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Research paper

# Incidence of drying on microstructure and drug release profiles from tablets of MCC–lactose–Carbopol® and MCC–dicalcium phosphate–Carbopol® pellets

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**Abstract**

The influence of intragranular excipients (lactose or dicalcium phosphate) and the drying procedure and conditions (oven-drying and freeze-drying after freezing at −30 or −196 °C) on the properties of tablets of MCC–Carbopol® pellets was evaluated. The drying procedure caused remarkable differences in pellet size and porosity (freeze-dried pellets were 3-fold more porous than those oven dried). Theophylline release from pellets was completed in less than 30 min and followed first-order kinetics, with a rate closely related to the intragranular porosity. The total porosity of the tablets (5–10%) was conditioned by the compression force (10–20 N), the drying procedure applied to the pellets and the coexcipient nature. Their intergranular porosity ranged inversely to the initial porosity of pellets due to the greater deformability of the most porous ones. A wide range of theophylline release rates were achieved depending on the drying procedure; tablets prepared from freeze-dried pellets sustained the release for 3 h. Most profiles showed a bimodal kinetics with an initial zero-order release (while the tablets did not completely disintegrate) that changed, after a certain time, to a first-order kinetics. The intergranular porosity determined drug release rate up to disintegration. Then, the release kinetics became first-order and the rate constant, which was conditioned by the intragranular porosity, showed a complex dependence on the drying procedure, the compression force, and the nature of coexcipient. In sum, the modulation of drug release profiles from tablets of MCC–Carbopol® pellets through an adequate control of the effects of the coexcipient nature, the drying procedure of pellets, and the compression force on the inter- and intragranular porosity opens interesting possibilities to control the release of hydrosoluble drugs.
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*Keywords:* Freeze-drying; Oven-drying; Pellets; Controlled release; Mercury porosimetry; Tabletting

## 1. Introduction

Compression of pellets has been of considerable interest to modulate drug release [1–3]. To optimize the performance of the tablets, the pellets should maintain their integrity and, thus, have to be plastic enough to deform without breaking apart when compressed [1,4–8]. Different approaches have been assayed to improve the tabletting of pellets, to avoid fragmentation, and to make the recovery of individual pellets possible after tablet disintegration, such as (i) extragranular mixing with microcrystalline cellulose (MCC) [2,9,10], lactose [11], pregelatinized starch [10] and magnesium stearate [10,12]; (ii) intragranular addition of lactose [13], dicalcium phosphate [10] or their mixtures [14]; and (iii) compression of placebo pellets together with the drug loaded pellets [15,16].

Deformation of pellets during tabletting entails the rearrangement of their primary particles [17]. Since empty spaces are required for enabling these particles to move,

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an adequate control of the inner structure of the pellets is required to avoid fragmentation during compression. Therefore, any rational approach to the tablets formulation requires taking into account any factor that can influence the porosity of the pellets. The composition of the granulation liquid [18–21] and the method and conditions of drying [22–24] are some of the most relevant factors that determine the porosity of granules. Some papers reported that the porosity of pellets and their mechanical strength, surface texture, and dimensions are conditioned by the drying technique, although a joint analysis of the data obtained with each specific technique is difficult due to differences in or absence of information on some critical process variables [25–27]. It has also been shown that the microporous structure of microcrystalline cellulose (MCC) pellets has a remarkable influence on their compression behavior, the tensile strength and the smoothness of the tablets [20,26,28] and the sensitivity of the drug release profile to the compaction process [19]. Santos et al. [29] have studied the dependence of the drug release rate from tablets on the intragranular porosity of MCC-based pellets containing 16% of xanthan gum. Nevertheless, a deeper knowledge on the effect of initial porosity of the pellets, particularly those containing high proportions of gelling excipients as controlled release agents, on the microstructural and drug release properties of tablets is required.

In a previous paper, we have shown that the microstructure of MCC–Carbopol® pellets can be modulated through the selection and rigorous control of the drying procedure [30]. The aim of the present work was to elucidate the influence of some intragranular excipients (lactose or dicalcium phosphate) and of the drying procedure and conditions (oven-drying and freeze-drying after slow or fast freezing) on the total porosity, pore size distribution and theophylline release behavior of MCC–Carbopol® pellets and their tablets.

## 2. Materials and methods

### 2.1. Materials

Theophylline anhydrous (batch 2740443, Sigma–Aldrich, Spain), Carbopol® 974P (batch AB17796, Noveon Inc., USA), MCC Avicel® PH101 (batch 6703C, FMC, Ireland), phosphate dicalcium dehydrated (DCP, batch K16409646, Merck, Germany), lactose QP (batch 872, C. Barcia, Spain), calcium chloride (batch TA882282, Merck, Germany). Purified water was obtained by reverse osmosis (resistively > 18.2 MOhm cm; MilliQ®, Millipore, Spain). All other reagents were of analytical grade.

### 2.2. Methods

#### 2.2.1. Preparation of pellets

Wet masses of Carbopol® 974P (60 g), MCC (30 g), DCP (10 g) or lactose (10 g) and theophylline (25 g) were prepared by adding 160 ml of $CaCl_2$ solution of enough concentration to provide a 0.29 salt:carbopol w/w ratio, and mixing the components for 1 h at 125 rpm in a RZR50 mixer (Heidolph, Germany) of 98 mm inner diameter and 1 l capacity. The wet mass was extruded through a 1 mm mesh size screen using a Model 10 extruder (Caleva Ltd., UK) at 60 rpm, and the extruded mass was spheronized (load 20 g) for 30 min at 575 rpm in a Model 120 spheronizer (Caleva Ltd., UK). Portions of the pellets were dried under various conditions as follows: (a) hot-air oven (J. Bonals, Spain) at 40 °C for 24 h; (b) slow freezing at −30 °C in a freezer for 24 h, followed by freeze-drying under vacuum at −30 °C for 48 h (Labconco Corp., USA); or (c) fast freezing at −196 °C (immersion in liquid nitrogen) followed by freeze-drying under vacuum at −30 °C for 48 h (Labconco Corp., USA). The identification codes of the resultant pellets are shown in Table 1. Once dried, the pellets were maintained with silica gel at 20 °C until assay.

#### 2.2.2. Characterization of pellets

*Shape and size*. Pellets were characterized throughout the analysis (PC Image VGA 24 v.2.1, Foster Findlay Ass., UK) of the digital images obtained with an Olympus SZ-CTV microscope (Japan) connected to a video camera (Olympus DP12, Japan). Size was estimated as the mean Feret diameter measured from four different angles (0°, 45°, 90° and 135°), for a minimum of 600 pellets per formulation; in all cases, the size data were best fitted by a normal distribution. Circularity was calculated as $4 \cdot \pi \cdot A/p^2$, where $A$ is the projection area and $p$ is the projection perimeter.

*Friability*. Pellets were sieved on a 250 μm mesh and samples of those collected on the sieve (5 g) were assayed for 30 min at 20 rpm in a PTF 10ER (PharmaTest, Germany) previously loaded with 100 spherical glasses (4 mm diameter). After, the pellets were removed, sieved and weighed again, and the percentage of loss in weight was calculated.

*Porosity*. Total porosity and pore size distribution were determined in triplicate by mercury-intrusion porosimetry with a Micromeritics 9305 pore sizer (Norcross, GA, USA), using a 3 ml powder penetrometer. Working pressures were in the range of 0.004–172.4 MPa. The following log-normal equation was used to analyze the bimodal pore size incremental distributions applying non-linear regression (GraphPad Prism v.3.02, GraphPad Software Inc., San Diego, CA):

$$V_p = \frac{PV_1}{2 \cdot \pi \cdot \mathrm{Ln}(\sigma_{g1})} \cdot e^{\left[-\frac{(\mathrm{Ln}(d) - \mathrm{Ln}(M_1))^2}{2 \cdot (\mathrm{Ln}(\sigma_{g1}))^2}\right]} + \frac{PV_2}{2 \cdot \pi \cdot \mathrm{Ln}(\sigma_{g2})} \cdot e^{\left[-\frac{(\mathrm{Ln}(d) - \mathrm{Ln}(M_2))^2}{2 \cdot (\mathrm{Ln}(\sigma_{g2}))^2}\right]} \quad (1)$$

Table 1
Composition, drying conditions and micromeritic properties of MCC:carbopol:theophylline pellets containing lactose (code L) or dicalcium phosphate (code F)

| Code | Drying process[a] | Feret diameter (μm) | Circularity | Porosity (%) | Mean pore size$_1$*, μm (SD**) | Pore volume$_1$ ($cm^3\ g^{-1}$) | Mean pore size$_2$*, μm (SD**) | Pore volume$_2$ ($cm^3\ g^{-1}$) |
|---|---|---|---|---|---|---|---|---|
| L1 | OD | 946.23 (168) | 0.90 (0.03) | 5.11 (0.16) | 93.3 (2.2) | 0.0157 (0.0001) | 0.16 (25.71) | 0.0037 (0.0006) |
| L2 | FD fast | 1223.79 (220) | 0.88 (0.03) | 23.72 (2.10) | 58.9 (1.8) | 0.0263 (0.0003) | 0.77 (3.02) | 0.1931 (0.0036) |
| L3 | FD slow | 1072.04 (187) | 0.88 (0.02) | 17.60 (0.31) | 91.2 (2.3) | 0.0261 (0.0003) | 0.77 (2.34) | 0.0935 (0.0012) |
| F1 | OD | 980.22 (165) | 0.90 (0.04) | 5.97 (0.34) | 112.2 (2.2) | 0.0157 (0.0002) | 0.24 (11.04) | 0.0041 (0.0008) |
| F2 | FD fast | 1271.68 (258) | 0.88 (0.03) | 32.08 (1.09) | 85.1 (2.0) | 0.0302 (0.0004) | 1.38 (1.70) | 0.3152 (0.0052) |
| F3 | FD slow | 1059.03 (246) | 0.88 (0.02) | 19.50 (1.07) | 50.1 (3.47) | 0.0320 (0.0004) | 0.82 (2.82) | 0.1368 (0.0028) |

*Geometric mean of the distribution and **geometric standard deviation of the distribution (fitting to the bimodal distribution, Eq. (1); $R^2 > 0.97$). Mean values and, in parentheses, standard deviations. The incremental distribution of pore volume was bimodal and its log-normal fitting to Eq. (1) enabled the estimation of the geometric mean pore size, the standard geometric deviation, and the volume corresponding to the inter- (subindex 1) and intra- (subindex 2) granular pores.
[a] OD, oven-drying; FD fast, freeze-drying after freezing by immersion in liquid nitrogen (−196 °C); FD slow, freeze-drying after freezing at −30 °C.

where $V_p$ is the total incremental pore volume, $PV_1$ and $PV_2$ are the pore volumes of the two distributions integrated in the bimodal model, and $M_1$, $M_2$, $\sigma_{g1}$ and $\sigma_{g2}$ are the mean and the geometric standard deviation of the corresponding distributions. The distribution with the greatest mean value was assumed to correspond to intergranular empty spaces (distribution 1) and that with the lowest mean value to intragranular empty spaces (distribution 2).

*Drug content*. 250 mg of pellets nominally containing 50 mg theophylline was stirred in 900 ml of water for 24 h and the drug concentration was spectrophotometrically determined at 271 nm (Agilent 8453, Germany). The experiments were carried out in triplicate.

*Theophylline physical stability*. X-ray spectra of pellets were recorded on a Phillips PW 1710 (Netherlands) diffractometer using Cu Kα radiation and scanning from 4 to 60° $2\theta$ at a rate of 1.5° $2\theta\ min^{-1}$.

*Drug release tests*. Drug release profiles from 250 mg of pellets were obtained, in sextuplicate, using a USP 24 type II (Turu Grau, Spain) apparatus at 50 rpm and 37 °C, in 900 ml of water. At given time intervals, 5 ml samples were withdrawn (and replaced with equal volume of medium) and drug concentration was determined spectrophotometrically at 271 nm (Agilent 8453, Germany). Drug release profiles were fitted by non-linear regression (GraphPad Prism v.3.02, GraphPad Software Inc., San Diego, CA) to the following equation that corresponds to a first-order process:

$$D = 1 - e^{-k_{1P} \cdot t} \tag{2}$$

where $D$ is the fraction of theophylline dose dissolved at time $t$ and $k_{1P}$ is the dissolution rate constant [31].

### 2.2.3. Preparation of tablets

The pellets were compressed in an eccentric tabletting machine (Korsch EKO, Erweka, Germany) fitted with 9 mm flat punches and control instrumentation of pressure and displacement (Sensing Electronics, Spain). Piezoelectric force and displacement transducer were calibrated by Lorenz Messtechnik GmbH (Germany). The die was manually filled with 250 mg of pellets and the compression force was 10 or 20 kN. No lubricant was used.

### 2.2.4. Characterization of tablets

*Tensile strength*. The tensile strength was calculated for each six tablets from the expression [32]:

$$TS = \frac{2 \cdot CS}{\pi \cdot TD \cdot E} \tag{3}$$

where CS is the crushing strength; TD and $E$ denote the tablet diameter and thickness, respectively. Parameters $E$ and CS were measured using a Mitutoyo digital micrometer (Japan) and a TB 2 A Erweka apparatus (Germany), respectively.

*Friability*. The weight loss (%) by friability was evaluated on 10 tablets from each batch and determined using a European Pharmacopeia (2004) apparatus (Erweka TAB, Erweka, Germany) for 15 min at 20 rpm.

*Porosity*. Total porosity and pore size distributions were determined using a 5 ml penetrometer and analyzed as described for pellets.

*Disintegration time*. Measurements were carried out using a Turu Grau apparatus (Spain) which conforms to the specifications exacted in USP 24-NF 19. Mean values were calculated from the disintegration times of six tablets in distilled water at 37 °C. The disintegration process ended when the tablet completely disintegrated in the constituent pellets or smaller particles.

*Dissolution profiles*. Time-course of theophylline release from the tablets of pellets was determined at 37 °C in a Turu Grau (Spain) apparatus adapted to meet the specifications of USP 24-NF 19, as described in Section 2.2.2. The profiles were analyzed by non-linear regression (GraphPad Prism v.3.02, GraphPad Software Inc., San Diego, CA) using the following functions:

$$D = k_{0T} \cdot t \text{ for } t \leqslant t_0$$
$$D = k_{0T} \cdot t_0 + (1 - k_{0T} \cdot t_0) \cdot (1 - e^{(-k_{1T} \cdot (t - t_0))}) \text{ for } t > t_0 \tag{4}$$

where $D$ is the theophylline fraction dissolved at time $t$, $k_{0T}$ and $k_{1T}$ are zero-order and first-order rate constants, respectively, and $t_0$ is the time that the zero-order kinetics fits the release process.

*2.2.5. Experimental design and statistical analysis*

To evaluate the effect of the addition of coexcipients and of the drying procedure on the pellets properties, these were prepared following a $2 \times 3$ factorial design: the coexcipient nature (A) coded as (−1) for lactose and (+1) for DCP, and the drying procedure (B) coded as (1 0) for oven-drying, (0 1) for freeze-drying after freezing in liquid nitrogen, and (−1 −1) for freeze-drying after freezing at −30 °C (Table 1). The response surface equations that quantify the effects of these variables on the properties of the pellets were obtained by regression using Design Expert software (v. 6.06, Stat-Ease Inc., Minneapolis, 2002). A stepwise regression with backward elimination was used; i.e. the two factors and their interaction terms were initially considered and, then, those that provided a significant level above 0.05 were discarded. In the case of the tablets of pellets, the compression force (C) coded as (−1) for 10 kN and (+1) for 20 kN was introduced as the third factor to conform a $2 \times 3 \times 2$ factorial design.

## 3. Results and discussion

To evaluate the changes induced by tabletting on the pellets structure and on the drug release rate, a detailed characterization of pellets before compression was carried out first.

### 3.1. Pellets

Addition of $CaCl_2$ in the wetting liquid can overcome the problems related to the tackiness effect of carbopol to the metallic elements of the extruder, making the extrusion and spheronization processes easier [33,34]. The use of a 0.29 $CaCl_2$:carbopol w/w ratio provided the wet masses chosen for the study with adequate processability, despite the high content in carbopol (40%) and regardless of the presence of lactose or dicalcium phosphate. Then, the pellets were dried by hot-air oven-drying or freeze-drying. Since freezing conditions may greatly determine the structure of water crystals and, consequently, of the porosity of pellets when water is removed, the incidence of a slow (in a freezer chamber at −30 °C) and fast freezing (by immersion in liquid nitrogen at −196 °C) was evaluated when the freeze-drying was applied. Main micromeritic properties of the resultant pellets are shown in Table 1. The remarkable differences observed mainly in size and porosity parameters are due to the drying procedure; the effect of the nature of the coexcipient not being statistically significant (Table 2). The regression equations have a notable predictive value (high regression coefficients). The important volumetric contraction of pellets dried in the oven [35–37] explains the greater diameter of freeze-dried pellets, especially if freezing occurs rapidly by immersion in liquid nitrogen. The values predicted by regression (Table 2) were 963.2 μm for the oven-dried pellets, and 1065.5 or 1247.7 μm for freeze-dried ones when freezing was carried out at −30 °C or by immersion in liquid nitrogen, respectively. All pellets were nearly spherical, with predicted circularity values of 0.90 for oven-dried pellets and 0.88 for the freeze-dried ones. Thus, the pellet spherical shape is not altered by the drying procedure [20,26,38].

Freeze-dried pellets were 3-fold more porous than the oven-dried ones, estimated by mercury intrusion porosimetry [39] (Table 1 and Fig. 1). The regression equation predicted 5.54% and 18.55% or 27.90% porosity for pellets that were dried in oven and for those freeze-dried after freezing at −30 or −196 °C, respectively. Once again, these findings are explained by the different volumetric contraction of pellets during drying due to the movement of water and, consequently of primary particles, inside the pellet when different drying procedures are applied [26,30]. The pore volume determined using mercury intrusion porosimetry is the sum of the inter- and intragranular empty spaces to which mercury can gain access [39]. To gain insight into the relative contribution of both types of spaces to the total porosity, a log-normal bimodal equation (Eq. (1)) was fitted to the incremental distribution of pore

Table 2
Dependence of the pellets properties on the drying procedure ($B$) coded as (1 0) for oven-drying (0 1), for freeze-drying after freezing in liquid nitrogen, and (−1 −1) for freeze-drying after freezing at −30 °C

| Property | Equation | $F$ | $R^2$ |
|---|---|---|---|
| Feret diameter (μm) | $F.D. = 1092.17 - 128.94B(1) + 155.57B(2)$ | $68.88^{a,**}$ | 0.98 |
| Circularity | $Circ. = 0.89 + 1.40 \times 10^{-2}B(1) - 6.50 \times 10^{-3}B(2)$ | $196.33^{a,**}$ | 0.99 |
| Porosity (%) | $Por. = 17.33 - 11.79B(1) + 10.57B(2)$ | $20.38^{a,*}$ | 0.93 |
| Pellets pore volume$_1$ ($cm^3\ g^{-1}$) | $PPV_1 = 0.024 - 8.66 \times 10^{-3}B(1) + 3.94 \times 10^{-3}B(2)$ | $13.60^{a,*}$ | 0.90 |
| Pellets pore volume$_2$ ($cm^3\ g^{-1}$) | $PPV_2 = 0.12 - 0.11B(1) + 0.13B(2)$ | $11.24^{a,*}$ | 0.88 |
| $k_{1P}$ ($h^{-1}$) | $k_{1P} = 14.73 - 7.82B(1) + 7.33B(2)$ | $30.24^{a,*}$ | 0.95 |

The effect of the coexcipient nature was not statistically significant. $B(1)$ and $B(2)$ represent the values of the first and second elements of the matrix, respectively.

[a] 2,3 degrees of freedom.

[*] $\alpha < 0.05$.

[**] $\alpha < 0.01$.

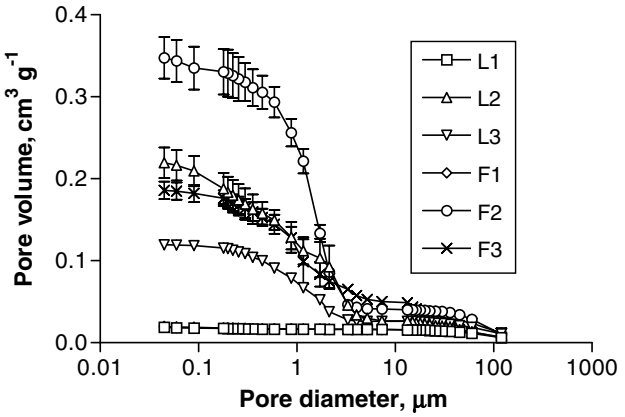


Fig. 1. Cumulative pore-diameter distribution plots of theophylline pellets prepared with MCC, carbopol, lactose (L) or dicalcium phosphate (F) that were dried by different procedures (1-oven-dried; 2-freeze-dried after frozen at −196 °C; 3-freeze-dried after frozen at −30 °C).

volume and two pore populations were distinguished (Table 1). The statistical analysis (Table 2) revealed that oven-dried pellets have a minor intragranular porous volume (predicted value 0.0039 $cm^3\ g^{-1}$) and that the intragranular porosity of freeze-dried pellets that were frozen at −196 °C (predicted value 0.2542 $cm^3\ g^{-1}$) is more than twice that of pellets frozen at −30 °C (predicted value 0.1152 $cm^3\ g^{-1}$). Despite these differences in porosity, all formulations had a considerable mechanical strength with friability values ca. 0%. The results obtained are in close agreement to those previously reported for pellets prepared with carbopol:MCC 60:40 without coexcipients [30]. Therefore, even when MCC is exchanged up to 25% for the soluble lactose coexcipient or the insoluble dicalcium phosphate, the drying procedure is still the key factor in the porosity. Theophylline release rate was strongly dependent on pellet microstructure (Fig. 2). The dissolution was complete in less than 30 min following first-order kinetics (Table 3), which suggests that the process is determined by the dissolution of the drug particles [40]. The response

Table 3
First-order kinetics fitting to the theophylline release profiles from pellets

| Code | $k_{1P}$ ($h^{-1}$) | $R^2$ |
|---|---|---|
| L1 | 7.19 (0.22) | 0.9852 |
| L2 | 19.89 (0.61) | 0.9963 |
| L3 | 14.25 (0.31) | 0.9966 |
| F1 | 6.63 (0.21) | 0.9846 |
| F2 | 24.22 (0.39) | 0.9951 |
| F3 | 16.19 (0.68) | 0.9904 |

surface (Table 2) predicts rate constant values of 6.91, 15.22 and 22.06 $h^{-1}$ for pellets that were oven dried, and freeze-dried after freezing at −30 and −196 °C, respectively. These findings are explained by the differences in intragranular porosity (Fig. 3) that determine the accessibility of the dissolution medium to the drug particles.

### 3.2. Tablets

Since the force and rate of compression may have a strong influence on the mechanical and drug release properties of the tablets [1,41,42], two compression forces, 10 and 20 kN, were applied to the pellets. These forces were enough to induce pellet cohesion to form strong monoliths (friability close to 0%). The control of maximum compression force instead of volumetric reduction, as proposed by other authors [43], is preferable in the case of pellets with so different porosity as those evaluated. In fact, in the range of forces that can be exerted by the eccentric machine, it was not possible to induce a volumetric reduction of the oven-dried pellets as high as that required for the freeze-dried pellets to form tablets of sufficient strength. Table 4 summarizes the characteristics of the tablets. The tensile strength values are not shown because the tablets did not break at the maximum force of the equipment (150 N), although formulations L3a and L3b significantly deformed.

Fig. 4 shows the cumulated distributions of pore volume. The total porosity, ranging between 5% and 10%,

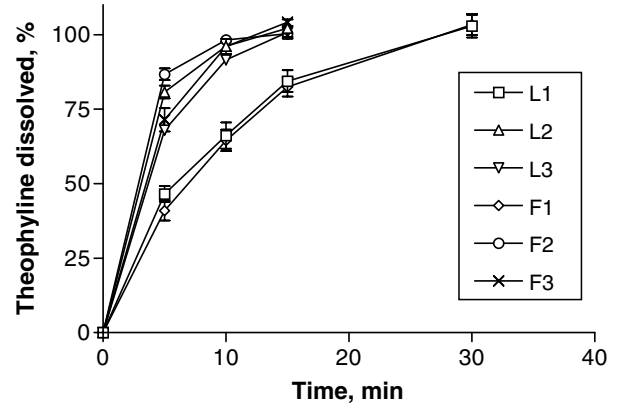


Fig. 2. Theophylline release profiles from pellets prepared with MCC, carbopol, lactose (L) or dicalcium phosphate (F) that were dried by different procedures (codes as in Fig. 1).

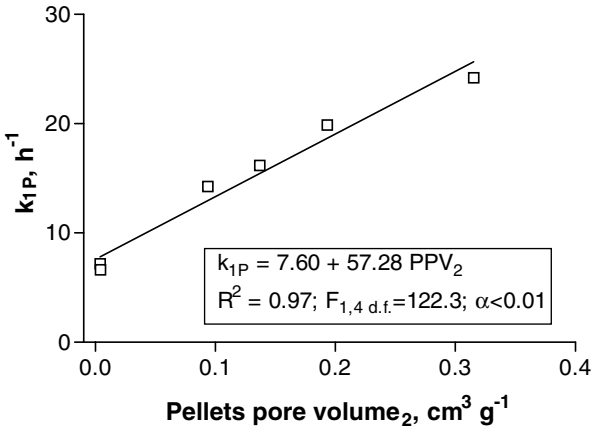


Fig. 3. Dependence of the theophylline first-order release kinetics on the intragranular pore volume of pellets.

Table 4
Compression conditions and properties of tablets obtained with MCC:carbopol: theophylline pellets containing lactose (code L) or dicalcium phosphate (code F)

| Code | Compression force (kN) | Thickness (mm) | Desintegration time (min) | Porosity (%) | Mean pore size$_1$*, μm (SD**) | Pore volume$_1$ ($cm^3\ g^{-1}$) | Mean pore size$_2$*, μm (SD**) | Pore volume$_2$ ($cm^3\ g^{-1}$) |
|---|---|---|---|---|---|---|---|---|
| L1a | 10 | 3.10 (0.01) | 23.1 (2.2) | 9.14 (0.28) | 42.7 (1.9) | 0.0428 (0.0013) | 0.64 (5.06) | 0.0187 (0.0019) |
| L2a | 10 | 3.00 (0.01) | 44.4 (3.1) | 9.39 (0.56) | 34.7 (1.7) | 0.0049 (0.0012) | 0.26 (3.03) | 0.0447 (0.0036) |
| L3a | 10 | 3.03 (0.02) | 11.7 (1.2) | 6.70 (0.19) | 33.9 (1.7) | 0.0151 (0.0021) | 0.08 (6.97) | 0.0117 (0.0012) |
| F1a | 10 | 3.03 (0.01) | 23.3 (1.0) | 9.32 (0.44) | 45.0 (2.0) | 0.0441 (0.0032) | 0.53 (5.51) | 0.0151 (0.0008) |
| F2a | 10 | 2.97 (0.01) | 36.9 (3.4) | 7.81 (0.91) | 41.7 (2.1) | 0.0043 (0.0009) | 0.24 (3.28) | 0.0405 (0.0018) |
| F3a | 10 | 2.89 (0.01) | 18.2 (0.7) | 6.14 (0.34) | 37.1 (2.0) | 0.0116 (0.0016) | 0.25 (3.62) | 0.0270 (0.0010) |
| L1b | 20 | 2.88 (0.06) | 39.0 (1.4) | 5.38 (0.17) | 26.9 (1.8) | 0.0169 (0.0018) | 0.711 (5.51) | 0.0102 (0.0007) |
| L2b | 20 | 2.90 (0.03) | 56.0 (1.9) | 6.47 (0.52) | 45.7 (2.3) | 0.0040 (0.0007) | 0.15 (4.26) | 0.0201 (0.0011) |
| L3b | 20 | 2.98 (0.02) | 16.5 (0.8) | 5.97 (0.10) | 31.6 (1.8) | 0.0108 (0.0011) | 0.09 (6.93) | 0.0118 (0.0006) |
| F1b | 20 | 2.86 (0.02) | 38.8 (0.9) | 5.70 (0.22) | 33.9 (1.7) | 0.0180 (0.0010) | 0.43 (6.70) | 0.0094 (0.0005) |
| F2b | 20 | 2.86 (0.03) | 54.3 (0.5) | 4.80 (0.26) | 40.7 (2.0) | 0.0023 (0.0005) | 0.24 (5.37) | 0.0106 (0.0010) |
| F3b | 20 | 2.85 (0.01) | 24.4 (1.3) | 5.33 (0.13) | 46.8 (2.1) | 0.0067 (0.0009) | 0.27 (4.26) | 0.0218 (0.0012) |

*Geometric mean of the distribution and **geometric standard deviation of the distribution (fitting to the bimodal distribution, Eq. (1); $R^2 > 0.96$). Mean values and, in parentheses, standard deviations. The incremental distribution of pore volume was bimodal and its log-normal fitting to Eq. (1) enabled the estimation of the geometric mean pore size, the standard geometric deviation, and the volume corresponding to the inter- (subindex 1) and intra- (subindex 2) granular pores.

was conditioned by the three factors included in the experimental design (Table 5); the relevance of the compression force ($C$; $F_{1,3d.f.} = 2543.27$; $\alpha < 0.01$) being the greatest, which is in agreement with previous papers [18]. Nevertheless, the drying procedure ($B$; $F_{2,3d.f.} = 332.22$; $\alpha < 0.01$) and the coexcipient nature ($A$; $F_{1,3d.f.} = 230.48$; $\alpha < 0.01$), as well as the $C \cdot B$ ($F_{2,3d.f.} = 304.31$; $\alpha < 0.01$) and $A \cdot B$ ($F_{2,3d.f.} = 104.23$; $\alpha < 0.01$) interactions, also significantly contribute to modulate the total porosity of the tablets. This complex dependence makes the effect of compression force less relevant in the case of tablets obtained with freeze-dried pellets that were frozen at −30 °C. Paradoxically, greater pore volume values were recorded for tablets of oven-dried pellets compressed at 10 kN, compared to the initial pellets. This is a consequence of that the upper measurement limit of mercury intrusion porosimetry is around 120 μm [44]. As compression progresses interparticular empty spaces greater than 120 μm disappear, while smaller pores are being generated. This effect is particularly relevant in the case of oven-dried pellets because of their lowest intragranular porosity; so the intergranular spaces to total porosity remarkably contribute to the total porosity of the tablets.

The fitting of a bimodal distribution (Eq. (1)) enabled the characterization of the intra- and intergranular porosity of the tablets (Table 4). Both depended on the three factors evaluated and their interactions (Table 5). The porosity of the initial pellets determined the magnitude of the intergranular porous space of the tablets. The intergranular empty volume of the tablets ranged inversely to the initial porosity of pellets, as follows: tablets made with oven-dried pellets > tablets made with freeze-dried pellets frozen at −30 °C > tablets made with freeze-dried pellets frozen at −196 °C. A similar behavior was previously reported for MCC–DCP pellets [45]. Porous pellets can undergo greater deformation under the same pressure, which enables the particles to fit better to each other leading to closer structures. In this sense, Bashaiwoldu et al. [26] found a direct dependence of the deformability on the porosity of MCC pellets obtained from masses wetted with water:ethanol 3:2 that were dried applying different techniques.

An increase in compression force from 10 to 20 kN had different repercussions on tablet porosity depending on the drying procedure (Table 4). Tablets made of the oven-dried pellets suffered the most important reduction in the intergranular pore volume (2.5-fold); those obtained from freeze-dried pellets behaving similar regardless of the freezing step (up to 1.8-fold). Tablets made of the freeze-dried pellets after frozen at −196 °C underwent the most relevant reduction in the intragranular porosity (up to 3.8-fold), compared to tablets made with oven-dried pellets (up to 1.8-fold) or with freeze-dried after frozen at −30 °C (no noticeable change). Such different behavior is undoubtedly related to the different intragranular pore volume of the initial pellets, which determines the easiness of rearrangement of the primary particles [45].

The next step was to evaluate how the different microstructure of pellets and their tablets may influence tablet performance when entering into contact with the aqueous medium, mainly in terms of their disintegration time (Table 4) and drug release rate (Table 6). The statistical analysis of disintegration time (ranging from 10 to 60 min) indicated the main influence of the drying procedure ($F_{2,8d.f.} = 50.92$; $\alpha < 0.01$) and, to less extent, of the compression force ($F_{1,8d.f.} = 23.54$; $\alpha < 0.01$) (Table 5). In contact with the liquid medium, the tablets firstly disintegrate into the constituent pellets, except formulation L2b that slowly eroded. In this process, the intergranular porosity may be a critical variable. When the disintegration time values were plotted against the intergranular pore volume of tablets (Fig. 5), the data clearly arrange themselves into two well-differentiated groups: one corresponding to tab-

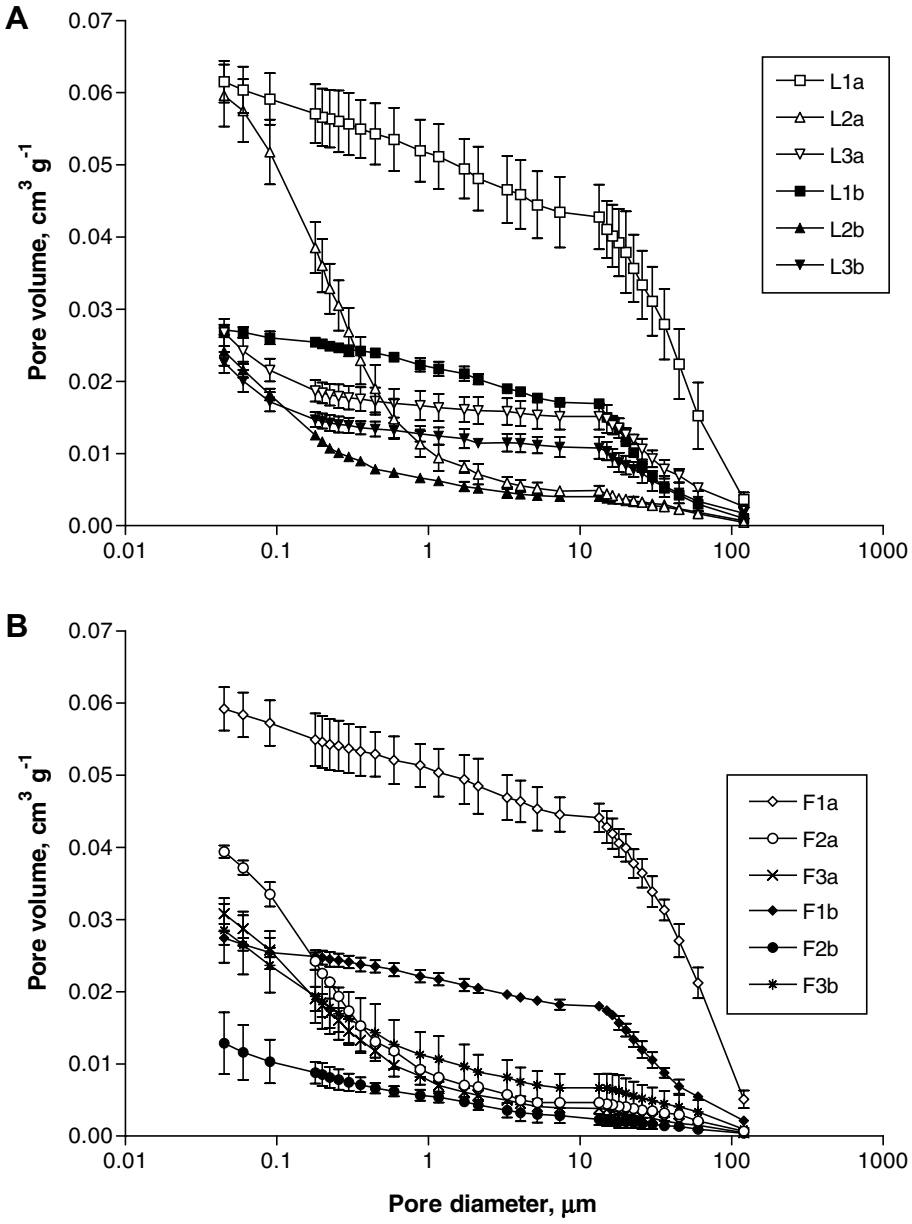


Fig. 4. Cumulative pore-diameter distribution plots of tablets made of theophylline pellets prepared with MCC, carbopol, lactose (plot A) or dicalcium phosphate (plot B), dried by different procedures after compression at 10 or 20 kN. Codes as in Table 4.

lets made of oven-dried pellets and the other for the tablets made of freeze-dried pellets. For a given intergranular per volume, the latter ones disintegrated faster than the former. The reason for such a behavior could be related to two main factors: (i) freeze-drying promotes the hydrophilicity of the pellet surface and thus, it may facilitate the wetting of the tablet surface [46,47]; and (ii) the different inner porosity of pellets may cause the compression force to be mainly directed at deformation of freeze-dried pellets, but in the case of oven-dried pellets, which are the hardest, it would contribute to force contact among them and thus promoting the cohesion of the pellets [38].

Different theophylline release profiles were observed; some formulations releasing all drug in less than 30 min while others requiring up to 3 h (Fig. 6). The profiles showed bimodal kinetics with an initial zero-order release that change, after a certain time ($t_0$), to first-order kinetics. Similar profiles were previously observed by Santos et al. [29] with tablets made of pellets of ibuprofen (10%), MCC (50%), PVP (8%), lactose monohydrate (16%), and the gelling agent xanthan gum (16%). The statistical analysis of the results (Table 5) shows that the time the zero-order kinetics fitted the release mainly depends on the drying procedure of the pellets ($F_{2,7\text{d.f.}} = 18.60$; $\alpha < 0.01$) and on the compression force ($F_{1,7\text{d.f.}} = 6.55$; $\alpha < 0.05$). This dependence is similar to that described above for the disintegration time. The strong linear correlation between $t_0$ and the disintegration time, with a slope close to 1 (Fig. 7),

Table 5
Dependence of the tablets properties on the compression force ($C$) coded as (−1) and (+1) for 10 and 20 kN, respectively; coexcipient nature ($A$) coded as (−1) and (+1) for the lactose and DCP, respectively, and the drying procedure ($B$) coded as (1 0) for oven-drying, (0 1) for freeze-drying after freezing in liquid nitrogen, and (−1 −1) for freeze-drying after freezing at −30 °C

| Property | Equation | $F$ | $R^2$ |
|---|---|---|---|
| Porosity (%) | $\text{Por.} = 6.88 - 1.20C - 0.36A + 0.61B(1) + 0.24B(2) - 0.54C \cdot B(1) - 0.28C \cdot B(2) + 0.39A \cdot B(1) - 0.45A \cdot B(2)$ | 531.91[b,**] | 0.99 |
| Intergranular pore volume$_1$ (cm$^3$ g$^{-1}$) | $\text{TPV}_1 = 0.015 - 5.37\times10^{-3}C - 5.89\times10^{-4}A + 0.015B(1) - 0.011B(2) - 7.62\times10^{-3}C \cdot B(1) + 4.65\times10^{-3}C \cdot B(2) + 1.19\times10^{-3}A \cdot B(1) + 2.17\times10^{-5}A \cdot B(2)$ | 1358.84[b,**] | 0.99 |
| Intragranular pore volume$_2$ (cm$^3$ g$^{-1}$) | $\text{TPV}_2 = 0.020 - 6.15\times10^{-3}C - 6.78\times10^{-3}B(1) + 8.84\times10^{-3}B(2) + 2.60\times10^{-3}C \cdot B(1) - 7.48\times10^{-3}C \cdot B(2) - 1.70\times10^{-3}A \cdot B(1) - 4.03\times10^{-3}A \cdot B(2)$ | 42.91[e,**] | 0.99 |
| Desintegration time (min) | $\text{DT} = 32.18 + 5.94C - 1.15B(1) + 15.68B(2)$ | 41.80[a,**] | 0.94 |
| Dissolution parameters | | | |
| $k_{0T}$ (% h$^{-1}$) | $k_{0T} = 77.01 - 10.14C + 9.74B(1) - 34.16B(2)$ | 13.06[a,**] | 0.83 |
| $t_0$ (h) | $t_0 = 0.47 + 0.088C - 0.014B(1) + 0.27B(2)$ | 13.47[c,**] | 0.85 |
| $k_{1T}$ (h$^{-1}$) | $k_{1T} = 6.68 - 0.98C + 0.51A + 0.71B(1) - 2.59B(2) + 0.20C \cdot B(1) - 1.08C \cdot B(2) - 0.58A \cdot B(1) + 0.85A \cdot B(2)$ | 115.04[d,**] | 0.99 |

$B(1)$ and $B(2)$ represent the values of the first and second elements of the matrix, respectively.
[a] 3,8.
[b] 8,3.
[c] 3,7.
[d] 8,2.
[e] 7,4 degrees of freedom.
** $\alpha < 0.01$.

Table 6
Release rate constants obtained by fitting of the bimodal function (Eq. 4) to the theophylline release profiles from tablets of pellets

| Code | $k_{0T}$ (% h$^{-1}$) | $t_0$ (h) | $k_{1T}$ (h$^{-1}$) | d.f. | $R^2$ |
|---|---|---|---|---|---|
| L1a | 111.9 (2.9) | 0.34 (0.05) | 8.26 (1.77) | 33 | 0.997 |
| L2a | 40.5 (1.9) | 0.69 (0.01) | 4.78 (0.16) | 51 | 0.995 |
| L3a | 119.0 (11.0) | 0.15 (0.01) | 8.53 (0.41) | 33 | 0.997 |
| F1a | 101.1 (3.7) | 0.39 (0.02) | 8.06 (1.09) | 39 | 0.996 |
| F2a | 58.4 (2.6) | 0.47 (0.01) | 7.51 (0.34) | 45 | 0.998 |
| F3a | 92.1 (4.5) | 0.23 (0.01) | 8.77 (0.43) | 39 | 0.998 |
| L1b | 64.7 (3.8) | 0.46 (0.01) | 6.64 (0.42) | 45 | 0.995 |
| L2b | 36.1 (0.4) | – | – | 76 | 0.988 |
| L3b | 114.9 (4.0) | 0.22 (0.01) | 8.10 (0.67) | 45 | 0.998 |
| F1b | 69.4 (1.5) | 0.62 (0.02) | 6.57 (0.69) | 51 | 0.997 |
| F2b | 36.4 (1.6) | 0.96 (0.01) | 3.39 (0.18) | 63 | 0.991 |
| F3b | 79.7 (4.6) | 0.24 (0.01) | 8.84 (0.42) | 33 | 0.998 |

Codes as in Table 4.

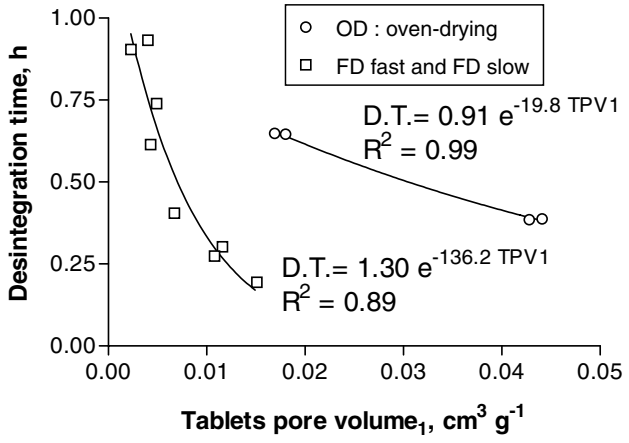


Fig. 5. Dependence of desintegration time of the tablets on their intergranular porous volume.

clearly indicates that the release at a constant rate is maintained while the tablets do not completely disintegrate. During this time, the $k_0$ values, which were also dependent on the drying procedure of the pellets ($F_{2,8\text{d.f.}} = 16.80$; $\alpha < 0.01$) and on the compression force ($F_{1,8\text{d.f.}} = 5.58$; $\alpha < 0.05$), showed a linear correlation with the intergranular porosity of the tablets (Fig. 8). Therefore, the intergranular porosity determines drug release rate while the tablet retains the integrity.

Once the tablets were disintegrated, the release kinetics became first-order. $k_{1T}$ showed a complex dependence on all factors evaluated (Table 5). In addition to the pellets drying procedure ($B$; $F_{2,2\text{d.f.}} = 332.04$; $\alpha < 0.01$) and the compression force ($C$; $F_{1,2\text{d.f.}} = 172.77$; $\alpha < 0.01$), there was also a dependence on the nature of coexcipient ($A$; $F_{1,2\text{d.f.}} = 35.47$; $\alpha < 0.05$) and on the $C \cdot B$ interaction ($F_{2,2\text{d.f.}} = 77.58$; $\alpha < 0.05$) and $A \cdot B$ ($F_{2,2\text{d.f.}} = 45.98$; $\alpha < 0.05$). The effect of the compression force and of the codiluent nature is particularly relevant to tablets made of the freeze-dried pellets after frozen at −196 °C.

The $k_{1T}$ values are related to the intragranular pore volume, i.e. to the porosity of the pellets that are released from the tablets. Since the intragranular porosity of oven-dried pellets is less sensitive to compression (compared to the other pellets), the values of the rate constant of the first-order kinetics obtained both for tablets ($k_{1T}$) and the initial pellets ($k_{1P}$) were similar. In fact, the intragranular pore volume of the tablets made of oven-dried pellets was even above that of the constituent pellets, which can be explained by indentations on pellet surface during compression, as found by Tunón and Alderborn [48] for MCC pellets. Fig. 9 shows that the changes in the first-order release constant of tablets relative to that

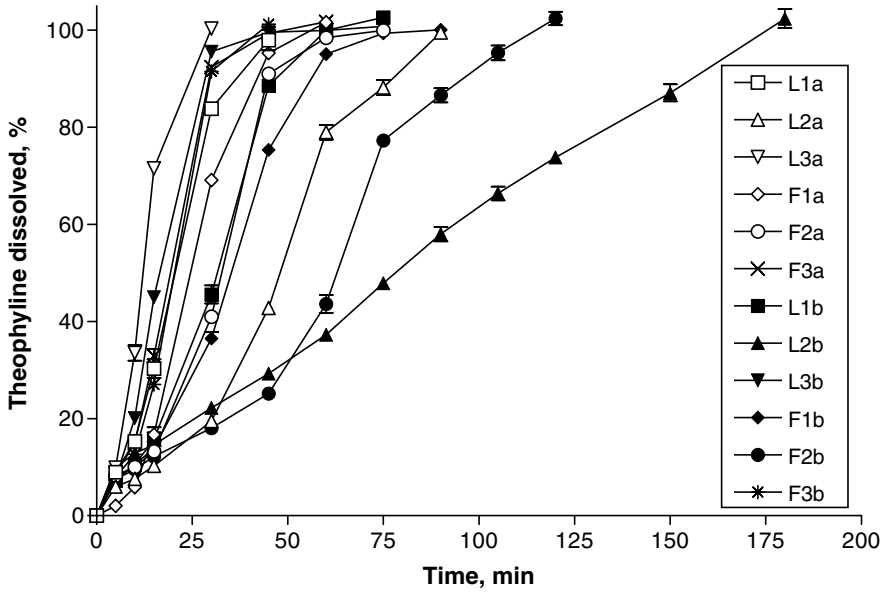


Fig. 6. Theophylline release profiles from tablets of pellets. Codes as in Table 4.

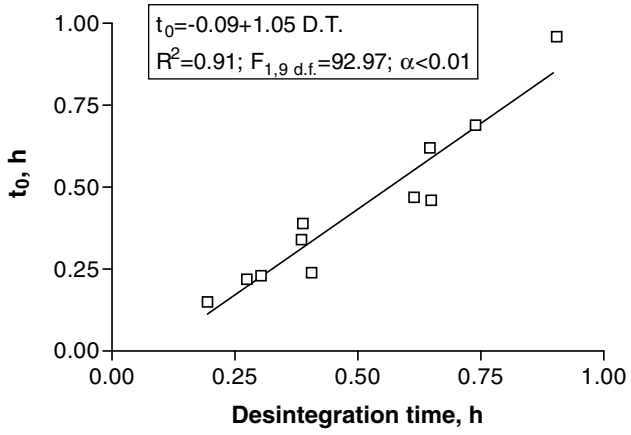


Fig. 7. Linear correlation of the disintegration time of the tablets on the time that the zero-order kinetics fits the release profile.

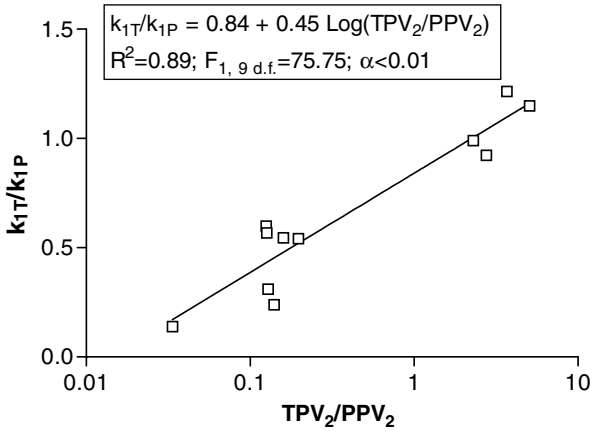


Fig. 9. Dependence of the change in the first-order release rate constant due to compression on the change in the intragranular porous volume of the pellets when tabletting.

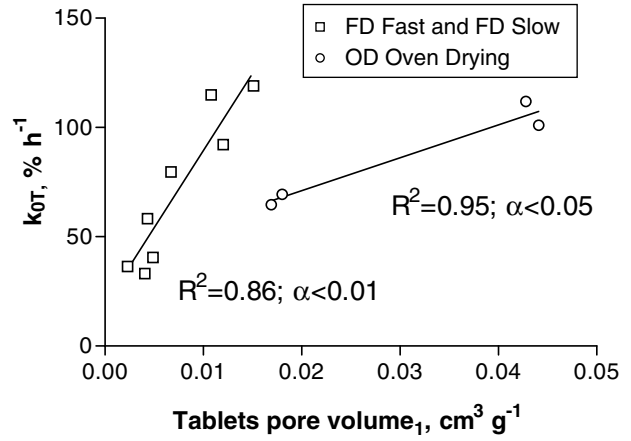


Fig. 8. Dependence of the zero-order release rate constant on the intergranular porous volume of the tablets.

of the corresponding pellets before compression are positively log-correlated to the changes undergone in the intragranular pore volume. This means that the intragranular porosity controls the release rate when the disintegration occurs. This behavior is a consequence of the mechanism of compression of pellets, which undergo deformation without breaking into the primary particles [17,29,49].

The modulable effect of the compression force and the coexcipient nature on the inter- and intragranular porosity of freeze-dried pellets opens the possibility of achieving a wide range of release rates and of adapting the performance of the formulations to specific therapeutic requirements. It should be noticed that freeze-dried pellets that were frozen at −196 °C, which released all dose in less than 15 min regardless of the coexcipient nature, are able after compression to sustain the release up to 3 h.

## 4. Conclusions

The drying procedure is critical for the features of theophylline pellets containing MCC, carbopol and lactose or DCP, because of its effect on the volumetric contraction of the wetted masses, the porosity and the hydrophilicity of the dried pellets. The compression process leads to remarkable changes in the drug release profiles compared to the constituent pellets; the pellets freeze-dried after frozen at −196 °C being the most sensitive. The intergranular porosity of the tablets mainly determines the disintegration time, while the intragranular porosity plays a key role on the release rate from the regenerated pellets. This leads to bimodal profiles with zero-order kinetics, before complete disintegration, followed by a first-order kinetics up to the end of the release process. The dependence of both the inter- and intragranular porosity on the coexcipient nature, the drying procedure of pellets and the compression force found in this work can be very helpful for a rational design of pellet-based tablets.

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