Carbohydrate Polymers 87 (2012) 2432–2438

Contents lists available at SciVerse ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

The release of active substances from selected carbohydrate biopolymer membranes

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ARTICLE INFO

Article history:
Received 20 September 2011
Received in revised form 1 November 2011
Accepted 4 November 2011
Available online 12 November 2011

Keywords:
Chitosan
Polylactid acid
Dibutyrylchitin
Drug release
Diffusion model

ABSTRACT

As a biopolymer application to control release systems is increasing at present, flat matrices (transdermal systems) should be highlighted. They constitute one of the most friendly form of drug administration to the patient. The present results concern investigations on the active substance release (ibuprofen and salicylic acid) from film matrices made from biopolymers: polylactid acid (PLA), dibutyrylchitin (DBC) and chitosan (CH). The amount of released active substance was examined with UV-VIS spectrophotometer. The release process was conducted in the medium of pH = 5.6 as the transdermal systems are applied to human skin surface of pH value approximating 5.6. Swelling of polymer samples was confirmed in the buffer of pH = 5.6 as well.

The paper comprises the analysis of obtained release results according to the proposed two stage complex diffusion model.

1. Introduction

Presently, in the field of medicine it is possible to observe the growth of biopolymer use to control release of active substance (drugs). The study (Patel, Patel, & Rakesh Patel, 2005) presents numerous uses of polymers in pharmacy. The authors discuss generality of polymer solid supports and describe their plurality of use. Another article (Illum, 1998) concerns numerous industrial applications of polymers in cleaning or detoxification of liquids and drugs transport. Next paper (Illum, 2008) presents the possibility of peptide transport by nasal way. From among popular polymer forms such as microcapsules, tablets or microspheres flat matrixes (transdermal systems) deserve great attention (Guy & Hadgraft, 2000; Prausnitz & Langer, 2008; Williams, 2003; Yogeshvar & Guy, 2001). As authors provide they constitute the most friendly form of drug application to patient, as it gently penetrates the skin pores reaching an organism tissue saving alimentary configuration. The number of substances delivered with this method are as follows: lidocaine, ibuprofen, and testosterone. Transdermal systems usually are composed of a layer with active substance and adherent to it located outside the protective layer (Farmacopea Poland pub. VI, 2002). Due to advantages of transdermal systems it found many applications as, for instance, plasters of analgesic activity, in antinicotine treatment, in heart illnesses and others.

Mechanism of active substance release from CRS (controlled release systems) array due to its complexity is difficult to describe, especially for matrixes composed of biopolymers. Its complexity comprises polymer surface erosion, volume erosion and drug diffusion. The paper (Siepmann & Gopferich, 2001) presents the mechanism of volume and surface erosion of selected polymers. Furthermore, mass transport from interior of the array is influenced by the number of factors: physicochemical properties of release substance, polymer hydrophylicity or pH of environment in which the release process occurs (Carrie et al., 2003; Costa & Sousa Lobo, 2001; Panos & Dokoumetzidis, 2000; Siepmann & Gopferich, 2001; Yogeshvar & Guy, 2001).

In the present paper the results concern the active substances release (ibuprofen, salicylic acid) from thin biopolymer films forming flat transdermal systems involving chitosan, dibutyrylchitin and polylactid acid swelling properties.

Polylactid acid (PLA) is a polyester belonging to very promising biodegradable synthetic materials. This polymer was widely examined considering safe medical and pharmaceutical applications and its perfect biocompatibility was also under scrutiny (Miyajima et al., 1999; Prokakis, Mamouzelos, Tarantili, & Andreopoulos, 2006).

Chitosan (CH) and dibutyrylchitin (DBC) are polysaccharides.

Dibutyrylochitin (DBC) is a derivative of chitin and it is also bioactive and biodegradable polymer displaying membrane- and fabric properties that contribute to obtain fibers, nonwoven fabric and different usable forms and can be applied to medicine (Błasińska, Krucińska, & Chrzanowski, 2004; Sobecki & Pabin-Szafko, 2010).

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doi:10.1016/j.carbpol.2011.11.013

Chitosan (CH) is also a derivative of chitin and belongs to the most widespread natural polymers. It displays valuables specific properties such as: biodegradability, bioactivity, biocompatibility and nontoxic properties (Catteneo & Demierre, 2001; Hemant & Shivakumar, 2010; Mucha, 2010; Shu & Zhu, 2002; Silva, Pereira, Ramalho, Pais, & Sousa, 2008). Chitosan is applied to many fields such as medicine and medical dressings applied on wounds, scalds and as solid support (matrix) for drug to control release and acting also as hydrogels (Kofuji, Ito, Murata, & Kawashima, 2000; Martinez-Ruvalcaba, Schanchez-Diaz, Becerra, & Cruz-Barba, 2009).

2. Drug release models

There are many mathematical models describing release kinetics of active substances – both semi-empirical models, based mostly on Fick's diffusion theory, and empirical ones. The obtained results are mostly fitted with zero-order kinetics model or the first-order kinetics model (Carrie et al., 2003; Costa & Sousa Lobo, 2001; Panos & Dokoumetzidis, 2000).

Assuming that the polymer does not undergo the disintegration (the inter phase does not change), the drug release is slow, no equilibrium conditions are obtained, the release kinetics can be described by Eq. (1):

$$f_t = k_0 \bullet t \tag{1}$$

where $f_t = (C_t/C_0)$ is a value representing the fraction of the released drug in time t, k_0 the rate constant of zero order release process [1/h]. Symbol C_0 denotes the initial amount of drug in CRS array (controlled release systems), however, C_t denotes the amount of the drug that was released in time t. Graph of function f_t and versus time is a straight line.

The application of zero-order kinetics is observed in the case of transdermal systems and tablets containing the substance of low solubility (Varelas & Steiner, 1995).

Another mathematical model defining the kinetics of active substance release is described by the Eq. (2):

$$f_t = (1 - \exp(-k_1 \cdot t) \tag{2}$$

where f_t denotes the same as in Eq. (1), k_1 constant of release rate of the first order.

Application of first order kinetics is found in the case of decreasing rate of substance release in time and for porous matrixes containing drugs soluble in water. The first stage of active substance (drug) release process is described with this model (Mulye & Turco, 1995).

Next mathematical model is Peppas Model (Korsmeyer, Gurny, Doelker, Buri, & Peppas, 1983) ('the power law') presented by Eq. (3). It constitutes the basic expression describing drug release kinetics used in various arrays with different geometry.

$$f_t = k \bullet t^n \tag{3}$$

where f_t means the same as in Eq. (1), k means the rate constant of release, n denotes an index describing the mechanism of release.

Higuchi Model presents Eq. (4):

$$f_t = k_H \bullet t^{1/2} \tag{4}$$

where f_t means the same as in Eq. (1), k_H is Higuchi rate constant. This model is based on the first Fick law (Crank, 1975; Peppas, 1985).

The paper (Lao, Venkatraman, & Peppas, 2008) presents three stage model of drug release with consideration of diffusion process.

3. Proposed complex model for presenting results

Analysis of the research results confirms that the drugs release from biodegradable polymers proceeds in a complex way. There are a number of factors influencing the process under scrutiny. Penetration of solvent (buffer) to the interior of polymer matrix should be mentioned as the first factor. A significant impact on this process is exerted by polymer hydrophilicity and pH of environment (buffer) in which the process progresses. Another factor is possible degradation of polymer chains (hydrolysis) that causes appearance of new free volumes for drug dissolution. In this case one may consider decisive factors such as susceptibility of polymer to erosion and physicochemical properties of drug. Transport conditions of drug by diffusion to the surrounding medium is a third factor. When polymer does not degrade in a significant way (that was confirmed in our case), first and third process should be considered. It is assumed that the release progress occurs in two stages. The first fast stage is called the "burst effect". It was assigned to drug particles release located close to the surface of swelled film and it can be described with first order kinetics. It is described with Eq. (5):

$$\frac{dC}{dt} = k_1(C_s - C), \tag{5}$$

In the case of drug release into the tested environment the concentration of saturated solution C_s is much lower than the maximum drug concentration in tested medium: $C_{max} << C_s$. Eq. (5) in case of drug release assumes the following form:

$$\frac{dC}{dt} = k_1(C_{max} - C), \tag{6}$$

The above equation should be integrated in the boundary of (0, t) and (0, C_t). Finally, drug release is described by the first order kinetics as Eq. (7):

$$f_t = 1 - \exp(-k_1 \bullet t) \tag{7}$$

In accordance with the above the release process is proportional to drug concentration inside the tested matrix whose rate is diminishing with time duration exponentially.

Considering the second stage of the drug release the process concerns the mass transfer and here the second Fick's law is applied. One-direction diffusion may be expressed in the form of Eq. (8):

$$\frac{dC}{dt} = D \bullet \left(\frac{d^2C}{dx^2}\right) \tag{8}$$

where C denotes the active substance (drug) concentration in a tested sample will change in time of the drug release process. D denotes the apparent diffusion coefficient.

It should be assumed that:

- Initial and boundary conditions are as follows: $C = C_0$; for $-L < x < L$ and $t = 0$ and $C = 0$ for $x = -L$ and $x = L$ where L constitutes half of swelled biopolymer film thickness.
- At the time of process duration:

  $t > 0$; $C = C_t$ for $x = -L$ and $x = L$ and $dC/dx = 0$, for $x = 0$

  where C_t is the amount of recorded drug in medium in which the release process is observed. The process proceeds to the moment of achieving equilibrium stage in a studied array. The participation of a drug released from a polymer film of thickness $2L$ describes Eq. (9) (Crank, 1975):

$$f_t = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \cdot \pi^2} \exp\left\{-\frac{(2n+1)^2 \cdot D \cdot \pi^2 \cdot t}{4L^2}\right\} \tag{9}$$

where n means the sum parameter (natural number).

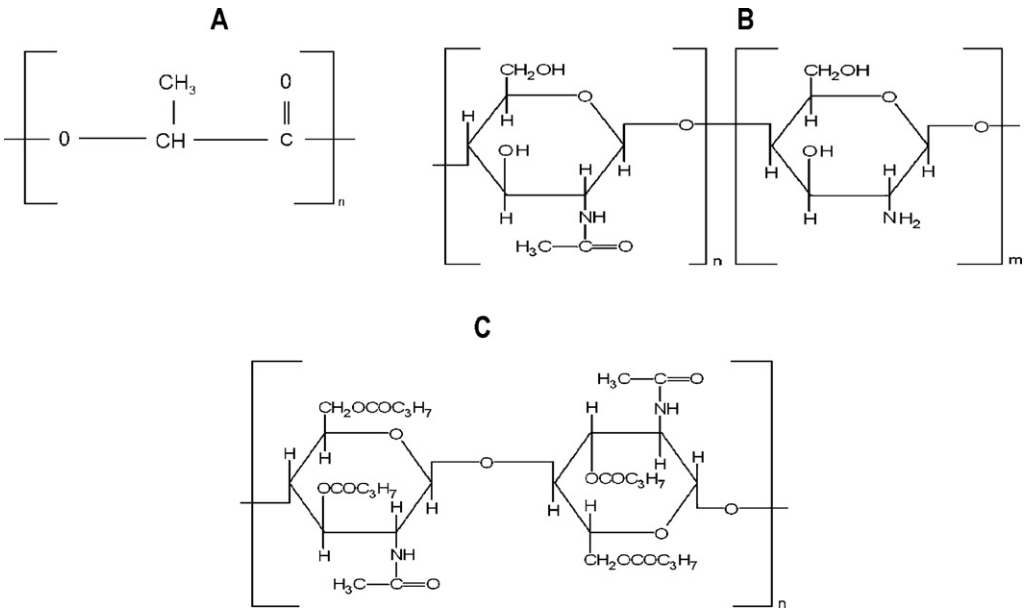

Fig. 1. Structural formulas: **A** Polylactid acid, **B** Chitosan, and **C** Dibutyrylchitin.

Considering that the total measured amount of released drug is the sum of the first and second stage finally it can be expressed by Eq. (10):

$$f_t = \varphi_1 [1 - \exp(-k_1 \cdot t)] + \varphi_2 \left(1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \cdot \pi^2} \exp \left\{ -\frac{(2n+1)^2 \cdot D \cdot \pi^2 \cdot t}{4L^2} \right\} \right) \quad (10)$$

where φ_1 and φ_2 are weight fractions of released drug in the course of the so-called 'burst effect' and on diffusion way respectively by $\varphi_1 + \varphi_2 = 1$. In the case when test data indicate the remaining small amount of drug in a matrix, this part should be considered as the weight fraction φ_3, then finally one obtains: $\varphi_1 + \varphi_2 + \varphi_3 = 1$.

Complex drug release from surface and volume of the polymer films were fitted to the experimental curves.

4. Experimental

4.1. Materials

The present results concern the studies of active substances release (ibuprofen and salicylic acid) to biopolymer film matrices that are as follows: polylactid acid (PLA), dibutyrylchitin (DBC) and chitosan (CH).

Fig. 1 presents structural formulas of applied biopolymers.

Polylactid acid (PLA) in the form of granulate used in the study was purchased from the Cargill Dow Polymers LLC company (polymer of M_w = 4000 Da). Methylene chloride was applied as its solvent.

Dibutyrylchitin (DBC) was provided by dr L. Szosland (the Technical University of Lodz) (polymer of M_w = 16,0000 Da). 96% ethyl alcohol was applied as a solvent.

Chitosan (CH) was purchased at BioLog company Biotechnology und Logistics GmbH (Chitosan 85/120/A1) of deacetylation degree 85 (polymer of M_w = 200,000 Da). 1% acetic acid was used as solvent of chitosan.

As an active substance ibuprofen (2-propionic ($C_{13}H_{18}O_2$) acid) and salicylic acid (-orto-hydroxybenzoic or 2-hydroxybenzoic (C_6H_4(OH)COOH) acid) were applied. Ibuprofen is a white or yellowish crystalline powder of characteristic smell. It is the substance easily solved in ethyl ether. It is widely used in medicine as an analgesic, antifever and anti-inflammatory drug (Leo, Forni, & Bernabei, 2000). Ibuprofen was purchased from Hubei Biocause Pharmaceutical Co., Ltd. Ibuprofen has it characteristic UV–Vis band of the absorbance λ_1 = 222.0 nm.

Salicylic acid occurs in the form of white crystalline powder or as colorless needles. It weakly dissolves in water and it is utilized for production of aceto-salicylic acid or p-amino-salicylic acid. The compound was purchased from Chempur Company. Salicylic acid has it characteristic UV–Vis band of the absorbance in λ_2 = 279.2 nm.

Fig. 2 shows structural formulas of active substances applied to the investigations.

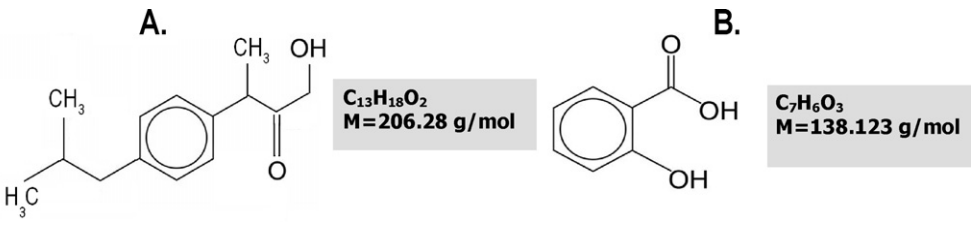

Fig. 2. Structural formulas: **A** Ibuprofen and **B** Salicylic acid.

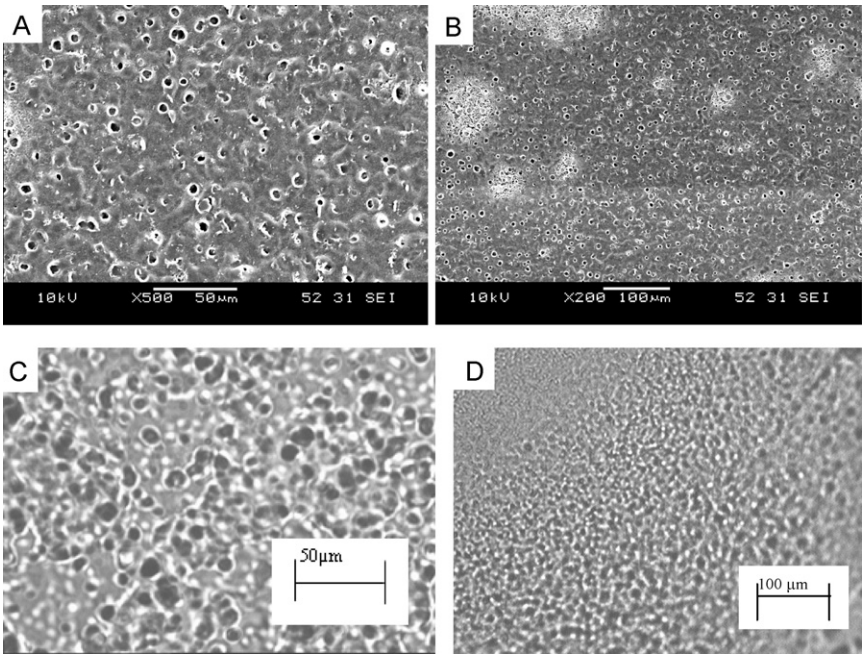

Fig. 3. Microphotographs from electron microscope of PLA films (A and B) and (C) from optical microscope of DBC film, after completed research of ibuprofen release and (D) microphotography of CH film after completed research of salicylic acid release.

4.2. Analytical methods

4.2.1. Films preparation

Transparent films were obtained by casting from DBC ethyl alcohol solution and PLA methylene chloride solution mixed with ibuprofen in mass ratio 5:1.

Chitosan films were prepared also by casting from the CH solution in 1% solution of acetic acid with salicylic acid in mass ratio 9:1. The solutions at appropriate volumes were poured on Petri plates and were left at the ambient temperature to evaporate the solvent. Subsequently, chitosan films were etched (for deactivation of acidic rests) in methyl alcohol. The following thicknesses of the films were obtained: 40 μm PLA, 80 μm DBC and 50 μm CH.

4.2.2. Swelling methods

The polymer films (without drug) applied for the study of swelling were dried at the temperature of 60 °C for 1 h. The films of the defined size (mass = 50 mg) were introduced to the proper environment (buffer solution at pH = 5.6) at the room temperature. The buffer solution is compatible with the Polish Pharmacopoeia the VIth and it composition is NaH_2PO_4–NaOH. At definite time intervals (every two minutes by first half an hour, then every 10 min by next half an hour) the films were weighted (surface dried up by tissue paper).

The experimental data were demonstrated in the form of the diagram presenting the dependence of the swelling degree (α) in the function of time (t) $\alpha = \left[(m_m - m_s)/m_s\right] \cdot 100\%$. Individual symbols denote: m_m mass of wet sample [mg], m_s mass of dry sample [mg].

Swelling kinetics was described by equation of first order kinetics:

$$\alpha = \alpha_\infty{}^\bullet(1 - \exp(-k_2{}^\bullet t)) \quad (11)$$

symbol α_∞ denotes the maximum swelling stage [%], k_2 is the constant of first order swelling kinetics [1/h]. At least three repetitions for swelling measurements were performed.

4.2.3. Release methods

The release of active substances was carried out in a glass vessel containing 50 cm^3 buffer medium of pH = 5.6. The investigations were carried out at the temperature of 37 °C (±0.5 °C). Polymer films containing an active substance of the known size and mass (30–50 mg) were introduced into the system. The glass vessel was covered against medium evaporation. Buffer medium containing an immersed film was stirred (by magnetic stirrer). The medium was sampled at a half distance of medium surface but no closer than 1 cm from the wall of the vessel (acc. Polish Pharmacopoeia). The sample of the medium was taken out at the definite time intervals for an analysis in the UV–Vis spectrophotometer. The concentration of active substance was determined (the model curve for both drugs has been determined) based on the absorbance in a characteristic band of λ = 222.0 nm for ibuprofen and λ = 279.2 nm for salicylic acid. Release drug fraction f_t was calculated. At least three repetitions for drug release measurements were performed.

4.2.4. Films morphology

Fig. 3 presents microphotographs of PLA films (from scanning electron microscope Jeol jsm5500LV) and microphotograph of DBC film (from polarized optical microscope Biolar PI) after the completed ibuprofen release process. Readings of SEM images were done by Scanning Electron Microscope JEOL JSM-5500LV in the Center of Molecular and Macromolecular Studies PAN (Polish Academy of Science). Samples before the morphology analysis were coated with gold under the pressure of 8 Pa. Voltage of Electron Microscope at work was 10 kV, the image was obtained by secondary electron detector (SEI). Fig. 3 presents also microphotography (from polarized optical microscope Biolar PI) of chitosan films after the completed salicylic acid release process.

In all cases the change of the films structure is observed. The presence of blowholes arised after the release of active substance. Morphological structure of samples before the release process is similar but out of the blowholes.

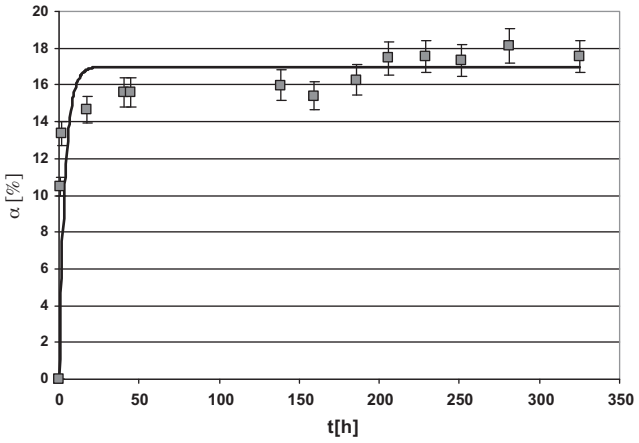

Fig. 4. Swelling kinetics of DBC film at pH = 5.6 ■ experimental points; ▬ first order fitting.

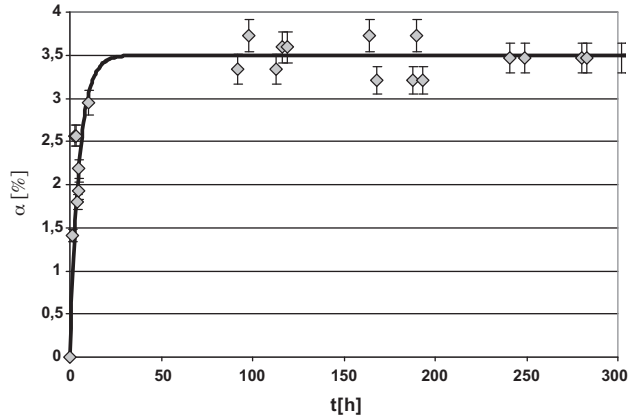

Fig. 5. Swelling kinetics of PLA film at pH = 5.6; ♦ experimental points; ▬ first order fitting.

5. Results and discussion

5.1. Swelling kinetics

Swelling kinetics of polymer samples was observed. The obtained test data were displayed in Figs. 4–6 presenting dependence of swelling degree (α) versus time (t). The best fitting to the curves presents the first order kinetics model (Eq. (11)). Maximal swelling degree for DBC oscillates around α_∞ = 17%, for PLA α_∞ = 3.5% and the highest one for CH α_∞ = 170%. Values

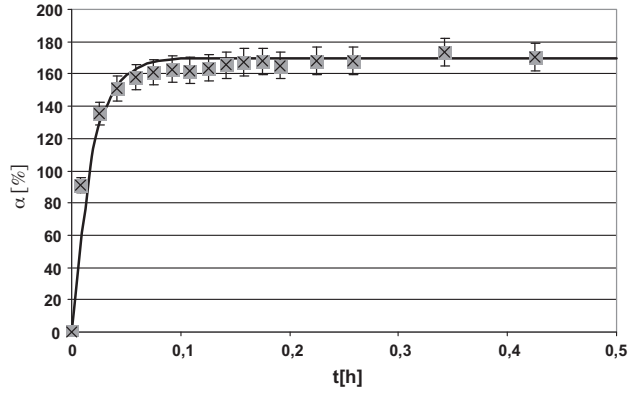

Fig. 6. Swelling kinetics of CH film at pH = 5.6; ▒ experimental points; ▬ first order fitting.

Table 1
Swelling kinetic parameters at pH 5.6.

Name	Chitosan (CH)	Dibutyrylchitin (DBC)	Polylactid acid (PLA)
α_∞ [%]	170	17	3.5
k_2 [1/h]	55	0.26	0.2

of swelling kinetic parameters are calculated and presented in Table 1.

Polymer swelling in buffer environment is lower for PLA and DBC, the highest one is for CH. The data show a high swelling rate (k_2) of chitosan in comparison with both other biopolymers. The smallest swelling rate is obtained for polylactid acid $k_{2CH} > k_{2DBC} > k_{2PLA}$. Experimental points show that the highest maximal swelling degree is obtained also for chitosan $\alpha_{\infty CH} > \alpha_{\infty DBC} > \alpha_{\infty PLA}$.

5.2. Release kinetics

Basing on obtained results the graphs of release fraction (f_t) of ibuprofen or salicylic acid as a function of time (t) were drawn. The appropriate mathematical model (Eq. (10)) was adjusted to those results. The effects of the fitting are presented in Figs. 7–9.

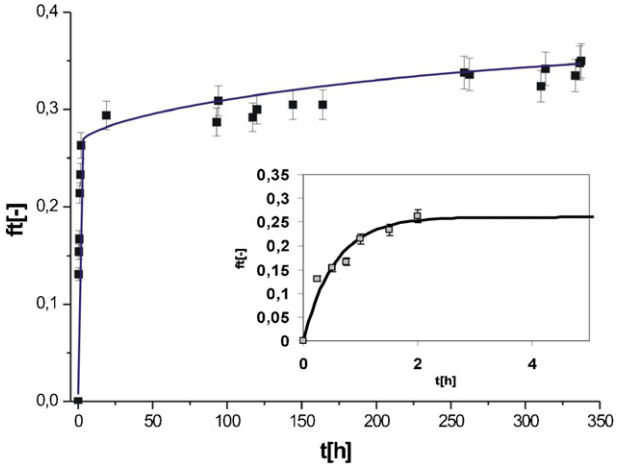

Fig. 7. Kinetics of ibuprofen release from DBC film at pH = 5.6; ■ experimental points; ▬ Complex Diffusive Model fitting (inside first order kinetics fitting for short time).

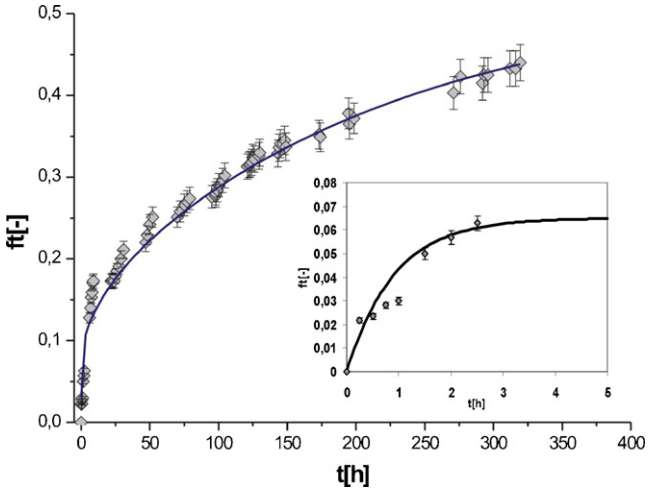

Fig. 8. Kinetics of ibuprofen release from PLA film at pH = 5.6; ♦ experimental points; ▬ Complex Diffusive Model fitting (inside first order kinetics fitting for a short time).

Table 2
Parameters of release kinetics into buffer of pH 5.6.

Name	Complex Diffusive Model						
	First order kinetics (first stage)		$2L^*$ [cm]	C_0 [mg/ml]	φ_2 [−]	φ_3 [−]	D [cm^2/s]
	φ_1 [−]	k_1 [1/h]					
Chitosan (CH) + salicylic acid	0.45	2.2	0.0216	0.148	0.53	0.02	1.94×10^{-10}
Dibutyrylochityna (DBC) + ibuprofen	0.26	1.6	0.00944	0.168	0.11	0.63	1.01×10^{-11}
Polylactid acid (PLA) + ibuprofen	0.064	1,0	0.00412	0.122	0.46	0.476	2.19×10^{-12}

The obtained experimental release results were described with the appropriate Eq. (10) fitted with Complex Diffusive Model (swelled film thicknesses $2L$ were included in calculations). This model assumes a two-stage release process. First stage is fast release – the so called 'burst effect' and originates from the area near the sample surface the so called 'skin layer'. It is described by the first order kinetics. The second stage is the release from the volume of the matrix and overlaps by diffusion.

Good fitting demonstrates our model indicating on a two-stage release process. Drug release at the initial stage (about 5 h) is a fast process that can be described with first order kinetics model (Eq. (7)) presented in Figs. 7–9 (inside small graphs). The behavior means that the main driving force of the first stage is the transport of dissolved drug through buffer swelled polymer (swelling is also first order process). Thus the rate of release process depends on swelling degree of biopolymer films.

The release of drug dissolved in biopolymer matrix is complex. It can originate from the non-uniform distribution of the drug in polymer matrix. In the case of preparation of the polymer films by casting from solution a fraction of dissolved low-molecular substances displays the tendency to partial sedimenting near the film surface creating the so called 'skin layer'. Thus the drug release in the first stage can be connected with that part of drug and the process occurred according to the first order model. That proved that the main driving force of this stage is a dissolution of drug in swelled polymer matrix (swelling is also the process described by the first order kinetics). Then at the second stage the drug diffuses from the matrix to external medium in which it is recorded. The surface effect is more visible when polymer swelling in buffer environment is lower (as for PLA and DBC). Adding both processes of drug release from surface (first order) and volume (diffusion effect) of the polymer film gives observed experimental release curve.

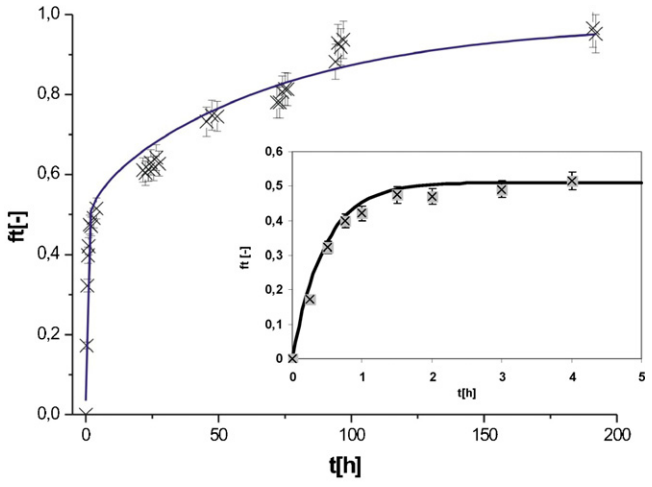

Fig. 9. Kinetics of salicylic acid release from CH films at pH = 5.6; ▒ experimental points; ▬ Complex Diffusive Model fitting (inside first order kinetics fitting for short time).

Comparison of release kinetics parameters of ibuprofen and salicylic acid from the examined transdermal systems is presented in Table 2.

*For theoretical analysis the thickness of swelled films were considered.

Values of calculated apparent diffusion coefficients D (second stage of the release process) are dependent on the swelling degree of biopolymer matrix: $D_{CH} > D_{DBC} > D_{PLA}$. They differ by one order of magnitude. Value of k_1 parameter of first order kinetics fitted to 'burst effect' (short time, first stage) is also the largest in the case of chitosan.

Complex Diffusive Model takes into account weight fractions of released drug in the so-called 'burst effect' and on diffusion way respectively, by $\varphi_1 + \varphi_2 = 1$. Fractions of release at the first stage φ_1 change from 0.45 for CH to 0.26 for DBC and 0.064 for PLA. The second stage is the release from the volume of the matrix and overlaps by diffusion φ_2. Fractions of release at the second stage φ_2 change from 0.53 for CH to 0.11 for DBC and 0.46 for PLA. In the case when test data indicate on remaining some amount of drug in the matrix, this part is considered as the weight fraction φ_3, then finally one obtains: $\varphi_1 + \varphi_2 + \varphi_3 = 1$. The obtained experimental results indicate that a certain amount of drug φ_3 remained in the interior of the matrix. The smallest amount of drug remained in the most swelled chitosan (CH) matrix. However, φ_3 value remains very high in PLA and DBC.

6. Conclusions

Swelling of the polymeric films in media, of pH = 5.6 is observed. Maximum swelling degree $\alpha_\infty = 17\%$ for DBC, $\alpha_\infty = 3.5\%$ for PLA, and $\alpha_\infty = 170\%$ for CH. Polymer swelling in buffer environment is lower for PLA and DBC, the highest one is for CH. The data show high swelling rate (k_2) of chitosan in comparison with both other biopolymers. The best fitting to the curves presents the first order kinetics model.

The initial stage (ca. 5 h) of the drug release process is fast and for all tested biopolymers it can be described using the first order model.

The obtained experimental release results were described with the appropriate fitted Complex Diffusive Model (the swelled films thicknesses were included as $2L$). This Model assumes a two-stage release process. The first stage is fast release of the so called 'burst effect' and originates from the area near the sample surface of the so called 'skin layer' φ_1. It is defined by the first order model. The second stage is the release from the volume of the matrix and overlaps by diffusion φ_2. Fractions of release at the second stage φ_2 change from 0.53 for CH to 0.11 for DBC and 0.46 for PLA. Values of calculated apparent diffusion coefficients D (the second stage of the release process) are dependent on the swelling degree of biopolymer matrix: $D_{CH} > D_{DBC} > D_{PLA}$.

In the case when test data indicate on remaining small amount of drug in a matrix this part is considered as the weight fraction φ_3, then, finally, one obtains: $\varphi_1 + \varphi_2 + \varphi_3 = 1$. The obtained experimental results indicate that a certain amount of the drug

remains inside the tested matrices. The smallest amount of the drug remained in the most swelled chitosan (CH) matrix.

Complex drug release model both from the surface and volume of the polymer films were fitted to the experimental curves.

Biopolymers applied to the study: chitosan, dibutyrylchitin and poly(lactic acid) can be used with a good result as flat matrices to release drugs in transdermal systems. Based on the obtained results various rates of the release process related primarily to different hydrophilicity and swelling in buffer of the samples under study may be observed.

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