Study of the Drug Diffusion Through Polymeric Membranes

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We present the studies carried out on the transport properties of some membranes obtained from synthetic polymers: polyurethane and ethylene-vinyl acetate copolymer, for use in the development of transdermal therapeutic systems with limiting membranes of speed. The properties of drug active substances transport through membranes were highlighted by performing studies with a diffusion cell. Experimental drug active substances were paracetamol and tetracycline. The experimental data obtained was processed using a general mathematical model for drug release from non-porous, non-swellable transdermal devices, which starts from Fick's second law and has terms that also take into account the possibility of retaining the drug in the membrane polymer. Even though the mathematical model does not take into account neither the swelling phenomenon nor the possibility of membrane erosion, a good agreement between model and experimental data was obtained. The values of effective diffusion coefficients of drug in the polymeric membranes were also determined.

Keywords: therapeutic transdermal delivery, Fick's diffusion law, drugs transport through polymeric membranes, modelling

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In several therapies controlled-release drug delivery systems have highlighted as a viable method of administering a large number of active substances [1].

Over the past two decades, the development of new types of biomaterials and drug active substances for pharmaceutical applications has seen a real breakthrough in which there is an important volume of experimental research. Beyond requirements for biocompatibility with the human body, the structure and transport properties of drugs through biomaterials should allow them to fit perfectly into the specific field of *in vivo* applications [2, 3].

In order to achieve a controlled-release system of an active substance, it is necessary to know the mechanism of drug transport by polymers [4]. Whether it is a matrix-type transdermal system or a reservoir type, in both cases the drug has to cross the polymeric material [5].

Transdermal drug delivery systems type reservoir contain the active substance that diffuse through the polymeric membrane at controllable rate [6]. The drug diffuses directly through the nonporous membrane polymeric material or diffuses through fluid-filled micropores of membranes [7].

The type of polymeric material must be in concordance with the drug used [8]. Polymers used in reservoir-based drug controlled release systems are required to be biostable and biocompatible, and they can consist in nonbiodegradable materials for diffusion controlled and biodegradable ones for chemically controlled systems [9]. Through nonbiodegradable polymers the thickness, area and permeability of polymeric membrane determine the release kinetics of the drug [10, 11]. The polymers that are used for rate-controlling membrane have to be approved to comply with the FDA regulations [12].

Non-degradable polymers used in drug delivery are characterized by tissue/blood compatibility, durability, robust structure and mechanical strength during *in vivo* application.

Among the materials used for rate-controlling membranes in transdermal delivery of drugs, there are used many polymers, nonbiodegradables: polyurethanes, polydimethylsiloxane, poly(ethylene vinyl acetate) (PEVA) and biodegradables: polyesters (such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactide-co-glycolide) (PLGA)), polyanhydride (poly(fatty acid dimer-sebacic acid), p(FAD-SA)), polysaccharides such as hydroxypropyl methylcellulose (HPMC) [13].

Substantial progress in design of transdermal delivery drug delivery systems is possible only on the basis of the in-depth knowledge of the physical mechanism and the mathematical models of mass transfer phenomena [14, 15].

In the chemical engineering activity, numerous attempts have been made to develop unitary mathematical models for the phenomena of transferring drug active substances through polymers, based on the similar physical mechanism. Choosing the right mathematical model for designing and

developing new drug delivery systems depends on many aspects, such as the route of administration, the drug type, and the release rate controlling excipients [16, 17].

The major advantages of these models are: (i) the elucidation of fundamental mass transport mechanisms, and (ii) the possibility of predicting the effect of the design parameters of the medical device (e.g shape, size and composition) on the rate of drug release, new pharmaceutical products. Conventional drug delivery systems such as tablets, implants, injectable microspheres, transdermal patches often release a high concentration of active substance at a higher than the maximum permissible value, followed by a rapid decrease in concentration at a level below the tolerated therapeutic dose [18].

Starting the previous results on tetracycline diffusion through biocellulose membrane, we extended our studies to evaluation of paracetamol and tetracycline transport through the polyurethane and ethylene vinylacetate copolymer membranes, as can constitue parts of a system with drug controlled delivery, type membrane and reservoir [19, 20]. We present studies on paracetamol and tetracycline release kinetics to obtain information of membrane material efficiency. We have analysed the transport mechanism depending on drug type and membrane polymeric material. The mathematical modeling will ease the understanding the release mechanism in the following systems that were analysed.

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In the present study we have used two type of thermoplastic polymers ethylene vinylacetate copolymer (EVA) as nonporous material and porous polyurethane (PU) for membrane.

EVA is a material those vinylacetate (VA) content can be adjusted to obtain different types of the copolymer. In the EVA material the the amorphousness, polarity and permeability increase with the vinylacetate percent. The diffusivity of polar drugs increase in EVA material with increasing VA content [21].

Polyurethanes (PUR) that are very used as result of their high biocompatibility and processability [22]. Polyurethane membranes are used for transport of hydrophilic polar drugs [23].

The study of transfer kinetics in diffusion processes is rather complicated. In order to perform a correct study, it is necessary to eliminate or be able to calculate exactly the diffusion resistance at mass transfer and to determine precisely the interfacial contact area [24, 25]. Also, a liquid / liquid contactor for successful use in kinetic studies must provide optimal hydrodynamic conditions, a short time for phase contact and no flow end effects.

Experimental part

Drugs used in the study, has the following molecular weights: paracetamol from Zentiva- 151 g/mol and tetracycline from Arena Group S.A.- 445 g/mol.

Membranes were performed from: polyurethane (PUR) obtained in the laboratory with porosity 0.02 and ethylene vinylacetate copolymer (EVA) with VA content 28% .

Researches for performing ethylene-vinylacetate copolymer microporous membranes with various pore sizes with application in the controlled release of drug active substances focused on the possibility of obtaining pre-membranes from two polymer compatible mixtures and selective solvent extraction of the soluble polyvinyl chloride component from them.

Two types of polymeric recipes have been proposed for obtaining membranes E1 (EVA60% / PVC 40%) and E2 (EVA 40% / PVC 60%) without compatibilizer, based on plasticized polyvinyl chloride and ethylene vinylacetate copolimer, that were performed by melt blending on Brabender plastograph. From the resulted polymeric recipes it were achieved films by melt pressing that constitute premembranes. PVC was extracted from premembranes in solvent cyclohexanone, resulting ethylene vinylacetate membranes.

Drug release studies

The diffusion cell (fig. 1) used in the study of transport of drugs through polymeric membranes consists of two compartments (donor and receptor) made of a transparent plastic (polymethyl methacrylate) to allow visualization of the fluid level inside. The two compartments are joined by mounting the polymeric membrane and separated from each other so that they do not come in contact with each other [26].

The tests were carried out as follows: polymeric membranes (PUR or EVA) were mounted in the diffusion cell; in the donor compartment was introduced the aqueous solution of the drug active substance; in the receptor compartment was introduced distilled water and mixing was started; at predetermined time intervals samples from drug aqueous solutions were taken from both compartments; the concentration of active drug substance in each compartment was determined spectrophotometrically; the amounts of drug delivered to the diffusion cell receptor compartment were evaluated by UV-Vis spectroscopy at constant wavelength 275.6 nm for paracetamol and 625nm for tetracyclines using a CINTRA 6 (GBS Scientific-Australia) spectrophotometer.

Experimental conditions in all experiments were the follows: 200 mL of (tetracycline, paracetamol) drug solution was fed into donor compartment of the diffusion cell, and 200 mL of distilled water was fed into the receptor compartment, the working temperature was 25 °C and speed rotation of the mixer n = 100 rpm.

Mathematical modeling of drug release

In a previous paper we have presented a study of tetracycline transport through bacterial cellulose membranes. Tetracycline diffusion coefficients have been calculated using a mathematical model that supposed that in the diffusion cell compartments the liquid is perfectly mixed (assumption valid since each cell compartment is equipped with a stirrer and the speed at which it was run was 100 rpm), and that drug delivery is convective from the drug solution located in the donor compartment to the membrane and from membrane to the pure solvent (receptor compartment) [27]. Also, within polymeric membrane the transport is diffusive and can be accompanied by drug adsorption in the material [28]. It is considered that the balance between external phases and membrane is established. Briefly, the model consists of the following equations:

$$\frac{\partial C_m}{\partial t} = D_m \frac{\partial^2 C_m}{\partial x^2} - \frac{(1-\varepsilon)}{\varepsilon}\frac{\partial q}{\partial t} \quad (1)$$

$$\frac{\partial q}{\partial t} = k_{ad}\left(q^* - q\right) \quad (2)$$

where:

$$q^* = K \cdot C_m \quad (3)$$

In the bulk phases for each compartment, the balance equations are:

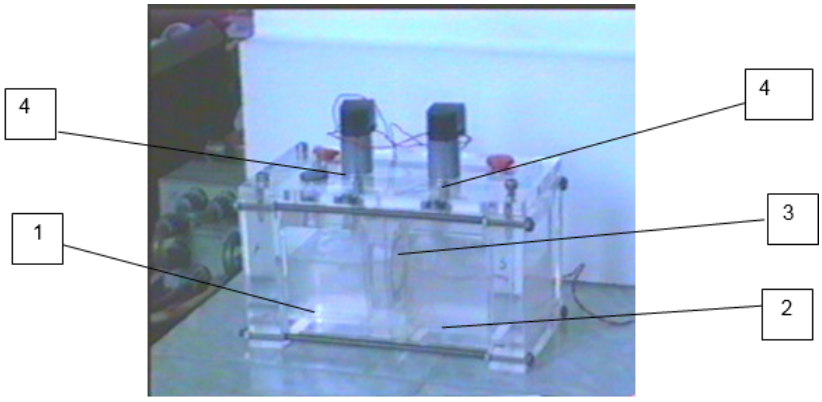

Fig.1. The diffusion cell used to performing studies for drug transfer through polymeric membranes: 1- donor compartment, 2 – receptor compartment, 3-polymeric membrane, 4 - mechanical stirrers

$$-V_1\frac{dC_1}{dt}=k_1S\left(C_1-\frac{C_m}{K}\right),\quad t=0,\ C_1=C_{1,0} \quad (4)$$

$$V_2\frac{dC_1}{dt}=k_2S\left(\frac{C_m}{K}-C_2\right),\quad t=0,\ C_2=C_{2,0} \quad (5)$$

Initial and boundary conditions are

$$\text{IC}\quad C_m=0,\quad t=0 \quad (6a)$$

$$q=0,\quad t=0 \quad (6b)$$

$$\text{BC}\quad D_m\frac{\partial C_m}{\partial x}=k_1\left(C_1-\frac{C_m}{K}\right)\quad x=0 \quad (7a)$$

$$D_m\frac{\partial C_m}{\partial x}=k_2\left(\frac{C_m}{K}-C_2\right)\quad x=\delta \quad (7b)$$

where: C_1 is bulk concentration in the donor compartment (kg/m^3), C_2 represents the bulk concentration in the receiver compartment (kg/m^3), k_1, k_2 are mass transfer rate in the donor compartment and receiver compartment, respectively (m/s), S is membrane area (m^2), V_1, V_2 denote volumes of donor and receiver compartment (m^3), K – distribution coefficient, C_{01} is the initial bulk concentration in donor chamber (kg/m^3), C_{02} means in the initial bulk concentration in receiver compartment (kg/m^3).

The model basic differential equations were solved numerically by means of finite difference method.

The experimental data were compared with predictions of the mathematical model, to obtain the diffusion coefficients. The model paramaters were expressed as follows: the distribution coefficients K and the thickness of the membrane were experimental determined; the mass transfer coefficients were calculated based on criterial relation from the literature [29].

The membranes porosity was calculated using *pat and weight* method and equation (1), taking into account the volume of the polymeric membrane and of the liquid that fill the pores [30]. Membrane pores were filled with distilled water and n-butanol.

$$Porosity\ (\theta)=\left[1-\frac{\left(\frac{m_f}{\rho_f}\right)}{\left(\frac{m_m}{\rho_m}+\frac{m_f}{\rho_f}\right)}\right] \quad (8)$$

where,

-porosity (θ) represent the overall porosity of the polymeric membrane,

-m_m is the mass of the dry sample polymer,

-ρ_m is the density of the polymer from the literature,

-m_f is the mass of the liquid filling the membrane pores,

-ρ_f is the density of the liquid filling the membrane pores.

The parameters effective diffusion coefficient D_{ef} of the drugs through the polymeric membrane and the adsorption constant were identified by overlapping the theoretical and experimental curves.

Results and discussions

Experimental results obtained on the transport of paracetamol through the polyurethane membrane

A solution of paracetamol with an initial concentration of c_0 = 269 mg/L was used in the donor compartment. The experimental results obtained for paracetamol transport through polyurethane membrane to receiver compartment in the diffusion cell, are shown in the figure 2.

From the experimental results it can observe that: the paracetamol transport was more intense in the first 360 minutes; after this time interval, the amount of drug transported through the polyurethane membrane was very low; in the range 1200-1260 min, the amount of paracetamol in the receptor compartment increased by

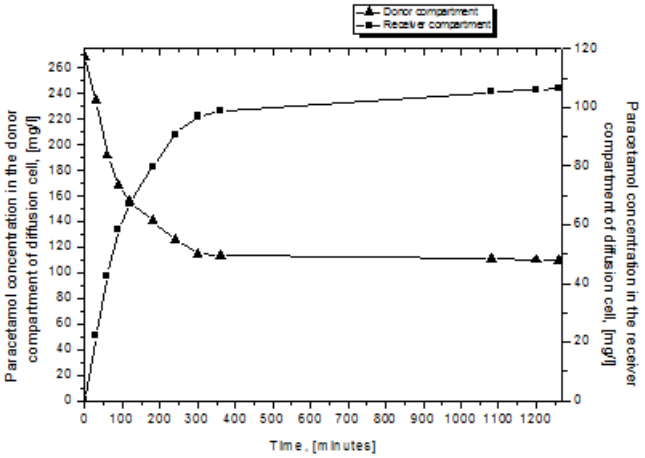

Fig. 2. The variation of the paracetamol concentration over time in the compartments of the diffusion cell

only 0.3 mg/L; after 1260 min, the amounts of drug in both compartments of the diffusion cell were almost equal, practically there was no increase in paracetamol concentration in the receptor compartment, and experimentation was discontinued; in receptor compartment of the diffusion cell was passed approximately 40.5% of the initial drug amount that was present in donor compartment; 18.9% of paracetamol was adsorbed within polymeric membrane; in the donor compartment remained 40.6% of the initial amount of drug.

Experimental results obtained on the tetracycline transport through polyurethane membranes

The experimental results are presented in the figure 3. The results obtained indicate that in the receptor compartment, about 53% of the initial quantity of tetracycline was passed from donor compartment. From the initial amount of drug 1% was adsorbed by the polyurethane membrane and 46% remained in the donor compartment. In the interval of 1140 and 1260 min, the amount of tetracycline in the receptor compartment increased by only 0.16 mg/L, which led to the interruption of the experiment after 1260 min.

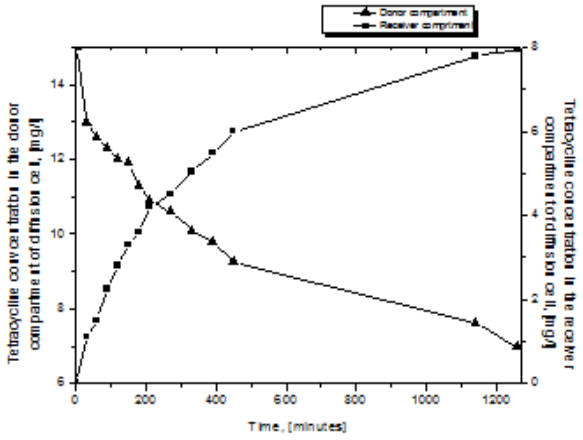

Fig. 3. The variation of the tetracycline concentration over time, in the diffusion cell compartments, at initial tetracycline concentration C_0= 15 mg/L

Experimental results obtained on the tetracycline transport through ethylene vinylacetate copolymer membranes

The membranes from ethylene vinylacetate copolymer performed in the laboratory were experienced in the diffusion cell, using aqueous solution of active substance tetracycline. Researches were performed in two experiments using ethylene vinylacetate copolymer membranes, E1 and E2 from EVA with 28% VA content,

with different porosity. The initial concentration of tetracycline in the aqueous solution present in donor compartment, was 275 mg/L, the same when used E1 and E2 membranes.

In the first experiment when was used membrane E1, from the analysis of the drug concentrations in the solutions from the two compartments of diffusion cell, it was found that through membrane E1 was transported 56.97% of tetracycline in the receiver compartment. In the donor compartment remained 42.33% of tetracycline. The transport of tetracycline through E1 membrane occured with an adsorbtion of 0.7% drug within EVA membrane (fig. 4).

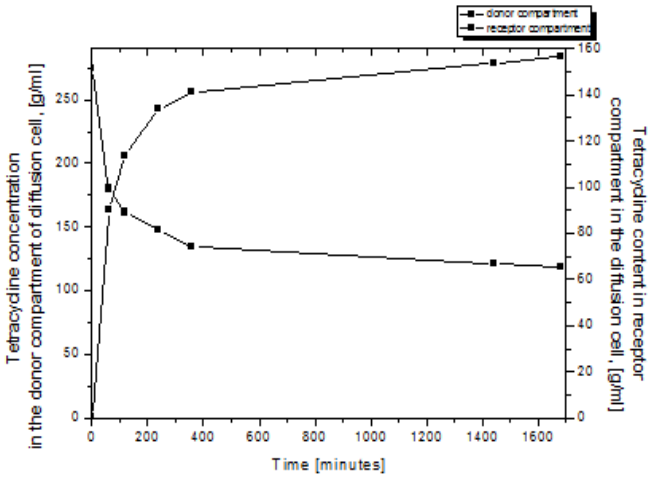

Fig. 4. Variation of tetracycline concentration in diffusion cell compartments using membrane from EVA grade E1, at initial concentration c_0=275mg/L

In the second experiment, membrane type E2 was used. As it can be seen, membrane E2 with higher porosity allowed the faster transport of tetracycline to the receiver compartment. Experimental results presented in figure 5. The results obtained exhibit that in 32.5 h 65.74% from tetracycline was transported in the receiver compartment of the diffusion cell, approximatelly 33.76% of tetracycline content remain in the donor compartment and approximatelly 0.5% of drug was adsorbed in the polymeric membrane.

In the present case, laboratory research has been conducted to study drug transport properties through membranes achieved experimentally, and the results can be used later in other experiments on the transport of drugs from a complex of conditioners excipients.

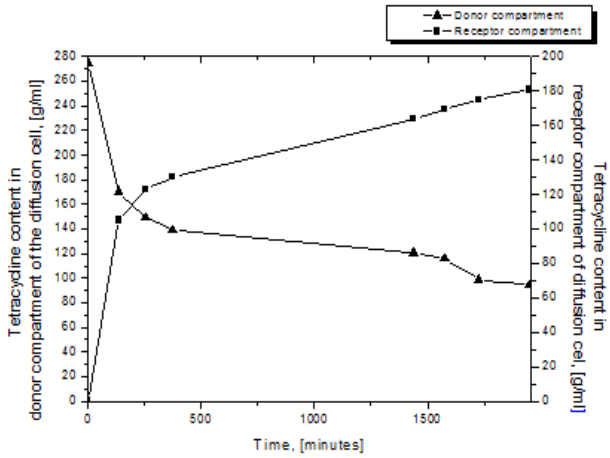

Fig. 5. Variation of tetracycline concentration in diffusion cell compartments using membrane from EVA grade E2, at initial concentration c_0=275mg/L

Thus, the results can be summarized in the table 1.

From the experimental data obtained, resulted that polyurethane membranes and ethylene vinylacetate copolymer showed acceptable transport properties for paracetamol and tetracycline.

Paracetamol and tetracycline drugs are found to have a high transport rate in the first 300-450 min during all the experiments performed, while under the action of agitation drug leaves the donor compartment and traverses the polymeric membrane reaching the receptor compartment.

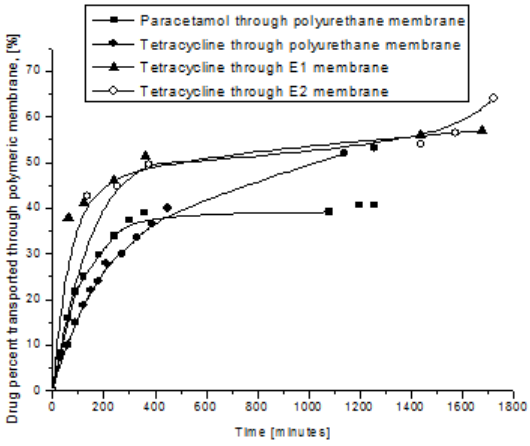

Fig. 6. Comparative variation of drug content in the diffusion cell compartments

Type of membrane / drug	Experiment time [h]	Drug present final in donor compartment	Drug adsorbed on polymeric membrane	Drug present final in receiver compartment
Polyurethane / paracetamol	21	40.6%	18.9%	40.5%
Polyurethane / tetracycline	21	46%	1%	53%
Ethylene vinylacetate E1 / tetracycline	28	41.33%	1.7%	56.97%
Ethylene vinylacetate E2 / tetracycline	32.5	32.76%	1.5%	65.74%

Table 1
COMPARATIVE RESULTS OF DRUG DELIVERY THROUGH POLYMERIC MEMBRANES

After this time, because of the adsorption of drugs in the polymers, the membrane pores become less accessible and the transport rate of the drug decreases considerably so that a smaller amount reaches the receptor compartment. The figure 6 shows the comparison between the drug concentrations variation in the diffusion cell compartments.

From the point of view of drug adsorption in membranes, drug loading was higher for paracetamol in polyurethane. The different values of the percentage of drug adsorbed are mainly due to the morphology of each polymer and the interactions between the drug and the polymeric chains.

Determination of the diffusion coefficient of paracetamol through polyurethane membranes

Applying the mathematical model, already presented, we have obtained the following results which will be presented in tables 2-4 for the different membranes which were tested. The values of parameters used in the modelling the transport of paracetamol through polyurethane membrane and the diffusion coefficient are presented in table 2.

Figure 7 presents a comparison of the experimental data with the theoretical curves resulting from the integration of the proposed model. It is observed that good agreement between the model and the experimental data was obtained.

The values of parameters used in the modelling the transport of tetracycline through polyurethane membrane and the diffusion coefficient are presented in table 3.

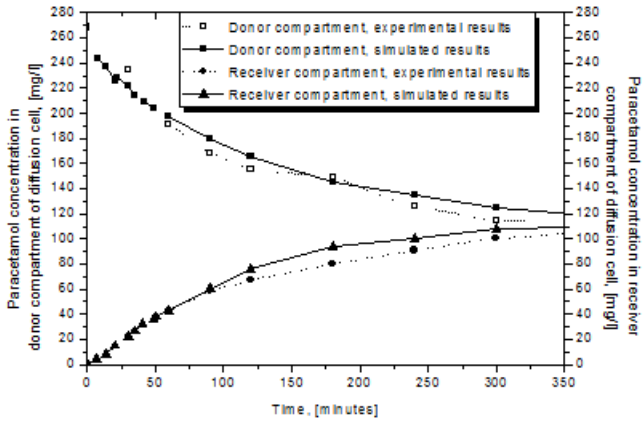

Fig. 7. Comparison of experimental data and theoretical curves obtained for diffusion of paracetamol through polyurethane membranes

Figure 8 presents a comparison of the experimental data with the theoretical curves resulting from the integration of the proposed model.

In this case, a better concordance between the model and the experimental data for the receiver compartment was obtained than for the donor compartment.

The values of parameters used in the modelling the transport of tetracycline through polyurethane membrane and the diffusion coefficient are presented in table 4.

Figures 9 and 10 presents a comparison of the experimental data with the theoretical curves resulting from the integration of the proposed model. It is observed that good agreement between the model and the experimental data was obtained.

Model parameters	**Observations**
Membrane thickness $\delta m=1.1x10^{-4}$ m	Measured with the digital micrometer
Membrane diameter $D_m=0.0375$ m	Measured with the digital micrometer
Distribution coefficient K=1	Experimentally determined [31]
Membrane porosity $\varepsilon=0.2$	Experimental determined [30]
Adsorbtion constant $k=10^{-5}$ m/s	Proposed
Mass transfer coefficients in aqueous phase $k_1=k_2=5x10^{-5}$ m/s	Calculated using criterial equations from literature
Effective diffusion coefficient $D_{ef}=9.7x10^{-12}$ m^2/s	Calculated

Table 2
THE VALUES OF THE PARAMETERS USED IN THE MODELLING OF THE PARACETAMOL TRANSPORT THROUGH POLYURETHANE MEMBRANE

Table 3
MODEL PARAMETERS USED TO CALCULATE THE EFFECTIVE DIFFUSION COEFFICIENTS OF TETRACYCLINE THROUGH POLYURETHANE MEMBRANES

Model parameters	**Observations**
Membrane thickness, $\delta m=1.1x10^{-4}$ m	Measured with the digital micrometer
Membrane diameter, $D_m=0.0375$ m	Measured with the digital micrometer
Distribution coefficient, K=1	Experimentally determined [31]
Membrane porosity, $\varepsilon=0.2$	Experimental determined [30]
Adsorbtion constant, $k=10^{-5}$ m/s	Proposed
Mass transfer coefficients in the aqueous phase $k_1=k_2=5x10^{-5}$ m/s	Calculated using criterial equations from literature
$D_{ef}=4x10^{-12}$ m^2/s	Calculated

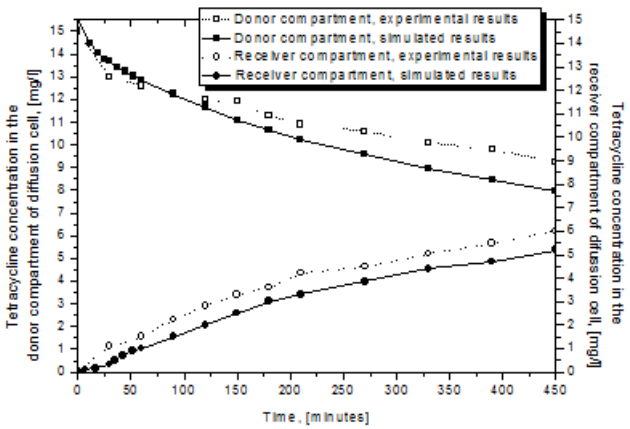

Fig. 8. Comparison of the experimental data and the theoretical curves obtained for diffusion of tetracycline through polyurethane membranes

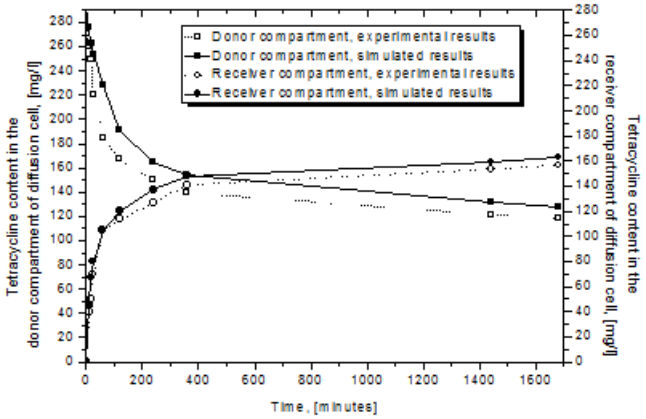

Fig. 9. Comparison of the experimental data and the theoretical curves obtained for diffusion of tetracycline through ethylene vinylacetate (E1) membranes

Table 4

THE MODEL PARAMETERS USED TO CALCULATE THE EFFECTIVE DIFFUSION COEFFICIENTS OF TETRACYCLINE THROUGH MEMBRANES FROM ETHYLENE VINYLACETATE COPOLYMER

Modeling parameters	**Membrane E1**	**Membrane E2**	**Observations**
Membrane thickness, δm	$1.0x10^{-4}$ m	$1.0x10^{-4}$ m	Measured with digital micrometer
Membrane diameter, D_m	0.0375 m	0.0375 m	Measured with digital micrometer
Distribution coefficient, K	1	1	Experimentally determined [31]
Membrane porosity, ε	0.24	0.28	Experimental determined [30]
Adsorbtion constant, k	10^{-5} m/s	10^{-5} m/s	Proposed
Mass transfer coefficients in the aqueous phase, $k_1=k_2$	$5x10^{-5}$ m/s	$5x10^{-5}$ m/s	Calculated using criterial equations from literature
Effective diffusion coeficient, D_{ef}	$6.89x10^{-12}$ m^2/s	$9.86x10^{-12}m^2/s$	Calculated

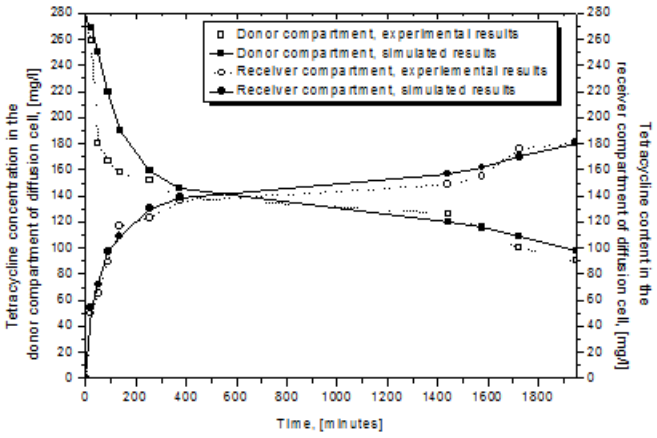

Fig. 10. Comparison of the experimental data and the theoretical curves obtained for diffusion of tetracycline through ethylene vinylacetate (E2) membranes

Conclusions

The experimental research presented in this article aimed to carry out studies of the transport of paracetamol and tetracycline drug active substances through polyurethane and ethylene vinylacetate copolymer membranes. Studies of the transport of active substances through the polymeric membranes were carried out with the aid of a mixing diffusion cell. Experimental results have shown that membranes obtained from ethylene vinylacetate copolymer have good transport properties for tetracycline. Also, polyurethane membranes are more permeable to tetracycline than to paracetamol. Compared to other literature data, the polyurethane membranes and ethylene vinylacetate copolymer were within acceptable limits of the amount of drug transported.

The experimental data obtained on the transport of the paracetamol and tetracycline drugs through polyurethane and ethylene vinylacetate copolymer membranes were processed using a model that starts from Fick's second law and has terms that also take into account the possibility of drug retention in the membrane polymer. Even though the model does not take into account the swelling phenomenon or the possibility of membrane erosion, a good agreement between model and experimental data is obtained. Effective drug diffusion coefficient values were determined in the types of membranes that were tested. The properties of the membranes studied for the transport of active drug substance have shown that they can be used to perform transdermal therapeutic systems.

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