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Starch Film as a Carrier of a Model Drug Substance from the Group of Non-Steroidal Anti-Inflammatory Drugs

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Abstract
The article describes the production of starch film as a carrier of a model drug substance from the group of non-steroidal anti-inflammatory drugs (NSAIDs). An analgesic/anti- inflammatory drug was put into aqueous starch solution, and next a film was formed. The following solid drug substances were included in the tests: acetylsalicylic acid, salicylic acid, ibuprofen lysine salt, naproxen in the form of acid, and sodium salt. Solutions were obtained from ibuprofen lysine salt and naproxen sodium, whereas the other drugs enabled to obtain aqueous suspensions. Such a drug substance was mixed with aqueous starch solution to obtain a film. Forming a film under laboratory conditions involved spreading aqueous starch solution containing a drug on a flat heated surface and evaporating water. The films obtained were transparent. They were then dried for a period of 24 hours at a temperature of 20 °C and 50% relative air humidity. Next their mechanical properties were studied. Starch films which contained therapeutic substances were characterised by Fourier transform infrared spectroscopy (FTIR). There were slight differences between the spectra of films containing a drug substance and those of films containing both starch and a drug substance, which implies weak intermolecular reactions. Scanning electron microscope (SEM) images of cross-sections of the starch films with a drug substance were taken, which indicated their uniform morphological structure. The release rate of the drug from each film to an acetate buffer pH 4.5 (acetylsalicylic acid and salicylic acid) or phosphate buffer pH 7.38 (ibuprofen lysine salt and naproxen) was determined in vitro with the paddle method. This procedure took up to 90 min. Acetylsalicylic acid and salicylic acid were almost completely released from the starch film as early as in the first minutes of the procedure, with a maximum value of around 90%. The release of ibuprofen lysine salt and naproxen in the form of acid from the starch film was partial, about 40%. The release of naproxen sodium from the starch film was time-proportional, and there was a tendency towards further release.

Key words: *starch, film, anti-inflammatory drugs, analgesics, drug substance release.*

Introduction

For a long time, polymers have had a great role in pharmacy as they are the auxiliary components of drugs of various forms, mainly tablets. They are more and more widely applied mainly due to their properties and the fact that other useful forms can be produced from them, e.g. nonwoven, sponges and films. Microcrystalline cellulose, starch, chitosan, alginate and other polysaccharides are common components of tablets – fillers, and disintegrating and binding agents. For some years, chitosan has been the subject of studies since it is hoped that it can become a controlled-release drug carrier. Microcrystalline chitosan has also been the focus of studies [1]. One of the renewable polymers, i.e. starch, is mainly used as a disintegrating and filling agent in the technology of solid drug forms [2]. Both polylactide (PLA) and thermoplastic starch (TPS), characterised by biocompatibility and biodegradability, have become the focus of great attention due to their potential application in pharmacy and other medical areas, e.g. in antineoplastic therapies. Studies conducted so far allow to believe that PLA and TPS, as biocompatible and biodegradable polymers, found in mixtures (the ratio 2:3 wt%), will be used to generate a system of prolonged drug release and applied, for example, in antineoplastic therapies [3]. The mixture of deproteinised natural rubber (DNR) latex and gelatinized starch and glycerine could be good agents for obtaining a film which would be a drug carrier, e.g. lidocaine in the transdermal therapeutic system [4]. Homogenous oral disintegrating films (ODF), which disintegrate in the oral cavity and are obtained from various concentrations of starch and gelatin, can serve as an antioxidant carrier, the role now being played by vitamin C [5]. The new generated utility form (film) will be more widely applied. Researchers from the Institute of Biopolymers and Chemical Fibres prepared a technology of obtaining films from aqueous solutions of polysaccharides, i.e. cellulose, chitosan, sodium alginate, and carrageenan. They films obtained from pure polysaccharides or polysaccharide mixtures were analysed in terms of their mechanical properties, oxygen barrier and water solubility. The results received allow a quick selection of films characterised by properties which are proper for drugs [6 - 8]. Non-steroidal anti-inflammatory drugs (NSAIDs), which are carboxylic acid derivatives, constitute the largest group of drugs, and are widely applied in pharmacotherapy. They are analgesic, antipyretic and anti-inflammatory drugs. Moreover some of them demonstrate anti-aggregation activity. The anti-inflammatory and analgesic mechanism of NSAIDs involves the inhibition of cyclooxygenase activity (COX), responsible for the generation of prostaglandins, which, in turn, induce inflammation. The antipyretic activity of NSAIDs is associated with depression, affecting thermoregulatory centres, localised in the hypothalamus. All substances belonging to this huge group of drugs, characterised by different chemical structures and acidic properties. This fact increases their affinity to inflamed tissues. Depending on

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the pharmaceutical form, the drugs are available by or without a prescription [9]. NSAIDs have lipophilic properties, hence they get easily absorbed. However, they are characterised by poor wettability, which results in low solubility. Most NSAIDs are low water soluble. Adding some auxiliary substances to NSAIDs improves their solubility, which might, in turn, improve their absorption and make the drugs therapeutically more effective. The application of a polymer drug carrier could be another solution [10, 11]. Acidum acetylsalicylicum (*Acetylsalicylic acid*), which is a derivative of salicylic acid, synthesised in the 19th century, was the first non-steroidal anti-inflammatory drug used on a great scale. Acidum salicylicum (*Salicylic acid*) is applied topically in preparations, demonstrating keratolytic, disinfectant, anti-inflammatory and analgesic activity. It inhibits inflammatory processes, decreases inflammation oedema, and penetrates epidermal tissues. Its maximal concentration can be observed after 4 – 8 h. An advantage of topical NSAIDs over orally administered drugs is their high concentration in the site of application and small risk of adverse effects. Acidum acetylsalicylicum is the strongest peripheral prostaglandin inhibitor of all salicylates. For some time, acetylsalicylic acid has been replaced by more innovative NSAIDs in most cases. These new generation drugs inhibit inflammatory processes and relieve pain more effectively. Acidum acetylsalicylicum still occupies first place in the prevention of cardiovascular events due to its anti-aggregation activity towards platelets. The introduction of acetylsalicylic acid into clinical practice was followed by the introduction of many other compounds from the NSAIDs group, such as naproxen, diclofenac and ibuprofen. Propionic acid derivatives: naproxen, ibuprofen and ketoprofen are strong analgesics but weaker anti-inflammatory drugs. NSAIDs for external use (e.g. ketoprofen, diclofenac, naproxen) can be administered to muscle and joint pains, traumas, dislocations and injuries (contusions). Naproxen demonstrates strong and long-lasting effects. Similar to ibuprofen, it effectively reduces the inflammatory process and pain. Undoubtedly, in comparison to other over-the-counter medications, naproxen is characterised by prolonged activity. One of the most common NSAIDs, applied topically and systemically, is ibuprofen – an analgesic [12]. The mechanism of ibuprofen is mainly associated with inhibition of the synthesis of prostaglandin, which are mediators in the development of an inflammatory reaction, e.g. E2 prostaglandin. Its level is extremely high in inflammatory exudates. Hence ibuprofen applied topically in the form of gel as an effective pain relief and anti-inflammatory drug. Currently 10% Ibuprofen lysine salt in the form of gel is available on the pharmaceutical market. Ibuprofen lysine salt is an innovative and modern form of ibuprofen due to better pharmacokinetic properties (higher solubility; time of C_{max} achievement is 2 – 4 times shorter) in comparison to the standard and commonly used acid form. The acidic form of ibuprofen, administered orally, is absorbed relatively slowly (maximal plasma concentration is observed after 90 – 120 min). Ibuprofen lysine salt is absorbed much faster. Its maximal level is observed after as little as 35 min. The difference results from the higher solubility of ibuprofen lysine salt in water [13].

The aim of the study was to obtain starch film which would be a carrier of a model drug substance from the group of non-steroidal anti-inflammatory drugs (NSAIDs). An analgesic/anti- inflammatory drug was put into aqueous starch solution, and next a film was formed. Mechanical and morphological tests were performed at the Institute of Biopolymers and Chemical Fibres in Lodz, whereas FTIR and the process of release of the drug substance from the film were performed at the Medical University of Lodz.

Experimental

Materials

Potato starch is one of the cheapest and most widely available kinds of starch in Poland. ***Table 1*** presents selected characteristics of native potato starch, used in tests.

Table 1. *Selected characteristics of native potato starch.*

Amylose content	wt%	28.6
Amylopectin content	wt%	71.4
Humidity	wt%	15.7
pH of aqueous extract	-	6.3
Number average molar mass, Mn	kDa	272
Weight average molar mass, Mw	kDa	1295
Polydispersity index (PDI)	-	4.8

Table 2. *List of selected drug substances.*

Name of drug substance	Abbreviation	Company
Acidum acetylsalicylicum	AAsa	Sigma
Acidum salicylicum	Asa	POCh
Ibuprofenum lysine salt	Ib	Sol. Chem. Italiana
Naproxenum natricum	NapNa	Sigma
Naproxenum	Nap	Sigma

As ***Table 1*** shows, the potato starch used in the tests is characterised with a high content of amylose (28.6%) and weight average molar mass, Mw = 1295 kDa. These characteristics should be enough to obtain films with proper mechanical parameters.

The following drug substances were included in the tests (***Table 2***).

Solutions were obtained from ibuprofen lysine salt and naproxen sodium, whereas the other drugs enabled to obtain aqueous suspensions. Such a drug substance was mixed with aqueous starch solution to obtain a film.

Methodology

Preparing aqueous solutions of starch containing drug substances

Aqueous starch solution of 18.27 wt% concentration was prepared. A proper amount of starch was introduced to a mixing tank with little demineralised water and stirred intensely. Next the remaining portion of water of a temperature of 20 °C was added. To make the preparation, a mixing tank was used equipped with a special system of band stirrers, running at 120 r.p.m, and three stirrers, running at 900 r.p.m. anti-clockwise. The procedure of dissolving starch was performed for 45 min at 95 °C. Next the aqueous suspension of a drug was added, whose temperature was 95 °C, and everything was stirred for 15 min. The procedure above enabled to obtain starch solution needed to prepare films.

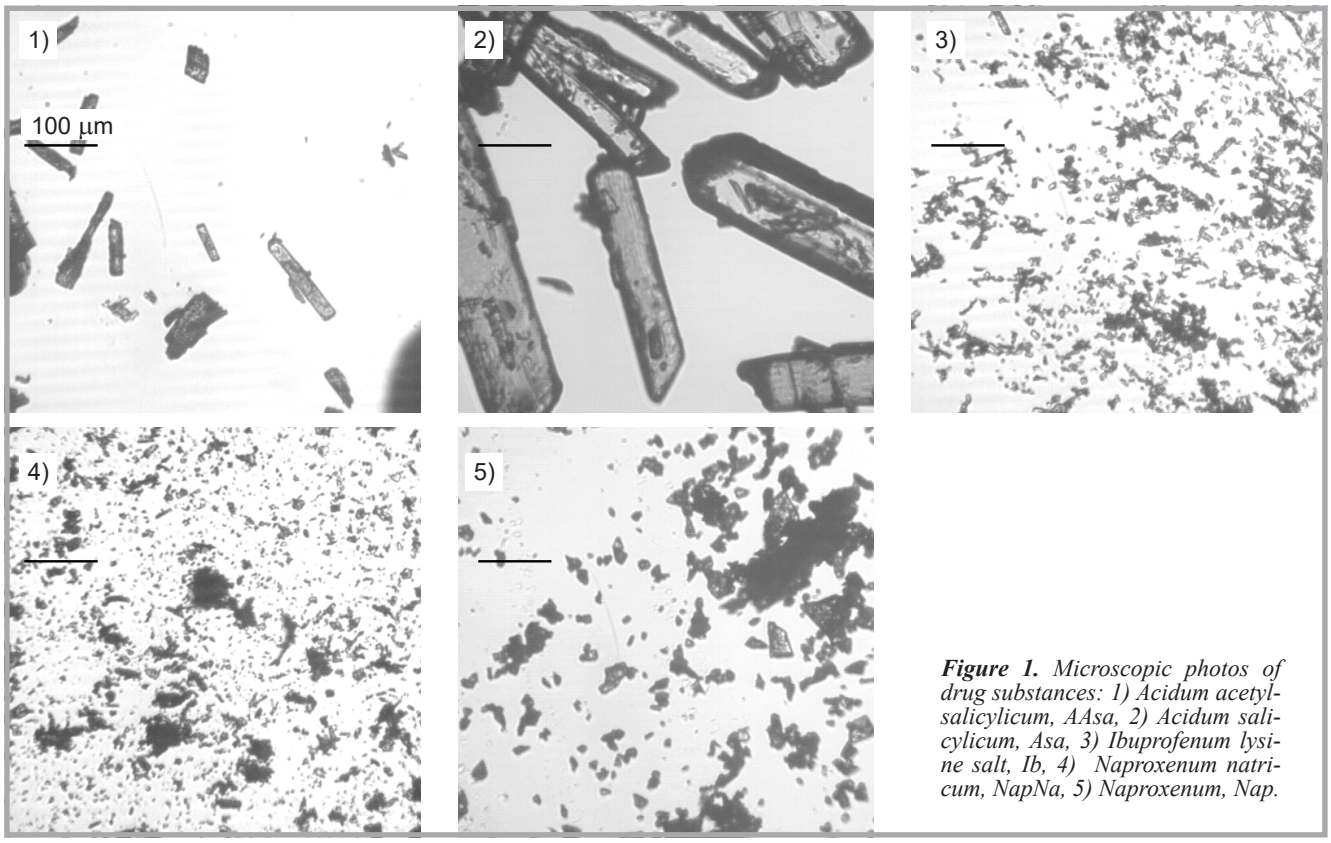


Figure 1. *Microscopic photos of drug substances: 1) Acidum acetylsalicylicum, AAsa, 2) Acidum salicylicum, Asa, 3) Ibuprofenum lysine salt, Ib, 4) Naproxenum natricum, NapNa, 5) Naproxenum, Nap.*

Obtaining starch films containing drug substances

Making films under laboratory conditions involved spreading aqueous starch solution whose temperature was 95 °C on a flat heated surface using a specially constructed slit tool. The height of the slot was 0.5 mm. The films were dried at 20 °C and 50% RH for 24 h. The films obtained after being stored at assumed humidity and temperature were analysed to identify their mechanical and morphological properties. The release rate of the drug substance was subject to an analysis made at the Medical University of Lodz.

Analytical methods

Determining the duration of the fall of a ball in aqueous starch solutions

The determination procedure involved measuring the period of the fall of a metal ball into the solution, in a glass cylinder, at a distance of 20 cm. A steel ball with a mass of 130 ± 1 mg and diameter of 3.17 mm was used. The glass cylinder was filled with the solution tested, just after it had been prepared at 95 °C and thermostated for 30 min. Afterwards the duration of the ball fall was measured. The result was an arithmetic mean of the two measurement values obtained within an accuracy of 1 s.

Analysis of aqueous starch solutions containing a drug substance with the application of optical microscopy

Images of aqueous starch solutions were taken with the use of a polarising microscope Biolar, PZO, Poland, equipped with a camera and IMAL computer image analyser.

Measuring the pH of water and aqueous solutions with a drug substance

The pH of the water and aqueous solutions with a drug substance was measured with the use of a pH-meter equipped with a combined electrode (METTLER-TOLEDO, Switzerland).

***Analysis of starch films with the use of* scanning electron microscopy *(*SEM/ESEM)**

A scanning electron microscope (Quanta 200 (W), FEI Co., US) was used in order to inspect the cross-section of surfaces of the films obtained.

Determining mechanical properties of starch films containing a drug substance

Mechanical properties of the starch films were estimated according to appropriate standards:

- thickness of the film: PN-EN ISO 4593:1999
- strength and elongation at maximal stress, according to PN-EN ISO 527-3:1998.

Tests of mechanical properties of the films were conducted on an Instron 5544 tensile tester, USA. The film samples tested were 10 mm long, 15 mm wide, and the elongation rate was 10 mm/min. The mechanical tests were carried out in an air-conditioned room at 65 ± 4% relative air humidity and at 20 ± 2 °C.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were obtained at the Department of Elementary and Spectroscopic Analysis of the Faculty of Pharmacy with the use of a FTIR spectrophotometer (Mattson, USA). Polymeric thin films were prepared for the FTIR studies. An analysis of spectra obtained in infrared spectroscopy in the wavelength range 4000 – 400 cm^{-1} at a spectral resolution of 4 cm^{-1} (10 scans in total) allowed to evaluate physicochemical reactions between the polymer (starch) and drug substance from the NSAIDs group. For comparison, the FTIR spectrum of a starch film without a drug substance is presented. FTIR spectra of a drug substance in the form of tablets in KBr (1 mg of

the studied material and 300 mg of KBr) were also obtained

Determining the release rate of a drug substance from starch films

A procedure to determine the release rate of a model drug substance from starch films was performed with the use of a technique appropriate for solid forms, in compliance with requirements of *Pharmacopeia Polonica Ed. VI* and *XI* [14, 15] in paddle apparatus containing 500 ml of acetate buffer pH 4.5 (acidum acetylsalicylicum and acidum salicylicum) or 100 ml of phosphate buffer pH 7.38 (ibuprofen lysine salt, naproxen and naproxen sodium) at 37 °C, with the stirrer running at 50 r.p.m. Three series of determinations were carried out. The solution for determining levels of the drug substance was collected at particular periods, after 1, 3, 5, 10, 15, 20, 30, 45, 60 & 90 min. The concentration of the drug substance released was determined with the spectrophotometric method. Prior to the procedure, the wavelength was analytically determined: around 265 nm (acetylsalicylic acid and salicylic acid), 221 nm (ibuprofen lysine salt), and 262 nm (naproxen and naproxen sodium), according to the detailed monograph of particular substances [14].

The kinetics of the release of a drug substance from a film can be presented in equations which describe various types of chemical reaction. Literature [16 - 18] mentions the following types of equations: zero-order and first-order, as well as semi-empirical models, as described by Higuchi and Krosmeyer-Peppas. When release profiles indicate a two-stage process, the application of a complex equation seems more justified [1, 19]. Analysis of the data obtained implies that the process of release of model substances from the NSAIDs group from a starch film consists of two stages. An equation comprising two first order equations was suggested (as if there was a similarity to subsequent reactions).

$$M_t/M_\infty = 100 - [a_1 \times \exp(k_1 \times t) + a_2 \times \exp(k_2 \times t)]$$

where, M_t – the amount of substance released after time t, M_∞ – total amount of the substance, a_1 and k_1 – constants describing stage I, a_2 and k_2 – constants describing stage II. The constant refers to the amount of substance at each stage.

The half-life of drug substance release is expressed by the following formula: $t_{0.5} = \ln 2/k = 0.6933/k$, indicating the period of time in which half of the substance will be released. It is assumed that at time $3t_{0.5}$, 95% of the substance, hence almost the whole of the amount, is released.

Mathematical computations – performed with the use of Microsoft Office 2018, specifically the Excel program.

Test results and discussion

While carrying out tests, the effect of minerals in water used as a solvent on the properties of the starch solution was noted. After many attempts, mineral water containing a definite amount of minerals, with definite electric conductance and pH was used [8].

Aqueous solutions with a drug substance

In the tests a drug substance was used, described in the section "Materials". ***Figure 1*** presents microscopic images of the solid drug substance.

As can be seen in ***Figure 1***, the size of particles of the drug substance is greatly different and depends on the type of drug. The size ranges from a few to a few hundred micrometres. Chemical properties of the substance have an influence on water solubility, whereas the size of particles has an effect on the stability of the suspension. An appropriate amount of the drug substance in the form of powder was added to demineralised water whose temperature was 20 °C. The procedure resulted in obtaining either a suspension or solution. After determining pH, the solution was heated until its temperature increased up to 95 °C. After that, it was introduced into the starch solution. The water suspension or solution with a drug substance were added to starch solution according to suggested methodology.

Table 3 presents characteristics of aqueous solutions/suspensions with drug substances.

Table 3. *Characteristics of aqueous solutions/suspensions with drug substances.*

Solution symbol	Drug substances		Form	pH at 20 °C
	Name	Concentration of drug in water, %		
	Demineralized water	-	-	6.48
AAsa/1	Acidum acetylsalicylicum	2.00	suspension	2.40
AAsa/2		4.00		2.35
AAsa/3		6.00		2.36
AAsa/4		8.00		2.36
Asa/1	Acidum salicylicum	1.00		2,38
Asa/2		2.00		2.37
Asa/3		3.00		2.39
Asa/4		4.00		2.38
Ib/1	Ibuprofenum lysine salt	0.50	solution	6.99
Ib/2		1.00		6.95
Ib/3		1.50		6.88
Ib/4		2.00		6.83
NaprNa/1	Naproxenum natricum	0.50		7.54
NaprNa/2		1.00		7.59
NaprNa/3		1.50		7.25
NaprNa/4		2.00		7.26
Napr/1	Naproxenum	0.50	suspension	3.93
Napr/2		1.00		3.89
Napr/3		1.50		3.43
Napr/4		2.00		2.75

Results presented in ***Table 3*** indicate that ibuprofen lysine salt and naproxen sodium completely dissolve in water and turn into solution, while the other drug substance turns into suspension.

Figure 2 presents some photos of aqueous solution with naproxen sodium (a),

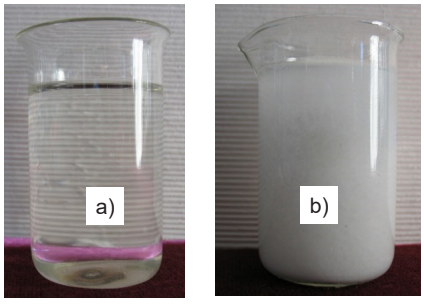


Figure 2. *Photos of aqueous solution with naproxen sodium (a), and aqueous suspension with naproxen in the form of acid (b).*

Table 4. *Parameters of aqueous starch solutions containing drug substances prepared. Concentration of starch 18.27%, tempreture of dissolution 95 °C, dissolution time at 95 °C - 45 min., mixing time at 95 °C - 15 min.*

Symbol of solution of drug substance	Initial temperature, °C	Duration of achievement of dissolution temperature, min	Total duration of dissolution, min	Ratio of concentration between drug substance and starch, wt%	Duration of ball fall/ temperature, s / °C
Starch solution	16	60	105	-	35 / 87
AAsa/1	15	100	145	0.91	331 / 82
AAsa/2	16	80	80	1.82	120 / 90
AAsa/3				2.74	188 / 87
AAsa/4				3.65	-
Asa/1	16	60	105	0.46	2 / 90
Asa/2	33			0.92	7 / 84
Asa/3	34			1.37	1 / 84
Asa/4	33			1.82	1 / 84
Ib/1	18			0.23	34 / 80
Ib/2	21			0.46	34 / 80
Ib/3	15			0.68	33 / 80
Ib/4	35			0.92	33 /80
NaprNa/1	17			0.23	115 / 82
NaprNa/2	36			0.46	55 / 82
NaprNa/3	34			0.68	-
NaprNa/4	17			0.92	-
Napr/1	34			0.23	23 / 82
Napr/2	32			0.46	25 / 82
Napr/3	20			0.68	21 / 82
Napr/4	15			0.92	22 / 82

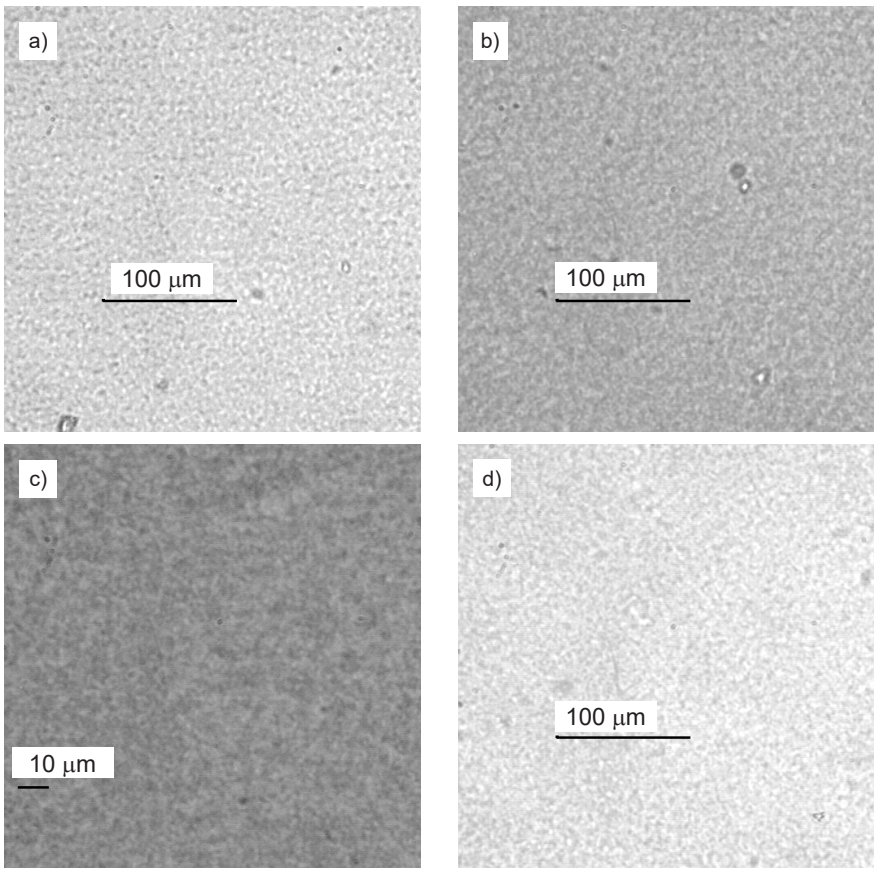


Figure 3. *Microscopic images of starch solutions containing a water-soluble drug substance –naproxen sodium (soluble form). a) Napr-Na/1, b) Napr-Na/2, c) Napr-Na/3, d) Napr-Na/4.*

and aqueous suspension with naproxen in the form of acid (b).

Preparing aqueous solution of starch containing drug substances

A drug substance, irrespective of its form (acid or salt, turning in water into suspension or solution), was added to starch solution. It was then stirred for 15 min at a temperature of 95 °C. Afterwards films were obtained from these solutions. While forming, the films did not show differences regarding the form of the drug in water (solution, suspension). It was noted that the solution and film made with the application of salicylic acid had a characteristic pink colour, not detected in other samples. Another interesting observation was made: Starch solutions containing salicylic acid demonstrated a reduced tendency to gelatinise. This observation refers to all drugs. An increase in the amount of the drug substance had an effect on the fluidity of the starch solution at 50 °C.

Table 4 presents parameters of the aqueous starch solutions containing a drug substance prepared.

After comparing the duration of the fall of a ball immersed in starch solution containing acetylsalicylic acid with that of the fall of a ball immersed only in starch solution, we can observe that the lowest concentration of acetylsalicylic acid (0.91 wt%) contributes to a rapid increase in the duration of the ball fall up to around 330 s. For higher concentrations, the duration of the ball fall is shorter than 180 s. For starch solutions with salicylic acid, kinematic viscosity decreases dramatically, which results in a decrease in the duration of the ball fall from 34 s to a few seconds, irrespective of the concentration of the solution. When we compare the durations of the ball fall in starch solutions containing ibuprofen lysine salt, we can conclude that the values are comparable, i.e. 34 s regardless of the concentration of the drug. A long duration of the ball fall (115 s) was observed in starch solution containing naproxen sodium at its lowest concentration (0.23 wt%). With regards to higher concentrations of naproxen sodium, a considerable decrease in the duration of the ball fall was noted. A comparison of durations of the ball falls in starch solutions containing naproxen in the form of

acid allows to conclude that the values are comparable (above 20 s) regardless of the drug level.

A microscopic analysis of solutions used for obtaining films revealed that they did not contain particles of the drug substance introduced into them in the form of suspension. This observation might imply that the particles get dissolved in starch solutions.

As an example, ***Figure 3*** presents microscopic images of starch solutions containing a water-soluble drug substance (naproxen sodium) in various concentrations.

Despite various concentrations of naproxen sodium in aqueous starch solution, the photos presented do not show more noticeable differences other than in the texture, which is characteristic for starch solutions.

As an example, ***Figure 4*** presents microscopic images of starch solution containing a drug substance introduced in the form of suspension (naproxen in the form of acid) at various concentrations.

The photos demonstrate that various concentrations of naproxen in aqueous starch solution contribute to differences in the texture, which is greatly affected by the temperature of starch solutions. Particles of low soluble drug substances are invisible in the photo.

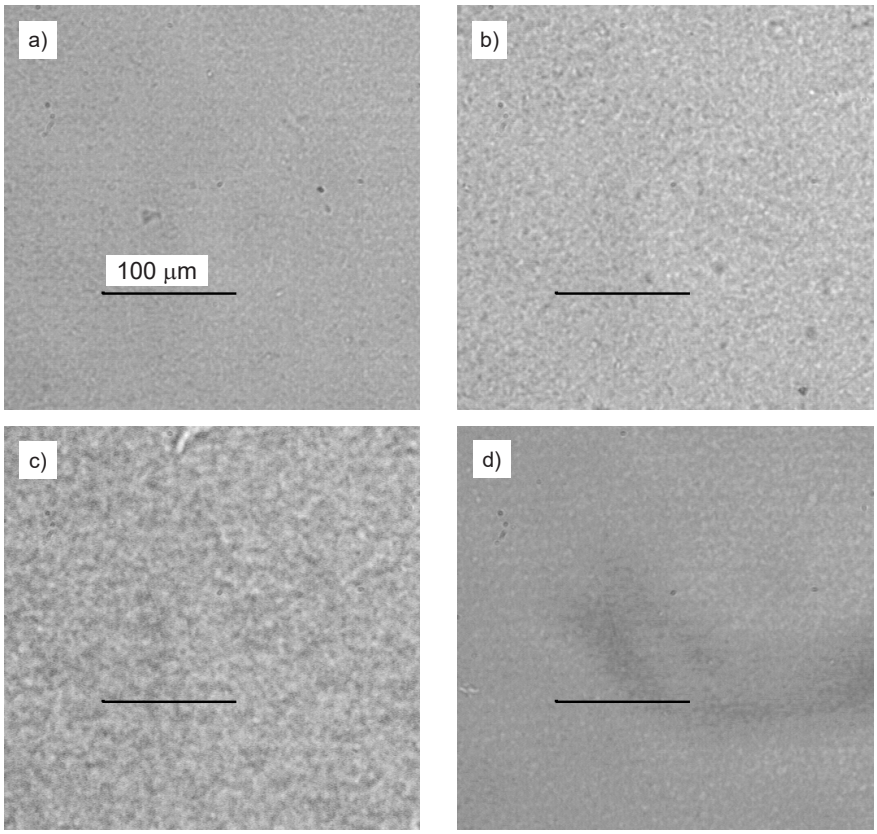


Figure 4. *Microscopic images of starch solution containing naproxen (low soluble form of acid). Naproxen. a) Napr/1, b) Napr/2, c) Napr/3, d) Napr/4.*

Starch films containing drug substances

The procedure of obtaining starch films containing a drug substance was carried

Table 5. *Mechanical properties of starch film containing drug substances.*

Film symbol	Drying time of the film / temperature of drying, h / °C	Air-conditioned room, 20 ± 2 °C, 65+ 4% RH						
		Thick-ness, mm	Thickness coefficient of variation, %	Max breaking force, N	Breaking force coefficient of variation, %	Tensile strength, MPa	Elongation at max stress, %	Elongation coefficient of variation, %
FS	24 / 20	0.046	11.8	28.4	9.08	41.3	4.64	16.0
AAsa/1	24 / 18	0.059	1.92	41.7	3.18	46.8	5.85	12.8
AAsa/2		0.053	11.9	34.3	21.0	43.2	6.74	37.4
AAsa/3		0.049	6.34	32.4	9.23	43.8	9.05	7.37
AAsa/4		0.034	14.8	19.6	17.1	38.4	7.91	16.4
Asa/1	24 / 20	0.027	6.68	16.7	9.11	41.5	7.78	10.2
Asa/2		0.043	8.40	28.2	13.4	44.5	10.1	17.3
Asa/3		0.049	7.64	29.0	9.57	39.8	7.99	22.3
Asa/4		0.060	6.15	38.3	10.8	42.4	6.85	12.4
Ib/1	24 / 18	0.021	5.41	13.2	21.6	41.1	5.45	15.2
Ib/2		0.052	8.17	32.6	7.17	41.7	7.54	20.1
Ib/3		0.054	4.61	36.7	6.17	45.0	4.61	7.29
Ib/4		0.049	4.44	29.4	11.1	40.1	5.75	41.6
NaprNa/1	24 / 18	0.061	4.02	39.1	5.20	42.7	9.06	14.7
NaprNa/2		0.051	5.19	33.5	7.91	43.8	9.35	17.9
NaprNa/3		0.048	2.36	33.0	2.60	45.4	9.06	7.96
NaprNa/4		0.042	8.60	23.0	13.6	36.7	3.05	31.0
Napr/1	24 / 16	0.032	2.63	17.2	20.8	36.1	3.96	19.2
Napr/2		0.046	5.10	27.3	4.43	39.7	7.95	18.2
Napr/3		0.036	6.83	14.8	14.1	37.5	6.83	31.4
Napr/4		0.037	15.1	20.3	15.2	36.3	7.91	12.1

Figure 5. *Photos of starch films containing: a) naproxen sodium (NapNa/2) and b) naproxen (Nap/4).*

out in compliance with parameters appropriate for starch film only. In most cases of the procedures of obtaining starch films containing drug substances, no differences were observed. Undissolved drugs did not pose a problem for the process of forming films. Only films generated from lower pH solutions appeared to be more fragile than others.

Figure 5 demonstrates images of a starch film containing naproxen sodium NapNa/2 and naproxen in the form of acid (Nap/4).

Starch films with soluble NapNa/2 and low soluble Nap/4, presented in ***Figure 6***, are not different in terms of appearance, transparency or feeling.

Mechanical properties of starch films containing drug substances

Samples of starch films and those containing drug substance were subject to tests in order to identify their mechanical properties. Mechanical tests were conducted in an air-conditioned room at 20 ± 2 °C and 65 ± 4% RH. Test results are presented in ***Table 5***.

Test results allowed to conclude that a small amount of acetylsalicylic acid (below 1.0%) contributed to the increased strength of the film (above 10%). The film which contained more acetylsalicylic acid, above 3.64%, demonstrated decreased strength (about 10%). There were no changes with respect to elongation. A comparison of the strength of the starch film containing salicylic acid and that without a drug substance allows to conclude that values of this parameter are similar. A similar observation could be made for films with ibuprofen lysine salt. The strength of starch films with naproxen sodium is up to 10% higher, while it is up to 10% lower for starch films with naproxen in the form of acid.

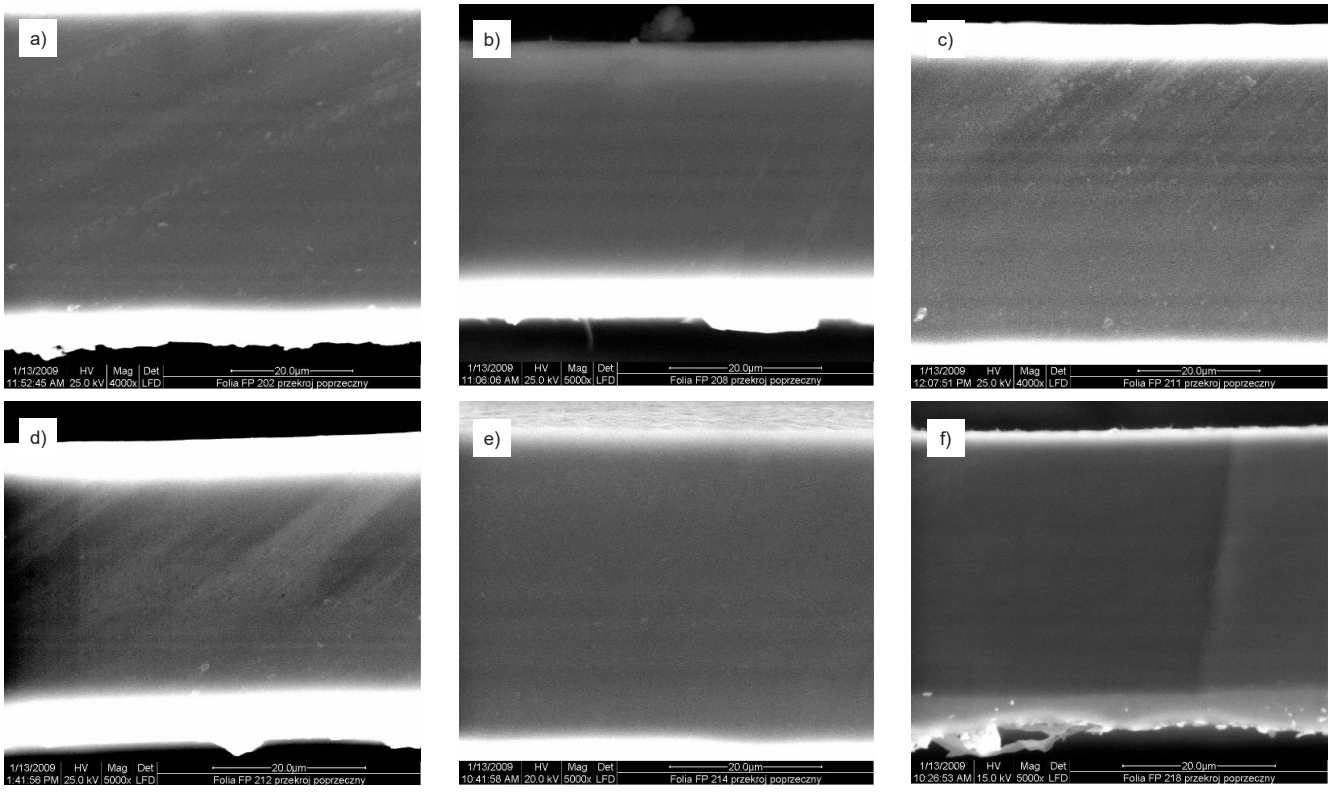


Figure 6. *SEM images of the cross-section of a starch film containing drug substances. a) AAsa/1, b) Asa/2, c) Ib/1, d) Ib/2, e) Ib/4, f) NapNa/1.*

With regards to film elongation, it can be said that irrespective of the drug substance, its value is the same, ranging between 5 and 10%.

Figure 6 presents SEM images of starch film containing a drug substance i.e. acetylsalicylic acid (AAsa/1), salicylic acid (Asa/2), ibuprofen lysine salt (Ib/1, Ib/2, Ib/4) and naproxen sodium (NapNa/1).

On the basis of SEM images of the cross-section of the starch film, it was concluded that the structure of the starch film is homogenous and compact (***Figure 6***). No changes in the structure of the film were observed regardless of the type and concentration of the drug substance. Starch films containing a drug substance are characterised by a homogenous structure, similar to that of starch film.

FTIR results

With the use of infrared spectroscopy (FTIR), an analysis was made of physicochemical reactions between the polymer (potato starch) and drug substances introduced into hydrogel prior to obtaining an appropriate film. In the FTIR spectrum of the starch film, two characteristic absorption bands were visible. The first of them, with the high wave-number side of the spectrum ranging from 3600 to 3100 cm^{-1}, due to the hydrogen – bond interaction, was attributed to O-H stretching vibrations. The other characteristic absorption band is a saccharide band, ranging from 1200 to 800 cm^{-1}. However, the fading of bands, typical for characteristic groups, found in particular drugs might indicate the formation of bonds between the polymer and substance. The bands are not visible in the spectrum of the polymer – a therapeutic substance, which might be associated with the fact that the substance spectrum is overlaid by an intensive polymer spectrum [20].

Infrared absorption spectra obtained for starch films containing selected NSAIDs as compared with those of films containing only polymer and a drug substance in the form of a tablet with KBr are presented in ***Figures 7 – 11***. The FTIR spectra are presented in two ranges: 4000 – 500 cm^{-1} and 1800 – 700 cm^{-1} in order to more effectively show reactions occurring in characteristic bands related to active groups of the compounds studied.

In ***Figure 7*** the presence of acetylsalicylic acid in the starch film is identified with greater visibility of the band and changed location of the peak 1550 cm^{-1} towards lower wave numbers - 1525 cm^{-1}, particularly for greater concentrations of AAsa/4-film. There are no new absorption bands related to the drug substance. Only in the spectrum of the film with a lower concentration of the drug substance, is a new absorption band visible at about 2500 cm^{-1}.

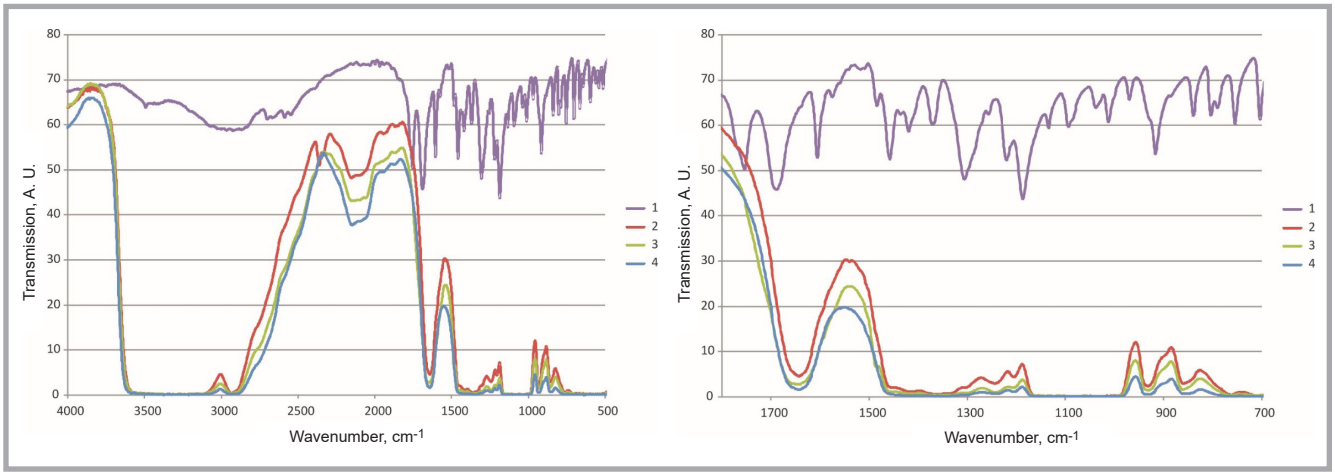


Figure 7. *FTIR spectra of starch films with various concentrations of acetylsalicylic acid (AAsa). 1 – AAsa substance, 2 – AAsa/1- film (0.91 wt%), 3 – AAsa/4 – film (3.65 wt%), 4 – starch film.*

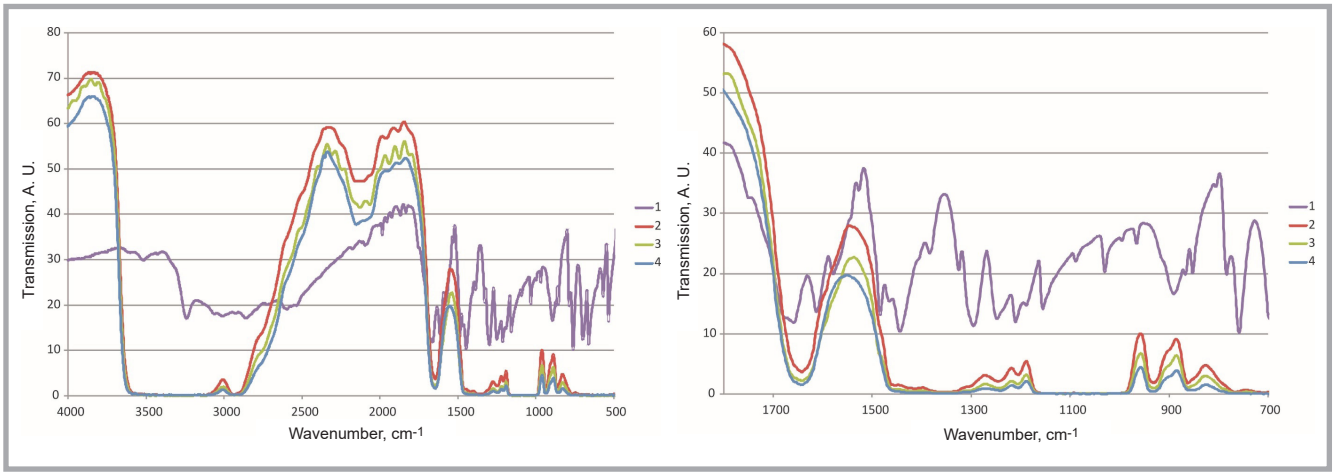


Figure 8. *FTIR spectra of starch films with various concentrations of salicylic acid (Asa). 1– Asa substance, 2 – Asa/1 film (0.46 wt%), 3 – Asa/2 film (0.91 wt%), 4 – starch film.*

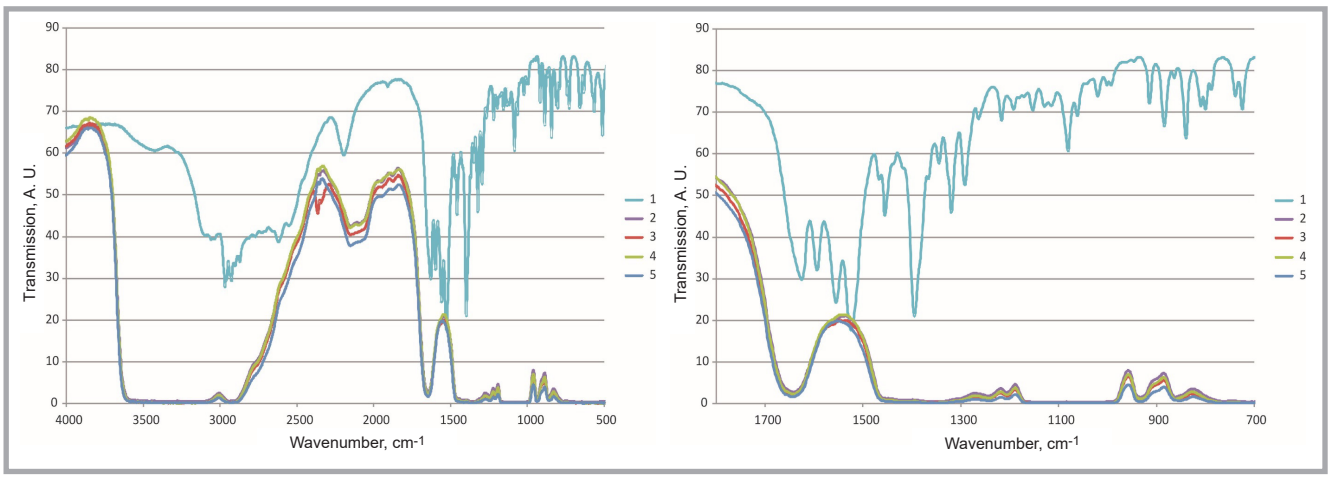


Figure 9. *FTIR spectra of starch films with various concentrations of ibuprofen lysine salt (Ib). 1 - Ib substance, 2 – Ib/2 film (0.46 wt%) 3 - Ib/3 film (0.68 wt%) 4 – Ib/4 film (0.91 wt%) 5 – starch film.*

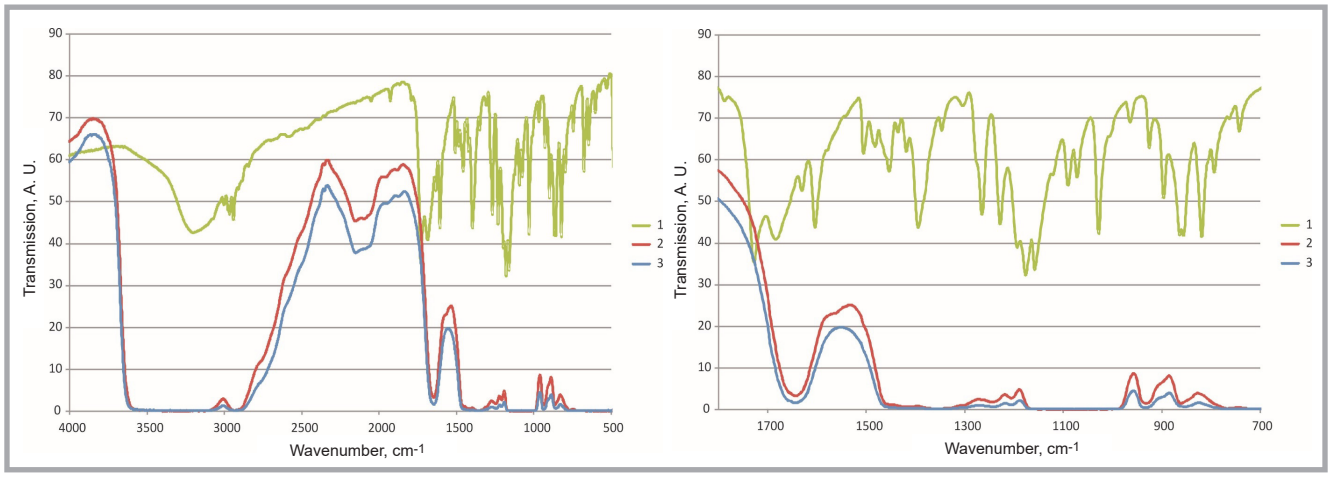


Figure 10. *FTIR spectra of a starch film containing naproxen sodium (NapNa). 1 – NapNa - substance, 2 – NapNa – film (0.46 wt%), 3 – starch film.*

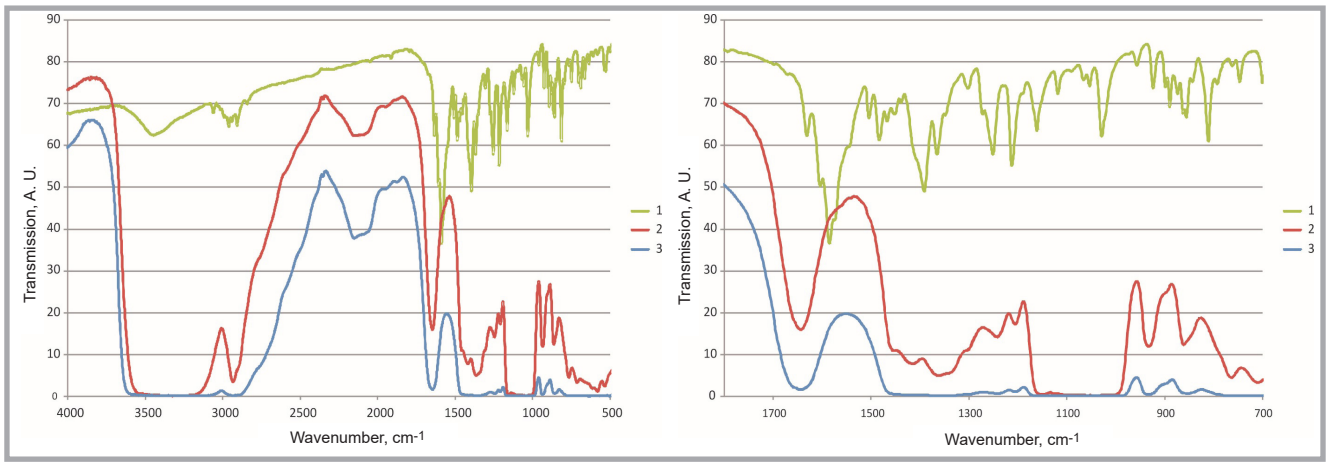


Figure 11. *FTIR spectra of starch film containing naproxen in the form of acid (Nap). 1 – Nap substance, 2 – Nap/1- film (0.46 wt%), 3 – starch film (FS).*

In ***Figure 8*** the presence of salicylic acid in the starch film is identified with greater visibility of the band in the whole range of the spectrum and with a changed location of the peak 1550 cm^{-1} towards lower wave numbers - 1525 cm^{-1}, particularly for greater concentrations of Asa/2-film. Besides, within the range 2200 - 1800 cm^{-1}, peaks related to the drug substance are visible.

In ***Figure 9*** the presence of ibuprofen lysine salt in the starch film slightly affects the visibility of bands in the whole spectrum range. There are no new bands in the spectrum of the starch film containing a drug substance, except for one

extra band shifted towards higher wave numbers up to about 2400 cm^{-1} in comparison to the spectrum of the same drug substance (2300 cm^{-1}).

In ***Figure 10*** the presence of naproxen sodium in the starch film slightly affects the visibility of bands in the whole spectrum range. There are no new bands in the spectrum of the starch film containing a drug substance, except for a marked change in the peak appearance at about 1600 cm^{-1} and a changed location of the peak 1550 cm^{-1} towards lower wave numbers - 1525 cm^{-1}.

In ***Figure 11*** the presence of naproxen in the form of acid in the starch film is identified with greater visibility of all bands and a changed location of the peak 1550 cm^{-1} towards lower wave numbers - 1525 cm^{-1}. There are no new absorption bands related to the drug substance.

Test results of kinetics of release of the drug substances from a starch film in *in vitro* conditions

Below in ***Table 6*** determined concentrations of a particular drug substance as compared with starch (wt%) in starch films are presented, selected for tests on the release rate of the drug substance (NSAIDs).

Figure 12 presents a comparison of results of the release of acidum acetylsalicylicum (AAsa) from starch films containing different concentrations of a drug substance.

The above figure shows that already in the first 5 minutes, soon after the commencement of the procedure, most of the substance was released. Later the release process slowed down. After 90 minutes, 90% of acidum acetylsalicylicum was released. In the case of the film with the highest acidum acetylsalicylicum content, 100% of the substance was released. Such a huge amount of acetylsalicylic acid released from starch films possibly results from the decreased mechanical strength of the films, which got defragmentated just after they had been placed in acetate buffer of pH 4.5.

Figure 13 presents a comparison of results of determinations of acidum salicylicum (Asa) from starch films containing different concentrations of a drug substance.

As ***Figure 13*** shows, the release profiles of acidum salicylicum from starch films in both procedures are similar. They differ only in the amount of substance released.

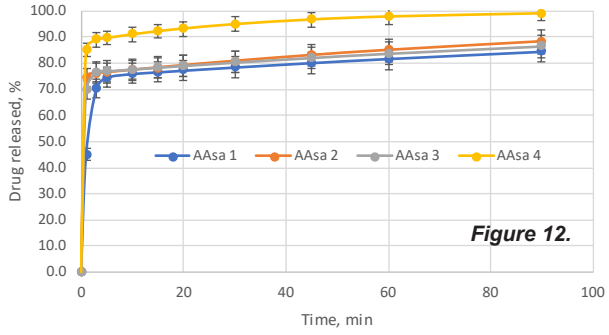
More substance was released to the acetate buffer from the Asa 1 film, in which the content of acidum salicylicum was twice as low as that observed in the Asa 2 film. A higher concentration of acidum salicylicum contributes to stronger reactions with starch and its slower release.

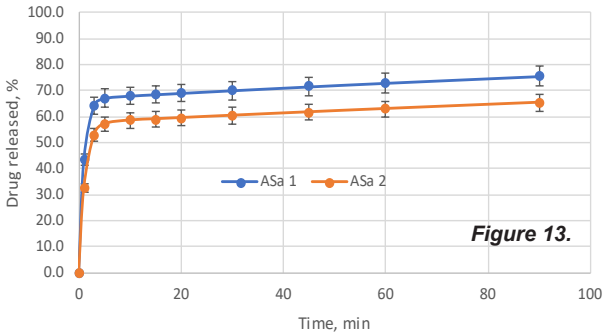
Table 6. *Determined concentrations of a particular drug substance as compared with starch (% wag) in starch films, selected for tests on the release rate of the drug substance (NSAIDs).*

Sample symbol	Name of drug	Determined concentration of drug substance in relation to starch, wt %
FS	-	-
AAsa 1	Acidum acetylsalicylicum	0.91
AAsa 2		1.82
AAsa 3		2.74
AAsa 4		3.65
Asa 1	Acidum salicylicum	0.91
Asa 2		1.82
Ib 2	Ibuprofen lysine salt	0.46
NapNa 2	Naproxen sodium	0.46
Nap 2	Naproxen	0.46

Measurement values of the release rate of ibuprofen lysine salt (Ib 2) as well as naproxen sodium and naproxen in the form of acid (NapNa 2 and Nap 2) from a starch film are presented in ***Figure 14***.

Figure 14 presents the release profile of ibuprofen lysine salt and naproxen in the form of acid and sodium. ***Figure 14*** shows that in the first 5 minutes, about 40% of ibuprofen lysine salt was released, and with time the value increased,





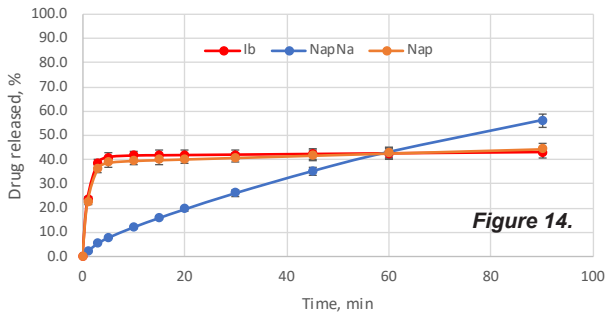


Figure 12. *Relationship between the amount of AAsa released from starch films containing acidum acetylsalicylicum in the following amounts: 0.91 wt% (AAsa 1), 1.82 wt% (AAsa 2), 2.74 wt% (AAsa 3), 3.65 wt% (AAsa 4) and time.*

Figure 13. *Relationship between the amount of Asa released from starch films containing acidum salicylicum in the following amounts: 0.91% wag (Asa 1), 1.82% wag (Asa 2) and time.*

Figure 14. *Relationship between the amount of released substances from starch films and time in the amount 0.46 wt%: ibuprofen lysine salt (Ib2), naproxen (NapNa2), naproxen (Nap2).*

Table 7. *Parameters of the kinetic equation referring to the release rate of a drug substance from the starch films tested - $t_{0.5}$ – half-time of release for each stage.*

Film symbol	Stage I			Stage II		
	a_1, %	k_1, min^{-1}	$t_{0.5}$, min	a_2, %	k_2, min^{-1}	$t_{0.5}$, min
AAsa 1	74.66	0.921	0.75	25.34	0.00549	126
AAsa 2	75.42	4.096	0.17	24.58	0.00816	85
AAsa 3	76.28	2.457	0.28	23.72	0.00632	110
AAsa 4	88.06	3.360	0.21	11.94	0.02883	24
Asa 1	66.91	1.033	0.67	33.08	0.00337	206
Asa 2	57.57	0.823	0.84	42.43	0.00223	310
Ib 2	41.40	0.847	0.82	58.60	0.00031	2235
NapNa 2	4.31	0.414	1.67	95.69	0.00866	80
Nap 2	39.02	0.859	0.81	60.98	0.00104	666

but only slightly, despite the good solubility of this drug.

The release of naproxen in the form of acid from the starch film was a rapid process (similar to ibuprofen lysine salt). Within 5 minutes, following the placement of the film in phosphate buffer, almost 40% of the substance got released, and later its content in the buffer slightly exceeded 40%. With regards to naproxen sodium, it released slowly, and after 90 minutes about 55% of the substance was released from the film to the phosphate buffer. Moreover it tended to further release.

All graphs presented in ***Figures 12 – 14*** can be expressed with a complex kinetic equation. ***Table 7*** presents parameters of this equation, which refers to the release rate of a drug substance from the starch films tested.

All the drugs studied are characterised by both release stages. The first is rapid, while the second is slow. In the case of AAsa, in the first stage, between 74 and 88% of the drug substance gets released within 1.0 – 2.3 h. In the second stage, between 12 and 25% of the agent gets released within 1.0 – 6.3 h. With regards to Asa, in the first stage, between 58 and 67% of the drug substance gets released within 1 – 3 minutes, with the remaining amount – between 10 and 15 h. In the case of Ib 2 and Nap 2, in the first 2.5 minutes, about 40% gets released, with the remaining amount within 112 h (Ib 2) and 33 h (Nap 2). With regards to NapNa 2, in the first stage, 4.3% of the drug gets released, with the remaining amount within 4 h.

Summary

A reduction in the gelling capacity of acidum salicylicum starch solutions and other therapeutic substances was observed at 50 °C, regardless of their concentration. It was found that drug substances introduced into the starch solutions in the form of a suspension are dissolved. Results of tests performed allowed to conclude that a small amount of acidum acetylsalicylicum of 0.912 g/100 g (AAsa 1) in a starch film increased the film strength by 10%. A concentration of acidum acetylsalicylicum exceeding 3.64% contributed to the decreased strength of the film by 10% and its increased elongation. The strength level of the starch film containing acidum salicylicum is the same as that of the starch film only. A similar observation was made for the film with ibuprofen lysine salt. The strength level of starch films with naproxen sodium is up to 10% higher, and with naproxen in the form of acid - up to 10% lower, in comparison to a starch film. With regards to the film elongation parameter, it can be concluded that it is higher (5 – 10%) irrespective of the type of drug substance. The elongation of the film is independent of the type of drug substance, being in the range of 5 - 10%. SEM images confirm that starch films containing a drug substance are characterised by a homogenous structure, similar to that of starch film. Cross-sections of the film, seen in the images, indicate that its structure is homogenous and morphological. There were slight differences in the FTIR spectra of films containing a drug in comparison to the spectrum of the starch only and the drug substance, which implies weak intermolecular reactions. The process of release of drug substances from the starch films obtained was of a two–phase nature. The first phase was characterised by rapid release, whereas the second was much slower. On the basis of the results obtained, we concluded that the release of acidum acetylsalicylicum and acidum salicylicum from starch films was almost complete and achieved the maximal value, i.e. about 90% as early as in the first minutes of the procedure conducted. The release of ibuprofen lysine salt and naproxen in the form of acid from the starch film was only partial, its value being about 40%. The release of naproxen sodium from the starch film was time-proportional and there was a tendency towards further release. This is positive with regard to the topical drug-application, which is for giving a prolonged therapeutic effect.

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