# MODIFICATION OF RELEASE RATE OF SALICYLIC ACID FROM CHITOSAN MEMBRANE

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**Abstract**
*Due to continued interest in biodegradable polymers, chitosan is one of the most commonly used polymers in the field of control release of active substances. Currently as carriers of drugs, among tablets, or micro spheres transdermal systems, called films, are used. The presented results apply to study a drug release in buffer of pH = 7.2 from chitosan film. To study the kinetics of controlled release salicylic acid was used as a model substance. Obtained films were cross-linked in TPP solution and were also modified by applying outsider layer to slow down the release process. Received transdermal systems were tested with swelling kinetics and the release kinetics of salicylic acid. The obtained systems were tested in relation to different temperature of cross-linking solution of chitosan, different thickness of studied matrices, the influence of outside layer and varying initial amount of salicylic acid.*

**Key words:** *crosslinking, release, transdermal systems, salicylic acid, chitosan.*

## 1. Introduction

Due to continued interest in biodegradable polymers, chitosan is one of the most commonly used polymers in the field of control release of active substances [1-3]. It is used as carriers of drugs, tablets, or microspheres and transdermal systems, called films. They are an alternative to the standard forms of active substance delivery in the human body. Transdermal system is a thin one or multilayer membrane of any shape and sizes. Transdermal system using one of the active functions of the skin delivers the drug, which gently diffuses by skin pores into the overall circulatory system. Because of its advantages these membranes gain on popularity among patients [4].

The presented results apply to study of drug release in buffer of pH = 7.2. As a model substance to study the kinetics of controlled release salicylic acid was used. It occurs in the form of white crystalline powder or as colorless needles. Salicylic acid weakly dissolves in water. It is utilized for production of aceto-salicylic acid or p-amino-salicylic acid.

As a matrix for salicylic acid release was used chitosan. Thanks to its valuable properties as biocompatibility or non-toxic is intensively studied as: a carrier for the drugs, in controlled release and hydrogels [5, 6] and many other fields.

Chitosan films as transdermal systems were made by casting of chitosan solution containing salicylic acid in 1% solution of acetic acid. Films obtained by evaporation of solvent were cross-linked in TPP solution [5, 7]. They were also modified by applying outsider layer to slow down the release process.

Received transdermal systems were tested by swelling and release kinetics of salicylic acid. The obtained systems were tested in relation to different temperature of cross-linking, different thicknesses of studied matrices, the influence of outside layer and varying the initial amount of salicylic acid. For obtained experimental results the appropriate mathematical model was fitted. That takes into account the influence of tested effects on both process as the swelling of films and the release of salicylic acid.

## 2. Materials and methods

The present results concern the studies of salicylic acid release from chitosan (CH) films.

### 2.1. Materials

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 Daltons). 1% acetic acid was used as solvent of chitosan.

Salicylic acid was purchased from Chempur company and has it characteristic UV-Vis band of the absorbance in $\lambda_2$ = 279.2 nm.

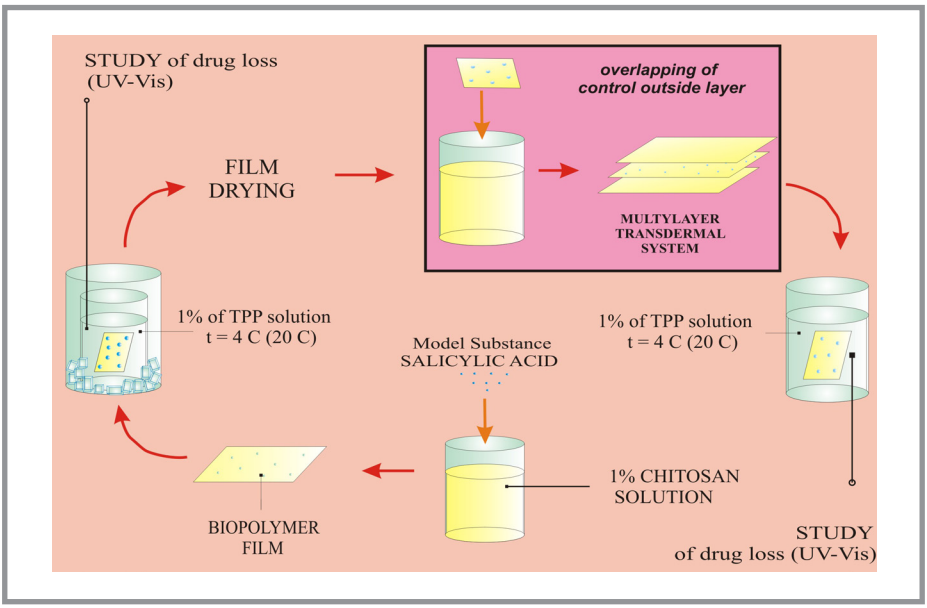


***Figure 1.*** *Receipt of transdermal systems.*

## 2.2. Methods

### *2.2.1 Films preparation*

Chitosan films were prepared 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. Chitosan films were crosslinked in 1% solution of TPP in acidic environment and temperature of 4 °C or in ambient temeperature [**7**]. Films of different thicknesses (80µm and 100 µm), different capacity of salicylic acid (10% and 20%) and also with extra layer (about 10 m) were obtained. Studies of swelling and release of active substance were done in environment of pH = 7.2. The receipt of the transdermal systems is present in ***Figure 1***.

### *2.2.2. Swelling process*

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 about 40 mg) were introduced to the buffer environment (pH = 7.2 of composition $NaH_2P0_4$-Na0H) at the room temperature. At definite time intervals (every two minutes by first half an hour, then every 10 minutes by next half an hour) the films were weighted (surface dried up by tissue paper).

The experimental data were presented in the form of the graph presenting the dependence of the swelling degree ($\alpha$) in the function of time (t) $\alpha = (m_m - m_s)/m_s \times 100\%$. Individual symbols signify: $m_m$ – mass of wet sample in mg, $m_s$ – mass of dry sample in mg.

Swelling kinetics was described by equation of first order kinetics ***Equation 1***:

$$\alpha = \alpha_{\infty} (1 - \exp(-k_1' \cdot t)) \quad (1)$$

Symbol $\alpha_{\infty}$ means the maximum swelling stage in %, $k_1'$ is the constant of first order swelling kinetics in 1/h.

### *2.2.3. Release process*

The release of salicylic acid was carried out in a glass vessel containing 50 $cm^3$ buffer medium of pH = 7.2. The investigations were carried out at the temperature of 37 ± 0.5 °C. Polymer films containing an active substance of the known size and mass (about 40 milligrams) were introduced into the buffer environment. 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 Pharmacopeia). 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 measured (the model curve for the drug was determined early) basing on the absorbance in a characteristic band of λ = 279.2 nm. Released drug fraction $f_t$ was calculated. Release kinetics was described by equation of first order kinetics [8 - 10], (***Equation 2***):

$$f_t = A_1 (1 - \exp(-k_1 \cdot t)) \quad (2)$$

Symbol $f_t$ means fraction of released drug in time $t$, $A_1$ is the amount of released drug in duration of the process in -, $k_1$ is the constant of first order release kinetics in 1/h.

## 3. Results and discussion

Swelling kinetics of polymer samples was observed and the obtained test data were displayed in graphs presenting dependence of swelling degree (α) versus time ($t$). The

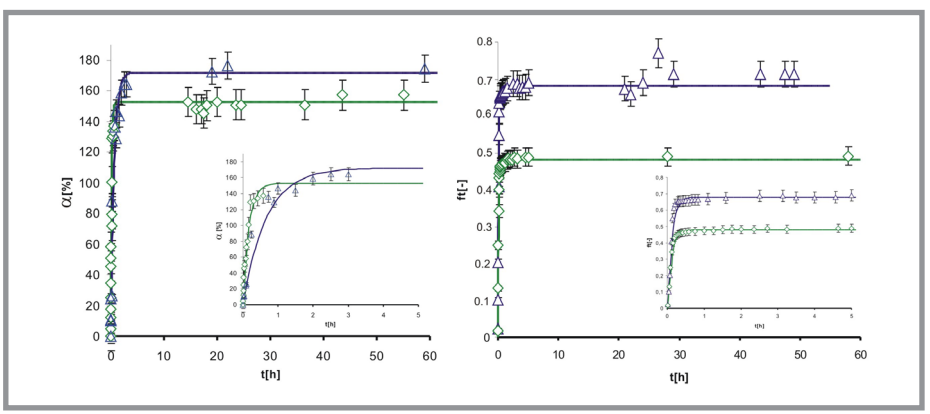


***Figure 2.*** *a) Swelling of modificated chitosan film. b) The release of salicylic acid from chitosan film Experimental points of crosslinked chitosan in solution of 4 °C △ ; and of 20 °C ◇; curves – first order kinetics (effect 1).*

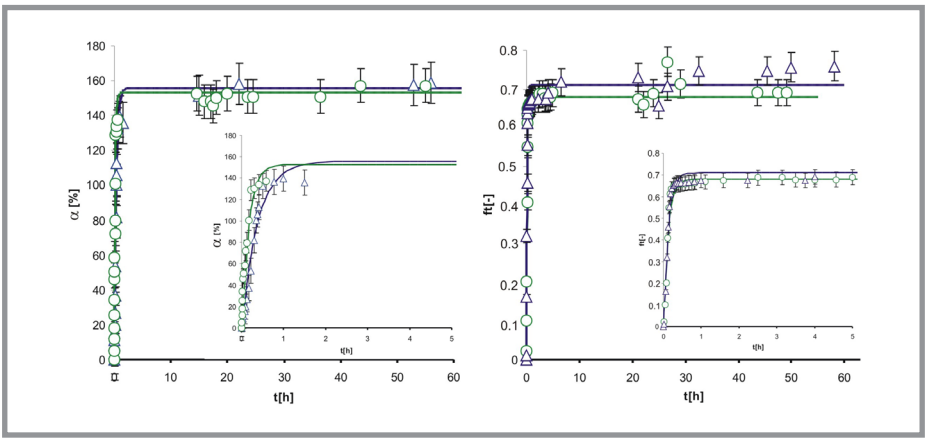


***Figure 3.*** *a) Swelling of modificated chitosan film. b) The release of salicylic acid from chitosan film Experimental points of chitosan film with thickness of 100 μm △ ; and with thickness of 80 μm ○; curves – first order kinetics (effect 2).*

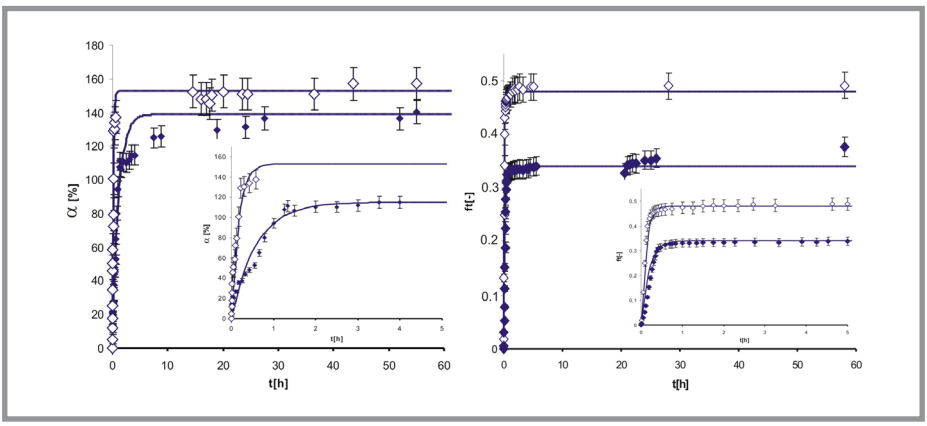


***Figure 4.*** *a) Swelling of modificated chitosan film. b) The release of salicylic acid from chitosan filmExperimental points of chitosan film without extra layer ◇; and with extra layer◆; curves – first order kinetics (effect 3).*

graphs of release fraction ($f_t$) of salicylic acid as a function of time (t) were also drawn. Swelling and release process ware tested in respect of studied effects and the results are presented in ***Figures 2 - 5***. The effects of study were: 1) the temperature of crosslinking, 2) different thickness of films (80 μm and 100 μm), 3) influence of added outside layer, 4) varying initial amount of salicylic acid (10% and 20%). To the achieved experimental points the first order kinetics model was fitted.

To each graph inside small diagram was introduced to present the initial rate of observed process. For the experimental results of release and swelling processes first or-

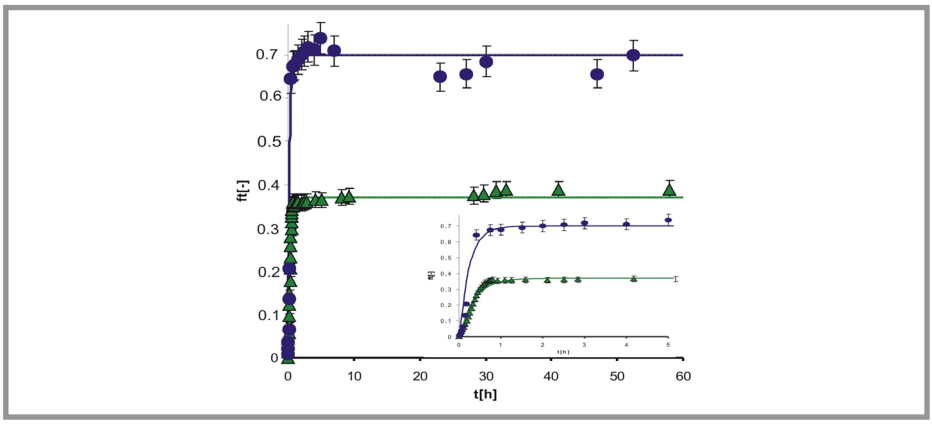


***Figure 5.*** *The release of salicylic acid from chitosan film; experimental points of chitosan film of initial amount of salicylic acid of 20% ● ; and of 10% ▲; curves – first order kinetics (effect 4).*

der model was fitted. In the graphs fast release is observed - the so called 'burst effect'. It originates from drug release from the surface area (so called 'skin layer'). Moreover it was proposed to divide the loaded amount of the substance into three characteristic fractions. The volume fraction of released substance in the main release process ($\phi_1$'), the released amount into TPP solution during crosslinking process ($\phi_2$') and also a substance left in the transdermal system after the main release ($\phi_3$') thus $\phi_1$'+ $\phi_2$'+$\phi_3$'=1.

The effect results of the study are presented in ***Tables 1*** and ***2***. In the case of release process the following effects were studied: 1) the temperature of crosslinking, 2) thickness of films (80 μm and 100 μm), 3) added outside layer, 4) varying initial amount of salicylic acid (10% and 20%). The effects of the study are presented in ***Table 1***. It is observed a smaller loss ($\phi_2$') of salicylic acid during crosslinking of the chitosan film in TPP solution of temperature 4 °C than of 20 °C. The thickness of the film does not influence significantly on studied release process. Moreover it was found that film with additioned layer indicates on smaller amount of released substance ($\phi_1$') in relation to the film without the layer. Bigger initial content of the drug in the sample influences on a higher maximal amount of released drug (see ***Figure 5***).

In the case of swelling process the following effects were studied: 1) the temperature of crosslinking, 2) thickness of films (80μm and 100μm) and 3) influence of additioned outside layer. The results of the effects are presented in ***Table 2.*** Visible influence of chitosan crosslinking temperature is observed. Samples crosslinked in TPP solution at 4 °C temperature show higher maximal swelling value ($\alpha_\infty$) than at ambient temperature (20 °C).

The thickness of the film in the studied region does not influence significantly on the swelling process. Moreover it was observed some influence of the extra layer on swelling process of the films.

***Table 1.*** *The results of studied effects on the release process; $k_1$ is the constant of first order release kinetics in 1/h, $A_1$ is the amount of released drug in duration of the process in -; the volume fraction of released substance in the main release process ($\phi_1$'), the released amount during crosslinking process ($\phi_2$') and also left substance inside the transdermal system after the release ($\phi_3$'); 1) the temperature of crosslinking, 2) thickness of films, 3) added outside layer, 4) varying initial amount of salicylic acid.*

| RELEASE (*acc. First Order Model*) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Effect of study | 1. | | 2. | | 3. | | 4. | |
| | 4 °C | 20 °C | 80 µm | 100 µm | with layer | without layer | 10% | 20% |
| $k_1$ | 8.00 | 8.70 | 8.00 | 8.00 | 5.50 | 8.70 | 2.80 | 4.10 |
| $A_1$ | 0.68 | 0.48 | 0.68 | 0.71 | 0.34 | 0.48 | 0.37 | 0.70 |
| $\varphi_1$ ' | 0.68 | 0.48 | 0.68 | 0.71 | 0.34 | 0.48 | 0.37 | 0.70 |
| $\varphi_2$ ' | 0.30 | 0.43 | 0.30 | 0.08 | 0.48 | 0.43 | 0.54 | 0.30 |
| $\varphi_3$ ' | 0.02 | 0.09 | 0.02 | 0.21 | 0.18 | 0.09 | 0.09 | 0.00 |

***Table 2.*** *The results of studied effects on the swelling process; $\alpha_\infty$ means the maximum swelling stage in %; $k_1$' is the constant of first order swelling kinetics in 1/h; 1) the temperature of crosslinking; 2) thickness of films and 3) influence of additioned outside layer.*

| SWELLING (*acc. First Order Model* ) | | | | | | |
|---|---|---|---|---|---|---|
| Effect of study | 1. | | 2. | | 3. | |
| | 4 °C | 20 °C | 80 µm | 100 µm | with layer | without layer |
| $k'_1$ | 1.5 | 5.8 | 5.8 | 2.6 | 0.9 | 5.8 |
| $\alpha_\infty$ | 185 | 153 | 153 | 156 | 139 | 153 |

Extra layer causes slowdown of the swelling process and insignificant reduction of maximal swelling value of the studied samples.

## 4. Conclusions

Swelling and release process of chitosan samples were tested in respect of the following effects: 1) the temperature of crosslinking (4 °C and 20 °C), 2) thickness of films (80 µm and 100 µm), 3) influence of added outside layer, 4) initial amount of salicylic acid (10% and 20%).

Obtained results showed that composition and structure of the matrix determines the rate of diffusion and dissolution of the active substance to the buffer environment. It is observed that the change of thicknesses of the films from 80 µm to 100 µm does not have significant influence on swelling process of the samples and on the rate of release process of active substance. It was found that extra layer (with thickness ~ 10 µm) causes reduction of the released fraction ($f_t$) of model substance about 18% and affects swelling process. The swelling process has influence on the release of model substance from modified matrix. Both processes are described by first order kinetics. The loss of salicylic acid in TPP solution during crosslinking is smaller at temperature 4 °C than at 20 °C. Chitosan films containing different initial amount of salicylic acid (10% and 20%) were studied. It was found

that initially higher percentage content of the drug is characterized by higher released drug fraction. Moreover it was proposed that the initial amount of active substance inside the film ($f_t = 1$) can be divided into three fractions: $\phi_1$' fraction of substance released in studied process, $\phi_2$' released fraction during crosslinking and $\phi_3$' fraction left inside the system. Thus: $\phi_1' + \phi_2' + \phi_3' = 1$.

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