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Study on the Usability of Polymer Complexes in the Form of Films Applied in Bedsore Treatments

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Abstract
Investigations are presented regarding the preparation of a complex dressing material on the basis of three biopolymers: chitosan, sodium alginate and sodium-calcium alginate with the addition of an analgesic. The dressing was prepared in the form of a film. Mechanical-, sorption- and imbibition properties of the film were tested and assessed. Investigation into the speed of delivery of the drug used as the acceptor fluid indicate that the process can be described with a complex kinetic equation of first order with two exponential functions.

Key words: *biopolymer complexes, single-layer film, dressing, bedsores, analgesic.*

Introduction

Bedsores are a serious clinical and economic problem mainly with bedridden patients receiving palliative care. The difficult-to-heal bedsores inflict pain and deepen suffering related to the main health problem. Bedsores are defects of the skin and deeper tissue caused by long-lasting or recurring pressure, resulting in ischaemia, bacterial growth, and, as a consequence, necrosis [1 - 3].

Demand increases for dressing materials that are capable of providing good protection and effective healing of bedsores. Such dressings need to be made of biodegradable polymers with adequate sorption, mechanical properties and healing ability.

Specific biological properties useful for the healing of wounds make chitosan and alginates appropriate substances in the treatment of bedsores. The biopolymers are biodegradable and partly resorbable in the vicinity of the wound, and reveal biostimulation action [4 - 7].

For a couple of years, investigations have been on-going in the Institute of Biopolymers and Chemical Fibres in biomaterials, regarding their uses in medicine, pharmacy, dentistry and veterinary areas [8 - 16].

This work presents investigations related to the preparation of a biodegradable dressing material in the form of a single-layer film made from the biopolymers chitosan, sodium alginate and sodium-calcium alginate, with the addition of the analgesic lidocaine.

Lidocaine is used for local anaesthesia as a transdermal aerosol or gel and as a pain-killing and anti-arrhythmia drug [17].

Materials and methods

Materials

- Chitosan: in the preparation of a useful form the material named ChitoClear®Primex fg 90 (USA) was used with the following parameters: average molecular mass ($\bar{M}_v$) = 338 kDa, deacetylation degree (DA) = 83.2%, ash content = 40 ppm.
- Modified chitosan lactate was used with the following parameters: pH = 6.20 – 6.65, polymer content = 1.96 - 1.97% wt. and $\bar{M}_v$ = 330.0 kDa, DA = 83.2%.
- Sodium alginate – Protanal LF10/60, supplied by FMC BioPolymer (USA).
- Plasticiser – pure glycerol for analysis was supplied by Fluka Co (USA).
- Active substance (analgesics) – lidocaine *2-(dietyloamino)-N-(2,6-dimetylofenylo)acetamide* was supplied by Sigma Co (USA).
- Lactic acid, pure for analysis, was supplied by POCh (Polish producer of reagents).
- Calcium chloride anhydrous, pure for analysis, was supplied by POCh.

Preparation of the chitosan alginate complex in the form of a film with the addition of an active substance

A modified chitosan lactate with a lower pH (6.2) and a solution of sodium alginate at concentration of 1.7% wt. were used in the preparation of the chitosan-alginate composite. The polymer solutions were blended in the following percentage proportion: 85:15; 75:25; 50:50. Next, the pH of the mixture was raised to 6.65 by the addition of a 5% NaOH solution. The composition of the composite was adopted from earlier studies performed by the Team of Biomaterials, at IBWCh.

Commercial lidocaine in an ethanol solution at an amount of 3% wt. on the dry mass of the polymers was added to the mixture. The amount of analgesics added was adopted on the basis of the dose recommended by the Polish Pharmacopeia (FP IX) for external use [18]. Glycerol in the amount of 0.5 wt. part on 1wt. part of the complex (dry mass) was added to the mixture to provide elasticity and contiguousness to the wounds. The mixture was cast onto Teflon plates forming a film with an assumed thickness in the range of 0.04 – 0.1 mm. The film was dried at 20 ± 1 °C for 48 hours.

Preparation of the chitosan-sodium-calcium alginate complex in the form of a film with the addition of the active substance

A solution of sodium-calcium alginate was blended in the proportion of 3:1 with a solution of modified chitosan lactate containing 1.96% wt. of the polymer to prepare the chitosan- and sodium-calcium alginate-containing complex. The analgesic lidocaine was added to the mixture at an amount of 3% wt. on the dry mass of the polymers. Glycerol in the amount of 0.5 wt part per 1 wt. part of the composite (dry mass) was added and the mixture was cast in the form of a film on Teflon plates. The composition of the blend was adopted from earlier studies performed by the Team of Biomaterials.

Analytical methods

Physical-mechanical properties

The mechanical testing was done at IBWCh[1)].

The following standards were applied and tests performed:

- PN-EN ISO 4593:1999 *"Resins. Film and plates estimation of thickness by mechanical scanning"* – thickness in mm;
- PN-EN ISO 527-3:1998 "*Resins. Estimation of mechanical properties at static drawing conditions in testing of film and plates"* – strength in MPa; and elongation at max stress in %;
- PN-EN 13726-4:2005 "*Non-active medical devices. Testing of direct wound dressings. Part 4: Ability to fit"* – ability to fit, durable deformation in % and extensibility in N/cm;
- PN-EN-13726-2:2005 "*Testing of direct wound dressings. Part 2: Transmission of humidity vapour through dressings with semi-permeable film"* – transmission of humidity vapour in $gm^{-2}\ 24h^{-1}$.

Assessment of absorption capacity

The absorption capacity of the materials was estimated using two parameters: 1) Water retention value (WRV), and 2) ability to absorb.

WRV was tested according to a standard method [19] and calculated from the following equation:

$$WRV = (m_1 - m_0)/m_0 \times 100\% \quad (1)$$

where m_1 denotes the mass of sample after immersion in water for 20 h and centrifuging for 10 min at 4000 r.p.m., and m_0 indicates the mass of sample after drying at 105 °C.

In the assessment of ability to absorb, samples (2 cm × 2 cm) were immersed in deionised water for a defined time (0.17; 0.25; 0.5; 3; 5 and 24 h). After a given time, the samples were taken out of the water, dried and weighed. The ability to absorb was expressed as the sorption coefficient, meaning the amount of water imbibed by 2 g of the dressing [20].

$$WS = (m_i - m_0)/m_0 \quad (2)$$

where m_i indicates the mass of the swollen sample after immersion in water for the given time t_i and drying in g, and m_0 denotes the mass of the dry sample before swelling in g.

Assessment of the release rate of the drug from the preparation to an acceptor fluid

The release rate of lidocaine from the film was tested according to the Polish Pharmacopeia (FP IX) – demands for solid drugs and transdermal systems [18, 21, 22]. Samples with a weight of 0.200 g were tested with the use of a paddle apparatus. Normal saline with a concentration of 0.9% wt. in the amount of 100 ml served as the acceptor fluid. Tests were performed in triplicate. The solution was taken after 1, 2, 5, 10, 15, 30, 60, 120, 180 minutes and 24 hours to measure the drug concentration. The concentration of the released drug was measured by photometry at wavelength of 264 nm. The testing was done by the Department of Applied Pharmacy of the Medical University of Lodz. The following preparations were tested: modified chitosan lactate, sodium alginate blended in the proportion of 85:15, 75:25, 50:50, and modified chitosan lactate and sodium/calcium alginate blended in the proportion of 3:1. Lidocaine and the plasticiser were added to both of the preparations.

Results and discussion

The primary goal of the investigation was the preparation of a complex materi-

Table 1. *Physical-mechanical parameters of the chitosan-sodium alginate film with and without lidocaine.*

Symbol of complex		Quantittive composition of the composite Chit : Alg, % wt.	Amount of lidocaine, % wt.	Strength, MPa	Elongation at max. stress, %	Permanent deformation, %	Extensibility, N/cm	Transmisssion of moisture vapour, $g \cdot m^{-2} \cdot 24h^{-1}$
B/K/MLCh/Alg/4	a)	85:15	-	6.61	171.0	-	-	-
B/K/MLCh/Alg/4/Lid	b)		3.0	4.80	103.0	4.42	1.02	7240
B/K/MLCh/Alg/5	c)	75:25	-	6.67	172.0	-	-	-
B/K/MLCh/Alg/5/Lid	d)		3.0	7.27	96.3	4.37	1.55	6580
B/K/MLCh/Alg/6	e)	50:50	-	9.75	85.8	-	-	-
B/K/MLCh/Alg/6/Lid	f)		3.0	7.24	81.1	4.86	1.77	5458

Table 2. *Physical-mechanical parameters of the chitosan–sodium/calcium alginate film with and without lidocaine.*

Symbol of the complex		Quantitative composition of composite Chit : Alg, % wt	Amount of lidocaine, % wt.	Strength, MPa	Elongation at max. stress, %
B/K/MLCh/AlgCa/1	g)	25:75	-	16.3	70.7
B/K/MLCh/AlgCa/1/Lid	h)		3.0	6.06	12.8

al in film form containing analgesics as a component of dressings for the treatment of difficult bedsores. Elasticity, durability, good fitting and the transmission of humidity vapours were the expected features of the dressing. Such a dressing was expected to provide good contact with the surface of the damaged tissue and, if applied in a motor limb, not to restrict the patient's mobility. Other potential attributes are: the ability to maintain proper moisture in the area surrounding the wound, thereby providing good delivery of the drug to the wound, and protection of the wound against further impairment by the accumulation of excessive fluids under the dressing [23].

Assessment of physical-mechanical properties

The main physical-mechanical parameters of the films containing the analgesic lidocaine at a concentration of 3% were tested. The impact of the substance upon the mechanical resistance of the film was examined. The film was 0.04 – 0.1 mm thick, and contained glycerol in the amount of 0.5 wt. parts per 1 wt. part of the complex (on dry mass).

Test results are compiled in ***Tables 1*** and ***2.***

On the basis of the strength parameters and humidity vapour transmission shown in ***Tables 1*** and ***2***, it can be concluded that the dressings in the form of a film allow the easy evaporation of excessive humidity from the wound surface, and, on the other hand, stop water and bacteria from penetrating the wound, thereby preventing infection. The film samples exhibit sufficient strength and very good elongation when drawn. However, the addition of the analgesic lidocaine causes an increase of elongation which is seen as insignificant for the practical use of the materials. The translucence of the material is an asset, as it permits visual inspection of the wound.

Assessment of the absorption and imbibition properties

Modern dressing devices designed for the healing of difficult wounds and bedsores are expected to provide not only an effective healing action of the contained drug but also comfort in application and use. A much desired feature is the ability to maintain proper humidity in the wound, which provides the opportunity of faster and more effective healing. The moist environment provides better penetration of the active substance to the interior of the wound. Another benefit is in the easier and less painful redressing without any danger of injuring the regenerated granulated tissue. Human skin, mainly its outer layer stratum corneum, is the main obstacle hindering the permeation of active substances to the interior of the patient. Hydration eases the transmission of the active substances from the carrier through the epidermis, as water improves the skin permeability by swelling the keratin and augmenting the inter-cell space [24].

Sorption and imbibition properties of the prepared film components were assessed in consecutive steps of the research. The sorption ability and WRV of the prepared compositions were measured. Results are presented in ***Figures 2 - 5***.

Results of the imbibition testing shown in ***Figures 1*** and ***3*** lead to the conclusion that the absorption ability of all of the tested films increases with prolonged

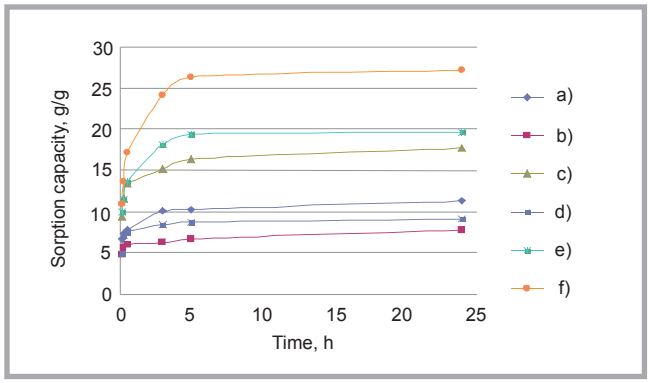

Figure 1. *Time-dependent change of absorption capacity of the chitosan-sodium alginate film, with and without the addition of lidocaine;* ***Abbreviations*** *as in* ***Table 1****.*

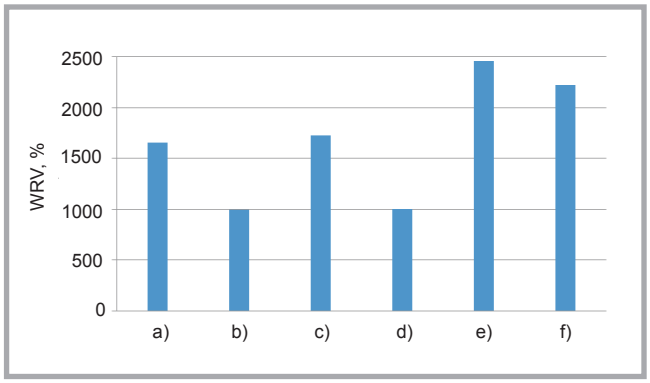

Figure 2. *WRV of chitosan–sodium alginate film, with and without the addition of lidocaine;* ***Abbreviations*** *as in* ***Table 1****.*

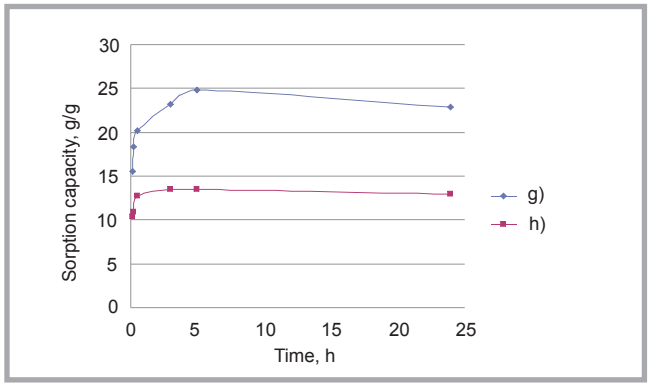

Figure 3. *Time-dependent change of absorption capacity of the chitosan-Na/Ca alginate film, with and without the addition of lidocaine;* ***Abbreviations*** *as in* ***Table 2****.*

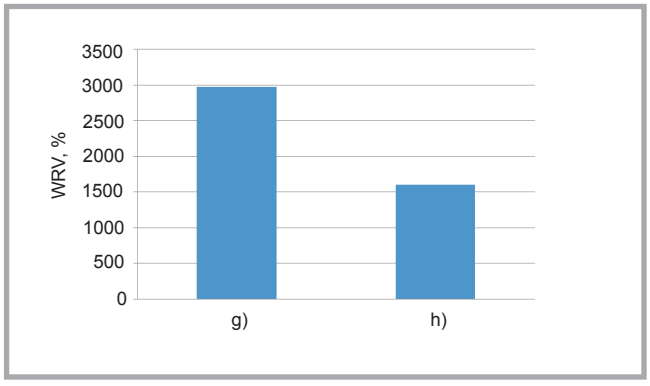

Figure 4. *WRV of chitosan-Na/Ca alginate, with (a) and without (b) the addition of lidocaine;* ***Abbreviations*** *as in* ***Table 2****.*

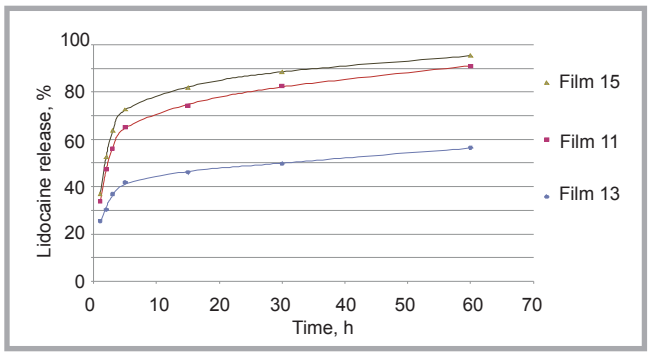

Figure 5. *Release profiles of lidocaine from the complexes: film 11 - B/K/MLCh/Alg/5/Lid; film 13 - B/K/MLCh/Alg/4/Lid; and film 15 - B/K/MLCh/Alg/6/Lid.*

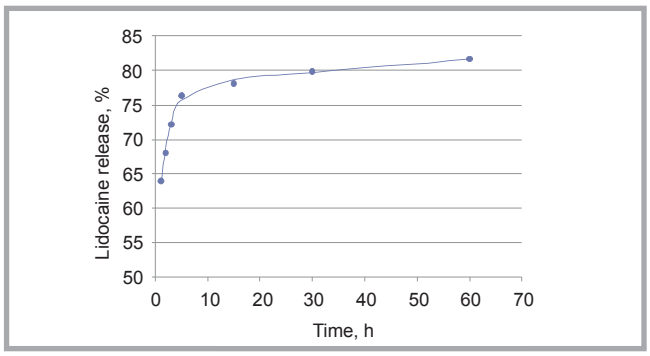

Figure 6. *Release profile of lidocaine from the complex film chitosan–Na/Ca alginate–B/K/MLCh/AlgCa/1/Lid.*

Table 3. *Parameters of the kinetics equation (3) defining the delivery rate of lidocaine from the examined chitosan alginate complex films.*

Type of complex	Symbol of complex	a_0, %	Phase I			Phase II		
			a_1, %	k_1, min $^{-1}$	$t_{0.5}$, min	a_2, %	$k_2 \times 10^3$, min $^{-1}$	$t_{0.5}$, min
chitosan-sodium alginate	B/K/MLCh/Alg/6/Lid	7.35	64.81	0.579	1.20	27.84	29.56	23.4
	B/K/MLCh/Alg/5/Lid	9.37	55.02	0.551	1.26	35.61	22.99	30.1
	B/K/MLCh/Alg/4/Lid	14.30	28.36	0.455	1.52	57.33	4.52	153.3
chitosan-Na/Ca alginate	B/K/MLCh/AlgCa/1/Lid	55.52	22.01	0.452	1.53	22.47	3.39	204.7

time of the in-water-immersion. From the results in ***Figures 2*** and ***4***, it can be seen that the WRV value depends upon the qualitative composition of the tested preparations. Preparations with a 50:50 proportion of chitosan to sodium alginate showed the highest retention of water in the structure.

It can also be seen that the addition of the analgesic lidocaine causes a worsening of the absorption capacity, and a decrease of WRV in both preparations. The commercial lidocaine used in the investigation is practically insoluble in water and dissolves readily in 95% ethanol. As a consequence, lidocaine was added to the biopolymer mixtures in its ethanol solution, which could have been the reason for the worsening of the imbibition and sorption properties caused by shrinking of the inner surface of the polymers. It is, therefore, suggested to use a water-soluble derivative of lidocaine in further research.

Examination of the release rate of the analgesics from the films

Release profiles of the active substance from the tested complexes are shown in ***Figures 5*** & ***6***.

From the results shown in ***Figure 5*** it can be concluded that the composition of the tested films is decisive when the release rate of lidocaine from the materials is concerned. The slowest release of the active substance occurred in the preparation containing the highest chitosan amount (B/K/MLCh/Alg/4/Lid (85:15)) from which 57% of the drug was released after 60 minutes. Lidocaine was released much faster by about 91 - 96% after 60 minutes from the remaining preparations (B/K/MLCh/Alg/5/Lid (75:25) and B/K/MLCh/Ag/6/Lid (50:50)).

The release profile for the preparation of Na/Ca alginate (***Figure 6***) reveals that about 82% of the lidocaine was released after 60 minutes. In ***Table 3***, values of the parameters of the kinetic equation are compiled, which defines the release process of lidocaine from the films.

$$y = 100 - a_1(1-\exp(-k_1 t)) + - a_2(1-\exp(-k_2 t)) \quad (3)$$

where a_0 denoted 100 - a_1 - a_2 – amount of "bound" lidocaine in %, a_1 and k_1 are constants describing phase I, and a_2 and k_2 indicate constants describing phase II.

By comparing the values of constants of release rates and half release times of lidocaine estimated for the singular types of the chitosan alginate complex, it can be concluded that, by changing the composition of the materials, one can control the release process of the active substance to a certain degree. Results confirmed that lidocaine is released the fastest from the films marked B/K/MLCh/Alg/6/Lid (50:50) and B/K/MLCh/Alg/5/Lid (75:25), in which the half-release times were $t_{0.5}$ = 23.4 min and 30.1 min, respectively. The slowest release of lidocaine proceeded from the chitosan-Na/Ca alginate preparation with a half-release time of $t_{0.5}$ = 204.7 min.

Summary

- A complex preparation in the form of a film was elaborated on the basis of modified chitosan lactate, sodium alginate and sodium/calcium alginate.
- The quantitative and qualitative composition of the chitosan alginate complex has a profound impact upon the release rate of the added active substance (lidocaine), mechanical properties like strength, elasticity, and permanent deformation, and the transmission of humidity fluid.
- Addition of the active substance (lidocaine) to the chitosan alginate complex film causes a distinct decrease of the water retention value and worsening of sorption properties.
- The use of a dissolvable lidocaine derivative is suggested in further investigations.
- The release of lidocaine from the chitosan alginate complex can be put into a complex kinetic equation of first range with two exponential functions.
- The prepared types of complex in film form satisfy basic mechanical and sorption criteria, which permit their use as dressing materials in the healing of bedsores.

Editorial notes

1) *The accredited Metrological Laboratory of IBWCh – certificate AB 338.*

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