Modulation of Tenoxicam Release from Hydrophilic Matrix: Modulator Membrane *versus* Rate-Controlling Membrane

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This paper describes the preparation of two layered device comprising of tenoxicam containing layer and a drug free membrane layer based on Geomatrix® Technology. Our device based on bilaminated films which produced by a casting/solvent evaporation technique. The drug–hydroxypropyl methylcellulose (HPMC) layer was covered by drug free membrane layer composed of a mixture of different ratios of HPMC and ethyl cellulose (EC). The prepared devices were evaluated for thickness, weight, drug content uniformity, water absorption capacity and *in-vitro* drug release. The films were also evaluated for appearance, smoothness and transparency. The influence of drug free membrane layer composition and thickness on the drug release pattern was studied on 12 devices (D1 to D12). The results indicate that, the release of drug from HPMC matrixes without the drug free membrane layer was fast and follows diffusion controlled mechanism. The release of drug from the devices D1, D4, D9 and D12 follow the same mechanism, while the release of drug from other devices become linear with time (zero order) and extended for long time especially when thickness and the ratio of EC was increased in the drug free membrane layer. From this study it is concluded that, changing the geometry of drug layer by addition of drug free membrane layer and changing its composition and thickness plays an important role in determining whether the drug free membrane layer is rate-controlling or modulator membrane. Hence it can facilitate the development of different pharmaceutical products with different release pattern.

Key words tenoxicam; bilayered device; hydrophilic matrix; water absorption capacity; release kinetics

Recently much attention has been focused on developing controlled drug delivery systems using polymers.[1)] Drug containing polymeric films have been prepared to achieve controlled drug release for topical, oral or other routes of administration either directly or in the form of coating. Drug release from matrix systems follows either a square root of time relationship or more complex patterns according to the diffusional character of the system. One of the major objectives in the development of controlled release drug delivery systems is to prepare devices which modulate the release of drugs at a constant rate for extended periods of time.[2)] The modification of the release surface exposed to the dissolution medium as a way of modulating the release performance of a matrix system was mainly investigated on inert non-swellable devices. Spherical, cylindrical as well as biconvex shapes and films have been evaluated.[3—5)] A new delivery device, in the form of a multilayer tablets, has recently been proposed for constant drug release: Geomatrix® Technology.[6)] It consists of a hydrophilic matrix core, containing the active ingredient, and one or two impermeable or semi-permeable polymeric coatings (films or compressed barriers) applied on one or both bases of the core (two and three layer systems). The presence of the coatings modifies the hydration/swelling rate of the core and reduces the surface area available for drug release. These coatings provide a modulation of drug dissolution profile from the device.[7—9)] Several workers[2,10—12)] investigated the use of laminated films to control the release of different drugs. They described the laminated films as drug reservoir layer and drug free layer called rate-controlling membrane layer. Borodkin and Tucker[11)] studied pentobarbital, salicylic acid and methapyrilene release from laminated films composed from drug in hydroxypropyl cellulose (HPC) as the reservoir layer and HPC–polyvinyl acetate as drug free membrane layer. Donbrow and Samuelov[10)] prepared laminated double layered films comprising of tripelennamine, barbitone, salicylic acid and caffeine dispersed in hydroxypropyl cellulose as drug layer and drug free layer composed of ethyl cellulose (EC) and polyethylene glycol or HPC. While Bodmeier and Paeratakul[2)] studied salicylic acid, chlorpheniramine maleate and propranolol HCl release from laminated polymeric films prepared from aqueous latexes.

The objective of this paper is to study the release pattern of tenoxicam, potent non-steroidal anti-inflammatory drug, from hydrophilic matrix (hydroxypropyl methylcellulose, HPMC) through the restriction of the releasing surface by addition of drug free membrane layer composed of HPMC and EC. Also to explore the drug free membrane layer is a rate-controlling or modulator layer.

Experimental

Materials Tenoxicam (Chemi Iberica SA, Roche, kindly supplied by EIPICO, Egypt), ethyl cellulose (ethoxyl content of 47.5—49%, BDH chemicals Ltd., Poole, England), Hydroxypropyl methylcellulose (Dow chemical Co. Midland, U.S.A.), Methylene chloride, methyl alcohol, propylene glycol, disodium hydrogen phosphate and potassium dihydrogen phosphate (El-Nasr Co. for pharmaceuticals, Egypt), Amir adhesive (General Electronic Corporation, Tokyo, Japan).

Methodology. Preparation of Tenoxicam Delivery Device Preparation of Tenoxicam Film Matrix: Medicated films (drug supply layer) were cast from solution containing drug and hydroxypropyl methylcellulose respectively with methylene chloride/methanol mixture (1 : 1) as solvent.[13)] HPMC (2.4 g) was added as a dry powder by slow addition to the vigorously stirring solution by a magnetic stirrer then tenoxicam (0.26 g) was added. The solution was then allowed to stand for about 30 min to remove entrapped air. Films were cast by pouring the solution containing drug and polymer on glass Petri dish.[13)] The rate of evaporation of the solvent was controlled by placing an inverted funnel over the Petri dish. The dry films were removed from the glass surface and kept in a desiccator until use.

Preparation of Drug Free Membrane Layer: The drug free membrane film layer was prepared separately from different weight ratios (2.7 g) of HPMC and ethyl cellulose, EC, by the same casting technique using methylene chloride/methanol (1 : 1) solutions containing 1.2% w/v of propylene glycol as plasticizer. The ratio of HPMC to EC in films was 9 : 1, 8 : 2, 6 : 4 and 5 : 5. Also, the membranes were cast from the solutions at various thicknesses by pouring different amounts of solutions in the Petri dishes.

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Preparation of Drug Delivery Device: The delivery device was prepared by cutting a section (3×3 cm) of drug supply film matrix (measuring its thickness in five different places with a micrometer) placing it on glass substrate, and spraying the other side with the casting solvent. A slightly larger part of the drug free membrane layer (thickness had been previously measured) was immediately pressed on the wet side of the drug film placed on a glass plate avoiding entrapment of air. The delivery system was allowed to air dry for 24 h and inspected to ensure complete adhesion between the two layers before use.

Physicochemical Characterization of Drug Delivery Device Drug Content of Drug Supply Layer: The drug containing layer was dissolved in the casting solvent and diluted subsequently with it and its absorbance was measured spectrophotometrically (UV spectrophotometer-161, Shimadzu, Japan), at λ 368 nm[14] against the blank casting solvent containing the same amount of polymer without drug. The results recorded were the mean of three determinations.

Device Thickness: The thickness of each layer of the device was determined at five separate points using a micrometer (Mitutoyo corporation, model Pk-1012E, Japan) before lamination. The thickness of the device was the sum of the thickness of the two layers.

Device Weight: The devices were subjected to weight variation by individually weighing three randomly selected devices.

Water Absorption Studies: The water absorption capacity of various devices was determined at 84% relative humidity (RH) according to the method described by Danjo *et al.*[15] Each device was attached to glass plates using Amir adhesive with the drug free membrane layer exposed and weighed. The device was then put in desiccator containing saturated solution of potassium chloride. After equilibrium was attained, the device was taken out from the desiccator and weighed. The water absorption capacity of the devices was calculated based on the change in the weight with respect to initial weight of the device.

***In-Vitro* Tenoxicam Release from the Device** Each device (3×3 cm) was attached to glass plates (5×4.5 cm) using Amir adhesive with the drug free membrane layer exposed to the dissolution medium. The edges of the device were covered with Amir adhesive to avoid direct drug release from edges. The drug release rate from the device was determined using USP dissolution tester[16] (USP dissolution tester, Apparatus Il, Pharma Test, Germany), maintained at 37±0.5 °C and stirred at 25 rpm. The glass plate device assembly was immersed in 200 ml of Sorensen phosphate buffer (pH=7.4). Samples were withdrawn at time intervals filtered and analyzed spectrophotometrically for drug content at λ=368 nm.[14] Drug free device was treated similarly to be used as a control. The experiment was carried out in triplicate and the mean value was calculated.

Release Data Treatment The release data were analyzed using various kinetic equations for zero order, first order and Higuchi equation.[17] The model of highest correlation coefficient is then selected.

Scanning Electron Microscopic Studies The surface morphologies of the drug free membrane layer films before and during drug release studies were examined by Scanning electron microscopy (SEM). The dried films were mounted on aluminum stubs using a double sticky cellophane tape, gold-coated in a vacuum evaporator and observed under Jeol (Jem 100S, Japan) Scanning electron microscope.

Results and Discussion

Twelve devices containing tenoxicam were prepared. Each drug delivery device contains two laminated film layers, drug supply layer and drug free membrane layer. Tenoxicam containing films (drug supply layer) was prepared using hydroxypropyl methylcellulose (HPMC) with film thickness equal to 0.09 mm±0.02. The second film layer without drug (drug free membrane layer) was formulated from different amounts of HPMC and ethyl cellulose (EC). The ratios of HPMC to EC used in the second layer are 9 : 1, 8 : 2, 6 : 4 and 5 : 5. These ratios were chosen on the basis of both to show the effect of doubling the amount of EC in the membrane layer and upon film elasticity. The drug free membrane layer was constructed using three different thickness, these are 0.09, 0.16 and 0.21 mm±0.02. The uniformity of drug free membrane polymeric films containing various ratios of HPMC and EC was evidenced by the low variation in thickness measurements. The drug supply layer yielded smooth flexible films as it folded 100 times. This was in a good agreement of Khanna *et al.*,[18] where they determined the folding endurance of the films by repeatedly folding one film at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties. This depends of course on the type and concentration of polymer used and film thickness. Incorporation of propylene glycol as a plasticizer in the drug free membrane layer yielded smooth films. As the ratio of EC increased in the drug free membrane layer, the transparency, smoothness and elasticity of the membrane was decreased. Increasing the concentration of EC above 50% resulted in the formation of brittle films. The drug content per device was within 14.49—15.00 mg. The specifications of the devices are shown in Table 1.

Table 1. Characteristic of Tenoxicam Devices

Device membrane composition HPMC : EC	Device number	Device drug content (mg)	Device thickness (±0.04 mm)	Device weight (g)	Amount of water absorbed per device (g)
9 : 1	D1	14.98	0.18	0.224	0.515
	D2	14.86	0.25	0.271	0.637
	D3	14.99	0.30	0.297	0.683
8 : 2	D4	15.00	0.17	0.222	0.500
	D5	15.00	0.25	0.268	0.611
	D6	14.99	0.31	0.299	0.688
6 : 4	D7	14.55	0.18	0.225	0.450
	D8	15.00	0.26	0.273	0.573
	D9	15.00	0.32	0.298	0.611
5 : 5	D10	14.49	0.18	0.235	0.447
	D11	14.70	0.26	0.272	0.530
	D12	15.00	0.32	0.299	0.598

Water absorption capacity of the device was increased as HPMC, hydrophilic polymer, fraction in the drug free membrane layer increased (Table 1). This result was in a good agreement with Rao *et al.*,[19] where they studied propranolol hydrochloride release from films containing different ratios of ethyl cellulose and polyvinyl pyrrolidone.

Figures 1—3 depict the different release pattern of tenoxicam from drug supply layer (control) and twelve devices (D1—D12) having different ratios of HPMC to EC in the drug free membrane layer. Tenoxicam released from control was ~90% after 30 min as shown in Fig. 1. The drug release was found to follow diffusion-controlled matrix model, in which the amount of drug released per unit area is proportional to the square root of time (Table 2). In case of different devices, the drug release was extended from 30 to 300 min with increasing EC fraction in the drug free membrane layer. The release of tenoxicam from devices D1, D4, D9 and D12 showed the same release pattern of drug from the drug supply layer (diffusion mechanism), while in the other devices the release mechanism changed to zero order. These results were in a good agreement with several workers,[2,10,11] where they found that addition of drug free membrane layer to the drug supply layer (reservoir layer) changed the release mechanism. These workers called this layer a rate controlling layer if it change or not change the release mechanism. In this study for devices (D1, D4, D9, D12) there is no change in the release mechanism so the drug free membrane layer is called a rate controlling membrane as it controls the release

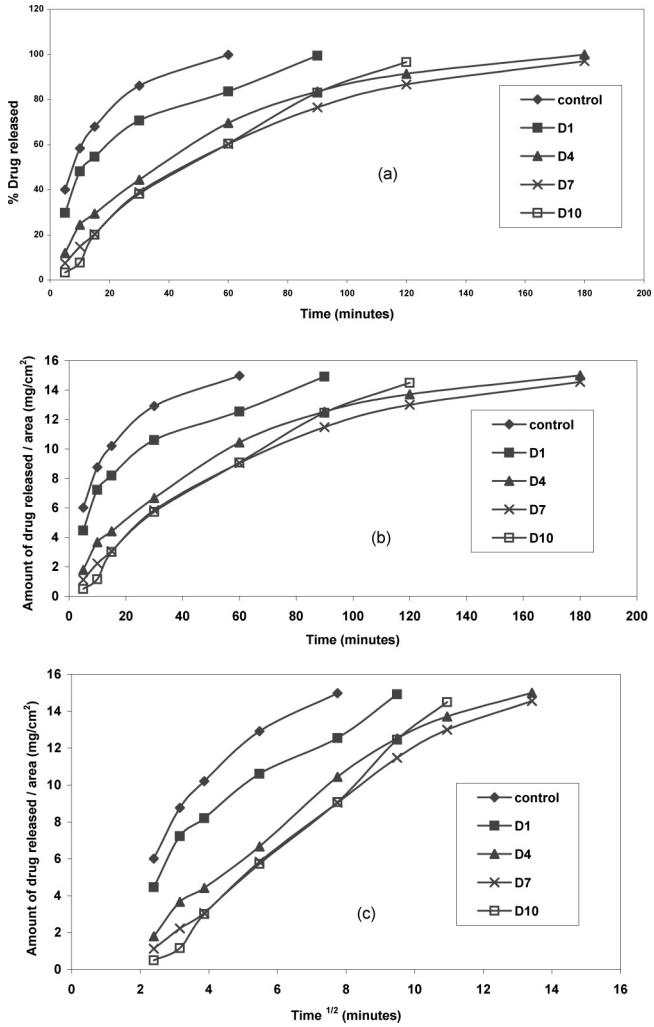

Fig. 1. *In-Vitro* Release of Tenoxicam from Different Devices through the Membrane Layer Thickness (0.09±0.02 mm) Having Different Ratios of HPMC and EC

(a) % release α time, (b) amount of drug release α time, (c) amount of drug release α time$^{1/2}$.

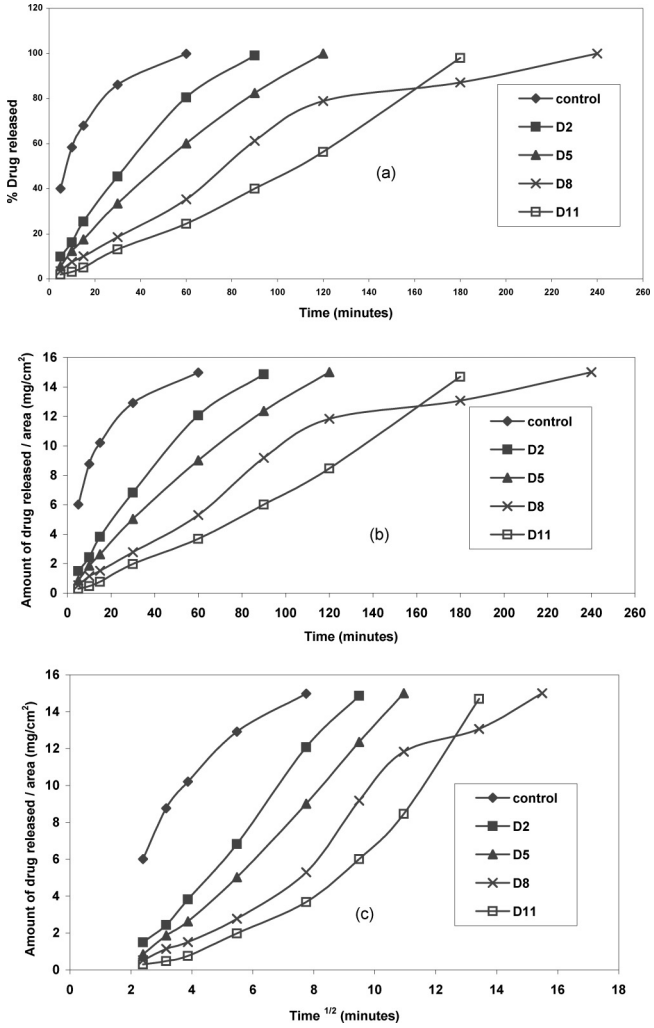

Fig. 2. *In-Vitro* Release of Tenoxicam from Different Devices through the Membrane Layer Thickness (0.16±0.02 mm) Having Different Ratios of HPMC and EC

(a) % release α time, (b) amount of drug release α time, (c) amount of drug release α time$^{1/2}$.

of drug. On the other hand, the rest of devices showed change in the release mechanism, so the drug free membrane layer is called modulator membrane (*i.e.* modulate the release mechanism of drug from diffusion mechanism to zero order). It was noticed that upon increasing the ratio of HPMC in the drug free membrane layer, the release of drug was increased. This may be due to the leaching of HPMC by the dissolution medium and pore formation which leads to an increase in the internal film area exposed to the release medium and porosity was increased. With an increase in porosity, the void volume would be expected to be occupied by external solvent diffusing into the drug supply layer. These results are in a good agreement with Shah and Sheth[13] where they studied the release of a dye from film matrix composed of EC with HPMC. They suggested that hydration and dissolution of HPMC results in pore formation in the film which facilitates transport of solute.[13] This was also confirmed by Scanning electron microscope (SEM) photographs taken before and during drug release studies Fig. 4. It was also found that as the water absorption capacity of the device increased, the release of drug from device was increased.

The effect of drug free membrane thickness on drug release is shown in Figs. 5—8. The film thickness of the drug free membrane layer was varied by varying the casting volumes. As drug free membrane layer thickness increased, the release of drug was decreased. Devices (D1, D4, D7, D10) with membrane thickness 0.09 mm, showed high drug release in the first 60 min than other devices. This may be attributed to the thickness of drug free membrane layer. In case of other devices, there is slight difference in the release pattern although the thickness of the drug free membrane layer is different. This could be explained on the other factor which is the composition of the drug free membrane layer (HPMC : EC ratio). A thickness independent rate constant could be calculated by multiplying the zero order rates by thickness. This allowed the comparison of the rate constants of devices of different composition.[2] A non linear relationship was observed for tenoxicam release from devices (Table 3). This result was in a good agreement with Bodmeier and Paeratakul,[2] where they found non linear relationship for salicylic acid release from Eudragit NE 30D laminates.

Conclusion

The results obtained confirm that the drug release rate and

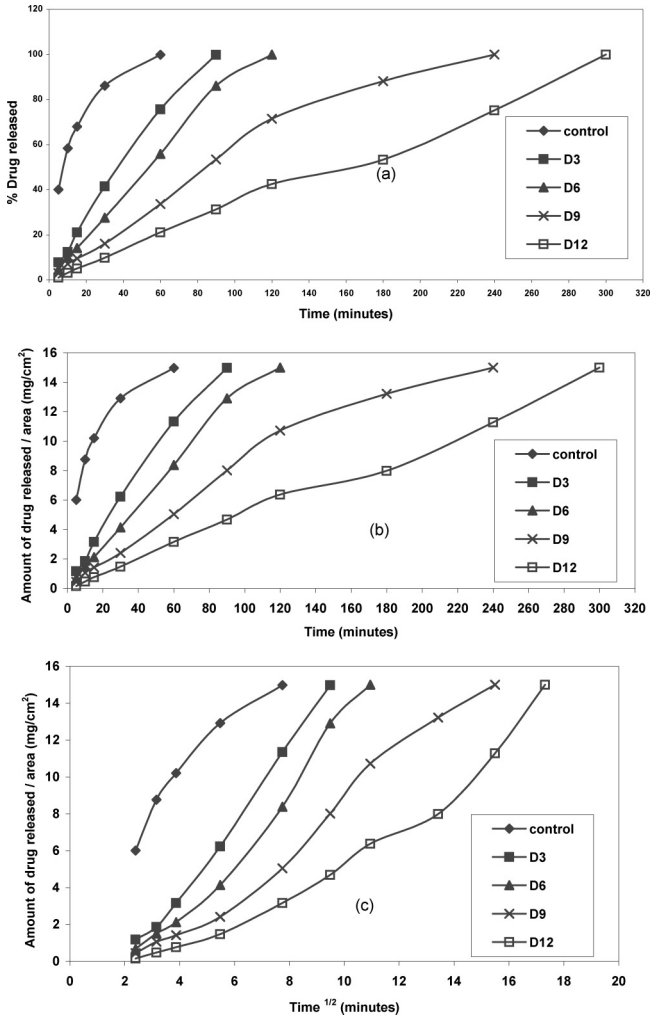

Fig. 3. *In-Vitro* Release of Tenoxicam from Different Devices through the Membrane Layer Thickness (0.21±0.02 mm) Having Different Ratios of HPMC and EC

(a) % release α time, (b) amount of drug release α time, (c) amount of drug release α time$^{1/2}$.

Table 2. Kinetic Analysis of Release Data of Tenoxicam from Different Devices

Device number	Correlation coefficient			Mechanism of release
	Zero order	First order	Diffusion	
Control[a)]	0.9264	0.8499	0.9782	Diffusion
D1	0.9056	0.8094	0.9636	Diffusion
D2	0.9969	0.9407	0.9853	Zero
D3	0.9954	0.9562	0.9703	Zero
D4	0.9523	0.8236	0.9881	Diffusion
D5	0.9977	0.8980	0.9920	Zero
D6	0.9982	0.9000	0.9904	Zero
D7	0.9988	0.9204	0.9886	Zero
D8	0.9936	0.8872	0.9943	Zero
D9	0.9803	0.8403	0.9985	Diffusion
D10	0.9808	0.8718	0.9724	Zero
D11	0.9818	0.9876	0.9320	Zero
D12	0.9954	0.8451	0.9963	Diffusion

a) Control=drug supply layer.

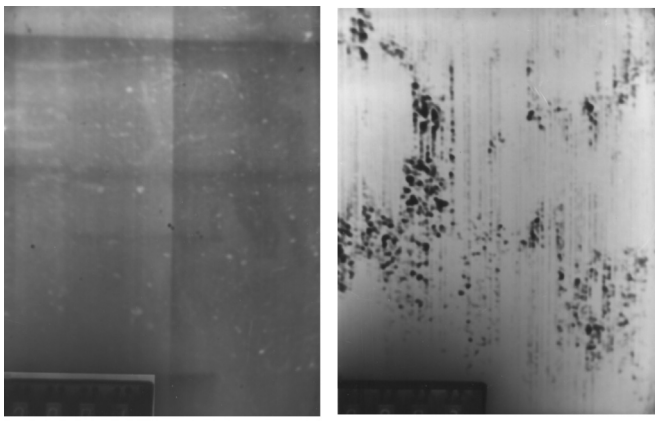

Fig. 4. Scanning Electron Micrographs of Films (HPMC: EC, 6 : 4) Showing Pore Formation

(a) Before release and (b) during release study.

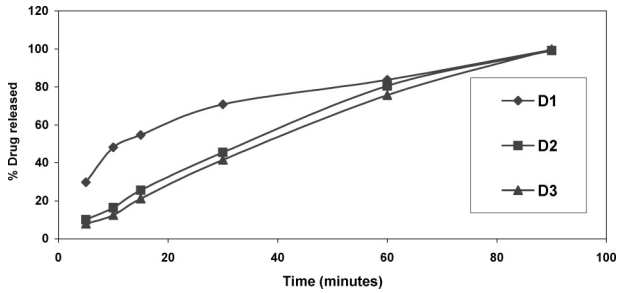

Fig. 5. Effect of Membrane Layer Thickness on Tenoxicam Release from Different Devices (Membrane Layer Having Ratio of HPMC and EC; 9 : 1)

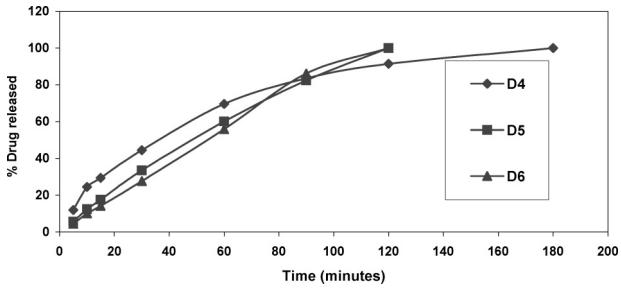

Fig. 6. Effect of Membrane Layer Thickness on Tenoxicam Release from Different Devices (Membrane Layer Having Ratio of HPMC and EC; 8 : 2)

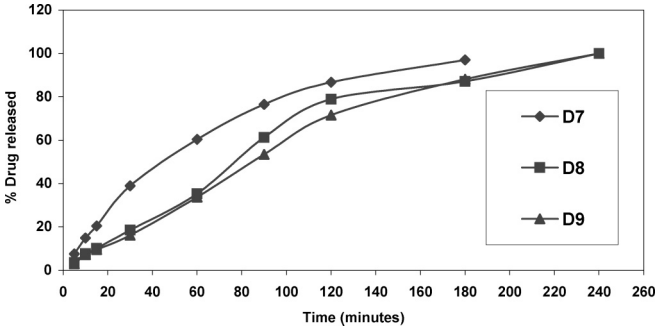

Fig. 7. Effect of Membrane Layer Thickness on Tenoxicam Release from Different Devices (Membrane Layer Having Ratio of HPMC and EC; 6 : 4)

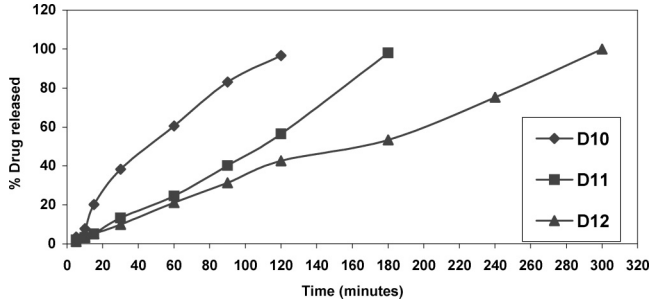

Fig. 8. Effect of Membrane Layer Thickness on Tenoxicam Release from Different Devices (Membrane Layer Having Ratio of HPMC and EC; 5 : 5)

Table 3. Zero-Order Release Rates (K) for Tenoxicam from Different Devices

Device number	K (mg/cm^2·min)	$k \cdot h^{a)}$ (mg/cm·min)
D2	0.228	0.0036
D3	0.207	0.0043
D5	0.168	0.0027
D6	0.138	0.0029
D7	0.195	0.0017
D8	0.088	0.0014
D10	0.191	0.0017
D11	0.066	0.0011

a) h=thickness of membrane layer.

its mechanism from hydrophilic matrix films can be widely modulated using this kind of drug free membrane layer and a suitable composition of membrane. Tenoxicam release kinetics from devices could be shifted from linearity with the square root of time (diffusion) to linearity with time (zero order) by laminating a modulator drug free membrane layer to the releasing surface. The device proposed allows the release performances of the matrix to modulate in a wide range of variation and different releases pattern can be fabricated.

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