KINETICS OF ACTIVE SUBSTANCE RELEASE FROM FLAT BIOPOLYMER MULTILAYER FILMS

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Abstract
Abstract. Polymer films were made of different biodegradable materials. Solid support of model active substance (salicylic acid) was unmodified and modified (crosslinked with glutaraldehyde) chitosan and outside layers were polylactid acid (PLA). The aim of the study was to obtain the controlled release kinetics of active substance, in medium of pH 5.6 which is similar to conditions occurring on the human skin surface. The chitosan films were investigated with swelling kinetics while multilayer films were studied with release kinetics of active substance (salicylic acid). The amount of salicylic acid released from film was measured using a UV-VIS spectrophotometer. The appropriate mathematical model was also adjusted to the experimental points. The results prove that the swelling process follows the first order kinetics but the results of release process are fitted with Peppas model.

Key words: *drug release, swelling kinetics, polymer films, chitosan, polylactid.*

1. Introduction

At present, we may observe an increase in the application of various polymer materials with the improved usable properties. In the recent years biopolymers in particular have found the application in pharmacy, especially as microcapsules or microspheres and transdermal systems with the aim of controlled drug release [1].

According to Farmacopea [2], transdermal systems are elastic multi-layer plasters of varied shape and size. A medical substance during use of systems should be released with a constant controlled rate.

Transdermal systems are intended to be applied to the skin which has not been changed by the disease. Medical substance is passed over to the general circulation by skin barrier.

It adheres to the skin by soft pressure of the palm or fingers. Removal does not cause any damage to the skin, or separation of the layers.

Transdermal systems are usually composed of layer with medical substance and adhered outside protective layer.

The focus of the research were thin multilayer polymer films containing drug which constituted the internal film of the transdermal system.

The results presented concern the research into the active substance release (salicylic acid) from biopolymer chitosan films. The present study is the continuation of the previous research into the controlled release of model substance from PLA films and dibutyrylchitin [3].

Description of active substance release from the controlled release systems (CRS) is a complex problem. Mass transfer from the system is influenced by many factors: hydrophilicity of the polymer (water sorption ability), the physico-chemical properties of the drug (first of all, its solubility in the water environment, but also the shape and size of the drug particles).

Nowadays, one may find many mathematical models describing the release kinetics of active substance- 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 [4]. 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 and the release kinetics may be presented by zero-order equation. It was observed zero-order kinetics in description of transdermal systems, tablets containing the active substance with low solubility or CRS in areolas.

Another model [4, 5] describing the first-order kinetics of the active substance release may be presented by equation (1):

$$f_t = (1 - e^{-k_1 \cdot t}) \quad (1)$$

Separate symbols mark: $f_t = C_1/C$ - coefficient representing a part of released drug in time t; C_0 – initial drug concentration in controlled release systems (CRS); C_t –drug concentration, released from matrix after time t; k_1 – kinetic constant of first-order release in 1/h.

The application of the first-order kinetics is when the rate of substance release decreases in time also for porous matrices containing drugs soluble in water.

A more universal model is a semi-empirical equation used to describe the drug release from polymer systems referred to as 'Power Law' or Peppas Model [4, 5], equation (2)

$$f_t = k \cdot t^n \quad (2)$$

Where: k_1 – kinetic constant of release process in 1/h; n - index describing the mechanism of drug release, dependent on the configuration geometry. As regards controlled drug release obeying the diffusion-degradation principle, n accepts the values for flat arrays in 0.5 and 1.0. Exponent n takes the value close to 0.5 when Fick's diffusion contributes to the release and close to 1.0 when the main driving force is polymer matrix degradation.

Peppas Model is used as a basic equation describing the drug kinetics release and applied to configurations with different geometry as well as to polymer matrices when the mechanism of release is not known [5].

2. Experimental

2.1. Materials

Two biodegradable polymers were used in the study. Chitosan was applied as the main matrix for the drug and polylactid acid was used as an outside layer.

Polylactid acid in the form of granulate used in the study was purchased from the Cargill Dow Polymers LLC company. Methylene chloride was applied as a solvent.

Chitosan is a natural, non-toxic, biodegradable copolymer of (1.4-β-)-2-amino-2-deoxy-D-glucopiranose and (1.4-β-)-2-acetamido-2-deoxy-D-glucopiranose. As a solvent of chitosan 1% acetic acid was used.

Salicylic acid was used as an active substance and it is also known as **- ortho-hydroxybenzoic or 2-hydroxybenzoic acid.** It is an aromatic carboxylic hydroxy-acid with the general formula $C_6H_4(OH)COOH$. It occurs in the form of white crystalline powder or as colorless needles. Salicylic acid weakly dissolves in water and better in ethanol. Salicylic acid is utilized for production of aceto-salicylic acid or p-amino-salicylic acid. It is used as a disinfectant and ceratolic agent (acne drugs). Salicylic acid shows an anti-fungal, anti-bacterial, anti-viral and anti-protozoan influence caused by the presence of a free phenol group in a salicylic anion. ***Figure 1***. presents the structural formula of salicylic acid.

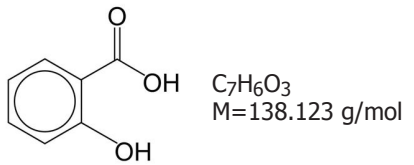

Figure 1. *Structural formula of salicylic acid.*

2.2. Analytical methods

2.2.1. Films preparation

Polymer films were prepared from the mixture of modified chitosan with 1% glutar aldehyde in solution of 1% acetic acid with salicylic acid and also from an unmodified chitosan mixture.

Outside layer of transdermal systems was obtained by dipping chitosan films in 1.5% PLA mixture were the solvent was chloride methylene. Chitosan solutions with volume of 15 ml were poured on Petri plates and were left to vaporize the solvent at the ambient temperature. Transparent unmodified chitosan films of thickness 45 - 50 μm and modified chitosan films of thickness 75-110 μm with a yellowish tint were obtained. The samples were also etched in methyl alcohol. The thickness of obtained PLA outside layer covering the modified chitosan film was 15 - 25 μm but the thickness for unmodified chitosan was equal to 120 μm. The films were analyzed.

2.2.2. Kinetics of swelling process

The investigation of the swelling kinetics of chitosan films was carried out in glass beakers containing 50 cm^3 medium of pH = 5.6. The films which did not contain salicylic acid and intended for examinations of swelling, were dried at the temperature 80 °C for 1 h. The polymer films of the defined size prepared in such a way were introduced to the proper environment. The studies were carried out at the ambient temperature. At the definite time intervals the films were again dried and weighted. 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). The formula (3) allows to determine the swelling degree of the polymers.

$$\alpha = \left(\frac{m_m - m_s}{m_s} \right) \cdot 100\% \tag{3}$$

Where: m_m - mass of wet sample [mg], m_s - mass of dry sample [mg], α - degree of swelling (percentage content of absorbed liquid) [%].

Swelling kinetics is described by the first-order equation:

$$\alpha = \alpha_\infty \cdot \left(1 - \exp\left(-k_1 \cdot t\right)\right) \tag{4}$$

Symbol α_∞ denotes the maximum swelling degree in %, k_1 is the first-order kinetic constant of swelling in 1/h.

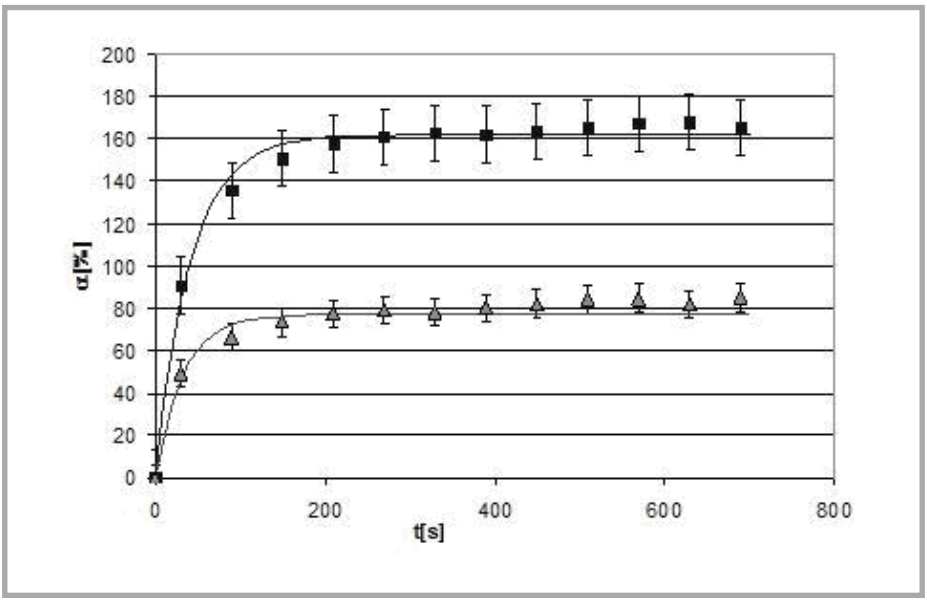

Figure 2. *Curves of swelling kinetics of films, pH = 5.6.* ■ *- unmodified chitosan* α_∞ *= 162%;* k_1 *= 0,024* h^{-1}*;* ▲ *- modified chitosan,* α_∞ *= 77%,* k_1 *= 0.031* h^{-1}*;* ━ *first-order kinetics fitting; tolerance of en error 3%.*

Figure 2 shows the graph of swelling degree of chitosan films in the environment of pH = 5.6.

From the analysis of ***Figure 2*** it follows that we can observe clear swelling of both polymeric samples. Due to the obtained results it is feasible to observe that the rate of water sorption for unmodified chitosan is higher than for modified chitosan. The swelling degree α is considerably higher for unmodified chitosan, α_{max} exceeds 100%.

2.2.3. Film morphology

Figure 3 see page 112 shows the microphotographs of (PLA) outside layer after completed investigations of salicylic acid release. We can observe that the structure of the tested samples changed and it is characterized by the presence of blowholes and numerous cracks. It indicates the hydrolytic degradation of polymer in the release process.

Figure 4 see page 112 presents microphotographs of chitosan films after the completed process of salicylic acid release. The microscopic photograph of chitosan film with added glutar aldehyde shows the cross-linked structure of chitosan. Structure of the examined unmodified chitosan films is altered and presence of blowholes is to be found. It indicates the hydrolytic degradation of polymer in the release process.

It is essential to add that chitosan films during the release process of active substance acquired a darker yellowish colour.

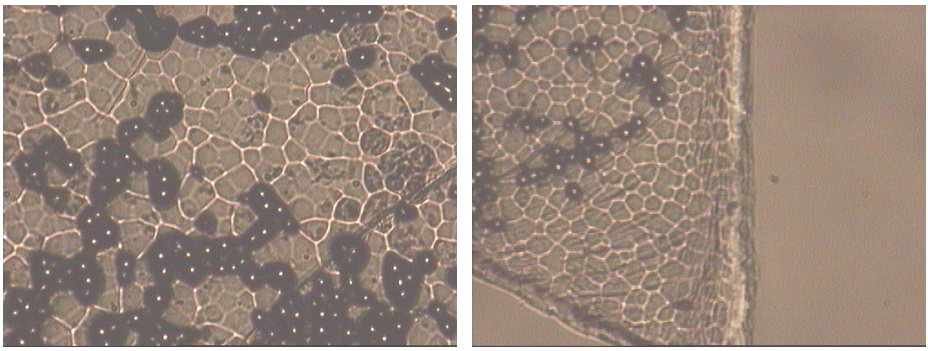

Figure 3. *Microphotographs of (PLA) outside layer film after the release process.*

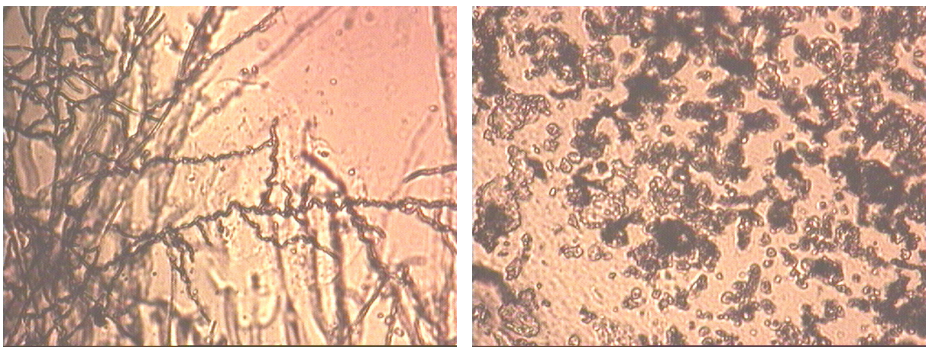

Figure 4. *Microphotographs of chitosan films, after finished release process of salicylic acid: A - modified chitosan film; B - unmodified chitosan film.*

2.2.4. Methodology of release

The release of salicylic acid was carried out in a glass beaker containing 50 cm^3 medium of pH = 5.6. The investigations were carried out at the temperature of 37 °C (± 0.5 °C). Medium of pH = 5.6 and the temperature 37 °C simulates the environment of human skin (transdermal release). Polymer films (containing salicylic acid) of the known size and mass were introduced into the system. Liquid with an immersed chitosan film, with and without PLA layer was subjected to mixing by magnetic stirrer. The beaker was covered to make it impossible for a liquid to evaporate. The amount of salicylic acid released from the film was measured with a UV-Vis spectrophotometer. The sample of the liquid was taken for an analysis in a quartz cuvette of the UV-Vis spectrophotometer at the definite time intervals. The concentration of salicylic acid was determined (the model curve had been determined previously) on the basis of the absorbance in a characteristic band of $\lambda = 279.2$ nm. The liquid was sampled at half of the distance of the upper edge of the mixer from the surface of the liquid but no closer than 1 cm from the wall of the beaker.

3. Results and discussion

Chitosan as a polymer with unique solubility, biological and chemical activity has attracted attention as a biomedical polymer [6]. Because of chitosan unique polymeric features, gel and film forming properties, since about fifteen years it is wide used in the pharmaceutical industry in the development of drug delivery systems. Up to now it is possible to observe many drug delivery formulations based on chitosan such as microspheres, films, ect. [7].

3.1. Release kinetics

The graph of salicylic acid release kinetics (f_t) in a function of time (t) was created on the basis of the obtained results. The appropriate mathematical model was adjusted for those values. The results of matching are presented in ***Figures 5 - 8***.

The obtained exponential data profile of salicylic acid release from the analyzed polymer films has been defined with Peppas Model.

As it results from ***Figure 8*** in the initial stadium, the release process occurs according to the first-order model (inside ***Figure 2***). This means that the main driving force of this stage of the process is drug solubility in a swelled polymer (swelling process obeys the rules of the first-order kinetics).

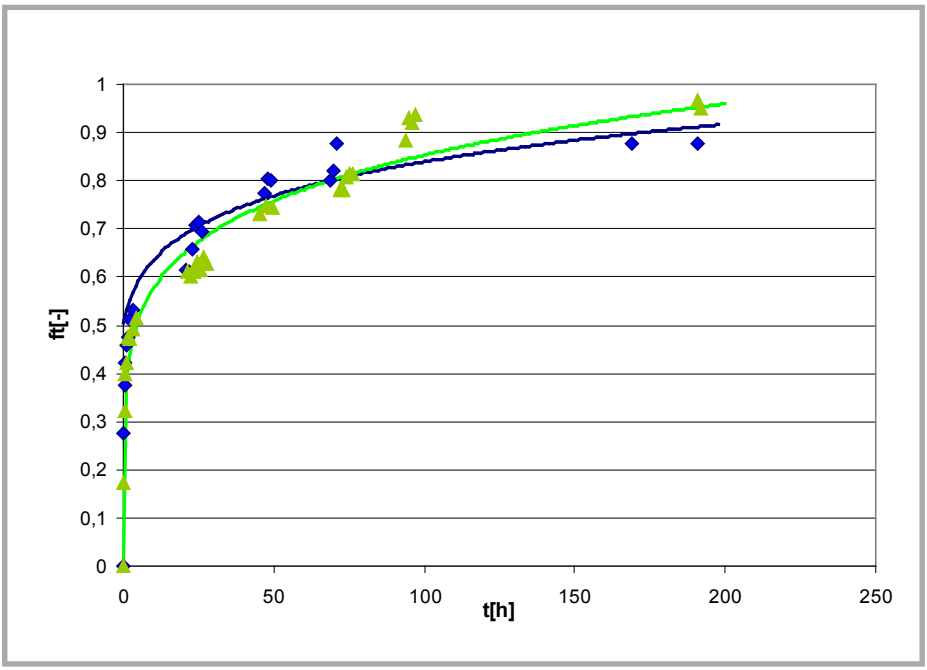

Figure 5. *Kinetics of salicylic acid release from chitosan film, pH= 5.6 ▲ - unmodified chitosan; ♦ - modified chitosan; Peppas model fitting.*

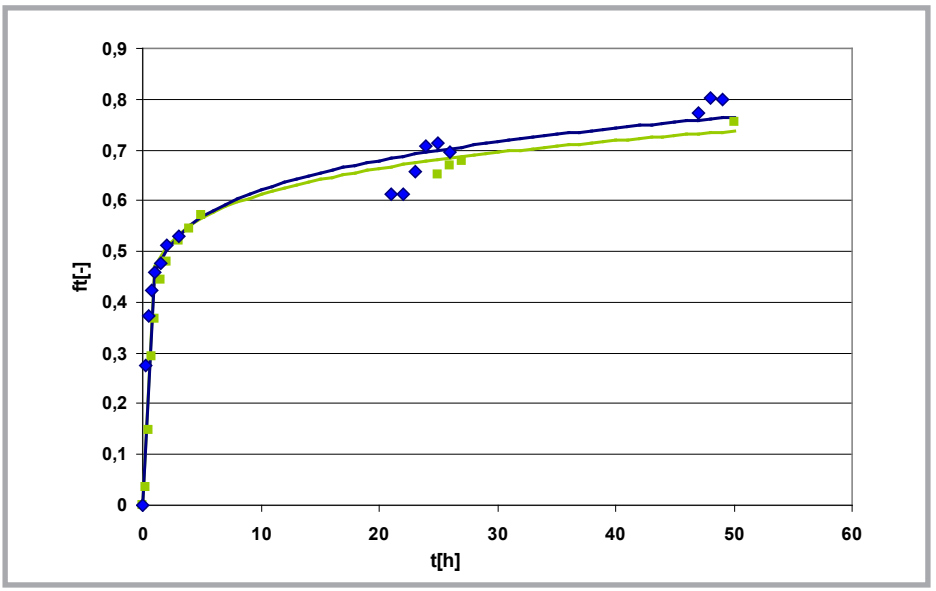

Figure 6. *Kinetics of salicylic acid release from chitosan film, pH= 5.6; ■ - Modified chitosan with PLA layer thickness of 15 μm; ● - modified chitosan without PLA layer; model fitting.*

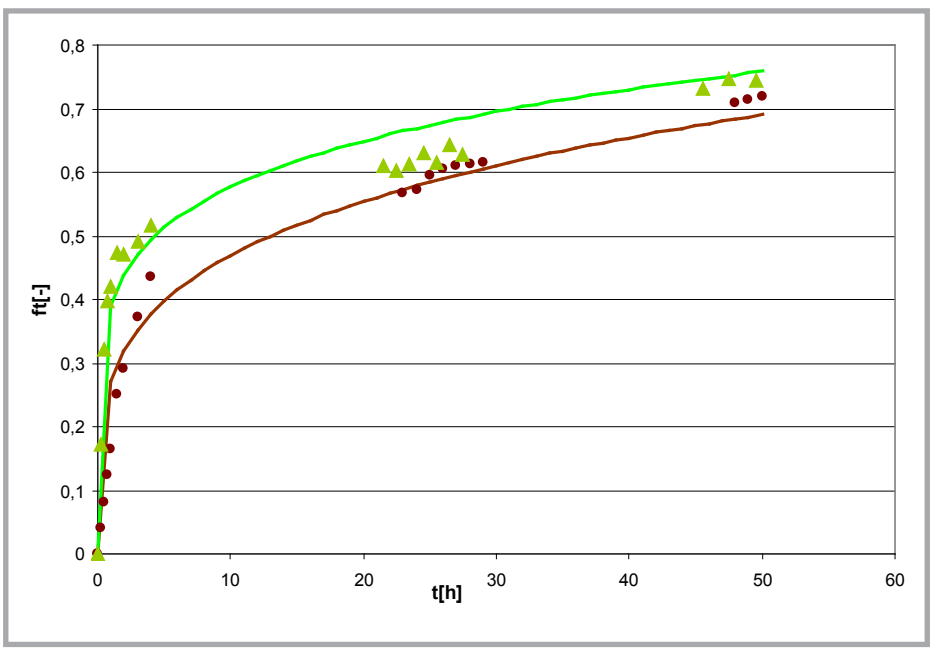

Figure 7. *Kinetics of salicylic acid release from chitosan film, pH= 5.6. ▲ - unmodified chitosan; ● - unmodified chitosan with PLA layer thickness of 120 μm; Peppas model fitting.*

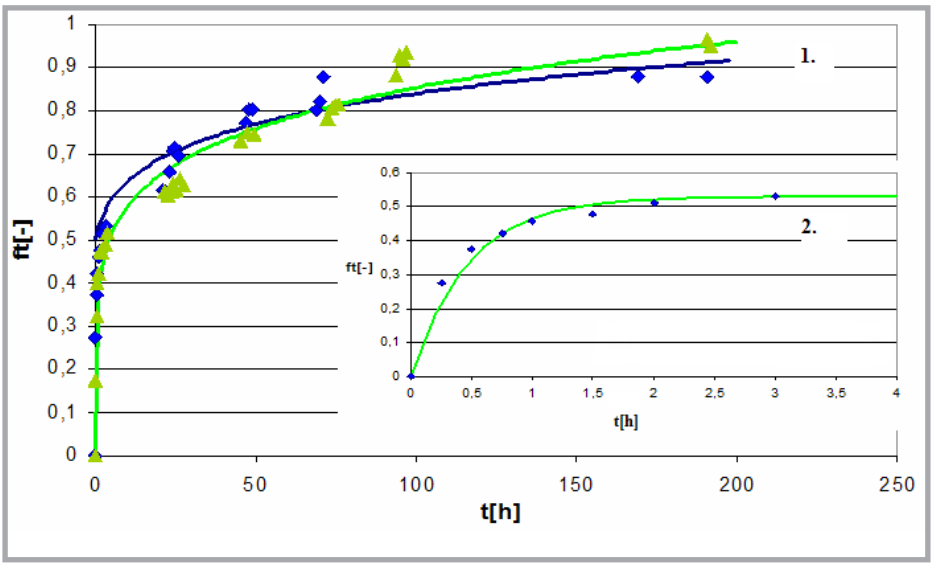

Figure 8. *Kinetics of salicylic acid release from chitosan film, pH = 5.6; ▲ - unmodified chitosan; ♦ - modified chitosan; 1. – Peppas model fitting; 2. – inside, first-order fitting.*

Composition of release kinetics of salicylic acid from chitosan films is shown in ***Table 1***.

Table 1. *Parameters of release kinetics (Peppas Model):*

Chitosan	Release			
	Modified	Modified with PLA layer (15 μm)	Unmodified	Unmodified with PLA layer (120 μm)
k, 1/h	0.46	0.47	0.39	0.27
n, -	0.13	0.12	0.17	0.24

4. Conclusions

Salicylic acid presents a good solubility in an aqueous chitosan solution. Microscopic analysis of chitosan films indicated dispersion of the drug as molecules (no crystals of salicylic acid in films). From the analysis of the obtained swelling kinetics results it follows that it is possible to observe clear swelling of both chitosan samples. The rate of water sorption for unmodified chitosan is faster than for modified chitosan. Swelling of the film contributes to loosening of the polymer structure and causes the release of active substance (salicylic acid). Swelling kinetics of the analyzed films has been described with good precision with the first-order equation.

Even though there are differences in the swelling rate of modified and unmodified chitosan films, the rate of release process does not depend on the sort of the films. This phenomenon and a big rate of release at the beginning of the process prove that the process is

superficial. The release of salicylic acid from the analyzed polymer films has been described with good precision for the majority of aforementioned cases using Peppas Model.

It can be observed that PLA outside layer has a negligible influence on the rate of the released substance. The reason for this phenomenon can be the separation of the layers during the process. It is possible to notice a clear decrease of the model active substance release rate only for unmodified chitosan film with PLA outside layer of thickness 120 μm. Film morphology after the release process shows a significant hydrolytic degradation of polymer during the release process of the drug.

5. Acknowledgments

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6. References

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