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**ORIGINAL ARTICLE**

# Two- and three-layer tablet drug delivery systems for oral sustained release of soluble and poorly soluble drugs

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**Abstract**

*Background*: Multilayer tablets are gaining importance in oral sustained drug delivery. They consist of an active matrix core and one or more layers applied during tableting which may act as barriers and regulate drug release. *Objective*: To examine the release performance of two model drugs, diclofenac sodium and furosemide, from two- and three-layer drug delivery systems using as carriers hydrophilic swellable polymers, namely, Metolose, Polyox, Xantham gum, and an erodible material Gantrez. *Results and discussion*: All prepared formulations demonstrated sustained release profiles. They also indicated that the carrier characteristics (particularly swelling-expansion, erosion-dissolution) and drug solubility in combination with tablet structure considerably influenced the performance of examined formulations as well as their mode and mechanisms of release. In general our findings show that the differences in drug release between the two- and three-layer tablets are small as it appears that two-layer tablets exhibit a slightly higher release. Because of its greater erosion Gantrez formulations displayed faster release relative to Xantham gum, as did Metolose formulations compared to Polyox formulations. A faster release rate was also noted with diclofenac formulations compared to those of furosemide because of diclofenac's higher solubility mainly seen at early time period. *Conclusions*: All three-layer Gantrez tablets containing either diclofenac or furosemide and the two-layer furosemide formulation demonstrated a biphasic release. The above indicate that both structures may be used successfully for sustained release drug delivery. In addition the use of multilayer tablets, consisting of materials with suitable properties, may result in modulation of drug release.

**Key words:** *Diclofenac; furosemide; polymers; release kinetics; sustained release; two- and three-layer tablets*

## Introduction

Different types of oral controlled release solid formulations such as matrix tablets[1] and capsules[2,3] have been developed to improve treatment and clinical efficiency. Recently multilayer tablets feature more frequently in the design of oral sustained drug delivery systems[4,5]. These systems consist of an active matrix core and one or more barriers applied during tabletting. The barriers delay the interaction of the core with the dissolution medium by reducing the surface available for drug release and thus limiting liquid penetration. These formulations are designed to deliver the drugs at a sustained and predetermined rate, thus maintaining their therapeutically effective concentrations in the systemic circulation for prolonged periods of time. Depending on material characteristics these systems may swell, gel, erode, and finally dissolve in the gastrointestinal tract. The control of overall release is primarily determined by the composition of each layer. Multilayer systems permit the production of various tablet structures possessing different release properties that result in 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 delayed release[6]. Most published articles have focused on the three-layer tablet system and only a limited number is on two-layer tablets[7,8].

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The basic ingredients, carriers of these systems, are the polymers. A variety of polymers are employed because their nature and characteristics may play a key role and significantly influence the behavior of these devices[9]. 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. To be more specific the effect is because of polymer molecular properties, such as the nature of the monomer, type, and degree of substitution and whether the polymer is mixed dry or dissolved.

The release of a drug from a delivery system differs depending on the type of polymer used, but the dissolution of the active compound is always a prior and necessary step of the release process. Inert polymer matrices consist of materials, which encompass the drug within the matrix. Drug release depends on successive dissolution and diffusion once the dissolution medium penetrates the matrix. Upon contact with the dissolution medium the swelling polymer matrix forms an outer gel layer during the hydration process. The entrapped drug dissolves and diffuses through the swollen network, which eventually undergoes erosion[10–13]. In this study multilayer tablets, two and three layers, were developed and evaluated, (Figure 1).

The aim of this study was to investigate the effect of (a) the structure of the system and (b) polymeric materials on the drug release rate and finally to (c) compare and evaluate the performance of the systems prepared and examined in this investigation. Polymeric materials of different nature and properties were employed as ingredients, carriers, to investigate how polymer characteristics may influence drug release from these systems. To thoroughly investigate and evaluate the behavior of these systems, a poor water-soluble drug (furosemide), a rather water-soluble drug (diclofenac sodium), three hydrophilic swellable polymers [hydroxylpropylmethyl cellulose (HPMC), polyethylene oxide (PEO), and xanthan gum (XG)], and an erodible material poly(methyl vinyl ether/maleic anhydride) (PMMA) were employed in this study.

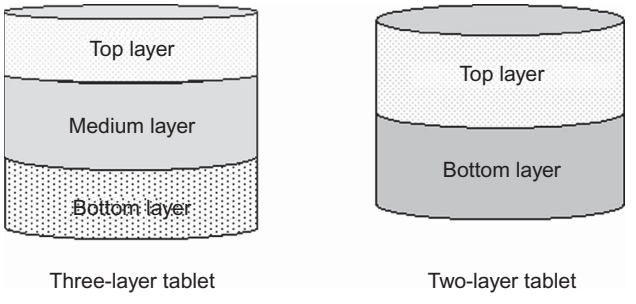


**Figure 1.** Schematic drawing of the two- and three-layer tablet systems.

## Materials and methods

### *Materials*

The following chemicals were obtained from commercial suppliers and used as received: diclofenac sodium (Sigma Chemical Co., St. Louis, MO, USA), furosemide (Hoechst, Frankfurt, Germany), HPMC (Shin-Etsu, Tokyo, Japan) [Metolose 90, SH.100.000 SR] (MW = 230,000), PEO (Union Carbide, Danbury, CT, USA) [Polyox NF, MW = 7 $\times$ $10^6$], XG (Aldrich) (MW = in the area of 2 $\times$ $10^6$), PMMA (ISP, GAF Chemicals, NJ, USA) [Gantrez AN-169 BF] (MW = 67,000), and magnesium stearate (BDH, Dorset, UK) was used as lubricants.

### *Tablet preparation*

The drug and the other excipients were mixed thoroughly in a Turbula-T2C mixer (Willy A. Bachofen AG, Basel, Switzerland) for 10 minutes. Tablets of 200 mg mass were compressed using 10-mm diameter flat-faced punches in a Carver laboratory hydraulic press (Fred S. Carver, Inc., Wabash, IN, USA) to a crushing strength 9–10 kg, measured in the Erweka hardness tester (Erweka, Heusenstamm, Germany). Similarly drug-free polymer matrix tablets (from each polymer alone) of 200 mg weight, 10 mm diameter, and crushing strength of 8–10 kg were prepared for swelling and erosion experiments.

Two- and three-layer tablets were prepared by directly compressing procedure. The die was accurately and progressively filled with weighed amounts of the different mixtures. Two-layer tablets (200 mg) were prepared by a procedure involving two consecutive steps. The first layer (100 mg) was placed in the bottom of the die and compressed at approximately 100 kg; the second layer (100 mg) was then added and compressed at approximately 500 kg.

Similarly, to prepare three-layer tablets (200 mg) the die was accurately and progressively filled with weighed amounts of different mixtures, that is, top layer, middle layer, and bottom layer. First, the bottom layer (50 mg) was placed in the bottom of the die and compressed at approximately 100 kg, the middle layer (100 mg) was then added and compressed at 100 kg followed finally by the top layer (50 mg), which was added and compressed at 500 kg (Figure 1). The two- and three-layer formulations and their compositions are listed in Tables 1 and 2, respectively.

### *In vitro drug release studies*

Tablets were subjected to the dissolution study at 37 $\pm$ 0.5°C with 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).

**Table 1.** Formulation compositions of three-layer tablets containing the drug in all layers (in mg).

| | | Ingredients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tablets | | Diclofenac sodium | Furosemide | Metolose (HPMC) | Xantham gum (XG) | Polyox (PEO) | Gantrez (PMMA) | Mg St | $t_{120\,min}$ | $t_{240\,min}$ | DE |
| 3PGD | TL | 24.75 | | | | | 24.75 | 0.5 | 32.0 | 62.0 | 53.0 |
| | ML | 49.50 | | | | 49.50 | | 1 | | | |
| | BL | 24.75 | | | | | 24.75 | 0.5 | | | |
| 3MGD | TL | 24.75 | | | | | 24.75 | 0.5 | 31.0 | 58.0 | 51.0 |
| | ML | 49.50 | | 49.50 | | | | 1 | | | |
| | BL | 24.75 | | | | | 24.75 | 0.5 | | | |
| 3PXD | TL | 24.75 | | | 24.75 | | | 0.5 | 24.0 | 48.0 | 45.5 |
| | ML | 49.50 | | | | 49.50 | | 1 | | | |
| | BL | 24.75 | | | 24.75 | | | 0.5 | | | |
| 3MXD | TL | 24.75 | | | 24.75 | | | 0.5 | 21.0 | 38.0 | 35.5 |
| | ML | 49.50 | | 49.50 | | | | 1 | | | |
| | BL | 24.75 | | | 24.75 | | | 0.5 | | | |
| 3PGF | TL | | 24.75 | | | | 24.75 | 0.5 | 11.5 | 26.0 | 32.5 |
| | ML | | 49.50 | | | 49.50 | | 1 | | | |
| | BL | | 24.75 | | | | 24.75 | 0.5 | | | |
| 3MGF | TL | | 24.75 | | | | 24.75 | 0.5 | 11.0 | 26.0 | 30.0 |
| | ML | | 49.50 | 49.50 | | | | 1 | | | |
| | BL | | 24.75 | | | | 24.75 | 0.5 | | | |
| 3PXF | TL | | 24.75 | | 24.75 | | | 0.5 | 16.0 | 27.0 | 26.0 |
| | ML | | 49.50 | | | 49.50 | | 1 | | | |
| | BL | | 24.75 | | 24.75 | | | 0.5 | | | |
| 3MXF | TL | | 24.75 | | 24.75 | | | 0.5 | 17.0 | 25.5 | 23.0 |
| | ML | | 49.50 | 49.50 | | | | 1 | | | |
| | BL | | 24.75 | | 24.75 | | | 0.5 | | | |

TL, top layer; ML, medium layer; BL, bottom layer; Mg St, Magnesium stearate.

**Table 2.** Formulation compositions of two-layer tablets containing the drug in both layers (in mg).

| | | Ingredients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tablets | | Diclofenac sodium | Furosemide | Metolose (HPMC) | Xantham gum (XG) | Polyox (PEO) | Gantrez (PMMA) | Mg St | $t_{120\,min}$ | $t_{240\,min}$ | DE |
| 2PGD | TL | 49.50 | | | | 49.50 | | 1 | 28.0 | 56.0 | 55.0 |
| | BL | 49.50 | | | | | 49.50 | 1 | | | |
| 2MGD | TL | 49.50 | | 49.50 | | | | 1 | 28.0 | 52.0 | 52.0 |
| | BL | 49.50 | | | | | 49.50 | 1 | | | |
| 2PXD | TL | 49.50 | | | | 49.50 | | 1 | 24.0 | 44.0 | 42.0 |
| | BL | 49.50 | | | 49.50 | | | 1 | | | |
| 2MXD | TL | 49.50 | | 49.50 | | | | 1 | 28.0 | 36.0 | 38.0 |
| | BL | 49.50 | | | 49.50 | | | 1 | | | |
| 2PGF | TL | | 49.50 | | | 49.50 | | 1 | 15.0 | 31.0 | 36.0 |
| | BL | | 49.50 | | | | 49.50 | 1 | | | |
| 2MGF | TL | | 49.50 | 49.50 | | | | 1 | 15.0 | 32.0 | 34.0 |
| | BL | | 49.50 | | | | 49.50 | 1 | | | |
| 2PXF | TL | | 49.50 | | | 49.50 | | 1 | 15.5 | 26.0 | 28.0 |
| | BL | | 49.50 | | 49.50 | | | 1 | | | |
| 2MXF | TL | | 49.50 | 49.50 | | | | 1 | 15.0 | 24.0 | 25.0 |
| | BL | | 49.50 | | 49.50 | | | 1 | | | |

TL, top layer; BL, bottom layer; Mg St, Magnesium stearate.

Samples (5 mL) were withdrawn at predetermined time intervals, filtered, and analyzed at $\lambda_{max}$ = 276 nm for sodium diclofenac and furosemide 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.

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

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

where $y$ is the percentage of dissolved product and DE is the area under the dissolution curve between time points $t_1$ and $t_2$ expressed as a percentage of the curve at maximum dissolution $y_{100}$ over the same time period. When a relationship is to be shown between dissolution and another variable, it is considered more realistic to use DE, which takes into account the dissolution profile as a whole[14]. In addition, where a quantitative comparison is required, DE is a more suitable parameter, and when limits are set on DE it can be used for quality control in place of the conventional dissolution level.

### *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-shaped 'tent' formed by a preweighted $4 \times 4$ 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 Sartrorius analytical balance. Then the wetted tablets were dried in an oven at 105°C for a 24-hour period, 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

$$E\% = \frac{(W_i - W_f)}{W_i} \times 100, \tag{2}$$

where $W_i$ and $W_f$ are the initial starting dry weight and final dry weight of the same dried and partially eroded tablet, respectively. Also, the increase in weight (water uptake) because of absorbed liquid ($A$) was calculated at each time point by

$$A\% = \frac{(W_w - W_f)}{W_f} \times 100, \tag{3}$$

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, Yokosuka, Japan) fitted with a zoom lens (Century Precision Optics AD-5870, Burbank, CA, USA) and connected to a monitor. The light system 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 with stirring at 100 rpm to allow one to observe changes in the device. The beaker was removed, at predetermined time intervals, from the dissolution apparatus and was transferred into the optical image setup. 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 tablet expansion. Results reported are averages for three different tablets.

### *Statistical analysis*

Results are given as mean ± SD. The DE values were analyzed using student's $t$-test ($P < 0.01$).

## Results and discussion

Polymeric materials commonly used in controlled delivery systems include hydrophobic, insoluble, erodible, or hydrophilic swellable polymers. In our study, the materials used were hydrophilic, swellable polymers, such as HPMC, PEO, XG, and an erodible material PMMA. As model drugs were used the poorly soluble furosemide and the rather soluble diclofenac sodium with solubilities of 8.9 and 18.79 mg/mL, respectively (in aqueous phosphate buffer pH 7.4), were used[15] as it is apparent that furosemide has half the solubility of diclofenac sodium. The structures of the prepared tablets are shown in Figure 1, and they represent the forms of the sustained release delivery systems developed and examined in this investigation. These tablets consisted of two or three layers and had at least one of their surfaces covered. In the next sections we will attempt to examine and evaluate their performance, release behavior, and consider how these are affected by the tablet's structure and composition.

### *Swelling and erosion studies of drug-free tablets*

From Tables 1 and 2 it is clear that tablet layers consist of different polymers. As previously mentioned these materials possess different characteristics that could influence their performance. Two important characteristics of the polymers employed, that is, their liquid uptake (swelling) and loss of weight (erosion), were thoroughly evaluated so as to allow us to determine whether these properties are interrelated and to what extent, with each formulation's behavior and how they influence the system's function and performance. For these studies drug-free polymer tablets of 200 mg weight, 10 mm diameter, and crushing strength of 8–10 kg were utilized. The results of the swelling studies are illustrated in Figure 2a, and they indicate the rates at which these tablets absorb water and swell. The changes in weight represent water uptake and maximum swelling.

Visual observations showed that the tablets appeared swollen almost from the beginning and a viscous gel mass was created when they came in contact with the liquid, with the exception of the PMMA tablets in which gel layer development appeared negligible. The swelling rate of the polymers increased with time, and the maximum was measured at 8 hours with the exception of the PMMA, which showed a gradual increase up to 4 hours (maximum swelling) and then started to decrease. From Figure 2a, it is apparent that XG demonstrated the fastest and greatest swelling (1700%) followed by PEO (900%), HPMC (550%), and lastly PMMA (380%).

Erosion results expressed here as loss of weight are shown in Figure 2b and reflect the amount of polymer dissolved. The greatest erosion was observed with the PMMA tablets followed by XG, PEO, and HPMC.

PMMA and XG displayed rapid erosion particularly after 3 and 4 hours, respectively. The former initially (up to 3 hours) exhibited a low erosion, then its erosion increased drastically, and it was completely eroded in 8 hours, whereas the latter eroded approximately 75% within this time.

PEO and HPMC tablets displayed a slower and progressive weight loss with time and their erosion appeared lower because only 35% and 12% eroded in 8 hours, a development that was also confirmed visually. It is noteworthy that although the degree of liquid uptake of XG is almost five times that of PMMA, its rate of erosion is lower than that of PMMA. This indicates that the gel formed with XG tablets is more durable.

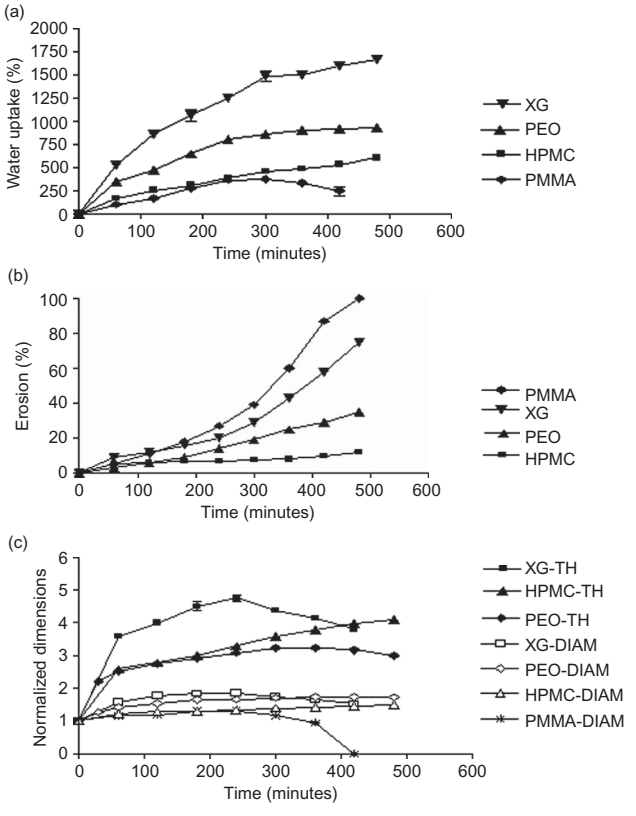


**Figure 2.** (a) Percentage of weight change (uptake/swelling) from drug-free tablets as a function of time for PMMA, XG, PEO, and HPMC; (b) Percentage of weight loss (erosion) from drug-free tablets for PMMA, XG, PEO, and HPMC; and (c) Normalized axial (TH) and radial (DIAM) dimensional changes for drug-free polymer tablets. Each point represents the mean value of the three samples and error bars show ± SD.

### *Radial/axial dimensional changes of drug-free tablets*

Figure 2c illustrates the normalized radial (diametrical) and axial (thickness) expansion of the pure polymer tablets. A fast initial expansion (particularly in axial direction) is observed in all cases followed by a decrease after 4 hours with the XG and 3 hours with the PMMA tablets. The axial expansion of PMMA is not illustrated because substantial deformation in the early stages did not allow us to record its changes. XG tablets demonstrated a maximum increase in thickness, 4.8-fold, between 180 and 240 minutes, followed by a rather fast decrease, which accelerated at $t > 240$ minutes. Unfortunately after 420 minutes, because of substantial deformation further recordings were not taken. HPMC tablets exhibit a fourfold increase in thickness, and the maximum value was observed at 480 minutes. Finally PEO tablets exhibited the lowest expansion, 3.3-fold, with a maximum recorded at 300 minutes followed by a small decrease in size.

Similarly, with respect to radial expansion, the diameter of the tablets increased by 1.8-, 1.45-, 1.75-, and 1.3-fold for XG, HPMC, PEO, and PMMA, respectively, clearly revealing a greater axial expansion in accordance with earlier findings[16]. It is notable that the diameter of

the PMMA tablets became smaller than the initial diameter after 300 minutes.

Moreover, PEO tablets exhibited mainly axial erosion after 300 minutes (Figure 2c), because after this time their thickness decreased whereas their diameter remained rather stable. XG tablets exhibited erosion both radially and axially after 240 minutes, whereas HPMC tablets displayed an increase in both dimensions during the time period of the experiment, which indicates that its swelling is higher than its erosion.

### *Swelling and erosion studies of multilayer tablets*

The results of swelling studies for the two- and three-layer tablets are shown in Figure 3. As mentioned earlier the change in weight represents water uptake and maximum swelling. Optical examination revealed that all tablets (particularly XG) were swollen almost from the beginning and a gel mass was formed when they came in contact with the liquid.

Diclofenac sodium tablets demonstrated higher swelling compared with furosemide. Also we did not detect considerable differences between diclofenac two- and three-layer tablets, whereas a few differences were observed among the equivalent furosemide formulations.

Three-layer tablets consisting of PEO–PMMA and PEO–XG showed the greatest swelling, whereas tablets consisting of HPMC–PMMA displayed the lowest. It was also noted that the tablets containing PEO in the middle layer exhibited a greater liquid uptake than the corresponding HPMC tablets. With the two-layer tablets the greatest swelling was observed with the PEO–XG formulations for both drugs whereas the lowest, once more, was that of the HPMC–PMMA formulations.

The erosion results are shown in Figure 4, and they are rather similar for the two- and three-layer tablets of both drugs. PMMA tablets demonstrated a greater erosion >80% (after 8 hours) than the XG formulations that displayed erosion <60% for the same time (with the exception of 3PXD). Formulations containing HPMC displayed lower erosion than the equivalent PEO preparations. These changes coincide with earlier erosion findings (section 'Swelling and erosion studies of drug-free tablets', Figure 2b). Finally diclofenac formulations containing XG displayed greater erosion than that of

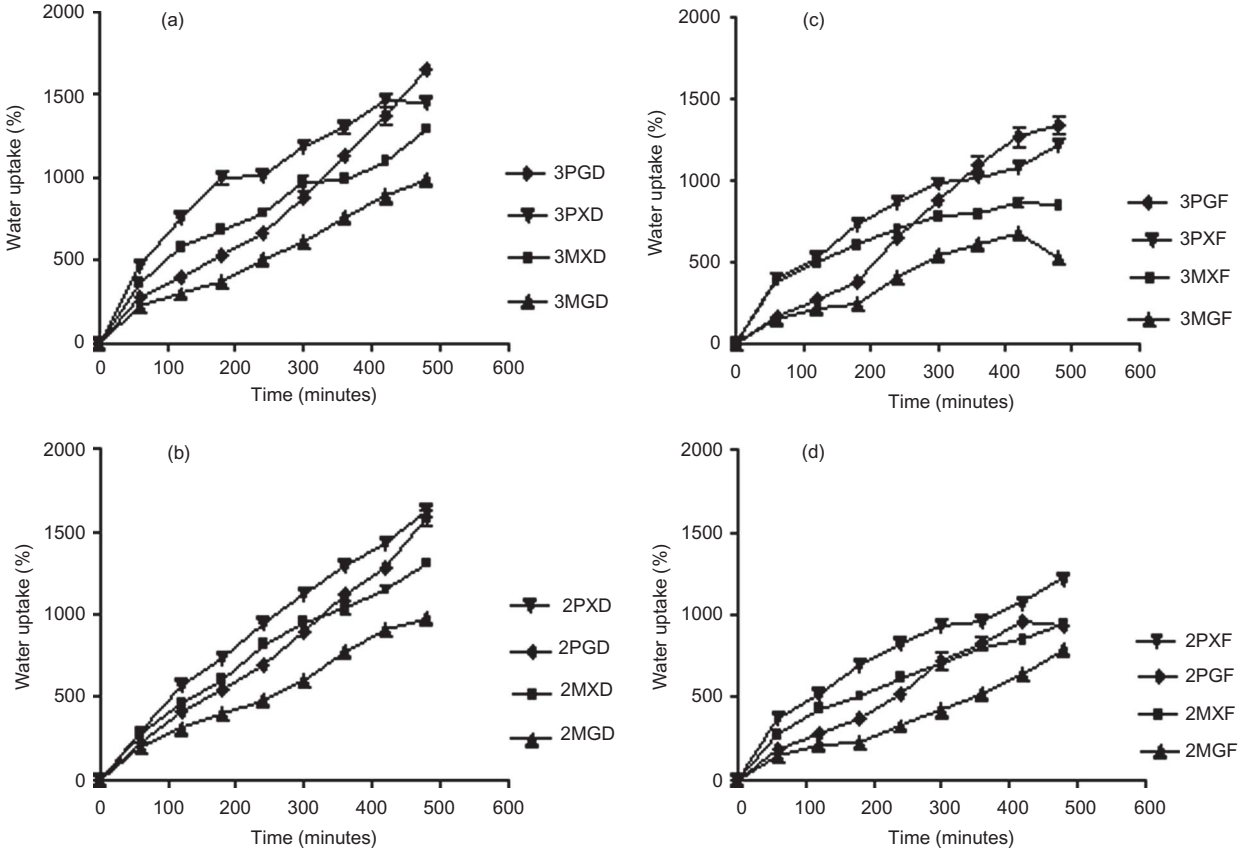


**Figure 3.** Percentage of weight change (uptake/swelling) as a function of time in phosphate buffer for diclofenac (a) three- and (b) two-layer tablets and for furosemide (c) three- and (d) two-layer tablets. Each point represents the mean value of the three samples and error bars show ±SD.

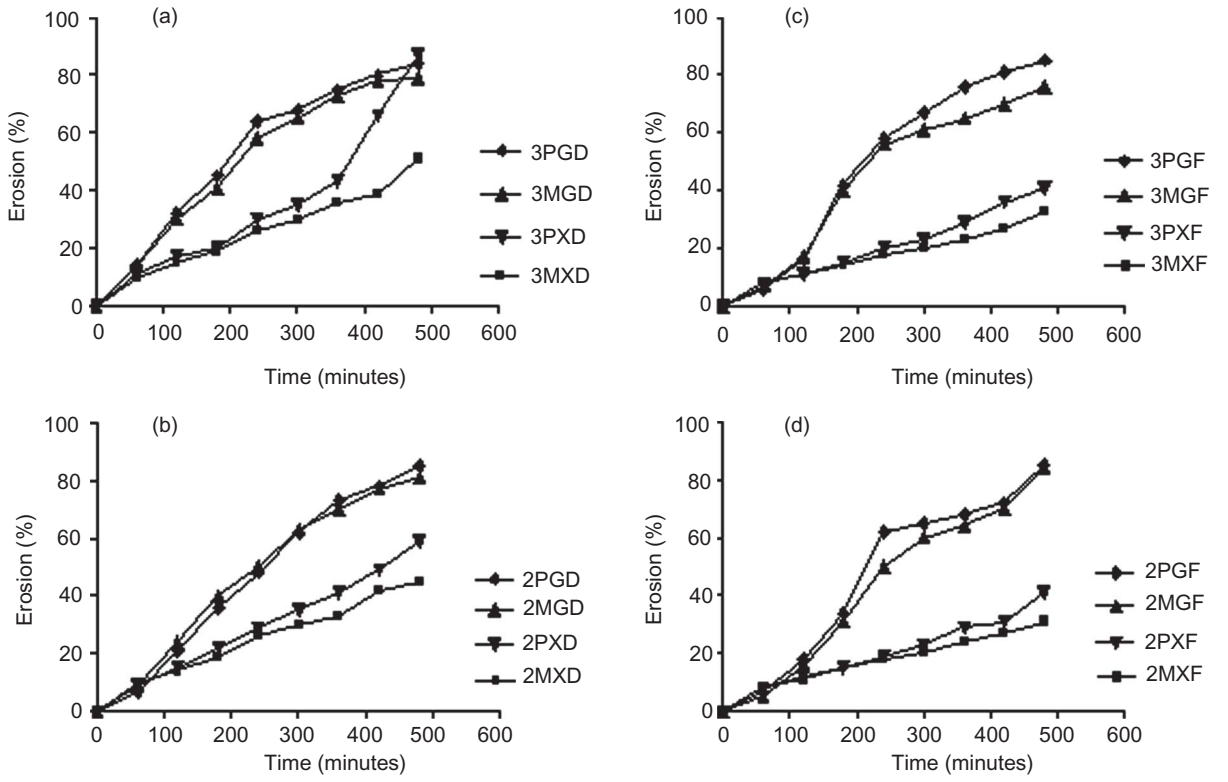


**Figure 4.** Percentage of weight loss (erosion) dried after exposure to phosphate buffer for diclofenac (a) three- and (b) two-layer tablets and for furosemide (c) three- and (d) two-layer tablets. Each point represents the mean value of the three samples and error bars show ±SD.

furosemide formulations whereas the erosion of the PMMA preparations was comparable.

### *Tablet morphological changes*

In Figure 5 typical images of diclofenac tablets undergoing hydration-swelling and the changes in their morphology after 60, 120, and 300 minutes are illustrated as example. Analogous changes were observed with the furosemide tablets (not shown). In these photographs the recorded time intervals were chosen to reveal some of the major changes that occur during the dissolution process. When the tablets come into contact with the liquid, all underwent fast hydration because of rapid liquid penetration and the swelled-expanded layers merged creating a rather solid polymer mass.

As can be observed, in Figure 5a, the external layers (of three-layer tablets) consisting of XG displayed greater swelling than the equivalent PMMA external layers resulting in greater overall (axial and radial) expansion. This was because of the different axial and radial expansion of the polymers (section 'Radial/axial dimensional changes of drug-free tablets'). It was also noted that the XG tablets formed a 'dumb-bell' shape. Furthermore PEO tablets became larger (predominantly to radial direction) than the equivalent HPMC tablets. Visual observations indicated that PMMA layers eroded rather rapidly after 3 hours. A comparable swelling-expansion was observed with two-layer tablets as well; however, the different swelling and enlargement of the XG and PMMA layers are clearly illustrated in Figure 5b.

These developments can obstruct the transport of drug molecules through the polymer mass and consequently influence drug release. The characteristics of the contained polymeric materials, namely, swelling, entanglement or disentanglement of polymer chains, and erosion, clearly influence the behavior of the system.

### *Device structure and drug release*

Drug release from the matrix system may be characterized as a mass transport phenomenon and usually involves three different steps. Liquid penetration into the matrix is the first step followed by dissolution of the drug and finally its diffusion. However, drug release from multipart preparations and particularly multilayer systems appears more complicated as the movement of drug molecules is considerably affected by the structure of the system and the existing barriers.

In Figures 6 and 7, the release profiles of diclofenac and furosemide are illustrated. As seen from the results the extent of drug release varies among the formulations and

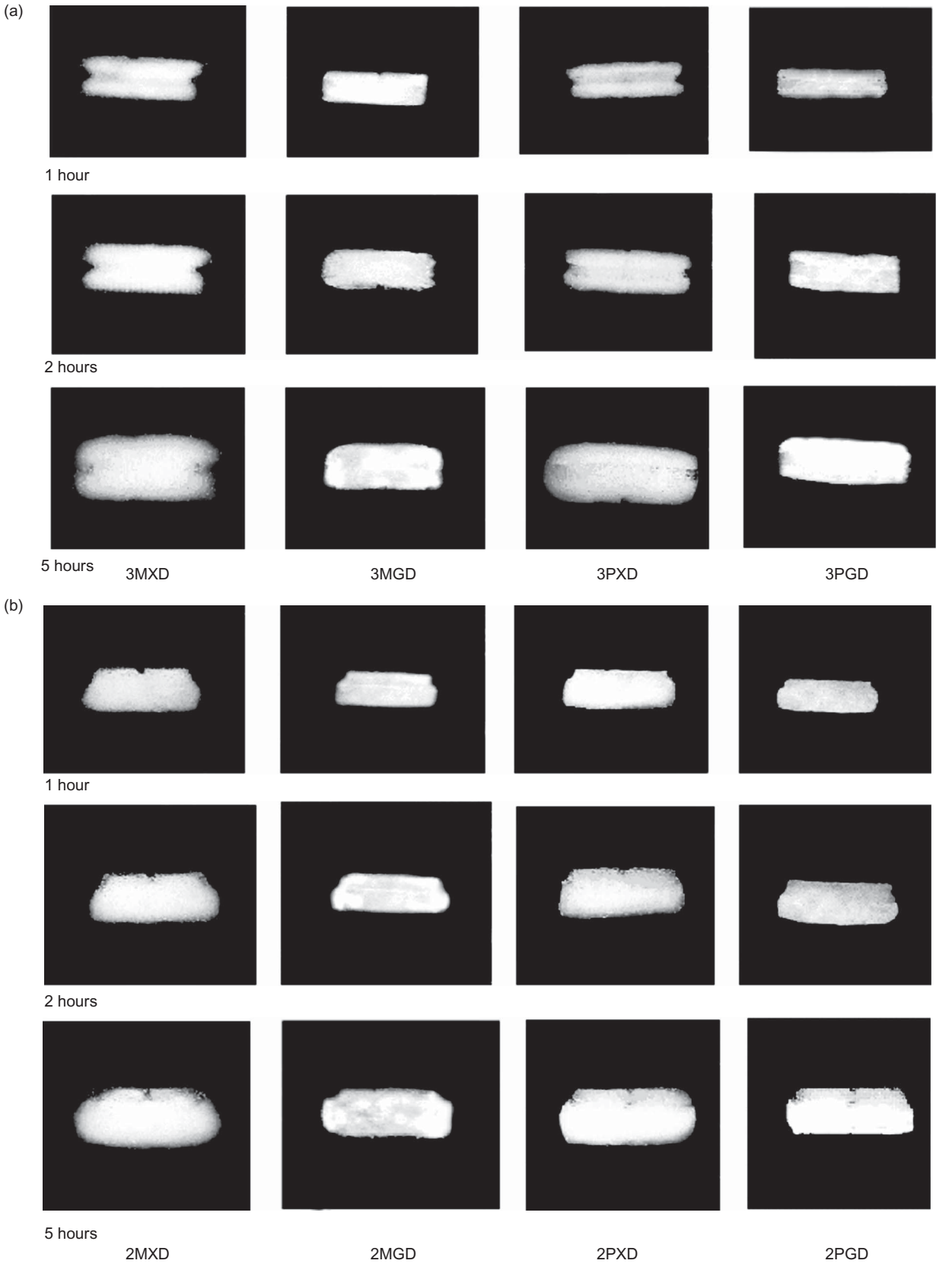


**Figure 5.** Morphological changes of the systems during dissolution after 1, 2, and 5 hours: (a) three- and (b) two-layer tablets.

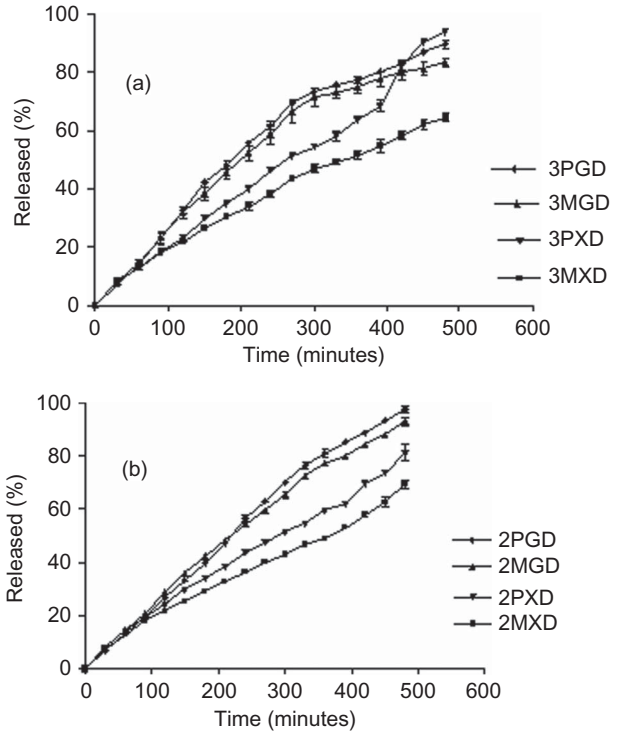


**Figure 6.** Release profiles of the diclofenac (a) three- and (b) two-layer formulations. Each point represents the mean value of the three samples and error bars show ±SD.

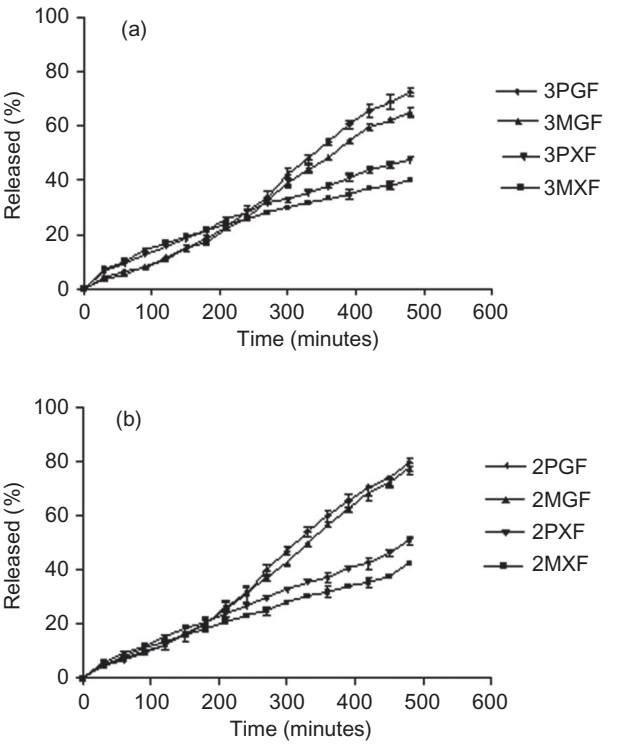


**Figure 7.** Release profiles of the furosemide (a) three- and (b) two-layer formulations. Each point represents the mean value of the three samples and error bars show ±SD.

is affected by the structure of the tablet and the properties of the contained materials. In all the cases the overall release and the release rate of diclofenac is higher than that of furosemide as clearly demonstrated by the $t$ and DE values (Tables 1 and 2).

From these findings it is evident that the solubility of the drug influences its release and release rate considerably. The diclofenac-loaded tablets demonstrated in most cases a 1.5- to 1.8-fold increase in the release compared with equivalent furosemide preparations and also higher release rates particularly at the early time period up to 4 hours as can be seen from their $t_{120}$ and $t_{240}$ values (Tables 1 and 2). In addition the overall drug release from two- and three-layer tablets differed only to a small extent as the two-layer formulations displayed a slightly greater total release, and this can be observed from the DE values (Tables 1 and 2) with the exception of 3PXD. This may be because the same quantity of the drug is embedded in two instead of three layers. Thus, in the latter system drug molecules have to overcome one more polymer barrier that obstructs their movement and also requires the drug to travel a longer distance to diffuse out. A similar tendency (involving two- and three-layer tablets) was shown in earlier studies[17,18] although in cases where the barrier layers were drug-free.

It is noteworthy that the presence of different excipients, contained in the tablets layers, resulted in considerable variations in the release rates of various formulations. The results show that in all the cases the presence of PMMA results in an increase in drug release while in contrast the presence of XG (with one exemption) appears to decrease the release (Tables 1 and 2).

To explain and evaluate these findings we considered it necessary to explore the factors that created the differences among the various formulations prepared and evaluated in our study. The differences may be attributed to a number of factors that we will attempt to discuss below.

In three-layer tablets the external layers usually act as barriers because typically they consist of pure polymer[6,9,17], and as a result they hinder drug dissolution and release. However, in our case these layers contained a quarter of the total drug quantity (i.e., 24.75 mg) to allow early drug release and consequently an earlier pharmacological effect. Thus, initially the layers act partly as barriers but as soon as they are sufficiently hydrated the embedded drug begins to dissolve and diffuse out in a delayed release mode.

Simultaneously the middle layer starts to hydrate and a fraction of the drug begins to be released from that layer too, mainly from the lateral surface. As hydration progressed the layers swelled, merged, and formed

a solid polymer mass. An analogous procedure seemed to occur also in the two-layer tablets.

The progressive elimination of the external layer (PMMA formulations) facilitates the contact between the liquid and the remaining mass and improves its hydration. From the above, it is apparent that hydration and liquid penetration into the tablets is a prerequisite step of drug release. In both structures of tablets it appears that drug release and the release rate are dependent on material properties, that is, swelling and erosion.

Drug release, initially, involves continuous diffusion from the hydrated external area. As time passes the swelled layers merge and the apparent release from the formed polymer mass is affected by the entanglement or disentanglement of polymer chains, the changes in the available surface area, the diffusional pathway, and the erosion of the system.

In PMMA three-layer tablets, the hydration process of the two external layers occurred with limited swelling followed by rapid erosion resulting in a smaller polymer mass and therefore a shorter diffusion path. This is primarily attributed to the high and rapid (after 3 hours, Figure 2b) erosion–dissolution of PMMA (Figure 4a and c), as it is the most erodible and less-swellable material followed by XG, PEO, and finally HPMC (Figure 2a and b). After the erosion of PMMA the drug continues to be released from the remaining solid mass consisting mainly of PEO or HPMC (Figure 5a). On the other hand the equivalent XG tablets exhibited increased swelling and less erosion, thus a larger solid mass, resulting in a longer diffusion path. Therefore, the drug molecules had to travel over a longer distance to reach the bulk solution, and the release of the drug from XG formulations was less than that of the PMMA formulations with the exception of 3PXD. Similar developments were noticed in the two-layer tablets as illustrated in Figure 5b.

From the DE values in Tables 1 and 2 and release profiles in Figures 6a and 7a it is evident that the three-layer tablets containing in their external layers either diclofenac or furosemide and PMMA exhibited greater release than the equivalent tablets containing XG. The composition of the middle layer also influences the release profile although to a lesser extent. More specifically tablets containing PEO in the middle layer demonstrated increased release than HPMC tablets, probably because of a higher erosion of the former. Similar results were reported in earlier studies[19]. A complete understanding of the release procedure and mechanisms involved is not easy as the process is complicated and is dependent not only on tablet structure and morphological changes (expansion) but also on polymer characteristics.

Diclofenac tablets containing PMMA (3PGD and 3MGD) (Figure 6a) displayed an identical release rate up to 120 minutes, then the PEO formulation, 3PGD, demonstrated a small increase in its release rate until completion. Similarly, XG formulations (3PXD and 3MXD) displayed equivalent release rates up to 120 minutes. Up to 400 minutes a notable difference of the release rate was observed for 3PXD. After that time an unexpected second rapid increase in rate was displayed until the end. This surprising and massive release is most likely because of an intense cracking and detachment of particles from the surface of the tablet (visual observation) and its subsequent disintegration and quick erosion after 400 minutes. Furosemide formulations demonstrated comparable results. The release rates appeared rather similar up to 240 minutes, afterward PMMA formulations exhibited higher release compared with XG. Once more the PEO formulations displayed greater release rates than these of HPMC formulations.

Moreover, all three-layer PMMA tablets containing either diclofenac or furosemide demonstrated a biphasic release. Notably, another important differentiation in the release behavior, of the two drugs, was revealed. Furosemide formulations exhibited a slow initial phase (0–210 minutes) followed by a fast phase (240–480 minutes), whereas diclofenac formulations exhibited the opposite phenomenon, that is, a fast initial phase (0–280 minutes) was followed by a slow one (300–480 minutes). This development may be attributed to the higher solubility of diclofenac particles and the development of increased osmotic pressure, which facilitates the rapid penetration of an increased amount of liquid into the tablet and the rapid creation of channels that assist increased dissolution. In contrast furosemide particles remained undissolved for a longer time obstructing liquid infiltration.

As pointed out above the release profiles from the two-layer tablets (Figures 6b and 7b) demonstrated a similar release behavior to that of the three-layer tablets. Diclofenac tablets displayed a higher release than the equivalent furosemide formulations and once more the PMMA tablets exhibited a greater release than the XG tablets as DE values indicated (Table 2). Similarly PEO formulations showed a higher release than the equivalent HPMC formulations. Once again the presence of PMMA results in a faster erosion (Figure 5b) and drug release. Among the two-layer tablets only furosemide–PMMA formulations 2MGF and 2PGF demonstrated biphasic release, a slow initial phase (0–210 minutes) followed by a fast phase (240–480 minutes).

Figures 4a, c, 6a, and 7a clearly illustrate that in three-layer tablets erosion plays a crucial role. The erosion data match with the equivalent release data. Erosion sharply increased after 180 minutes (Figure 4a and c) and as a consequence the release increased after 210–240 minutes. These developments are more pronounced in

the PMMA formulations. Their erosion shortens the travel distance of dissolved drug molecules from the dissolution front to the surrounding medium and this coincides with drug release, thus the operating mechanism could be mainly attributed to erosion/dissolution.

The phenomenon is more dominant in the last stages where erosion of the polymer mass becomes more intense. This is more apparent in the case of formulations containing XG where the lower erosion rate, compared with PMMA, was reflected in the lower drug release rate with the exception of 3PXD. This formulation showed exceptional erosion and drug release (Figures 4a and 6a).

Analogous erosion results were observed in two-layer tablets as well (Figure 4b and d). Once more PMMA tablets displayed a greater but expected release (Figures 6b and 7b) relative to the above-mentioned results. Furosemide formulations demonstrated sharp erosion after 180 minutes (Figure 4c and d), and as a consequence their release increased rapidly after 210–240 minutes (Figure 7b). On the other hand diclofenac formulations exhibited a more progressive erosion and release as seen in Figures 4b and 6b.

In PMMA three-layer tablets the external layers after the initial hydration began to erode and their thickness decreased as time passed, and consequently the drug continued to be released from the formed solid mass, that is, the remaining PMMA layer and the middle layer of PEO or HPMC. In contrast XG external layers swelled considerably, merged with the middle layer, and formed a swelled solid polymer mass. The swelling was greater and erosion, of the tablet, was less than that observed in the former; therefore drug release was smaller. A comparable procedure and changes were expected for the two-layer tablets.

The bar graphs in Figure 8 illustrate the release data from the preparations that did not exhibit bimodal release, presented as the drug release (percent dissolved per hour) versus time. The graph clearly shows that furosemide formulations displayed a fairly constant drug release rate, from both three- and two-layer tablets, which corresponds to about 5–7% per hour after the second hour (Figure 8a and b).

On the other hand diclofenac tablets displayed a different more complicated mode and an increased release rate compared to furosemide formulations. Thus, 3PXD tablets demonstrated an approximately 10% release per hour after the third hour until the end of the experiment, whereas 3MXD tablets also showed a 10% release rate from the second to fifth hour and for the remaining three hours the rate decreased to 5% per hour Figure 8c. In parallel the two-layer tablets presented a variable release rate and only 2MXD exhibited a fairly constant release rate in the region of 8% (Figure 8d). Finally, diclofenac three-layer tablets exhibited lower release rate compared with the analogous two-layer tablets.

With respect to the different solubility of the two drugs (furosemide has half the solubility of diclofenac sodium) it is apparent that this difference is not entirely

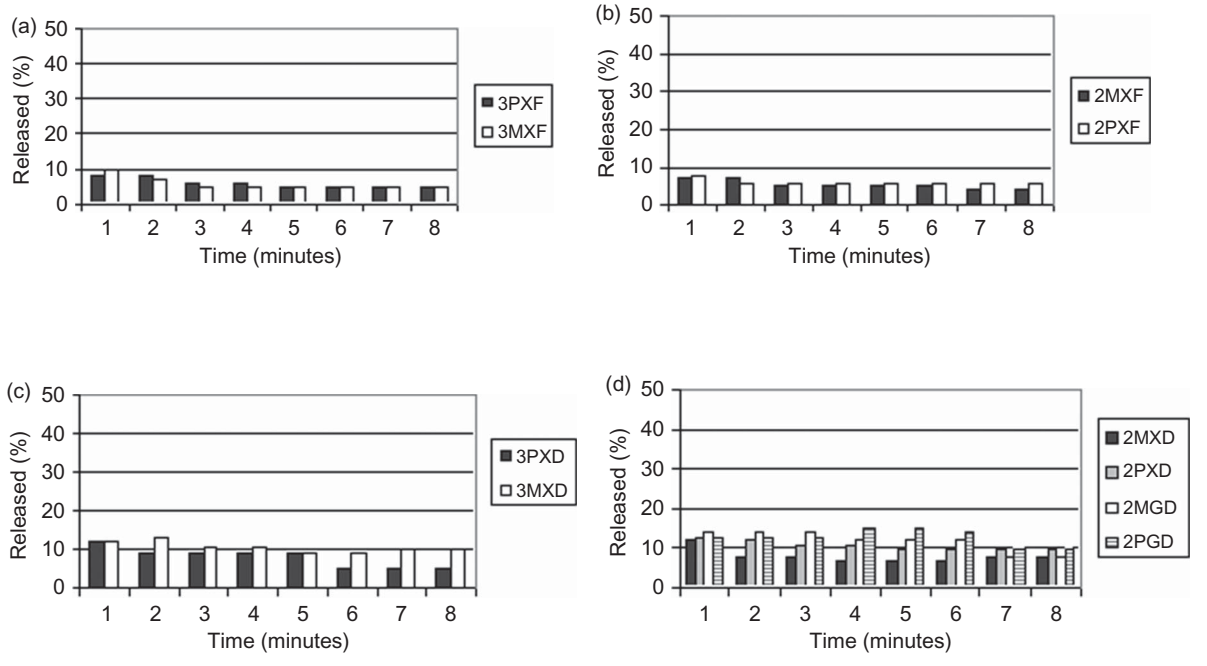


**Figure 8.** Rate of drug release (percentage of drug release per hour) as a function of time.

reflected in their release behavior or release rates. The total release from furosemide tablets is <25–30% of the corresponding release from diclofenac formulations. On the other hand their release rate per hour appeared rather comparable. It is noteworthy that in a recent study where HPMC was used as the only carrier the total release of furosemide from these matrices was almost half that of diclofenac[15].

The above results show that the differences in drug release between the two- and three-layer tablets are rather limited ($P < 0.05$). PMMA formulations displayed faster release because of its greater erosion relative to XG. Finally the release profiles (Figures 6 and 7) and DE values show that diclofenac formulations displayed a significantly higher ($P < 0.01$) release rate initially than furosemide formulations because of diclofenac's higher solubility[19,20].

### *Kinetics and mechanism of drug release*

From the above it is evident that the structure and the morphology of the tablet during dissolution do not influence the drug release and release rate to a significant extent. As seen above a biphasic release was demonstrated by a number of formulations and was also reported in earlier studies[21–24].

Bimodal release seemed to involve two phases. An initial gelation phase (where the gel layer expands because of water penetration) during which there was some initial erosion of the polymer and therefore an initial burst in drug release because of rapid dissolution. In the second phase, upon complete hydration of the polymer mass, disintegration of the gel occurred, which resulted in another increase in the rate of drug release. Similar results were reported by Shah et al.[22] and Munday[24]. This behavior was attributed either to erosion[23] or to separation of the layers[25].

In our study biphasic release is clearly associated with the presence and the properties of PMMA in respective formulations. All furosemide formulations with PMMA (Figure 7a and b) and diclofenac's three-layer tablets exhibited biphasic release (Figure 6a). Visual observations revealed that after hydration of the tablets and as the procedure advanced particles of the material were gradually removed from the PMMA layer. Subsequently the detached particles slowly dissolved and this process was continued until the layer was entirely eroded.

In Table 3 the release rate constants for each phase, using zero-order model, are listed.

The zero-order release can be represented by the following equation:

$$M = M_0 - k_0 t, \tag{4}$$

where $M$ is the amount of drug remaining undissolved at time $t$, $M_0$ is the initial amount of drug in the pharmaceutical dosage form, and $k$ is the release rate constant. Judging by the correlation coefficients following regression analysis, both the initial and the terminal release phases exhibit a zero-order-type release kinetics.

To elucidate the mechanism of drug release the data were further analyzed using the familiar equation proposed by Korsmeyer and Peppas[26].

$$\frac{M_t}{M_\infty} = kt^n, \tag{5}$$

where $M_t$ is the amount of the drug released at time $t$, $M_\infty$ is the amount of drug released over a very long time that corresponds in principle to the initial loading, $k$ is the kinetic constant, and $n$ is the diffusional exponent that 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 obtained for the diffusional exponent, $n$, ranged from 0.63 to 1.14, demonstrating that the release mechanism varies. The calculated $n$ values are shown in Table 4. All PMMA formulations displayed $n$ values >0.89 indicating a close to zero-order release mechanism, which may be attributed to swelling and erosion/dissolution of the polymer—a fact confirmed by the

**Table 3.** Kinetic parameters of diclofenac and furosemide tablets using zero-order model.

| | Total release (0–480 minutes) | | | Initial release (0–210 minutes) | | | Terminal release (210–480 minutes) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Tablets | $K$ (min$^{-1}$) | ±SD | $r^2$ | $k_1$(min$^{-1}$) | ±SD | $r^2$ | $k_2$(min$^{-1}$) | ±SD | $r^2$ | $k_2/k_1$ |
| 3MGF | 0.1392 | 0.0005 | 0.981 | 0.0955 | 0.0047 | 0.991 | 0.1794 | 0.0004 | 0.998 | 1.8785 |
| 3PGF | 0.1543 | 0.0006 | 0.973 | 0.0874 | 0.0009 | 0.990 | 0.2032 | 0.0003 | 0.997 | 2.3249 |
| 2MGF | 0.1582 | 0.0003 | 0.980 | 0.1013 | 0.0016 | 0.989 | 0.2213 | 0.0016 | 0.998 | 2.1846 |
| 2PGF | 0.1671 | 0.0008 | 0.972 | 0.1004 | 0.0021 | 0.988 | 0.1964 | 0.0008 | 0.996 | 1.9561 |
| 3MGD | 0.1653 | 0.0007 | 0.913 | 0.2402 | 0.0008 | 0.997 | 0.0692 | 0.0009 | 0.990 | 0.2881 |
| 3PGD | 0.1764 | 0.0004 | 0.949 | 0.2493 | 0.0007 | 0.992 | 0.0824 | 0.0003 | 0.989 | 0.3305 |

**Table 4.** Analysis of release data utilizing Korsmeyer and Peppas model.

| Tablets | $n$(±SD) | $r^2$ |
|---|---|---|
| 3PGD | 0.96 ± 0.02 | 0.997 |
| 3MGD | 0.96 ± 0.03 | 0.998 |
| 3PXD | 0.86 ± 0.02 | 0.998 |
| 3MXD | 0.76 ± 0.01 | 0.998 |
| 2PGD | 0.97 ± 0.03 | 0.998 |
| 2MGD | 0.94 ± 0.03 | 0.999 |
| 2PXD | 0.81 ± 0.02 | 0.998 |
| 2MXD | 0.72 ± 0.02 | 0.999 |
| 3MXF | 0.63 ± 0.01 | 0.999 |
| 3PXF | 0.80 ± 0.02 | 0.998 |
| 3PGF | 1.14 ± 0.04 | 0.978 |
| 3MGF | 1.12 ± 0.03 | 0.980 |
| 2PXF | 0.81 ± 0.02 | 0.999 |
| 2MXF | 0.76 ± 0.02 | 0.999 |
| 2PGF | 1.12 ± 0.04 | 0.975 |
| 2MGF | 1.10 ± 0.03 | 0.977 |

$n$, diffusional exponent; $r^2$, correlation coefficient.

swelling and erosion studies. On the other hand XG formulations displayed $n$ values <0.89 suggesting a coupling of diffusional and relaxation mechanisms, the so-called anomalous diffusion.

## Conclusion

Our findings show that two- and three-layer tablet formulations consisting of an appropriate combination of polymeric materials demonstrate sustained release and could modulate drug release. As seen the differences in drug release between the two- and three-layer tablets were found to be limited and as a result both structures may be used successfully for sustained release drug delivery. The barriers consisting of polymeric materials with suitable properties considerably influence (depending on the material's properties) the dissolution of the drug molecules by controlling the penetration of the surrounded dissolution medium, thus modifying the diffusion path. PMMA formulations displayed a faster release because of its less swelling and greater erosion than the equivalent XG formulation; moreover, HPMC formulations displayed an increased release compared with corresponding PEO formulations. Diclofenac formulations displayed a greater release and release rate compared with furosemide because of diclofenac's higher solubility mainly detected at early time period. All three-layer PMMA tablets containing either diclofenac or furosemide and the two-layer furosemide formulation demonstrated a biphasic release. Overall it appears that drug solubility, tablet structure, and the properties of the polymers considerably influence drug release, release rates, and mechanisms of release.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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