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Design and evaluation of oral delivery formulations based on dextran with theophylline.

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Abstract

The purpose of this investigation was to develop and evaluate different oral drug release delivery formulations namely, tablets and capsules, based on dextran, in order to determine how the quantity of dextran and the form-structure of the delivery systems influence drug release and release mechanisms. Theophylline was used as the model drug. All matrix tablets and one capsule formulation demonstrated sustained release profiles. The amount of dextran and its properties (particularly erosion) along with the form of the preparation were found to considerably affect the performance of the system, the release profiles and the mechanism of release. In all cases an increase in the quantity of dextran resulted in a decrease in the release rate indicating that acted as a kind of barrier and hindered the release of drug molecules from these formulations. Significant differences were also observed among the different preparations under examination, with the matrix tablets exhibiting the slowest drug release followed by the capsules. By altering the dextran/theophylline ratio or the form of the preparation it is possible to obtain appropriate drug release. Consequently dextran appears to be a versatile material and a promising vehicle for the preparation of various oral sustained release drug delivery systems and relevant devices.

Keywords: Dextran, theophylline, tablets, capsules, sustained release, release

Introduction

Hydrogels have attracted considerable attention in recent years as sustained release preparations for drug delivery. Dextran hydrogels can be used for oral sustained release systems particularly in the colon area [1]. Up till now only a few articles [2-4] have been published on this subject but only in one of them pure dextran was used as a carrier [4]. Dextran it is derived from the bacterium Leuconostoc mesenteroides and can be described as a glucose homopolysaccharide with a linear polymer backbone structure in which linkages are almost entirely of the 1,6-a D-type(95%) the remaining 5% being 1,3-a-D- linkages. The 1,6-a D-glycosid linkages of dextran are hydrolyzed by dextranases. The majority of dexran splitters in the human colon are anaerobic intestinal bacteria mainly of the genus Bacteroides, which produce dextranases. The bacteroides produce both endo- and exodextran-ases which cleave randomly along the dextran chain and at the terminal linkages, respectively [5,6]. Thus we believe that our contribution will help researchers by providing them some essential information needed to design and manufacture sustained release oral preparations based on dextran.

Today a number of design options are available to control or modulate the drug release from a drug delivery system. Most of the oral controlled release dosage forms are either matrix or capsule systems [7-11]. These preparations may swell, gel and finally erode thus modulating the release process [8,12,13].

The aim of the present investigation was to develop and evaluate new oral sustained release delivery systems using dextran as a carrier and theophylline a rather water soluble drug (11.2 mg/mL) as a model drug. Secondly we aimed to examine the effect of the formulations on the rate of drug release. Two different formulations were prepared and evaluated, namely capsules and matrix tablets.

Materials and Methods

Materials

The chemicals were obtained from commercial suppliers and used as received: theophylline (Sigma Chemical Co, USA), dextran from Leukonostoc mesenteroides, MW $5x10^6$ – $40x10^6$(Sigma Chemical Co, USA) and magnesium stearate (BDH Poole, England).

Matrix tablet and Capsule preparation

The matrix tablets, (M), and capsules,(C), contained various quantities of theophylline with dextran(see Table 1) and 1% w/w of magnesium stearate. They were mixed for 10 min in a Turbula

–T2C mixer (Willy A. Bachofen AG. Basel, Switzerland), then the tablets were compressed at a compressing pressure of 1400kg to a crushing strength of 8-10 kg, measured in the Erweka hardness tester (Erweka Heusenstamm, Germany). The diameter of the flat face tablets was 9 mm and the height was 3 mm.

Weight variation test was performed by taking 20 tablets or capsules using an analytical balance (Sartorius AG, Goettingen, Germany) according to the official method. Weight variation was found to fall within the USP limit (± 0.5%).

Friability of the tablets was determined by testing 10 tablets in a Roche friabilator (Erweka TA, Erweka Heusenstamm, Germany) for 5 minutes at 25 rpm performed in triplicate.

Tablet friability was found in the region of 1 %. The mixing process described above was also followed for the powders filled into the capsules. The exact weight of powder was filled manually into each capsule of size 1 for 200mg/20mg and size 0 for 200mg/35mg and 200mg/60mg mixtures, (see Table 1). The filling was performed at maximum bulk density. Each capsule was individually weighed before filling. All formulations are shown in Table 1.

In vitro drug release studies

The dissolution study of theophylline tablets or capsules was carried out in a USP dissolution tester, paddle method for tablets (apparatus 2) and basket method (apparatus 1) for capsules (Pharmatest, Hainberg, Germany), in 900 ml with stirring at 100 rpm, at 37 ± 0.5 ^{0}C. The dissolution media consisted of 0.1N HCl, pH 1.2, for 2h, and then phosphate buffer pH 6.8, for 6h. Samples were withdrawn in selected time interval filtered and analyzed at 275 nm, 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. Results are given as mean ± standard deviation.

Dissolution efficiency values (D.E.), first suggested by Khan [14], is a parameter useful for the evaluation of in vitro dissolution. D.E. is defined as follows:

$$D.E. = \frac{\int_{t_1}^{t_2} y.dt}{y_{100}(t_2 - t_1)} x100\% \qquad (1)$$

where y is the percentage of dissolved product and D.E. 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 realistic to use D.E. which takes into account the dissolution profile as a whole [14]. Besides, where a quantitative comparison is required, D.E. is a more suitable parameter and when limits are set on D.E. it can be used for quality control in place of the conventional dissolution level.

Erosion studies

Weighted tablets were placed in dissolution vessels, containing 900 ml under stirring at 100 rpm, at 37 ± 0.5 ^{0}C. The dissolution media consisted of 1N HCl (pH 1.2) for 2h and then phosphate buffer pH 6.8. To prevent floating, tablets were placed under a "tent" which was formed from a pre-weighted 4 cm x 4 cm metal mesh (no 10) square. At selected time intervals an individual tablet was withdrawn using the mesh " tent ". The mesh and the tablet were blotted to remove excess water and then weighted on a Sartrorius analytical balance. The wetted tablets were dried in an oven at 65 ^{0}C for a 24 h period then, before weighing, cooled in a desicator and finally weighted. This 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

$$E\% = 100 (Wi-Wf) / Wi \qquad (2)$$

Where Wi and Wf are the initial starting dry weight and final dry weight of the same dried and partially eroded tablet, respectively.

Optical examination of matrix tablets

The system and the method we used were similar to the technique described in a previous study [15,16]. The recorded images were collected and analyzed with a Leica image analysis system (Leica Q 5001 W). A 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 consisted of a fluorescent tube fitted under the beaker. The beaker was covered to prevent external light. The tablet was held on a pin and placed in a dissolution beaker (of a dissolution apparatus Pharmatest, Hainburg, Germany) containing the appropriate medium. It was mounted in a vertical or horizontal direction to allow the observation of swelling in the axial or radial direction. The beaker was removed, at predetermined time intervals from the dissolution apparatus and was transferred to 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 sharp, bright white ring around the tablet 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. The swelling values of axial, radial and gel layer were 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 reported are averages for three different tablets.

Statistical analysis

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

Results and Discussion

During the dissolution process liquid penetration into the mass of a matrix tablet or capsule is the first step followed by dissolution of the drug contained within and finally its diffusion.

In vitro drug release

In Figure 1, we illustrate the release profiles of theophylline from the different formulations. As seen from the results the extent of drug release varies among the formulations and was affected by the type of the formulation and the amount of dextran contained. Capsules displayed the highest release and release rate followed by the matrices as clearly demonstrated by the t50 and D.E. values and this was probably because the powder in the capsules was not compressed. Furthermore, in all cases an increase in dextran content resulted in a lower overall drug release and a higher t50 (Table 1) supporting earlier studies [6].

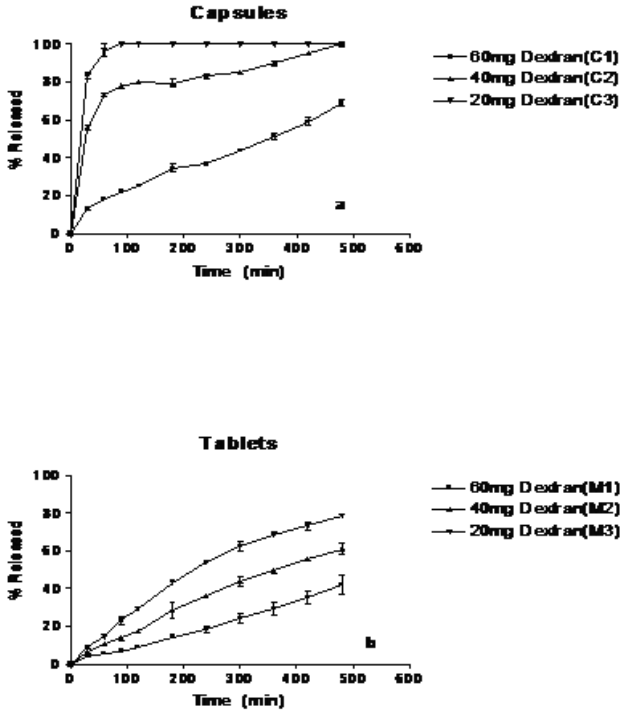

Figure 1. Dissolution profiles of capsules and tablets. Each point represents the mean value of the three samples and error bars show ± S.D.

From Figure 1a it is apparent that the capsule with the smallest amount of dextan (20mg) (C3) exhibited the highest release and the drug was completely released within 90-100 min, while the capsule containing the intermediate amount (40mg) (C2) of dextran released the drug in 480 min. The preparation with the largest amount (60mg) (C1) of dextran released only 70% of the drug after 8h.

Matrix tablets exhibited a slower release of the drug i.e. 80, 60 and 42% was release with a dextran content of 20 (M3), 40 (M2) and 60 (M1) mg, respectively (Fig. 1b). These results showed that the polymer may act as a strong barrier, controlling drug release from the matrices. This could be attributed to the high Tg value of dextran(>150 ^{0}C) [15] which could influence the transition of dextran from its glassy to a rubbery state. As a result the liquid penetration into the dry polymer mass is delayed and drug dissolution and release is decreased.

Previous studies on dextran mixtures tablets [2] containing soluble propranolol HCl (50 mg/ml in water) exhibited complete release of the drug, while in our findings with pure dextran tablets containing the less soluble theophylline (11.2 mg/mL) incomplete release was observed. Consequently it is possible that a decrease in dextran content might result in complete drug release.

The erosion results are shown in Figure 2. The capsules exhibited a very high erosion, almost twice that of the matrices (after 8 h). More specifically 40 and 20 mg capsules displayed 100 % erosion, while the formulation containing 60mg dextran displayed 80 % erosion, Figure 2a. In contrast tablets containing 20, 40 and 60 mg dextran respectively, exhibited lower erosion i.e. 75, 60 and 45% respectively, Figure 2b.

The higher erosion exhibited by capsules, compared to tablets, could be attributed to the fact that capsules are uncompacted preparations with a loose structure that facilitates liquid penetration into their mass and increases erosion and drug release.

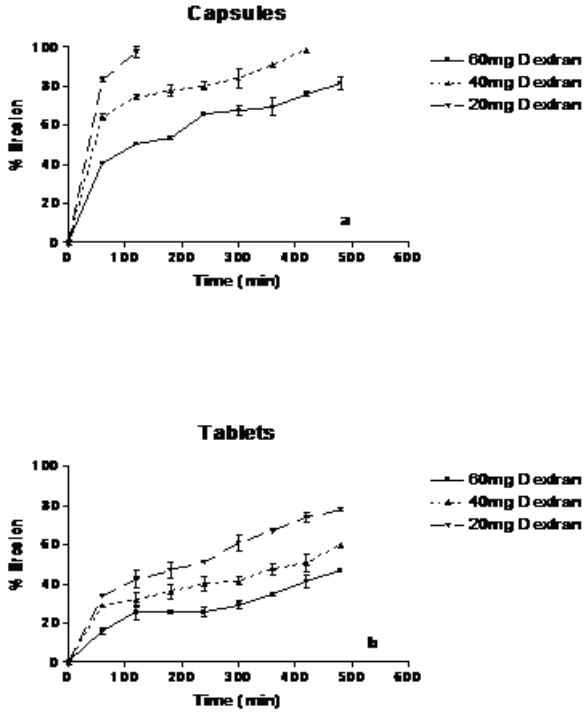

Figure 2. Percentage of erosion for capsules and tablets as a function of time. Each point represents the mean value of the three samples and error bars show ± S.D.

In general the formulations with lower concentrations of dextran demonstrated greater erosion and these results were consistent with the release data.

Tablet dimensional and gel layer changes.

On placing the tablet in liquid, a rapid and substantial increase in size was observed in both radially and axially directions. Due to rapid liquid penetration, all tablets underwent fast hydration. They swelled/expanded and created a rather thick gelatinous polymer mass. Three features are clearly visible from the images: a) the evolution of the gel layer with time, b) the change in size of the dry core of the polymer as more of the polymer becomes hydrated, and c) an increase in the dimensions of the tablet with time.

In Figure 3, typical images of dextran-theophylline tablets undergoing hydration- swelling and the changes in their morphology after 30, 90 and 420 min are shown. In images undergoing hydration after 30, 90 and 420 min. these photographs the recorded time intervals were chosen in order to expose some of the major changes that occur during the dissolution process.

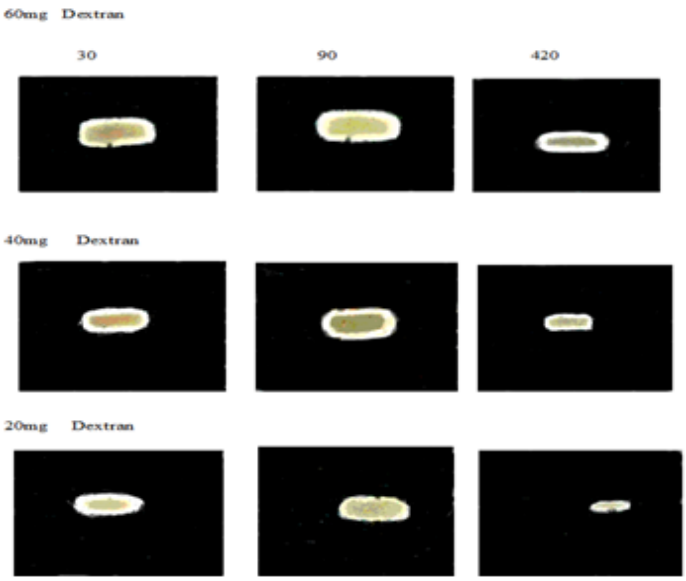

Figure 3. Morphological changes of the tablets during dissolution. Typical

The radial (RAD) and axial (AX) dimensional changes with time (normalized to the dry tablet) for all tablets were computed. The normalized tablet dimensions are defined as R(t)/R(0) for the radial direction and A(t)/A(0) for the axial direction, respectively, where R(0) and A(0) are the dimensions at time = 0; R(t) and A(t) are the dimensions at time = t.

Visual observations reveal that there was considerable expansion in both directions and all tablets displayed anisotropic swelling behavior with preferential axial expansion in accordance with previous studies [16].

Moreover an increase in dextran's content resulted in an increase in tablet dimensions. More specifically the 20 mg formulation exhibited a 1.60 fold axial expansion the 40 mg formulation a 1.70 fold expansion and the 60 mg a 1.78 fold expansion, while radial expansion was smaller ranging from 1.20 to 1.25 folds, (not shown here). It is noteworthy that after initial expansion, particularly after the 3rd hour, a gradual decrease in both dimensions was observed until the end of the experiment. The determination of the diameter(RAD) and thickness(AX) of the expanded tablet allowed us to calculate the corresponding total surface area using the formula, Area = 2r (r+h). The results obtained were normalized to the surface of a dry tablet and are shown in Figure 4. These results match with erosion data, (Fig. 2b) and support each other. It is obvious that tablets containing larger amounts of dextran exhibited greater surface areas, due to their greater axial and radial expansion.

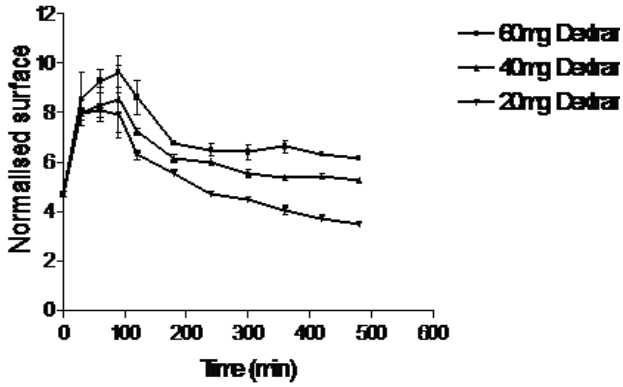

Figure 4. Surface changes of the tablets during hydration. Each point represents the mean value of the three samples and error bars show ± S.D.

Our visual examination showed that around the surface of the swelled tablets a highly viscous gel layer was created, Figure 3. The relative movement of the erosion and swelling fronts represents the gel layer thickness. The gel layer thickness and its changes appear to play an important role and determine the drug release from swellable delivery systems [17,18]. Therefore it was important to investigate the development of a gel for the dextran tablets under examination.

The next step we made was to determine the evolution of the gel layer and the changes of its thickness with time. The distance from the gel/core interface to the outer surface of the gel was taken as a measurement of the thickness of the layer. It was detected that the rate and the extent of gel growth was different for both the radial and the axial dimensions. In earlier studies [17,18] it was suggested that, for better precision and evaluation, it is preferable to use the average radial and axial gel thickness. It

was apparent with all tablets that the gel thickness increased rapidly in the beginning up to the 2th hour; (Figure. 5).
Afterwards the rate of growth and the thickness decreased followed by a plateau until the end of the experiment. This finding indicated that there was a synchronization of swelling and erosion fronts and stabilization of gel thickness. The gel thickness of the 60 mg matrices was greater reaching a maximum 1.85mm, followed by the 40 and 20 matrices with 1.50 and 1.25 mm respectively. The above results may explain the smaller release and release rate from the 60 mg matrices compared to the 40 and 20 mg matrices, since the greater thickness of the gel layer acts as a strong barrier that decreases the diffusion rate of drug molecules from the matrix.

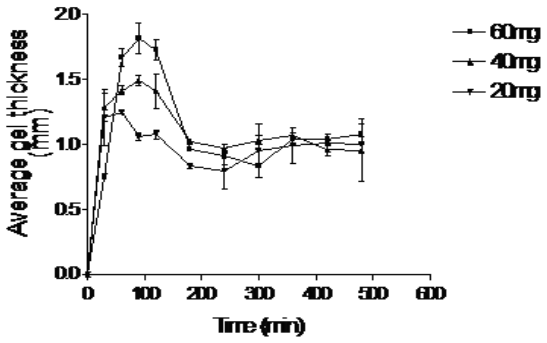

Figure 5. Gel thickness increase versus time. Each point represents the mean
value of the three samples and error bars show ± S.D.

Capsule morphological changes

Visual observations showed that 10-15 minutes after the capsule was immersed in our dissolution medium the capsule shell was dissolved and the remaining mass tent to form gel-like cylinder as the polymer hydrated and swelled. With time became an amorphous mass. Observations during the dissolution procedure showed that the polymer mass was reduced gradually in all cases.
Drug release from this mass was controlled by the viscous gel layer formed around the capsule mass. The layer acted as a barrier to drug release by obstructing the movement of dissolved solutes out of the polymer mass [19].
As time elapsed the polymer mass decreased as a result of erosion and dissolution of the polymer, resulting in increased drug release (Figs 1a,2a). In Figure 6, this procedure is clearly illustrated as well as the shrinking of the polymer mass for the capsules containing 60 mg of Dextran(as an example) from the beginning till the end of the experiment. Photos displayed in Figure 6 confirm these findings. In these photographs the recorded time intervals were chosen in order to demonstrate some of the major changes that occur during the dissolution process.
Gradual erosion started a little after 30 min and by 480 min only 80% of the mass had eroded. As is apparent the erosion can be compared to the progressive release of the drug, (Figs 1a and 2a). Capsules with 20 or 40 mg of Dextran exhibited a more rapid erosion and release compared to the 60 mg formulation.

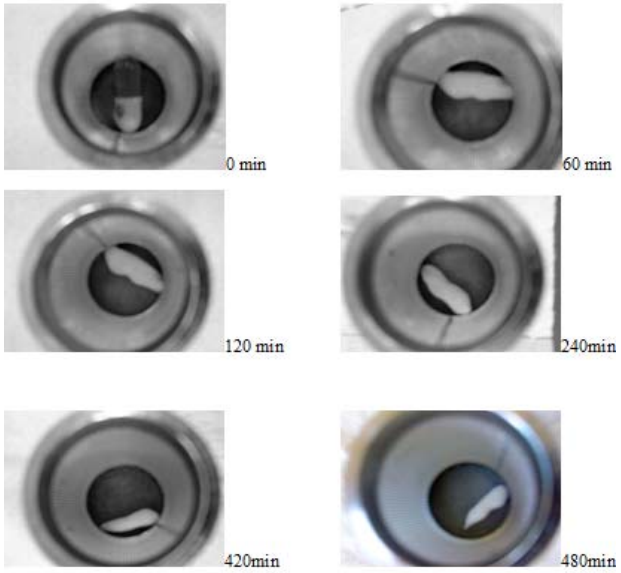

Figure 6. Morphological changes of the capsules during dissolution. Typical
images undergoing hydration after 0, 60, 120, 240, 420 480 min.

Effects of erosion on drug release

Figure 7 demonstrates the relationship between drug release and erosion for the 60 mg formulations. The results reveal that erosion plays a decisive role; it decreases the total surface area and subsequently shortens the distance that the dissolved drug has to travel from the interior of the formulation to the dissolution front and the surrounding medium. Thus with the decrease in surface area an increase in drug release was observed (Fig 8).
Polymer erosion could be attributed to its' dissolution as a result of chain disentanglement leading to shrinking of the gel layer and therefore increased drug release.
As seen in the graphs, (Figure 7), the association between release and erosion is comparable for these formulations. Greater erosion corresponds with increased drug release. From these results it appears that drug release could be attributed to both a swelling and a erosion/dissolution mechanism. The latter

dominates the last stages when erosion of the polymer mass becomes more intense. This fact was also confirmed by visual inspection during the dissolution studies.

Figure 9 illustrates the relationship between the amounts of Dextran and the D.E. It is obvious that the matrix tablets exhibit a linear correlation in contrast to the capsules.

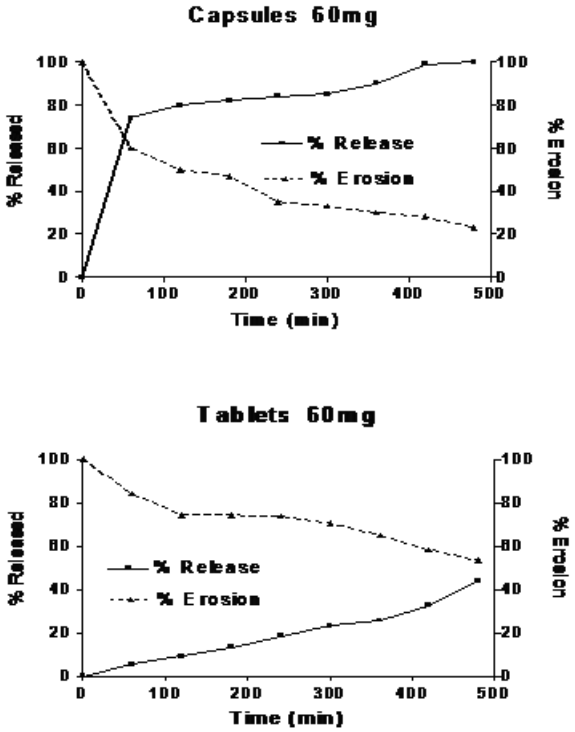

Figure 7. Dissolution profiles and erosion from capsules and tablets.

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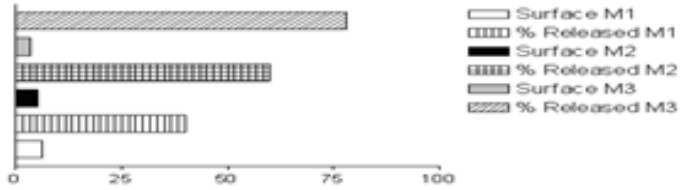

Figure 8. Relationship of drug release with surface area

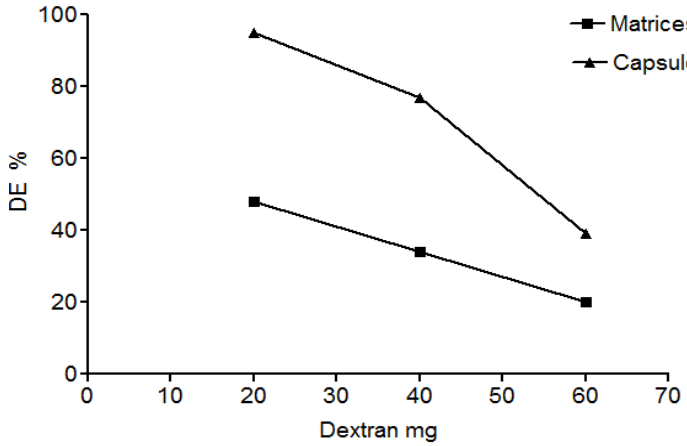

Figure 9. Relationship between the quantities of Dextran and the D.E

Table 1. Formulation compositions

Formulations	Ingredients in mg					
	Theophylline	Dextran	Mg. st.	t50 min	D.E.(8h)	n
M1 Matrix	200	60	2.6	>480	20.0±0.7	1.01
M2 >>	>>	40	2.4	370	34.0±0.9	0.84
M3 >>	>>	20	2.2	220	48.0±1.0	0.80
C1 Capsules	>>	60	2.6	340	39.0±1.2	0.66
C2 >>	>>	40	2.4	25	80.0±1.5	N.A.
C3 >>	>>	20	2.2	16	95.0±1.5	N.A.

Mg. st. = magnesium stearate, D.E. = Dissolution efficiency, N.A. = we do not have sufficient data for the calculation of n values.

Kinetics and mechanism of drug release

In order to clarify, identify and explain the mechanism of drug release, the data were further analyzed, up to 60% drug release, using the familiar empirical equation proposed by Korsmeyer and Peppas [20,21]:

$$M_t / M_\infty = k\, t^n \quad (3)$$

where M_t / M_∞ is the fractional release of the drug released at time t, k is the kinetic constant and n is the diffusional exponent for drug released which depends on the release mechanism. Values n = 0.45 indicate Fickian release, 0.45<n<1 indicate anomalous non-Fickian release kinetics (coupled diffusion/relaxation) and n =

1 for Case II transport (zero order release also known as purely relaxation-controlled drug release)(19).
The n values obtained (listed in Table 1), ranged from 0.67 to 1.01. The n values for the matrices M1, M2 and M3 (1.01, 0.84 and 0.80, respectively) indicate that drug release mechanism was due mainly to a macromolecular relaxation and erosion mechanism exhibiting a near zero-order release. It is apparent from our findings that an increase in the n value is associated with an increase in the dextran contained in a preparation. On other hand the C1 capsule preparation displayed a rather Fickian diffusion, n =0.66. For the preparations C2 and C3 we could not calculate the n values due to lack of data.

Conclusions

The influence of dextran and the form-structure of the examined formulations were investigated. All matrix tablets and one of the capsule formulations exhibited sustained release profiles. It was demonstrated that the amount of dextran and its erosion along with the structure of the formulation considerably affect the performance of the formulation as well as the release profiles and the mechanism of release. An increase in dextran quantity results in a decrease in the release rate indicating that dextran is a strong barrier that may obstruct the release of drug molecules from these formulations. Our findings show that marked differences were observed between these preparations, and the matrix tablets exhibited the slowest release followed by the capsules. By altering the dextran/theophylline ratio or the form structure it is possible to obtain appropriate drug release.

Declaration of interest

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

Acknowledgements

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