Rheological and textural properties of hydrogels, containing sulfur as a model drug, made using different polymers types

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Abstract: The preparation technology and the optimal composition of hydrogels with sulfur prepared using various types of polymers – hydroxyethyl cellulose (HEC), Carbopol 980, and sodium alginate – have been developed. Designed hydrogels were evaluated microscopically, for pH, viscosity and mechanical parameters. In addition, *ex vivo* bioadhesive properties of obtained hydrogels with hairless mice skin model as adhesive layer were estimated. Hydrogels with sulfur based on sodium alginate possessed the most favorable application properties and were stable at different temperature and humidity conditions during 90 days of storage.

Keywords: hydrogel, HEC, Carbopol 980, sodium alginate, sulfur, bioadhesion.

Właściwości reologiczne i mechaniczne hydrożeli, zawierających siarkę jako modelową substancję leczniczą, sporządzonych z wykorzystaniem różnych polimerów

Streszczenie: Opracowano technologię otrzymywania i optymalny skład hydrożeli z siarką sporządzonych z wykorzystaniem różnych rodzajów polimerów: hydroksyetylocelulozy (HEC), Carbopolu 980 oraz alginianu sodu. Przygotowane hydrożele oceniano mikroskopowo, poprzez pomiary pH i lepkości oraz na podstawie analizy ich właściwości mechanicznych. Ponadto przeprowadzono badanie bioadhezji *ex vivo* z wykorzystaniem skóry bezwłosych myszy jako modelu warstwy adhezyjnej. Hydrożele z siarką na bazie alginianu sodu charakteryzowały się najlepszymi właściwościami aplikacyjnymi i były trwałe podczas 90 dni przechowywania w różnych warunkach temperatury i wilgotności.

Słowa kluczowe: hydrożel, HEC, Carbopol 980, alginian sodu, siarka, bioadhezja.

Hydrogels have been defined as two- or multicomponent systems consisting of a three-dimensional network of polymer chains and water that fills the space between macromolecules. Within the major group of semisolid preparations, the use of gel systems has expanded both in pharmaceutical preparations and in cosmetics. Hydrogels for dermatological use have several favorable properties such as thixotropy, greaseless, good spreadability, ease of removal, moreover they are non-comedogenic preparations. They are highly biocompatible with a lower risk of irritation or other adverse reactions. Moreover, hydrogels tend to be most effective because they often provide faster release of drug substance, independent of drug water solubility, compared with creams and ointments [1–4].

Sulfur is a well-established therapeutic agent useful in a variety of skin disorders. It is characterized by antimicrobial activity and acts as a keratolytic agent. Precipitated and colloidal sulfur is used, in form of lotions, creams, ointments, powders and soaps for the treatment of acne vulgaris, acne rosacea, seborrhoeic dermatitis and scabies. Its keratolytic action is due to formation of hydrogen sulfide through a reaction that depends upon direct interaction between sulfur particles and keratinocytes. Adverse effects from topically applied sulfur are uncommon and are mainly limited to the skin. Sulfur is insoluble in water but soluble in carbon disulfide and, to a lesser extent, in other nonpolar organic solvents, such as benzene and toluene [5, 6].

The aim of this study was to evaluate the influence of the polymer type on physicochemical, rheological and texture properties of designed hydrogels containing sulfur as a model drug with poor water solubility.

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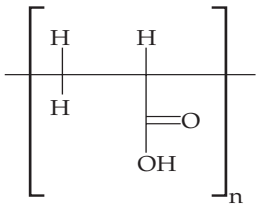
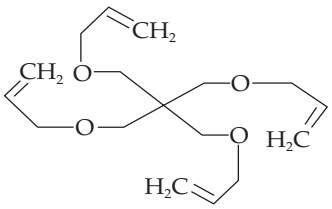
EXPERIMENTAL PART

Materials

– Carbopol 980, high molecular weight polymer of acrylic acid cross-linked with allyl ethers of pentaerythritol [Formulas (I), (II)], 56.0–68.0 % of carboxylic acid groups and with viscosity 40 000–60 000 mPa · s of 0.5 % aqueous dispersion was received as a gift sample from Lubrizol (Cleveland, USA);



(I)



(II)

– sodium alginate of low viscosity, with viscosity 132.6 mPa · s of 2 % solution at 25 °C, molecular weight about 147 000, 61 % mannuronic acid and 39 % guluronic acid, and 2-bromo-2-nitropropane-1,3-diol (bronopol) were purchased from Sigma Aldrich, Steinheim, Germany;

– sulfur was from Fagron, Kraków, Poland;

– glycerol 85 % was from PPH Galfarm Sp. z o.o., Kraków, Poland;

– hydroxyethyl cellulose – HEC, Natrosol HR, with viscosity 2000 mPa · s of 2 % solution in water was from A.C.E.F., Piacenza, Italy;

– calcium chloride anhydrous and trimethylamine (TEA) were purchased from POCH S.A., Gliwice, Poland.

All chemicals used were of analytical grade.

Hairless mice skin was obtained from Experimental Medicine Center of the Medical University of Białystok. The skin has been collected from Cby.Cg-Foxn1nu/cmdb hairless mice intended for collection of organs and this procedure did not require the approval of the Local Ethical Committee on Animal Testing.

Preparation of hydrogels

Hydrogels were prepared by gradually dispersing the different types of gelling agents: sodium alginate, HEC, Carbopol 980 in an aqueous-based solution containing glycerol 85 % (10 % w/w, as a humectant) and bronopol (0.02 % w/w, as a preservative), with the help of mechanical stirrer RZR 2020 (Heidolph Instruments, Schabach, Germany) at a moderate speed. Mixing was continued until a homogenous dispersions of polymer or a transparent gel were received. Formulation based on Carbopol 980 was neutralized with triethanolamine (TEA) to allow gel formation and to receive desirable viscosity (about 5500–6000 mPa · s). In the case of alginate cross-linked hydrogel, sodium alginate powder (5.0 % w/w) was dissolved in an aqueous-based solution containing glycerol 85 % and bronopol with the use of mechanical stirrer. As cross-linking agent, 0.5 % $CaCl_2$ solution was applied. 0.5 % $CaCl_2$ solution was added dropwise in amount of 2.0 g into the sodium alginate solution and stirred until homogenous gel possessing viscosity about 9000 mPa · s was obtained. Process was carried out at 25 °C. Sulfur at 2.0 % w/w concentration was uniformly dispersed in hydrogel vehicle. The concentration of active ingredient was set based on commercially available products. A control hydrogel formulations without sulfur H1, H2, H3, H4 (placebo) were also prepared. The compositions of designed hydrogels are listed in Table 1.

Methods of testing

Determination of pH

The pH was measured by a glass electrode of pH-meter Orion 3 Star (Thermo Scientific, Waltham, MA, USA)

T a b l e 1. Composition of designed hydrogels

Ingredient	Formulation code							
	H1	HS1	H2	HS2	H3	HS3	H4	HS4
	Content, g							
Sulfur	–	2.0	–	2.0	–	2.0	–	2.0
HEC	2.75	2.75	–	–	–	–	–	–
Carbopol 980	–	–	0.25	0.25	–	–	–	–
Sodium alginate	–	–	–	–	7.0	7.0	5.0	5.0
Bronopol	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Glycerol 85 %	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
TEA	–	–	1 drop	1 drop	–	–	–	–
0.5 % $CaCl_2$	–	–	–	–	–	–	2.0	2.0
Purified water, up to	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

which was calibrated before each use with standard buffer solutions. Each measurement was carried out six times and average pH was calculated. Results are presented as the mean ± standard deviation (*SD*).

Particle size analysis

Samples of hydrogels containing sulfur (in quantity corresponding to 10 μg of active substance) were observed under magnification 100x and particle size was analyzed by using optical microscope Motic BA 400 equipped with a camera (Moticon, Wetzlar, Germany) [7].

Viscosity measurement and determination of rheological properties

The viscosity of prepared hydrogels was determined using Brookfield viscometer (RVDV-III Ultra, Brookfield Engineering Laboratories, Middlebro, MA, USA) equipped with the cone/plate type CPA52Z (plate diameter 24 mm, cone angle 3°) at 25 ± 1 °C. The viscosity at shear rate 10.0 s^{-1} was recorded and the rheograms were evaluated by plotting the obtained values of shear stress *versus* shear rate (2.0–20.0 s^{-1}). Results are presented as the mean ± standard deviation (*SD*) based on six independent measurement.

Texture analysis

Texture properties such as firmness, compressibility and adhesiveness of prepared hydrogels were examined using a Texture Analyser TA.XT Plus (Stable Micro System, Godalming, UK) for backwards extrusion measurements. A disc (35 mm diameter) was pushed at a speed of 2 mm/s for a distance of 5 mm into the hydrogels sample (30 g) and redrawn. Data collection and data analysis were performed using Texture Exponent 32 software package [8–10].

Mechanical properties of prepared hydrogels including tensile strength and Young's modulus were also conducted. The tensile strength and Young's modulus (modulus of elasticity, Pa) were calculated using the following equations:

$$\text{Tensile strength} = F/A \tag{1}$$

$$\text{Young's modulus} = \frac{F/A}{\Delta l / l} \tag{2}$$

in which: F [N] represents the force applied to the gel, A [m^2] displays the calculated cross-sectional area of the gel cylinder, Δl [m] represents the length deformation and l [m] represents the original sample length. Young's modulus is a measure of the "stiffness" (mechanical response) of a material, the material's ability to recapture its original shape after deformation and reflects the number and length of elastic segments [11, 12].

***Ex vivo* bioadhesive properties**

Evaluation of bioadhesiveness was performed using TA.XT.plus Texture Analyser (Stable Micro Systems, Godalming, UK) and hairless mice skin as adhesive layer. Samples of the skin were frozen at -20 °C and stored no longer than 4 weeks. On the day of the experiment skin was defrosted and cut into 5 mm diameter pieces, then skin samples were thawed in physiological saline solution (0.9 % NaCl) at 25 ± 0.5 °C for 30 min. Next mice skin was attached to the lower end of a cylindrical probe using a cyanoacrylate glue and hydrogels samples in amount of 0.5 g were placed below the probe. The experiment was carried out at 32 ± 0.5 °C (water bath) to mimic skin temperature. Experimental parameters of the process were chosen during preliminary tests and set as follows: pre-test speed 0.5 mm/s, test speed 0.1 mm/s, contact time 120 s, post-test speed 0.1 mm/s, applied force 0.5 N. The adhesive properties were determined as the maximum detachment force (F_{max}) and the work of adhesion (W_{ad}) – calculated from the area under the force *versus* distance curve, expressed in μJ. The work of adhesion (W_{ad}) was calculated using the following formula:

$$W_{ad} = A \cdot 0.1 \cdot 1000 \tag{3}$$

where: A – area under the force *versus* distance curve, multiplication by 0.1 – conversion time measurement to distance (the sampler was raised at 0.1 mm/s), then multiply by 1000 in order to express the result in units of work μJ [13, 14]. The results were reported as the means of six tests.

Stability study

The prepared hydrogels containing sulfur were stored over a period of 90 days in sealed polyethylene containers at three different temperature and humidity conditions [4 ± 2 °C, 25 ± 2 °C and 60 ± 5 % relative humidity (*RH*), 40 ± 2 °C and 75 ± 5 % *RH*] in climatic test chambers (CTC 256, Memmert, Schwabach, Germany; KBF 115, Binder, Tuttlingen, Germany). Formulations were evaluated periodically for viscosity, pH, particle size and inspected visually for homogeneity, phase separation and change in their color or odor [15].

Statistical analysis

Results are presented as the mean ± standard deviation (*SD*) based on six independent experiments. Statistical analysis was done by one-way analysis of variance (ANOVA) using Statistica 10.0 software (StatSoft, Kraków, Poland). A probability level of $p < 0.05$ was considered as significant.

RESULTS AND DISCUSSION

A wide choice of polymer vehicles ranging from liquid to semisolid forms has been used for skin care and topi-

cal treatment of dermatological diseases. During designing topical formulations, the choice of the appropriate polymer and selection of suitable excipients is particularly important aspect, which influences the quality of the formulation, its efficacy and stability [16, 17]. High molecular weight water soluble polymers of cellulose derivatives – hydroxyethyl cellulose (HEC), cross-linked polyacrylate polymer – Carbopol 980 or sodium alginate are reported to be useful in formation of hydrogels. HEC is a non-ionic water soluble cellulose derivative widely used in pharmaceutical products. HEC in water solutions is stable at pH 2–12, it can be used with a wide variety of antimicrobial preservatives and possesses good tolerance for electrolytes. HEC is generally regarded as an essentially nontoxic and nonirritant material [18]. Carbopol 980 is polyacrylic acid polymer with highly ionized carboxyl groups after neutralization that leads to gel formation due to the electrostatic repulsion among the charged polymer chains. It is effective in low concentrations and the hydrogels of Carbopol 980 are homogeneous, transparent, with good adhesive properties. The viscosity of Carbopol formulations is considerably reduced at pH values less than 3 or greater than 12, or in the presence of strong electrolytes [17, 18]. Alginate is a naturally derived polysaccharide that has been widely used in drug delivery systems. It is composed of (1→4) β-D-mannuronic acid and α-L-guluronic acid residues linked either randomly or as homopolymeric blocks. The cross-linking and gelation of the polymer are mainly achieved by the exchange of sodium ions from the guluronic acids with the divalent cations and the stacking of these guluronic groups to form the characteristic "egg-box" structure. Sodium alginate has been frequently used as gelling agent for hydrogels preparation because of its biocompatibility, low toxicity, nonimmunogenicity, and mild gelation behavior with divalent cations [18, 19]. The present study was conducted to determine how the type of polymer used as a gelling agent effects on the properties of hydrogel formulations with sulfur.

T a b l e 2. pH, particle size and viscosity of prepared hydrogels

Formulation code	pH	Particle size in hydrogels μm	Viscosity* mPa · s
H1	4.9 ± 0.02	–	10 352 ± 75
H2	4.4 ± 0.02	–	5477 ± 94
H3	7.4 ± 0.01	–	10 557 ± 191
H4	7.2 ± 0.02	–	8819 ± 79
HS1	5.1 ± 0.03	22.2 ± 16.1	12 144 ± 161
HS2	4.8 ± 0.01	23.2 ± 13.7	6582 ± 127
HS3	7.4 ± 0.01	20.1 ± 11.7	10 650 ± 136
HS4	7.2 ± 0.02	19.1 ± 9.5	9095 ± 78

* Viscosity was measured at the shear rate 10.00 s^{-1}.

All designed hydrogels were characterized by smooth, uniform consistency with absence of syneresis, and they

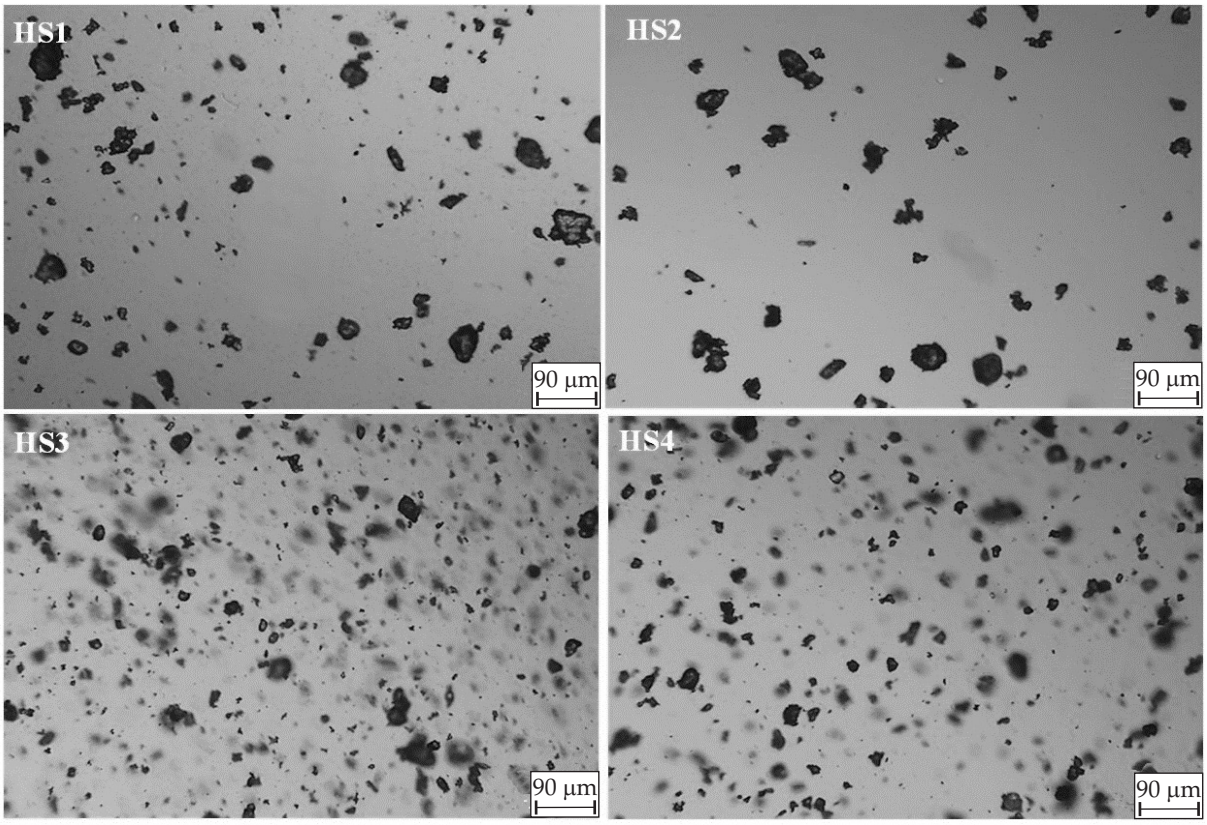


Fig. 1. Microscopic images of hydrogels containing sulfur (HS1–HS4) under magnification 100×

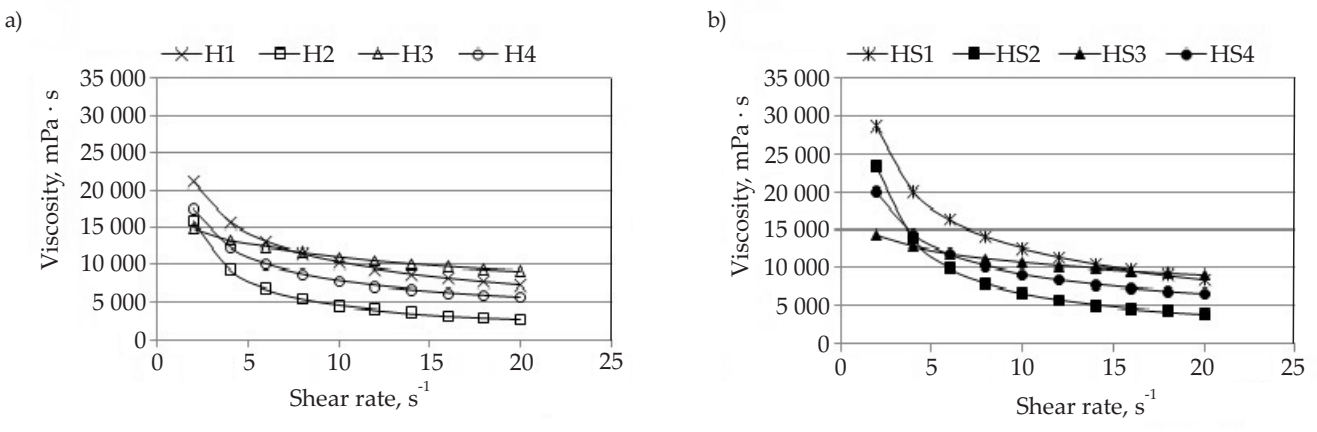


Fig. 2. Viscosity curves of: a) control hydrogels H1–H4, b) hydrogels containing sulfur HS1–HS4

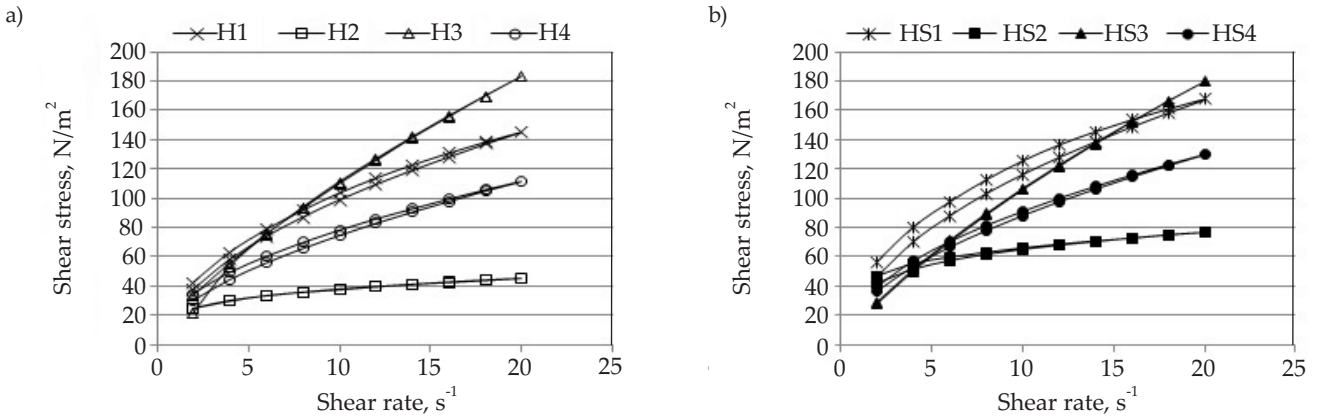


Fig. 3. Rheograms of: a) control hydrogels H1–H4, b) hydrogels containing sulfur HS1–HS4

were easily spreadable. The presence of sulfur gave the preparations a light yellow color. The pH value of obtained formulations was in the range of 4.8–7.4 and it was comparable with placebo hydrogels (Table 2). Furthermore, pH values of hydrogels containing sulfur were suitable for topical delivery providing application without the risk of skin irritation [20]. Additionally, there was no significant change in pH values as a function of time for all formulations. It was observed that particle size of sulfur dispersed in hydrogels was not higher than acceptable 90 μm (Table 2, Fig. 1).

Rheology is the science of the flow and deformation of matter under the effect of an applied force. In pharmaceutical field, rheological characterization is important to understanding the fundamental nature of a system, study the effect of different parameters on the product quality, predicting changes upon storage or even consumer acceptance. Many pharmaceutical processes such as ingredient selections, designing formulation, and shelf storage are associated with a complex flow of materials. Viscosity and rheological properties of semisolid topical dosage forms are related to application behavior such as spreading and contact time with the skin surface [10, 21]. A topical dosage form needs to have semisolid consistency, to be easily spreadable on the skin and able to remain in the application site. Obtained hydrogel formulations containing sulfur were found to have different viscosity values (Table 2). The highest viscosity was noticed in the case of HEC hydrogel HS1 (12 144 mPa · s) and the lowest viscosity possessed Carbopol 980 hydrogel HS2 (6582 mPa · s). The addition of sulfur increased viscosity values, which was particularly noticeable in formulation obtained with HEC.

From the viscosity curves (Fig. 2) it was observed that with the increase of the shear rate the viscosity was decreased which indicates that all formulations are shear-thinning pseudoplastic in nature. Furthermore, all formulations possessed thixotropic properties, as evidenced by the hysteresis loops visible on the rheograms (Fig. 3). A thixotropic system exhibits loss in apparent viscosity over time at a constant shear rate, while the shear stress is removed, the apparent viscosity gradually rises and returns to its primary value.

Texture profile analysis provides information on the response to the external force. It is valuable to predict samples behavior under the physiological conditions, such as the application of a stress during sample administration, and verify the ease of semisolid formulation to remove from the container package or its spreadability on the skin surface. Topical preparations should exhibit appropriate mechanical properties, such as firmness, adhesiveness and compressibility. Firmness is the maximum force produced during probe penetration, compressibility – positive area

covered by the force-time curve. This value represents the work needed to overcome the internal bonds of the material. Firmness and compressibility quantify sample deformation under compression and shear. They are related to sample consistency. Low values of firmness and compressibility would ensure that minimum work is required to remove the formulation from the container and administer to the skin surface. Adhesiveness is the negative area covered by the force-time curve and its value represents the work required to remove the probe from the sample and it is related to the breaking of cohesive bonds. In case of topical hydrogels, higher values are more favorable to ensure prolonged adhesion [10, 22].

T a b l e 3. Textural properties of designed hydrogels

Formulation code	Firmness g	Compressibility g · s	Adhesiveness g · s
H1	80.0 ± 1.6	160.0 ± 2.6	-182.2 ± 3.8
H2	63.1 ± 0.9	121.8 ± 2.7	-108.9 ± 4.4
H3	69.5 ± 2.8	136.9 ± 5.5	-146.6 ± 2.6
H4	101.8 ± 5.2	206.9 ± 5.8	-167.8 ± 5.3
HS1	137.5 ± 0.5	266.5 ± 4.6	-323.2 ± 3.8
HS2	71.4 ± 0.9	141.3 ± 0.7	-122.1 ± 1.6
HS3	72.1 ± 3.3	144.3 ± 4.4	-154.1 ± 3.1
HS4	104.6 ± 4.9	213.9 ± 3.2	-172.0 ± 4.9

The results of the texture analysis are presented in Table 3. Placebo formulations possessed slightly lower firmness, compressibility and adhesiveness compared with hydrogels containing sulfur. The highest values of mechanical parameters were recorded in the case of HEC and alginate hydrogels containing sulfur, while the lowest – for Carbopol 980 hydrogel, what can be attributed to the nature of the polymers used in formulation. Cross-linked alginate hydrogel, despite the use of relatively low concentration of polymer was characterized by high values of firmness, compressibility and adhesiveness. Sodium alginate gelation can be induced in the presence of divalent cations and most commonly used are Ca^{2+} ions which act as cross-linkers for polymer chains. Gelation process is a result of ionic interaction and intramolecular bonding between the carboxylic acid groups located on the polymer backbone and the Ca^{2+} ions. Regions of guluronate monomers in one alginate molecule can be linked to a similar region in another molecule by means of Ca^{2+}. The result is a chain of Ca^{2+}-linked alginate strands that form gels with ordered structure and high stiffness described as "egg-box" structure [19, 23].

Additionally, it is clearly seen that the polymer type applied in the formulation influenced strength of designed hydrogels (Fig. 4). The highest stiffness was observed for cross-linked alginate hydrogel (H4) and in case of alginate formulations cross-linking process significantly increased gel strength. Carbopol 980 formulation (H2) was characterized by the highest elasticity. Moreover, it is worth to note that only for formulation based on HEC, addition of sulfur considerably increased gel strength (HS1).

Bioadhesion is the term described as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by in-

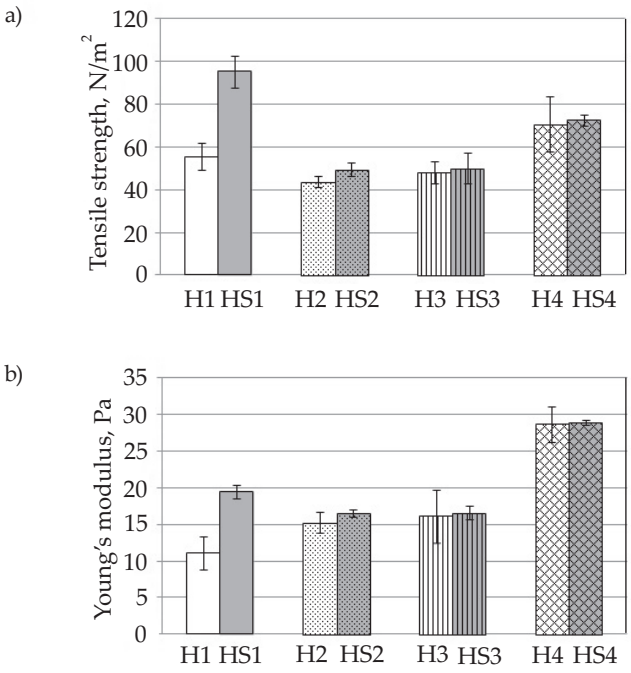


Fig. 4. Comparison of: a) tensile strength profiles for control hydrogels H1–H4 and hydrogels containing sulfur HS1–HS4, b) Young's modulus for control hydrogels H1–H4 and hydrogels containing sulfur HS1–HS4

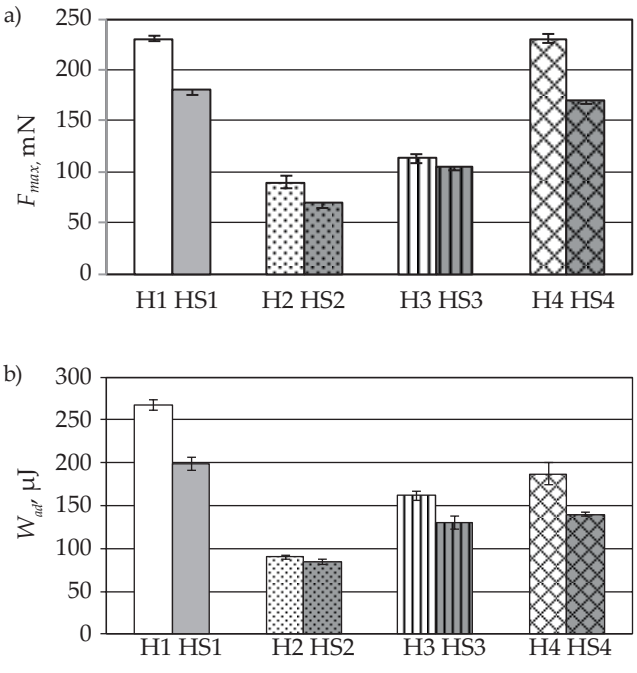


Fig. 5. *Ex vivo* bioadhesive properties of placebo hydrogels (H1–H4) and hydrogels containing sulfur (HS1–HS4) determined as: a) the maximum detachment force F_{max}, b) the work of adhesion W_{ad}

terfacial forces. The bioadhesive properties of the vehicles used as topical drug carriers enable them adhere to the skin surface and in the consequence prolong the retention time of the dosage form at the site of application [10, 24]. The results of tests performed using the hairless mice skin as adhesive layer are presented in Fig. 5. All prepared hydrogels containing sulfur were characterized by bioadhesive properties and the greatest values of F_{max} and W_{ad} were noticed in case of HEC (HS1) and cross-linked alginate (HS4) hydrogels, characterized by high values of mechanical parameters (Table 3) and viscosity (Table 2). Addition of sulfur slightly reduced the bioadhesive properties of designed hydrogels.

To completely assess the influence of polymer type on properties of designed hydrogels containing sulfur, stability studies were performed. Hydrogels were subjected to three different storage conditions according to EMA (European Medicines Agency) – 4 ± 2 °C, 25 ± 2 °C and 60 ± 5 % *RH*, 40 ± 2 °C and 75 ± 5 % *RH* – for a 90 days period [25]. All prepared formulations were found to be stable over 90 days of storage and no significant changes were observed in their physical appearance, rheological properties and particle size (data not shown). However, hydrogels based on HEC (HS1) and Carbopol 980 (HS2) after 90 days of storage at 40 ± 2 °C and 75 ± 5 % *RH* have become more fluid. In the case of these formulations, a clear aggregation and sedimentation of sulfur suspended in hydrogels was additionally noticed. The sedimentation of sulfur particles was probably caused by the decrease in the viscosity of hydrogels under the influence of high temperature (Fig. 6).

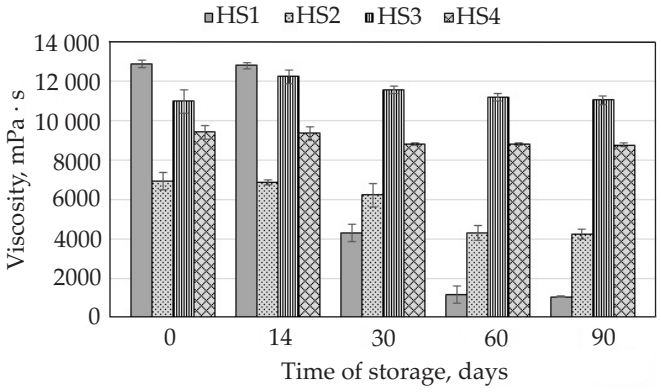


Fig. 6. Viscosity of hydrogels containing sulfur (HS1–HS4) directly after preparation (0 day) and after 14, 30, 60 and 90 days of storage at 40 ± 2 °C and 75 ± 5 % *RH*

CONCLUSIONS

All designed hydrogels exhibited acceptable physicochemical features for topical application: proper homogeneity, particle size, pH, viscosity, and textural properties. Obtained preparations were non-Newtonian systems, showing a shear-thinning behavior with thixotropic properties. Moreover, it was noticed that all formulations were characterized by favorable bioadhesiveness. Optimal physicochemical properties and better stability exhibited hydrogels containing sulfur based on sodium alginate. Alginate hydrogels were stable at different conditions of temperature and relative humidity and no significant changes in their organoleptic properties, pH and viscosity were noticed during 90 days of storage. Due to the most favorable physicochemical properties, adequate viscosity, mechanical features, good bioadhesion and better stability, designed alginate hydrogels may present promising potential as topical vehicles for sulfur – model substance insoluble in water. However, to fully evaluate these vehicles, further research including the determination of sulfur release profiles are necessary.

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