Controlled Release of Tramadol from Mixed Matrix Membranes

L. Donato, G. Barbaro, E. Drioli and C. Algieri*

National Research Council - Institute for Membrane Technology (ITM–CNR), c/o The University of Calabria, cubo 17C, Via Pietro BUCCI, 87036 Rende CS, Italy

Abstract: In this work mixed matrix membranes (zeolite loaded) were prepared and tested as potential devices for the controlled release of tramadol hydrochloride. Due to the hydrophilic nature of the drug, a hydrophobic polymer (polydimethylsiloxane) was chosen for the membrane preparation. NaX zeolites was added to PDMS matrix as modulating agent with the aim to obtain a linear and adequate delivery of the drug in the time as required by the therapeutic needs of this opioid.

About the different investigated systems, the PDMS membrane containing 17 wt% of zeolite and 0.2 wt% of drug seems to be the most promising for application as transdermal device. Different mathematical models (Zero order, First order, Higuchi, Bhaskar, and Korsemeyer-Peppas) were used to interpret the drug release mechanism from the different Mixed matrix membranes. The experimental data showed good fit with three different models: Higuchi, Bhaskar and Korsemeyer-Peppas.

Keywords: Tramadol hydrochloride, transdermal drug delivery, polydimethylsiloxane, FAU zeolite, NaX-PDMS membranes.

INTRODUCTION

Controlled release technology is a science rapidly growing due to the development of different polymers (polyurethanes, polyanhydrides and siloxanes) [1-4] and for the advantages over conventional dosage forms, including improved efficacy and reduced toxicity [5]. Today, transdermal drug delivery is an alternative route for systemic drug release because provides different advantages with respect to the conventional therapeutic treatments [6] as the possibility to avoid the metabolism variations and improve the patients compliance [6-7].

Recently, synthetic zeolites were studied in order to investigate their ability to encapsulate and to release drugs [8]. Zeolites are alumino-silicate materials with crystalline structure and micropore aperture size in the range of molecular dimensions (3–10 Å). It is possible to change their adsorption properties varying the Si/Al ratio during the synthesis [9]. Dermal uptake of the zeolite is negligible for long time on the undamaged skin [10]. These materials for their characteristics are used in the pharmacological field. For example, pharmaceutical zeolite-based compositions containing zinc and erythromycin have been used in the treatment of acne [11]. FAU zeolite acts as a slow release agent for different antihelmintic drugs [12].

Up to date, mixed matrix membranes (zeolite loaded) were studied for gas and liquid mixture separations [13-15] but the possibility to use them for a sustained drug release was not yet explored. Polymeric materials do not meet the current demands of membrane technology. Mixed matrix membranes (MMMs), consisting of organic polymer with dispersed inorganic fillers (such as zeolite, carbon molecular sieves, silica and carbon nanotubes), combine the properties of the polymer and of the inorganic materials [16]. As demonstrated deeply in the open literature [16], a limit of MMMs is their application in the gas separation processes where the use of glassy polymer is required as matrix host for the inorganic particles. In fact, MMMs prepared with rubbery polymers do not present defects due to the high mobility of the polymeric chains [13]. When glassy polymers are used, the membranes present defects at the polymer-zeolite interface owing to the high rigidity of the polymeric chains [16].

In this work MMMs loaded with NaX zeolite (faujasite topology) were prepared and investigated as a new transdermal delivery devices of the model drug tramadol hydrochloride (tramadol). The latter is a synthetic opioid from the aminocyclohexanol group widely used for the treatment of the pain caused by surgical operation and chronic disease [17, 18]. The half-life of the drug is about 5.5 hours and in order to maintain the effective plasma concentration it dosage regimen is 50 to 100 mg every 4 to 6 hours with a maximum dosage of 400 mg/day [19].

In this study, the release of tramadol from the MMMs (zeolite loaded) was explored with the aim to evaluate the effect of zeolite on the release kinetic of

*Address corresponding to this author at the National Research Council - Institute for Membrane Technology (ITM–CNR), c/o The University of Calabria, cubo 17C, Via Pietro BUCCI, 87036 Rende CS, Italy; Tel: +39-0984-492030; Fax: +39-0984-402103; E-mail: c.algieri@itm.cnr.it

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the drug. Different mathematical models (Zero order, First order, Higuchi, Bhaskar, and Korsemeyer-Peppas) were also used to interpret the drug release mechanism from the different MMMs.

MATERIAL AND METHODS

Materials

Tramadol ($C_{16}H_{25}NO_2 \cdot HCl$, ≥99%) having molecular weight of 299.84 Da was purchased from Sigma Aldrich (Figure **1a**).

Polydimethylsiloxane (PDMS) (Sylgard (R) 184 silicone elastomer) (Figure **1b**) supplied by Dow Corning Co. has a kit containing a base (specific gravity at 25 °C 1.05 g/cm^3, viscosity 5000 cSt) and a curing agent (specific gravity at 25 °C 1.03 g/cm^3, viscosity 110 cSt).

Dichloromethane (CH_2Cl_2, 99.5%) and tetrahydrofuran (C_4H_8O, 99.9%) were purchased from Carlo Erba Reagenti.

NaX zeolite (Figure **1c**) was purchased by Aldrich (particle size ~2 μm and Si/Al=1.2). Before using, zeolite crystals were purified using a series of centrifugation and rinsing steps to remove the amorphous materials. The procedure was repeated until to low the pH value from 10 to 7. Finally, the zeolite particles were activated at 500 °C and stored into a dryer to avoid water adsorption.

HPLC Analysis

The quantitative determination of the drug was performed on a LaChrom D7000 HPLC system (Hitachi) equipped with L-7400 UV detector. Analysis were carried out using the column Prevail C18, 5 μm, 250·4.6 mm (Alltech, Italy). The mobile phase was acetonitrile/ KH_2PO_4 50 mM at pH = 3 (25/75 v/v). The operating conditions were: flow rate of 1.05 mL min^{-1}, temperature of 25 °C, pressure of 120 bar and wavelength of 220 nm.

Membrane Preparation

The membranes were prepared by the phase inversion technique using the dry method [19]. It consists in a dissolution of a polymer in a proper solvent and cast the solution on a suitable plate. Subsequently, the solvent is evaporated to obtain a dense homogeneous membrane.

In this paper the PDMS polymer was dissolved in CH_2Cl_2 (curing agent and base with a ratio 1:10 on weight basis). Afterwards, the tramadol was added to the polymer solution with the aim to evaluate the release of this drug from the membrane. The membranes PDMS-TRAMA based were obtained pouring the solution on a Teflon plate that in turn was put in an oven for 12 hours at 60 °C to allow the solvent evaporation and the cross-linking of the polymeric material.

To fabricate MMMs, the zeolite particles were dispersed in the solvent in an ultrasonic bath for 15 min. The polymer and the drug were then added and the resulted dispersion was stirred magnetically at room temperature for 4 hours. In addition, during this period, three sonications of 15 min each one were done to guarantee a well-dispersed suspension. Subsequently, the dispersion was poured on a Teflon

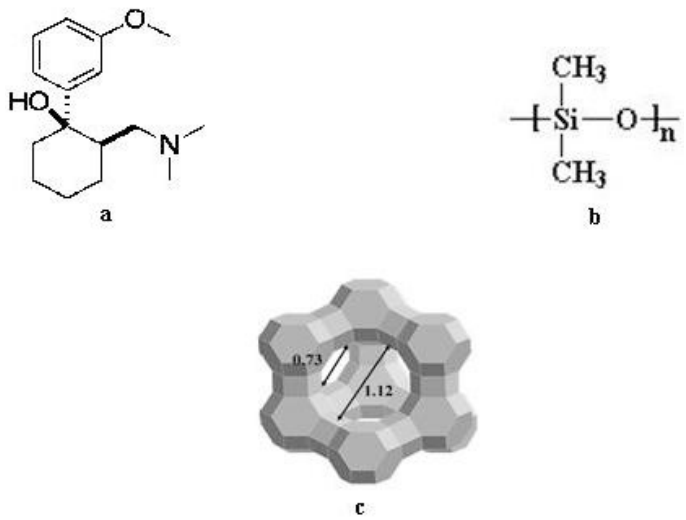

Figure 1: Structure of: (**a**) tramadol; (**b**) PDMS; (**c**) NaX zeolite.

Table 1: Composition of the Different Prepared Membranes

Sample	PDMS (wt%)	NaX (wt%)	Tramadol (wt%)
PDMS-TRAMA 0.2% DL	99.8	-	0.2
PDMS-TRAMA 0.4% DL	99.6	-	0.4
PDMS-TRAMA 0.6% DL	99.4	-	0.6
PDMS-NaX 8%-0.2% DL	91.8	8	0.2
PDMS-NaX 17%-0.2% DL	82.8	17	0.2
PDMS-NaX 17%-0.4% DL	82.6	17	0.4
PDMS-NaX 17%-0.6% DL	82.4	17	0.6
PDMS-NaX 34%-0.2% DL	65.8	34	0.2

plate that was placed in an oven for 12 hours at 60 °C to allow the cross-linking of the material and the membrane formation.

The composition of the different prepared samples (in terms of drug loading (DL) and zeolite content) was reported in Table **1**.

Membrane Characterization

Morphological Analysis

Top view and cross-section of the prepared samples were analysed by using a Cambridge Zeiss LEO 400 scanning electron microscope (SEM). Membranes were broken in liquid nitrogen to keep unalterated the film structure.

The thickness of the membranes was measured by using a digital micrometer (Carl Mahr D7300 Esslingen a.N.) averaging 15 measurements. The standard deviation calculated on the sample was about 8%.

Water Contact Angle Measurements

The wettability of the membranes was evaluated by means of water contact angle (WCA) measurements. Contact angle of water droplets were measured at room temperature with a CAM 200 contact angle meter (KSV Instruments LTD, Helsinki, Finland). The drop was formed depositing water onto the membrane surface with an automatic microsyringe. Both sides of the membrane were tested. At least 30 measurements on different regions of each sample were averaged per each CA value. Standard deviations are indicated as error.

In Vitro Release

The drug release tests were carried out as reported in the literature [20-22]. The experiments were performed immersing the membranes (area of 28.16 cm^2) in 0.5 L of phosphate-buffered solution (50 mM, pH 7.4) maintained at 37 °C under continuous stirring (200 rpm). During the experiments 500 µl were withdrawn (each twenty minutes during the first hours and then deferred over time). The concentration of the drug present in the medium was estimated by HPLC analysis and the drug release percent was determined using the following equation:

$$\text{Drug release } (\%) = \left(\frac{M_t}{M_i}\right) \cdot 100 \quad (1)$$

Where, M_i and M_t are the initial amount of drug and the amount of drug released at the time t, respectively. All the experiments were repeated three times. Due to a concentration gradient of the drug between the membrane and release medium, the tramadol migrates from the initial position in the membrane to the medium.

Release Profile Analysis

The release data were fitted with different mathematical models (Zero order, First order, Higuchi, Bhaskar and Korsemeyer-Peppas) to interpret the drug release mechanism from the membranes.

The zero order equation (2) is:

$$Q_t = Q_0 + k_0 t \quad (2)$$

Where Q_t is the amount of drug dissolved in the time t, Q_0 is the initial amount of drug in the solution and k_0 is the zero order release constant [23]. This model represents the drug release from matrix tablet and transdermal devices [24].

The drug release that follows the first-order kinetics is expressed by the equation (3):

$$-\log(1-\frac{M_t}{M_\infty}) = \frac{kt}{2.303} \quad (3)$$

Where M_t is the amount of the drug release at time t, M_∞ is the amount of the drug release after infinite time and *k* is a release rate constant. This model is used to describe the release of water-soluble drug [23].

The Higuchi model is described by the equation (4):

$$\frac{M_t}{M_\infty} = k_H t^{\frac{1}{2}} \quad (4)$$

Where k_H is the Higuchi dissolution constant. This model is based on the following hypotheses: 1) initial drug concentration in the matrix is higher than drug solubility; 2) drug diffusion occurs only in one dimension; 3) drug particles are smaller than system thickness; 4) matrix swelling and dissolution are negligible; 5) drug diffusivity is constant [24]. This model can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as some transdermal systems and matrix tablets with water soluble drugs [25,26].

The equation (5) describes the Bhaskar model:

$$-\log(1-\frac{M_t}{M_\infty}) = Bt^{0.65} \quad (5)$$

B is the kinetic constant. This model is used to describe the drug diffusion through the resins and inorganic materials [27,28].

The Korsemeyer-Peppas model is expressed by the equation (6):

$$\log\frac{M_t}{M_\infty} = \log k + n\log t \quad (6)$$

k is a release rate constant that incorporates structural and geometric characteristics of the tablet and n is a diffusional exponent indicative of the release mechanism as reported in Table **2** [29].

Table 2: Interpretation of Diffusional Release Mechanisms from Polymeric Films

Release exponent (n)	Drug transport mechanism
0.5	Fickian release
>0.5 <1	Non Fickian release (anomalous)
1	Case II transport

RESULTS AND DISCUSSION

Top-view and cross-section of the different samples PDMS based are shown in Figures **2a-2e**. The top-view of the PDMS membranes loaded only with the tramadol is very smooth (Figure **2a** and **2b**). Referring to the mixed matrix membranes, all micrographs show the crystals well embedded in the rubbery matrix indicating a good interaction between the two different materials due to the high mobility of the polymeric chains. The cross sections confirm a good crystals distribution for the all membranes (see Figure **2c-2e**).

The thickness of the all prepared membranes, measured using a digital micrometer, ranged from 1.1-1.6 mm.

Contact angle measurements showed that all the prepared membranes exhibited a hydrophobic character even if the addition of the zeolite has determined changes of the contact angle values for both sides of the membranes. In fact, air and Teflon side of the pure PDMS present the same hydrophobic character that remains constant also after the addition of tramadol, as it is shown in Figure **3** for the samples containing 0.2% DL. On the other hand, in the case of MMMs increasing the zeolite content (from 8 wt% to 17 wt%) also increases the contact angle value of the side exposed to the air. This because an increase of the zeolite content determines a higher particles sedimentation on the membrane side exposed to the Teflon plate (for the action of the gravitational force as also reported in literature [30]). Consequently, the hydrogen bonds between the different oxydrilic groups of the zeolites are mainly formed both inside and on the Teflon side of the membrane. Therefore, the zeolite particles exposed to the air their hydrophobic portion (Si-O-Si). Hence, the Teflon side of the membrane presents a lower contact angle value.

Figure **4** reports the release profile of tramadol for the PDMS-TRAMA membranes at different drug loading.

As it is shown, the release kinetic was not influenced by DL. Taking into account the high solubility of tramadol in the aqueous medium, the use of a hydrophobic polymer like PDMS ensured a slow release of the drug in the time. However, the release kinetics are not enough linear as required by the therapeutic needs of this opioid [31]. On the basis of these results a modulating agent such as zeolite was added into the polymeric matrix with the aim to promote

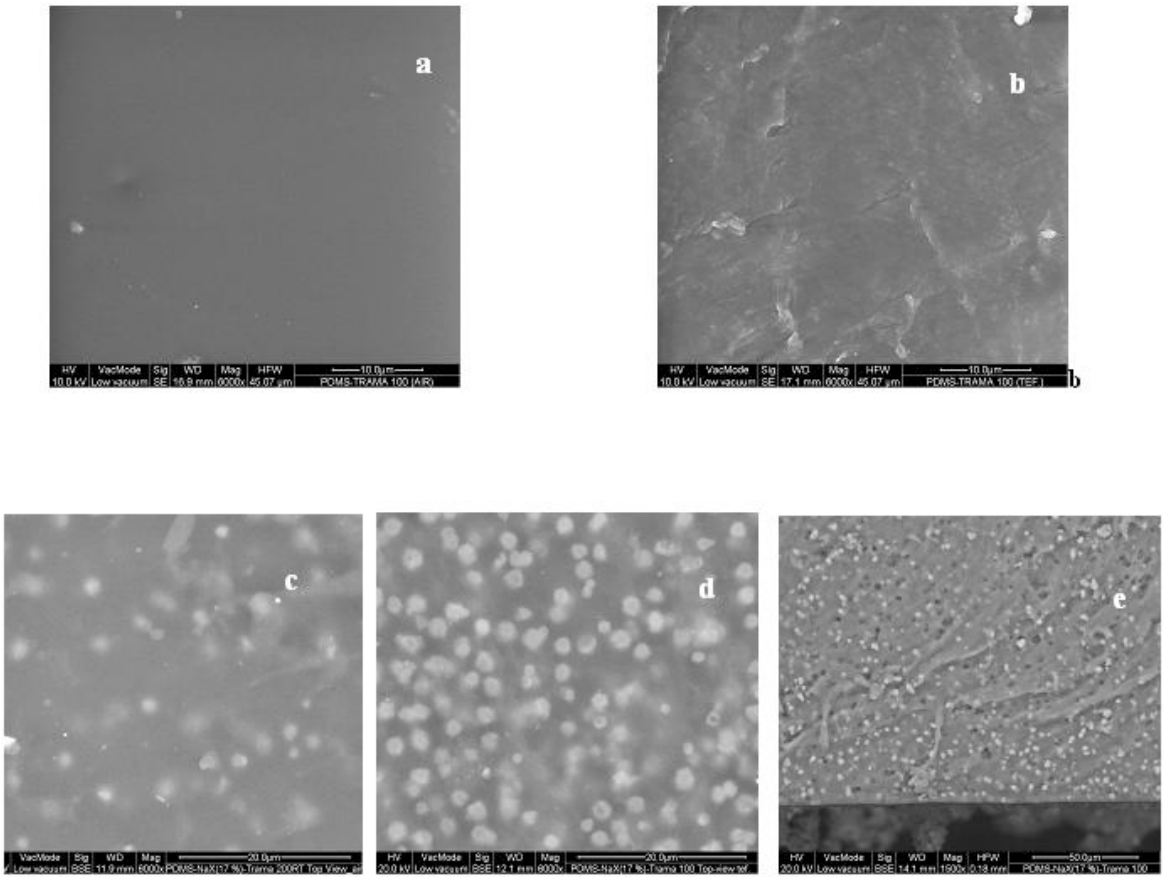

Figure 2: SEM micrographs of different membranes: Top-view of **a**) air side and **b**) Teflon side of PDMS-TRAMA 0.2 % DL. **c**) air side; **d**) Teflon side and **e**) cross-section of PDMS-NaX17%-0.2 % DL.

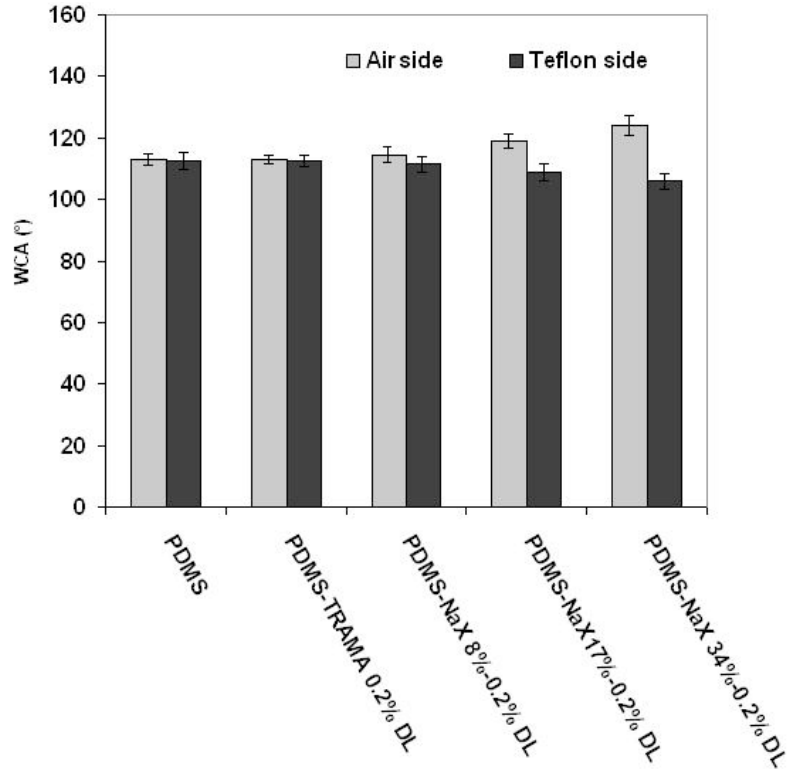

Figure 3: WCA values of the different prepared membranes.

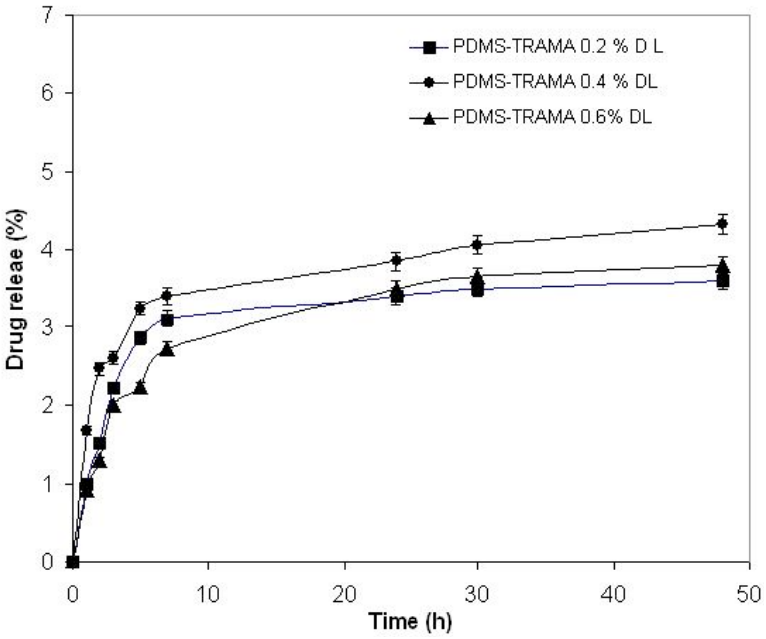

Figure 4: Release profile of tramadol from PDMS-TRAMA membranes at different DL.

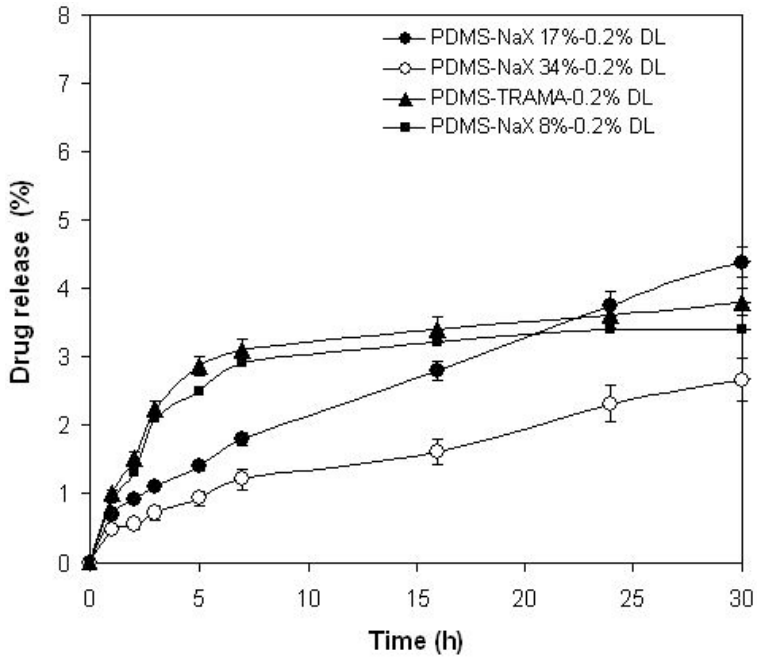

Figure 5: Effect of zeolite content on tramadol release from PDMS-NaX membranes (0.2 % DL).

a more linear and adequate delivery in the time. In this perspective, various MMMs at 0.2 % DL and low, medium and high zeolite content were prepared and tested. The effect of the zeolite on the release profile of tramadol from the MMMs is shown in Figure **5**.

As it can be seen, at low NaX content (8 wt%) in the polymeric matrix was not observed any significant effect of the zeolite on the release rate. Increasing further the zeolite amount (17 wt%) a more linear release behaviour was obtained. This results is due to the interaction of the hydrophilic zeolite with the polar molecules of tramadol [32] which leads to a slower delivery to the medium. However, at high zeolite content (34 wt%) an excessive delay of the release rate was observed. This last result is due to two different aspects. First of all, the formation of zeolite clusters into the polymeric matrix that hinderd the release of the drug. Secondly, the increase of the zeolite content from 17 wt% to 34 wt% determined a more tortuous diffusion pathway of the drug into the polymeric matrix.

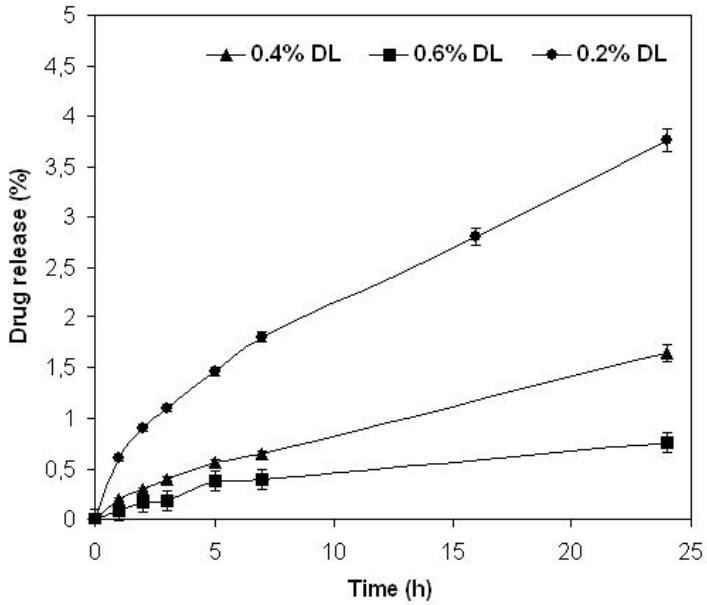

Figure 6: Effect of DL on tramadol release from mixed matrix membranes (NaX 17 wt%).

On the basis of these results, other MMMs at 17 wt% of zeolite content were prepared increasing the DL. Results are shown in Figure **6**.

An Increase of DL from 0.2 % to 0.6 % determined a decrease of the drug release rate. This behaviour can be attributed to the precipitation of the drug into the polymer matrix when its amount exceeds the solubility limit in the polymer as also confirmed by literature [33]. About the different investigated systems, the PDMS-NaX 17%-0.2% DL membrane seems to be the most promising for application as transdermal device.

Different mathematical models (Zero order, First order, Higuchi, Bhaskar and Korsemeyer-Peppas) were used to interpret the drug release mechanism from the MMMs loaded with 0.2% DL. The model that best fits the release data was evaluated by correlation coefficient (R^2). The release constant and the R^2 values are given in Table **3**. The experimental data showed good fit with three different mathematical models: Higuchi, Bhaskar and Korsemeyer-Peppas. The latter model (see Table **3**) indicated a non-Fickian transport behaviour of the drug from the devices exhibiting a relase exponent in the range 0.5<n<1.

CONCLUSIONS

In this work was demonstrated that mixed matrix membranes NaX-loaded can be used as devices for the transdermal controlled release of tramadol. The obtained results evidenced as the release of a polar drug requires the use of a hydrophobic polymer to avoid a fast release. Besides, the presence of the zeolite particles have permitted to obtain a more linear release kinetic. This results is due to the interaction of the hydrophilic zeolite with the polar molecules of the tramadol. However, a high zeolite content (34 wt%) into the polymeric matrix has determined an excessive decrease of the release rate. About the different investigated systems, the PDMS membrane containing 17 wt% of zeolite and 0.2 % DL seems to be the most promising for application as transdermal device.

Different mathematical models (Zero order, First order, Higuchi, Bhaskar, and Korsemeyer-Peppas) were used to interpret the drug release mechanism from the different MMMs. The experimental data showed good fit with three different models: Higuchi, Bhaskar and Korsemeyer-Peppas.

Table 3:

	Zero-order		First-order		Bhaskar		Higuchi		Korsemeyer-Peppas	
	K_0	R^2	K	R^2	B	R^2	K	R^2	n	R^2
PDMS-NaX 8wt%-0.2 DL	0.02	0.92	0.04	0.94	0.04	0.97	0.052	0.97	0.51	0.98
PDMS-NaX 17%-0.2% DL	0.002	0.88	0.02	0.95	0.02	0.99	0.07	0.99	0.55	0.99
PDMS-NaX 34%-0.2% DL	0.001	0.84	0.01	0.89	0.01	0.98	0.005	0.98	0.52	0.98

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