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Development of Mixed Matrix Membranes for Controlled Release of Ibuprofen

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ABSTRACT: In this work was studied the effect of different zeolite topologies on the release of ibuprofen from mixed matrix membranes (MMMs). The main parameters investigated were: zeolite concentration, its hydrophilic/hydrophobic character, and drug loading. About the different investigated systems, the PDMS NaX (I) membrane seems to be the most promising for its application as transdermal device. The release data were fitted with different mathematical models (zero order, first order, Higuchi, Bhaskar, and Korsemeyer-Peppas) to give a possible explanation of the release mechanism of the drug from MMMs. The release data of the drug from pure PDMS membranes (PDMS IBU) were fitted by the Higuchi model (R^2 pari a 0.97). In the case of MMMs, the correlation coefficients are very far from the unit value except for the PDMS NaX (I) system that obeys to the Korsmeyer–Peppas (0.98) and Bashkar (0.99) models. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

KEYWORDS: controlled release; mixed matrix membranes; FAU zeolite; LTA zeolite; Ibuprofen; transdermal patches

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INTRODUCTION

Ibuprofen (2-(4-isobutylphenyl) propionic acid) is a nonsteroidal anti-inflammatory drug used widely in rheumatoid arthritis, osteoarthritis, and in other painful conditions. Using conventional formulations, ibuprofen is rapidly absorbed, and the peak serum concentrations occur within 1–2 h.[1,2] Its short biological half life (~2 h) requires multiple daily dosing. To reduce the frequency of administration and to improve the patient compliance, a controlled release is necessary. Today, many polymers such as polyurethanes, polyanhydrides, and siloxanes are used for the development of controlled drug delivery devices.[3–5] In this context, different papers present in the open literature are focused on the oral sustained release of ibuprofen.[6–9] Transdermal patches are innovative drug delivery systems that give the possibility to by-pass the gastrointestinal tract avoiding both its irritation that normally occurs and partial first-pass inactivation by the liver.[10–13] Up to date, mixed matrix membranes (MMMs) were studied for gas and liquid mixture separations,[14–16] but the possibility to use them for a sustained drug release was not yet explored. In this work, MMMs loaded with different zeolite topologies [Faujasite (FAU) and Linde Type A (LTA)] were studied as a novel transdermal devices for the controlled release of ibuprofen. Zeolites are alumino-silicate materials having crystalline structure with 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.[17] These materials are used in different fields: industrial, agricultural, and pharmacological.[18] Several toxicological studies showed that the natural zeolite clinoptiolite is a nontoxic and safe material used in human and veterinary medicine.[19] It is ascertained as dermal uptake of the zeolite is negligible for long time on the undamaged skin.[20,21] For example, pharmaceutical zeolite-based compositions containing zinc and erythromycin have been used in the treatment of acne.[22] Besides, FAU zeolite acts as a slow release agent for different anthelmintic drugs.[23]

In this study, the release of ibuprofen from the MMMs was investigated with the aim to evaluate the effect of zeolite adsorption properties on the release kinetics. Besides, different mathematical models were used to determine the kinetics of drug release from drug delivery systems.

EXPERIMENTAL

Materials

Ibuprofen ((*RS*)-2-(4-(2-methylpropyl)phenyl) propanoic acid, $C_{13}H_{18}O_2$) was kindly supplied by Centro Ricerche per le Energie Non Convenzionali–Istituto Eni Donegani di Novara (Italy). Polydimethylsiloxane (PDMS, Sylgard (R) 184 silicone elastomer) polymer, used to prepare the membranes, was supplied by Dow Corning Co. NaX (Faujasite) and NaA (Linde type A)

Table I. Membranes with Different Drug and Zeolite Loadings

Membrane	PDMS (wt %)	Zeolite (wt %)	DL (wt %)
PDMS-IBU	98	-	2
PDMS-NaA(I)	93	5	2
PDMS NaA (II)	88	10	2
PDMS NaA (III)	78	20	2
PDMS NaX (I)	93	5	2
PDMS NaX (II)	88	10	2
PDMS NaX (III)	78	20	2
PDMS NaX (IV)	92	5	3
PDMS NaX (V)	91	5	4
PDMS NaY (I)	98	-	2
PDMS NaY (II)	93	5	2
PDMS NaY (III)	88	10	2

zeolites used to prepare the MMMs were purchased by Aldrich, whereas the NaY ((Faujasite) zeolite was kindly furnished by UOP. Zeolite crystals before using were purified by means of a centrifugation to enable the separation of the crystal fraction from the mother liquid. The solid phase was redispersed in distilled water and centrifuged again. 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. Acetonitrile (ACN, 99.9%) and dichloromethane (DCM, 99.5%) were purchased from Carlo Erba Reagenti (Italy).

HPLC Analysis

The quantitative determination of ibuprofen 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 m*M*, pH 7 (35/65 v/v). The operating conditions were: flow rate of 1.0 mL min^{-1}, temperature of 25°C, pressure of 110 bar, and wavelength of 220 nm.

Membrane Preparation

All the membranes were prepared *via* phase inversion technique using the dry method. PDMS membranes were obtained dissolving the two components of the polymer (curing agent and base with a ratio 1: 10 on weight basis) and the drug in DCM. The resulting solution was stirred magnetically for 3 h at room temperature and including three intervals of sonication (each of 10 min) to ensure a good dispersion of the drug. Afterward, the solution was poured in a Teflon plate and then it was put in an oven for 12 h at 60°C to allow the cross-linking of the material.

MMMs were prepared dispersing the zeolite in the solvent by sonication. Subsequently, the polymer and the drug were added to the zeolite suspension. The resulting slurry was stirred magnetically for 3 h, and the MMMs were prepared using the protocol already used for the PDMS membranes.

Table I shows the prepared membranes formulation at different zeolite type, concentration, and drug loading (DL).

Zeolite and Membrane Characterization

The morphology of the zeolites and of the prepared membranes were investigated by scanning electron microscopy (SEM) using a Cambridge Zeiss LEO 400 microscope. The Si/Al ratio of the zeolite crystals was determined by means of energy dispersive X-ray (EDX) performed with EDAX-Phoenix (SUTW Detector, analyzer: Si/Li crystal). Powder X-ray diffractometry (XRD) with a Philips PW 1730/10 X-ray diffractometer (using Ni filtered Cu $K_{\alpha 1} + K_{\alpha 2}$, $k =$ 1.542 Å) was also performed on zeolites to confirm their topology.

The thickness of the membranes has been measured by using a digital micrometer (Carl Mahr D7300 Esslingen a.N.) averaging 15 measurements, the standard deviation calculated on the sample was always lower than 5%.

In Vitro Release

The drug release tests were carried out as reported in the literature.[24,25] The membranes were immersed in 0.5 L of phosphate-buffer solution (50 m*M*, pH 7.4) and placed inside the incubator maintained at 37°C under continuous stirring. At predetermined time intervals, 500 μL of medium was withdrawn. 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:

$$\text{Drug release}\,(\%) = {}^{M_t}/_{M_i} \cdot 100 \tag{1}$$

where M_i is the initial amount of drug and M_t is the amount of drug released at the time t, respectively. All experiments were repeated three times, and the results were in agreement within ±4% standard error.

Release Profile Analysis

The release data were fitted with different mathematical models (zero order, first order, Higuchi, Bhaskar, and Korsemeyer-Peppas) to give a possible explanation of the release mechanism of the drug from MMMs.

The zero order equation is:

$$Q_t = Q_0 + k_0 t \tag{2}$$

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.[26] This model represents the drug release from matrix tablet and transdermal devices.[27]

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

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

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.[26]

The Higuchi model is described by the eq. (4):

$$\frac{M_t}{M_\infty} = k_H t^{\frac{1}{2}} \tag{4}$$

Table II. Interpretation of Diffusional Release Mechanisms from Polymeric Films

Release exponent (*n*)	Drug transport mechanism
0.5	Fickian release
>0.5 <1	Non Fickian release
1	Anomalous release

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, and (5) drug diffusivity is constant.[26] 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.[28,29]

The eq. (5) describes the Bhaskar model:

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

where B is the kinetic constant. This model is used to describe the drug diffusion through the resins and inorganic materials.[30,31]

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

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

where k is a release rate constant that incorporates structural and geometric characteristics of the release device and n is the release exponent indicative of the release mechanism as reported in Table II.[32]

RESULTS AND DISCUSSION

Zeolite and Membrane Characterization

The morphology of the different zeolites is shown in Figure 1. They present different dimensions: 5 μm for NaA (a), 4 μm for NaX (b), and 0.4 μm for NaY (c).

The Si/Al ratio is 1.0 for NaA, 1.23 for NaX, and 54 for NaY. The results indicate that the zeolites NaA and NaX present hydrophilic properties (low Si/Al ratio), whereas NaY is the most hydrophobic (high Si/Al ratio). The hydrophilic character of zeolite is due to the presence of aluminum in the structure. In fact, aluminum occurs in nature as trivalent specie, but in the zeolite structure it is tetra-coordinated and presents a negative charge. Moreover, being the zeolite a neutral system, the negative aluminum charge is counterbalanced by extra-structural metal cations (such as Na^+ and Ca^{2+}).[33]

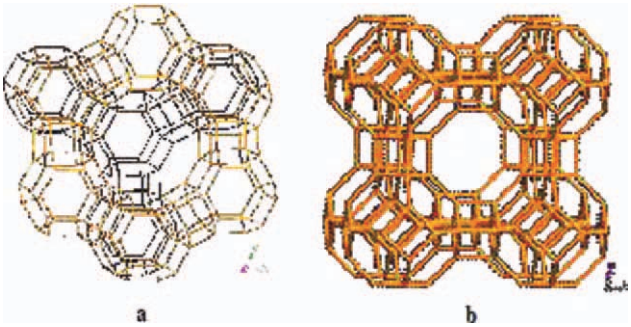

Figure 2. (a) FAU and b) LTA topologies.[34] [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

XRD analyses confirmed Faujasite (FAU) topology for NaX and NaY zeolites. This topology is characterized by the presence of supercages with a diameter of 13 Å interconnected by pores of about 7 Å [see Figure 2(a)]. The NaA exhibits a Linde Type A (LTA) topology showing pores of about 4 Å [see Figure 2(b)].

SEM micrographs of the air and Teflon side are shown in Figure 3(a–f).

The top-view of the PDMS-IBU membranes is very smooth [Figure 3(a,b)]. The SEM analysis of MMMs showed the same morphological characteristics. Air and Teflon sides of PDMS-NaA loaded with 5 wt % [Figure 3(c,d)] and 20 wt % [Figure 3(e,f)] of zeolite are also showed. All micrographs show that the crystals are well embedded in the rubbery matrix indicating a good interaction between the two different materials. The absence of defects is due to the choice of an elastomer as polymer characterized of a high mobility of its polymeric chains that ensure a good interaction with the inorganic particles.[14]

At high zeolite concentration (20 wt %), the formation of zeolite clusters occurs. This phenomenon is more evident when NaY zeolite is used due to its small particle size (see Figure 4).

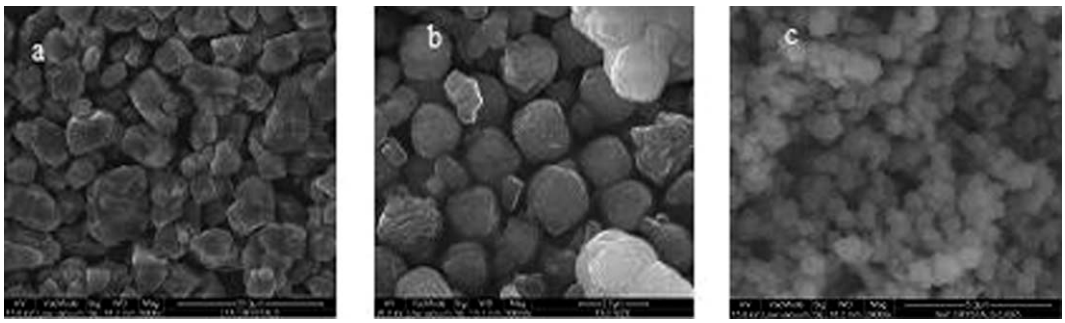

Figure 1. SEM images of the zeolites: NaA (a), NaX (b), and NaY (c).

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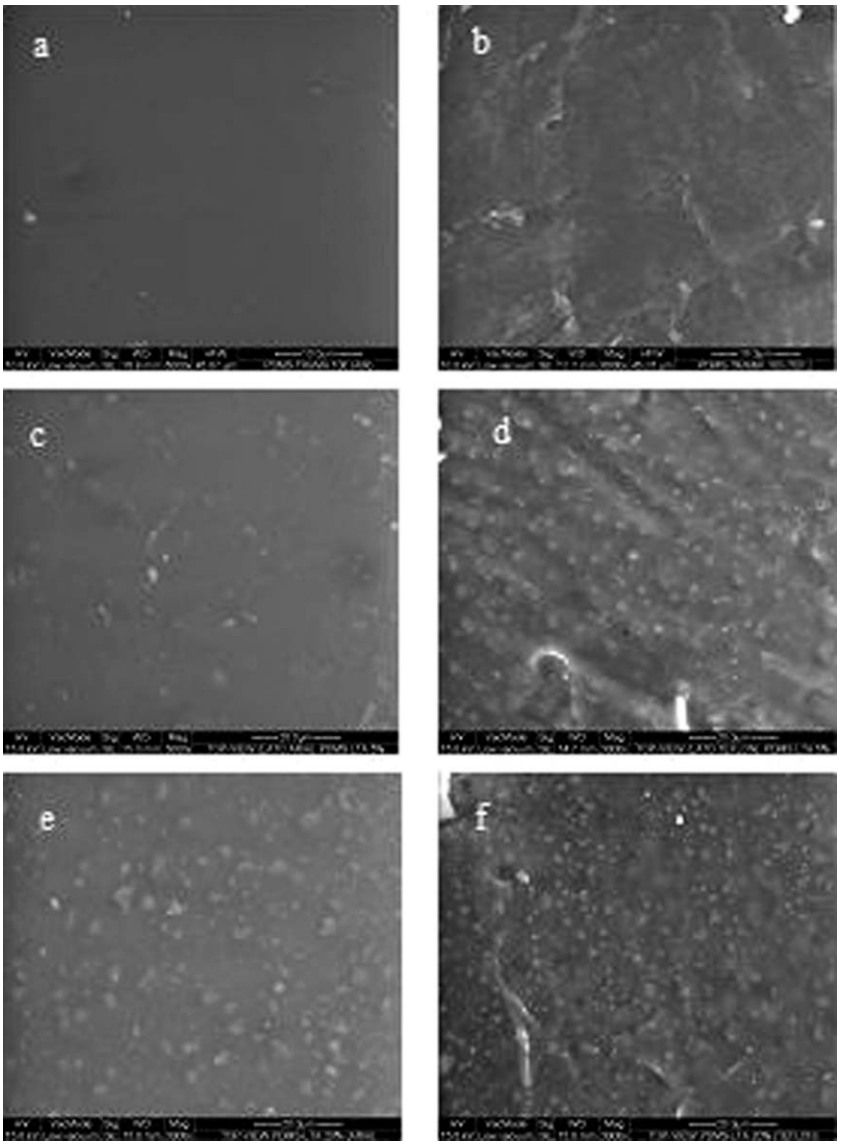

Figure 3. PDMS-IBU: (a) air and (b) Teflon side. PDMS-NaA (I): (c) air side and (d) Teflon side. PDMS-NaA (III): (e) air and (f) Teflon side.

The thickness of the prepared membranes ranged from 500 to 700 μm. Measurements performed by SEM analysis are in agreement with the results obtained by using the digital micrometer.

Release Studies

After membrane preparation and morphology characterization, studies *in vitro* were performed to evaluate the effect of some factors on the release of ibuprofen. The main parameters investigated were: zeolite concentration, its hydrophilic/hydrophobic character, and DL.

Figure 5 shows the release behavior of ibuprofen from MMMs loaded with 5 wt % of different zeolite types and 2% DL.

In the case of the PDMS-based membrane, the kinetic release was low due to the hydrophobic properties of this material that hindered the interactions between the drug and the release medium. About the MMMs, the presence of the zeolites determined a higher release kinetic owing to their hydrophilic

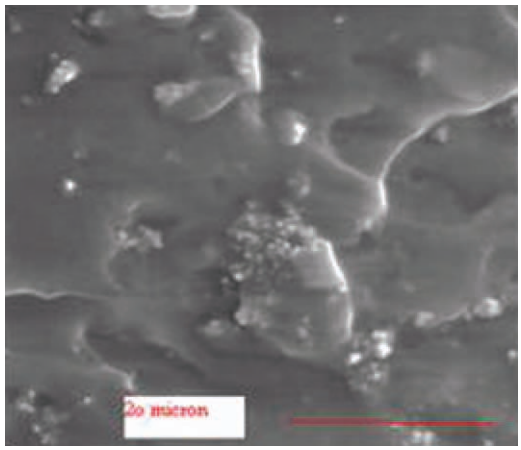

Figure 4. Cross section of the PDMS-NaY (III). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

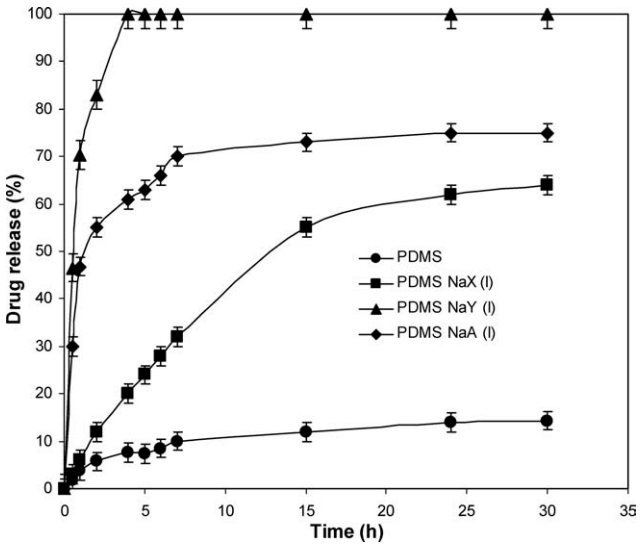

Figure 5. Effect of zeolite type on ibuprofen release from mixed matrix membranes containing 5 wt % of zeolite and 2% DL.

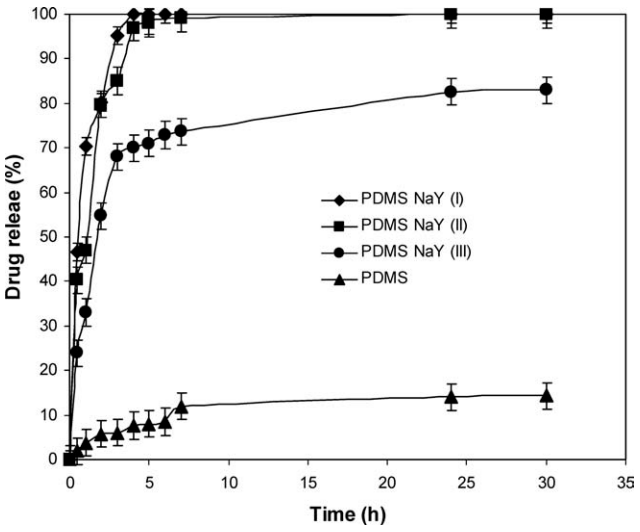

Figure 7. Effect of zeolite concentration on ibuprofen release from PDMS-NaY membranes (2% DL).

character with respect to the pure PDMS. However, the release profile changed as a function of the different type of zeolite due to their different aluminum content. Above all, as the Al content increases (low Si/Al ratio) the interaction of the drug with the zeolite crystals also increases leading to a less pronounced delivery to the medium. In fact, as reported by Horcajada and coworkers[9] in the zeolites with higher aluminum content, the ibuprofen is more strongly bounded to the zeolite surface (by coordinative bound of ibuprofenate and Al species). When the Al content is low (high Si/Al ratio), the Van der Waals interactions between the drug and the silicon present in the zeolite framework are predominant. This determines a high release rate. In fact, the PDMS NaY (I) showed a "burst effect." This because the NaY zeolite is characterized by a low aluminum content (Si/Al = 54) with respect to the NaX (Si/Al = 1.23) and NaA (Si/Al = 1.0) zeolites. Considering the other two zeolite types, the release profile of the MMMs containing NaX crystals was more linear and slower in the time than the system containing the zeolite NaA, despite in the latter the Al content is highest. This result can be explained considering that ibuprofen can enter in the supercages (13 Å) of the NaX zeolite leading to a slow down in drug release.[9] The effect of the zeolite concentration on the drug release for the different systems investigated is shown in the Figures 6–8.

In all cases, it is possible to note a threshold value for the zeolite concentration above which the release rate decreases. This result is due to two different aspects. First of all, the formation of zeolite clusters (at high zeolite concentration) into the polymeric matrix that hinder the release of the drug. Second, the increase of the zeolite concentration from 10 to 20 wt %

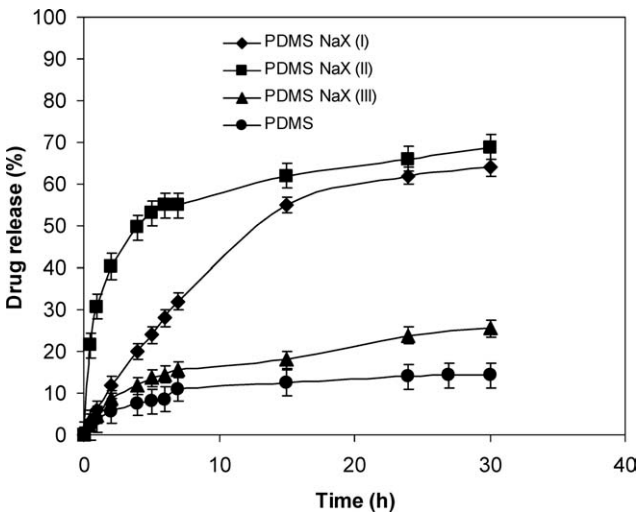

Figure 6. Effect of zeolite concentration on ibuprofen release from PDMS-NaX membranes (2% DL).

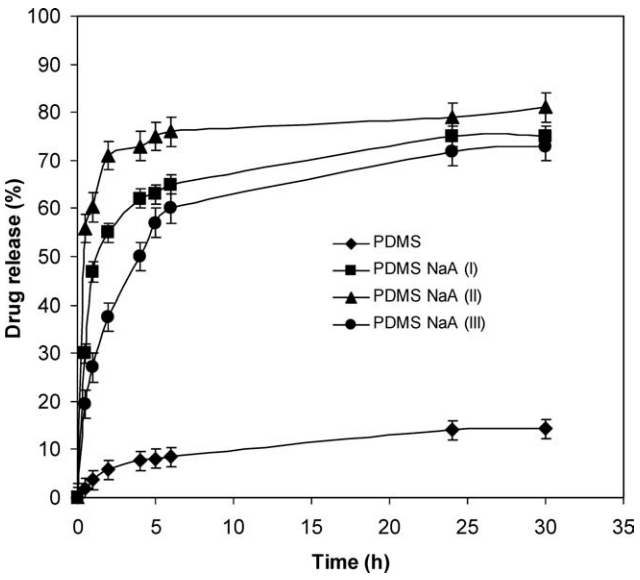

Figure 8. Effect of zeolite concentration on ibuprofen release from PDMS-NaA membranes (2% DL).

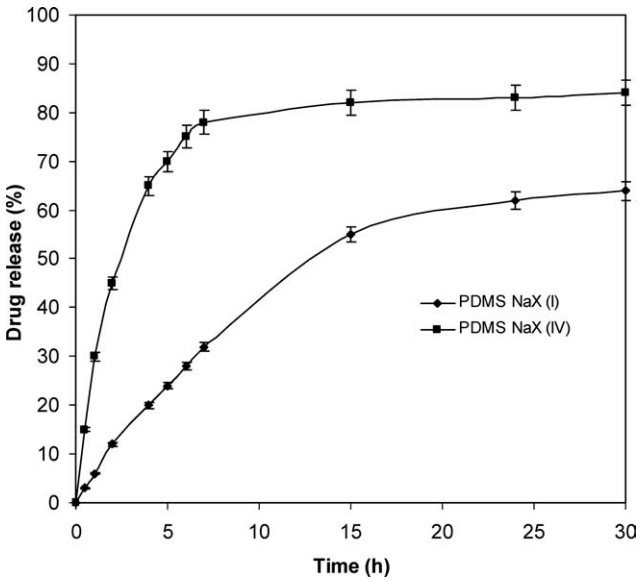

Figure 9. Effect of drug loading on the release of ibuprofen from PDMS NaX membranes.

determines a more tortuous diffusion pathway of the drug into the polymeric matrix.[35]

About the different investigated systems, the PDMS NaX (I) membrane seems to be the most promising for application as transdermal device. On the basis of these results, other PDMS NaX membranes loaded with the same amount of the zeolite (5 wt %) and different drug amount (3% DL and 4% DL) were prepared and tested. Figure 9 shows as increasing the DL from 2 to 3% the release of ibuprofen in the time also increases but the profile is no longer linear. This behavior is due to an increase of the drug concentration gradient between membrane and release medium.

Membranes prepared with 4% DL were not useful for release study because the drug crystallized and precipitated in the membrane matrix probably because its amount exceeds the solubility limit in the polymer.[25]

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 model that best fits the release data was evaluated by correlation coefficient (R^2). The fitting equations and the R^2 are given in Table III.

The kinetic data of the PDMS IBU showed good fit with the Higuchi model (R^2 pari a 0.97). In the case of MMMs, the correlation coefficients are very far from the unit value except for the PDMS NaX (I) system that obeys to the Korsmeyer–Peppas (0.98) and Bashkar (0.99) models. Regarding the Korsmeyer–Peppas's model, this membrane system exhibited a release exponent of 0.60 indicating a non-Fickian transport behavior of the drug from the device. However, these mathematical models do not describe very well this transdermal device because they do not take into account the presence of filler into the polymer.

CONCLUSIONS

In this work was demonstrated that PDMS NaX (I) membranes are promising as devices for the transdermal controlled release of ibuprofen. The experimental data indicate as this hydrophilic zeolite allowed to modulate the ibuprofen release with respect to the pure PDMS membrane. 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 kinetic data of the PDMS IBU showed good fit with the Higuchi model (R^2 pari a 0.97). In the case of MMMs, the correlation coefficients are very far from the unit value except for the PDMS NaX (I) system that obeys to the Korsmeyer–Peppas (0.98) and Bashkar (0.99) models. Regarding the Korsmeyer–Peppas's model, this membrane system exhibited a release exponent of 0.60 indicating a non-Fickian transport behavior of the drug from the device.

Table III. Kinetics of Drug Release from MMMs

	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-IBU	0.52	0.85	0.04	0.87	0.05	0.95	0.03	0.97	0.45	0.95
PDMS-NaA(I)	0.32	0.49	0.03	0.70	0.04	0.87	0.11	0.71	0.20	0.87
PDMS NaA (II)	0.13	0.32	0.03	0.54	0.04	0.85	0.10	0.51	0.10	0.90
PDMS NaA (III)	0.12	0.40	0.03	0.50	0.03	0.65	0.10	0.67	0.30	0.84
PDMS NaX (I)	0.02	0.90	0.03	0.97	**0.05**	**0.99**	0.12	0.95	**0.60**	**0.98**
PDMS NaX (II)	0.06	0.53	0.03	0.70	0.04	0.85	0.11	0.80	0.31	0.92
PDMS NaX (III)	0.07	0.81	0.07	0.87	0.01	0.95	0.04	0.95	0.52	0.95
PDMS NaX (IV)	0.17	0.48	0.04	0.64	0.06	0.80	0.13	0.75	0.34	0.90
PDMS NaX (V)	0.02	0.50	0.05	0.71	0.08	0.85	0.15	0.75	0.38	0.95
PDMS NaY (I)	0.15	0.37	0.08	0.47	0.13	0.50	0.13	0.61	0.21	0.83
PDMS NaY (II)	0.01	0.40	0.06	0.49	0.11	0.50	0.11	0.50	0.20	0.68
PDMS NaY (III)	0.01	0.42	0.02	0.57	0.10	0.57	0.10	0.57	0.40	0.88

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