Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 323 (2006) 93–100
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Compressed mini-tablets as a biphasic delivery system

Carla M. Lopes [a,*], José Manuel Sousa Lobo [a], João F. Pinto [b], Paulo Costa [a]

[a] *Departamento de Tecnologia Farmacêutica, Faculdade de Farmácia, Universidade do Porto, Rua Aníbal Cunha 164, 4050-047 Porto, Portugal*
[b] *Departamento de Tecnologia Farmacêutica, Faculdade de Farmácia, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*

Received 20 January 2006; received in revised form 9 May 2006; accepted 24 May 2006
Available online 6 June 2006

Abstract

Compressed mini-tablets systems are presented as a biphasic delivery system designed for zero-order sustained drug release. The outer layer that fills the void spaces between the mini-tablets was formulated to release the drug in a very short time (fast release), while the mini-tablets provided a prolonged release. Different composition (HPMC or EC) and number (10 or 21) of mini-tablets were used to obtain different drug release rates. The in vitro performance of these systems showed the desired biphasic behaviour: the drug contained in the fast releasing phase (powder enrobing the mini-tablets) dissolved within the first 2 min, whereas the drug contained in the mini-tablets was released at different rates, depending up on formulation. Based on the release kinetic parameters calculated, it can be concluded that mini-tablets containing HPMC were particularly suitable approaching to zero-order (constant) release over 8 h time periods.

Keywords: Biphasic release; Multiple unit dosage form; Compaction of mini-tablets; Tablet characteristics; Tablet dissolution

1. Introduction

Oral controlled release drug delivery systems can be classified in two broad groups: single unit dosage forms (SUDFs), such as tablets or capsules, and multiple unit dosage forms (MUDFs), such as granules, pellets or mini-tablets. The concept of MUDFs was initially introduced in the early 1950s. The production of MUDFs is a common strategy to control the release of a drug, as shown by the reproducibility of the release profiles when compared to the ones obtained with SUDFs (Borgquist et al., 2004).

The development of mini-matrices is a promising area in pharmaceutical research concerned with a high control over the release rate of the drug combined with a high flexibility on the adjustment of both the dose and the release of a drug or drugs (Gandhi et al., 1999), and has attracted some attention in the 1990s (Colombo et al., 1985; Sujja-Areevath et al., 1998; Cox et al., 1999; De Brabander et al., 2000). The concept of MUDFs is characterised by the fact that the dose is administered as a number of subunits, each one containing the drug. The dose is then the sum of the quantity of the drug in each subunit and the functionality of the entire dose is directly correlated to the functionality of the individual subunits (Gross et al., 1986; Hoffman et al., 1986; Mathiowitz and Brannon-Peppas, 1999).

Mini-tablets are tablets with a diameter equal to, or smaller than, 2–3 mm (Lennartz and Mielck, 1998). The production of mini-matrices using a tabletting technique is an attractive alternative to the production of pellets, as the presence of solvents (e.g. water) is avoided and high production yields like the ones observed in extrusion and spheronization are obtained. Furthermore, due to the manufacturing process, defined size and strengths can easily be produced, with small variability within and between batches (Rouge et al., 1997).

Like other MUDFs, several mini-tablets can be either filled into hard capsules or compacted into bigger tablets that, after disintegration, release these subunits as multiple dosage forms (Fig. 1). There has been an increasing interest in the development of MUDFs incorporated into tablets instead of hard gelatine capsules, in order to overcome the higher production costs of capsules (Marshall and Rudnick, 1990; Celik, 1994). Because of their size uniformity, regular shape, smooth surface, low porosity and high attainable strength, mini-tablets can maintain their structure and shape in a more reproducible way than usual pellets or granules, once they have been compressed into a tablet system. It can be hypothesized that when shape irregularity and surface roughness of the mini-particles (i.e., pellets and granules) increases, the compression behaviour changes towards a

* Corresponding author. Tel.: +351 222 078 900; fax: +351 222 003 977.
E-mail address: clopes@ff.up.pt (C.M. Lopes).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.05.063

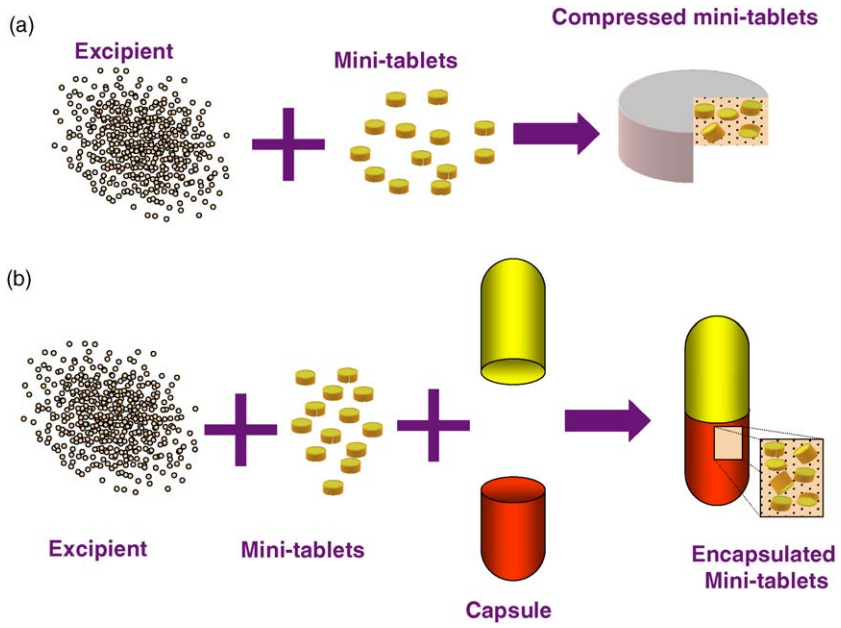

Fig. 1. Mini-tablets delivered as a tablet (a) or a capsule (b).

more complex process that, besides deformation and densification, includes also fragmentation and attrition of the subunits (Johansson and Alderborn, 2001; Santos et al., 2004).

This concept can be used to produce a biphasic delivery system combining a fast release together with the slow release period of the drug, provided that the excipient powder that fills the void spaces between the mini-tablets incorporates a part of the total drug dose. This system can produce a rapid rise in the plasmatic concentrations for some drugs (such as analgesic, anti-inflammatory, antihypertensive and antihistaminic agents) that are requested to promptly exercise the therapeutic effect, followed by an extended release phase in order to avoid repeated administrations (Maggi et al., 1999).

Although some references can be found in the literature (Li and Zhu, 2004; Santos et al., 2004), the full preparation and characterization of a tablet, as SUDF, with mini-tablets containing ethylcellulose (EC) or hydroxypropylmethylcellulose (HPMC) are not common. The biphasic delivery system was able to deliver a first fraction of the dose in a short time (a few minutes) and to deliver a second fraction for a longer period of time at a constant rate. Moreover, the flexibility of the dosage regimen was also studied by the combination of a different number of mini-tablets in the prolonged release component and a different dose of the drug in the fast release component. Previously, the lowest relationship between the amount of powder enrobing the mini-tablets and the weight of mini-tablets, from which tablets could be prepared, was evaluated and this relationship was found to be 3/1 w/w. This could be explained because lower quantities of powders were insufficient to fill the voids between the subunits, and consequently major damages were observed in their structure after the tabletting.

In order to delay the drug release, corresponding to the prolonged release component of the biphasic system, EC and HPMC were used as matricial agents to control release of the drug from the mini-tablets. In matricial systems, the characteristics of the matrix forming agent play an important role in the release mechanism(s) of the drug. Among the hydrophilic polymers, HPMC is one of the most commonly used carriers for the preparation of oral controlled drug delivery systems due to its ability to swell upon jellification once in contact with water. The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution (Colombo et al., 2000; Kiil and Dam-Johansen, 2003). In the other hand, hydrophobic polymers, such as EC, can be alternatives to the swelling polymers by forming an inert matrix, with no physiological action and stable at different pH values and moisture levels. When a tablet with a hydrophobic matrix is placed in the dissolution medium, the drug at the surface is released quickly, with a possible burst effect, requiring its replacement by drug from inner layers that must diffuse through the pores until it reaches the surface.

Ibuprofen is an analgesic and anti-inflammatory drug (NSAID), widely prescribed for the treatment of inflammatory pain or rheumatism, and was used as a model drug.

The major objectives of this study were: (i) to develop and to evaluate compressed mini-tablets systems, in order to achieve a fast/slow drug release; (ii) to investigate formulation parameters affecting in vitro performance; (iii) to obtain a compressed mini-tablet formulation, which has the ability to release the drug at a zero-order rate (constant release).

2. Materials and methods

2.1. Materials

Ibuprofen, a slightly soluble drug (supplied by Laboratórios Medinfar, Lisboa, Portugal) was incorporated in both components of the biphasic delivery system. For the preparation of the prolonged release component (mini-tablets), ethylcellulose (EC, Ethocel®, Fluxa Biochemika, Germany) and hydroxypropyl-

methylcellulose (HPMC, Methocel® K100M, Colorcon, Orpington, UK) were considered, whereas for the fast release component, microcrystalline cellulose (Avicel PH 102, FMC Corporation, USA) and sodium croscarmellose (Ac-Di-Sol, FMC Corporation, USA) were used.

2.2. Preparation of the biphasic delivery system

The qualitative and quantitative composition of the different formulations of the biphasic delivery system can be seen in Table 1.

2.2.1. Prolonged-release component (mini-tablets)

The mini-tablets contained either HPMC or EC as controlling agents. EC was milled (Electric Mill, Ika model A10, Germany) before use. All materials were sieved and the fractions below 63 μm were considered to minimize the lag time observed during drug release when coarse fractions were used and to prevent changes on properties of the tablets due to changes on the size of particles. The formulations contained 50% (w/w) of ibuprofen for HPMC K100M mini-tablets and 85% (w/w) of ibuprofen for EC mini-tablets in order to delay the release of ibuprofen throughout 8 h (Lopes et al., 2006). Mini-tablets, weighing 12.0 ± 1.0 mg, were prepared by direct compression with flat tip punches and dies with 2.5 mm diameter. The punches and dies were fit to an instrumented mechanical press (Lloyds Instruments, LR 50K, UK) that controlled and recorded the pressure (100 ± 5 N/mm^2) and the displacement of the punches.

2.2.2. Fast release component

Microcrystalline cellulose (Avicel PH 102) was used because of its good compaction and disintegration properties. Sodium croscarmellose was used as a super disintegrant to obtain an immediate release of the drug.

2.3. Compressed mini-tablets system

For the preparation of the biphasic delivery system the die of the tabletting machine was progressively filled by hand with the weighed amounts of the fast release component and the mini-tablets (Table 1) prior to compression. Two different ratios of powder to mini-tablets (w/w) were employed: 750/250 and 880/120.

Biphasic formulations, weighing 1000.0 ± 20.0 mg were prepared by direct compression, with flat tip punches and dies with 13 mm diameter at 5 kN, as mentioned previously for the mini-tablets.

Table 1
Composition of biphasic delivery systems (quantities in mg)

Composition	Formulation no.			
	1	2	3	4
Fast release component (weight/biphasic system)				
Ibuprofen	200	235	200	235
Avicel PH 102	545	639	545	639
Ac-Di-Sol	5	6	5	6
Prolonged release component				
Number of mini-tablets/biphasic system	21	10	21	10
Mini-tablet component (weight/mini-tablet)				
Ibuprofen	6	6	10.8	10.8
HPMC K100M	6	6	–	–
EC	–	–	1.2	1.2

2.4. Physical characterization of the compressed mini-tablets system

Compressed mini-tablets were characterized for weight variation ($n = 15$, analytical balance METTLER AE 200, Mettler Toledo, Switzerland), thickness ($n = 15$, electronic digital micrometer, Palmer), crushing strength ($n = 3$, Erweka, model TBH 28, Germany) and friability ($n = 5$, Roche type friabilometer, 25 rpm for 4 min, Sotax model F1 Friabilator, Switzerland).

The crushing strength of a compact was determined by compressing the compact diametrically. The radial tensile strength (σ_X) was calculated from the compact crushing strength and thickness according to Fell and Newton equation (Fell and Newton, 1968):

$$\sigma_X = \frac{2F}{\pi D h} \quad (1)$$

where σ_X is the tensile strength (MPa), F the force required to cause failure in tension (N), D the diameter (mm) and h is the thickness of the compact (mm).

The mini-tablets tested for the crushing strength were red coloured using a sudan dye in ethanol solution in order to observe the structure of mini-tablets after compression (Fig. 2).

2.5. Dissolution testing

In vitro dissolution tests were performed according to the USP paddle method at 150 rpm using an automated dissolution apparatus (Sotax model AT7, Switzerland) containing 900 ml

Fig. 2. Fracture equatorial showing surfaces of the compressed EC mini-tablets system.

of phosphate buffer (pH 7.2) at 37 ± 0.5 °C. The drug released was quantified spectrophotometrically on-line through a UV–vis spectrophotometer (Jasco, model V-530, Tokyo, Japan) set at 265 nm. The cumulative fraction of the drug released was calculated from the total amount of ibuprofen and plotted as a function of time. Dissolution studies ($n = 3$) was carried out on both compressed mini-tablets and original mini-tablets to investigate the effect of compression on the dissolution behaviour.

The dissolution profiles from compressed and non-compressed mini-tablets were compared using a similarity factor (f_2) (Morre and Flanner, 1996). The FDA and EMEA suggested that two dissolution profiles were declared similar if f_2 was between 50 and 100 (CDER, 1995; EMEA, 1999). Comparisons of the n exponent values between the compressed and non-compressed mini-tablets were made with analysis of variance (ANOVA, $\alpha = 0.05$). All statistical analysis were performed with the SPSS software package (SPSS for Windows 14.0, SPSS, Chicago, USA).

2.6. Release drug data modelling

The suitability of several equations, which are reported in the literature to identify the mechanism(s) for the release of ibuprofen (Costa and Sousa Lobo, 2001), was tested with respect to the release data. Some diffusion models (Korsmeyer–Peppas) are expected to be valid only up to approximately 60% cumulative drug released (Ritger and Peppas, 1987) and the data for analysis were therefore restricted to that range excluding also the lag time. The data were evaluated according to the following equations:

- Zero-order model (Donbrow and Samuelov, 1980):

$$M_t = M_0 + K_0 t \quad (2)$$

- Higuchi model (Higuchi, 1961, 1963):

$$M_t = M_0 + K_H t^{0.5} \quad (3)$$

- Korsmeyer–Peppas model (Korsmeyer et al., 1983; Peppas, 1985):

$$M_t = M_0 + K_K t^n \quad (4)$$

where M_t is the amount of drug dissolved in time t, M_0 the initial amount of drug, K_0 the zero-order release constant, K_H the Higuchi rate constant, K_K the release constant and n is the release exponent, which characterizes the mechanism of drug release. The magnitude of the exponent n indicates the release mechanism as Fickian diffusion, as case II transport, or as anomalous transport. In the present study (cylindrical shape) the limits considered were $n = 0.45$ (indicates a classical Fickian diffusion-controlled drug release) and $n = 0.89$ (indicates a case II relaxational release transport: polymer relaxation controls drug delivery). Values of n between 0.45 and 0.89 can be regarded as indicators of both phenomena (transport corresponding to coupled drug diffusion in the hydrated matrix and polymer relaxation) commonly called anomalous non-Fickian transport. Values of n greater than 0.89 indicates a super case II transport, in which a pronounced acceleration in solute release by a film occurs toward the latter stages of release experiments, resulting in a more rapid relaxation-controlled transport (Jacques et al., 1974).

3. Results and discussion

3.1. Physical properties of the compressed mini-tablets systems

Table 2 lists the physical properties (weight, thickness, tensile strength and friability) of the compressed mini-tablets systems.

One of the major characteristics of the mini-tablets is that they should not fuse into a non-disintegrating matrix during compaction. It was observed that red coloured mini-tablets were able to withstand the compression force after the crushing test. Generally, discrete mini-tablets could clearly be distinguished within the compact system although the distance between the mini-tablets in formulations one and three was very low due to the higher number of mini-tablets in relation to the amount of powder mixture around them.

Visual inspection of the fracture surfaces of the biphasic system revealed that the appearance of the mini-tablets in the compact system was similar to the original mini-tablets. Thus, these subunits tended to keep their integrity when compacted and remained as coherent individual units after the process of tabletting (Fig. 2). These units did not fragment into smaller units after the compaction process. This lack of fragmentation might be caused by the unique stress conditions of the mini-tablets during uniaxial compression in the die, i.e., the mini-tablets are stressed from several directions simultaneously, making the fracturing of these subunits relatively difficult.

Johansson et al. (1995, 1998) and Johansson and Alderborn (2001) have suggested that the degree of deformation of the pellets seemed to be controlled by their porosity before compression, rather than by their ability to withstand an applied force as individual pellets. A deformation of a pellet during compression is probably caused by the repositioning of the primary particles which constitute the pellet. Due to the production process of

Table 2
Physical properties of the compressed mini-tablets systems

Formulation	Weight (mg), mean ± S.D.	Thickness (mm), mean ± S.D.	Tensile strength (MPa), mean ± S.D.	Friability (%)
1	1020.03 ± 3.36	7.21 ± 0.03	0.63 ± 0.05	0.99
2	1014.01 ± 1.72	7.07 ± 0.01	0.71 ± 0.06	0.92
3	1010.95 ± 6.34	7.15 ± 0.02	0.62 ± 0.03	1.01
4	1014.16 ± 4.27	7.07 ± 0.04	0.73 ± 0.06	0.96

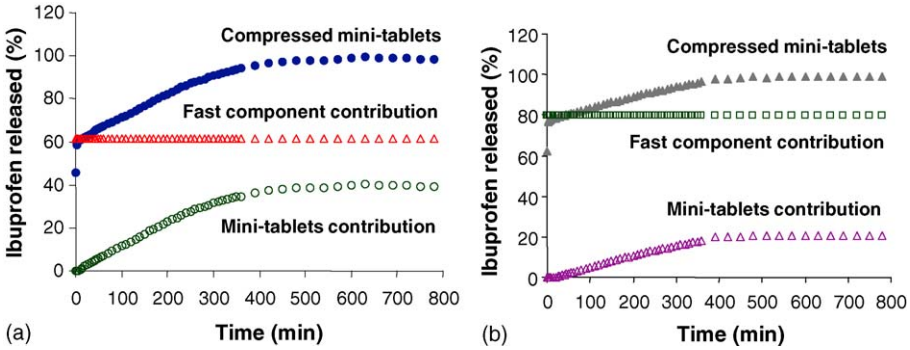

Fig. 3. In vitro ibuprofen release profiles from compressed mini-tablets systems, fast component and mini-tablets contribution at different ratios of mass fraction of powder/HPMC mini-tablets component (mg/mg): (a) 750/250 (formulation 1); (b) 880/120 (formulation 2).

mini-tablets, a low porosity will be expected for these multiple units. In this case, the possibility for the primary particles to find a sufficient space to move into when the mini-tablets are stressed will be limited, and the degree of deformation which the mini-tablets undergo during compression will be low. Furthermore, at low porosities, the primary particles might be rigidly positioned one to each other, which can also affect the possibility of the particles to change its position.

After compaction, some mini-tablets showed slight compression-induced changes in shape, as could be noticed by visual inspection. As it was previously observed with pellets, this is an indication that the deformation of mini-tablets seemed to occur mainly in the same direction as the stress applied during compression (Johansson et al., 1995). This also implies that volume reduction of these subunits can be an important change induced during compression.

3.2. Dissolution testing of the compressed mini-tablets system

Figs. 3 and 4 show the ibuprofen release profiles from compressed mini-tablets systems and the corresponding mixtures of the components in the formulation, including different ratios of powder/mini-tablets containing either HPMC or EC as prolonged release component. These figures also show the contribution of each component (fast/mini-tablets) in the release of the drug. To evaluate the contribution of the ibuprofen mini-tablets release, the amount of drug contained in the fast component was subtracted to the ibuprofen released.

For the compressed mini-tablets systems under investigation, the release profiles are characterized by a burst release of ibuprofen, followed by a slow release phase, typical of a biphasic delivery system. For all formulations, the large tablets were rapidly disintegrated into both powder (releasing the immediate dose of the drug) and individual mini-tablets, which sustained the release of the drug. In fact, the dissolution profile of the fast release component occurs within a few minutes (less than 2 min), due to the prompt disintegration of the system in contact with the dissolution media. The percentage of ibuprofen released during the initial phase and the lag time for prolonged release were different due to the nature of the polymer component of the mini-tablets. The mini-tablets, upon dispersion in the dissolution media, controlled the ibuprofen release at a slow rate for almost 8 h. During the dissolution test an initial lag time was evident, as well as an anisotropic swelling phenomenon (i.e., more swelling in the axial direction than in the radial direction after exposure to water) for HPMC mini-tablets after the disintegration of the biphasic system (Fig. 3). A similar phenomenon was observed in previous studies of HPMC non-compressed mini-tablets by Lopes et al. (2006) and by Papadimitriou et al. (1993), who related the predominantly axial relaxation of the HPMC compacts to the relief of stress induced during compaction, and unidirectional swelling to the orientation of molecules during compression.

In the release phase for mini-tablets it was observed a different behaviour in the dissolution profiles (HPMC or EC). From plots in Figs. 3 and 4 it can be seen that release rates are affected

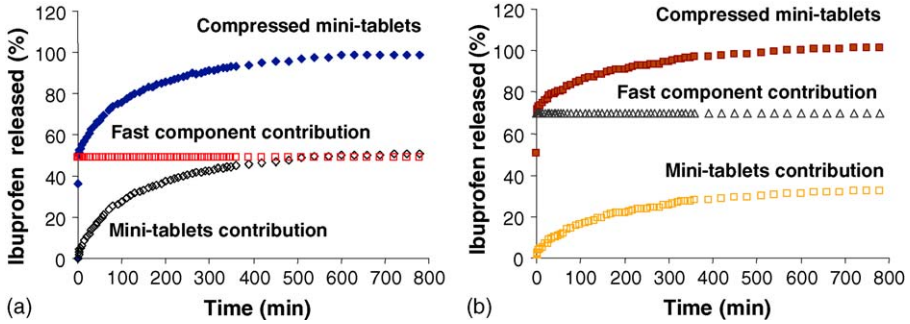

Fig. 4. In vitro ibuprofen release profiles from compressed mini-tablets systems, fast component and mini-tablets contribution (open symbols) at different ratios of mass fraction of powder/EC mini-tablets component (mg/mg): (a) 750/250 (formulation 3); (b) 880/120 (formulation 4).

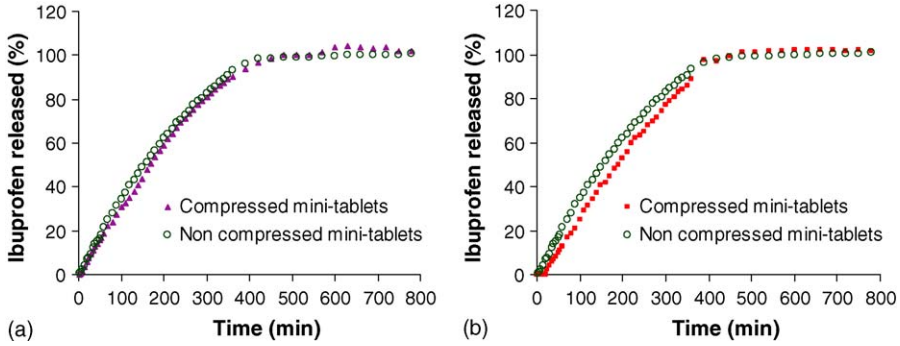

Fig. 5. In vitro ibuprofen release profiles from original HPMC mini-tablets (filled symbols) and mini-tablets compressed (open symbols) at different ratios of mass fraction of powder/HPMC mini-tablets component (mg/mg): (a) 750/250 (formulation 1); (b) 880/120 (formulation 2).

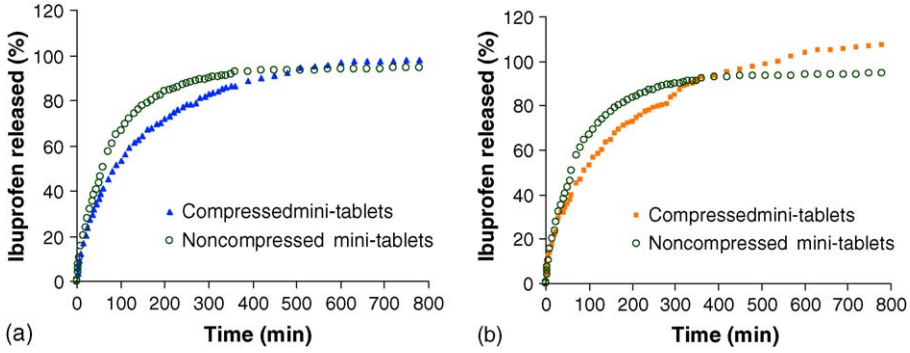

Fig. 6. In vitro ibuprofen release profiles from original EC mini-tablets (filled symbols) and mini-tablets compressed (open symbols) at different ratios of mass fraction of powder/EC mini-tablets component (mg/mg): (a) 750/250 (formulation 3); (b) 880/120 (formulation 4).

by the composition of mini-tablets present in the biphasic system.

Ideally, drug release should not be affected by the compaction process. The aim of most studies on the compaction of mini-tablets is to convert MUDFs into a SUDF containing the multi mini-particles, with this single unit formulation having the same properties, in particular drug release properties, as the individual mini-particles. In some cases, the application of a compaction pressure could lead to structural changes in these subunits and, consequently, to the modification of drug release.

In order to compare the ibuprofen release from mini-tablets, the contribution of the ibuprofen fast release was not considered in Figs. 5 and 6. These figures show the in vitro ibuprofen release obtained from compressed mini-tablets systems and compares it with the release obtained from original non-compressed mini-tablets containing HPMC and EC, respectively.

The biphasic formulations containing 21 and 10 compressed HPMC mini-tablets show the ability to release the intact mini-tablets in a dissolution medium while maintaining a similar dissolution profile to the original mini-tablets ($f_2 = 78$ and 57, respectively), suggesting their physical integrity (Fig. 5). In the case of formulations containing EC mini-tablets (Fig. 6), it was observed a lower release rate compared to the non-compressed mini-tablets. Despite, the apparent difference in the dissolution profiles between original and biphasic formulations containing compressed 21 and 10 EC mini-tablets, the f_2 value was 51 for both comparisons, indicating their similarity.

3.3. Drug release from compressed mini-tablets system

The results for the fitting of the kinetics model for ibuprofen release from compressed and non-compressed mini-tablets are shown in Tables 3 and 4, respectively (release rate constants, K_0, K_H, K_K, the determination coefficients, R^2, and the release exponent, n). The correlation coefficient (R^2) was used as indicator of the best fitting, for each of the models considered.

Table 3
Fitting of the kinetics model (release rate constants, K_0, K_H, K_K, and exponent n, together with the determination coefficients, R^2) for compressed mini-tablets system

Formulation	Zero-order equation		Higuchi equation		K–P equation		
	K_0	R^2	K_H	R^2	K_K	R^2	n
1	0.1132	0.9947	1.8550	0.9653	0.2049	0.9965	0.90
2	0.0589	0.9932	1.0367	0.9682	0.1354	0.9969	0.87
3	0.2402	0.9532	3.0415	0.9980	2.6200	0.9972	0.53
4	0.1243	0.9468	1.6773	0.9930	1.6444	0.9937	0.51

Table 4
Fitting of the kinetics model (release rate constants, K_0, K_H, K_K, and exponent n, together with the determination coefficients, R^2) for original mini-tablets (non-compressed)

Non-compressed mini-tablets	Zero-order equation		Higuchi equation		K–P equation		
	K_0	R^2	K_H	R^2	K_K	R^2	n
HPMC	0.3234	0.9946	5.2774	0.9775	0.7579	0.9978	0.84
EC	0.7700	0.9790	7.3100	0.9930	5.8714	0.9966	0.64

In the case of EC mini-tablets formulations, the values of the release constant in Tables 3 and 4 are higher for the original mini-tablets. This means that the decrease of the release rate is probably consequence of the mini-tablets deformation occurred during the compression of mini-tablets.

Some release mechanisms can be better elucidated indirectly, either on basis of exponent n, in Eq. (4), or comparing the fitting of the models of pure diffusion, Eq. (3), and of relaxational polymer and matrix erosion, Eq. (2). From the results given in Tables 3 and 4 we can say the following:

In the case of compressed mini-tablets systems containing 21 or 10 HPMC mini-tablets, the model which fits the best is the zero-order model (Eq. (2)), with $R^2 = 0.9947$ and 0.9932, respectively. The n values for these systems are 0.90 and 0.87, respectively. This means that n values and the comparison of model fitting lead to the same conclusion: the mechanism of release, for HPMC mini-tablets contribution in the biphasic system, is closer to case II relaxational transport. Regarding the results for original (non-compressed) HPMC mini-tablets, $R^2 = 0.9946$ (zero-order model) and $n = 0.84$, similar conclusions can be obtained for the release mechanism (case II transport). Comparison of the exponent n values between non-compressed and compressed HPMC mini-tablets based on ANOVA analysis revealed no statistical difference ($p > 0.1$). This is confirmed by a similar in vitro ibuprofen release profile obtained from the contribution of mini-tablets in the release of the biphasic system and of non-compressed mini-tablets based on the f_2 value. Thus, during the dissolution test, the HPMC mini-tablets were subjected to two simultaneous processes: (a) the formation of a gel layer and (b) its progressive erosion. Although the erosion of the gel is generally influenced by the hydrodynamic conditions, in this case the synchronisation of the two processes led to a nearly constant release rate. It can be concluded that relaxation of polymeric chain and the erosion of the matrix were a very important factor that controls the release rate of the drug from these mini-tablets.

In the case of compressed mini-tablets systems containing 21 or 10 EC mini-tablets, the best fitting model is obtained with pure diffusion model (Eq. (2)) with $R^2 = 0.9980$ and 0.9930, respectively. Taking also into account the n values, 0.53 and 0.51, respectively, we can say that the mechanism controlling the release is closer to a Fickian pure diffusion of the drug through the matrices in the EC mini-tablets than to an anomalous diffusion. For original EC mini-tablets, the R^2 of Eq. (2) and n exponent are, respectively, 0.9930 and 0.64. In this case, both results suggest that the release mechanism is an anomalous diffusion. Despite the f_2 value does not detect differences, there is a significant difference in the dissolution profiles obtained from non-compressed and compressed EC mini-tablets formulations based on the exponent n value (ANOVA, $p < 0.05$) probably due to the hydrophobic nature of the polymeric agent that tends to form inert porous structure matrix systems (Salomon and Doelker, 1980; Buri, 1984). The release of the drug from this type of matrices is mainly controlled by the size of the pore and the interconnected channels formed on the system throughout the process of dissolution. These results suggest that the drug diffusion from EC mini-tablets of biphasic delivery system was perhaps disturbed by the powder released from the fast component that interacted with the surface of the porous structure of the EC mini-tablets. Furthermore, the compaction pressure of mini-tablets could also contribute to modify the release profile compared to non-compressed mini-tablets. Based on the values of crushing strength from non-compressed HPMC and EC mini-tablets, respectively, 2.7 and 1.9 MPa (Lopes et al., 2006), it can be concluded that the structure presented by the HPMC mini-tablets is more resistant to deformation during the compression process than the EC mini-tablets.

4. Conclusions

A biphasic oral delivery system was developed by compressing mini-tablets into a tablet dosage form. The compressed mini-tablets showed slight deformation and no fragmentation. Because of their physical characteristics, mini-tablets tend to keep their integrity after compression, making more difficult the fracturing process of these subunits. This technology may be achieved by fast/slow delivery system. This is characterized by an initial rapid release phase, corresponding to the drug release contained in the powder layer filled between mini-tablets, followed by a period of slow release, corresponding to the drug release of mini-tablets. The proposed fast/slow delivery devices show a wide flexibility in the modulation of the delivery program. The two different release phases can be easily adjusted in a wide range of values of both delivery rate and ratio of the dose fractions, on the basis of the pharmacokinetics and therapeutic needs, to perform the desired in vivo profile. Key variables of this study included the external powder/mini-tablets ratio and type of matrix mini-tablets. The results show that the release profile is strongly dependent on the number and/or composition of subunits, making up the drug sustained dose. After the disintegration of this system, the HPMC mini-tablets were able to release a second fraction of the dose in a prolonged time (8 h) at a constant rate and with an identical dissolution profile to the non-compressed mini-tablets, suggesting their physical integrity after compression. In the case of EC mini-tablets, the powder released from fast component in biphasic formulations

and/or compression pressure induced some changes in the release mechanism and in the release time, which was prolonged compared to non-compressed mini-tablets.

Acknowledgements

The authors are thankful to Laboratórios Medinfar (Lisboa, Portugal) and Univete (Colorcon representative, Lisboa, Portugal) for the gifts of ibuprofen and HPMCs, respectively. This work was supported financially by FCT and FSE, doctoral grant (SFRH/BD/7002/2001).

References

Borgquist, P., Nevsten, P., Nilsson, B., Wallenberg, L.R., Axelsson, A., 2004. Simulation of the release from a multiparticulate system validated by single pellet and dose release experiments. J. Contr. Release 97, 453–465.

Buri, P., 1984. Définition et classification des systèmes matriciels. S.T.P. Pharm. Sci. 3, 193–199.

Celik, M., 1994. Compaction of multiparticulate oral dosage forms. In: Ghebre-Sellassier, I. (Ed.), Multiparticulate Oral Drug Delivery. Marcel Dekker, New York, pp. 181–216.

Center for Drug Evaluation and Research, 1995. Guidance for industry immediate release solid oral dosage forms scale-up and postapproval changes: chemistry, manufacturing, and controls, in vitro dissolution testing and in vivo bioequivalence documentation, CMC 5.

Colombo, P., Conte, U., Caramella, C., Gazzaniga, A., La Manna, A., 1985. Compressed polymeric mini-matrices for drug release control. J. Contr. Release 1, 283–289.

Colombo, P., Bettini, R., Santi, P., Peppas, N.A., 2000. Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. PSTT 3, 198–204.

Costa, P., Sousa Lobo, J.M., 2001. Modelling and comparison of dissolution profiles. Eur. J. Pharm. Sci. 13, 123–133.

Cox, P.J., Khan, K.A., Munday, D.L., Sujja-areevath, J., 1999. Development and evaluation of a multiple unit oral sustained release dosage form for *S*(+)-ibuprofen: preparation and release kinetics. Int. J. Pharm. 193, 73–84.

De Brabander, C., Vervaet, C., Fiermans, L., Remon, J.P., 2000. Matrix minitablets based on starch/microcrystalline wax mixtures. Int. J. Pharm. 199, 195–203.

Donbrow, M., Samuelov, Y., 1980. Zero order drug delivery from double-layered porous films: release rate profiles from ethyl cellulose, hydroxypropyl cellulose and polyethylene glycol mixtures. J. Pharm. Pharmacol. 32, 463–470.

EMEA, 1999. European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit, Note for Guidance on Quality of Modified Release Products: A. Oral Dosage Forms; B. Transdermal Dosage Forms; Section I (Quality), CPMP/QWP/604/96.

Fell, J.T., Newton, J.M., 1968. The tensile strength of lactose tablets. J. Pharm. Pharmacol. 20, 205–212.

Gandhi, R., Kaul, C.L., Panchagnula, R., 1999. Extrusion and spheronization in the development of oral controlled release dosage forms. PSST 2, 160–170.

Gross, S.T., Hoffman, A., Donbrow, M., Benita, S., 1986. Fundamentals of the release mechanism interpretation in multiparticulate systems: the prediction of the commonly observed release equations from statistical population models for particle ensembles. Int. J. Pharm. 29, 213–222.

Higuchi, T., 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. J. Pharm. Sci. 50, 874–875.

Higuchi, T., 1963. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145–1149.

Hoffman, A., Donbrow, M., Gross, S.T., Benita, S., Bahat, R., 1986. Fundamentals of release mechanism interpretation in multiparticulate systems: determination of substrate release from single microcapsules and relation between individual and ensemble release kinetics. Int. J. Pharm. 29, 195–211.

Jacques, C.H.M., Hopfenberg, H.B., Stannett, V., 1974. Super case II transport of organic vapors in glassy polymers. In: Hopfenberger, H.B. (Ed.), Permeability of Plastic Films and Coatings to Gases, Vapors, and Liquids. Plenum Press, New York, pp. 73–86.

Johansson, B., Wikberg, M., Ek, R., Alderborn, G., 1995. Compression behaviour and compactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical properties. Int. J. Pharm. 117, 57–73.

Johansson, B., Nicklasson, F., Alderborn, G., 1998. Effect of pellet size on degree of deformation and densification during compression and on compactability of microcrystalline cellulose pellets. Int. J. Pharm. 163, 35–48.

Johansson, B., Alderborn, G., 2001. The effect of shape and porosity on the compression behaviour and tablet forming ability of granular materials formed from microscrystalline cellulose. Eur. J. Pharm. Biopharm. 52, 347–357.

Kiil, S., Dam-Johansen, K., 2003. Controlled drug delivery from swellable hydroxypropylmethylcellulose matrices: model-based analysis of observed radial front movements. J. Contr. Release 90, 1–21.

Korsmeyer, R.W., Gurny, R., Doelker, E.M., Buri, P., Peppas, N.A., 1983. Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm. 15, 25–35.

Lennartz, P., Mielck, J.B., 1998. Minitabletting: improving the compactability of paracetamol powder mixtures. Int. J. Pharm. 173, 75–85.

Li, Y., Zhu, J., 2004. Modulation of combined-release behaviours from a novel "tablets-in-capsule system". J. Contr. Release 95, 381–389.

Lopes, C.M., Sousa Lobo, J.M., Pinto, J.F., Costa, P., 2006. Directly compressed mini matrix tablets containing ibuprofen: preparation and evaluation of sustained release. Drug Develop. Ind. Pharm. 32, 95–106.

Maggi, L., Machiste, E.O., Torre, M.L., Conte, U., 1999. Formulation of biphasic release tablets containing slightly soluble drugs. Eur. J. Pharm. Biopharm. 48, 37–42.

Marshall, k., Rudnick, E.M., 1990. Tablet dosage form. In: Banler, G.S., Rhodes, C.T. (Eds.), Drugs and the Pharmaceutical Sciences—Modern Pharmaceutics, vol. 40. Marcel Dekker, New York, pp. 355–426.

Mathiowitz, E., Brannon-Peppas, L., 1999. In: Mathiowitz, E. (Ed.), Encyclopedia of Controlled Drug Delivery. Wiley, New York, pp. 493–546.

Morre, J.W., Flanner, H.H., 1996. Mathematical comparison of dissolution profiles. Pharm. Tech. 20, 64–74.

Papadimitriou, E., Buckton, G., Efentakis, M., 1993. Probing the mechanisms of swelling of hydroxypropyl methylcellulose matrices. Int. J. Pharm. 98, 57–62.

Peppas, N.A., 1985. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. 60, 110–111.

Ritger, P.L., Peppas, N.A., 1987. A simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J. Contr. Release 5, 23–36.

Rouge, N., Cole, E.T., Doelker, E., Buri, P., 1997. Screening of potentially floating excipients for minitablets. S.T.P. Pharm. Sci. 7, 386–392.

Salomon, J.L., Doelker, E., 1980. Formulation des comprimés à libération prolongée. I. Matrices inertes. Pharm. Acta Helv. 55, 174–182.

Santos, H., Veiga, F., Pina, M.E., Sousa, J.J., 2004. Compaction, compression and drug release characteristics of xanthan gum pellets of different compositions. Eur. J. Pharm. Sci. 21, 271–281.

Sujja-Areevath, J., Munday, D.L., Cox, P.J., Khan, K.A., 1998. Relationship between swelling, erosion and drug release in hydrophilic natural gum mini-matrix formulation. Eur. J. Pharm. Sci. 6, 207–217.