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Mixed matrix membranes as potential transdermal devices for gemfibrozil release

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ABSTRACT: Aim of this work was the development of mixed matrix membranes as potential devices for transdermal controlled release of gemfibrozil (2,2-dimethyl-5-(2,5-dimethylphenoxy) pentanoic acid). The effect of the hydrophilic NaX zeolite and of drug loading on the release kinetics of the drug was investigated. The material used as membrane matrix was polydimethylsiloxane. Scanning electron microscopy analysis showed as zeolite crystals were well embedded into the polymeric matrix. Membrane characterizations by means of swelling ratio, moisture uptake, and erosion degree determination indicated low swelling degree and moisture uptake, and the absence of erosion. This results confirmed as these membranes did not promote bacterial growth and skin irritation. The performance of the membranes was evaluated by performing *in vitro* release studies and percutaneous tests through the stratum corneum taken from the skin of rabbit ear. *In vitro* experiments indicated as the best system was the membrane containing 12 wt % of zeolite and 2.6 wt % of gemfibrozil (PDMS-2.6GEM-12NaX) and so it was used in the percutaneous tests. In this case, the permeation rate was lower owing to the presence of an additional resistance applied by rabbit skin. An interesting result was the linear behavior indicating that the permeation of the drug thorough the device occurred with zero-order kinetic which is the feature of the transdermal controlled delivery systems. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 41698.

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INTRODUCTION

Controlled drug delivery science has been rapidly developed and became one of the most important field in modern medication. Particular attention was focused on the development of innovative transdermal delivery devices owing to their advantages over the traditional dosage forms. The extremely interesting aspect of this kind of administration is the possibility to by-pass the gastrointestinal tract avoiding both side gastric effects and the partial first-pass inactivation at liver level.[1–4] Additional beneficial impacts are the reduction of the administration frequency and the improvement of patient compliance.[5] For these reasons and taking into account the possibility to synthesize a wide range of polymeric materials like polyurethanes, polyanhydrides and siloxanes,[6–9] the transdermal administration route by means of patches rapidly attracted the attention of the scientists. Transdermal delivery patches are medicated adhesives that are placed on the skin to release an exact dose of drug through the skin into the blood circulation.[10]

In this work, for the first time, were developed mixed matrix membranes as potential devices for the transdermal controlled release of gemfibrozil (GEM). This drug is a lipid-lowering agent used in dyslipidemic disease which is characterized by an increase in triglycerides and decreased of HDL cholesterol concentrations.[11] Currently, the drug is administered orally but it presents some weaknesses like short half life (~1.5 h),[12] gastric side effects, and the requirement of multiple daily dosage. Owing to these disadvantages, the possibility to administer the drug via controlled transdermal route may be convenient to avoid the different side effects.

Until a few years ago, mixed matrix membranes (MMMs) were used for gas and liquid separations.[13–15] In a mixed matrix membrane inorganic fillers (such as zeolites, carbon molecular sieves, silica and carbon nanotubes) are dispersed into a polymeric matrix. This system combines the characteristics of the polymer with the peculiar properties of the inorganic materials.[16] The use of a rubbery polymers permits to prepare defect free mixed matrix membranes owing to the high mobility of the polymeric chains that well incorporate the inorganic particles.[13] On the contrary, when glassy polymers are used, membranes present defects at the organic–inorganic interface due to the high rigidity of the polymeric chains.[16] Recently, Algieri *et al.*[17] and Donato *et al.*[18] demonstrated as MMMs could be used as

transdermal drug delivery devices. In this work was successfully established the possibility to administer the GEM via transdermal route instead of the conventional dosage form using MMMs (NaX zeolite loaded) as potential patches. Polydimethylsiloxane (PDMS) was used as membrane forming material. This polymer was used due to its biocompatibility and high chains mobility.

Zeolites are alumino-silicate microporous (pore size in the range 3–10 Å) materials having a crystalline structure. It is possible to change the adsorption properties of the zeolites varying the Si/Al ratio during the synthesis.[19] Different studies have demonstrated the possibility to use these materials in pharmacological field.[16,17,20–24] Various toxicological researches evidenced also as the dermal uptake of the zeolite on the undamaged skin is negligible for long time.[20–22] These materials, for their characteristics, are used in the treatment of acne and as a slow release agent of different anthelmintic drugs.[21–23]

The NaX zeolite used in this work was chosen as filler owing to its hydrophilic properties which allowed to reduce the hydrophobic nature of PDMS and therefore to increase the release kinetics. The performance of the membranes was evaluated by means of the study of the effect of the zeolite and drug content on the release behavior of GEM.

Different mathematical models (zero order, first order, Higuchi, Bhaskar, and Korsemeyer–Peppas) were used to interpret the drug release mechanism from the system that exhibited the best performance.

EXPERIMENTAL

Materials

Gemfibrozil (2,2-dimethyl-5-(2,5-dimethylphenoxy) pentanoic acid, $C_{15}H_{22}O_3$) was purchased from Sigma Aldrich. Polydimethylsiloxane (PDMS) (Sylgard (R) 184 silicone elastomer) was supplied by Dow Corning. It presents 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). Hexane (C_6H_{14}, 98.5%) and acetonitrile (ACN, 99.9%) were purchased from Sigma Aldrich. NaX zeolite (faujasite type) was provided by Aldrich (Si/Al = 1.23). Before using, zeolite crystals were purified using a series of centrifugation and rinsing steps to remove the amorphous materials. The procedure was repeated to reduce the pH value from 10 to 7. Finally, the zeolite particles were activated at 500°C and stored into a dryer to avoid moisture adsorption.

Membrane Preparation

Membranes were prepared via the phase inversion technique by means of the dry method.[18] Referring to the pure PDMS, the procedure was initiated dissolving the two components of the polymer (curing agent and base with a ratio 1 : 10 on weight basis) and the drug in the solvent (hexane). The solution was stirred magnetically for 2 h at room temperature and then was uniformly casted onto a Teflon support by means of a hand-casting knife (knife gap was set at 350 μm). Afterwards, the support was left in contact with the air for overnight and then put in an oven for 12 h at 40°C to consent the cross-linking of the polymeric material.

Table I. Composition of the Different Prepared Membranes

Membrane	PDMS (wt %)	NaX (wt %)	DL (wt %)
PDMS	100	–	–
PDMS-1.4GEM	98.6	–	1.4
PDMS-1.4GEM-5NaX	93.6	5	1.4
PDMS-1.4GEM-12NaX	86.6	12	1.4
PDMS-1.4GEM-16NaX	82.6	16	1.4
PDMS-1.4GEM-20NaX	78.6	20	1.4
PDMS-2.6GEM	97.4	–	2.6
PDMS-2.6GEM-5NaX	92.4	5	2.6
PDMS-2.6GEM-12NaX	85.4	12	2.6
PDMS-2.6GEM-16NaX	81.4	16	2.6
PDMS-2.6GEM-20NaX	77.4	20	2.6

The preparation of MMMs was started solubilizing the drug in the solvent and dispersing, then, the zeolite. Subsequently, to the slurry was added the polymer and the system was stirred for 3 h.

Afterwards, the suspension was casted onto a Teflon support with a casting knife having a gap of 350 μm. After, it was left in contact with the air for overnight and then put in an oven for 12 h at 40°C.

Table I shows the composition, in terms of polymer, zeolite, and drug loading (DL) of the different prepared membranes.

Morphological Analysis

Top-view and cross-section of the prepared membranes were observed by scanning electron microscopy (SEM) using a Cambridge Zeiss LEO 400 microscope.

The thickness of the membranes was measured 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%.

Measurement of Swelling Erosion and Moisture Uptake

Swelling ratio, erosion, and moisture uptake determinations were carried on the different samples.[25] The swelling ratio and erosion tests were performed by drying films (area of 4 cm^2) at 60°C for the time required to eliminate moisture of the sample (constant weight). The films were weighed (W_0) and immersed in 15 mL of distilled water at 37°C for the time necessary to reach constant weight.[26] After removal of water excess, the hydrated films were re-weighed (W_s). The percentage of swelling ratio was calculated using the following equation:

$$\text{Swelling ratio}\,(\%) = \left(\frac{W_s - W_0}{W_0}\right) \times 100. \qquad (1)$$

After the swelling test, the same samples were again dried at 60°C overnight and weighed (W_d). The percentage of erosion was calculated as the loss of weight ($W_0 - W_d$) compared to the initial film weight (W_0).

$$\text{Erosion}\,(\%)=\left(\frac{W_0-W_d}{W_d}\right)\times 100. \quad (2)$$

The moisture uptake tests were performed putting samples having an area of 4 cm^2 into a desiccators (with silica gel beads) for 24 h. Membranes were then weighed to obtain an initial value (W_0) and transferred into desiccators under a saturated sodium chloride environment that generates a 75% relative humidity. The specimens were removed and weighed in the time until their weight was constant (W_f). The percentage of moisture uptake was calculated as the increased weight ($W_f - W_0$) compared to the initial weight (W_0).

$$\text{Moisture uptake}\,(\%)=\left(\frac{W_f-W_0}{W_0}\right)\times 100. \quad (3)$$

In Vitro Release Studies

The drug release tests were performed as described in literature.[26,27] The membranes were incubated in 0.5 L of phosphate-buffer solution (50 m*M*, pH 7.4) and maintained at 37°C under stirring. The release media were collected at regular intervals of time. The concentration of the drug present in the medium was determined by HPLC analysis using a LaChrom D7000 HPLC system (Hitachi) equipped with L-7400 UV detector. Analysis was done using the column Alltima HP C18, 5 μm, 250 × 4.6 mm^2 (Grace, Milano). The mobile phase was acetonitrile/PBS 50 m*M* at pH = 7.4 (40/60, v/v). The operating conditions were: flow rate of 1.00 mL/min, temperature of 30°C, pressure of 119 bar, and wavelength of 200 nm.

The cumulative percentage of released GEM percent was calculated using the following equation:

$$\text{Drug release}\ (\%)=\frac{M_t}{M_i}\times 100, \quad (4)$$

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

Transdermal Permeation Studies

In vitro skin permeation studies were performed using a vertical diffusion Franz cell[28] with an effective diffusion area of 4.9 cm^2 (see Figure 1).

The experiments were performed using the stratum corneum of rabbit ear skin. The skin, previously frozen at −18°C, was pre-equilibrated in physiological solution at room temperature for 2 h before the experiments. A circular piece of this skin was sandwiched securely between the receptor and donor compartments: epidermal side of the skin was exposed to ambient condition while dermal side was kept facing to receptor solution. The donor compartment was empty and the donor phase was the membrane which was strictly put in contact with the epidermal side of rabbit skin. The receptor compartment was filled with 20 mL of phosphate-buffered (pH = 7.4) which was maintained at 37 ± 0.5°C and stirred by means of a magnetic bar. Before starting the experiments the donor cell was sealed with parafilm. At regular intervals up to 24 h the medium in the receiving compartment was removed and replaced with an equal volume of pre-heated (37 ± 0.5°C) fresh buffer. The concentration of GEM in the collected samples was analyzed by HPLC. Each experiment was performed in triplicate and the results were in agreement within ±4% standard error.

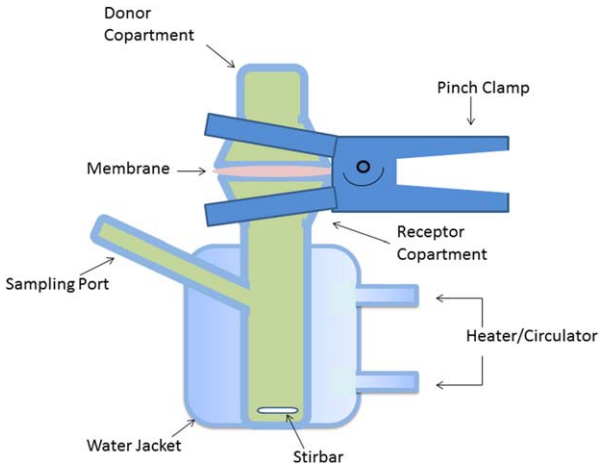

Figure 1. Scheme of the Franz diffusion cell. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Release Profile Analysis

Different mathematical models (zero order, first order, Higuchi, Bhaskar, and Korsemeyer–Peppas) were fitted with the release data for interpreting the release mechanism of the GEM from the membranes. The zero-order equation is:

$$Q_t = Q_0 + k_0 t, \quad (5)$$

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.[29] This model describes the drug release from transdermal devices and matrix tablet.[30]

The first-order kinetics is expressed by the eq. (6):

$$-\log\left(1-\frac{M_t}{M_\infty}\right)=\frac{kt}{2.303}, \quad (6)$$

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 study the release of the drug soluble in water.[29]

The Higuchi model is described by the following equation:

$$\frac{M_t}{M_\infty}=k_H t^{\frac{1}{2}}, \quad (7)$$

where k_H is the Higuchi dissolution constant. This model is adapted to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as some transdermal systems and matrix tablets using water soluble drugs.[31,32]

The Bhaskar model is used to describe the release process where the diffusion through inorganic and resinate particles is the rate-limiting step[33,34]:

$$-\log\left(1-\frac{M_t}{M_\infty}\right)=Bt^{0,65}. \quad (8)$$

In this equation, B is the kinetic constant.

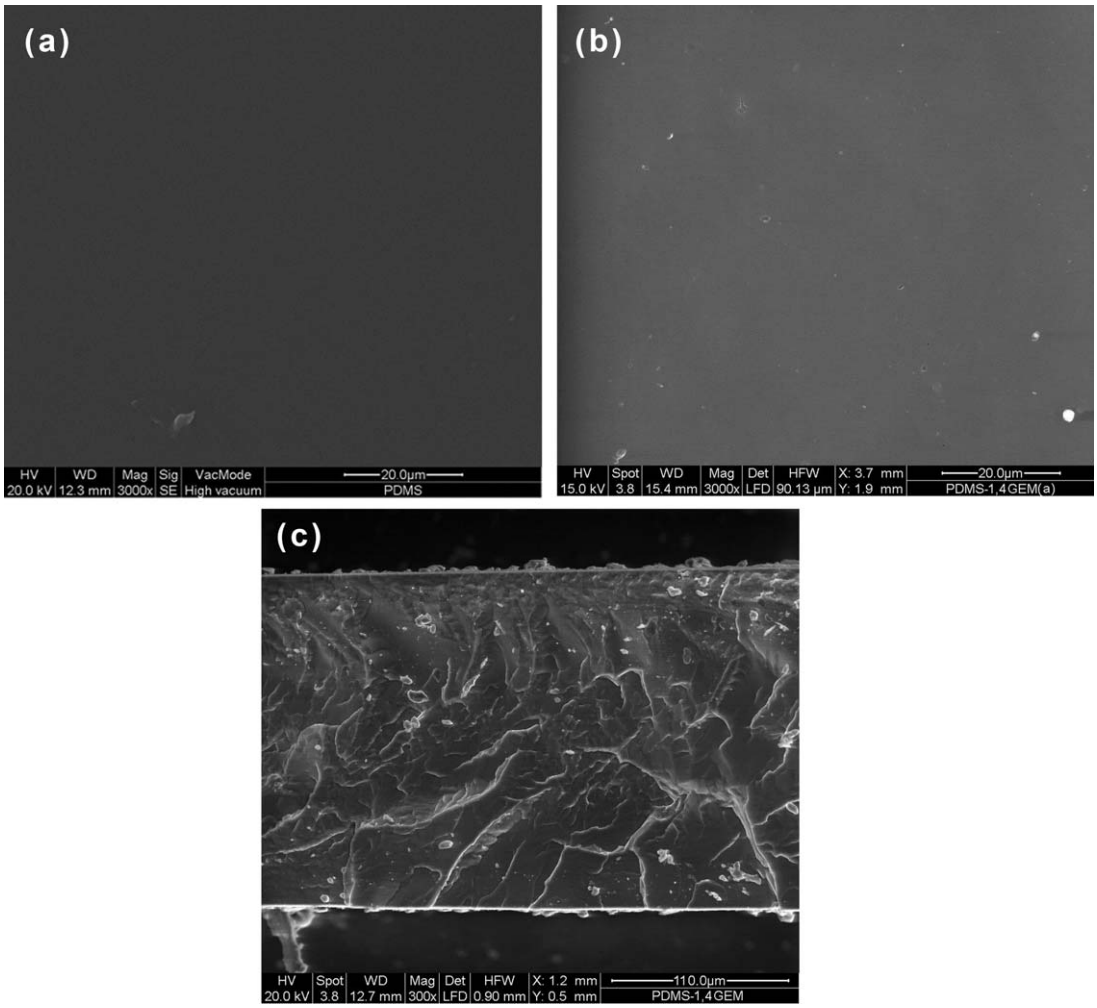

Figure 2. SEM images of: (a) top-view of PDMS membrane; (b) top-view and (c) cross-section of PDMS-1.4GEM membrane.

The Korsemeyer–Peppas model is expressed by the following equation:

$$\log \frac{M_t}{M_\infty} = \log k + n \log t, \quad (9)$$

where k is a release rate constant that incorporates structural and geometric characteristics of the release device and n is the release exponent.[35]

RESULTS AND DISCUSSION

SEM analysis revealed as the top-view (air side) of the pure PDMS and PDMS-1.4 GEM membranes exhibited a very smooth surface [Figure 2(a,b)], demonstrating as the presence of the drug into the polymeric matrix did not change the morphology. In addition, the cross-section of PDMS-1.4 GEM [Figure 2(c)] clearly showed a good distribution of the biomolecules into the membrane.

SEM analyses of MMMs evidenced crystals well embedded into the polymeric matrix indicating the absence of defects (owing to a good interaction between the two different materials). The absence of defects is due to the high mobility of the polymeric chains of the PDMS.[14,17,18]

Air and Teflon sides and cross-section of the PDMS-2.6GEM-5NaX sample are shown in Figure 3(a–c). The presence of zeolite clusters along the cross-section of the membranes containing 16 wt % and 20 wt % of zeolite is observable in Figure 3(d,e), respectively. For comparison, the cross-section of the membrane loaded at 12 wt % of NaX is shown in Figure 3(f). The formation of clusters can be explained taking into account that when the zeolite concentration increases also raise the cohesive forces between the particles.[36] Figure 3(g) shows the NaX zeolite crystals used for preparing MMMs. As it can be seen, the size of crystals is about 2 μm.

The thickness of the prepared membranes ranged from 230 to 430 μm (see Table II). Measurements performed by SEM analysis were in agreement with the results obtained using the digital micrometer.

The swelling of the PDMS membranes was negligible. The addition of the hydrophilic zeolite (5 wt % and 12 wt %) into the polymeric matrix determined a slight increase of the swelling

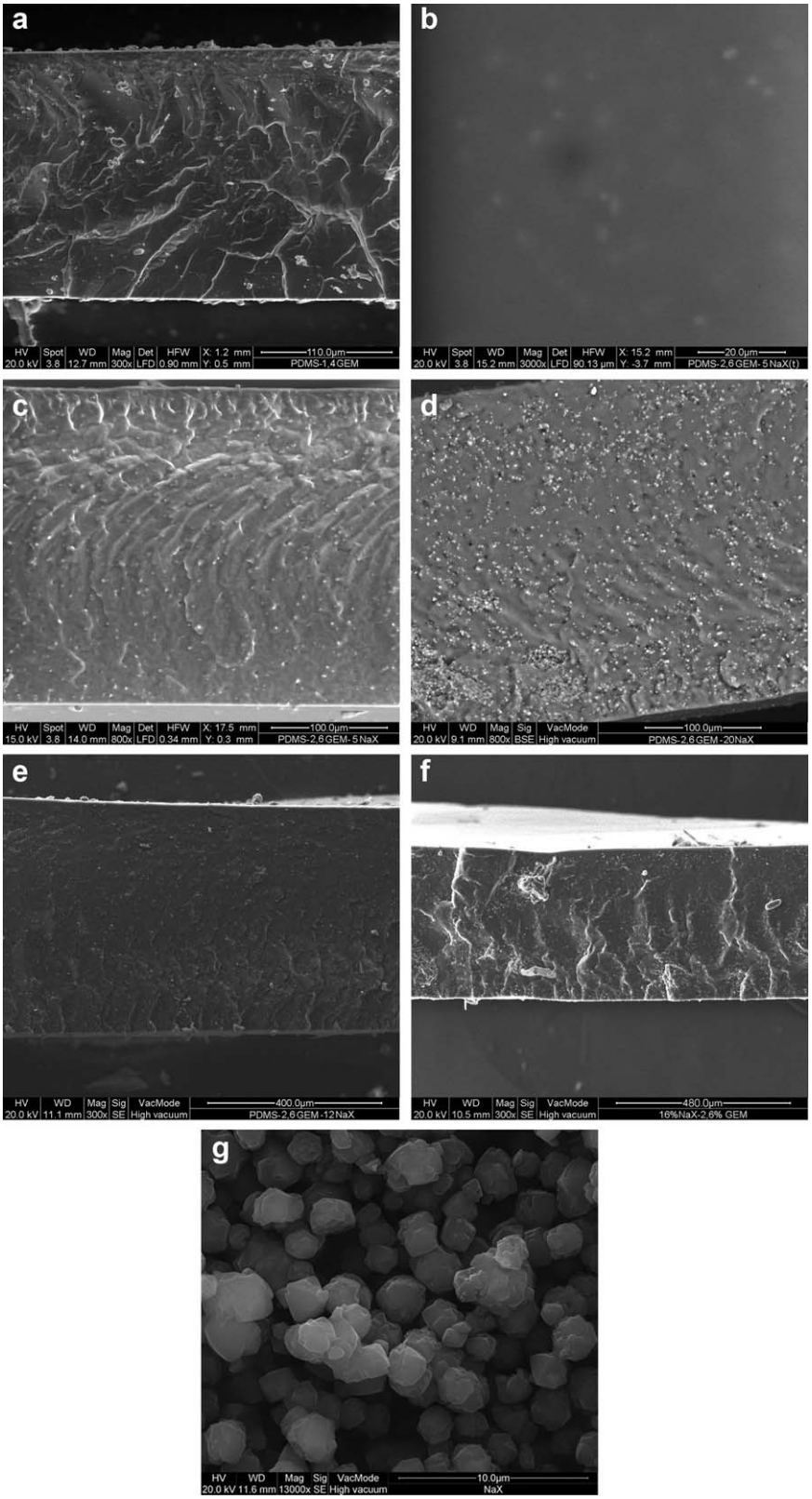

Figure 3. SEM images of: PDMS-2.6GEM-5 NaX (a) air side; (b) teflon side; and (c) cross-section; PDMS-2.6GEM-16NaX (d) cross-section; PDMS-2.6GEM-20NaX (e) cross-section; PDMS-2.6GEM-12NaX (f) cross-section; NaX zeolite crystals (g).

Table II. Thickness of the Different Membranes

Sample	Thickness (μm)
PDMS	240
PDMS-1.4GEM	231
PDMS-2.6GEM	274
PDMS-1.4GEM-5NaX	290
PDMS-1.4GEM-12NaX	336
PDMS-1.4GEM-16NaX	409
PDMS-1.4GEM-20NaX	432
PDMS-2.6GEM-5NaX	310
PDMS-2.6GEM-12NaX	351
PDMS-2.6GEM-16NaX	415
PDMS-2.6GEM-20NaX	426

(see Table III). However, a further increase of the zeolite content from 12 to 20 wt % caused a decrease of the swelling because the flexibility of the polymer chains in the zeolite-filled membranes decreased.[37,38] As a consequence, the free volume of the polymer was reduced and therefore the membrane acquired less sorption ability.[38,39] As it is reported in Table III, low moisture uptake and the absence of erosion were observed independently of zeolite content and DL. All these results evidenced as the prepared membranes could be used as transdermal patches as they do not favor both the microbial growth and the irritation of the skin. In fact, it is well known that moisture causes skin damage determining at the same time the onset of related problems (like bacterial and fungal infections and allergic dermatitis).[40,41] In addition, as it is confirmed in literature, the small moisture content of transdermal patches helps them to remain stable and protected from microbial contamination.[42]

The performance of the membranes was investigated realizing *in vitro* release studies aiming to evaluate the effect of zeolite content and DL on the release kinetics of GEM. The release profile of the GEM from pure PDMS and from mixed matrix membranes at fixed DL (1.4 and 2.6) and different zeolite content (from 5 to 20 wt %) is shown in Figure 4. In the case of the PDMS membrane, the release was very low due to the high hydrophobicity of this polymer that hindered the interactions between the drug and the release medium. The addition of the hydrophilic NaX zeolite into the polymeric matrix determined an increase of the release rate because the zeolite crystals increased the wettability of the membranes. However, a threshold value was observed at 12 wt % of zeolite above which the release rate decreased. This behavior is due to the combination of different effects: the decrease of polymer chains flexibility (as reported above), the hydrophilic nature of the filler, and the presence of zeolite clusters that englobes some drug molecules preventing their release. In addition, the GEM molecules encountered a more tortuous pathway into the membrane matrix.[23,36]

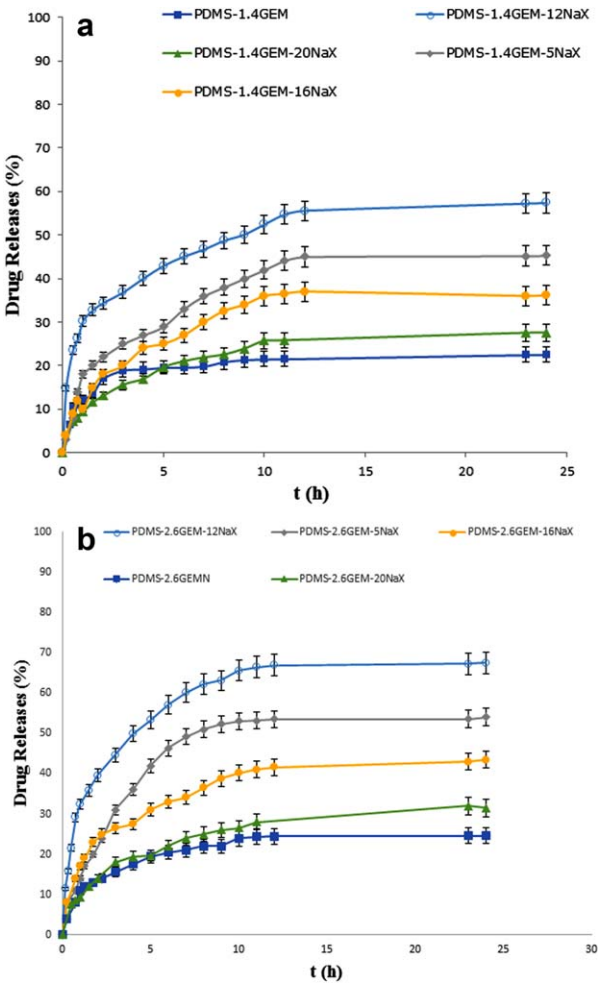

Figure 4. (a) Effect of the zeolite content on GEM release from pure PDMS membrane and MMMs (1.4 DL); (b) effect of the zeolite content on GEM release from pure PDMS membrane and MMMs (2.6 DL). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table III. Swelling Ratio, Erosion, and Moisture Uptake of the Prepared Membranes

Membrane	Swelling ratio (%)	Erosion (%)	Moisture uptake (%)	Moisture content (%)
PDMS	0.07	0.07	0.13	0.07
PDMS-1.4GEM	0.08	0.09	0.14	0.07
PDMS-1.4GEM-5NaX	0.85	0.06	0.52	0.51
PDMS-1.4GEM-12NaX	1.00	0.10	0.63	0.73
PDMS-1.4GEM-16NaX	0.70	0.8	0.71	0.68
PDMS-1.4GEM-20NaX	0.50	1.0	0.80	0.60
PDMS-2.6GEM	0.09	0.10	0.16	0.09
PDMS-2.6GEM-5NaX	0.75	0.41	0.42	0.56
PDMS-2.6GEM-12NaX	1.2	0.63	1.10	1.05
PDMS-2.6GEM-16NaX	0.80	0.85	1.03	0.91
PDMS-2.6GEM-20NaX	0.58	1.0	0.90	0.80

About the influence of the membrane thickness on the release rate, the experimental results evidenced a marked effect at high zeolite content (16 wt % and 20 wt %). On the contrary, at

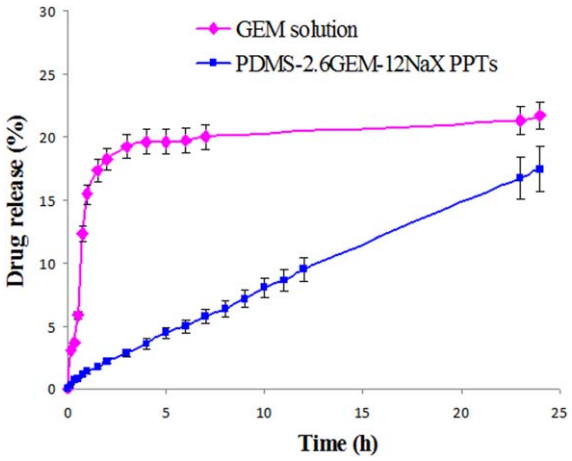

Figure 5. GEM permeation from: PDMS-2.6GEM-12NaX and free GEM solution. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

lower zeolite content (5 wt % and 12 wt %), the effect of the filler was predominant. In fact, moving from 5 to 12 wt % of zeolite, the thickness increased and the release also increased. This trend was observed for samples with 1.4 DL [Figure 4(a)] and 2.6 DL [Figure 4(b)]. However, for membranes at higher DL value, the release kinetics slightly increased (about 10%) in comparison with samples loaded at 1.4 DL. This trend was observed for all the different content of zeolite. Considering that an increase of DL from 1.4 to 2.6 did not change the overall membrane morphology, this phenomenon was attributed to an increase of the drug concentration gradient between membranes loaded at 2.6 DL and the release medium. As a consequence, the amount of GEM released in the time also increased.[27]

Among the different investigated systems, the PDMS-2.6 GEM NaX membrane exhibited the best performances. Therefore, this sample was used to perform the percutaneous permeation tests (PPTs) through the stratum corneum of ear rabbit skin using a Franz diffusion cell. The permeation pattern (Figure 5) was lower than that one observed during *in vitro* experiments. This was probably due to the presence of an additional resistance to the transport applied by the skin.

About the permeation tests, the release rate of the drug from the membrane was significantly slower compared to that from the solution. A possible explanation is due to the combined action of two effects: the hydrophobic nature of the polymer and the presence of the zeolite. The first caused a slower release of the drug. The second one permitted to modulate the release rate as also demonstrated in other works.[23,43,44] An interesting aspect is represented by the linearity of the drug release kinetic (see Figure 5) with the membrane indicating a constant release of the GEM in the time. This data reflect one of the main features of a controlled release devices namely the zero-order release kinetic. Results of this study underline the potential application of the mixed matrix membranes (zeolite loaded) as transdermal devices for the transdermal release of gemfibrozil.

The analysis of the drug release mechanism from the best system (PDMS-2.6GEM-12NaX) was performed using different mathematical models by fitting the results obtained in the "*in vitro*" and in "*ex vivo*" studies. The value of the correlation coefficient indicates the model that best describes the release mechanism. A value close to unity of the correlation coefficient indicates that the model well describes the mechanism of drug release. The fitting equations and the R^2 are given in Table IV.

Bhaskar's model described very well the release mechanism from the MMM used in *in vitro* experiments. The release pattern of the experiments performed in a Franz diffusion cell is excellently described by the zero-order model.

CONCLUSIONS

Mixed matrix membranes (PDMS based) were successfully developed as potential patches for the transdermal delivery of gemfibrozil. The hydrophilic properties of the NaX zeolite used as filler allowed to reduce the hydrophobic nature of PDMS and to modulate and to increase the release kinetics. At lower zeolite content (5 wt % and 12 wt %), the effect of the filler was predominant. In fact, moving from 5 to 12 wt % of zeolite, the thickness increased and the release also increased. A threshold value was observed at 12 wt % of zeolite above which the release rate decreased. This behavior is due to the combination of different effects: the decrease of polymer chains flexibility (as reported above), the hydrophilic nature of the filler, and the presence of zeolite clusters that englobes some drug molecules preventing their release. Besides, the GEM molecules encountered a more tortuous pathway into the membrane matrix. The best release system of *in vitro* experiments was the PDMS-2.6GEM-12NaX. This membrane was therefore used to perform percutaneous permeation tests (PPTs) through the stratum corneum of ear rabbit skin using a Franz diffusion cell. The permeation pattern was lower than that one observed during *in vitro* experiments. This was probably due to the presence of an additional resistance to the transport applied by the skin. An interesting aspect is represented by the linearity of the drug release

Table IV. 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-2.6GEM-12NaX	0.1	0.11	0.17	0.71	0.1	0.99	0.2	0.97	0.42	0.97
PDMS-2.6GEM-12NaX[a]	0.004	0.99	0.30	0.83	-	-	0.01	0.97		

[a] Percutaneous permeation tests.

kinetic (with the membrane indicating a constant release of the GEM in the time). This data reflect one of the main features of a controlled release devices that is the zero-order release kinetic.

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