

MODIFIED DIBUTYRYLCHITIN FILMS AS MATRICES FOR CONTROLLED IBUPROFEN RELEASE

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Abstract

In view of ongoing interest in biodegradable polymers, dibutrylchitin was used as a matrix for controlled release of a model substance. Transdermal systems (films) are presently more commonly used as an alternative to standard forms of drug delivery. The presented results are concerned with the release of ibuprofen from dibutrylchitin film. The obtained transdermal films were modified by applying a control layer to slow down the release process. The matrices were also modified by adding nanoclay (Nanofil 2). Dibutrylchitin matrices were tested for swelling and release kinetics using UV-Vis spectrophotometer. The drug kinetics release was studied in phosphorus buffer of pH = 5.5 at the temperature of 35 °C. Structural investigations of the obtained matrices were carried out by optical microscopy and FTIR spectrophotometry. An appropriate mathematical model was also fitted to the obtained experimental data.

Key words: *controlled release, transdermal systems, ibuprofen, dibutrylchitin, nanoclay.*

1. Introduction

Analysis of active substance release from transdermal systems is an important area of scientific research for human health. Transdermal systems are presently more commonly [1 - 4] used. They are thin, single or multilayer membranes of any shape and size. Films are an alternative to standard forms of active substances delivery into the human body. Because of their numerous advantages, the membranes gain popularity among patients. Due to a current global trend towards the use of environmentally friendly polymers derived from renewable sources, dibutylchitin (DBC) was chosen and used as a drug carrier in the present study.

The presented results are concerned with the release of ibuprofen from DBC film into the buffer of pH = 5.5. DBC is a natural biodegradable and bioactive polymer which is an ester derivative of chitin. It is easily dissolved in organic solvents. DBC easily forms films, fibers and other formulations used in medicine [5 - 8].

Model drug substance used for the controlled release study was ibuprofen (IBU). It is widely used in medicine as an analgesic, antipyretic and anti-inflammatory agent.

The obtained matrices were modified by applying an outside control layer (to slow down the release process) by dipping or by spraying dibutylchitin solution on the surfaces. Films were also modified by adding nanoclay.

The kinetics of ibuprofen release from the transdermal systems was investigated using UV-Vis spectrophotometer. Ibuprofen release was studied in phosphorus buffer of pH=5.5 at the temperature of 35°C. Appropriate mathematical models were fitted to the obtained experimental data.

2. Materials and methods

The aim of the research was to study ibuprofen release from dibutylchitin modified films.

2.1. Materials

Dibutylchitin (DBC) of $M_w = 160 \times 10^3$ was produced at our laboratory. 96% ethyl alcohol was used as a solvent.

Ibuprofen (IBU) (2-propionic acid $C_{13}H_{18}O_2$) was applied as an active substance. Ibuprofen with a molecular mass of 206.28 g/mol was purchased from Cardinal Pharma Trade, Poland. IBU has characteristic UV-Vis absorbance bands at $\lambda_1 = 222.2$ nm and $\lambda_2 = 264.4$ nm.

Nanoclay (Nanofil 2) was the nanoadditive used as an active nanofiller for polymer applications [9]. It is an originally modified nanodispersible layered silicate with a long-chain hydrocarbon/benzyl group.

2.2. Methods

2.2.1 Films preparation

Dibutylchitin films were prepared by casting from the DBC (with ibuprofen in mass ratio 9:1) solution in 96% ethyl alcohol. The solutions of appropriate volumes were poured onto Petri plates and left in dry air conditions at ambient temperature to evaporate the solvent. Transparent films of different thicknesses (80 μm and 110 μm) were obtained. Extra layers of different thicknesses (20 μm – 40 μm) were added by spraying and dipping methods using DBC solution. Kinetics studies of swelling and release of the active substance were carried out in phosphorus buffer environment of pH = 5.5. Preparation of transdermal systems is presented in *Figure 1*.

2.2.2 Spectral results

The FTIR spectra of ibuprofen -3 (IBU), dibutylchitin -1 (DBC) film and the mixture - 2 of 30% of IBU in DBC film were compared with different characteristic functional groups. The assigned bands of ibuprofen and dibutylchitin correspond with the spectral assignments for their functional groups reported in the literature [5, 14]. FTIR spectra (*Figure 2*) were recorded in the frequency range from 500 to 2000 cm^{-1} . The results were obtained using Jasco V-630 spectrophotometer.

2.2.3. Swelling process

Dibutylchitin films (without drug) for swelling were dried at the temperature of 70 $^{\circ}\text{C}$ for 1 h. The dried samples of the defined mass ($m_s \sim 40$ mg) were introduced to the buffer environment (pH = 5.5; composition: NaH_2PO_4 -NaOH acc. to FP VI) at room temperature. At

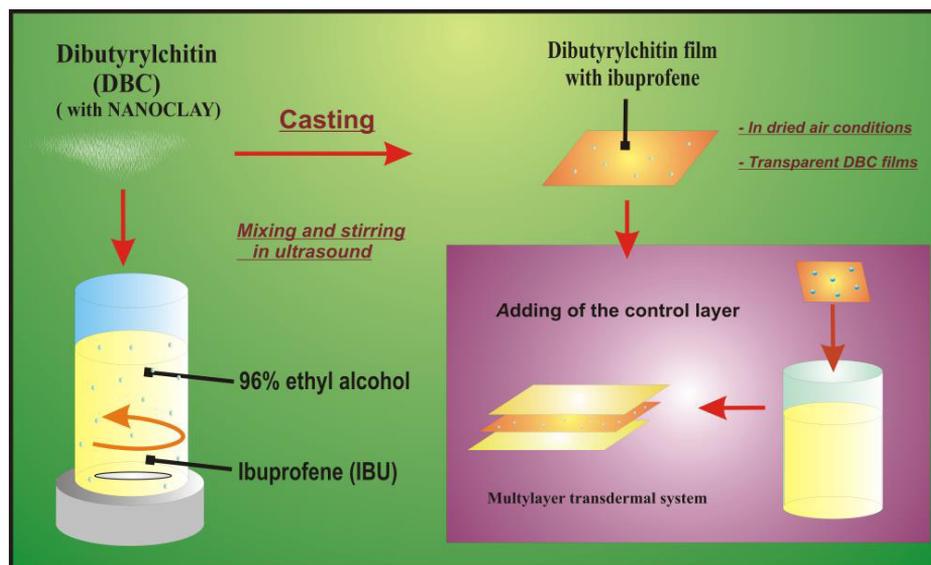


Figure 1. Preparation of the investigated transdermal systems.

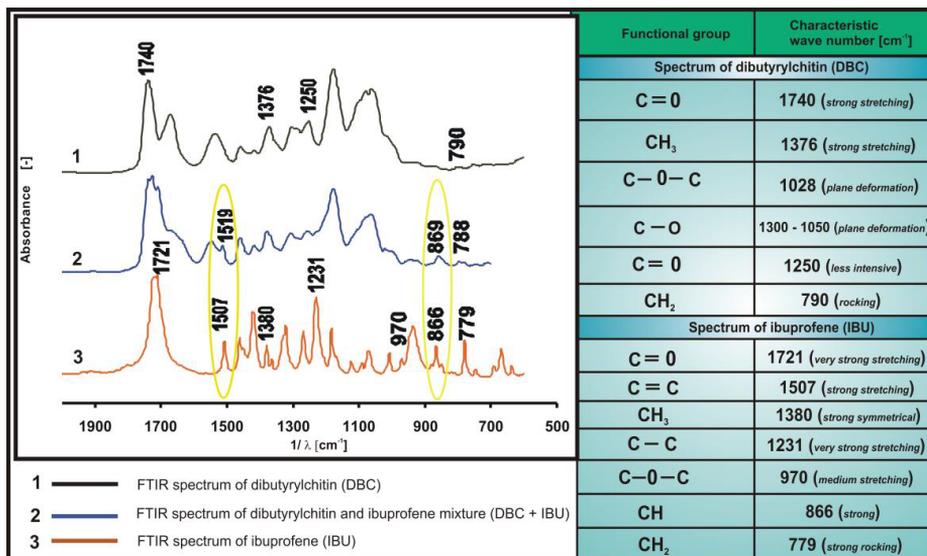


Figure 2. Spectrophotometric study of FTIR.

definite time intervals (every two minutes over the first half an hour, then every 10 minutes over the next half an hour) the films were surface dried by tissue paper and weighed (m_m).

Experimental data was presented in the form of a graph as a dependence of the swelling degree (α) as a function of time (t) where $\alpha = [(m_m - m_s)/m_s] \cdot 100\%$, m_m – mass of swollen sample in mg, m_s – mass of dry sample in mg.

Swelling kinetics was described by Peppas model equation [10], (Equation 1):

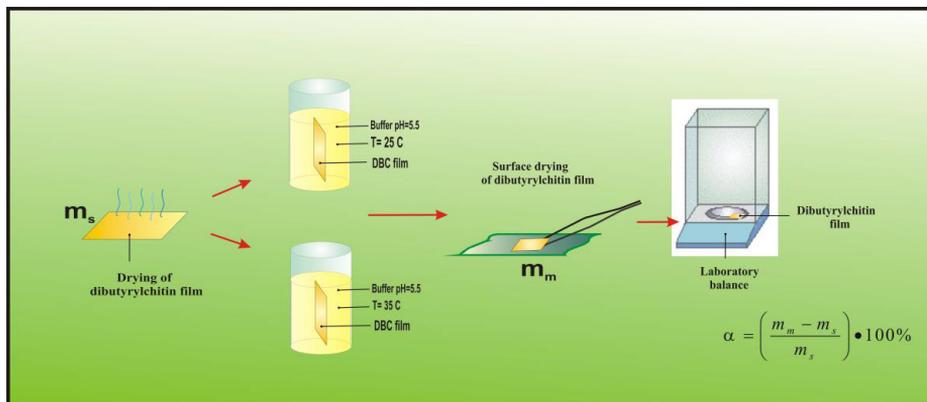


Figure 3. Swelling procedure for the systems.

$$\alpha = k \cdot t^n \quad (1)$$

where α is the swelling degree in %, k is the constant of Peppas swelling kinetics in 1/h, exponent n describes kinetics and mechanism of the process in -. The diagram of the swelling process is presented in **Figure 3**.

2.2.3. Release process

The release of ibuprofen was carried out in a glass vessel containing 50 cm³ phosphorus buffer medium of pH = 5.5. Investigations were carried out at the temperature of 35 ± 0.5 °C. Polymer films containing IBU (about 10%) of the known size and mass (about 40 milligrams) were introduced into the buffer environment. Glass vessel was covered to prevent liquid evaporation. Buffer medium containing an immersed film was stirred using a magnetic stirrer. The medium was sampled at a half distance of medium surface but no closer than 1 cm from the vessel wall (acc. to the Polish Pharmacopeia FP VI) [11]. A sample of the medium was taken out at definite time intervals for analysis using UV-Vis spectrophotometer. Drug concentration was measured (the model curve for the drug was determined earlier) basing on the absorbance in a characteristic band of $\lambda = 222.2$ nm and $\lambda = 264.2$ nm. Released drug fraction f_t was calculated. Release kinetics was described using an equation developed by Gallagher & Corrigan [12, 13], (**Equation 2**):

$$f_t = f_{t_{max}} \cdot (1 - e^{-k_1 t}) + (f_{t_{max}} - f_b) \cdot \left(\frac{e^{k_2 \cdot (t - t_{2max})}}{1 + e^{k_2 \cdot (t - t_{2max})}} \right) \quad (2)$$

f_t is a fraction of the released substance in time t , $f_{t_{max}}$ indicates maximum amount of the released drug during the process in -, f_b is a fraction of drug released during the 1st stage - the burst effect in -, k_1 is the first order kinetics constant in 1/h (1st stage of release), k_2 is a kinetics constant for the 2nd stage of release in 1/h and t_{2max} means time to maximum drug release rate in h. Graphic interpretation of Gallagher & Corrigan model is presented in **Figure 4**.

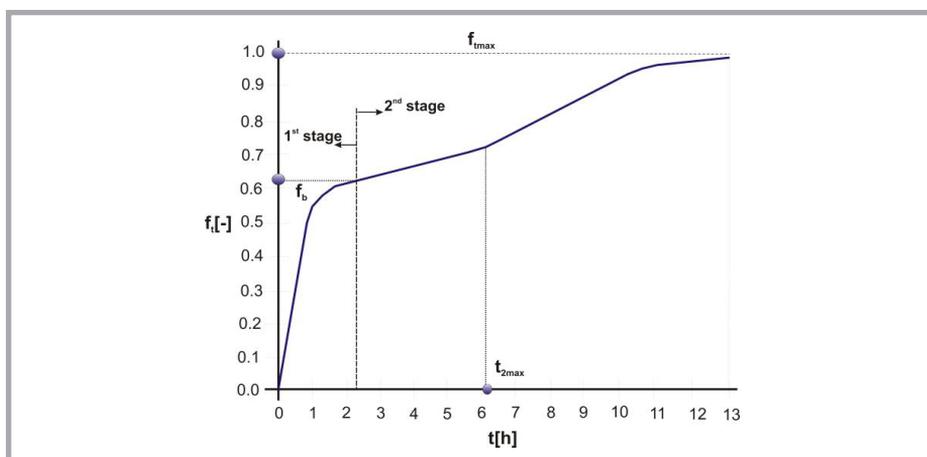


Figure 4. Graphic interpretation of Gallagher & Corrigan model.

3. Results and discussion

3.1. Swelling results

Swelling of the tested polymer was measured also with nanoclay. The process graph as the dependence of swelling degree (α) versus time (t) was presented in **Figure 5**.

Dibutylchitin film with the addition of nanoclay shows a higher equilibrium degree of swelling ($\alpha_{1\max} = 18\%$) in comparison with a film without an additive ($\alpha_{2\max} = 13\%$). Nanofil 2 is a hydrophilic modified nanoclay.

3.2. Release results

The obtained results of the IBU release can be described by a two stage process. In the Gallagher and Corrigan model the process of release is considered a combination of surface burst effect and release from bulk matrix modified by polymer degradation. The so-called ‘burst effect’ occurs at an early stage of release and is characterized by the first order kinetics curve. After this stage there occurs a diffusion of IBU molecules into the surrounding medium, accompanied by hydrolytic degradation (swelling) of the polymer matrix. The fitting results are shown in **Figure 6**.

Our experimental data (**Figure 6**) is accurately fitted by Gallagher and Corrigan equation (2). During the first stage (~100 hours) a significant amount of the drug fb was released in the so-called ‘burst effect’. After the first stage another mechanism of release was observed. The final release fraction of ibuprofen (f_{\max}) was achieved after about 325 hours. However, polymer hydrolysis (without mass loss – no mass loss was observed during swelling) may lead to chain loosening and thus to the increase of the release rate. The results of the release study are presented in **Table 1**.

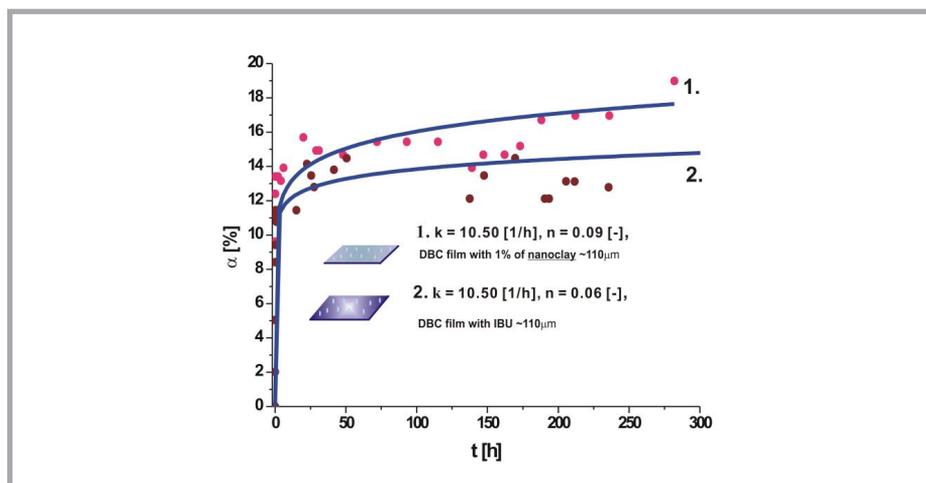


Figure 5. The influence of nanoclay on swelling process of dibutylchitin film. 1. Experimental points of DBC film with 1% of nanoclay, 2. Experimental points of DBC film. Fitting with Peppas model.

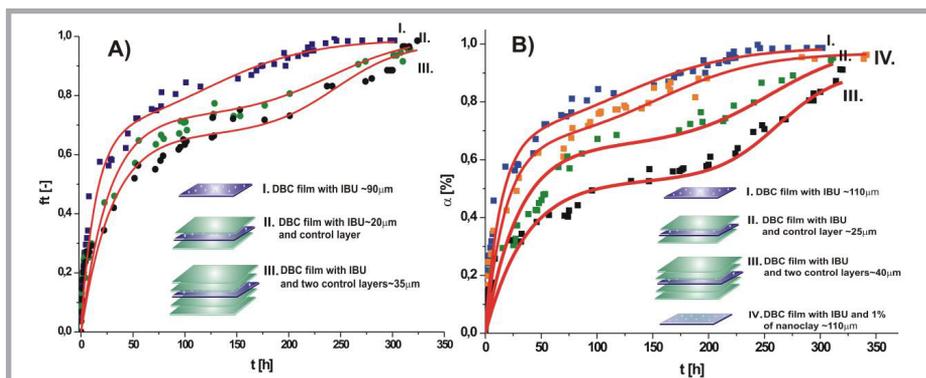


Figure 6. The influence of added control layers on the process of ibuprofen release from dibutylchitin film. I. Experimental points of DBC film with IBU and without a control layer, II. and III. Experimental points of DBC film with IBU and with control layers, IV. Experimental points of DBC film with IBU modified by adding 1% of nanoclay, A) Control layer added by spraying, B) Control layer added by dipping. Fitted with Gallagher and Corrigan model.

Table 1. Experimental results of the study of ibuprofen release from dibutylchitin film fitted to equation 2. f_t - fraction of released substance in time t , f_{tmax} - maximum, final fraction of released drug [-], f_b - fraction of drug released during 1st stage - the burst effect [-], k_1 - first order kinetics constant [1/h] (1st stage of release), k_2 - kinetics constant for 2nd stage of release [1/h], t_{2max} - time to maximum drug release rate [h], **I.** DBC film without layer, **II.** DBC film with one layer, **III.** DBC film with two layers, **IV.** DBC film with nanoclay.

Release process (control layers added by dipping)							
Name	Indication		f_b [-]	f_{tmax} [-]	k_1 [1/h]	k_2 [1/h]	t_{2max} [h]
Dibutylchitin +ibuprofene	DBC	I. Film without layer	0.66	1	0.070	0.020	121
		II. Film with one layer	0.65	1	0.034	0.025	255
		III. Film with two layers	0.53	1	0.028	0.036	262
	DBC + Nanoclay	IV. Film without layers	0.65	1	0.055	0.022	156
Release process (control layers added by spraying)							
Dibutylchitin +ibuprofene	DBC		f_b [-]	f_{tmax} [-]	k_1 [1/h]	k_2 [1/h]	t_{2max} [h]
		I. Film without layer	0.66	1	0.070	0.020	121
		II. Film with one layer	0.73	1	0.038	0.024	240
	III. Film with two layers	0.67	1	0.034	0.030	245	

Introduction of an outside control layer onto polymer matrix results in the lowering of the release rate. It is indicated by lower value of rate constant k_1 characteristic for the first stage of the release. Significant reduction of the drug release rate is observed. It is easy to see by comparing $k_1 = 0.070 \text{ h}^{-1}$ for film without layer (I.) and $k_1 = 0.028 \text{ h}^{-1}$ for film with two layers (III.). At the same time the reduction of drug fraction released in the first stage of the process (f_b) is observed. In the second stage, in which the IBU release is accompanied by hydrolytic degradation/swelling of the polymer, an increase of the k_2 rate constant is observed. By comparing $k_2 = 0.020 \text{ h}^{-1}$ film without layer (I.) and $k_2 = 0.0236 \text{ h}^{-1}$ for film with two layers (III.) it shows that the presence of additional control layers also resulted in the extension of the time to maximum drug release rate (t_{2max}).

Moreover, the system with outside control layers prepared by dipping results in higher reduction of ibuprofen release rate than the system with outside control layers prepared by spraying.

Introduction of nanoadditive (curve IV.) into the dibutylchitin film did not cause a significant reduction of the ibuprofen release rate from the tested matrix.

4. Conclusions

The results of swelling kinetics indicate the influence of hydrophilic nanoclay. Dibutylchitin film with an addition of nanoclay shows a higher equilibrium degree of swelling ($\alpha_{1max} = 18\%$) in comparison with film without the additive ($\alpha_{2max} = 13\%$). Peppas model was fitted to the obtained experimental data of swelling process.

The obtained results on the release rate were described by two stage model proposed by Gallagher and Corrigan. Polymer hydrolysis (without mass loss – no mass loss was observed during swelling) may lead to polymer chain loosening and thus to the increase of the release rate.

Clear effect of additional layers on the release process of ibuprofen from the dibutylchitin transdermal system was observed. Introduction of outside control layer on polymer matrix causes lowering of the release rate. It is indicated by lower value of rate constant k_1 characteristic for the first stage of the release. In the second stage in which the IBU release is accompanied by hydrolytic degradation/swelling of the polymer, an increase of the k_2 rate constant is observed. The presence of additional control layers also resulted in the extension of the time to maximum drug release rate (t_{2max}).

The way control layer is added is also important. The system with outside control layers prepared by dipping demonstrates higher reduction of ibuprofen release rate than the system with outside control layers prepared by spraying.

Introduction of nanoadditive into the dibutylchitin film did not cause a low reduction of the ibuprofen release rate from the tested matrix. The results show that the composition

and structure of the matrix determine the rate of diffusion and dissolution of the active substance in the buffer environment.

5. Acknowledgments

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6. References

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