Drug Development and Industrial Pharmacy, 2011, 37(1): 113–120

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI:10.3109/03639045.2010.495753

informa
healthcare

ORIGINAL ARTICLE

Effect of core size and excipients on the lag time and drug release from a pulsatile drug delivery system

M. Efentakis, A. Iliopoyloy and A. Siamidi

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Athens, Athens, Greece

Abstract

Background: Pulsatile drug delivery system, based on a core-in-cup dry-coated tablet was examined and evaluated. The system consisted of three different parts: a core tablet (with increasing diameter), containing the active ingredient acting as reservoir; an impermeable outer shell; and a top cover layer barrier. The core tablet contained either caffeine or theophylline as model drugs. *Objective*: To investigate and evaluate how the geometrical characteristics of the core tablets, drugs, and excipients influence the behavior of the system presented, namely, lag time and drug release. *Results and Discussion*: Drug release exhibited a lag time period dependent on the core tablet size, drug solubility, and characteristics of polymer and polymer mixtures. The lag time was increased by increasing the core tablet diameter and the quantity of soluble lactose in the top cover layer. *Conclusions*: The quantity and characteristics of materials, the core tablet size, and the erosion of the top cover layer were found to be important factors in controlling the lag time and release. Increase in core tablet diameter resulted in lower lag times and greater release and release rates. Similarly, by increasing sufficiently the quantity of the soluble excipient lactose, in the top layer we observed a decrease of the lag times and an increase of release.

Key words: Caffeine, erosion, lag time, pulsatile drug delivery, swellable polymers, theophylline

Introduction

Controlled release drug delivery systems offer many advantages. Among them important ones are improved patient compliance, the maintenance of their therapeutic effects for extended periods, a smaller dose requirement, minimized side effects, and finally their cost effectiveness. On the other hand, for certain therapies a pulsatile drug release pattern is more appropriate. Pulsatile drug delivery systems release the drug rapidly after a definite predetermined lag time, and they have gained increasing research interest lately[1].

Recent studies have shown that most of the bodily functions display circadian rhythms, for example, the heart rate, the stroke volume, the blood pressure, the blood flow, the body temperature, and the gastric-pH. Moreover, most of our organ functions vary with the time of the day. It is well documented that there are rhythmic and temporal patterns in the manifestation of numerous disease states. The symptoms of many diseases, such as bronchial asthma, myocardial infraction, angina pectoris, hypertension, and rheumatic diseases, follow a circadian rhythm.

In several reports[2–5], day–night variations of dyspnea attacks in asthmatic patients and variations in the incidence of myocardial infractions are mentioned. Delthefsen and Repges[6] reported a sharp increase in the incidence of asthmatic attacks throughout the early morning hours. Based on all these observations it is evident that drug delivery and therapy should be modified to achieve an efficient drug level at the required time. Pulsatile administration could be useful for the treatment of a number of diseases, for instance, asthma, gastric ulcer, hypertension, ischemic heart disease, and arthritis, which exhibit circadian rhythms[6].

Systems displaying pulsatile release are mainly based on polymers and can be classified into single-pulse, double-pulse, and mixed-pulse systems[7]. Most pulsatile systems are of the reservoir type and are usually surrounded with a diffusional barrier. This barrier can be dissolved, eroded, or removed at a predetermined period of time after which the drug is dissolved and rapidly released.

Address for correspondence: Dr. M. Efentakis, Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Athens, Panepistimiopolis, Zografou, 157 71 Athens, Greece. Tel: +30 210 7274025, Fax: +30 210 7274 027. E-mail: efentakis@pharm.uoa.gr

(Received 8 March 2010; accepted 18 May 2010)

In recent times, several pulsatile delivery systems have been developed and examined including tablet and capsule formulations[8–11]. Most of the tablet formulations are of the reservoir-type devices with a barrier coating. In parallel, capsule-based pulsatile release systems, preparations, such as Pulsincap, have also been developed[12–15]. These systems consist of a water-impermeable or semi-impermeable capsule, half filled with the drug formulation and sealed by means of a hydrogel polymer plug. Contact with the gastrointestinal fluids results in their erosion and removal or ejection of the polymer plug followed by the rapid release of the drug.

In our previous studies[16], we have presented a novel pulsatile drug delivery system consisting of an impermeable cup and a swellable top cover layer. The top cover layer would allow greater versatility and adjustment of lag time. More specifically, the system is a dry-coated preparation and an alternative to the existing, until now, one-pulse drug delivery devices. The system consists of three parts: a core tablet containing the active ingredient, an impermeable outer shell, and a top cover layer barrier. The system could be described as a hybrid system in which the top layer consists of a gel-forming part and the inner part a conventional tablet acting as drug reservoir. It was found[16] that the characteristics of materials contained in core and top layer substantially affect the lag times of the system's performance.

For the preparation of tablets a press coating method was employed. This method is one of the modern methods utilized for the manufacturing of sustained release preparations and offers a number of advantages such as a nonsolvent process, a short processing time, limited steps, and low energy requirements[17].

The purpose of this study was to further investigate and evaluate how the geometrical characteristics of the core tablets and excipients influence the behavior of the system suggested. Three different polymers, two hydrophilic (polyethylene oxide, guar gum) and a hydrophobic (cellulose acetate propionate), were used. Polyox are hydrophilic, swellable, uncrosslinked, nonanionic polyethylene oxide polymers, soluble in water with a variety of molecular weights ranging between 100,000 and 8,000,000. As they are nonanionic no interaction between drug and polymers was expected. Further they are capable of forming strong hydrogen bonds with water, a characteristic that is responsible for their high water uptake and eventual dissolution[18]. We should note that the above materials have regularly been used in research as controlled drug delivery carriers[19,20].

Guar gum is a nonionic polysaccharide made of the sugars galactose and mannose. It consists of linear chains and has a molecular weight of 220,000 approximately. It is stable over a wide pH range and its viscosity is the same in both acidic and alkaline media[21]. In pharmaceutical formulations it is used frequently as a sustained release carrier. This gelling retards the drug release from solid dosage forms[22]. Further, guar gum is being used to deliver a drug to the colon because of its drug release retarding property and susceptibility to microbial degradation in the large intestine[23,24]. Cellulose acetate propionate is a cellulose ester wherein hydroxyl groups of cellulose are substituted with acetyl and propionyl, practically insoluble in water[25].

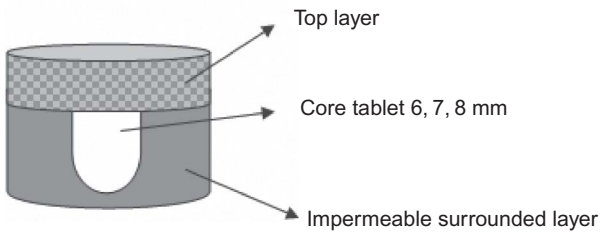

Figure 1. Structure of the drug delivery system.

As model drugs caffeine (very soluble in water) and theophylline (less soluble in water) were employed. The developed system consisted of three different parts: a core tablet containing the drug (acting as reservoir) and it was surrounded by an impermeable outer shell and a top cover layer barrier which was removed or eroded at programmed time (Figure 1).

Materials and methods

Materials

The chemicals were obtained from commercial suppliers and used as received: caffeine, theophylline (Sigma Chemical Co., St. Louis, MO, USA), cellulose acetate propionate (CAP 482-20, M.W. 75,000, Eastman Chemical Company, Kingsport, TN, USA), polyethylene oxide (Polyox M.W. 0.9×10^6, Union Carbide, Danbury, CT, USA), guar gum (Sigma Chemical Co.), lactose (Mendel, East Hanover, NJ, USA). The viscosities of Polyox and guar gum were 380 and 4850 cps, respectively (2% solution); the measurement was carried out using a viscosity meter Brookfield, model DV-II (Brookfield Engineering Lab., Middleboron, MA, USA).

Tablet preparation

The tablets were prepared using a Carver laboratory hydraulic press with suitable flat faces punches (Fred S. Carver, Inc., Menomonee Falls, WI, USA). The system consists of a core-in-cup tablet (Figure 1). The core tablet was made of 100 mg of pure drug using flat punches (8 mm diameter) under a compression pressure of 1000 kg. Both cores had 2 mm thickness. Their friability was 1.4% and 1.5% for theophylline and caffeine cores, respectively, and was determined using a Roche friability tester (Erweka TA, Erweka, Heusenstamm, Germany). The crushing strength was 2.0 and 2.25 kg, respectively, measured in the Erweka hardness tester (Erweka).

An impermeable coating cup consisting of cellulose acetate propionate was applied under the bottom and

around the core tablet. The cellulose acetate propionate powder (100 mg) used in the under bottom coating layer was filled into a die of 11 mm diameter and then was gently compacted to make a powder bed with a flat surface. The core tablet was in turn carefully placed in the center of the powder bed. Next, the die was filled with the remainder of the coating powder (65 mg) so that the surface around the core tablet was fully covered. On the top was added the hydrophilic swellable material (120 mg), which consists of polyethylene oxide, guar gum, and their mixtures. Last, the bed was compressed at 2000 kg to produce the desired core-in-cup system.

In vitro drug release studies

The dissolution study of caffeine and theophylline tablets was carried out in a USP dissolution tester, paddle method (Pharmatest, Hainberg, Germany), in 900 mL under stirring at 100 rpm, at 37 ± 0.5°C. The dissolution media consisted of 1 N HCI (pH 1.2) for 2 hours and then phosphate buffer pH 6.8. Samples were withdrawn in selected time intervals and filtered and analyzed at 272 nm for caffeine and 275 nm for theophylline using a Perkin Elmer UV spectrophotometer (Norwalk, CT, USA). An equivalent volume of temperature-equilibrated fluid was replaced into the dissolution bath following the removal of each sample. The data represent the mean values of at least three separate experiments. Results are given as mean ± standard deviation.

Dissolution efficiency (DE), first suggested by Khan[26], is a parameter useful for the evaluation of in vitro dissolution. DE is defined as follows:

$$\mathrm{DE} = \frac{\int_{t_1}^{t_2} y\,\mathrm{d}t}{y_{100}(t_2 - t_1)} \times 100\%, \tag{1}$$

where y is the percentage of dissolved product and DE the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, y_{100}, over the same time period. When a relationship is to be shown between dissolution and another variable, it is considered more realistic to use DE which takes into account the dissolution profile as a whole[26]. Besides, where a quantitative comparison is required, DE is a more suitable parameter and when limits are set on DE it can be used for quality control in place of the conventional dissolution level.

Erosion studies and optical examination

The techniques used for determining the erosion studies and optical examination were described in earlier studies[27].

The extent of erosion (E) was determined from

$$E\% = \frac{100(W_\mathrm{i} - W_\mathrm{f})}{W_\mathrm{i}}, \tag{2}$$

where W_i and W_f are the initial starting dry weight and final dry weight of the same dried and partially eroded tablet, respectively.

Statistical analysis

Results given as mean ± standard deviation (SD) were analyzed using Student's t-test ($P < 0.05$).

Results and discussion

As mentioned above, a press coating method was used for the preparation of the tablets because it offers several advantages and makes this method ideal for their fabrication.

The pulsatile drug delivery systems are designed to release the drug after a well-defined lag time and for a number of drugs or therapies this is a major advantage. The pulsatile system developed herein consists of three different parts: the core tablet made of pure drug, the impermeable surrounding (lateral) layer, and the top cover layer (Figure 1). Both external layers consist of polymers; the surrounding layer (lateral) contains a hydrophobic impermeable polymer material (cellulose acetate propionate), whereas the top cover layer contains a hydrophilic swellable polymer or their mixtures. The external layers are intended to control the function of the system and modify the drug release and its rate. This device could be described as a hybrid system in which the top cover layer consists of a hydrophilic gel-forming layer and the core tablet acts as a drug reservoir.

Visual observations reveal that upon contact of the hydrophilic top layer with the dissolution medium, it starts to absorb liquid, hydrates, and as a result the polymer swells and an expansion of the layer is observed. With time the expansion of the top layer increases creating a significant barrier which may delay the contact of the liquid with the core tablet. This development varies and depends on the properties of the polymer used. Moreover, this expansion of the top layer may result in the destabilization of this layer because of disintegration and erosion of the polymer mass. As the time passes the layer is entirely eroded/dissolved followed by a rapid dissolution of the core drug tablet because of the enhanced penetration of the medium. The extent by which the medium penetrates into the core tablet controls the dissolution of the drug and the more rapid the penetration, the faster its dissolution. Hence, the balance between expansion and erosion of the top layer controls behavior and performance of the system.

Figures 2 and 3 show the release data of caffeine and theophylline. The release profiles had a typical shape and development. It is also clear that in all cases no drug release was observed during lag time. A rather slow release followed by a rapid one occurred particularly in the case of Polyox. The relative time periods for the

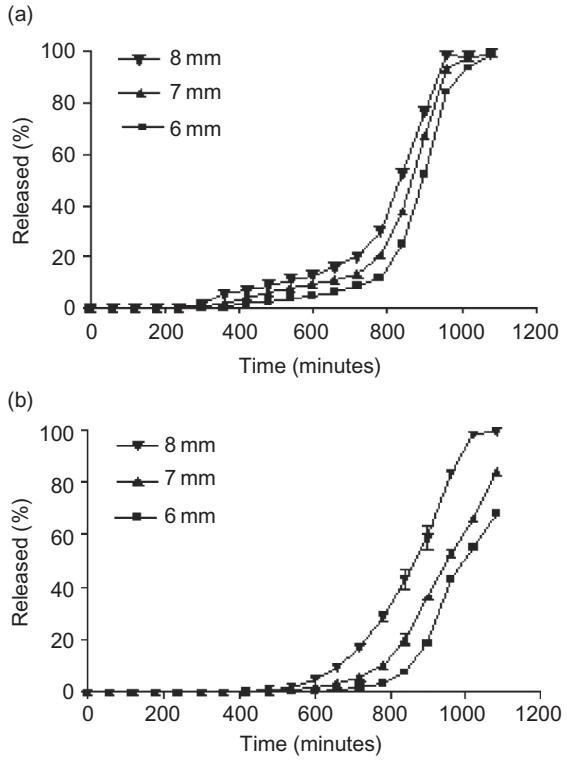

Figure 2. Effect of core tablet size on the release rate of (a) caffeine and (b) theophylline from Polyox tablets. Each point represents the mean value of the three samples and error bars show ±SD.

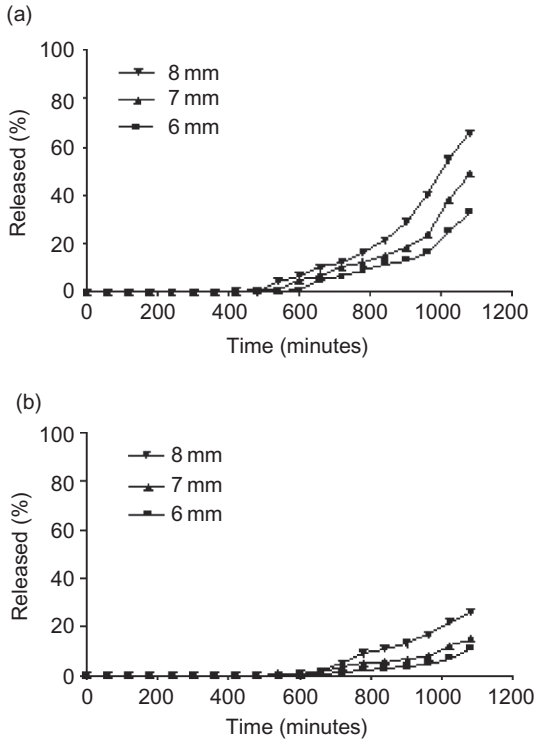

Figure 3. Effect of core tablet size on the release rate of (a) caffeine and (b) theophylline from guar gum tablets. Each point represents the mean value of the three samples and error bars show ±SD.

above procedures are different for these two drugs. The lag time of caffeine tablets is in all cases shorter than the theophylline case. Furthermore, the release profiles between the two drugs are quite different and this could be attributed to the different solubilities. The core tablets wider in diameter (8 mm) demonstrated in all cases the highest release followed by the 7 and 6 mm (see Table 1).

In Polyox formulations (Figure 2a and b), the core tablets of 8, 7, and 6 mm diameter displayed lag times in the region of 300, 360, and 420 minutes, for caffeine and 600, 660, and 720 minutes, for the theophylline, respectively. In parallel, the shorter lag time corresponds to greater DE values (Table 1).

At the rapid release stage, the release of caffeine is fast and completed approximately within 18 minutes for all three tablets. Moreover, its release is much faster, from all formulations, compared to the equivalent theophylline ones (as seen from T_{50} values, Table 1), whereas only the 8 mm tablets demonstrated complete release.

On the other hand, guar gum tablets displayed different profiles (Figure 3a and b). Their corresponding lag times are more extensive and the total drug release for both drugs is much lower compared to Polyox, as seen from the DE values in Table 1. Guar gum core tablets of diameter 8, 7, and 6 mm exhibited lag times in the region of 480, 540, and 600 minutes for caffeine, whereas all theophylline preparations displayed lag times greater than 720 minutes and very low release as it is demonstrated from DE values (Table 1).

The results clearly indicate that the core tablet size, polymer properties, and drug solubility play a substantial role in modifying the lag time and total drug release. An increase of core size results, in all cases, in a parallel decrease of the lag time and an increase of drug release rate from the system. This could be attributed to the fact that the tablets with the greater diametrical plane (consequently and surface) exhibit increased hydration followed by greater dissolution and drug release.

Polyox tablets exhibit shorter lag times than that of the guar gum. The release of caffeine, in all cases, is substantially faster than that of the theophylline. The longer lag times of the guar gum tablets may be because of its much higher viscosity as mentioned above. The higher viscosity in turn indicates that the gel formed in top layer is more durable and has the ability to form a gel mass, where the polymer chains have increased entanglement that in sequence slows down drug dissolution and diffusion.

Next, to modify the release and release rates from these tablets we have incorporated various amounts of a soluble filler, such as lactose (1 g dissolves in 8 mL water) in the top cover layer of the 8 mm tablets. The layer consisted of three different ratios of Polyox or guar gum/lactose mixtures, namely 25/75%, 50/50%, and 75/25%. Figure 4 displays the release profiles from these formulations.

Table 1. Characteristics of the different formulations.

Formulations	Lag time (minutes)	DE % (18 hours) ± SD	T_{50} (minutes)
Polyox 8 mm Caffeine	300	27.0 ± 1.0	830
Polyox 7 mm Caffeine	360	23.5 ± 0.9	860
Polyox 6 mm Caffeine	420	19.0 ± 0.7	900
Guar gum 8 mm Caffeine	480	13.0 ± 0.6	1000
Guar gum 7 mm Caffeine	540	8.5 ± 0.3	1060
Guar gum 6 mm Caffeine	600	6.0 ± 0.2	>1080
Polyox 8 mm Theophylline	600	22.0 ± 0.7	880
Polyox 7 mm Theophylline	660	13.0 ± 0.5	950
Polyox 6 mm Theophylline	720	9.0 ± 0.2	1000
Guar gum 8 mm Theophylline	>720	6.5 ± .1	>1080
Guar gum 7 mm Theophylline	>720	3.0 ± 0.1	>1080
Guar gum 6 mm Theophylline	>720	1.5 ± 0.2	>1080
Guar gum/lactose 25/75 Caffeine	60	83.0 ± 2.2	170
Guar gum/lactose 50/50 Caffeine	180	69.0 ± 1.8	330
Guar gum/lactose 75/25 Caffeine	540	15.0 ± 0.5	950
Polyox/lactose 25/75 Caffeine	180	71.0 ± 1.8	300
Polyox/lactose 50/50 Caffeine	360	42.0 ± 1.0	620
Polyox/lactose 75/25 Caffeine	660	9.5 ± 0.4	1010
Guar gum/lactose 25/75 Theophylline	60	74.0 ± 2.0	285
Guar gum/lactose 50/50 Theophylline	180	61.0 ± 1.6	420
Guar gum/lactose 75/25 Theophylline	540	8.0 ± 0.3	1070
Polyox/lactose 25/75 Theophylline	240	57.0 ± 1.4	465
Polyox/lactose 50/50 Theophylline	420	36.0 ± 0.8	700
Polyox/lactose 75/25 Theophylline	720	6.0 ± 0.2	>1080

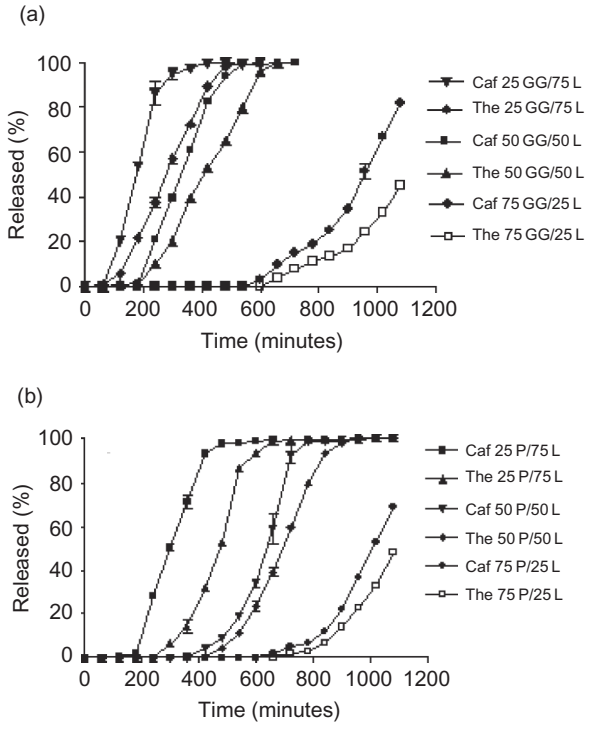

Figure 4. Effect of (a) guar gum–lactose (GG/L) and (b) Polyox–lactose (P/L) mixture tablets on the release rate of caffeine and theophylline. Each point represents the mean value of the three samples and error bars show ±SD.

All mixtures demonstrated pulsatile release profiles, smaller lag times, and greater overall release (except the 75/25 ratio of Polyox–lactose mixtures) than the formulations containing pure polymer, as it can be seen from DE values.

It is apparent that high lactose solubility facilitates liquid penetration following the creation of pores and then channels in the top layer resulting in a faster contact of the medium with the core tablet. The dissolved drug subsequently diffuses out of the core into the external dissolution medium. The results show that the incorporation of lactose displayed certain worth-mentioning findings. Its presence in the polymer mixtures appears to modify considerably the behavior and characteristics of both polymers by changing the nature of the polymer mass. Indeed, it appears to increase greatly the drug release from the tablets of both polymer mixtures and particularly from those of guar gum compared to the equivalent of Polyox.

It is evident that an increase of lactose quantity in the mixture results in a decrease of lag times and an increase of total drug release and release rates (except the 75/25 ratio of Polyox–lactose mixtures). As expected, caffeine formulations displayed lower lag times and faster release than theophylline.

Guar gum–lactose formulations (Figure 4a) exhibited shorter lag times compared to the equivalent Polyox–lactose (see Figure 4b). Surprisingly, the lag times of guar

gum–lactose are identical for both drugs; to be precise, for 25/75, 50/50, and 75/25 ratios the lag time is 60, 180, and 540 minutes, respectively. However, their release mode and release rates are entirely different as demonstrated from DE and T_{50} values (Table 1); again caffeine displayed greater total release and release rates.

On the other hand, Polyox–lactose tablets demonstrated different lag times and release profiles. Caffeine exhibited shorter lag times and T_{50} but greater DE values than that of theophylline (Table 1). The lag times for 25/75, 50/50, and 75/25 ratio is 180, 360, and 660 minutes, respectively, for caffeine, whereas the equivalent theophylline tablets demonstrated longer times such as 240, 420, and 720 minutes, respectively.

Furthermore, it is noteworthy that although in all cases the 25/75 and 50/50 mixtures exhibited greater and faster release compared to pure polymer, the 75/25 ratio displayed lower release as seen from the DE values in Table 1.

This is rather hard to explain and possibly depends on gel microstructure because of the presence of lactose. A reasonable explanation is that this could be attributed to the entanglement–disentanglement of Polyox chains and the influence of internal bond forces because of the presence of lactose. When lactose is in low concentrations, the formed gel is strengthened most likely because of an increase in the viscosity of the microenvironment of the gel during liquid penetration. To be precise, the contact between the polymer mixture mass and the liquid results in a more mobile network and subsequently in a stronger entanglement between polymer chains.

On the other hand, higher concentrations of lactose act in an entirely different way and facilitate disentanglement. This may be a result of its high solubility and osmotic effect which result in increased liquid concentrations.

The dissolution of lactose is followed by polymer chain disentanglement and the formation of porous channels in the polymer mass. The outcome is increased destruction of top layer and erosion/dissolution of the polymer, which facilitates drug dissolution.

At the stage of rapid release, the release of caffeine from the guar gum–lactose mixtures is faster and was completed approximately within 300 and 360 minutes (for the 25/75% and 50/50% mixtures, respectively); similarly for theophylline it was 420 and 480 minutes. For the Polyox–lactose equivalent mixtures, the release was completed within 360 and 420 minutes for caffeine and 420 and 540 minutes for theophylline, respectively.

Figure 5 illustrates the influence of core diameter size and lactose amount contained in the top layer on the T_{50} (the mean time required to dissolve 50% of the drug content). It is apparent (Figure 5a) that an increase of core diameter results in a decrease of T_{50}, in Polyox formulations. Unfortunately, because of low release, it was not possible to show this relationship for the guar gum formulations. Figure 5b illustrates the influence of the amount of lactose contained in the top layer on T_{50}

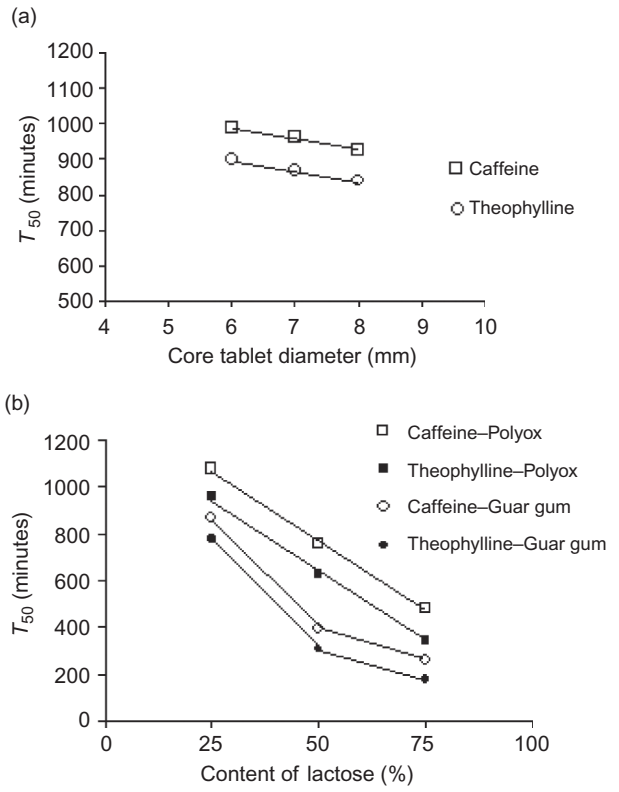

Figure 5. (a) Time taken for T_{50} drug release as a function of the core tablet size. (b) Time taken for T_{50} as a function of the percent weight content of lactose in the tablet.

(preparations with 8 mm core tablet). Clearly, in all Polyox formulations, T_{50} was dependent on the amount of lactose contained and a significant linear correlation between T_{50} and the lactose percentage was observed ($P < 0.05$). On the contrary, guar gum formulations displayed a nonlinear dependence.

Another finding worth mentioning is that although both caffeine and theophylline formulations showed an overall shorter lag time than that of the guar gum formulations, the opposite was observed when lactose was added. A possible explanation is that lactose causes greater erosion in the guar gum mass than in the Polyox mass (as shown in the Erosion Studies section below) stimulating a faster liquid penetration into the guar gum and thus decreasing the lag time in these formulations.

These findings show that apart from the drug solubility and core size, also the soluble excipients contained in the top layer (acting as pore formers) influence considerably the lag time and drug release. Thus, all these characteristics constitute critical factors and regulate the lag time periods, drug release, and its rates from these systems.

Erosion studies

Taking into consideration the above findings and the fact that the top layer characteristics influence considerably lag times and total release of the drug from the system,

we attempted to examine polymer erosion as it is a characteristic which may affect considerably the polymer behavior. Such investigation would allow us to explore whether the properties of lactose (a soluble material) are interrelated and to what extent they may affect the performance of the top layer. The experiments were carried out with identical tablets but without the drug. The drug amount was replaced by an equal quantity of cellulose acetate propionate.

From Figure 6 it is evident that the polymer erosion between the two mixtures appears entirely different. The erosion of Polyox–lactose mixtures was gradual and progressive (Figure 6a). The fastest erosion has been observed in the mixture of 25/75% tablets (completed approximately in 180 minutes) followed by the 50/50 (in 420 minutes) and the 75/25 (in 540 minutes) mixtures.

It is apparent that 25/75% tablets show a lag time in the region of 180–240 minutes (Figure 4). This time coincides with the period of time required to complete the erosion of the top layer (180 minutes). Similarly, the lag times (360–420 minutes) for 50/50 and (600–660 minutes) for 75/25% mixtures are comparable with their erosion times of 420 and 540 minutes, respectively.

On the other hand, guar gum–lactose mixtures displayed different profiles (Figure 6b): 25/75 and 50/50 ratio demonstrated a very similar fast erosion, completed in 60 and 180 minutes, respectively, whereas in the 75/25 ratio the erosion was in the range of 70% at the same time. Once more, lag times coincide with erosion times. The lag times for 25/75 and 50/50 mixtures, 60 and 180 minutes, respectively, are identical to the erosion times. On the contrary, for the 75/25 mixture it is obvious that the release for both drugs was incomplete and their erosion was 70% till 600 minutes. In parallel, their lag times are greater than 600 minutes.

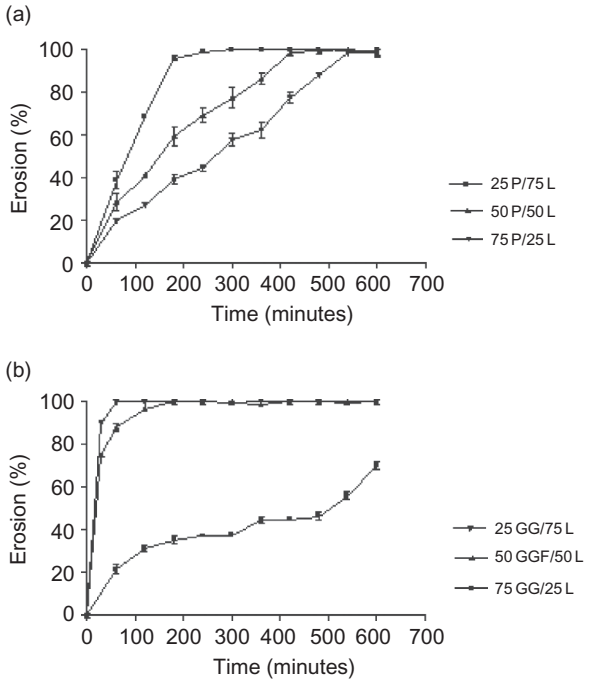

Figure 6. Percentage of weight loss (erosion) from tablets of pure polymer containing in top layer (a) Polyox (P)–lactose (L); and (b) guar gum (GG)–lactose (L) mixtures. Each point represents the mean value of the three samples and error bars show ±SD.

These findings indicate that the presence of lactose, particularly in high quantities, affects considerably the character of polymer. As mentioned earlier, this is probably because of the large disruption of polymer mass, followed by rapid erosion–dissolution, which as a result increases drug release from the system. In addition, these may explain the different release behaviors between the two mixtures and it is obvious that the erosion of the top layer plays a very important role in systems' performance considering that erosion times coincide with lag times.

Visual observations revealed that as soon as the top layer came into contact with the liquid, the top layer started to hydrate and expanded; a highly viscous gel layer was created around the surface of the tablets. Afterward, the layer started to erode and shrink as illustrated in the photos (Figure 7). In these photos, the changes of gel evolution with time are demonstrated for the Polyox–lactose, 25/75%, tablet mixture (with caffeine core) as an example. Recorded times were selected to illustrate major changes that occurred with time during dissolution. Following contact of the top layer with the liquid a gelatinous polymer mass was formed and it expanded with time, as seen in Figure 7A and B, which corresponds to 60 and 180 minutes, respectively. The maximum swelling was achieved at 180 minutes followed afterward by progressive erosion as can be seen in Figure 7C–E, and completed at 540 minutes (Figure 7F). It is apparent that the erosion started in the region of 180 minutes (Figure 7B), and it is comparable with the lag time for this mixture as seen in Figure 4. After that time, the release of the drug starts to increase and at 240 minutes approximately 30% was released. Then a very rapid release was observed in

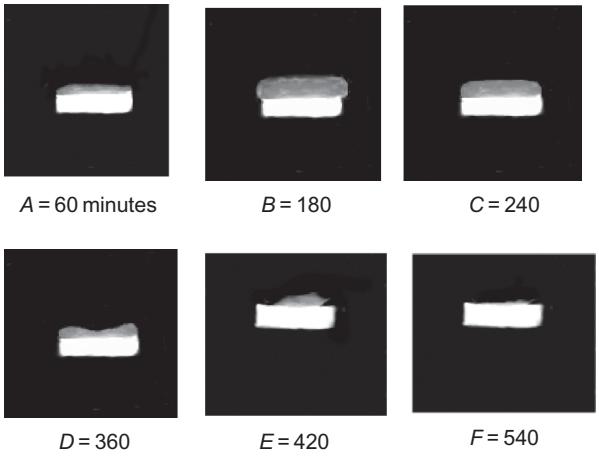

Figure 7. Morphological changes of the system during dissolution. (A) 60 minutes, (B) 180 minutes, (C) 240 minutes, (D) 360 minutes, (E) 420 minutes, (F) 540 minutes.

the region of 420 minutes (Figure 7E). When the top layer was almost eroded the surface of the core is practically fully exposed to the medium and approximately 90% of the caffeine was released. At 540 minutes (Figure 7F), the top layer is entirely removed and the dissolution of the drug is completed. From visual examination a similar procedure was observed with the other mixtures too.

Conclusions

The results of our investigation demonstrated that the developed system exhibited a pulsatile drug release. The properties of the used materials, particularly the solubility, affect considerably the behavior and performance of the system. Moreover, the diameter of core tablets as well as the characteristics and the quantity of the excipients contained in the top layer influences considerably the lag times, drug release, and release rates. The erosion of the top cover layer also plays an important role in regulating these characteristics. An increase in core tablet diameter resulted in lower lag times and greater release and release rates. Similarly, by increasing sufficiently the quantity of the soluble excipient lactose in the top layer, we observed decrease of the lag times and increase of release.

Declaration of interest

This work was partially supported by a grant from University of Athens. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Anal A. (2007). Time controlled pulsatile delivery systems for bioactive compounds. Recent Pat Drug Deliv Formul, 1:73–9.
2. Smolensky M, D' Alonso G. (1988). Biologic rhythms and medicine. Am J Med 85:34–46.
3. Lemmer B. (1991). Circadian rhythms and drug delivery. J Control Release, 16:63–74.
4. Lemmer, B. (1999). Chronopharmacokinetics: Implications for drug treatment. J Pharm Pharmacol, 51:887–90.
5. Junginger H. (1993). Oral applications of pulsatile drug delivery. In: Gurny R, Junginger H, Peppas N, eds. Pulsatile drug delivery. Stuttgart: Wissenseschaftliche Verlagsgesellschaft mbH, 113–34.
6. Dethlefsen U, Repges R. (1985). Ein neues therapieprinzip bei nachtlichem Asthma. Med Klin, 80:44–7.
7. Peppas N. (1993). Fundamental of pH and temperature sensitive delivery systems. In: Gurny R, Junginger H, Peppas N, eds. Pulsatile drug delivery. Stuttgart: Wissenseschaftliche Verlagsgesellschaft mbH, 41–70.
8. Ishido R, Yoshino H, Hirakawa Y, Noda K. (1992). Design and preparation of pulsatile release tablet as new oral drug delivery system. Chem Pharm Bull, 40:3036–41.
9. Ueda S, Yamaguchi H, Kotani M, Kimura S, Tokunaga K, Kagayama A, et al. (1994). Development of a novel drug release system, time controlled explosion system (TES). II. Design of multiparticulate TES and in vitro drug release properties. Chem Pharm Bull, 42:359–63.
10. Ueda S, Ibuki R, Kimura S, Murata S, Takahasi T, Tokunaga K, et al. (1994). Development of a novel drug release system, time controlled explosion system (TES). III. Relation between lag time and membrane thickness. Chem Pharm Bull, 42:364–7.
11. Yang S. (2001). Micronized ethylcellulose used for designing a directly compressed time controlled disintegration tablet. J Control Release, 70:321–8.
12. McNeill M, Rashid A, Stevens H. (1994). Drug dispensing device. US Patent 5 342624.
13. Krogel I, Bodmeier R. (1998). Pulsatile release from an insoluble capsule body controlled by an erodible plug. Pharm Res, 3:474–80.
14. Busseme T, Bodmeier R. (2003). Formulation parameters affecting the performance of coated gelatin capsules with pulsatile release profiles. Int J Pharm, 267:59–68.
15. Ross, A. (2000). Chronopharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion. J Pharm Pharmacol, 52:903–9.
16. Efentakis M, Koligliati S, Vlachou M. (2006). Design and evaluation of a dry-coated drug delivery system with an impermeable cup, swellable top layer and pulsatile release. Int J Pharm 311:147–56.
17. Lin S, Li M, Li K. (2004). Hydrophilic excipients modulate the time lag of time-controlled disintegrating press-coated tablets. AAPS PharmSciTech, 5:(4) Article 54.
18. Moroni A, Ghebre-Sellassie I. (1995). Application of poly(oxyethylene) homopolymers in sustained release solid formulations. Drug Dev Ind Pharm, 21:1411–28.
19. Efentakis M, Vlachou M. (2000). Evaluation of high molecular weight poly(oxyethylene) (Polyox) polymer: Studies of flow properties release rate of furosemide and captopril from controlled release hard gelatin capsules. Pharm Dev Technol 5:339–46.
20. Kim G. (1998). Effects on drug solubility, drug loading, and polymer molecular weight on drug release from Polyox tablets. Drug Dev Ind Pharm, 24:645–51.
21. Goldstein A, Alter E, Seaman J. (1973). Guar gum. In: Whistler R, ed. Industrial gums. New York: Academic Press, 315.
22. Khullar P, Khar R, Agarwal S. (1998). Evaluation of guar gum in the preparation of sustained-release matrix tablets. Drug Dev Ind Pharm, 24:1095–9.
23. Krishnaiah Y, Satyanaryana S, Rama Praady Y. (1999). Studies of guar gum compression coated 5-aminosaliscylic acid for colon specific drug delivery. Drug Dev Ind Pharm, 33:651–7.
24. Mundargi R, Patil S, Agnihotri S, Aminabhavi T. (2007). Development of polysaccharide-based colon targeted drug delivery systems for the treatment of amoebiasis. Drug Dev Ind Pharm, 33:255–64.
25. Guiomar AJ, Evans SD, Guthri J. (2001). Evaluation of the permeability of modified cellulose acetate propionate membranes for use in biosensors based on hydrogen peroxide detection. *Cellulose*, 8:297–301.
26. Khan K. (1983). The concept of dissolution efficiency. J Pharm Pharmacol, 27:48–9.
27. Efentakis M, Hani N, Vlachou M. (2010). Two and three layer tablet drug delivery systems for oral sustained release of soluble and poorly soluble drugs. Drug Dev Ind Pharm, in press.