confirmed that the lower the content of water, the higher the dust formation during forward steps. Conversely, the larger the amount of water, the larger the trend of the extrudate or pellets to agglomerate during the spheronization process.

Preliminary experiments were also carried out to identify appropriate conditions for successful coating.

2.4. Experimental design

A factorial design was used to study the effect of the water in pellets characteristics. Three factors were choosen:

(1) The amount of water required for mixing: 10.8 (W1); 11.2 (W2) and 11.6 parts (W3).
(2) The lag time between massing and extrusion: immediately prior to extrusion (E1); after 12 h storage in a closed container (E2).
(3) The drying process: in a tray oven (D1); in a fluid bed dryer (D2).

The factorial design comprised 12 experiments as shown on Table 1. All the other experimental conditions, described below were constant.

2.5. Extrusion/spheronization process

The pellets were produced by the following process.

Table 1
Experimental design

Prep. No.	Level		
	W[a]	E[b]	D[c]
1	1	1	1
2	1	1	2
3	1	2	1
4	1	2	2
5	2	1	1
6	2	1	2
7	2	2	1
8	2	2	2
9	3	1	1
10	3	1	2
11	3	2	1
12	3	2	2

[a]Water content.
[b]Pre-extruser storage time.
[c]Drying process.

2.5.1. Dry mixing

Dry powders were weighed (eletronic balance, Mettler PC 1616, Mettler Instruments AG, Greifensee, Zürich, Switzerland) and mixed in a planetary mixer (Chef KN 201, Kenwood, Woking, UK) for 10 min.

2.5.2. Wet mass

The water required for each mix was added, and allowed to mix for further 10 min.

2.5.3. Extrusion

According to the experimental design, Preparations 1, 2, 5, 6, 9 and 10 were extruded immediately after the wetting phase (E1); preparations 3, 4, 7, 8, 11 and 12 were stored for 12 h in a well closed plastic bag (E2) before extrusion.

For all the preparations, the wet mass was extruded through a 1 mm/4 mm (diameter/length) die, using a ram extruder fitted to a physical testing instrument (Lloyds MX 50, Lloyds Instruments, Southampton, UK) fitted with a 50 KN load cell, at a constant cross-head speed of 250 mm/min.

2.5.4. Spheronization

A spheronizer (Caleva, Sturminster Newton, Dorset, UK) fitted with a radial plate with 203.2 mm/diameter was used. Extrudates were left to round for 10 min at a fixed speed of 1000 rpm.

2.5.5. Drying

Preparations 1, 3, 5, 7, 9, and 11 (D1) were dried for 24 h in a tray oven equiped with a fan (Hotbox oven, Size 1, Gallenkamp, Leicester, UK) at 35°C. Preparations 2, 4, 6, 8, 10 and 12 (D2) were dried in a fluid bed dryer (model, FBD/L70, PRI Engineering, Mostyn, Flintshire, UK) at 35°C for 30 min.

2.5.6. Coating

All the preparations were coated with a ethylcellulose latex preparation, Surelease E-7050 (Colorcon, Orpington, Kent, UK), previously diluted to 15% total solids, to give 10% weight gain in a fluid bed coater (Strea 1, Aeromatic, Bubendorf, Switzerland). The coating conditions are shown on Table 2. Each cycle took on average 15 min.

Table 2
Coating conditions

Coating parameters	Set values
Batch size (g)	40
Inlet air temperature (°C)	50
Outlet air temperature (°C)	40
Atomizing air (bar)	0.2
Air pressure	35
Air volume (m^3/h)	100
Feed rate (ml/min.)	3

2.6. Analysis of the spheres

2.6.1. Determination of drug content

A sample of pellets was ground and the resultant powder was suspended in water, shaken and filtered. An amount equivalent to 3 mg of drug was diluted to perform 100 ml with water and analysed for propranolol content in a UV spectrophotometer at 288 nm (model 554, Bodenseewerk Perkin Elmer, GmbH, Überlingen, Germany).

2.6.2. Sieve analysis

Pellets were analysed for size using a mechanical method (Sieve shaker, Endecotts, London, UK). Each preparation (100 g) was shaken for 10 min. The mesh diameter of the British Standard followed a $\sqrt{2}$ progression between 500 and 2000 μm.

2.6.3. 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 module, Rengo, Toyohashi, Japan) connected to a zoom lens (18-108/2-5, Olympus, Hamburg, Germany) and analysed for shape as descibed by Podczeck and Newton (1994). According to these authors, the characterization of the shape of a particle, taking in account the surface roughness, is based on a shape factor, E_r, calculated as follow:

$$E_r = \frac{2\pi r}{P_m} - \sqrt{1 - (b/\lambda)^2} \quad (1)$$

where P_m is the measured perimeter, r the mean radius of the circle, λ the length of the elipse and b the breadth of the ellipse, representing the largest distance perpendicular to the length axis. Eq. (1) related the surface roughness (first part) and the linear eccentricity (part under the square root signal). According to Eq. (1) only a circle can have an E_r value of 1.0. However, due to the fact that the image is projected as a two dimensional shape, light can reflect due to shadows resulting in change of the real image which was confirmed (Podczeck and Newton, 1994) when a perfect sphere (ball bearing) was found to have a E_r of 0.766, using a light table (the image of the pellets was thus black on a bright backgroung, and dark shadows could alter the image).

To cary out this analysis, 40 spheres were mounted in a petri dish previously painted with non reflective black ink. The pellets were lit from the top using a cold light source (Olympus, Hamburg, Germany). The image was thus white pellets on a black background, and the dark shadows only influenced the shape to a small extent.

2.6.4. Density and porosity

Samples of pellets were weighed (Oertling YP4 balance, Orpington, UK) and placed in the air pycnometer (Beckman model 930, Irvin, USA) using ambient air as a gaseous medium. The mean of three samples was determined. Porosity was then calculated from the following Eq. (2):

$$\text{Porosity} = 1 - (\text{granule density}/\text{particle density}) \quad (2)$$

2.6.5. Crushing strength

Twenty pellets of each formulation were evaluated by diametrical crushing force using a tablet strength tester (CT40 Engineering Systems, Nottingham, UK).

2.6.6. Water content

The residual water present in the pellets after drying was determined by thermogravimetric analysis (TGA Hi-Res TGA 2950 Thermogravimetric Analyser connected with a Thermal Analyst 2000, TA Instruments, New Castle, Delaware, USA).

Table 3
Results of the physical tests performed on uncoated pellets

	Preparation number											
	1	2	3	4	5	6	7	8	9	10	11	12
E_r	0.58	0.602	0.603	0.612	0.616	0.636	0.598	0.613	0.574	0.605	0.568	0.596
A.R.	1.11	1.09	1.09	1.10	1.10	1.08	1.09	1.10	1.12	1.11	1.12	1.11
Per	3218	3349	3141	3306	3589	3482	3582	3520	4225	4318	4551	4480
Den	2.14	2.15	2.14	2.14	2.12	2.14	2.14	2.12	2.08	2.14	2.13	2.14
Por	0.24	0.23	0.24	0.24	0.24	0.24	0.24	0.24	0.26	0.24	0.24	0.24
C.F.	0.70	0.70	0.83	0.79	0.88	0.77	1.03	1.00	1.38	1.28	1.38	1.40
RW	1.89	1.99	1.96	1.98	1.75	1.81	1.78	1.82	1.81	1.81	1.83	1.78
SA		1.46				2.58				2.98		
Dc	102.1	101.6	99.8	100.1	100.0	100.0	101.1	99.8	98.9	101.5	100.6	100.6

E_r, Shape factor ($n = 40$); AR, aspect ratio ($n = 40$); Per, perimeter (mm) ($n = 40$); SA, specific area (m^2/g); Den, density (g/cm^3) ($n = 3$); Por, porosity; CF, crushing force (N) ($n = 20$); RW, residual water (%) ($n = 3$); Dc, drug content (%).

2.6.7. SEM

Scanning eletron microphotographs (SEM) of the surface, structure and membrane thickness were taken before and after dissolution test (Philips, serie 2000, Philips Technology, Eidhoven, The Netherlands).

2.6.8. DSC

Samples of pellets as well as the powder blends (typically 5–7 mg) were sealed in an aluminium seal and heated at 10°C/min. from room temperature to 300°C in a calorimeter (Shimadzu, Tokyo, Japan) under inert atmosphere of nitrogen.

2.6.9. Specific area

Samples from preparations 2, 6 and 10 (corresponding to each level of water) were analysed by BET technique for specific area using the gas adsorption technique with Krypton (ASAP 2000, Micrometrics Instruments, Norcross, USA).

2.6.10. Dissolution tests

Dissolution studies were performed according to the paddle method USP XXII, apparatus 2 (Pharmatest PTWS, Tredegar, Kent, UK), fitted with a pump (Ismatec IPS, Surrey, UK) and a sample collector (model PTFC II, Pharmatest, Tredegar, Gwent, UK), at a rotational speed of 100 rev/min.

From all the batches, three samples of uncoated (150 mg < > 3 mg of propranolol) and three of coated pellets (165 mg), were analysed.

Samples of the dissolution medium were taken after 15 min and at each hour for 12 h and analysed for propranolol content by a UV spectrophotometer at 288 nm.

3. Results and discussion

Table 3 shows the general characteristics of the pellets obtained.

3.1. Size distribution

The amount of water used during the wetting phase causes an increase in the median pellet size, whatever the following conditions of extrusion or drying process. Fig. 1 shows the level of water on the resultant median size of pellets obtained when the level of the influence of other variables (E and D) change.

3.2. Crushing strength and density

The strength data records the moment when the pellets first broke. Sometimes some pellets showed only a partial fraction but this was considered as the end point of the experiment. Fig. 2 shows the influence of the water content on this variable, when both the conditions of drying and the lag time before extrusion changed. It also can be seen

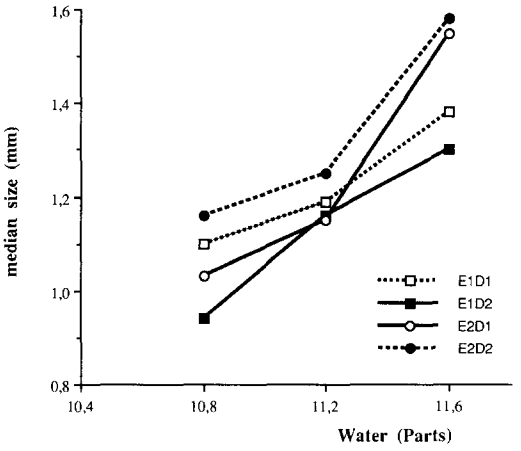

Fig. 1. Influence of the amount of water in the median size of pellets. □, E1D1; ■, E1D2; ○, E2D1; ●, E2D2.

that the absolute value of pellets crushing strength increased with the amount of water (Table 1). This is probably due to the 'water bridges' built after partial dissolution of a powder. Since the dry formulation was the same, an increase in the water level (W) or in the time which it was allowed to disperse within the mass, is responsable for a great number of those strong bonds which lead to a strong structure. It should be pointed out that in all the batches the residual moisture was lower than 2% (w/w).

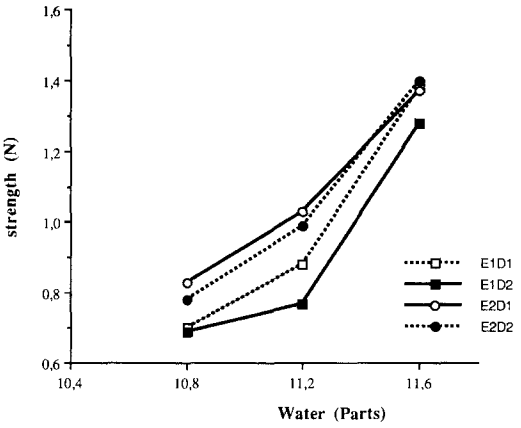

Fig. 2. Influence of production variables on the strength of pellets. Symbols are the same as for Fig 1.

Table 4
Influence of the independent variables on the strength of pellets

Variable	DF	F values
W[a]	2	409.59***
E[b]	1	43.85***
D[c]	1	6.71**
W/E	2	4.41*
W/D	2	0.60
E/D	1	2.27
W/E/D	2	1.90

[a]Water content.
[b]Preextruser storage time.
[c]Drying process.
***$P \leq 0.001$.
**$P \leq 0.01$.
*$P \leq 0.05$; degree of freedom for variance within the group: 228; degree of freedom for total variance: 239;

3.3. Statistical analysis

The analysis of variance for this dependent variable (Table 4) shows that only the factor 'drying' acts as an independent variable. Althought the extrusion lag time and water level show a positive effect they are included in the first degree of interaction (W/E), and therefore their single influence cannot be considered as influence factor. This results are in accordance with a previous paper (Bataille et al., 1993) which compared the strength of pellets dried in an oven tray and a microwave. Due to the high penetration of heat in the second process which give a quasi-immediate release of the water molecules the pellets became more porous and less strong (Bataille et al., 1993). As can be seen in Table 4, by comparison between pairs of preparations, pellets dried in fluid bed dryer are less strong than the correspondent pellets dried in an oven tray.

The analysis of the changes in density however did not show any differences, which means that this factor is only dependent on the density of the raw materials used. As residual water in all the batches is about 2% and as the composition is the same for all pellets the results also confirm the effectiveness of both drying methods. Differences between them should be considered in the speed of removal and the implications in structure

rather than in the residual moisture. Porosity was also identical in all batches.

3.4. Shape

Analysis of variance of the data obtained for perimeter, aspect ratio and shape factor, E_r, are shown in Table 5. The three independent variables act together and due to this interaction none of them, individually, can be responsible for the different results obtained for aspect ratio and shape factor, E_r. However, as seen for the mean pellet size, the perimeter value increases with the water content (Table 3). Changes are small and the pellets are all quite round.

3.5. DSC

As no significant differences were seen between the batches analysed, it can be concluded that the water which remained within the pellets is present as free water which may be readily lost by evaporation, confirming the findings of Fielden et al. (1988).

Table 5
ANOVA for diameter, aspect ratio and shape factor, E_r

Variable	DF	F values		
		Perimeter	Aspect ratio	Shape factor
W[a]	2	161.73***	91.10***	28.43***
E[b]	1	203.03***	186.16***	25.03***
D[c]	1	40.15***	209.27***	81.45***
W/E	2	138.93***	28.35***	10.51***
W/D	2	3.13**	19.41***	11.85***
E/D	1	15.34***	26.23***	14.08***
W/E/D	2	47.03***	1.35	1.19

[a]Water content.
[b]Preextruser storage time.
[c]Drying process.
*** $P \leq 0.001$.
** $P \leq 0.01$.
* $P \leq 0.05$; degree of freedom for variance within the group: 342; degree of freedom for total variance: 353.

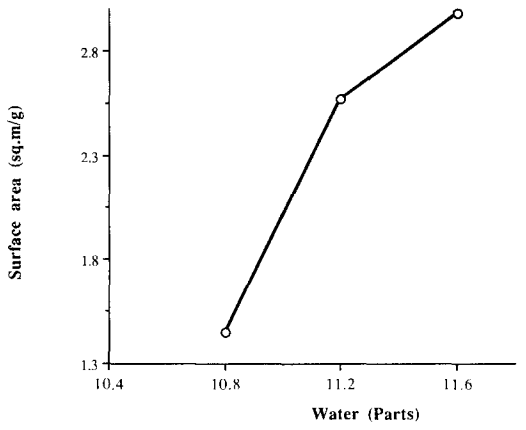

Fig. 3. Influence of water level in the specific surface area.

3.6. Specific area

Preparations 2, 6 and 10 were analysed for specific area by krypton adsorption. The results clearly demonstrated (Fig. 3) that the higher the level of water used the higher the specific area which may be related to the swelling properties of the insoluble fillers present in the formulation. Although porosity values of the different pellets are similar, the surface area determinations show that there are major changes in pellet structure.

3.7. Dissolution studies

The introduction of statistical moments in the characterization of the dissolution profiles (Brockmeier, 1986) has often been widely used in an effort to correlate in vitro and in vivo data.

One important approach is modelling the dissolution release profile of a drug. According Voegele et al. (1988) the first step to carry this out is the calculation of the mean and variance of dissolution times, considering the cumulative distribution function $F(t)$ which is the statistical representation of the the fraction of drug release in the time t, and the probability density function $f(t)$ which are conversible:

$$dF(t)/dt = f(t) \text{ and } \int f(t)\,dt = \int dF(t) = F(t) \quad (3)$$

Various different moments can be calculated during the residence time of the drug in the dosage form:

$$m_k = \int_0^t t^k \cdot f(t) \cdot d(t) = \int_0^t t^k \, dF(t) \quad (4)$$

the limits of zero and infinity (or the final time).

If K equals unity, the mean of dissolution time is achieved, representing the first moment,

$$m_1 = \int t \cdot f(t) \cdot dt \quad (5)$$

Again, when K is equal to 2:

$$m_2 = \int t^2 \cdot f(t) \cdot dt \quad (6)$$

the second moment is generated.

Voegele et al. (1988) defined the variance of dissolution times (VDT) as the difference between the second common moment and the squared mean:

$$m_2 - MDT^2 = VDT \quad (7)$$

It follows that the calculation of the relative dispersion of dissolution times (RDC) can be obtain as:

$$RDC = VDT/MT^2 \quad (8)$$

This is used as a measure of the width of a distribution and serves as a discriminator in the specification of which model function best fits the data obtained.

With these values, simple equations (Table 6) can be drawn to define the rate constants for zero order release, first order release, square root law and cube route law, which only requires the mean dissolution time to define these standardized dissolutions profiles (Voegele et al., 1988).

Table 6
Relation between relative dispersion and model dissolution behaviour according to Voegele et al. (1988)

Dissolution model	Eqs.	Relative dispersion
Zero-order	$K = 1/(2 \cdot MT)$	0.333
First order	$K = 1/MT$	1.0
Square root	$K = 1/(3 \cdot MT)^{1/2}$	0.8
Cube root	$K = 1/(4 \cdot MT)$	0.6

However, when the Weibull function is applied, the relation between the amount of drug release up to the time t, designated as $M(t)$ and the final amount released Mo, is given by the expression:

$$M(t)/Mo = 1 - e^{-(k-t)^{\beta}} \quad (9)$$

In order to derive the model parameters k and β by mean and variance of dissolution times, it is necessary to use the gamma-function in order to carry out the integration step. With this approach, there is an initial relation between β and the relative dispersion, and the rate constant, k, is related to the mean and a value of the γ-function of

$$\frac{1}{\beta + 1} \quad (10)$$

The release profile will be sigmoidal when RDC is smaller than unity and conversely shows steepness when RDC is larger than unity (Voegele et al., 1988). When RDC is 1, a first order release is achieved.

Analysing the influence of the independent variables and their interaction on the relative dispersion factor (Table 7), it can be seen that the drying process is actually acting as an independent factor and that there is an interaction between water level and extrusion lag time (Fig. 4).

Considering the mathematical approaches presented by Voegele et al. (1988) for the RDC values, it seems that for the first level of water, the release profile switch between a non-Fickian release for pellets dried in tray oven and a zero-order profile for those dried in fluid-bed coater. For pellets produced with a medium level of water, the release profile pattern is closely related to a square root model. On the other hand, pellets obtained with the highest level of water, show a zero order release for the extrusion conditions designated as E2 while for E1 the release profile only can be explained by the Weibull-function showing an initial steep on the dissolution pattern. However, the characterisation of the different release profiles obtained can also be carried out by analysis of other dissolution properties. The values of area

Table 7
Area under the % drug dissolved time profile (AUC), mean dissolution time (MDT), variance of dissolution time (VDT), relative dispersion coefficient (RDC) and release at 12 h (Rel. 12 h)

Experiment no.	AUC (mg l^{-1} h)	MDT (h)	VDT (h^2)	RDC	Rel. 12 H (mg/100 ml)
1	103.3 ± 6.6	5.05 ± 0.27	13.26 ± 0.88	0.53 ± 0.05	20.36 ± 0.26
2	65.5 ± 2.1	6.9 ± 0.26	15.87 ± 2.4	0.34 ± 0.07	9.43 ± 0.20
3	118.3 ± 3.3	4.54 ± 0.21	15.00 ± 0.78	0.69 ± 0.07	25.58 ± 1.02
4	113.7 ± 15.7	5.90 ± 0.67	14.23 ± 2.45	0.39 ± 0.17	19.02 ± 0.54
5	147.8 ± 17.1	4.55 ± 0.50	14.44 ± 0.90	0.80 ± 0.19	34.5 ± 1.01
6	54.2 ± 4.0	4.93 ± 0.25	17.85 ± 1.69	0.81 ± 0.11	10.94 ± 0.42
7	171.4 ± 17.6	4.09 ± 0.49	14.03 ± 0.50	0.75 ± 0.21	42.91 ± 1.80
8	82.6 ± 2.5	4.25 ± 0.06	12.54 ± 0.30	0.70 ± 0.01	19.35 ± 0.44
9	155.3 ± 11.0	2.02 ± 0.12	8.65 ± 0.85	2.11 ± 0.09	77.07 ± 1.37
10	153.4 ± 31.4	1.76 ± 0.34	5.67 ± 1.20	2.08 ± 0.60	87.16 ± 2.27
11	442.0 ± 3.3	5.10 ± 0.06	7.42 ± 0.47	0.29 ± 0.02	86.49 ± 0.35
12	474.2 ± 3.0	5.28 ± 0.03	6.01 ± 0.15	0.22 ± 0.01	89.86 ± 0.17

For the formulations under study (results are the mean and standard deviation of three replicates).

under the curve (AUC), mean dissolution time (MDT), variance of dissolution time (VDT), percentage of drug released after 12 h (Rel. 12 h) and the relative dispersion coefficient (RDC) for the preparations under study are shown on Table 7.

It can be seen that the higher level of water (W3) leads to the fastest release independently of the extrusion lag time or the drying method. All the four preparations on this sub-group, reached high drug release which seem not be related to the other two variables. For the levels W1 and W2, the amount of drug released was considerably smaller. The influence of the lag time before extrusion also indicates differences on the release profile. The longer the time that water was allowed to disperse within the mass, the faster the release, when compared with preparations immediately extruded after the wet mix. These results can only be explained if we take into consideration the previous results obtained for physical characteristics of the pellets. It is obvious that when the same amount of coating material is sprayed onto spheres with different sizes and shape the thickness of the resultant film will not be the same, resulting in different drug release profiles.

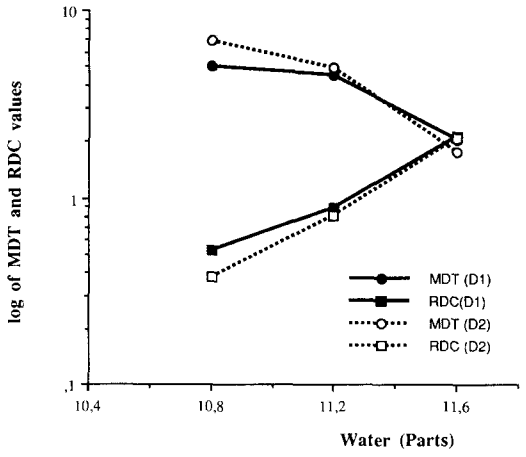

Fig. 4. Influence of water content on MDT and RDC values obtained with pellets dried under D1 and D2 conditions; ●, MDT(D1); ■, RDC(D1); ○, MDT(D2), □, RDC(D2).

The results of ANOVA (Table 8) for these variables show that for AUC and MDT no single factor acts alone and only the interaction should be considered. Conversely, the cumulative release profile up to 12 h of the dissolution test is influenced by the extrusion lag time (E) which indeed acts as a single factor plus the interaction between all the three variables.

4. Conclusions

The role of the water during the preparation of pellets by the extrusion/spheronization process seems to influence not only the physical character-

Table 8
ANOVA for AUC, MDT, RDC and cumulative release after 12 h

Factor	DF	F values			
		AUC	MDT	RDC	12 h
W	2	927.95***	113.85***	27.80***	14000***
E	1	760.85***	35.63***	61.37***	443.16***
D	1	55.16***	29.36***	5.77*	564.96***
WE	2	440.86***	141.10***	79.73***	1.58
WD	2	51.11***	20.21***	0.34	608.48***
ED	1	7.59**	0.13	0.03	1.19
WED	2	1.22	1.41	0.33	23.27***

[a]Water content
[b]Pre-extruser storage time;
[c]Drying process.
***$P \leq 0.001$.
**$P \leq 0.01$.
*$P \leq 0.05$; degree of freedom for variance within the group: 24; degree of freedom for total variance: 35.

istics of the resultant pellets but also the release pattern of the drugs entrapped in their structure.

A clear relation between the amount of water and the particle size distribution can be pointed out in this study. Moreover, the surface area, shape and structure are related not only to the amount but also to the drying process. On the other hand, while the density and porosity seems to be only related to the raw materials, the strength is influenced by the water level and the lag time between massing and extrusion.

All the preparations under study gave different release profiles that are not related to the film thickeness as this was a constant parameter. The differences were the different structures of the pellets obtained. Due to the inability of finding a relationship between the independent variables and the release behaviour, it can be concluded that not only the formulation itself but the process conditions are of paramount importance in the preformulation study of sustained release pellets obtained by extrusion/spheronization.

Acknowledgements

The authors would thanks to Professor Doutora Margarida Figueiredo and Eng. M. José (Instituto Pedro Nunes, Coimbra, Portugal) for the help conducting the specific surface analysis. João José Sousa is grateful to JNICT (Portugal) for financial support.

References

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

Bataille, B., Ligarski, K., Jacob, M., Thomas, C. and Duru, C., Study of the influence of spheronization and drying conditions on the physico-mechanical properties of neutral spheroids containing Avicel PH 101 and lactose. *Drug Dev. Ind. Pharm.*, 19 (1993) 653–671.

Brockmeier, D., In vitro/in vivo correlation of dissolution using moments of dissolution and transit times. *Acta Pharm. Techn.*, 32 (1986) 164–174.

Dyer, A.M., Khan, K.A. and Aulton, M.E., Effect of the drying method on the mechanical and drug release properties of pellets prepared by extrusion-spheronization. *Drug Dev. Ind. Pharm.*, 20 (1994) 3045–3068.

Fielden, K.E. Newton, J.M., O'Brien, P. and Rowe, R.C., Thermal stduies on the intercation of water and microcrystalline cellulose. *J. Pharm. Pharmacol.*, 40 (1988) 674–678.

Follonier, N. and Doelker, E., Biopharmaceutical comparison of oral multiple-unit and single-unit sustained-release dosage forms.: *STP Pharma Sci*, 2 (1992) 141–158.

Hasznos, L. Langer, I. and Gyarmathy, M., Some factors influencing pellet characteristics made by an extrusion/spheronization process. Part I: effects on size characteristics and moisture content decrease of pellets. *Drug Dev. Ind. Phar.*, 18 (1992) 409–437.

Hileman, G.A., Goskonda, S.R., Spalitto, A.J. and Upadrashta, S.M., A factorial approach to high dose product development by an extrusion/spheronization process. *Drug Dev. Ind. Pharm.*, 19 (1993) 483–491.

Kleinebudde, P., Shrinking and swelling properties of pellets containing microcrystalline cellulose and low substituted hydroxypropylcellulose: I. Shrinking properties. *Int. J. Pharm.*, 109 (1994a) 209–219.

Kleinebudde, P., Shrinking and swelling properties of pellets containing microcrystalline cellulose and low substituted hydroxypropylcellulose: II. Swelling properties. *Int. J. Pharm.*, 109 (1994b) 221–227.

Ligarski, K., Bataille, B., Jacob, M. and Cassanas, G., Influence des paramètres technologiques sur la dureté de minigranules fabriqués par extrusion/spheronization. *STP Pharma Sci.*, 1 (1991) 256–261.

Lindner, H. and Kleinebudde, P., Use of powdered cellulose for the production of pellets by extrusion/spheronization. *J. Pharm. Pharmacol.*, 46 (1994) 2–7.

Newton, J.M., The preparation of spherical granules by extrusion/spheronisation. *STP Pharma.*, 6 (1990) 396–398.

Noché, C. Barochez, B.H., Brossard, C., Horvath, S. and Cuiné, A., Optimizing the Manufacturing Process for Controlled Release Pellets. *Pharm. Techn. Eur.*, 4 (1994) 39–46.

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

Vervaet, C., Baert, L., Risha, P.A. and Remon, J.P., The influence of the extrusion screen on pellet quality using an instrumental basket extruder. *Int. J. Pharma.*, 107 (1994) 29–39.

Voegele, D., Brockmeier, D. and Hattingberg, H.M., Modelling of input function to drug absorption by moments. In *Proc. Symp Compartmental and Noncompartmental modelling in pharmaceutics, Czechoslovakia*, 1988, September 12–16.