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Design and evaluation of a dry coated drug delivery system with an impermeable cup, swellable top layer and pulsatile release

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Abstract

In this investigation a novel oral pulsatile drug delivery system based on a core-in-cup dry coated tablet, where the core tablet surrounded on the bottom and circumference wall with inactive material, is proposed. The system consists of three different parts, a core tablet, containing the active ingredient, an impermeable outer shell and a top cover layer-barrier of a soluble polymer. The core contained either diclofenac sodium or ketoprofen as model drugs. The impermeable coating cup consisted of cellulose acetate propionate and the top cover layer of hydrophilic swellable materials, such as polyethylene oxide, sodium alginate or sodium carboxymethyl cellulose. The effect of the core, the polymer characteristics and quantity at the top cover layer, on the lag time and drug release was investigated. The results show that the system release of the drug after a certain lag time generally due to the erosion of the top cover layer. The quantity of the material, its characteristics (viscosity, swelling, gel layer thickness) and the drug solubility was found to modify lag time and drug release. The lag time increased when the quantity of top layer increased, whereas drug release decreased. The use of sodium carboxymethyl cellulose resulted in the greatest swelling, gel thickness and lag time, but the lowest drug release from the system. Polyethylene oxide showed an intermediate behaviour while, the sodium alginate exhibited the smallest swelling, gel thickness and the shortest lag time, but the fastest release. These findings suggest that drug delivery can be controlled by manipulation of these formulations.

Keywords: Pulsatile release tablets; Lag time; Diclofenac sodium; Ketoprofen; Swellable polymers; Erosion

1. Introduction

Oral controlled release drug delivery systems offer a number of advantages over the conventional immediate release delivery preparations. These systems are designed to deliver the drugs at a controlled and predetermined rate thus maintaining their therapeutically effective concentration in systemic circulation for prolonged periods. On the other hand, for certain therapies a pulsatile drug release pattern, where the drug is released after well-defined lag time, exhibits significant advantages. It is well documented that most of the body functions display circadian rhythms, e.g. heart rate, stroke volume, blood pressure, blood flow, body temperature, gastric-pH (Lemmer, 1999). Moreover, in a number of organs their functions vary with the time of the day. It is increasingly recognized that there are rhythmic and temporal patterns in the manifestation of many disease states. The symptoms for a number of diseases, such as bronchial asthma, myocardial infraction, angina pectoris, hypertension, rheumatic diseases, etc. follow a circadian rhythm.

In a number of reports (Smolensky and D'Alonso, 1988; Lemmer, 1991, 1999; Junginger, 1993) day–night variations of dyspnoea attacks in asthmatic patients and variations in the incidence of myocardial infractions are mentioned. Dethlefsen and Repges (1985), reported a sharp increase in the incidence of asthmatic attacks during the early morning hours. Based on these findings drug delivery and therapy should be modified to achieve an effective drug level at the required time. This can be achieved by adapting a pulsatile drug delivery system of a suitable drug. Consequently, the administration of a drug formulated in such a delivery system, i.e. taken at bedtime with a programmed start of drug release in early morning hours, could offer a more effective therapy than a typical controlled release drug delivery system, provided that the most appropriate drugs are administrated.

Oral pulsatile administration could be useful for the treatment of certain diseases, such as asthma, gastric ulcer, hypertension, ischemic heart disease, arthritis, etc., which exhibit circadian

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rhythms (Junginger, 1993). Pulsatile drug delivery denotes the capability of a controlled release preparation to deliver the drug at varying rates from very low to high over a desirable time. Such a system should be able to rapidly release the active agents after a specified lag time. It also should be capable of releasing its drug content at either a predetermined time or at a specific site in the gastrointestinal tract.

Controlled release systems displaying pulsatile release are mainly based on polymeric materials. These systems can be classified into one pulse, double pulse and mixed pulse systems (Peppas, 1993). Most pulsatile systems are reservoir systems and usually covered with a barrier. This barrier can be dissolved, eroded or removed at a predetermined period of time after which the drug is dissolved and rapidly released.

The last decade several pulsatile delivery systems have been proposed including tablet and capsule formulations. Ishido et al. (1992), Ueda et al. (1994a,b), Conte et al. (1989) and Shan-Yang (2001), have developed different technologies referring to tablet pulsatile release systems. Most of the tablet formulations are reservoir type devices with a barrier coating. Besides capsule-based pulsatile release systems, formulations, such as Pulsicap have also been developed (McNeill et al., 1994). Similar or analogous systems were proposed and evaluated by Krogel and Bodmeier (1998), Ross (2000), Bussemer and Bodmeier (2003) and McConville et al. (2005). These systems consist of a water-impermeable or semi-impermeable capsule half with the drug formulation contained within the capsule and sealed by means of a hydrogel polymer plug. Contact of the dissolution media or gastrointestinal fluids with the barrier or the plug results to its removal or ejection followed by the rapid release of the drug.

The aim of the present investigation was to develop and evaluate an alternative, simple, orally applicable one-pulse drug delivery system based on a dry coated tablet preparation. The system consists of three different components, a core tablet containing the active ingredient, an impermeable outer shell and a top cover layer-barrier that should be removed at predetermined time (Fig. 1). Ideally, the drug should be released after a complete removal of the top cover layer, with the lag time being controlled by the characteristic properties of the material in the top cover. In order to thoroughly investigate and evaluate the behaviour of the system, two different drugs, a water insoluble (ketoprofen) and a rather water soluble (diclofenac sodium) and three hydrophilic swellable polymers (polyethylene oxide, sodium alginate or sodium carboxymethyl cellulose) were employed in this study.

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: ketoprofen, diclofenac sodium (Sigma Chemical Co., USA), cellulose acetate propionate CAP 482-20, M_W 75,000 (Eastmam Chemical Company, USA), polyethylene oxide (Polyox M_W 0.9×10^6, Union Carbide, Danbury, CT, USA), sodium alginate (SA) Low Viscosity (Sigma Chemical Co., USA) and sodium carboxymethyl cellulose (NaCMC), (Hercules, Dusseldorf, Germany). The viscosities of Polyox, SA and NaCMC, are 320, 240 and 500 cps, respectively [2% solution]. The measurement was carried out using a viscosity meter Brookfield, model DV-II (Brookfield Engineering Lab., Massachusetts, USA)

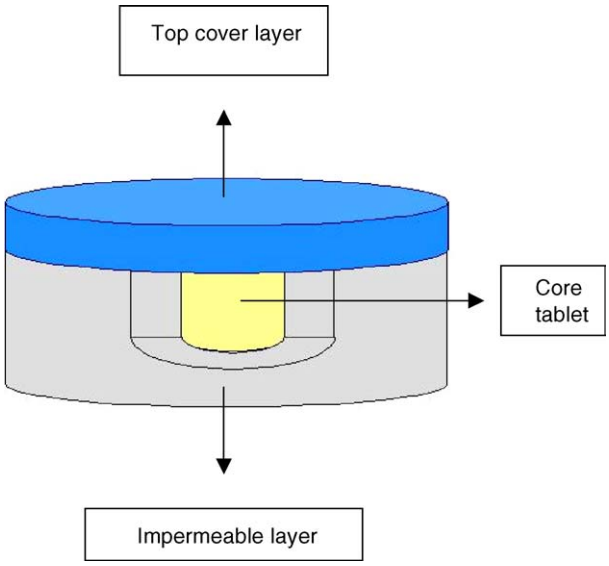

Fig. 1. Schematic representation of pulsatile drug delivery system.

2.2. 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 is consisted of a core-in-cup tablet (Fig. 1). The core tablet was made of 200 mg of pure drug using flat punches (8 mm) under a compression pressure of 1000 kg. 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 surrounding surfaces of the core tablet was fully covered. On the top was added the hydrophilic swellable material (60, 90 or 120 mg), which consists of polyethylene oxide, sodium alginate or sodium carboxymethyl cellulose. Last, the bed was compressed at 2000 kg to produce the desired core-in-cup system (total weight 425, 455 or 485 mg).

2.3. In vitro drug release studies

The dissolution of ketoprofen and diclofenac sodium tablets was monitored in a USP dissolution tester, paddle method (Pharmatest, Hainberg, Germany), under stirring at 100 rpm. The dissolution media consisted of 900 ml of simulated intestinal fluid (pH 7.4) at $37 \pm 0.5\,^{\circ}C$. Samples were withdrawn every

30 min filtered and analyzed at 272 nm for ketoprofen, and 275 nm for diclofenac sodium 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 six separate experiments.

2.4. Uptake and erosion studies

Preparations without drug were placed in flat bottom dissolution vessels, containing 900 ml of simulated intestinal fluid under the temperature and stirring conditions described in the drug release studies section above. To prevent floating, tablets were placed under a bell shape "tent" which was formed from a pre-weighed 4 cm × 4 cm metal mesh (no. 10) square. At a selected time interval, an individual tablet was withdrawn using the mesh "tent". The mesh and the tablet were blotted to remove excess liquid and then weighed on a Sartrorius analytical balance (Sartrorius AG, Goettingen, Germany). The wetted tablets were then dried in an oven at 105 °C for 24 h, cooled in a desiccator and weighed again. This procedure was repeated until constant weight was achieved (final dry weight). Three different tablets were measured for each time point and fresh tablets were used for each individual time point.

The extent of erosion (E) was determined from

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

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. The increase in weight (uptake) due to absorbed liquid (A) was calculated at each time point from

$$A\,(\%) = 100 \times \frac{(W_\mathrm{w} - W_\mathrm{f})}{W_\mathrm{f}}$$

where W_w is the mass of the wet tablet before drying.

2.5. Measurement of top cover layer expansion—Optical image analysis

The method used in the present study for top cover layer expansion measurements is similar to that described in a previous investigation (Papadimitriou et al., 1993). The recorded images were collected and analyzed with a Leica image analysis system (Leica Q 5001 W). The video camera (JVC TK-C11381, Japan) was fitted with a zoom lens (Century Precision Optics AD-5870, USA) and connected to a monitor. The light system consists of a fluorescent tube fitted under the beaker. The beaker was covered to prevent incoming external light. The tablet was placed in a beaker (of a dissolution apparatus) containing 900 ml of intestinal fluid at 37 ± 0.5 °C stirred at 100 rpm.

It was held under the liquid surface by mounting on a pin, which was glued to the base of the beaker to allow the observation of swelling in the axial or radial direction, respectively. At predetermined time intervals, the beaker was removed from the dissolution apparatus and was transferred into the optical image set up. The tablet was photographed by means of a video camera to record the axial and radial changes of the swelled tablet and to estimate the gel thickness growth. The gel layer appears as a light ring due to the scattering of light by the hydrated polymer. The glassy core and the medium appear black, as they do not permit scattering of the incoming light (Gao and Meury, 1996a). The swelling–expansion was obtained by calibration of the obtained image. The dimensional scale was calibrated from the known tablet size and measurement of the image obtained at $t = 0$. Results are averages of three different tablets and are given as mean standard deviation values.

2.6. Statistical analysis

Results given as mean ± standard deviation (S.D.), were analyzed using student's t-test ($P < 0.05$).

3. Results and discussion

3.1. Formulation structure and release

The novel pulsatile system described herein consists of three different components, the central core tablet made of pure drug, the impermeable surrounding (lateral) layer and the top cover layer (Fig. 1). Both external layers consist of polymer materials and are intended to regulate the function of the system and modify the release of the drug. This type of tablet could be described as a hybrid system in which the top cover layer consists of a gel forming layer and the inner part of a conventional tablet acting as a drug reservoir.

From visual observations it becomes apparent that upon contact of the tablet with the liquid the top cover layer, consisting of the hydrophilic polymer, starts to absorb liquid. As a consequence the polymer swells and shortly after an expansion of the layer is noticed.

As the time passes the swelling and the expansion of the top layer increases creating a considerable barrier which may delay to some extent the contact of the bulk liquid with the surface of the core drug tablet. This process varies with the nature of the polymer used.

It is also possible that the swelling process of the top cover layer could act as a disintegrating force, which facilitates firstly the destabilisation of the layer itself and additionally the system when material is prone to disintegration/erosion. Therefore, the balance between these two forces, swelling and disintegration, controls the behaviour of the top cover layer (i.e. the erosion process of the polymer) and consequently the performance of the system. Finally, and depending on the properties of each polymer the cover is completely eroded or removed and as a result the dissolution of the core drug tablet increases sharply due to increased access of liquid into the core of the tablet.

In Fig. 2, these significant changes in the top cover layer consisting of Polyox 120 mg, of diclofenac sodium tablets are illustrated. In these photographs the recorded time intervals were carefully chosen in order to reveal some of the major changes that occur in the top layer during the dissolution process. Thus, after the contact of the top hydrophilic layer with the liquid, a rapid absorption of the liquid observed and the swelled–expanded

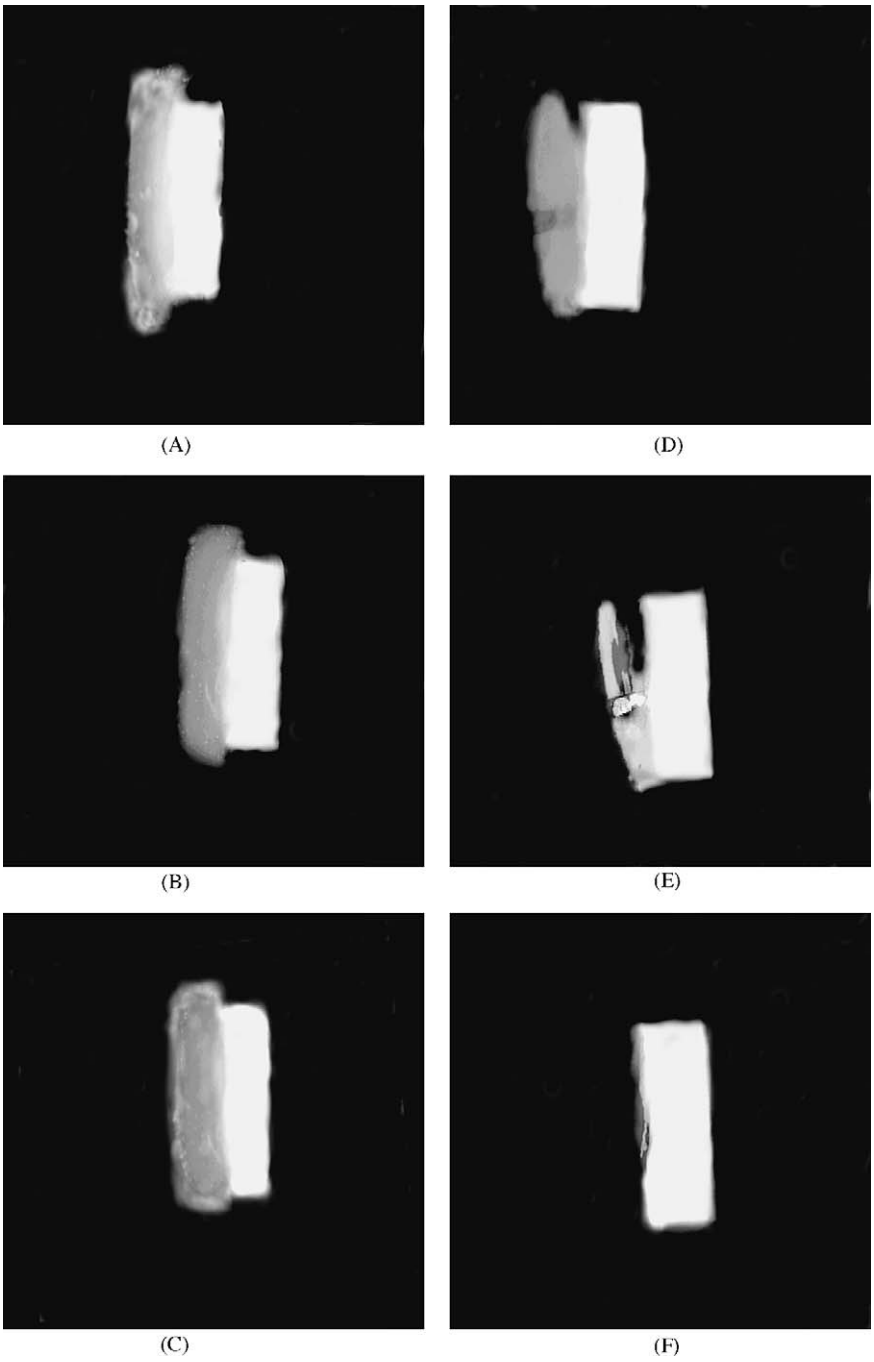

Fig. 2. Morphological changes of the system during dissolution. (A) 30 min, (B) 90 min, (C) 120 min, (D) 240 min, (E) 300 min, and (F) 330 min.

polymer layer practically covers the top of the tablet as it can be seen in Fig. 2(A)–(C), which correspond to 30, 90 and 120 min, respectively. After the swelling of the top layer due to excessive liquid uptake is completed (180 min), it is noticed a gradual decrease of polymer mass and this procedure is more obvious after 210 min. At the same time the release of the drug starts to increase. At $t = 240$ (Fig. 2(D)), the layer is partly eroded and slowly separates from the surface of the core tablet. At this stage, approximately 45% of the drug is released. Later, at $t = 300$ (Fig. 2(E)), the top layer is almost completely eroded and separated; as a result the surface of diclofenac sodium is nearly fully exposed to the dissolution medium facilitating rapid liquid penetration accordingly, 85% of the drug is released. Finally, at $t = 330$ (Fig. 2(F)), the top layer is totally eroded or removed and the dissolution of the drug, as demonstrated in the dissolution graph of diclofenac sodium, is completed. A similar behaviour was also noticed in the case of the other two polymers.

Determination of the diameter and thickness of the expanded cover layer allowed us to calculate the corresponding bulk swelling using the formula of a cylinder: $V = \pi r^2 h$. The results obtained were plotted and are shown in Fig. 3. Volume changes are shown up to 180, 210 and 240 min for SA, Polyox and

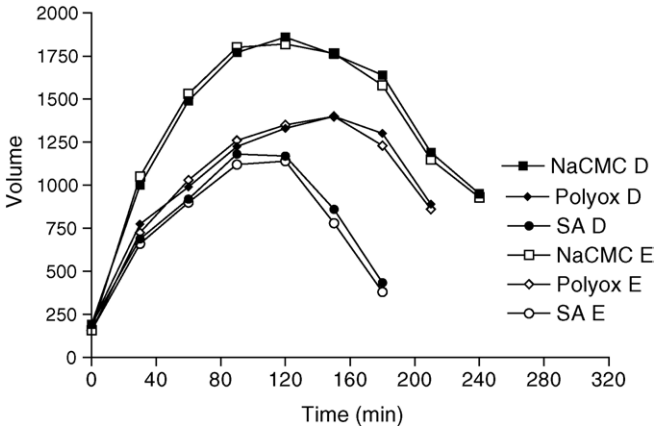

Fig. 3. Bulk volume changes of the top layer in formulations with drug (D) and without drug (E) vs. time. Each point represents the mean value of the three samples and error bars show ±S.D.

NaCMC, respectively, since at longer times it was difficult to accurately determine the diameter and thickness of the expanded top layer due to deformation. These results suggest that NaCMC (with the higher viscosity 500 cps) displays the most rapid and the greatest bulk swelling which lasts longer, followed by Polyox and SA with viscosities 350 and 250 cps, respectively. After maximum swelling was achieved a tendency to decline was observed. The decline appeared to be greater for SA, followed by Polyox and NaCMC. Thus, the greatest bulk swelling is achieved with the polymer with the highest viscosity and the opposite applies with respect to the decline. Apparently, the polymer with the maximum volume increase exhibited the maximum lag times and the smaller drug release as it is shown below. In ketoprofen tablets a comparable process is observed.

In Fig. 4(a)–(c), the release data of diclofenac sodium and ketoprofen are shown. The release profiles had a typical pulsatile shape. It is clear that in all cases no drug release occurs during the lag time. Afterwards a rapid release phase, especially in the case of diclofenac sodium, is noticed. The relative periods for the abovementioned procedures are different for the two drugs, the lag time of diclofenac sodium tablets is in all cases shorter than in ketoprofen tablets. Moreover, the release profiles of the two drugs are quite different. This could be attributed to the different solubility properties of the two drugs.

At the stage of rapid release, the release of diclofenac sodium is faster and terminates approximately within 3 h for all three-polymer tablets. On the other hand, the release of ketoprofen is much slower. It lasts more than 6 h demonstrating a rather sustained release profile due to the poor solubility of ketoprofen.

These results suggest that apart from the drug solubility the top cover layer also plays a significant role in modifying the lag time and the drug release. The polymer properties and the quantity of the polymer material contained in this layer control the performance and the function of the system. As it can be seen, three different quantities of those materials were examined in order to determine how this difference in weight could affect the system performance and functioning.

It is apparent that the release of both drugs, Fig. 4, is considerably dependent on the materials and the quantity used. An

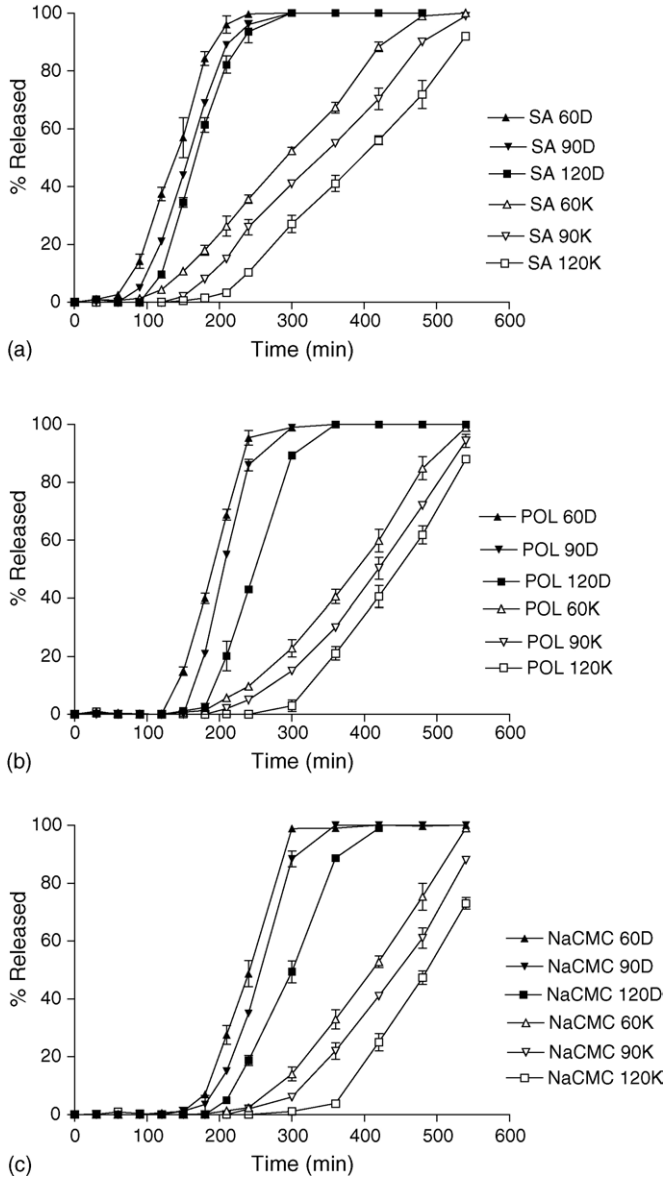

Fig. 4. (a) Effect of sodium alginate quantity on the release rate of diclofenac sodium and ketoprofen, (b) effect of Polyox quantity on the release rate of diclofenac sodium and ketoprofen, (c) effect of sodium carboxymethyl cellulose quantity on the release rate of diclofenac sodium and ketoprofen. Each point represents the mean value of the six samples and error bars show ±S.D.

increase in the polymer quantity results to a parallel increase of the lag time and a decrease of the release rate of the drug from the system. The SA tablets exhibit the shorter lag time followed by Polyox and NaCMC. The lag time accordingly depends on the polymer quantity contained in the top layer and an increase of its mass results to a substantial increase of the lag time.

Fig. 4(a) reveals these differences when the top layer contains SA. Ketoprofen exhibits a longer lag time than diclofenac sodium and consequently the release of diclofenac sodium is considerably faster than that of ketoprofen. Thus, the top layer of the 60, 90 and 120 mg tablets displays approximately lag times of 50, 65 and 85 min for diclofenac sodium and 85,125, and 155 min for ketoprofen. Fig. 4(b) shows the results when the

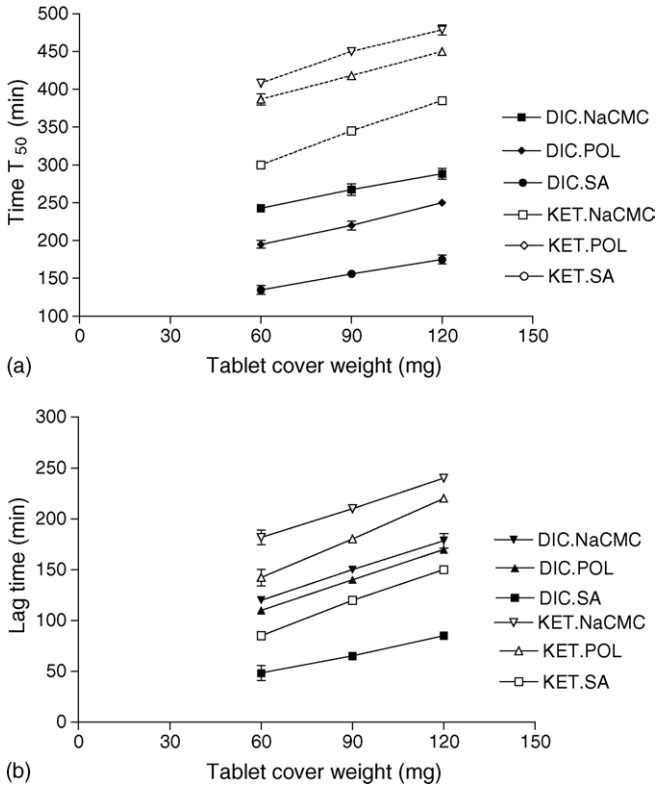

Fig. 5. (a) Time taken for T_{50} drug release as a function of the weight of the tablet top cover layer, (b) time taken for lag time as a function of the weight of the tablet top cover layer.

top layer is consisted of Polyox. The lag times are 120, 140 and 160 min for diclofenac sodium and 150, 180 and 220 min for ketoprofen. Finally, Fig. 4(c) illustrates the results for NaCMC, where the lag times are 125, 150 and 180 min for diclofenac sodium and 185, 210 and 245 min for ketoprofen, respectively. Diclofenac sodium displays a rapid release profile after the lag time while ketoprofen is released over extended period of time after the lag time.

Fig. 5(a) demonstrates the influence of the amount of the polymer contained in the top cover layer on the T_{50} (the mean time required to dissolve 50% of the drug content).

T_{50} was significantly dependent on the amount of polymer present as for all formulations, a significant linear correlation between T_{50} and tablet cover weight was observed ($P < 0.001$). The same applies for the effect of the amount of polymer on lag time ($P < 0.001$) and this is shown in Fig. 5(b). A weight increase of the top layer results to an increase of the lag time. Consequently, the lag time could be adjusted by the weight of this layer. Thus, the quantity of the polymer in the top layer constitutes a critical factor for the time of erosion and regulates the lag time period and drug release. In view of the above findings and also based on the fact that the top cover layer influences the lag times and drug release from the system, we investigated two important characteristics of the polymers empolyed, i.e. their liquid uptake-swelling and erosion.

Such a study would allow us to examine whether these characteristics are interrelated and to what extent with respect to the

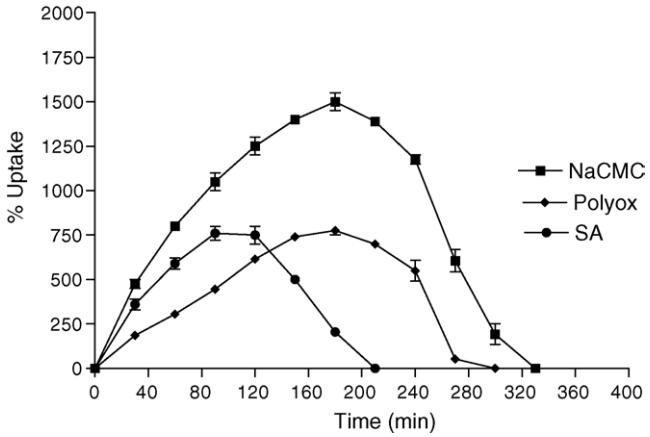

Fig. 6. Percentage of weight change as a function of time in intestinal fluid, for sodium alginate, Polyox and sodium carboxymethyl cellulose tablets. Each point represents the mean value of the three samples and error bars show ±S.D.

behaviour (erosion or separation) of the top cover layer. This in turn would reveal their influence on the function of the system.

3.2. Swelling and erosion studies

The experiments were performed with preparations without drug but the same formulation type and a top cover layer of 120 mg, a quantity that corresponds to the formulation previously used for the determination of bulk volume swelling. The drug was replaced by equal quantity of cellulose acetate propionate. The data, in Figs. 6 and 7, reflect the extent of liquid uptake and the loss of weight (erosion) of NaCMC, Polyox and SA layers (since the cellulose acetate propionate does not swell or erode).

Visual observation indicates that all three-polymers swell and create a viscous gel at the top layer surface when they are exposed to the liquid. During the course of the experiments, a maximum swelling achieved followed by erosion of the hydrophilic polymer layer. NaCMC preparations exhibit the highest weight uptake-swelling, Fig. 6, followed by Polyox and SA, which

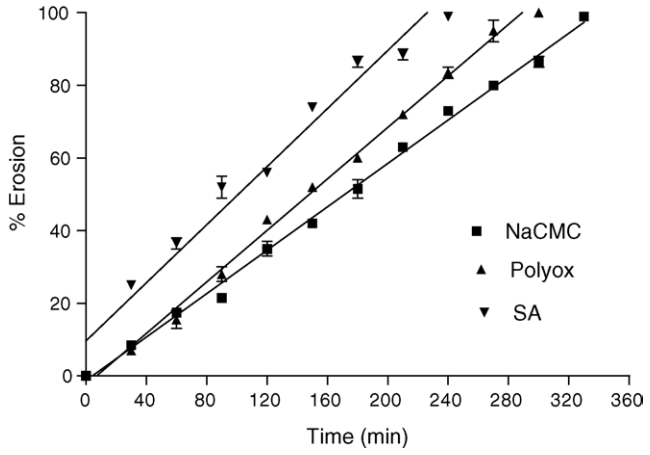

Fig. 7. Percentage of weight loss (erosion) from tablets dried after exposure to buffer for sodium alginate, Polyox and sodium carboxymethyl cellulose. Each point represents the mean value of the three samples and error bars show ±S.D.

both give similar maximum values but at different times. These changes in weight parallel the erosion data, Fig. 7, and they reflect the amount of polymer eroded.

Thus, SA layers display a fast liquid uptake-swelling, the maximum being observed between 90 and 120 min, followed by a rather gradual decrease due to erosion, which was completed at 210 min. Polyox layers exhibit an approximately linear and slower liquid uptake up to the maximum, which was observed between 150 and 180 min, whereas their erosion was terminated at 300 min. Finally, the maximum uptake-swelling of the NaCMC layers was achieved between 180 and 210 min. The complete erosion at this case took place at $t = 330$ min. Their liquid uptake was rapid and almost linear up to the time point where the maximum values were achieved. From this set of data, it is evident that NaCMC layers display the fastest and highest uptake, 1600%, followed by Polyox and SA, which both exhibit a similar uptake increase, approximately 850%, Fig. 6.

Polymer erosion is demonstrated in Fig. 7, the fastest erosion being observed in SA layers followed by Polyox and NaCMC. The percent weight loss was rather linear and the rates of erosion were 0.300, 0.366 and 0.400%/min for NaCMC, Polyox and SA, respectively, Fig. 7. Although the degree of liquid uptake of NaCMC is almost twice as high of that of Polyox and SA, its rate of erosion is lower than those of SA and Polyox, as it can be concluded from the recorded values. This indicates that the gel formed around the NaCMC layers is more durable, and NaCMC has the ability to form at the gel surface polymer chains with increased entanglement, compare to other polymers. This in turn results in slower erosion as reported in an earlier study (Bonferoni et al., 1992). These workers have also suggested that higher polymer viscosity reflects a stronger ability of the polymeric chains to produce entanglements and consequently matrices with slower erosion. Our results show that there is a dependence of polymer erosion (which can described as chain disentanglement and dissolution of polymer chains, Bonferoni et al., 1995) on viscosity. SA with the lowest viscosity displayed the highest erosion followed by Polyox with intermediate behaviour, while NaCMC with the highest viscosity exhibited smaller erosion. Consequently, the greater the viscosity of the material the more resistant the gel is to dilution and erosion.

It is evident from the data presented in Fig. 4(a) that diclofenac sodium tablets with a top cover layer consisting of SA show a lag time in the region of 100 min. This time coincides with the analogous time of 90–120 min where after the maximum swelling starts its decrease and a noteworthy (≈35%) loss of weight, due to the erosion of the polymer layer, Fig. 6. Further, the time required for the relatively total release of diclofenac sodium (240 min) is approximately the same to that needed for the complete erosion of the SA layer (in 210 min). Likewise, the lag time for the ketoprofen tablets (in the region of 180 min) coincides with the time needed for the erosion to be almost complete (between 180 and 210 min).

Polyox tablets, Fig. 4(b), demonstrate a similar behaviour; the lag time for the diclofenac sodium tablets (close to 180 min) corresponds to the time where the erosion of the polymer layer started after 180 min, Fig. 6. The time for the complete release of diclofenac sodium (roughly 300 min) is the same time needed

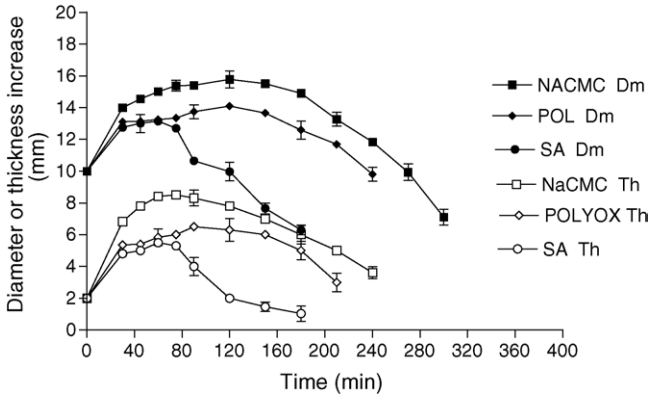

Fig. 8. Radial (diameter, Dm) and axial (thickness, Th) top layer dimensions changes for sodium alginate, Polyox and sodium carboxymethyl cellulose tablets. Each point represents the mean value of the three samples and error bars show ±S.D.

for the complete erosion of the polymer layer namely 310 min. The lag time of ketoprofen tablets (approximately 250 min) is similar to the time required for the near completion of the erosion of the polymer layer (280 min).

In the case of NaCMC Fig. 4(c), the diclofenac sodium tablets have shown a lag time of almost 180 min, which corresponds to the time where the erosion of the polymer starts, Fig. 6. Moreover, the time for the nearly complete release of the drug, 360 min, is more or less the same to that needed for the erosion of the polymer (330 min). On the other hand, the lag time for ketoprofen tablets (approximately 300 min) is not that different to the time demanded for complete erosion of the polymer layers, i.e. 330 min.

These findings indicate that in diclofenac sodium tablets, drug molecules are released by diffusion out of the gelatinous layer once the polymer top layer has being fully hydrated and the liquid molecules come in contact with the core tablet. As time passes, the erosion of the polymer and the progress of the dissolution of the drug occur almost simultaneously and termination of drug release coincides approximately with erosion of the top layer. On the other hand, in the case of the ketopro-

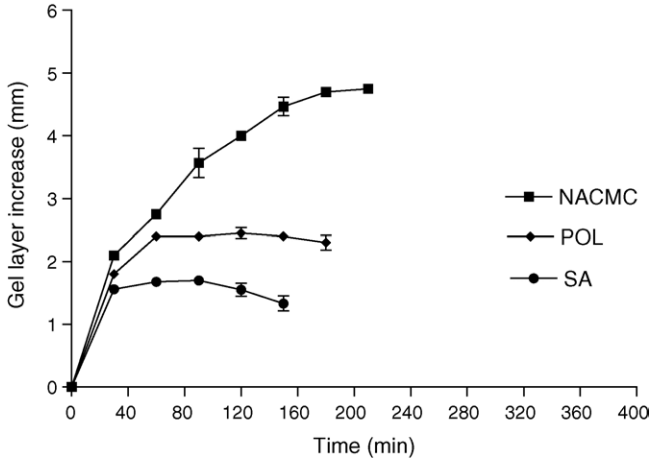

Fig. 9. Gel thickness increase vs. time. Each point represents the mean value of the three samples and error bars show ±S.D.

fen tablets the dissolution apparently starts when the polymer layer is nearly fully eroded or removed and the core tablet fully exposed to the dissolution liquid. Therefore, the release starts at a later stage since the poor solubility of the drug delays further its dissolution and increases the time required for its complete release.

3.3. Radial and axial dimensional changes

Fig. 8 illustrates the radial and axial expansion of the polymers top layers. A fast initial expansion is observed which is followed by a decrease at later times. In the case of SA layers the maximum increase in diameter, 1.3-fold, is demonstrated between 45 and 60 min, which is then followed by a rapid and sharp decrease. This decrease is accelerated at $t > 75$ min and the diameter of the wetted layer becomes, after 120 min, smaller than that of the initial layer. Polyox layers exhibit a 1.4-fold increase in diameter and the maximum value observed between 90 and 120 min. The diameter remains almost unchanged up to 150 min and then starts to decrease becoming smaller than the initial diameter at $t > 240$ min. Finally, the NaCMC layers exhibit the greatest expansion, 1.6-fold. The maximum values were recorded between 90 and 150 min and the diameter remains almost unchanged up to 180 min; then it starts to decrease becoming smaller than the initial diameter after 270 min.

Similarly, the axial expansion (thickness) was increased by 2.7, 3.2 and 4.2-fold for SA, Polyox and NaCMC, respectively, revealing clearly a preference in axial expansion. The axial increase or decrease in each of the above polymers coincides with the analogous diametetrical changes. For the SA, Polyox and NaCMC polymers, the diametetrical dimensions were measured for 180, 240 and 300 min; also, thickness was measured for 180, 210 and 240 min, respectively. Unfortunately, due to substantial deformation further recordings were not taken.

The change in the bulk volume of the preparations without drug (E) is analogous to that of the preparations with drug (D), Fig. 3. The minor differences observed may be attributed to the slightly modified conditions of each experiment.

Recent studies have shown that changes in the thickness of the gel layer (Colombo et al., 1995; Bettini et al., 2001) can modify drug release since the hydrated gel is the factor, which determines the diffusion path of drug molecules through the polymer into the dissolution medium. In Fig. 9, the average gel layer changes with respect to time are illustrated (Gao et al., 1996b). Gel layer thickness development occurs up to 210, 180 and 150 min, for NaCMC, Polyox and SA, respectively.

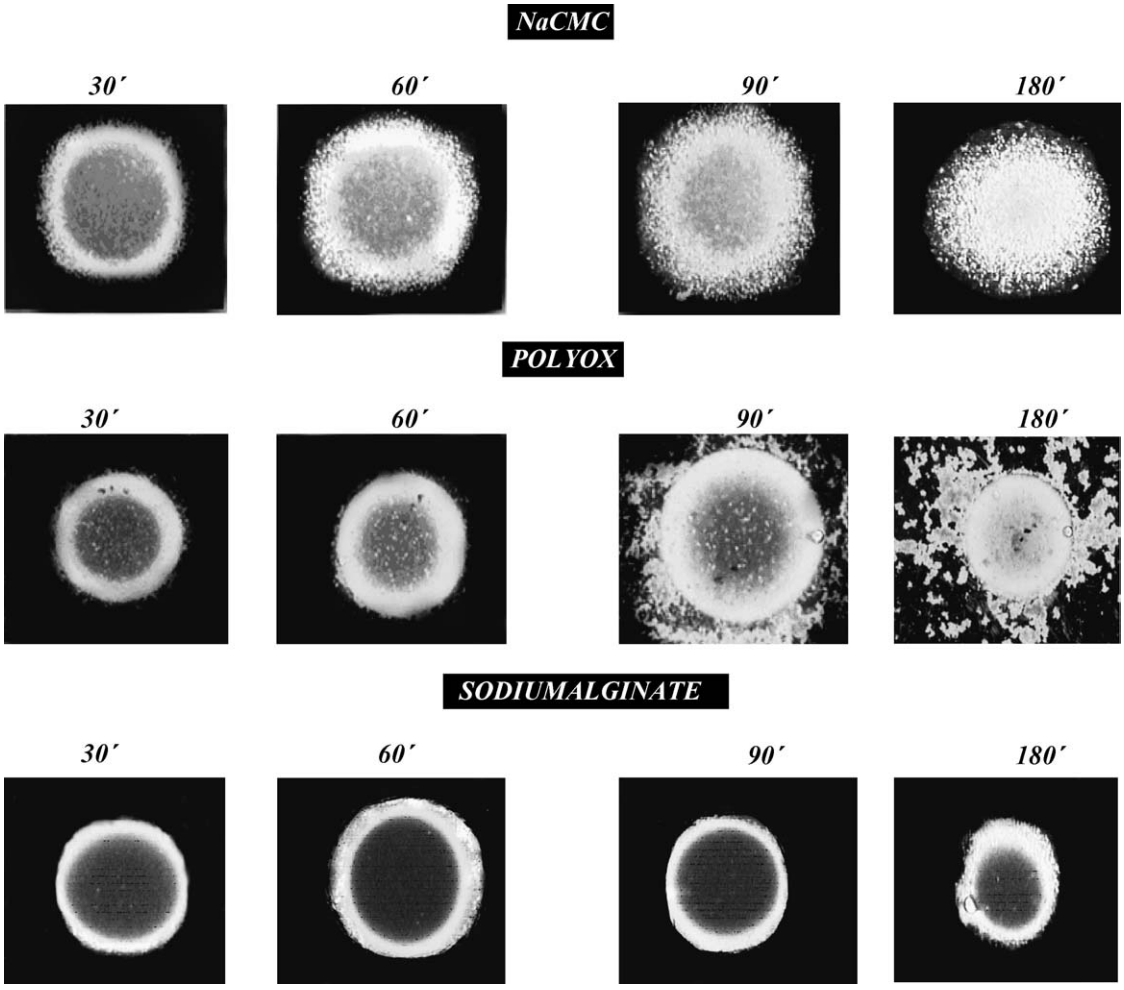

Fig. 10. Morphological changes in diameter of sodium alginate, Polyox and sodium carboxymethyl cellulose layers.

As previously, due to deformation further measurements could not be taken. NaCMC exhibits the maximum gel layer thickness and a continuous increase, Polyox follows an intermediate trend, while SA shows a substantial decrease after 120 min. The results indicate that these differentiations in the gel growth may be associated with the drug release modifying the diffusion pathway.

Fig. 10 shows the top layer changes with respect to their diameter at different critical time intervals. At $t = 30$ min, the swelling is already well advanced and a thick gel layer is being formed. The diameter of NaCMC increases more than that of the other two polymers. Further, at $t = 60$ min, the growth in diameter is continued in a similar fashion to the thickness of the gel layer. In the next set of photographs show that at $t = 90$ min, the sizes of the NaCMC and Polyox layers keep on increasing, while that of the SA layer starts to decrease. As time progress, the diametrical expansions terminated. The decrease due to erosion of the polymer starts at different times for each polymer.

From the graph in Fig. 8 and from visual observations is clear that the decrease of SA starts to occur after 75 min, of Polyox after 120 min and of NaCMC after 150 min. These changes in the diameter are better demonstrated in Fig. 10. Specifically, considerable erosion is observed in the Polyox layer where particles start to separate from the polymer mass. Similarly, a substantial decrease is detected in NaCMC layers, although this material exhibits the lowest shrink. It is worth mentioning that at 180 min NaCMC and Polyox layers were completely wetted, while SA layers, which exhibit the greatest erosion, maintain their core rather unwetted. This indicates that in SA layers the erosion of the gel is faster than the liquid penetration into the polymer mass. Equally, the layer thickness exhibits parallel changes (not shown) however, this is evident from the results illustrated in Fig. 8.

In general, SA layers display the fastest (radial, axial and bulk) reduction after the maximum expansion was achieved, followed by Polyox and NaCMC. The results obtained from these expansions coincide entirely with the uptake-swelling growth and thus parallel the procedure illustrated in Figs. 3, 6 and 8. Regarding the erosion of the polymer layers, by means of liquid uptake or expansion, these were found to be identical with both methods.

The study of expansion coupled with the swelling–erosion may reasonably explain the behaviour of the top cover layer. Therefore, as the time passes the increased swelling and expansion of the top layer have a significant effect on drug release. A large increase in the expanding volume decreases the release of the drug and consequently NaCMC, which exhibits the greatest swelling/expansion and gel thickness, but the lower erosion, has the smallest release. Polyox, which exhibits a less profound swelling/expansion and erosion, shows an intermediate release. Last, SA with the lower swelling/expansion and gel thickness and yet the highest erosion, displays a faster release. Thus, the changes of the top layer play undoubtedly a determining role on system's performance. Sungthongjeen et al. (2004) have recently reported an analogous finding suggesting that the level of a swelling layer in a coated system, which consists of Ac–Di–Sol, influences considerably the lag time of the system.

4. Conclusions

A novel core-in-cup pulsatile drug delivery system for oral use was developed and evaluated. The formulation consisted of a core tablet, containing the drug, an impermeable outer shell and a top cover swellable layer. The results suggested that the described system released the drug after a certain lag time, which could be modified by several factors. The quantity of material in the top layer, polymer characteristics and drug solubility are important factors in controlling the lag time and drug release. The lag time increases by increasing the quantity of the hydrophilic top cover layer. In contrast, drug release was found to decrease. Thus, we concluded that the top cover layer and especially the erodible polymeric material, from which this layer consists, regulate the performance of the system. The polymers contained in the top layer demonstrated considerable differences. NaCMC exhibited the greatest top layer expansion, maximum gel thickness and lag time but the lowest drug release from the system. Polyox showed an intermediate behaviour while SA, with the smallest expansion and gel thickness as well as the shortest lag time, exhibited a much faster release. Overall, the results confirm that these systems might offer a desired release profile for drug delivery at predetermined times.

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