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Modeling of Association Properties of Cetylpyridinium Halides (Cl, Br) and their Influence on Liberation and Rheological and pH Balances of Hydrogels with Ibuprofen

The paper studies the influences of two cationic surfactants – cetylpyridinium chloride (CPCl) and cetylpyridinium bromide (CPBr) – at concentrations 10-times below and 10-times above the CMC – at 25 °C–40 °C on the release of ibuprofen from hydrogels, rheological properties and pH. The association of surfactants in the water solutions was studied by conductometry. It was found that the temperature dependences of the surfactants' CMCs are not linear and the CMCs of CPCl are higher than that of CPBr. The concentrations of the polymer (chitosan) and the drug were kept constant. Amounts of the released drug increased with the increasing temperature. From the hydrogels with CPBr and CPCl, whose surfactant concentration was below the respective CMC, higher amounts of the active ingredient were released than from the hydrogels with surfactant concentrations above the respective CMC. It is shown that for increasing temperature the hydrogels exhibit gradual transition for pseudo plastic to thixotropic system, what is advantageous for their practical application. The hydrogels' pH values were in the interval 5.10–5.46, which is ideal for their application on the skin and for the chitosan swelling. The presented topic is a precondition of synthesis of the on-line and off-line control algorithms of an optimal release kinetics, elaborated by the authors.

Key words: Surfactants, ibuprofen, chitosan, hydrogel, association, release, rheology, pH

Modellierung der Assoziationseigenschaften von Cetylpyridiniumhalogeniden (Cl, Br) und ihr Einfluss auf das rheologische Gleichgewicht, das pH-Gleichgewicht und die Ibuprofenfreisetzung aus Hydrogelen. Der Beitrag untersucht den Einfluss der beiden kationischen Tenside Cetylpyridiniumchlorid (CPCl) und Cetylpyridiniumbromid (CPBr) auf die Freisetzung von Ibuprofen aus Hydrogelen, die rheologischen Eigenschaften und den pH-Wert im Temperaturbereich von 25 °C bis 40 °C. Die Tensidkonzentrationen waren 10-mal niedriger und 10-mal höher als die CMC. Die Assoziation der Tenside in den wässrigen Lösungen wurde mittels Konduktometrie untersucht. Es wurde festgestellt, dass die Temperaturabhängigkeit der CMCs der beiden Tenside nicht linear ist und die CMCs von CPCl höher sind als die von CPBr. Die Konzentrationen von Polymer (Chitosan) und Wirkstoff (Ibuprofen) wurden konstant gehalten. Die Mengen des freigesetzten Wirkstoffs nahmen mit steigender Temperatur zu. Aus den Hydrogelen mit CPBr und CPCl, deren Tensidkonzentration unterhalb der jeweiligen CMC lag, wurden höhere Mengen des Wirkstoffes freigesetzt als aus den Hydrogelen mit Tensidkonzentrationen oberhalb der jeweiligen CMC. Es zeigt sich, dass die Hydrogele bei steigender Temperatur einen graduellen Übergang vom pseudoplastischen zum thixotropen System zeigen, was für ihre praktische Anwendung vorteilhaft ist. Die pH-Werte der Hydrogele lagen im Bereich von 5,10–5,46, was sowohl für ihre Anwendung auf der Haut und als auch für die Chitosan-Quellung ideal ist. Das vorgestellte Thema ist eine Voraussetzung für die Synthese der Online- und Offline-Kontrollalgorithmen einer optimalen Freisetzungskinetik, die die Autoren ausgearbeitet haben.

Stichwörter: Tenside, Ibuprofen, Chitosan, Hydrogel, Assoziation, Freisetzung, Rheologie, pH

1 Introduction

The thermodynamically driven self-assembly of amphiphilic molecules into mesomorphic structures has been the object of intensive studies [1–3]. Surfactants have widespread applications in the emulsification for micellar-enhanced ultrafiltration for tracing contaminants from waste water [4]. The micelles are used as drug delivery agents [5, 6] and are similar to biomembranes, proteins, liposomes and enzymes [7, 8], dosage forms, disinfectants, antiseptics, emulsifiers [9, 10]. Cationic surfactants proved to be excellent carriers for the drug delivery [11]. They are also widely utilized in various industries [12]. Besides, the study of thermodynamic and aggregation properties of the drugs in solutions provide an invaluable source of knowledge that is used in pharmaceutical applications. The experimental data obtained by conductometric measurements can be utilized for the evaluation of various parameters that are discussed in terms of drug-drug, drug-water, and drug-surfactant interaction [5].

Nowadays, many research teams devote to the preparation of new biomaterials that may help to healing cutaneous wounds. In accordance with [13] the reasons for their wide use are:

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- Owing to their three-dimensional hydrophilic and polymeric structures they can adsorb liquids on the body surface.
- Due to their large water content they maintain the wettability of wound sites.
- They simulate structures of natural living tissues, which accelerates tissue formation and enhances of wound healing.

Hydrogels as dosage forms consist of a gel-forming material (polymer-natural or synthetic), and drug and auxiliary substances (often surfactants). During the last two decades the natural polymers have been substituted by synthetic ones, which have a longer lifetime, a high absorption of water and a high strength. Fortunately, the synthetic polymers have well defined structures, which can be modified to ensure good disintegration and function [14].

It was found [15] that the release from the semi-solid dermatological hydrogels can be determined by the evaluation of three factors: the properties of the active agent, the kind of vehicle and interactions between the active agent and vehicle.

Ibuprofen (Fig. 1a) is the first of the approved derivatives of propionic acid that is used as a nonsteroidal anti-inflammatory drug (NSAID). It is indicated for the relief of the inflammations and some diseases like headache, kinesialgia, toothache, rachialgia etc. [16, 17].

Chitosan (poly-D-glucosamine) is a natural polymer prepared either by chemical deacetylation with sodium hydroxide or enzymatic deacetylation by N-deacetylase [18]. It has special properties for use in the pharmaceutical, biomedical, food industry, health and agriculture due to biocompatibility, biodegradability and non-toxic nature. However, the high molecular weight and poor solubility at neutral pH limit its industrial applications [19, 20]. When the chitosan bonds with the drug, a macromolecular prodrug conjugate is formed that enters the cell by endocytosis. This supports the drug transport to the target cells and maintains a suitable drug concentration from a carrier. There were described antibacterial, antitumor and antioxidant properties of the chitosan as such and also of it's modified forms [20].

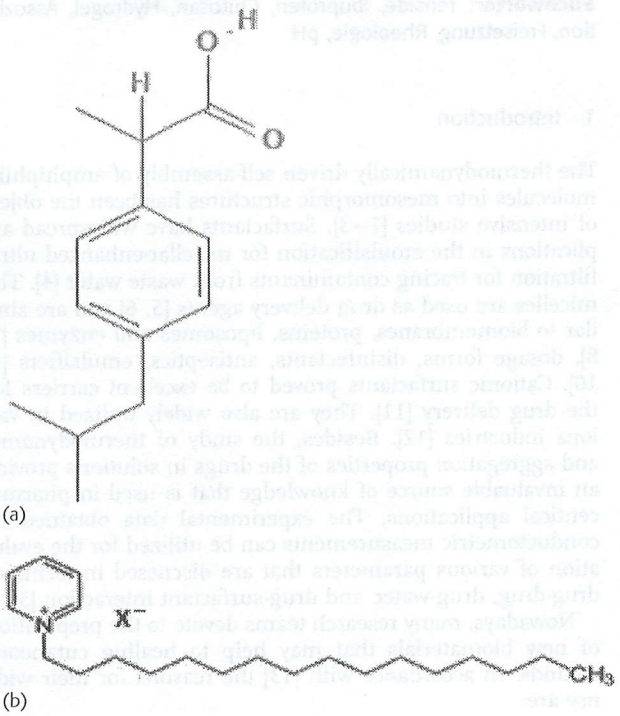

Figure 1 a – structure of ibuprofen, b – structure of studied surfactants, X^- stands for Cl^- or Br^-

Based on this knowledge the authors have decided to analyze of the micellar properties of cationic surfactants, namely cetylpyridinium bromide and chloride in water solutions in the temperature range 25 °C–40 °C. The results obtained from associative (in particular conductometric) studies of the chosen alkylpyridinium halogenides we use in the preparation of hydrogels containing the macromolecular substance – chitosan, the *non-steroidal* anti-inflammatory – ibuprofen and the surfactants at concentrations, which are the 10-times higher and 10-times lower than their CMC values. The preparation of hydrogels is described in [22]. The obtained results serve for decisions on the suitability of hydrogels for dermatological use.

2 Experimental

2.1 Chemicals

The hydrogels were composed from chitosan (CHIT, M_r = 190 000–375 000 g/mol (Sigma Aldrich Chemie GmbH, Germany)), ibuprofen (RS)-2-[4-(2 methylpropyl) phenyl] propane acid, (Merck Chemical Company, Germany, see Fig. 1a), two cationic surfactant – hexadecyl pyridinium chloride and hexadecyl pyridinium bromide (see Fig. 1b), lactic acid solution (LA Merck Chemical Company, Germany) and redistilled water (as solvent). The basic characteristics of surfactants can be found in [21].

2.2 Instruments and measurements methods

2.2.1 Determination of the CMC

– Conductivity

The conductivity was measured by conductometric titration in the temperature range 25 °C–45 °C (conductometer Ino Lab, Germany) with double conductivity cell and platinum electrode (cell constant K = 0.474 cm^{-1}). Precision of the measurements was ± 0.01 μS cm^{-1}. The systems were continually stirred and thermostated by a thermostat (JULABO 5E, Swiss) the precision was ± 0.1 °C.

– Spectrophotometry

The absorbance (*A*) of the hydrogel solutions was measured by UV VIS spectrometer (Hewlett Packard 8452A (diode array)). Redistilled water was used as a blank.

– Preparation of hydrogels

The mass concentration of chitosan in hydrogels was constant (W = 2.5 %). Lactic acid of the mass concentration W = 1 % was used for the neutralization of the hydrogels. The measurements were done in absence and in presence of surfactants. The surfactant concentration was above and below of the CMC repectively. In the hydrogels mass concentration of the drug-ibuprofen was constant at W = 0.1 %. The masses of surfactants in hydrogels at the different temperatures are summarized in Table 1.

T/°C	Mass of CPCl/g			Mass of CPBr/g		
	at CMC	below CMC	above CMC	at CMC	below CMC	above CMC
25	0.0168	0.00168	0.1680	0.0146	0.00146	0.1460
30	0.0176	0.00176	0.1760	0.0148	0.00148	0.1480
35	0.0185	0.00185	0.1850	0.0152	0.00152	0.1520
40	0,0201	0.00201	0.2010	0.0165	0.00165	0.1650

Table 1 Masses of surfactants in hydrogels at different temperatures

– In vitro release

The *in vitro* release experiments are described in detail in the reference [22]. Conditions of the experiment were the following: $T = 25\,^{\circ}C - 40\,^{\circ}C$, in 1.0 cm cuvettes at $\lambda_{max} = 224$ nm, specific absorption coefficient ($A^{1\%}_{1cm} = 354$).

– Rheological properties of hydrogels

We used the rotating viscometer (Viscotester VT 500, Germany). The outer stationary cylinder was filled up to the lubber line with the hydrogel and the inner cylinder was inserted. The system was kept at the temperature (25 °C–40 °C). The system has 20 speed degrees that indicated the revolutions of the inner cylinder. The measurement started ascending from the smallest until the highest degrees and the rotating moment M_d was readout at the every degree. After reaching the highest degree, the measurement continued in descending way.

Rheological measurements were done 24 h after the sample preparation. From the obtained values the basic rheological parameters were calculated: the shear strain (τ), speed gradient (D), and dynamic viscosity (η). Finally the rheograms τ-D were constructed. The expressions used for calculation of rheological parameters:

$$\tau = \frac{M_d f}{10} \quad (1)$$

M_d is a torque [N cm], f is a factor of the system ($f = 3754$)

$$D = \frac{Mn}{1\,000} \quad (2)$$

M is a system factor ($M = 1\,290$), n means the revolutions [min^{-1}]

$$\eta = \frac{\tau}{D} \quad (3)$$

where η is in [Pa s].

3 Results and Discussion

3.1 Critical micelle concentration

To analyze the influences of the counter ion and the temperature (25 °C–40 °C) on the CMC, we studied two cationic surfactants (hexadecyl pyridinium chloride and hexadecyl pyridinium bromide) by conductometry. The critical micelle concentration is established by the intersection of the two straight lines of the conductivity (κ) *vs.* molarity (c) plots. The obtained CMCs are in good agreement with the results of other authors [23–25] and they are summarized in Fig. 2a.

Galán at all. [23] also studied tetradecyl pyridinium chloride (CPCl) and tetradecyl pyridinium bromide (CPBr) and they presented the table of CMCs of alkylpyridinium halides with the number of carbon atoms in the alkyl chain $N_C = 8–15$ at 25 °C. We have completed those results with the CMCs for $N_C = 16$. The dependences ln CMC *vs. Nc* of the both CPCl and CPBr are graphically presented by the straight lines (Fig. 2b). We have established the CMCs of these surfactants for $N_C = 16$ and, as it can be seen, all values lie on the straight lines.

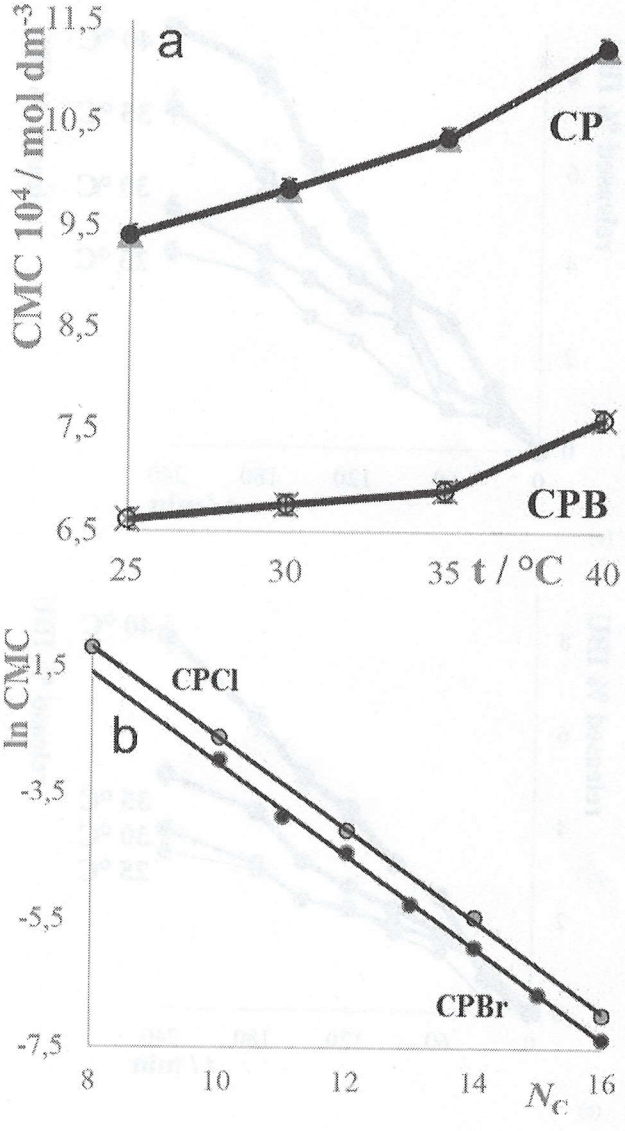

Figure 2 a – CMC as function of temperature of studied surfactants; b – ln CMC as function Nc of alkylpyridinium halides at 25 °C

Let us remark that CMCs of ionic surfactants are influenced not only by the temperature but also other factors like their structure, additives, solvent, pressure and others.

The obtained values of CMC were used for preparation of hydrogels containing gel creation base – chitosan W = 2.5%), drug – ibuprofen (W = 1%), and surfactants at concentration which are 10-times higher and 10-times lower than their CMCs (see Table 1).

3.2 Liberation balances

Liberation dependences of ibuprofen at 25 °C–40 °C are summarized in Fig. 3.

From Fig. 3 follows that the mass percentages of ibuprofen released from hydrogels having a surfactant concentration that is below the CMC concentration is higher than the release from a hydrogel having a surfactant concentration above CMC. The same applies to hydrogels with CPBr, which released a higher amount of ibuprofen than the CPCl-containing hydrogels. Such a behavior can be attributed to the relatively high value of the CMC (Fig. 2a) and also to the hydration radii of the two anions of the surfactants. The amount of the drug released from the hydrogels was small (not more than 9.0%). Ganje et al. [26] proposed to evaluate the kinetic parameters of the drug release using some models presented in the following text.

– Zero order model (model 1)

Basic formula:

$$c = k t \tag{4}$$

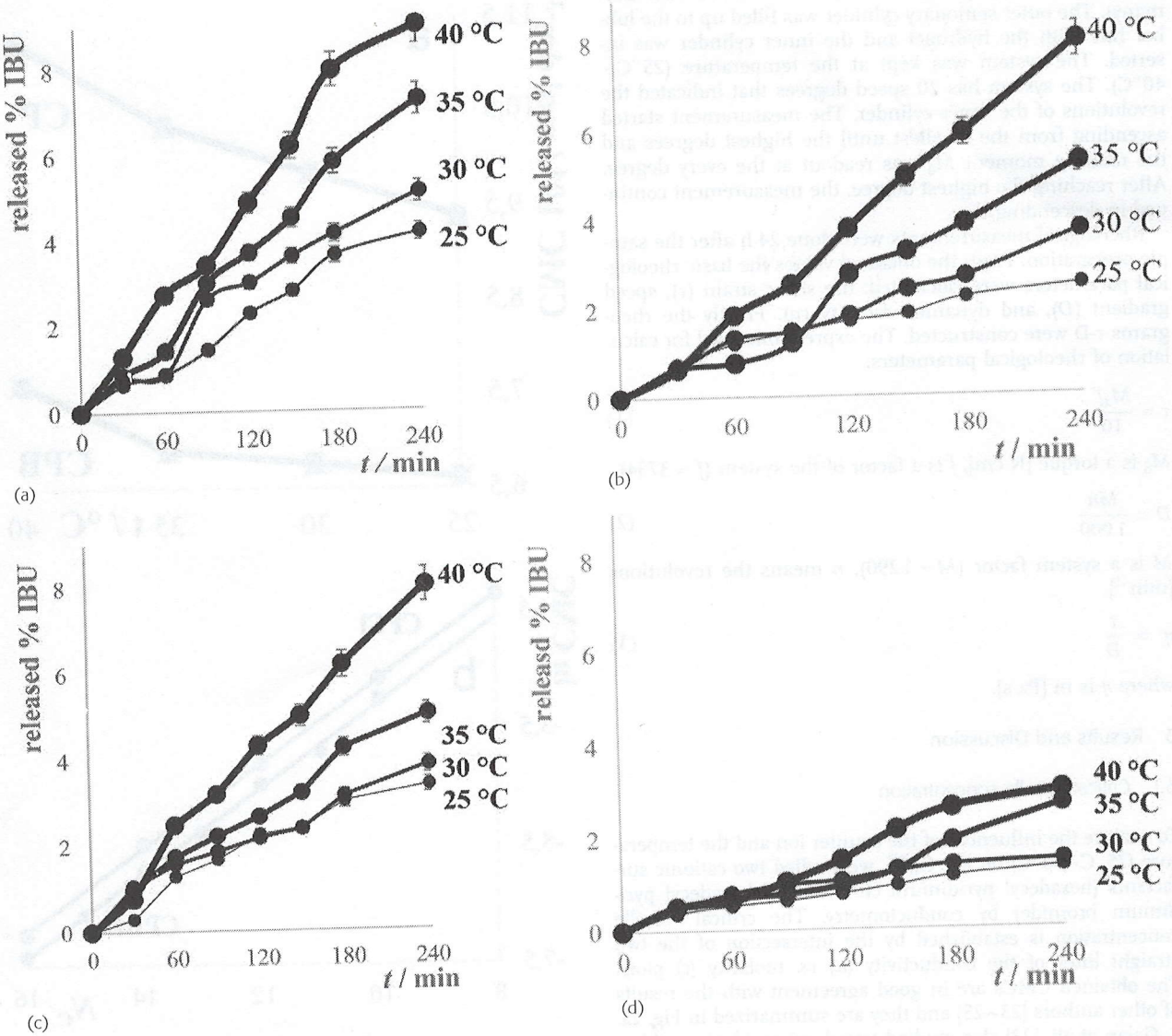

Figure 3 Cumulative amounts of released ibuprofen from prepared hydrogels with surfactant CPBr. **a** – below CMC, **b** – above CMC and with surfactant CPCl **c** – below CMC, **d** – above CMC

where c is the amount of the released ibuprofen in time t. Values of k and coefficient of correlation r of prepared hydrogels are summarized in the Table 2.

The values of k for zero order model are higher for hydrogels with the surfactant CPBr than with CPCl. They are also for systems with concentration of surfactants below CMC than above CMC. Values of correlation coefficients are sufficiently high.

– First order model (model 2)

Basic formula:

$$\mathrm{Ln}\, c = k t \qquad (5)$$

Values of k and r of the prepared hydrogels are summarized in the Table 3.

From the Table 3 one can deduce the same trend of the increasing values of k, but the values of correlation coefficients are lower than those shown in the Table 2. This indicates that the first order model is not sufficiently suitable for description of the drug release from hydrogels.

– Higuchi's model (model 3)

Basic formula:

$$C = k t^{0.5} \qquad (6)$$

Values of parameters k and r of the prepared hydrogels are summarized in the Table 4.

$(k \pm s) \cdot 10^3$/% min^{-1}					
T/°C	Hydrogels without surfactant	Hydrogels with CPBr		Hydrogels with CPCl	
		below CMC	above CMC	below CMC	above CMC
25	12.8 ± 1.01 r = 0.981	18.3 ± 1.10 r = 0.991	9.7 ± 1,10 r = 0.963	14.7 ± 1.30 r = 0.977	5.2 ± 0.40 r = 0.985
30		22.2 ± 1.70 r = 0.981	14.50 ± 0.70 r = 0.993	15.0 ± 1.20 r = 0.981	5.7 ± 0.80 r = 0.939
35		31.2 ± 1.10 r = 0.995	22.7 ± 1.50 r = 0.986	20.5 ± 1.00 r = 0.991	10.2 ± 1.00 r = 0.972
40		40.2 ± 1.60 r = 0.996	33.5 ± 0.80 r = 0.997	34.30 ± 1.40 r = 0.995	13.1 ± 0.80 r = 0.987

* Standard deviation

Table 2 Calculated values of k and r for the released ibuprofen from hydrogels according to zero order model at the different temperatures

$(k \pm s) \cdot 10^3$/min^{-1}					
T/°C	Hydrogels without surfactant	Hydrogels with CPBr		Hydrogels with CPCl	
		below CMC	above CMC	below CMC	above CMC
25	7.7 ± 1.40 r = 0.926	9.5 ± 1.25 r = 0.958	5.3 ± 0.83 r = 0.942	5.4 ± 0.81 r = 0.948	3.9 ± 0.85 r = 0.956
30		9.8 ± 1.65 r = 0.936	7.6 ± 1.04 r = 0.956	5.9 ± 0.56 r = 0.977	4.5 ± 0.76 r = 0.936
35		10.1 ± 1.58 r = 0.943	9.1 ± 1.00 r = 0.943	7.4 ± 0.94 r = 0.961	6.0 ± 1.04 r = 0.881
40		11.4 ± 1.21 r = 0.963	10.5 ± 1.91 r = 0.931	9.3 ± 1.09 r = 0.917	7.2 ± 1.10 r = 0.940

Table 3 Calculated parameters of released ibuprofen from hydrogels according to the first order model at different temperatures

$(k \pm s) \cdot 10^3$/mol dm^{-3} min$^{-1/2}$					
T/°C	Hydrogels without surfactant	Hydrogels with CPBr		Hydrogels with CPCl	
		below CMC	above CMC	below CMC	above CMC
25	12.4 ± 0.67 r = 0.976	18.7 ± 1.07 r = 0.981	8.3 ± 0.31 r = 0.986	10.7 ± 0.87 r = 0.989	4.1 ± 0.34 r = 0.986
30		23.1 ± 0.98 r = 0.980	14.0 ± 1.30 r = 0.983	13.0 ± 1.30 r = 0.980	4.7 ± 0.24 r = 0.990
35		32.0 ± 1.00 r = 0.980	23.8 ± 1.80 r = 0.980	19.7 ± 1.60 r = 0.984	7.5 ± 0.97 r = 0.980
40		40.5 ± 1.63 r = 0.986	34.9 ± 1.99 r = 0.989	31.6 ± 1.30 r = 0.980	9.8 ± 1.04 r = 0.987

Table 4 Calculated parameters of released ibuprofen from hydrogels according Higuchi's model at different temperatures

Correlation coefficients in the Table 4 are sufficiently high for all liberation experiments. The least of them is 0.980. This indicates suitability of the Higuchi's model for study of the drug liberation from the prepared hydrogels.

– Pseudo-first order model (model 4)

Basic formula for calculation:

$$kt = -\ln\frac{c_{sat} - c_t}{c_{sat}} \quad (7)$$

where c_t is a concentration in time t, c_{sat} is a saturated concentration, k is a rate constant [27].

Values of k and r of the prepared hydrogels are summarized in the Table 5.

From Tables 2–5 can be concluded, that for increasing the temperature of the hydrogels the rate constants of the drug liberation are also increasing. This is in conformity with the theory of the temperature influence on the rate of processes. The highest values of correlation coefficients are in the tables of the mathematical models 3 and 4. Therefore, the rate constants from the Table 4 were used for calculation of activation energies of the release. The calculation was done in accordance with the expression:

$$k = Ae^{-\frac{E}{RT}} \quad (8)$$

The symbol A is a pre-exponential factor, T is thermodynamic temperature in Kelvins, R is molar gas constant. Dependences $\ln k = f(1/T)$, which are linear, were used for calculation of the activation energy. Calculated activation energies are summarized in the Table 6.

Activation energies of the drug liberation from hydrogels are higher for the systems with the concentration of surfactants above their CMCs. The highest value was reached for hydrogels with the concentration of the surfactant CPBr below CMC.

3.2 Rheological properties

Interaction between hydrogels and the drug can be easily determined by measuring of the viscosity of hydrogels. The obtained flow curves (dependences of the shear stress – τ *vs.* the rate of shear – D) for the prepared hydrogels are shown in Fig. 4.

One may observe (Fig. 4) the gradual transition of the time independent non-Newtonian pseudo plastic systems to the time-dependent thixotropic (or rheopexic) due to the increased temperatures of experiments. The temperature decreases the shear stress (τ) of the prepared hydrogels. The linear dependence of the shear stress on the temperature appears for the highest values of the rate of shear D. Therefore, the dependences $\tau = f(D_{max})$ have their correlation coefficients in the range $r = 0.983–0.996$. In accordance to [15, 28] the mutual interaction between the hydrogel and the drug may be expressed by the equation

$$\tau = \tau_0 D^n \quad (9)$$

where τ_0 is the shear stress at $D = 0$, the D is the rate of shear and n is a constant characterized the type of the flow. The calculated value of n is in the interval 0.483–0.532, and τ_0 is from interval 11.66–17.37 Pa and thus the differences between them can be neglected.

3.3 pH measurements

The last experiment consists in the establishing pH of the prepared hydrogels. The obtained values of pH are in the range 5.10–5.46, that is ideal for their application on the skin (pH = 4.50–6.70). These values of pH are also suitable for the preparation of hydrogels with chitosan, which is used as the hydrogel base.

4 Conclusions

The association, liberation, rheological and pH balances of two cationic surfactants with the same cationic group – alkylpyridinium and different anionic group – halides chloride (CPCl) and bromide (CPBr) were studied in the temperature range 25 °C–40 °C.

The plots CMC vs. temperature are increasing non-linear functions and for CPCl they are higher in comparison to CPBr. That can be explained by the sizes of the ions (Br > Cl) and by hydration layer around the ions.

Hydrogels	$(E \pm s)$/kJ mol^{-1}
CPBr below CMC	44.88 ± 2.99
CPBr above CMC	76.77 ± 3.32
CPCl below CMC	51.15 ± 4.16
CPCl above CMC	52.72 ± 4.45

Table 6 Activation energy of drug liberation from hydrogels

$(k \pm s) \cdot 10^3$/mol dm^{-3} min^{-1}					
T/°C	Hydrogels without surfactant	Hydrogels with CPBr		Hydrogels with CPCl	
		below CMC	above CMC	below CMC	above CMC
25	0.12 ± 0.011 r = 0.980	0.18 ± 0.015 r = 0.989	0.08 ± 0.006 r = 0.986	0.12 ± 0.016 r = 0.989	0.04 ± 0.002 r = 0.996
30		0.23 ± 0.018 r = 0.992	0.14 ± 0.008 r = 0.993	0.14 ± 0.016 r = 0.989	0.05 ± 0.005 r = 0.990
35		0.32 ± 0.014 r = 0.995	0.24 ± 0.015 r = 0.986	0.20 ± 0.010 r = 0.993	0.09 ± 0.010 r = 0.981
40		0.42 ± 0.021 r = 0.993	0.35 ± 0.008 r = 0.998	0.38 ± 0.020 r = 0.992	0.13 ± 10.011 r = 0.989

Table 5 Parameters for released of ibuprofen form hydrogels according pseudo-first order model at different temperatures

4.1 Liberation balances

The amounts of ibuprofen released from the hydrogels with CPBr are higher than the amount released from the hydrogels with CPCl. If the surfactant concentration is below the CMC, a larger amount of the drug permeates through the semipermeable membrane than above the CMC. This is because in the latter case the drug is trapped in the micelles. The release rate constants from the hydrogels investigated are also higher in the systems with a surfactant concentration below the CMC concentration. To evaluate the experiments, the rate constants of drug release from hydrogels were calculated using four kinetic models. Based on this one can conclude that the release kinetics fits to the Higuchi's model and/or the pseudo first-order model. The reason for this is that the concentration approaches its saturation values, the rate of its increase decreases. The models are necessary parts of the compartment models used within the frame of synthesis of optimal control algorithms of the drug delivery.

4.2 Rheological properties

All evaluated hydrogels exhibit non-Newtonian pseudo-plastic flow that transits into tixoplastic flow if the temperature increases. The coefficient n characterizes the type of the hydrogel flow. The differences between hydrogels' pHs are not statistically significantly influenced by the temperature. The measured values of pH were within the interval 5.10–5.46.

In the end it is worth noting that the knowledge extracted from the experiments performed here is inevitable for optimization of dosage forms. The sense of the optimization is to find the release kinetics which keeps the drug concentration close to the middle of the therapeutic window and, at

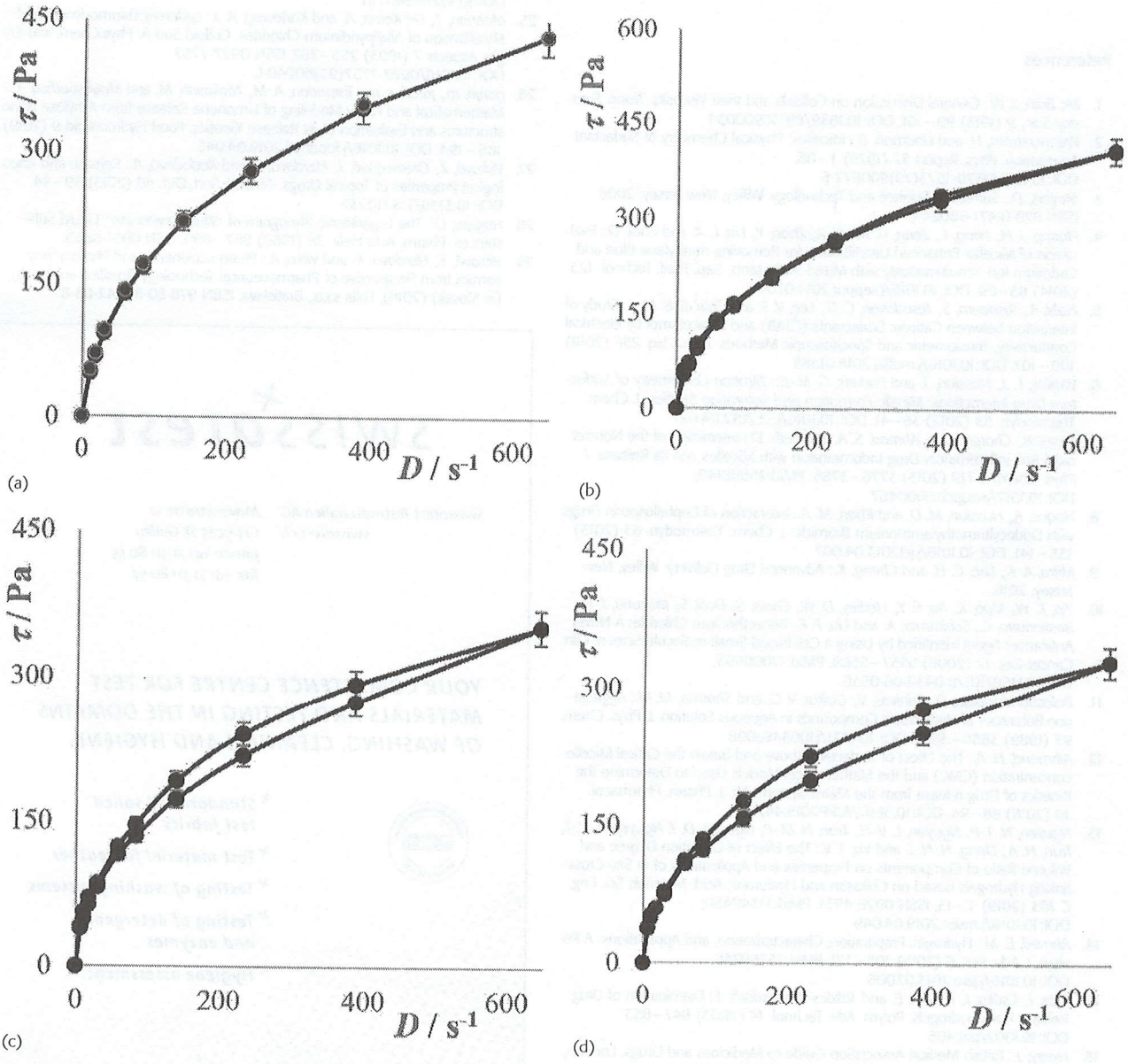

Figure 4 Rheological dependences $\tau = f(D)$ for hydrogels with CPBr (above CMC) at different temperatures: a – 25 °C, b – 30 °C, c – 35 °C, d – 40 °C

the same time, secures an optimal therapeutics effect. To this end the authors possess all relevant *in-vivo* data of the drug ibuprofen. Therefore, the team's research activity is now focused on the incorporation of all here obtained findings into appropriate models, both the deterministic and statistic pharmacokinetic models and the pharmacodynamic E_{max} model so as to be able to predict of the optimal release kinetic. That knowledge is a prerequisite of the development of an *on-line/off-line* automatic control of the release kinetics for reaching the desired therapeutic effect. This is a main incentive of this research. See also [29, 30].

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