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Utilization of Hydrophilic Swellable Polymers as Carriers for Sustained Drug Delivery from Matrices and Three Layer Tablet Systems

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Abstract: The purpose of this research was to develop and evaluate different sustained release preparations, using swellable polymers as carriers in the form of matrices and three-layer tablets. These preparations may offer a number of therapeutic advantages over immediate release dosage forms in drug delivery. The materials used for the fabrication of these systems were hydrophilic swellable polymers namely Metolose, Polyox, Xanthan gum and an erodible material Gantrez, acting as drug (diclofenac sodium) carriers. The powder characteristics determined for these polymers suggest good flowability with the exception of Gantrez. The addition of 1% of magnesium stearate resulted in improved flow properties for all polymers including Gantrez. Tablets were prepared by direct compression whereas three-layer tablets were prepared by compressing polymer barrier layers on both sides of the core containing the drug. Our findings show that both preparations exhibit sustained release characteristics; also the structure of the device considerably affects the drug release and the release rate. Furthermore erosion and swelling greatly influence the overall behavior, function and performance of the systems. Finally kinetic analysis studies indicated that the drug release mechanisms were also affected by these effects.

Keywords: Sustained release, swelling, erosion, matrix, three layer tablets.

INTRODUCTION

The preparation of suitable drug delivery systems is dependent on the selection of the appropriate carrier/ingredient capable of controlling delivery. Most sustained release preparations are based on polymeric materials. These materials, in particular hydrophilic swellable polymers are promising versatile carriers for the manufacturing of sustained release systems. These systems may offer a number of therapeutic advantages in drug delivery over conventional (immediate release) dosage forms of some drugs since they allow the release of various therapeutic agents to be controlled, and thus play a significant role in the development of novel oral dosage forms. The characteristic feature of these systems is that the rate of drug absorption may be adjusted through a controlled rate of drug release from the dosage forms. Their advantages include extended pharmacological cover, reduced dosing frequency, a decreased incidence of adverse effects and a reduction in drug plasma fluctuation resulting in a more constant therapeutic effect [1].

Different types of oral controlled release formulations such as matrix tablets [2], capsules [3,4] and mini matrices [5] have been developed to improve treatment and clinical efficiency. Recently multi-layer tablets are gaining importance in the design of oral sustained drug delivery systems [6,7]. These systems consist of an active matrix core and one or more barriers applied during tableting. The barriers delay the interaction of the core with the dissolution medium by reducing the surface available for drug release by limiting

liquid penetration. These formulations are designed to deliver the drugs at controlled and predetermined rate, thus maintaining their therapeutically effective concentrations in systemic circulation for prolonged periods of time. Depending on the material properties these formulations may swell, gel, erode and finally dissolve in the gastrointestinal tract. The control of the release is mainly determined by the composition of each layer. The multi-layer systems permit the production of various tablet structures of different release properties achieving thus a range of dissolution profiles. Layered tablets show a number of advantages and greater flexibility in obtaining different drug release profiles such as zero order, bimodal, pulsatile and controlled release [6]. The most frequently used ingredients-carriers of these systems as mentioned above are the polymers. A variety of polymers is employed since their nature and characteristics may play a key role and significantly influence the behavior of these devices [8]. The controlling effect of a polymer material on drug release depends on its physicochemical properties and the way it is mixed during the manufacture of the system. Specifically this effect is due to the polymers' molecular properties, such as the nature of the monomer, type and degree of substitution and whether the polymer is mixed dry or dissolved. In general three main types of polymers may be used: natural, synthetic and semi-synthetic [9]. These materials may swell or not, can be porous, non-porous, semipermeable, impermeable, erodible, non-erodible, etc.

In the present study matrix tablets and multi-layer tablet system were developed and evaluated. The aim of this study was to prepare matrices and three layer tablet system and then investigate the effect of a) the structure of the system b) the influence of the features of the particular polymeric materials on the drug release rate and c) to evaluate the behavior

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of the systems prepared in this investigation. Three hydrophilic swellable polymers hydroxyl propylmethyl cellulose, polyethylene oxide, xanthan gum and a rather erodible and moderately swellable material poly(methyl vinyl ether/ maleic anhydride), of different nature and properties were employed as ingredients-carriers. In order to investigate and evaluate their behavior, a rather water soluble drug diclofenac sodium was used as model drug.

EXPERIMENTAL

Materials

The following chemicals were obtained from commercial suppliers and used as received: Diclofenac sodium (D) (Sigma Chemical Co, USA), hydroxypropylmethyl cellulose [Metolose 90,100.000 SR] (M),(Shin-Etsu, Tokyo, Japan), polyethylene oxide [Polyox NF,MW 7×10^6] (P) (Union Carbide, Danbury, CT, USA), Xanthan gum (XG) (Aldrich, USA), poly(methyl vinyl ether/maleic anhydride) [Gantrez AN-169 BF] (G) (CAF, N.J. USA) and magnesium stearate (BD-H, Dorset,UK). Also, a well known commercial sustained release product (VOLTAREN marketed by Novartis) in the form of sustained release coated tablet was examined too. All chemicals used in this study were of analytical quality.

Powder Characteristics

The techniques used for the determining the powder characteristics were described in earlier studies [4].

Tablet Preparation

The matrix tablets were consisted of 49.5 w/w % of diclofenac sodium, 49.5% of polymers and 1% of magnesium stearate, and are listed in Table 1. The drug and the polymers were mixed in a Turbula (Type T2C) mixer (Willy A. Bachofen AG, Basel, Switzerland) for 10 min. Tablets of 200 mg mass were compressed using 10 mm diameter flat faced punches in a Carver laboratory hydraulic press (Fred S. Carver, Inc., Menomonee Falls, W) to a crushing strength 10 kg, measured in the Erweka hardness tester(Erweka, Heusenstamm, Germany).

Three-layer tablets were similarly prepared by direct compression procedure using, 10 mm diameter flat faced punches. The die was accurately and progressively filled with

weighed amounts of different mixtures, i.e. barrier layer, core layer and barrier layer once again. First, the barrier layer was placed in the bottom of the die and compressed at approximately 100 kg, the core layer was then added and compressed at 100 kg followed finally by the top layer barrier which was added and compressed at 500 kg. The core layer was consisted of Polyox or Metolose and diclofenac sodium whereas the barrier layers consisted of pure polymer. The three-layer tablet formulations prepared are listed in Table 2. The number 3 indicates three-layer tablet formulations. For tablet composition and notations see Tables 1 and 2 below.

In Vitro Drug Release Studies

Tablets were subjected to the dissolution study at 37 ± 0.5 °C under stirring at 100 rpm (paddle method) in the USP XXIII dissolution apparatus II (Pharmatest, Hainburg, Germany), in 900 ml of phosphate buffer(pH 7.4). Samples(5 ml) were withdrawn at predetermined time intervals, filtered and analyzed at 276 nm for sodium diclofenac using a Perkin-Elmer UV spectrophotometer (Norwalk, CT, USA). An equivalent volume of temperature-equilibrated fluid was replaced in the dissolution bath following removal of every sample. The data represent the mean values of at least three separate experiments. Results are given as mean \pm standard deviation.

Dissolution efficiency (DE) data were obtained using the following equation. The concept of DE was introduced first by Khan and Rhodes who suggested that it is a parameter useful for the evaluation of *in vitro* dissolution.

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

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 [10]. 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 [10]. In addition, where a quantitative comparison is required, DE is

Table 1. Formulation Compositions of Matrix Tablets (in mg).

	Tablets				Ingredients				
	Diclofenac Sodium	Metolose	Xanthan Gum	Gantrez	Polyox	Mg.St	t240	DE \pm S.D.	n
PGD	99			49.5	49.5	2	15	16.5 \pm 0.5	1.05
MGD	99	49.5		49.5		2	75	63.5 \pm 2.1	1.20
PXD	99		49.5		49.5	2	44	40.5 \pm 0.9	0.80
MXD	99	49.5	49.5			2	38	37.0 \pm 2.0	0.81
Voltaren							50	47.0 \pm 1.6	

Mg.St = Magnesium stearate

t240 = % drug released at 240 min

Table 2. Formulation Compositions of Three Layer Tablets (in mg).

Tablets		Diclofenac Sodium	Metolose	Xanthan Gum	Polyox	Gantrez	Mg.St	DE±S.D.	n
3MDX	TL			24.75			0.25	19.0±0.8	1.00
	ML	99	49.5				1.5		
	BL			24.75			0.25		
3MDG	TL					24.75	0.25	25.0±1.4	B.R.
	ML	99	49.5				1.5		
	BL					24.75	0.25		
3MDM	TL		24.75				0.25	22.5±1.2	0.96
	ML	99	49.5				1.5		
	BL		24.75				0.25		
3PDX	TL			24.75			0.25	23.0±1.1	0.89
	ML	99			49.5		1.5		
	BL			24.75			0.25		
3PDG	TL					24.75	0.25	26.0±1.7	B.R.
	ML	99			49.5		1.5		
	BL					24.75	0.25		
3PDP	TL				24.75		0.25	21.5±0.9	0.90
	ML	99			49.5		1.5		
	BL				24.75		0.25		

TL = top layer, ML = medium layer, BL = bottom layer B.R. = Bimodal release
Mg.St = Magnesium stearate .

a more suitable parameter and when limits are set on DE it can be used in quality control in place of the conventional dissolution level.

Uptake and Erosion Studies

Weighed tablets were placed in flat bottom dissolution vessels, containing the dissolution medium under the conditions of temperature and stirring described in the dissolution studies section above. To prevent floating, tablets were placed under a bell shape “tent” formed by 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 weighed on a Sartorius analytical balance. Then the wetted tablets were dried in an oven at 60 °C for a 48 hours period after that, before weighing. They were cooled in a desiccator and finally weighed. This process was repeated until a constant weight was achieved (final dry weight). Three different tablets were measured at each time point, and fresh tablets were used for each individual time point. The extent of erosion (E) was determined by,

$$E\% = 100 (W_i - W_f) / W_i \quad (2)$$

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. Also, the increase in weight (water uptake) due to absorbed liquid (A) was calculated at each time point by

$$A\% = 100 (W_w - W_f) / W_f \quad (3)$$

Where, W_w is the mass of the wet tablet before drying.

Optical Examination

Morphological tablet changes were examined with a video camera (JVC TK-C11381, Japan) fitted with a zoom lens (Century Precision Optics AD-5870, USA) and connected to a monitor. The light system was consisted of a fluorescent tube fitted under the beaker. The beaker was covered to exclude external light. The tablet was held on a pin and placed in a dissolution beaker with 900 ml of dissolution medium at 37 ± 0.5 °C under stirring at 100 rpm, to allow observation of changes in the device. The beaker was removed, at predetermined time intervals, from the dissolution apparatus and photographed by means of the video camera.

Statistical Analysis

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

RESULTS AND DISCUSSION

Polymeric materials used in controlled delivery formulations include hydrophobic, insoluble and erodible or hydrophilic polymers. In this study, the materials used were mentioned earlier in the introduction. As model drug was used a

rather soluble drug, diclofenac sodium, with solubility of 18.8 mg/ml [11].

The powder characteristics determined for the polymers are summarized in Table 3. The Hausner ratio and compressibility (%) were used to evaluate the flow properties of polymers. These parameters are commonly used to assess powder flowability and are useful indices, which reflect the flow and packing behavior of powders. The Hausner ratio values display very good flow properties for all polymers with the exception of Gantrez. The percentage compressibility was computed from the density data shown in Table 3. The compressibility values coincide with the Hausner ratio values, suggesting good flowability for these materials. The addition of 1% of magnesium stearate resulted in improved flow properties for all polymers including Gantrez (Table 3). Thus, these materials are suitable used for the preparation of tablet drug delivery systems.

The structure of the three layers devices are shown in Fig. (1). It is clear that in these formulations the core (or middle layer) has both surfaces (top and bottom) covered. Upon contact with the dissolution medium, swellable polymer matrices form a viscous gelatinous mass. As the hydration progresses the entrapped drug dissolves and diffuses through the swollen network, which after a while undergoes erosion. In three layer tablets the external layers cover the core tablet and usually act as barriers, since typically they consist of pure polymer [6,7,12]. With time they hydrate, swell and as a result they hinder drug dissolution and release. At the end of the process they tend to erode and the surface available for drug release slowly increases.

As seen in Table 1, the matrices are composed of polymer mixtures and diclofenac sodium. Three layer tablets contained drug only in the middle layer (core) while top and bottom layers, Fig. (1) were drug free acting as barriers (Table 2).

In the next sections we provide an evaluation of their performance, release behavior and a mechanistic approach of how these are affected by tablet's structure and composition.

Swelling and Erosion Studies

It is clear from, Tables 1 and 2, that the formulations examined consist of different polymers or polymer mixtures. As mentioned earlier these materials have different characteristics, which could influence their performance. Two im-

portant characteristics of the polymers employed, i.e. their liquid uptake (swelling) and loss of weight (erosion) were evaluated in order to examine whether these properties are interrelated and to what extent, with each formulations' behavior and how they affect the system's function and performance.

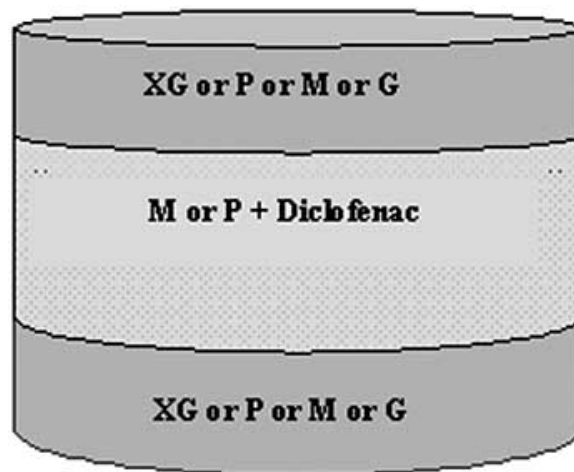


Fig. (1). Schematic diagram of the three layer tablet system.

The results obtained are illustrated in Figs. (2 and 3). The changes in weight represent water uptake and maximum swelling. Visual observations showed that the tablets appeared swollen almost from the beginning of the experiment. The only exception was the Gantrez tablets in which gel development appeared rather negligible. The swelling of the matrices increased gradually with time and the maximum being measured at 8 h. MGD, however, showed a gradual increase up to 4 h (maximum swelling) and then started to decrease drastically Fig. (2). It is clear that PGD showed the fastest and greatest swelling (1600%), followed by PXD (1400%), MXD(1300%) and last MGD(650 %).

The swelling results of three layer tablets are illustrated in Fig. (3). The uptake of these tablets appeared comparable and increased gradually until the end of the experiment, displaying maximum swelling in the region of 1500%, with the exception of Gantrez tablets which exhibited their maximum approximately at 6 h and after that time a rapid decrease was noticed.

Table 3. Powder Characteristics.

Polymer	Bulk Density is dB \pm SD		Tap Density is dT \pm SD		Compressibility % (Carr Index) dT - dB/dT \pm SD		Hausner Ratio dT/dB \pm SD	
	Mg.St=0	Mg.St=1%	Mg.St=0	Mg.St=1%	Mg.St=0	Mg.St=1%	Mg.St=0	Mg.St=1%
Metolose	0.40 \pm 0.012	0.42 \pm 0.011	0.47 \pm 0.010	0.48 \pm 0.012	14.00 \pm 0.12	12.00 \pm 0.13	1.17 \pm 0.007	1.14 \pm 0.009
Polyox	0.34 \pm 0.009	0.38 \pm 0.009	0.39 \pm 0.008	0.42 \pm 0.011	12.00 \pm 0.11	10.00 \pm 0.11	1.14 \pm 0.006	1.11 \pm 0.007
Xanthan gum	0.61 \pm 0.015	0.64 \pm 0.017	0.73 \pm 0.014	0.75 \pm 0.016	16.40 \pm 0.10	14.50 \pm 0.13	1.20 \pm 0.005	1.17 \pm 0.008
Gantrez	0.22 \pm 0.007	0.26 \pm 0.010	0.29 \pm 0.006	0.32 \pm 0.010	24.00 \pm 0.12	19.00 \pm 0.15	1.31 \pm 0.008	1.23 \pm 0.011

Data shown are means n = 5

Mg.St = magnesium stearate

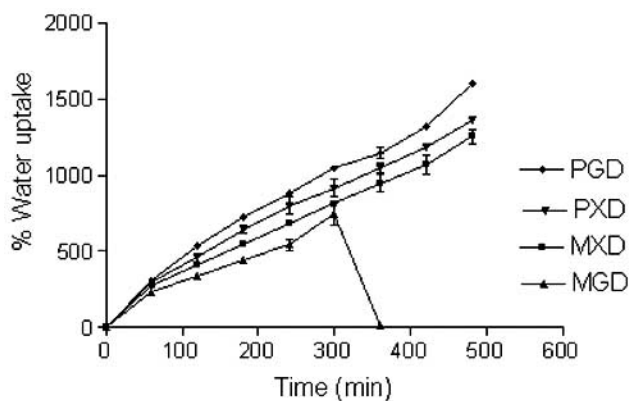


Fig. (2). Percentage of weight changes (water uptake) as function of time for matrices. Each point represents the mean value of the three samples and error bars show \pm S.D.

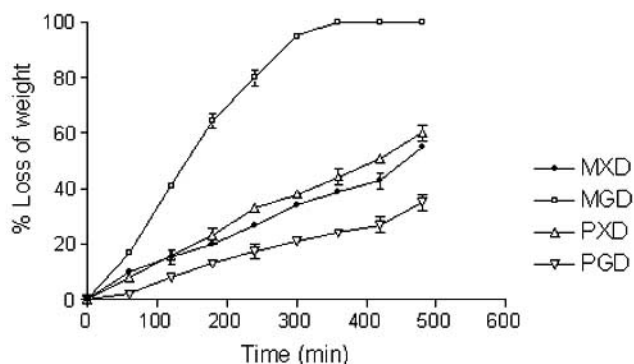


Fig. (4). Percentage of weight loss (erosion) from matrices after exposure to the medium. Each point represents the mean value of the three samples and error bars show \pm S.D.

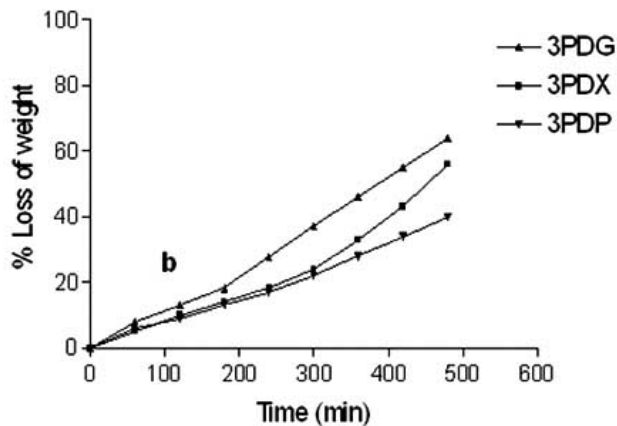
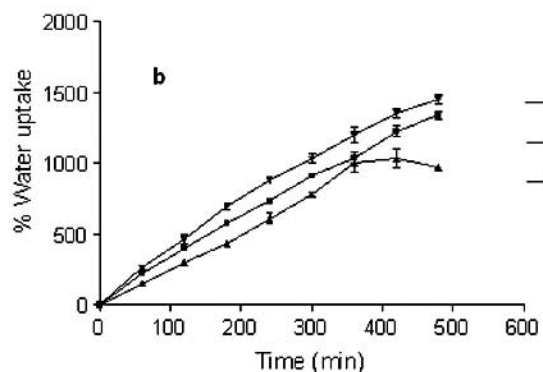
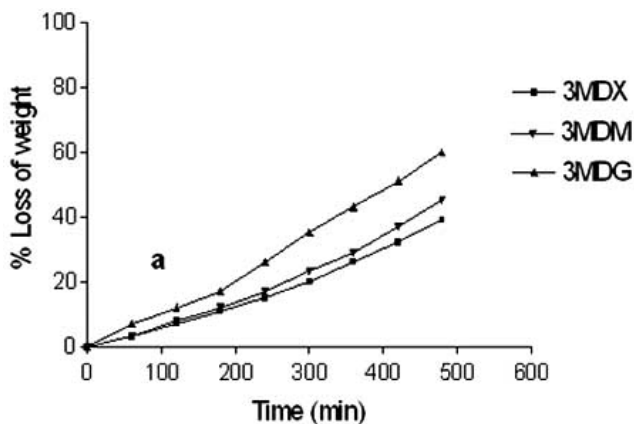
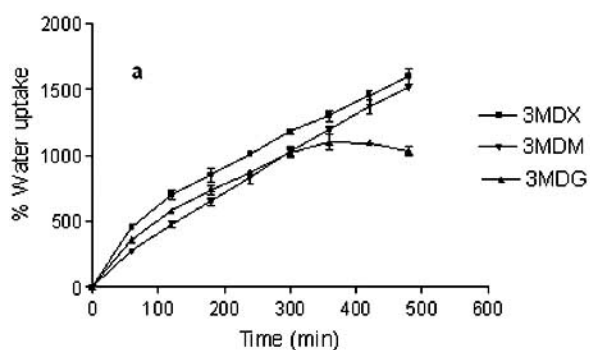


Fig. (3). Percentage of weight changes (water uptake) as function of time for three layer tablets. Each point represents the mean value of the three samples and error bars show \pm S.D.

Fig. (5). Percentage of weight loss (erosion) from three layer tablets after exposure to the medium. Each point represents the mean value of the three samples and error bars show \pm S.D.

Erosion results, expressed here by loss of weight, are shown in Figs. (4 and 5). The highest degree of erosion was observed in MGD matrices (totally eroded in 6 h), followed by PXD, MXD and PGD, which displayed a slower and progressive weight loss with time Fig. (4). Their erosion appeared to be lower than that of MGD since only between 35 to 60% eroded, a process which was also visually noticed.

Similarly, in Fig. (5) three layer's tablet erosion results are shown. The erosion of Metolose formulations Fig. (5a) are comparable to these of 3MDG and it is clear that the latter displayed the highest erosion(60%) followed by 3MDM and 3MDX with 45% and 40%, respectively. As far as the Polyox formulations are concerned, 3PDG displayed the hig-

hest erosion(65%), followed by 3PDX with 56% and then 3PDP with 40%, Fig. (5b).

Device Structure and Drug Release

The release profile depends on the type and properties of the polymer used, but dissolution of the active compound is always a prior and necessary step of the release process. Liquid penetration into the matrix is the first step followed by dissolution of the drug and finally its diffusion. The procedure depends on successive dissolution and diffusion, once the dissolution medium penetrates the matrix.

In Figs. (6 and 7) the release profiles of diclofenac sodium are illustrated. In Fig. (6) the VOLTAREN profile is included for comparison although it is a different form of sustained release (membrane release), manufactured by a different methodology.

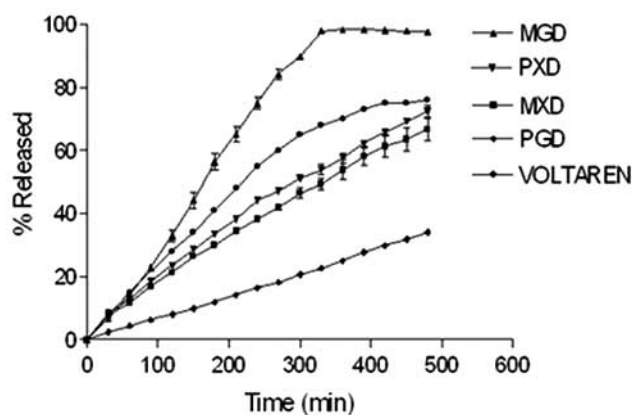


Fig. (6). Release profiles from diclofenac sodium matrices and VOLTAREN. Each point represents the mean value of the three samples and error bars show \pm S.D.

As can be observed in Figs. (6 and 7) the drug release and release rates differ considerably between the matrices and three layer tablets. All three layer tablets exhibited a significant ($P < 0.01$) lower release than the matrices with the exception of PGD. Moreover, all formulations demonstrated a sustained mode of release.

As it can be seen from the release profiles depicted in Fig. (6) the extent of drug release varies among the formulations and is affected by the composition of the tablet and the properties of the contained materials as indicated by the t_{240} and D.E. values (Table 1). Among the matrices, MGD showed the highest drug release (it was fully released in 6 h) followed by VOLTAREN, PXD, MXD and the PGD, which exhibited approximately 73%, 72%, 65% and 35% release in 8 h, respectively. It is apparent that no remarkable differences exist between VOLTAREN and PXD, MXD.

Findings from earlier studies revealed that the release of diclofenac sodium from HPMC matrices [11] was in the range of 60%, at the same time, while its release from Xanthan gum formulations varied, depending on the drug/polymer ratio and matrices dimensions [13,14]. Image analysis photos show that at 2 to 3 h period MGD matrices were suffered from increased shrinking compared to PGD Fig. (8).

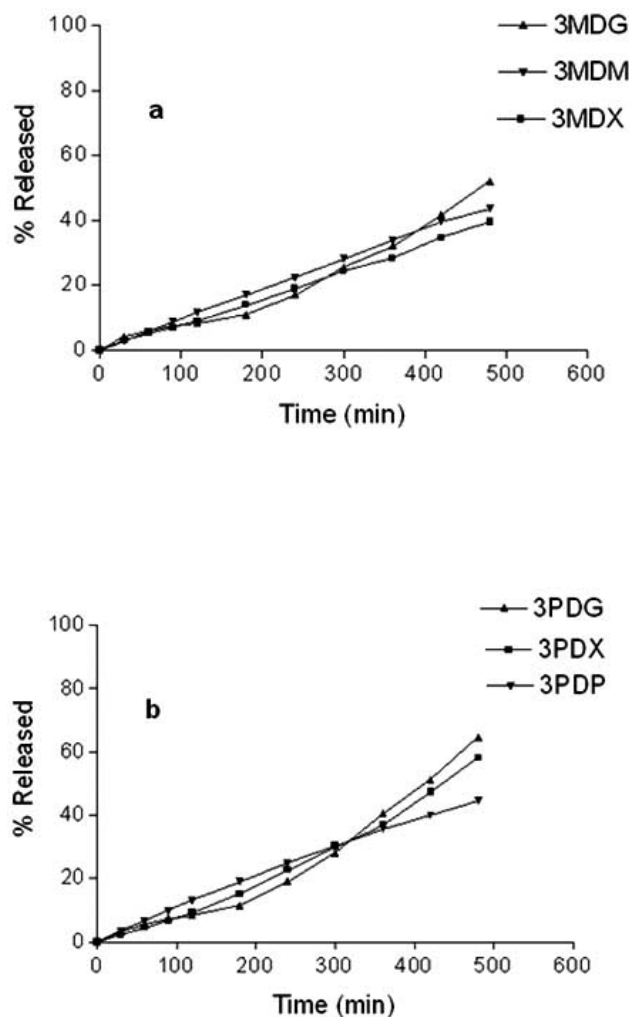


Fig. (7). Release profiles from diclofenac sodium three layer tablets. Each point represents the mean value of the three samples and error bars show \pm S.D.

Moreover, polymer particles probably Gantrez detached from the surface of MGD matrices and gradually dissolved, Fig. (8) resulting in the erosion and deterioration of the matrix. On the contrary, this phenomenon was not observed in PGD matrices, which maintained their integrity whilst their mass expanded, Fig. (8) and as a result lower drug release was noticed in this case. This different behavior could be attributed to the limited swelling-expansion of Metolose tablets compared to the corresponding Polyox. Due to its greater swelling, Polyox, can hold in more efficiently the Gantrez particles and hence blockade their detachment and erosion/dissolution. Thus, drug release results clearly coincide with the swelling and erosion properties of the different types of polymers used. In parallel, Xanthan gum matrices, PXD and MXD, demonstrated an intermediate level of swelling, erosion and consequently drug release. A comparison between these formulations with VOLTAREN is rather inappropriate due to the difference in the release procedure and mechanism.

On the other hand, drug release particularly, from multi-layer systems, appears more complicated since the move-

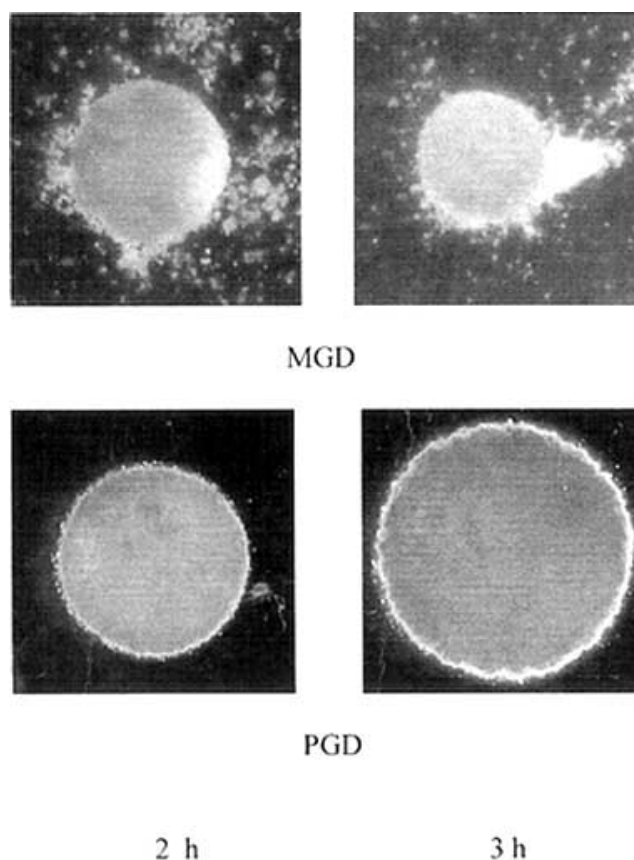


Fig. (8). Morphological changes in radial plane of the matrices during dissolution after 2 and 3 hours.

ment of drug molecules is also affected by the structure of the system and the existing barriers. It is known that in multilayer systems the matrix core usually contains the drug and the external layers incorporated during tableting modulate (delay) the interaction of the drug with the dissolution medium by limiting the surface available for the solute release and at the same time controlling liquid penetration. Thus they act as barriers since typically they consist of pure polymer [7,12] and as a result they obstruct drug dissolution and release. This is achieved by intercepting water penetration, into the protected core for a period of time and this reduces hydration rate and controlled area for solute release at the core. During the dissolution process, the barriers may swell

(hydrophilic polymers) and expand. With time these swollen barriers tend to erode and the surface available for drug release slowly increases.

With the exception of PGD Fig. (6) three layer tablets displayed lower release Fig. (7) compared to the matrices. In parallel, these tablets up to 90 min displayed a similar behavior and then their release mode tends to differentiate. The presence of the different polymers (Polyox or Metolose), contained in the middle tablet layer (core), did not differentiate their release rates, as seen from the DE values, of Table 2. Tablets containing Polyox demonstrated a slightly higher release compared to corresponding Metolose tablets. In parallel, the presence of Gantrez and Xanthan gum in external layers did not alter the systems performance considerably, even though Gantrez formulations displayed a higher release. It is therefore reasonable to expect that a modification of external layer thickness or an increase in the quantity of polymer in these layers could considerably affect drug release from these multilayer delivery systems.

Visual observations point out, that the external layers absorb liquid and expand creating a swellable barrier. This results to a substantial increase in the diffusion pathway for the drug molecules and consequently the drug release is decreased. At the same time the middle layer starts to hydrate and a fraction of the drug was released from that layer, mainly from the lateral surface. As hydration progressed, the layers continued to swell and then merged and formed a solid polymer mass [7]. This development facilitates the hindrance of drug molecules movement and additionally decreases their diffusion out.

In general, drug release from the solid polymer mass is affected by the entanglement or disentanglement of polymer chains and particularly by the rate of detachment of the polymer chains from the matrix surface [15], causing changes in the diffusional pathway and finally erosion of the system. Indeed Polyox formulations exhibited greater erosion than the respective Metolose Fig. (5).

In Fig. (9) typical images of diclofenac three layer tablets undergoing hydration-swelling and the changes in their morphology after 60,120 and 360 min are illustrated. Analogous changes were observed with all the three layer tablets examined (not shown). In these photographs the recorded time intervals were chosen in order to reveal some of the major changes occurring during the dissolution process.



Fig. (9). Morphological changes of the three layer tablets during dissolution 1, 2 and 6 hours.

Moreover, Gantrez tablets 3MDG and 3PDG demonstrated a biphasic release, Fig. (7). Both formulations exhibited a slow initial release phase (0-180min), followed by a fast release phase(240-480min). These coincide with their erosion, which is sharply increased after 180 min Figs. (5a, b) and as a consequence the release increased after 210-240 min. Erosion shortens the travel distance of dissolved drug molecules from the dissolution front to the surrounding medium and this matches the increase of drug release.

The bar graphs shown in Fig. (10) illustrate the release data from 3MDM, 3PDP and 3MDX preparations, presented as the rate of drug release (percent dissolved per hour) versus time. The graph clearly shows that these formulations displayed a fairly constant drug release rate, which corresponds to about 5-7% per hour.

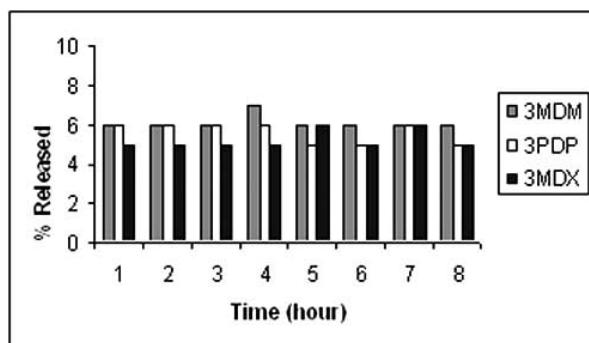


Fig. (10). Rate of drug release (% of drug release / hour) as a function of time.

The findings indicate that in the three layered tablet system formulations and in particular 3MDG and 3PDG, the polymers act as carriers. These formulations represent a very promising dosage form for the administration of rather soluble drugs, such as diclofenac sodium with a bimodal release. As previously mentioned above bimodal release involves two variable release phases: slow drug delivery at the beginning of the dissolution procedure, followed by a faster release in a subsequent phase. This bimodal release could be particularly suitable for the treatment of symptoms exhibiting circadian rhythms[16]. Naturally bioavailability studies would offer a more comprehensive picture of the pharmacological and therapeutic capabilities of these formulations; however these could be the subject of another study.

Kinetics and Mechanism of Drug Release

From the data presented above it becomes obvious that the properties of the polymers, the structure and the morphology of the tablet considerably influence the drug release and release rate. Furthermore a biphasic release was demonstrated by 3MDG and 3PDG, a development which was also reported in earlier studies [16,17]. Bimodal release seemed to occur in two phases. An initial gelation phase (where the gel mass expands due to water penetration) during which some initial erosion of the polymer was noticed and a fraction of the drug is released, followed by a second phase, where, upon complete hydration of the polymer mass fragmentation of the gel occurred, which resulted in another increase in the rate of drug release. Similar results were reported by Shah *et al* and Munday [17-19]. This behaviour

was attributed either to pH changes [18] or separation of the layers [20] or due to the different polymer properties [4].

In our investigation biphasic release is apparently associated with the presence and the properties of Gantrez in the respective formulations. Visual observations revealed, as previously mentioned, that after hydration of the tablets and as the process advances, particles of the material were gradually removed from the Gantrez tablets. Subsequently, the detached particles slowly dissolved and this was continued until the material was entirely eroded.

Fig. (7) shows the biphasic release of these formulations. Clearly, the curves are comprised of an initial and terminal release phase. The “break” between the two phases becomes apparent at 180 min.

In Table 4 the release rate constants for each phase are listed. Judging by the correlation coefficients, following regression analysis, both the initial and terminal release phases exhibit zero-order type release kinetics.

In order to elucidate the mechanism of drug release, the data were further analyzed using the familiar equation proposed by Korsmeyer and Peppas [21].

$$M_t / M_\infty = k t^n \quad (4)$$

M_t is the amount of the drug released at time t , M_∞ is the amount of drug released over a very long time, which corresponds in principle to the initial loading, k is the kinetic constant and n is the diffusional exponent which depends on the release mechanism. For a cylindrical matrix values $n = 0.5$ indicate Fickian release, values $0.45 < n < 0.89$ indicate anomalous release kinetics (coupled diffusion /relaxation) and $0.89 < n < 1$ indicate a zero order release also known as purely relaxation-controlled drug release.

The values we obtained for the diffusional exponent, n , ranged from 0.80 to 1.21 demonstrating that the release mechanism varies. The calculated n values are shown in Tables 1 and 2. The VOLTAREN n value was not estimated since the above equation can be used only for swellable matrices. Gantrez matrices displayed n values > 1 , indicating near zero order release mechanism, which may be attributed to swelling and erosion/dissolution of the polymer a fact confirmed by the swelling and erosion studies [22]. On the other hand Xantham gum formulations displayed n values < 0.89 suggesting a coupling of diffusional and relaxation mechanisms, called anomalous diffusion. Three layer tablets displayed n values $0.89 < n < 1$ indicating a zero order release.

CONCLUSIONS

It is evident that all preparations exhibited sustained release delivery. Moreover, it was demonstrated that the composition of the mixture may influence and modulate the drug release and the rate of release from the matrices used. It is also apparent that the properties of materials (particularly erosion) contained in the matrix affect considerably the release mode. Similarly, modulation of drug release also achieved in the three layer tablets and was influenced by the polymer properties and the drug release behavior of the system. The polymeric barriers modified (depending on the material's properties) the dissolution of the drug molecules by controlling the penetration of the surrounded dissolution

Table 4. Kinetic Parameters of Diclofenac Sodium Tablets Using Zero-Order Model.

Tablets	Total Release 0 - 480 Min			Initial Release 0 - 180 Min			Terminal Release 240 - 480 Min			k_2/k_1
	$k(\text{min}^{-1})$	\pm S.D.	r^2	$k_1(\text{min}^{-1})$	\pm S.D.	r^2	$k_2(\text{min}^{-1})$	\pm S.D.	r^2	
3MDG	0.1011	0.0005	0.957	0.0334	0.0047	0.989	0.1442	0.0004	0.995	4.31
3PDG	0.1282	0.0006	0.946	0.0452	0.0009	0.982	0.1913	0.0003	0.996	4.23

medium altering thus the diffusion path. It is therefore up to the formulator to select which dosage forms cover better the required specifications. Gantrez formulations displayed faster release due to its less swelling and greater erosion. Moreover, Metolose formulations displayed an increased release compared to the corresponding Polyox formulations. Overall, it appears that tablet structure and the properties of the materials containing in the dosage forms used considerably influence drug release, release rates and mechanism of release. In addition, due to their bimodal release mode, 3MDG and 3PDG, seem appropriate for the treatment of symptoms exhibiting circadian rhythms.

ACKNOWLEDGEMENT

This investigation was partially supported by a grand from University of Athens

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