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Study on the rheological properties of microcrystalline chitosan hydrogels used as drug carriers

Summary — The flow behavior of gel-like water dispersions containing 2—4 wt. % of microcrystalline chitosan (MCCh) (Table 1), selected anti-inflammatory drugs (diclofenac acid, ketoprofen acid, diclofenac Na, ibuprofen Na) (Table 2), and various auxiliary substances (triethanolamine, glycerol, *etc.), viz.,* viscosity (η) and yield stress (τ_0), were studied in relation to MCCh content, drug content (Table 4), temperature, shear rate, and storage time. Methylcellulose was used as a model gel-forming substance. The power-law Ostwald—de Waele [12] (eqn. 1) and the Herschel—Bulkley (eqn. 2) models were used for the diluted and for the MCCh-rich hydrogels, respectively; the adjustable parameters, k and n, and activation energy (E_a) were established (Tables 3, 4, Fig. 5). Measurements were carried out immediately after preparation and after a year's long storage (Table 5). Low-polymer MCCh hydrogels are non-Newtonian fluids with $n < 1$, shear-thinned, and with no yield stress. Polymer-rich hydrogels, $n < 1$ and $\tau_0 > 0$, are viscoelastic fluids, shear-thinned; they have a yield stress. As the temperature was raised, τ_0 decreased. For most hydrogel systems, the Arrhenius equation adequately described the variation of apparent viscosity with temperature. As the shear rate was increased, η and E_a decreased. In one year's long storage at 20°C the viscosity of the MCCh hydrogel was lower and that of the hydrogel containing an active substance was slightly higher. The polymer content decides whether the MCCh hydrogel is a pseudoplastic or a plastic fluid. Glycerol and 1,2-propylene glycol as hydrophilizing agents and methylcellulose hydrogel were found to be useful additives ensuring spreading over, and adhesion to, the surface of the human skin.
Key words: microcrystalline chitosan, hydrogel, apparent viscosity, yield stress, effect of temperature and storage time, energy of activation for viscous flow.

Natural polymers have received much attention as drug carriers especially in view of their safety and non-toxicity. Among these polymers, chitosan, *i.e.*, *N*-deacetylated chitin, is becoming increasingly important in the pharmaceutical field owing to its good biocompatibility, non-toxicity, and biodegradability [1—3]. Biodegradation of chitosan leads to oligoaminosaccharides, which are responsible for the bioactivity of this polymer. More recently chitosan has been reported to be a mucoadhesive [4, 5]. As a polycation, chitosan has been used for the production of transparent gels of an ointment consistence. Stable gels, containing therapeutic substances of various solubilities and at various concentrations, have been produced by using chitosan as a vehicle of the high deacetylation degree, dissolved in lactic acid [6]. Studies on chitosan as a drug carrier have been concentrated on its colloidal solutions and gels [7]. Low-chitosan hydrocolloids exhibit a relatively high viscosity attributable to the increased effective volume of the polymer molecules caused by repulsion of like charges in the chains. The mechanism of chitosan gel formation is not exactly known.

Recently, chitosan derivatives of a well-defined degree of deacetylation and depolymerization have been found of interest because of their considerably different physicochemical properties (especially solubility in water). As a weak base, chitosan requires some minimum amount of acid to have the glucosamine units converted into the positively charged ($-NH_3^+$) water-soluble form. Most chitosan molecules lose their charge and

precipitate from the solution at a neutral pH. The physical state of chitosan (flakes, powder, dispersion) and consequently the behavior of its reacting surface determine the physicochemical properties of this polymer.

Quantitative studies [8, 9] have confirmed the superior properties of microcrystalline chitosan as a gel-like water dispersion over its non-modified form, *i.e.* flakes. Microcrystalline chitosan (MCCh) is the modified form of chitosan obtained by aggregation of glucosamine macromolecules from an aqueous solution of an organic acid [10]. The specific properties of MCCh such as the ability of forming membranes directly from water dispersions, the developed reacting surface, the high water retention value (WRV) and the increased susceptibility to biodegradation as compared with the non-modified form of chitosan are promising as regards its applicability in medicine, pharmacy, and other areas [11].

The rheological properties of gel-like water dispersions of microcrystalline chitosan have not been studied so far. The aim of this work is to study the flow behavior of plain MCCh hydrogel at concentrations from 2.0 to 4.0 wt. % as well as of microcrystalline chitosan hydrogel systems containing selected non-steroidal anti-inflammatory drugs (NSAIDs). Diclofenac sodium was taken as a model therapeutic substance. Methylcellulose (MC) was taken as a model gel-forming substance. The rheological properties of microcrystalline chitosan were studied in relation to polymer content, presence of therapeutic substances, temperature, shear rate, and storage time. The Ostwald—de Waele power model [12] was applied to detemine the rheological characteristics of diluted hydrogels. The Herschel—Bulkley model involving three rheological parameters, describes the flow behavior of MCCh hydrogels of higher polymer contents.

EXPERIMENTAL

Materials

Microcrystalline chitosan (MCCh) was prepared by an unconventional method [10] from non-modified chitosan (Pandalus AS, Norway, and Chemopol Co., India). Selected property data on the non-modified and microcrystalline chitosans are presented in Table 1.

Table 1. Some properties of non-modified and microcrystalline chitosans

Sample	Pandalus AS		Chemopol Co.	
	non-modified	MCCh	non-modified	MCCh
Average molecular weight ($\overline{M}_w$), kDa	140.6	110.0	178.6	100.0
Degree of deacetylation (*DD*), %	90.0	85.7	60.5	95.0
Water retention value (*WRV*), %	72.6	950	63.0	1060

The therapeutic substances with acidic properties: diclofenac (DA), ketoprofen (KTA), and salts, *viz.*, diclofenac sodium (DS) and ibuprofen sodium (IBS) (Sigma Chemical Co.); ethanol (98%), glycerol (G), triethanolamine (TEA) (POCh, Gliwice, Poland); 1,2-propylene glycol (PG), methylparaben (MP) (Fluka); methylcellulose (MC), $\overline{M}_w$ = 41 kDa (Sigma Chemical Co.); Carbopol 940 (CP) (Polfarmex, Kutno, Poland), and distilled water were used. All chemical substances were of analytical grade.

Preparation of hydrogels

Microcrystalline chitosan was used as a vehicle for drugs in the form of a gel-like water dispersion at varying polymer contents (Table 2). Therapeutic substances (1.0 wt. %, IBS, KTA, DS) were dissolved or dispersed (DA) in the MCCh hydrogel by thoroughly triturating the drugs with a little gel and then mixing with the rest of the gel. In addition, a complex hydrogel was prepared by adding a methylcellulose (MC) hydrogel to the gel-like water dispersion of MCCh. The MC hydrogel was obtained *ex tempore* by mixing the powder with water. In order to obtain a proper base consistence avoiding excessive water evaporation, small amounts of a hydrophilizing agent such as glycerol or 1,2-propylene glycol and also a conserving agent, methylparaben, were added to the MCCh hydrogel (Table 2). All the types of the hydrogel vehicles were mixed until a homogeneous structure was produced.

For comparison, a Carbopol 940 hydrogel was combined with the gel-like water dispersion of MCCh in the following way: Carbopol 940, 0.5 g, was slowly added to a portion of distilled water and mixed until swollen. During the mixing (Stirring Motors, KIKA LABORTECHNIK) (1000 rpm) a diclofenac solution (1g DA in 30 g ethanol) was added to the swelling Carbopol 940 and then triethanolamine (TEA) dissolved in the MCCh dispersion (1 g TEA in 20 g of 2.0 wt. % MCCh) was added. This mixture was completed with 100 g of distilled water with continuous stirring to produce an opalescent gel. In the case of the Carbopol 940 gel (F7), after diclofenac had been completely dissolved in ethanol (1 g DA in 25 g ethanol) and Carbopol 940 (1 g) had been swollen in a portion of distilled water, the resulting mixture was neutralized with 1 g TEA. The mixture was completed with 100 g of distilled water with continuous stirring to produce a transparent gel.

The resulting hydrogel systems were left in a dark place for 24 h and then used for rheological studies.

Methods

A rotary rheometer (Rheotron BRABENDER) equipped with a concentric cylinder, was used to study the rheological properties of MCCh hydrogels and other systems, at 20 and 37°C or at 20, 30, and 40°C, and at shear rates ranging from $5 \cdot 10^{-1}$ to 10^3 s^{-1}. The flow cu-

T a b l e 2. Composition of hydrogel systems (wt. %)

Components	H1	H2	F1	F2	H3	F3	F4	F5	H4	H5	H6	H7	F6	F7
MCCh	2	3	3	3	4	4	4	4	3	3	—	—	0.5	—
DS	—	—	1	—	—	—	—	—	—	—	—	—	—	—
DA	—	—	—	—	—	1	—	1	—	—	—	—	1	1
KTA	—	—	—	—	—	—	1	—	—	—	—	—	—	—
IBS	—	—	—	1	—	—	—	—	—	—	—	—	—	—
TEA	—	—	—	—	—	—	—	0.5	—	—	—	—	1	1
G	—	—	—	—	—	—	—	1	0.5	—	—	—	—	—
PG	—	—	—	—	—	—	—	1	0.5	—	—	—	—	—
CP	—	—	—	—	—	—	—	—	—	—	—	—	0.5	1
MC	—	—	—	—	—	—	—	2	—	1	2	3	—	—
Et	—	—	—	—	—	—	—	1	—	—	—	—	30	25
MP	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
H_2O to	100	100	100	100	100	100	100	100	100	100	100	100	100	100
pH*)	6.87	6.87	7.08	6.94	6.94	5.88	5.30	7.09	6.90	6.20	6.70	7.70	8.47	8.15

H — code of hydrogel, F — code of formulation (hydrogel + therapeutic substance), MCCh — Microcrystalline Chitosan, CP — Carbopol 940, MC — Methylcellulose. Therapeutic substance: DS — Diclofenac Sodium, DA — Diclofenac Acid, KTA — Ketoprofen Acid, IBS — Ibuprofen Sodium. Auxiliary substance: TEA — Triethanolamine, G — Glycerol, PG — 1,2-Propylene Glycol, Et — Ethanol, MP — Methylparaben.
*) pH of 1 g gel in 10 ml H_2O, temp. 20°C.

rves and apparent viscosities were used to evaluate the rheogical properties of the hydrogels. The viscosity and the yield stress of the microcrystalline chitosan hydrogel were also studied in relation to the content of therapeutic substances. The measurements were performed for the hydrogels of microcrystalline chitosan and methylcellulose at varying polymer contents, and for the combinations of the therapeutic and auxiliary substances used in various proportions (Table 2).

The flow properties of the diluted hydrogels, *viz.*, MCCh (H1), MC (H6), and MC (H7), obey the power-law relationship of the Ostwald—de Waele model [12]:

$$\tau = k \cdot \gamma^n \text{ and } \eta = k \cdot \gamma^{n-1} \quad (1)$$

where: τ — *shear stress, Pa;* γ — *shear rate,* s^{-1}; η — *apparent viscosity, Pa · s; n, k — rheological parameters evaluated as the intercepts of the plot of the logarithm of shear stress versus the logarithm of shear rate.*

The simplest rheological model of the flow curves of MCCh hydrogels of higher polymer contents is the Herschel—Bulkley model:

$$\tau = \tau_0 + k \cdot \gamma^n \quad (2)$$

with the three rheological parameters: τ_0, k and n (where τ_0 — *is the yield stress*). There are many other models describing viscous properties of non-Newtonian fluids. However, the models presented above are simple enough to be used in our studies. The shear stress (τ, Pa) as a function of shear rate (γ, s^{-1}) was plotted as log (τ - τ_0) = f(log γ), whereas Ostwald's model was applicable only over low shear rates ($5 \cdot 10^{-1}$ to 10^2 s^{-1}). All the rheological parameters such as τ_0, n and k, were calculated and discussed.

To determine temporal changes in rheological properties, the hydrogels were stored at 20°C for up to 1 year, and then examined.

RESULTS AND DISCUSSION

The flow curves and the apparent viscosity plots *vs.* shear rate are presented (Fig. 1) for the MCCh hydrogels of varying polymer contents.

The flow curve for the MCCh diluted hydrogel (H1) (Fig. 1, curve 1) is typical for a non-Newtonian shear-thinning liquid without yield stress. The shear stress is less than proportionally related to the shear rate and the increase in shear rate is accompanied by a decrease in apparent viscosity.

In order to assess the rheological parameters k and n, the flow curves for the diluted hydrogels MCCh (H1),

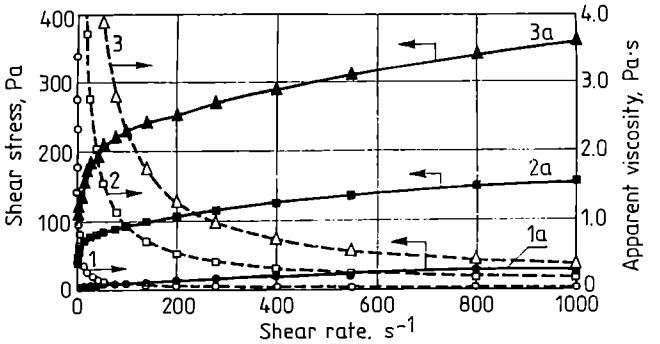

Fig. 1. Apparent viscosity (1, 2, 3) and shear stress (1a, 2a, 3a) in relation to shear rate for the MCCh hydrogels of different concentrations: 1, 1a — 2.0 wt. % (H1); 2, 2a — 3.0 wt. % (H2); 3, 3a — 4.0 wt. % (H3)

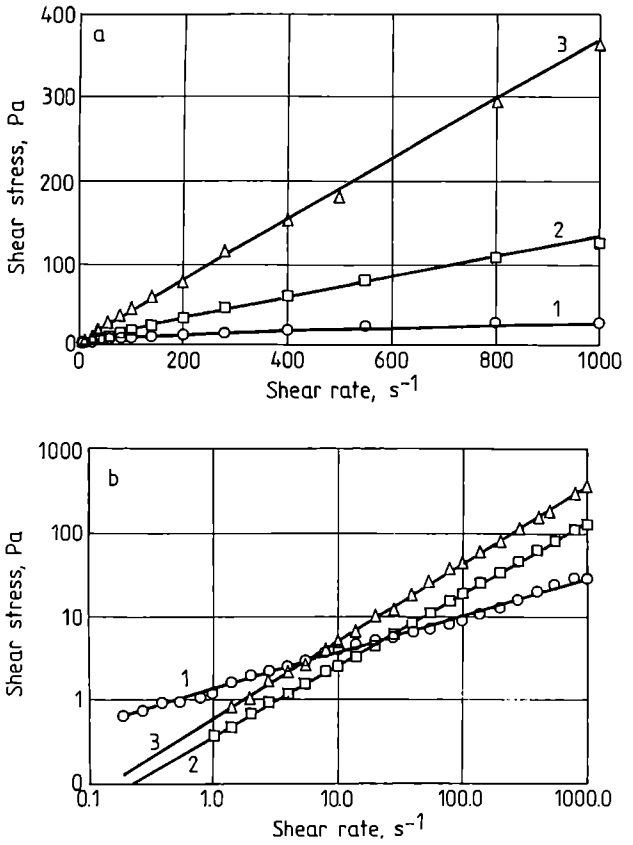

Fig. 2. a) Shear stress (τ) versus shear rate (γ), b) logarithm of shear stress (τ) versus logarithm of shear rate (γ) plots for hydrogels of low polymer contents: 1 — MCCh 2.0 wt. % (H1), 2 — MC 2.0 wt. % (H6), 3 — MC 3.0 wt. % (H7); 1) τ = 1.3376 + 0.4450 γ (r^2 = 0.9966); 2) τ = 0.3577 + 0.8594 γ (r^2 = 0.9997); 3) τ = 0.5874 + 0.9336 γ (r^2 = 0.9990)

MC (H6) and for the hydrogel MC (H7) (Fig. 2a) were linearized (Fig. 2b) as log τ = f(log γ).

The values of the rheological parameter k and n for the diluted systems (MCCh, MC), and hydrogel MC are given in Table 3.

In each system, the rheological parameter n is lower than unity and therefore each system is a liquid shear-thinned substance. However, methylcellulose, hydrogels, especially hydrogel H7 (MC, 3.0 wt. %), are closer to a Newtonian liquid in nature than is the diluted hydrogel of microcrystalline chitosan (H1). The parameters k and n show the H1, H6, and H7 systems to behave as pseudoplastic materials, shear-thinned without yield stress. The diluted hydrogel MCCh (H1) is characterized by a greater instability. After the hydrogel had been prepared, separation into the water phase and the dispersed phase took place immediately.

T a b l e 3. Comparison of rheological parameters n and k (in Ostwald—de Waele model) for hydrogel systems of low polymer contents at 20°C; ($5 \cdot 10^{-1}$ s^{-1} < γ < 10^3 s^{-1}); 35 measuring points

Type of hydrogel	$\tau = k \cdot \gamma^n$		
	k	n	r^2
MCCh (H1)	1.34±0.12	0.445±0.012	0.9966
MCCh (H1)*)	0.45±0.06	0.441±0.016	0.9896
MC (H6)	0.36±0.01	0.859±0.022	0.9997
MC (H6)*)	0.20±0.05	0.858±0.026	0.9997
MC (H7)	0.59±0.02	0.933±0.025	0.9990

*) 37°C.

The flow curves of the hydrogels MCCh with higher polymer contents are shown in Fig. 1 (curves 2 and 3). The rheological parameters τ_0, k and n for the hydrogels and formulations are presented in Table 4.

The parameter $n < 1$ as well as the parameter τ_0 show that the hy lrogels behave as visco-plastic shear-thinned materials with a yield stress. In each case, the correlation coefficient is high ($r^2 > 0.98$), which confirms that the Herschel-Bulkley model is applicable.

The parameters τ_0 and k of the MCCh hydrogels containing a therapeutic substance are higher when compared with those of the neat MCCh hydrogels (H2, F1, F2) and (H3, F3, F4, F5) (Table 4). The increase in the viscosity of the hydrogels caused by the presence of therapeutic substances (F3 and F4) as compared with the neat hydrogel (H3) is suggestive of physicochemical interactions of the anionic drugs (DA, KTA) with the excipient (free amine groups of MCCh). Salt formation ($COO^-NH_3^+$) is confirmed by the decrease of pH value after introduction of the anionic drugs, especially KTA (Table 2).

Addition of the hydrophilizing agents (glycerol and 1,2-propylene glycol) and methylcellulose hydrogel (MC) as well as triethanolamine (TEA) induced a significant increase in the apparent viscosity of the complex hydrogel MCCh/DA (F5). However, the effect is smaller as compared with that in the hydrogel MCCh/DA (F3) containing a single drug, with no auxiliary substances (G, PG, MC, and TEA) added.

The MCCh/DS (F1) hydrogel formulation involving a neutral drug (DS) is characterized by a higher viscosity as compared with the neat hydrogel (H2) (Table 4). Addition of the glycerol and 1,2-propylene glycol caused a decrease in the apparent viscosity of the MCCh hydrogel (H4). As compared with the neat hydrogel (H2), the hydrogel MCCh modified with MC (H5) showed insignificant change in yield stress.

The rheological properties of the Carbopol hydrogels (F6 and F7) show the yield stress of the Carbopol complex formulation (F6) to have decreased on combination of the MCCh hydrogel with Carbopol 940.

Storage time effect

The stability of microcrystalline chitosan depends on the degree of deacetylation and on the polymer content [9]. Small changes in properties were observed in MCCh as gel-like water dispersion with a high deacetylation degree (above 90%) containing from 3.0 to 4.0 wt. % of polymer. MCCh of a similar deacetylation degree

Table 4. Comparison of rheological parameters τ_0, k and n (in Herschel-Bulkley model) for hydrogel systems of higher polymer contents ($5 \cdot 10^{-1}$ $s^{-1} < \gamma < 10^3$ s^{-1}); 35 measuring points

Type of hydrogel	Temperature, °C	$\tau = \tau_0 + k \cdot \gamma^n$			
		τ_0, Pa	k	n	r^2
MCCh(H2)	20	27.0±0.3	20.2±1.2	0.266±0.021	0.9899
	37	16.1±0.2	18.2±0.9	0.268±0.028	0.9823
	20*)	20.2±0.3	21.6±1.2	0.253±0.022	0.9851
	37*)	18.1±0.2	16.3±0.7	0.271±0.023	0.9825
MCCh/DS (Fl)	20	35.0±0.5	13.2±0.4	0.350±0.024	0.9847
	37	31.0±0.4	8.65±0.1	0.376±0.021	0.9900
	20*)	55.0±0.6	24.3±1.2	0.332±0.026	0.9822
	37*)	50.0±0.4	15.8±0.7	0.344±0.020	0.9831
MCCh/IBS (F2)	20	76.0±0.5	13.5±0.	0.552±0.048	0.9886
	30	38.0±0.4	12.6±0.1	0.372±0.032	0.9837
	40	25.0±0.2	1 8.7±0.1	0.401±0.036	0.9803
MCCh/G/PG (H4)	20	12.0±0.2	14.7±0.5	0.433±0.038	0.9827
	37	10.5±0.1	14.3±0.3	0.411±0.038	0.9875
	20*)	17.0±0.3	15.3±0.6	0.477±0.041	0.9933
	37*)	15.0±0.4	13.9±0.4	0.430±0.038	0.9851
MCCh/MC (H5)	20	28.0±0.3	11.9±0.1	0427±0.035	0/9836
	30	27.0±0.3	10.4±0.1	0.430±0.037	0.9867
	40	18.0±0.2	10.1±0.1	0.425±0.031	0.9826
MCCh (H3)	20	85.0±0.7	35.2±1.4	0.305±0.026	0.9903
	37	80.0±0.3	33.1±1.2	0.314±0.021	0.9933
	20*)	80.0±0.8	42.3±1.8	0.330±0.027	0.9889
	37*)	75.0±0.3	37.5±1.7	0.340±0.026	0.9938
MCCh/DA (F3)	20	154.2±1.7	44.3±1.7	0.309±0.022	0.9921
	37	140.0±1.5	41.7±1.5	0.315±0.025	0.9922
	20*)	158.4±1.9	47.8±1.8	0.285±0.028	0.9887
	37*)	144.5±1.6	45.6±1.6	0.294±0.032	0.9916
MCCh/KTA (F4)**)	37	140.0±1.6	49.5±1.5	0.380±0.019	0.9856
	37*)	150.0±1.5	56.0±1.3	0.303±0.022	0.9906
MCCh/DA (F5)	20	112.5±1.2	97.6±2.4	0.266±0.028	0.9917
	37	104.0±1.0	93.4±2.3	0.275±0,006	0.9882
MCCh/CP/DA (F6)	20	62.0±0.7	41.0±0.4	0.392±0.031	0.9973
	30	60.0±0.6	41.0±0.3	0.366±0.032	0.9964
	40	58.0±0.8	32.9±0.3	0.355±0.032	0.9919
CP/DA (F7)**)	37	80.0±0.8	55.8±0.5	0.366±0.038	0.9828

*) After 1 year. **) Measured only at 37°C; k, n, τ_0 evaluated iteratively by using the Statgraphic Plus 2.1 computer program.

but a higher polymer content, 4.5 wt. %, hardened after a prolonged storage time (1 year). The MCCh of low deacetylation degree was less stable and liquefied after a short storage time (25 weeks). Differences in absorption spectra (UV/VIS) confirm the changes in MCCh (dissolved in 0.1 M $HN0_3$). At $\nu \sim 36 \cdot 10^3$ cm^{-1}, a new band was formed, additional to the band at $\nu \sim 33 \cdot 10^3$ cm^{-1}. In 1 year's long storage, the intensity of the new band rose and shifted towards higher wavenumbers, whereas the band at $\nu \sim 33 \cdot 10^3$ cm^{-1} progressively disappeared, and a new band at $\nu \sim 28 \cdot 10^3$ cm^{-1} was formed. Therefore, studies on the usefulness of MCCh as a drug carrier were based on gel-like water dispersions with a high DD containing from 3.0 to 4.0 wt.% of polymer of high stability (above 1 year).

The effect of storage time on the yield stress and on the apparent viscosity of the hydrogel systems is presented in Table 5. The apparent viscosity is shown in Fig. 3 as a function of shear rate.

The yield stress determined for the MCCh hydrogels would suggest a plastic behavior of the system. Nevertheless, in 1 year, the value was lower. It can be assumed that the plastic behavior of the system would become less eminent as the storage time is prolonged. Wi-

T a b l e 5. Changes in yield stress and apparent viscosity of hydrogel systems with storage time at 20°C

Type of hydrogel		τ_0 Pa	Shear rate, s^{-1}			
			10	100	550	1000
			Apparent viscosity, Pa s			
MCCh (H2)	after preparation	27.0	7.05	0.93	0.25	0.16
	after 1 year	20.2	6.20	0.89	0.23	0.15
MCCh /DS (F1)	after preparation	35.0	6.67	1.03	0.28	0.18
	after 1 month	28.5	5.52	1.11	0.33	0.22
	after 1 year	55.0	10.40	1.71	0.46	0.30

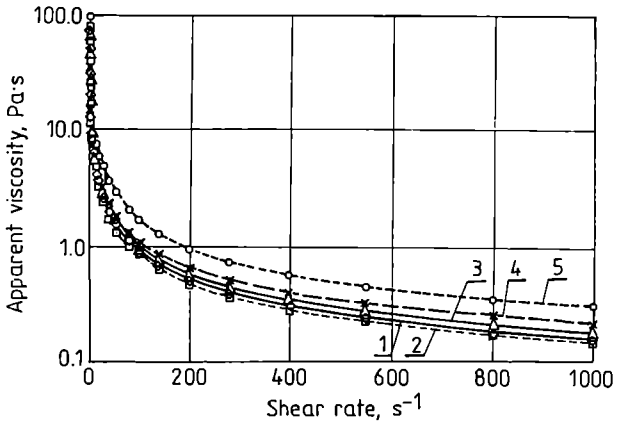

Fig. 3. Viscosities of MCCh (H2) and MCCh/DS (F1) hydrogel systems: 1 — MCCh (H2), 2 — MCCh (H2) after 1 year, 3 — MCCh/DS (F1), 4 — MCCh/DS (F1) after 1 month, 5 — MCCh/DS (F1) after 1 year

thin 1 year (storage at 20°C), the apparent viscosity of the MCCh hydrogel decreased slightly.

In 1 month, the yield stress of the MCCh hydrogel containing a therapeutic substance (DS) first decreased and then increased. Simultaneously, the apparent viscosity rose but slightly. Only the viscosity measured at a low shear rate was in one month of storage smaller than that measured directly after the preparation. Another MCCh/IBS (F2) hydrogel system showed syneresis after a short storage time, which indicated to interactions of the drug with the gel structure.

Temperature effect

The rheological measurements of the hydrogels were carried out at various temperatures (20 and 37°C or 20, 30 and 40°C). Still higher temperatures were not used to avoid thermal degradation. The effect of temperature on the rheological parameters of the hydrogel systems is presented in Table 4 and an example is shown in Figure 4.

For the hydrogel systems, the yield stress decreased as the temperature was increased (Fig. 4a). The parameter k, similar in value to the consistency index (k'), decreased, too (Fig. 4b). As the temperature was increased,

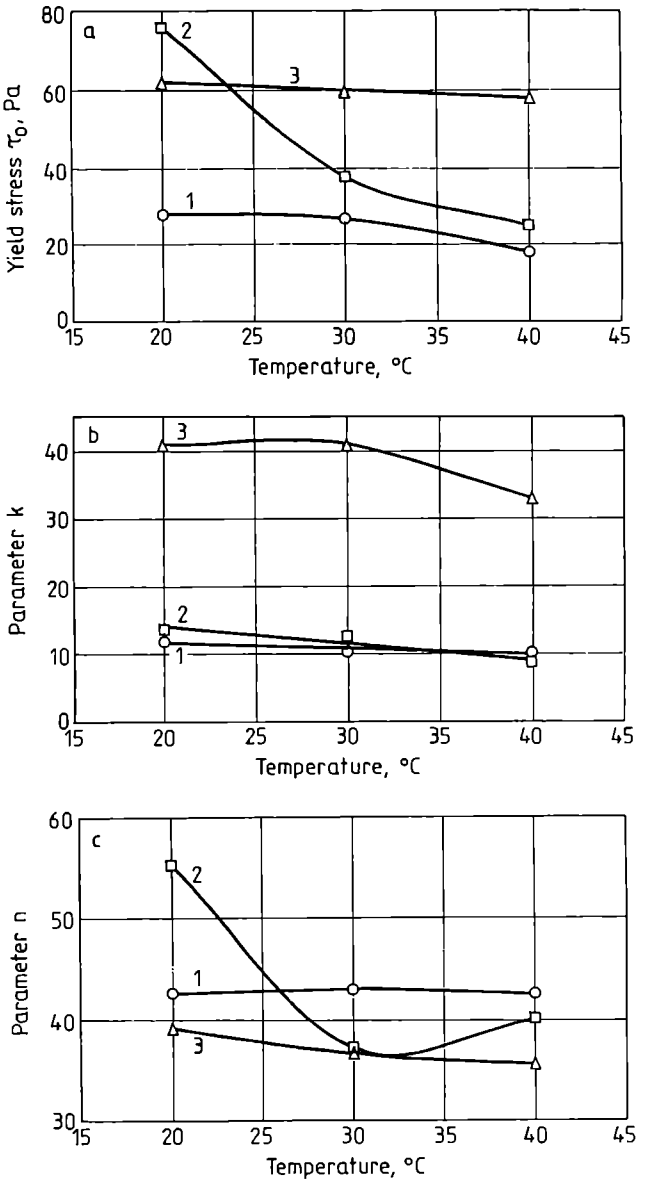

Fig. 4. Rheological parameters (a — yield stress τ_0, b — parameter k, c — parameter n) as a function temperature: 1 — MCCh/MC (H5), 2 — MCCh/IBS (F2), 3 — MCCh/CP/DA (F6) ($5 \cdot 10^{-1}\ s^{-1} < \gamma < 10^3\ s^{-1}$; 35 measuring points)

the rheological parameter n slightly rose in the MCCh hydrogel (H2), MCCh/DS (F1) (Table 4) and MCCh/MC (H5) (Fig. 4c, curve 1). Solutions of chitosan in a weak acetic acid have also been reported to behave as non-Newtonian liquids with the rheological parameter $n < 1$ [13]. The rheological parameter n increases as the temperature is increased. No such dependence was observed for the hydrogel system MCCh/IBS (F2) (Fig. 4c, curve 2). However, for the hydrogel MCCh with the addition of a hydrophilizing substance (H4) (Table 4) and for the complex MCCh/CP/DA hydrogel system (F6) (Fig. 4c, curve 3), the rheological parameter n decreased as the temperature was increased.

The activation energy for the viscous flow (E_a) of the hydrogel systems was determined from the Arrhenius equation

$$\eta = A_0 \exp [E_a/(RT)] \quad (3)$$

where: A_0 *represents the pre-exponential parameter.*

The activation energy is presented (Fig. 5) in relation to shear rate.

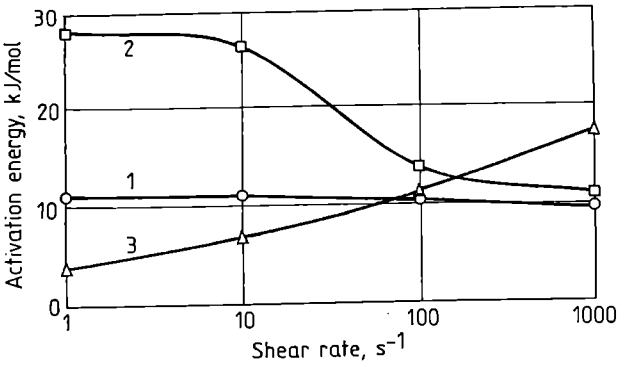

Fig. 5. Activation energy for viscous flow (E_a) in relation to shear rate (γ): 1 — MCCh/MC (H5), 2 — MCCh/IBS (F2), 3 — MCCh/CP/DA (F6)

For most of the present hydrogel systems the apparent viscosity varies with temperature as described by the Arrhenius equation within the limits of experimental error (0.5%). For the complex MCCh/CP/DA hydrogel system (F6), the E_a increases as the shear rate is raised (Fig. 5), because of intermolecular attraction forces. Dolz *et al.* [14] have studied extensively the rheological behavior and thixotropic properties of Carbopol 940 hydrogels at various concentrations and at low shear rates. The rheological parameters $n < 1$ confirm the pseudoplastic behavior of the Carbopol hydrogels. The viscosity of the Carbopol hydrogels decreased markedly as the shear rate was increased particularly at low shear rates [14]. The Carbopol 940 hydrogel containing a therapeutic substance exhibited a decrease in viscosity as compared with the control sample. This decrease is connected with interactions between the drug and the Carbopol 940 hydrogel basis [15].

For the MCCh diluted hydrogel (H1), two compensating effects occurring at elevated temperatures can explain the observed near constancy of E_a with temperature. The first effect includes the decrease of the apparent viscosity of the continuous phase, described by the Arrhenius equation. The second is the rate of structure formation that increases as the continuous phase becomes more liquid and the dispersed particles acquire more energy. The subsequent tendency for viscosity to rise means that the fall in the viscosity of the continuos phase can be more than compensated for by the increase in the suspension viscosity.

For the MCCh hydrogel of a higher polymer content (H2) and for the hydrogel system MCCh/DS (F1) an increase in the shear rate resulted in a decreased apparent viscosity and activation energy for the viscous flow and also of the activation energy for chitosan solutions in acetic acid calculated from the Arrhenius equation [13].

The decrease in E_a as the shear rate is increased indicates to the flexibility of the MCCh polymer chain. Relatively low E_a indicates a small temperature effect on the crucial points of the polymer complex structure. A maximum value of about 28 kJ/mol at very low shear rates for the diluted hydrogel MC (H6) and hydrogel system MCCh/IBS (F2) indicates that the polymer structure is rigid and that temperature affects intermolecular attraction forces.

CONCLUSIONS

The MCCh and MC hydrogels of low polymer contents behave as non-Newtonian shear-thinning liquids without a yield stress, with the power-law parameter $n < 1$. The MCCh hydrogels of higher polymer contents behave as non-linear viscoplastic shear-thinning materials with a yield stress.

The apparent viscosity of the MCCh hydrogel containing a therapeutical substance was found to increase in a year's long storage time. Changes in the apparent viscosity of MCCh hydrogel, induced by the presence of therapeutic substance and by storage time, are suggestive of physicochemical interactions between these substances. The more stable hydrogel systems containing a therapeutic substance were produced by using MCCh hydrogels of higher polymer contents.

In the majority of the hydrogel systems, the effect of temperature on apparent viscosity is described by the Arrhenius equation. Only in the case of the Carbopol 940 hydrogel modified by chitosan, the activation energy for the viscous flow (E_a) increased as the shear rate is increased which is due to the increase in intermolecular attraction forces.

The microcrystalline chitosan as gel-like water dispersion with glycerol, 1,2-propylene glycol and methylcellulose hydrogel added, appears to be the useful vehicle. The high yield stress of this hydrogel system is an advantageous property. This property ensures good spreading and adhesion to the skin surface, which in turn determines uniform distribution of the therapeutic substance.

The results of rheological studies of hydrogel systems suggest a complex nature of the system, which can be pseudoplastic or plastic depending on the kind and content of the polymer and also on the presence of other substances and occurrence of physicochemical interactions between the polymer and these substances.

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