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Preparation in high-shear mixer of sustained-release pellets by melt pelletisation

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Abstract

The preparation of sustained-release pellets by melt pelletisation was investigated in a 10-l high shear mixer and ternary mixtures containing stearic acid as a melting binder, anhydrous lactose as a filler and theophylline as a model drug. A translated Doehlert matrix was applied for the optimisation of process variables and quality control of pellets characteristics. After determination of size distribution, the pellets were characterised with scanning electron microscopy, X-ray photoelectron spectroscopy and porosimetric analysis. Finally, the in vitro release from every single size fraction was evaluated and the release mechanism was analysed. Since the drug release rate decreased when enhancing the pellet size fraction, the 2000-μm fraction, exhibiting a substantially zero-order release, was selected for further in vivo biovailability studies. These data demonstrated that pellets based on the combination of stearic acid and lactose can be used to formulate sustained release pellets for theophylline.

Keywords: Doehlert design; Melt pelletisation; High shear mixer; Sustained release

1. Introduction

Melt agglomeration is a process by which agglomeration is promoted through the addition of either a molten binder liquid, a solid binder that melts during the process. The product temperature is risen to above the binder melting point either by a heating jacket or by the heat of friction generated by the impeller blades when the impeller speed is high enough. This technique offers several advantages compared to the conventional wet granulation. Since the drying phase is eliminated, the process is less consuming in terms of time and energy (McTaggart et al., 1984).

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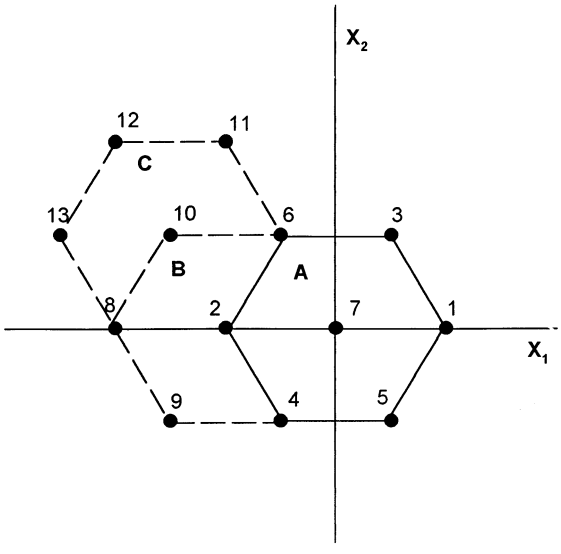
Even though various equipment have been used for melt agglomeration, high shear mixers are preferable for this technology. Schaefer (1997) has elucidated the variables that affect melt agglomeration using polyethylene glycols in different molecular weights as a melting binder in a Pellmix 10, Niro. The melt agglomeration technique was also proved to be a viable means for fabricating matrix pellets using a combination of a hydrophobic material and a starch derivative in a Grall 10 Collette high shear mixer (Zhou et al., 1996). This experience also demonstrated a further advantage of the melt granulation technique, that is, achieving a sustained drug release without any coating procedure. More recently, Thies and Kleinebudde (1999) applied the melt granulation technique to manufacture pellets containing an hygroscopic drug and glycerol monostearate as a binder in Diosna P10.

In our previous study an explorative analysis of the application of this technique for preparing granulates and pellets in a 10-l high shear mixer Roto J. Zanchetta has been carried out (Campisi et al., 1999). Then, with the same equipment, the effect of several process variables on melt agglomeration process had been studied (Voinovich et al., 1999). This work proved the feasibility of the melt granulation process and defined the experimental conditions and equipment modifications that permit to obtain a granulate or a pellet. In the present investigation, this technique has been applied to develop a sustained-release formulation of theophylline, using anhydrous lactose as a filler and stearic acid as a melting binder.



Experimental matrix	Exp.	X_1	X_2
A	1	1	0
	2	-1	0
	3	0.5	0.866
	4	-0.5	-0.866
	5	0.5	-0.866
	6	-0.5	0.866
	7	0	0
B	8	-2	0
	9	-1.5	-0.866
	10	-1.5	0.866
C	11	-1	1.732
	12	-2	1.732
	13	-2.5	0.866

Fig. 1. Doehlert matrix design and distribution of the experimental points in the space of two variables. Initial matrix (—), translated Doehlert matrix (---). The process variables (X_i) are expressed in terms of normalised values.

2. Experimental design

To reduce the number of runs needed to obtain the highest amount of information on product performance, the screening was planned using an experimental design. In particular, a Doehlert matrix (Doehlert, 1970) was employed for the optimisation of process variables and for quality control of granulation characteristics. The design has particular characteristics such as the possibility of translation and rotation, so each variable can take different number of distinct levels. These properties have been already described (Mathieu et al., 1999) and successfully exploited in preformulation studies of a granulation and in wet pelletisation of paracetamol (Vojnovic et al., 1993) and theophylline (Vojnovic et al., 1995) in a high shear mixer. The design is composed of seven uniformly distributed points in the experimental domain (Fig. 1). The process variables with their relative experimental values are reported in Table 1.

Table 1
Process variables (X_i) with their levels and measured responses (Y_i) for Doehlert design[a]

Normalised level	Experimental values
X_1 impeller speed (rpm)	
1	500
0	450
−1	400
X_2 massing time (min)	
1	17
0	11
−1	5

[a] Measured response. Y_1, percentage yield (w/w) of pellet size fraction.

3. Materials and methods

3.1. Materials

Anhydrous theophylline reagent-grade (Faravelli, Milano, Italy), stearic acid reagent-grade (Galeno, Milano, Italy), and monohydrate lactose EP-grade (Pharmatose 200 mesh, Meggle, Wasserburg, Germany) were used as starting materials.

3.2. Granulation manufacture

The granules were prepared in the 10-l laboratory scale Zanchetta Roto J. high shear mixer equipped with an electrically heated jacket (maximum temperature 100°C), already described in a previous work (Vojnovic et al., 1993).

The granulation procedure was standardised on the basis of preliminary trials, and the temperature of the powders inside the bowl was continuously recorded by a thermo-resistance probe fixed on the bowl lid and dipped in the powder mass.

The mixture composed of theophylline (60%), lactose (20%) and stearic acid (20%) was dry-mixed using an impeller speed of 100 rpm for 10 min. Successively, the mixture was heated up to 62°C. Impeller speed, and massing time were varied according to the experimental plan (Table 2). At the end of the granulation process the granules were cooled at room temperature by spreading them out in thin layers on trays.

3.3. Granule characterisation

The cooled granules were sieved in order to remove lumps larger than 3 mm and stored in well closed bags for 10 days.

Table 2
Experimental plan and observed response values[a]

Experiment	Process variables					Responses Y_1 (%)	
	X_1 (rpm)	X_2 (min)	2000 μm	1250 μm	800 μm	630 μm	<630 μm
1	500	11	27.89 ± 4.10	22.13 ± 3.75	11.94 ± 2.68	8.5 ± 1.00	29.54 ± 2.10
2	400	11	89.71 ± 1.40	9.64 ± 2.21	0.65 ± 0.18	0	0
3	475	16	20.32 ± 3.10	30.09 ± 1.70	23.30 ± 2.17	12.11 ± 1.47	14.18 ± 0.79
4	425	6	13.05 ± 2.75	19.27 ± 2.40	14.78 ± 3.12	5.84 ± 0.80	47.06 ± 1.18
5	475	6	10.61 ± 3.12	19.99 ± 2.68	17.45 ± 3.38	8.41 ± 1.02	43.54 ± 2.17
6	425	16	37.99 ± 0.17	42.95 ± 0.25	8.99 ± 0.90	2.56 ± 0.50	29.54 ± 1.32
7	450	11	50.36 ± 3.87	19.99 ± 2.46	30.54 ± 1.18	4.04 ± 0.76	6.58 ± 0.40
8	350	11	14.70 ± 2.80	42.95 ± 1.87	25.81 ± 2.81	1.65 ± 0.53	14.98 ± 3.01
9	375	6	5.89 ± 1.41	20.82 ± 1.12	28.65 ± 1.76	6.92 ± 1.36	37.72 ± 2.62
10	375	16	73.92 ± 0.80	25.16 ± 2.00	0.81 ± 0.02	0	0
11	400	21	Uncontrolled ball growth				
12	350	21	96.81 ± 2.12	3.19 ± 1.05	0	0	0
13	325	16	36.41 ± 3.20	51.92 ± 0.90	11.36 ± 2.80	0.31 ± 0.10	0

[a] Mean ± S.D., $n = 3$.

A vibrating apparatus (Octagon 200, Endecotts, London, UK) and a set of sieves (2000, 1250, 800, 630 μm) were used for size distribution determinations. The yield of each size fraction was evaluated after removal of lumps larger than 3 mm.

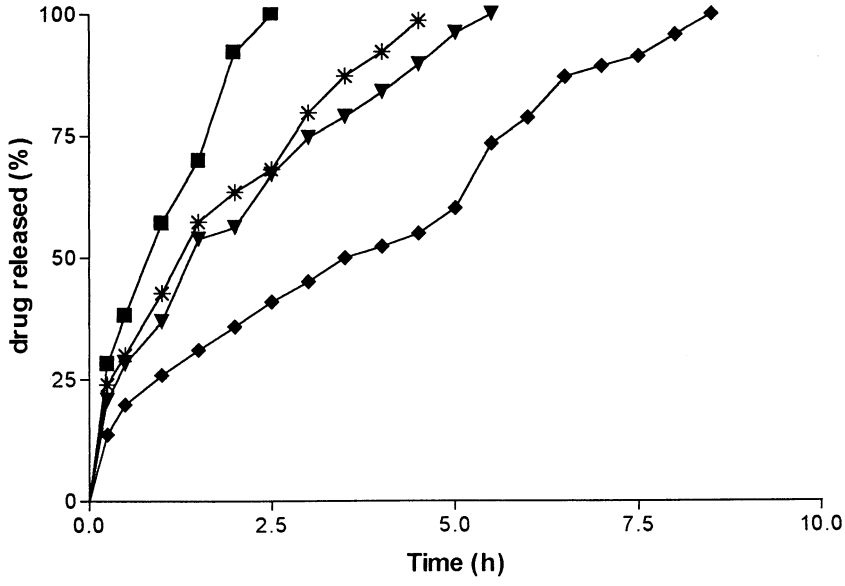


Fig. 2. In vitro dissolution tests at pH 7.4: 2000 μm (◆); 1250 μm (▼); 800 μm (*); 630 μm (■) size fraction pellets.

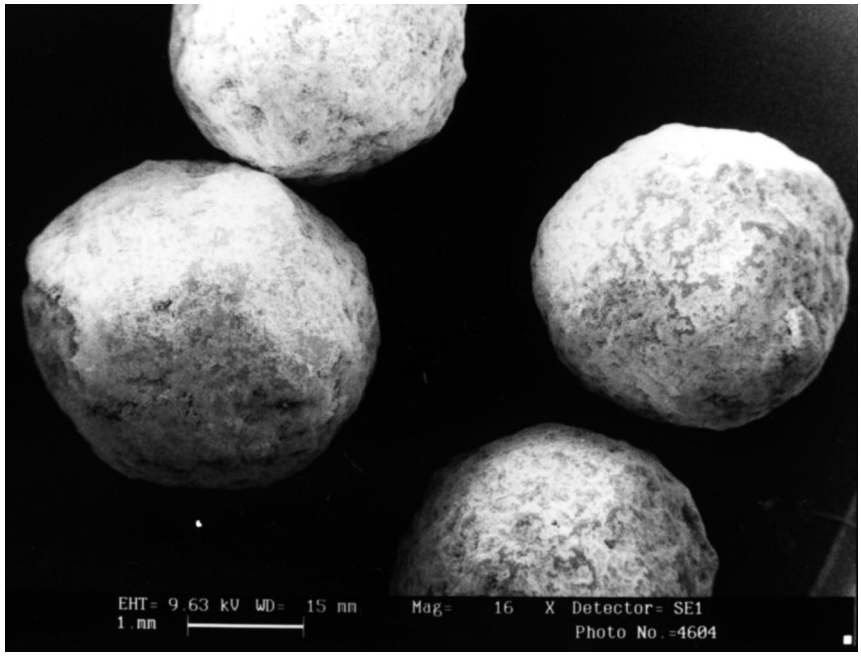


Fig. 3. SEM photograph of 2000 μm size fraction pellets produced with 21 min of massing time and 350 rpm of impeller speed.

3.4. Scanning electron microscopy

Photographs of the granules were taken using a scanning electron microscope (SEM), (Jeal JSH 5200, Japan).

3.5. Porosimetric analysis

The pore size of pellets before and after dissolution was determined using mercury porosimetry (Autopore III 9420 system, Micrometrics Instrum. Corp., Norcross, GA, USA). For the calculation of the porosity of pellets, the pores larger than 50 μm have been ignored to eliminate the influence of voids between the pellets.

3.6. X-ray photoelectron spectroscopy (XPS)

Samples were prepared by pressing a suitable amount of pellets onto a foil or pure indium (99.999% purity, Goodfellow, UK) and placed in an XPS-AES instrument (Physical Electronic Inc., PHI Mod. 548) using Al-K_α (1.448.6 eV) as anode material. A base pressure of 3×10^{-7} Pa was obtained in the analysis chamber.

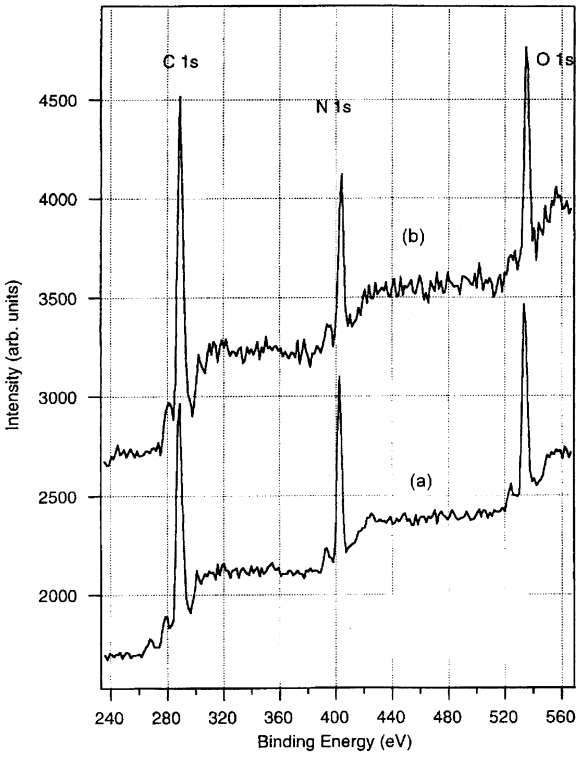


Fig. 4. X-ray photoemission spectra: (a) theophylline powder; (b) 2000 μm size fraction pellets.

3.7. In vitro dissolution studies

The USP XIII rotating basket apparatus (Mod. DT-1, Erweka, Italy) was used with a stirring rate of 100 rpm and maintained at 37 ± 0.1°C. The composition of the dissolution media was 0.2 M NaCl/0.2 M HCl (pH 1.2) or 0.2 M KH_2PO_4/0.2 M NaOH (pH 7.4) according to USP XXIII. Samples of pellets, containing a suitable amount (250 mg) of theophylline for sink condition ($C < < Cs$) were added over the surface of 900 ml of dissolution medium. Samples of 3 ml were extracted at regular time intervals (0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8 h), filtered and assayed spectrophotometrically at 271 nm. The aliquot withdrawn for analysis was immediately replaced with equal volume of fresh dissolution medium at the same temperature. The carriers did not interfere with the UV analysis. The results were averaged from at least triplicate experiments and the S.D.s were within 5% of mean value.

3.8. Dissolution kinetic

In order to investigate the mechanism of release of theophylline from cores the release data were analysed with the following mathematical models: (1) zero order kinetic (Eq. (1)); (2) first order kinetic (Eq. (2)); (3) Higuchi equation (Eq. (3)); and (4) Peppas equation (Eq. (4)).

$$Q = Q_0 - k_0 t \quad (1)$$

$$Q = 100(1 - e^{-k_1 t}) \quad (2)$$

$$Q = k_H t^{1/2} \quad (3)$$

$$Q = k_P t^n \quad (4)$$

where Q is the percent of drug released at time t, Q_0 is the initial drug content, k_0, k_1, k_H and k_P are the coefficients of the equations. In the case of Higuchi model, the release constant k_H reflects the

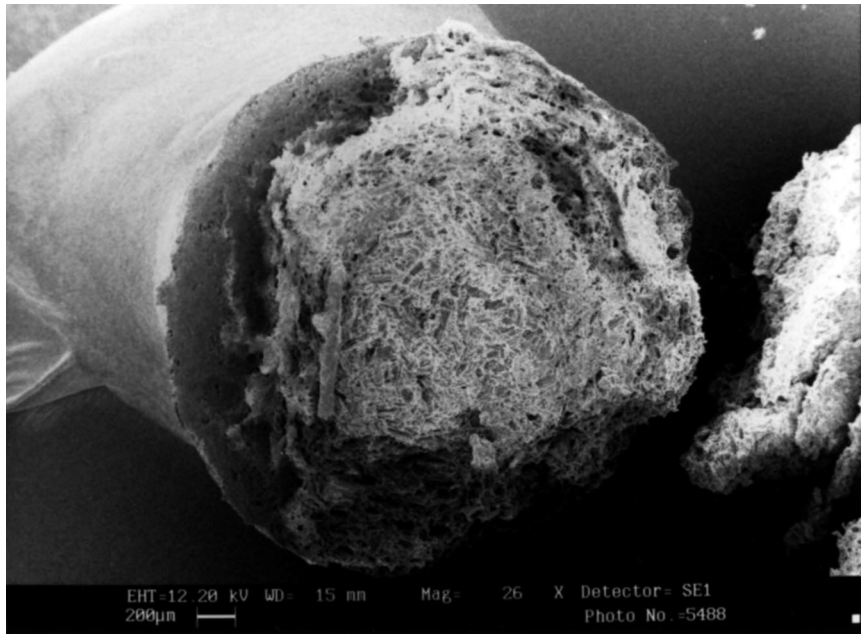


Fig. 5. SEM photograph of cross section of a pellet.

shape of the matrix, the internal structure of the matrix as it effects the tortuosity and porosity of the matrix and the drug concentration and solubility.

3.9. In vivo studies

Four healthy volunteers, two males and two females, aged between 27 and 40 years (mean age 33.75 years) and weighing 55–85 kg (mean weighing 73.8 kg) participated in this study. Written informed consent was signed by each subject participating in the study. All the volunteers had normal hepatic and renal function. All subjects were asked not to take any drugs 1 week before and to fast from 12 h before capsule administration until lunch on the treatment day. They were also not allowed to smoke, nor to take coffee or alcoholic beverages 12 h before and 48 h after the study drug administration. The subjects were all given a standard lunch 3.5 h after the dosing, and were allowed to drink water during the treatment period.

Blood samples (5 ml) were drawn at 0, 1, 2, 4, 6, 8, 12, 18, 24 h following capsule administration. Each sample was collected in a heparinised tube, and plasma was immediately separated by centrifugation (at 1500 rpm for 10 min), subsequently frozen and stored at -20°C until assayed.

Table 3
Parameters of theophylline release from pellets employing the Eqs. (1) and (4)

pH of the medium	Zero order model		First order model		Higuchi model		Peppas model		
	k_0 (%·h^{-1})	r^2	k_1 (%·h^{-1})	r^2	k_H (% h$^{-1/2}$)	r^2	k_p (h^{-n})	r^2	n
1.2	11.11	0.976	0.275	0.945	36.45	0.979	21.48	0.985	0.707
7.4	10.39	0.989	0.110	0.957	36.64	0.954	10.19	0.989	1.00

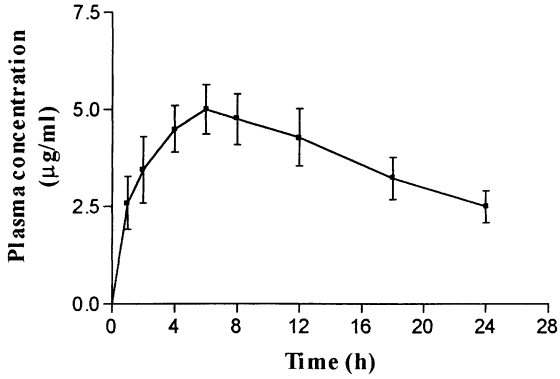


Fig. 6. Mean plasma concentration–time profiles (± S.D.; $n = 4$) obtained after oral administration of 300 mg theophylline as matrix pellets.

3.10. Analytical procedure

Theophylline in plasma samples was measured using a reversed phase high-performance liquid chromatography following the method described by Yuen et al. (1993). The HPLC system consisted of a Hewlett Packard series 1100, a Diode Array variable wavelength detector, an autosampling equipment, and an integrator. The column used was a 12.5 cm × 4 mm stainless steel Lichrosorb RP-18 (Merk). The mobile phase comprised 1.5% tetrahydrofuran (THF) in 0.01 M sodium acetate buffer adjusted to pH 4.3 with glacial acetic acid. Analysis was run at flow rate of 1.0 ml/min with the detector operating at 271 nm.

Before the analysis, the drug was extracted from the serum using the following procedure. A 0.5-ml aliquot of serum sample was added of 0.5 ml methanol, and 0.050 ml hydrochloric acid, followed by the addition of 0.050 ml of 2.5 mg/100 ml β-hydroxyethyltheophylline (BHET) internal standard solution. The mixture was sonicated for 5 min and then centrifuged at 5000 rpm for 2 min. Twenty μl volume of the supernatant was removed, filtered and then injected onto the column.

Theophylline standards were prepared by spiking drug-free serum in concentration range of 1–8 μg/ml. Standard curves, recoveries and precision studies were performed using these serum standards. The recovery values for both theophylline and internal standard (BHET) were greater than 95%, whilst the coefficients of variation were smaller than 4% assays in this concentration range. In addition, detector linearity, determined with theophylline standards prepared in water in a concentration range 0.5–10 μg/ml of was found to be linear.

3.11. Pharmacokinetic analysis

Plasma concentration–time data were analysed by non-compartmental pharmacokinetic method using WinNonlin version 2.1 (Pharsight, Palo Alto, USA). Maximum plasma concentration (C_{max}) and corresponding sampling time (t_{max}) were recorded as observed from the individual plasma concentration–time profiles. Half-life of the terminal phase ($t_{1/2,z}$) was calculated as 0.693 divided by the slope (z) of the linear regression line of the terminal log–linear portion of the concentration–time curve. Area under the plasma concentration versus time curve ($AUC_{0\rightarrow 24}$) was calculated by the linear trapezoidal rule and extrapolated to infinite time ($AUC_{0\rightarrow\infty}$) by addition of the term $C(24)/z$, where $C(24)$ is theophylline plasma concentration at the last sampling time (24 h).

Table 4
Bioavailability parameters after oral administration of 300 mg of theophylline for every single subject and mean values (± S.D.; $n = 4$)

Subject	F-1	F-2	F-3	F-4	Mean
t_{max} (h)	8	6	4	4	5.50 ± 1.91
C_{max} (μg/ml)	5.3	6.5	6	4	5.45 ± 1.08
$t_{1/2,z}$ (h)	11.65	15.72	19.95	18.40	16.43 ± 3.63
$AUC_{0\rightarrow 24}$ (μg h/ml)	87.15	110.9	103.15	55.8	89.25 ± 24.39
$AUC_{0\rightarrow\infty}$ (μg h/ml)	127.50	185.78	186.62	92.97	148.22 ± 46.07

4. Results and discussion

After verifying the feasibility of experimental plan, the first seven trials, corresponding to experimental plan A shown in Fig. 1 and Table 2, were run randomly. The relative results are also reported in Table 2.

From the results reported in Table 2 it can be noticed the poor homogeneity in particle size of the product. Therefore, in order to continue the explorative analysis and define the optimal conditions for the two considered process variables it has been necessary to analyse every single size fraction from the dissolution point of view. This way, it will be possible to select the optimal size fraction for the purpose of the research, that is, a sustained release of the drug.

The dissolution profiles clearly demonstrated that drug release was function of the pellet size. For the sake of brevity, in Fig. 2 only the results obtained from experiment number 2 (Table 2) at pH 7.4 are reported, being not significantly different ($P = 0.05$) the profiles at pH 1.2 and 7.4. The 2000 μm size fraction showed the slowest drug release, achieving the total release of the drug at pH 7.4 after 8.5 h, and at pH 1.2 after 7.5 h.

Following these results, an extension of the yield of this size fraction was attempted, translating the Doehlert matrix plan A toward the point corresponding to the experiment 2 equal to 89.71%. With the aid of only three further experiments it has been possible to design a second experimental plan B. Unfortunately the results of these experiments were not satisfactory, the maximum yield obtained being only 73.92% (see experiments 8–10, Table 2). Thus, in order to obtain a further increase of the yield, the experimental plan B was translated toward the experiment 10, being this one the only possible direction to obtain a spherical product following the restriction imposed on the process variables. This way, plan C was designed to achieve a yield of 96.81% in the 2000 μm size fraction (see experiments 11–13, Table 2). The experimental plan and experimental matrices are reported in Table 2 and Fig. 1, respectively.

After selection of the 2000 μm size fractions produced during each experiment from 8 to 13, the dissolution tests were carried out. Significant differences between these results and the profiles previously shown (Fig. 2) could not be found. Further experiments have been carried out using the pellets produced during the experiment 12, corresponding to the maximum yield. These pellets showed a satisfactory regular spherical shape (see Fig. 3).

With the aim of describing the mechanism of drug release from this device, a further characterisation of the system was performed.

Firstly, in order to explain the initial rapid release within the dissolution profile, the presence of theophylline on pellets surface was analysed. The chemical composition of the surface layer can be obtained from XPS spectra (Carli and Garbassi, 1985). The nitrogen peak, present in the theophylline molecule at about 405 eV, and still present in the spectrum of the pellets, demonstrated the presence of the drug onto the surface of the pellets (Fig. 4).

Then, the pore distribution was determined, carrying out this analysis at pH 1.2 to avoid the swelling phenomena noticed at pH 7.4. The shift in the pore analysis before and after drug release was noticed, as the pore size distribution shifted from 18.39 mm^3/g to larger pore size (703 mm^3/g) after dissolution. This phenomenon, already reported (Adeyeye and Price, 1994; Zhou et al., 1996), indicated that the pore diffusion layer can play a role in the drug release mechanism. A further confirmation of this fact was obtained from SEM analysis of pellet cross section (Fig. 5).

The results from analysis of release data with Eqs. (1)–(4) (previously explained under Section 2) are presented in Table 3. The release of theophylline from pellets was relative unaffected by the different pH media likely to be experienced in the gastro-intestinal tract. The highest correlations ($r^2 = 0.985$ and 0.989) were observed when the release data were fitted with Peppas equation (Eq. (4)). That is a simple empirical equation to describe general solute behaviour from controlled release polymeric matrices and assumes that release occurs as soon as the matrix is placed in contact with fluid and thus predicts an intercepts at the origin. The value of the exponent n can be used to characterise the mechanism for both sol-

vent penetration and drug release. Peppas (1985) described that, for $n = 0.5$, the release kinetics follow a Fickian diffusion mechanism and, for $0.5 < n < 1.0$, non-Fickian (anomalous) diffusion behaviour is observed. Furthermore, he explained that $n = 1$ (a special case of non-Fickian diffusion) gives rise to a zero-order transport mechanism known as case II transport. When the value of n approaches 1.0, phenomenologically one may conclude that the release is approaching zero-order. The release exponent $n = 1.0$, was obtained for theophylline release form pellets at pH 7.4.

After investigation of the in vitro release, the bioavailability in vivo was evaluated. The theophylline plasma concentration time profiles, obtained after the administration of capsules containing a theophylline dose of 300 mg, are shown in Fig. 6, while the pharmacokinetic parameters are listed in Table 4. The results demonstrated that the tested size fraction behaved as a sustained-release formulation, as indicated by the relatively high levels of t_{max}. This finding is further supported by the values of $t_{1/2,z}$. Since the observed values of $t_{1/2,z}$ are much higher than reported theophylline elimination half life of 6–10 h (Jonkman et al., 1989), a flip–flop phenomenon can be hypothesised. Therefore, the rate of absorption is manifested in the terminal phase slope of the concentration–time curve. Even though the presence of a flip–flop phenomenon may limit reliability of $AUC_{0 \rightarrow \infty}$ estimation, bioavailability of the tested formulation appears to be advantageous compared to some other theophylline sustained release formulations (Henrist et al., 1999). However in consideration of the little number of involved subjects and the variability among these subjects, further in vivo multiple-dose studies will be carried out onto a larger sample of volunteers in order to find the optimal sustained release characteristics that will allow once daily dosing.

5. Conclusion

It can be concluded that melt pelletisation technique in high shear mixer is a viable method to produce in a single step sustained-release pellets for theophylline, by using stearic acid as a melting binder and anhydrous lactose as a filler. The sustained-release can be achieved even with a high drug concentration, without the need of any coating procedure. Applying a translated Doehlert matrix for the optimisation of process variables and quality control of pellets characteristics, it was possible to increase the yield of the optimal size fraction to obtain a sustained-release formulation (2000 μm). The in vitro release from these pellets, unaffected from the pH, could be associated to a substantially zero-order release. The further in vivo studies confirmed the achievement of the purpose of the research, demonstrating a sustained release of theophylline on the tested four healthy volunteers.

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