

SALICYLIC ACID RELEASE FROM CHITOSAN PELLETS COATED WITH POLYLACTIDE

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Abstract

The aim of the study was to prepare a bi-polymer drug carrier composed of chitosan pellets (CS) coated with polylactide shell (PLA) providing prolonged model drug – salicylic acid (SA) release into phosphate buffer of pH = 7.2. Pellets were obtained through a coacervation followed by a freeze-drying process. In a terms of model drug loading, porous pellets were impregnated with a SA solution under vacuum. Afterwards, loaded and dried beads were coated with PLA films through their dipping in a PLA organic solution. FTIR spectroscopy was implemented to analyse the effectiveness of SA loading process. The UV-Vis spectrophotometry kinetic studies of a model drug release from PLA coated and non-coated pellets into phosphate buffer were conducted. Increasing time of CS pellets impregnation with SA solution resulted in decrease of salicylic acid release rate. This tendency was more evident for the SA release from pellets coated with an additional layer of PLA. Model drug release kinetic points were well approximated with first order kinetics model.

Key words: *chitosan, polylactide, salicylic acid, prolonged drug release, first order kinetics.*

1. Introduction

Controlled release systems (CRS), composed of drug molecules or crystals enclosed within polymeric matrix, have been widely investigated for last thirty years [1,2]. A spectrum of polymers, natural as well as synthetic [3] were successfully introduced to medicine as active substances carriers. The main goal of novel CRS drug forms preparation is to maintain the drug concentration on therapeutic level in a specific site of action in human organism.

Among others, chitosan (CS) and polylactide (PLA) are perfect candidates to form matrices in CRS. Chitosan is natural aminopolysaccharide widely known for its non-toxicity, well biocompatibility and ability to biodegradation due to bonds hydrolysis in aqueous environment [4]. Polylactide, on the other hand, represents synthetic group of biodegradable polymers – polyesters [5]. PLA is characteristic for a variety of structures like: stents, resorbable guts, microspheres [6] or films, which can be obtained from this polyester.

In this paper, analysis of novel CRS carriers in a form of chitosan pellets coated with polylactide films are presented. As a model drug encapsulated in polymeric matrices, salicylic acid (SA) [7] was selected. Bi-polymeric drug carriers were prepared through a complex process including chitosan pellets coacervation and freeze-drying, vacuum impregnation with SA solution and dip-coating in PLA organic solution.

Morphological studies of obtained pellets as well as FTIR spectroscopic salicylic acid encapsulation investigation are discussed. Moreover, kinetic studies of SA release from pellets coated and non-coated with PLA films into phosphate buffer (pH = 7.2) are presented.

2. Materials and methods

2.1. Materials

Polymeric pellets were prepared from chitosan (CS) powder of molecular weight $M_w = 4.5 \cdot 10^5$ and deacetylation degree equal to 73.3%, produced at the Sea Fisheries Institute in Gdynia. Polylactide (PLA) granulate of glass transition at $T_g = 57$ °C, purchased from NatureWorks LLC (USA) had been selected to be material for pellets coating. The polymer solvents were 1% acetic acid and ethyl acetate respectively.

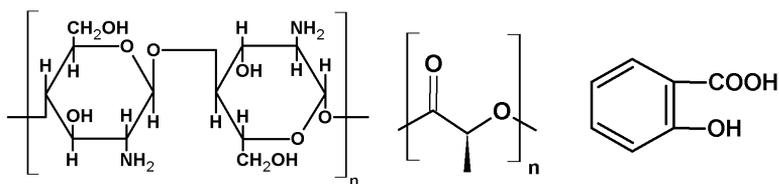


Figure 1. Chemical structures of used materials: A) chitosan (CS); B) polylactide (PLA); C) salicylic acid (SA).

Salicylic acid (SA) powder of molecular weight of 138.12 g/mol, provided by Chempur, Poland, was used as a model therapeutic substance.

The coacervation of chitosan was carried out in the sodium tripolyphosphate (Sigma Aldrich Chemie GmbH Steinheim, Germany) water solution.

Chemical structures of macromolecules forming CRS matrices as well as model drug are shown in *Figure 1*.

2.2. Drug loaded chitosan pellets preparation and their coating with PLA film procedure

First step of pellets preparation was chitosan coacervation process, which was carried out by adding dropwise viscous CS solution in 1% acetic acid into 1% aqueous solution of sodium tripolyphosphate (TPP). As a result of electrostatic attraction between positively charged CS molecules and phosphorous anions of TPP [8], hydrogel CS pellets obtained in solution.

Secondly, beads of average diameter approximately equal to 1.5 mm, were collected on sieve and freeze dried in Christ Alpha 2-4 lyophilizer for 24 hours at $-25\text{ }^{\circ}\text{C}$ and 63.0 Pa.

Lastly, vacuum (200 Pa) pellets impregnation with model drug solution were conducted at ambient temperature. Impregnation was carried out for 5 min, 15 min or 30 min. Complex process of SA impregnated chitosan pellets preparation is presented in scheme below (*Figure 2*).

Afterwards, pellets impregnated with model drug solution were dried at $60\text{ }^{\circ}\text{C}$ in oven until constant mass. After this step, average diameter of pellets was determined to be equal to 1 mm. Eventually, some amount of all pellets samples was coated with PLA film

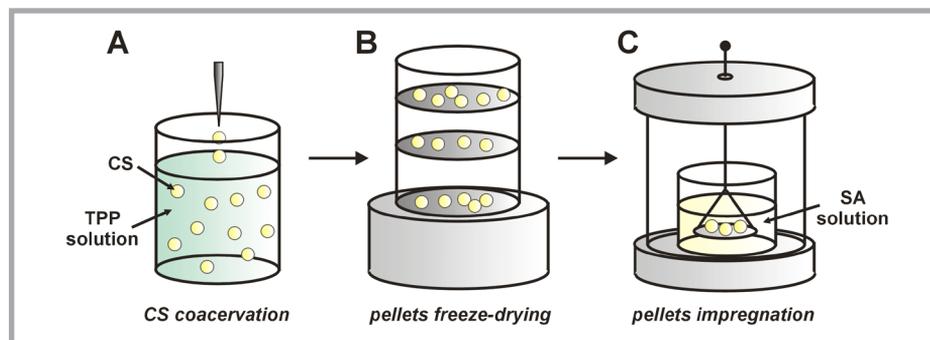


Figure 2. A scheme of three stage SA loaded chitosan pellets preparation: A) CS droplets coacervation in TPP solution; B) freeze-drying of hydrogel CS pellets; C) pellets impregnation with SA solution under vacuum.

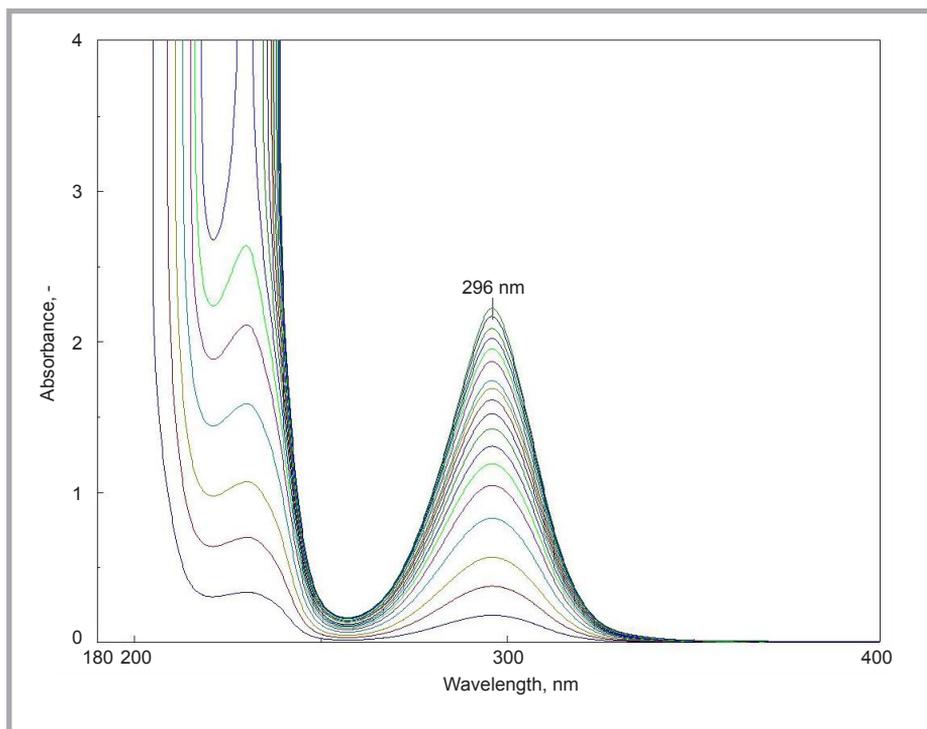


Figure 3. UV-Vis spectra of SA during release into $pH = 7.2$ from PLA coated CS beads impregnated for 30 min.

by dipping CS structures in polylactide organic solution followed by drying them at $50\text{ }^{\circ}\text{C}$. Coating process was repeated twice, obtained PLA layers were statistically $5\text{ }\mu\text{m}$ thick.

2.3. FTIR spectroscopy samples preparation

Spectroscopic FTIR analysis of chitosan pellets spectrum after their impregnation with SA solution was conducted to examine the effectiveness of model drug encapsulation. FTIR sample was prepared by mixing 3mg of dry CS pellets with 200 mg of KBr powder, able to transmit IR radiation in whole range of its spectrum, in a porcelain mortar. Obtained mixture was then compressed to form an uniform tablet, which was eventually analysed with Mattson Genesis II FTIR apparatus.

2.4. Drug release process methodology

Model drug release process was carried out in a vessel containing known amount of phosphorous buffer solution ($pH = 7.2$) at $37\text{ }^{\circ}\text{C}$. Kinetics of SA release from PLA coated and non-coated chitosan pellets impregnated for 5 min, 15 min and 30 min was analysed. Kinetic points of release process were obtained according to Pharmacopaea [9] by UV-Vis spectrophotometric analysis of the height of characteristic peak of model drug (296 nm).

In **Figure 3**, an exemplary UV-Vis spectra of SA during release from biopolymeric carriers are presented.

3. Results and discussion

3.1. Microscopic analysis

Morphology of obtained polymeric structures is presented in **Figures 4.** and **5.** SEM microphotographs of freeze-dried chitosan pellets (**Figure 5**) depict porous surface of this carriers as well as their cellular inner structure. Such a morphology let us assume that salicylic acid could be effectively incorporated into chitosan pellets by a vacuum impregnation technique.

The difference in morphology of chitosan pellets before and after impregnation and PLA film coating are shown in **Figure 5**. One can see that vacuum impregnation, dip-coating and drying at 60 °C resulted in a significant decrease of spherical CS pellets diameters. Our conclusion is that mentioned processes led to collapse of the porous biopolymeric structure, which can be beneficial in terms of prolonged drug release from this carriers.

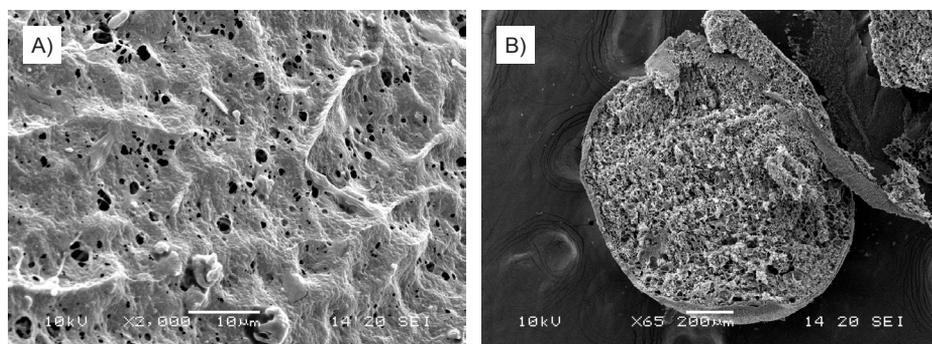


Figure 4. SEM microphotographs of chitosan freeze-dried pellet: A) surface structure; B) cross-section.

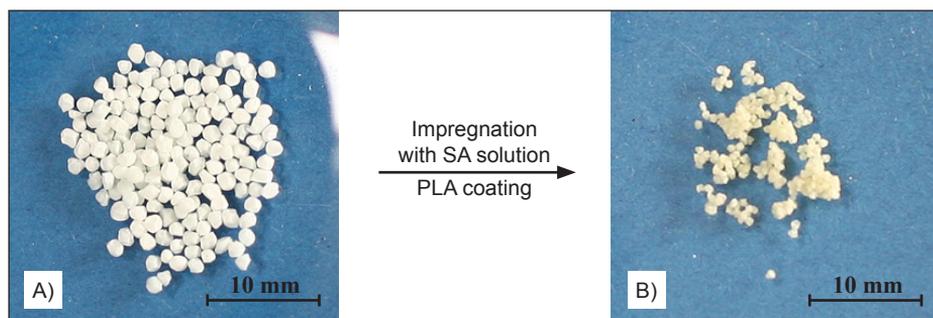


Figure 5. CS pellets before (A) and after (B) impregnation process with SA solution and coating with a PLA shells.

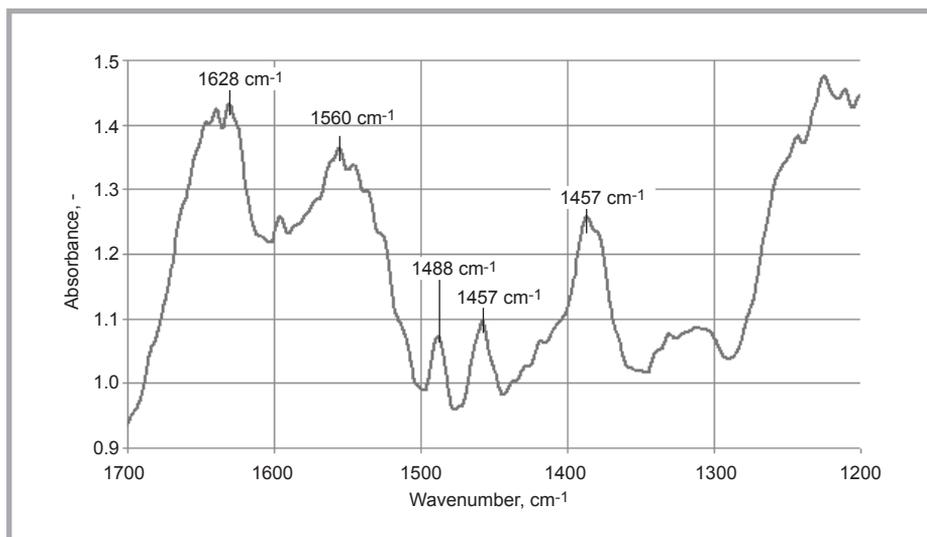


Figure 6. FTIR spectrum of non-coated CS beads impregnated with SA solution.

3.2. FTIR studies of salicylic acid loading

Infrared spectrophotometry was chosen as a method of indication of a salicylic acid molecules presence inside impregnated CS pellets. According to literature [10], salicylic acid FTIR spectrum reveals absorbance peaks at 1656 cm⁻¹, 1481 cm⁻¹, 1465 cm⁻¹ as well as at 1442 cm⁻¹. On the other hand, chitosan absorbs IR radiation at 1660 cm⁻¹ (I amide bond), 1565 cm⁻¹ (II amide bond) and at 1380 cm⁻¹ [11].

FTIR spectrum of chitosan pellets impregnated with SA solution was presented in **Figure 6**. Characteristic infrared bands were marked. One can see that beside chitosan absorbance peaks (1560 cm⁻¹, 1384 cm⁻¹ and 1628 cm⁻¹), two characteristic SA peaks are also present (1448 cm⁻¹ and 1457 cm⁻¹). This confirms an effectiveness of drug loading by vacuum impregnation technique. Another conclusion is that absorbance peaks for CS pellets with drug molecules are slightly shifted in comparison to spectra of pure substances, which may denote interactions between CS macromolecules and salicylic acid.

3.3. Analysis of model drug (SA) release kinetics

Experimental points of model drug release were gained through UV-Vis spectroscopic analysis of SA concentration in the release medium and well approximated with the I order kinetic model **Equation 1** [12]:

$$\frac{dC}{dt} = k_1 \cdot (C_{\max} - C) \quad (1)$$

After integration of equation (1) from 0 to t and from 0 to C_t , a final form of I-order kinetic model is obtained **Equation 2**:

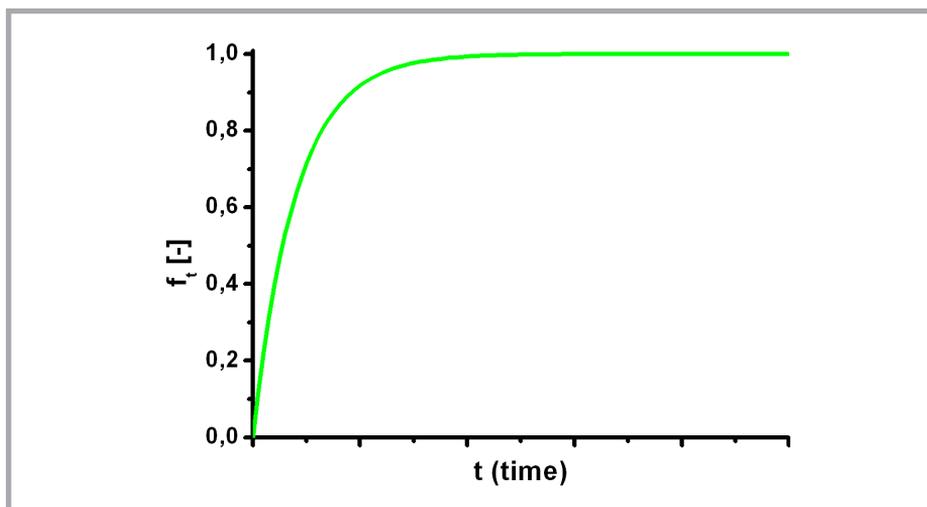


Figure 7. The first order kinetic curve.

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

where:

$f_t = C_t / C_{\max}$ – drug fraction released to medium during the time t without unit;

k_1 – first order kinetic constant in min^{-1} ;

t – time of drug release process in min.

One can conclude from **Equation 2** that the fraction of drug being released throughout the process undergoing the I order kinetics changes from 0 to 1 and the rate of release decreases in an exponential manner. Such a trend is depicted in **Figure 7**.

The kinetic results of ibuprofen release process are presented as a function of salicylic acid fraction released f_t in time t ($f_t = C_t / C_0$, where: C_t – concentration of drug released in t time in mg/cm^3 , C_0 – maximum drug concentration obtained during the release process in mg/cm^3). In each case, maximum drug concentration in release medium $C_t = C_0$ ($f_t = 1$) was achieved within 2.5 hours.

Experimental points were approximated with high accuracy with I order kinetic model (1). Kinetic curves of SA release are depicted in **Figures 8** and **9**. Furthermore, parameters values of I order equation are presented in **Table 1**.

On the basis of presented kinetic profiles analysis we conclude that the process of coating pellets with medicine with PLA shells is beneficial for achieving an extended release effect. It was also observed that with increasing time of pellets impregnation, the subsequent rate of SA release from biopolymeric carriers decreases. Moreover, the impact of time of impregnation with SA solution on drug release profile is more evident for pellets coated with an additional layer of PLA.

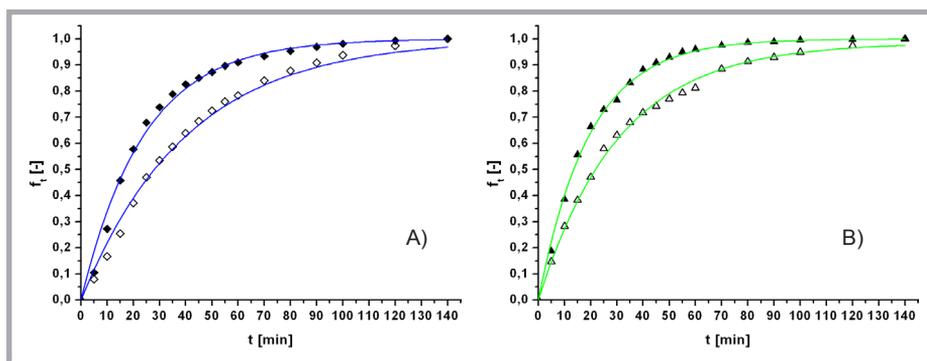


Figure 8. Kinetic curves of SA release from non-coated and PLA-coated CS pellets for: A) pellets impregnated for 15 min; B) pellets impregnated for 30 min.

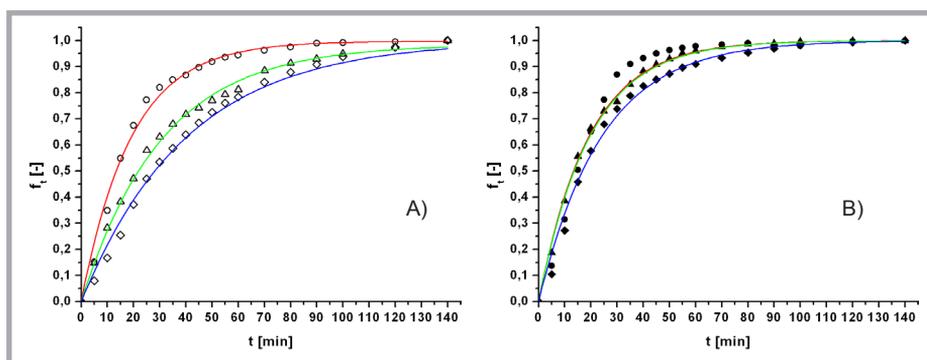


Figure 9. Kinetic curves of SA release from CS pellets impregnated for 5 min, 15 min and 30 min: A) pellets non-coated with PLA film; B) pellets PLA-coated (symbols are described in Table 1).

Table 1. Analysis of 1 order kinetic model parameters values for SA release.

model equation: $f_t = 1 - \exp(-k_1 \cdot t)$				
sample description		symbol	k_1 , 1/min	R ²
CS-SA pellets	impregnation time, min			
non-coated	5	●	0.0522	0.976
	15	▲	0.0513	0.998
	30	◆	0.0415	0.991
PLA-coated	5	○	0.0523	0.991
	15	△	0.0324	0.997
	30	◇	0.0247	0.993

4. Conclusions

On the basis of experimental data analysis, one can conclude that an impregnation under vacuum of CS pellets with SA solution resulted in incorporating of model drug into chitosan beads. Due to CS pellets dip coating with PLA films an extension of model drug release was achieved. Increasing time of CS pellets impregnation resulted in decrease of salicylic acid release rate into phosphate buffer (pH = 7.2), especially for pellets coated with an additional layer of PLA. Last but not least, SA release kinetic points were well approximated with I-order kinetics model. Correlation coefficient (R^2) values were equal to 0.976 or higher in all cases of experimental points approximation.

5. Acknowledgments

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6. References

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