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AUXILIARY SUBSTANCES AND APPLICATIVE PROPERTIES OF MODEL DENTAL GELS WITH KETOPROFEN AND THERAPEUTIC SALINE

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Abstract: The aim of the study was to produce a model form of a drug of anti-inflammatory activity designed for application in oral cavity. An attempt was made to choose hydrogel vehicle which would ensure not only high pharmaceutical availability of the therapeutic agent but appropriate rheological properties of the drug as well. Variant prescriptions with ketoprofen were worked out which differed in the kind of the used vehicle (xanthan gum, guar gum, hydroxyethylcellulose, carboxymethylcellulose sodium salt). Introduction of polyelectrolyte solution of therapeutic salts in the form of iodic-bromic-boronic saline into the composition of the preparation aimed at not only optimizing the hydrogel therapeutic activity but also at increasing ketoprofen pharmaceutical availability. The process of ketoprofen release is most effective from a model form of a drug with cellulose derivatives (CMC-Na and HEC) being the hydrogel vehiculum in the quantity ratio 1:1. It is a system demonstrating appropriate rheological properties such as: low value of yield stress and structural viscosity, insignificant water loss at 37^{o}C and good extensibility.

Keywords: dental anti-inflammatory hydrogels, ketoprofen, saline, pharmaceutical availability, rheology

In paradontal diseases there comes to shifts in microelement composition of tooth hard tissue (enamel, dentin), tissues surrounding the tooth, as well as in saliva and blood serum (1, 2). In the course of paradontitis, calcium, magnesium, sodium and phosphorus are mainly taken into account, the content of which in the gingival tissue is different in the course of the disease from that in the healthy tissue (3).

The soothing effect of therapeutic salts on inflammatory process in paradontium is associated with the content of mineral components affecting the healing process of pathologically changed soft tissue. Salines, polyelectrolyte solutions of therapeutic salts rich in magnesium, calcium, iron, bromine and also iodine which has a local disinfecting and bactericidal activity, have a beneficial effect (4). Besides all advantages resulting from the content of the mentioned mineral components, salines have antiseptic function. It is the influence of sodium chloride which in low concentrations has strong osmotic activity and does not decrease surface tension. Therapeutic salts have been demonstrated to increase salivation, which limits indirectly formation of bacterial dental plaque and dental calculus considered to be the main etiological factors of paradontosis (5-7).

The assumption of the undertaken study was to work out a model drug in the form of dental hydrogel of potential anti-inflammatory activity. Ketoprofen was suggested as basic therapeutic agent, which through blocking prostaglandins production, characteristic for nonsteroidal anti-inflammatory drugs, may inhibit gingivitis and decrease advancing bone destruction (8, 9). Introduction of polyelectrolyte solution of saline type into the preparation composition aimed at not only optimizing the hydrogel therapeutic activity but also at increasing ketoprofen pharmaceutical availability.

An attempt was made to select, from among variant prescriptions, an optimal hydrogel composition, which would provide not only high pharmaceutical availability of ketoprofen but also appropriate rheological properties of the drug form affecting its applicative properties.

EXPERIMENTAL

Materials

– Ketoprofen, Sigma-Aldrich Chemie GmbH, Germany;
– natural iodic-bromic-boronic saline „Zabłocka Mgiełka", Mine and Saltworks Lokal-Serwis Ltd, Dębowiec, Poland;

– xanthan gum, Sigma-Aldrich Chemie GmbH, Germany;
– guar gum, Sigma-Aldrich Chemie GmbH, Germany;
– carboxymethylcellulose sodium salt, Fluka Chemie GmbH, Switzerland;
– hydroxyethylcellulose, Fluka Chemie GmbH, Switzerland;
– Rofam R-15, Chemical Plant Rokita in Brzeg Dolny, Poland;
– Methyl hydroxybenzoate – Nipagine P, Fluka Chemie GmbH, Switzerland.

Preparation of anti-inflammatory hydrogels for application on oral cavity mucosa

Prescription of model preparations:

ketoprofen (K)	0.75
saline	32.25
gelating component *	3.00
Rofam R-15	1.00
Nipagine M	0.10
Nipagine P	0.10
water	to 100.00

* preparations of the same composition differed with the kind of the applied gelating component.

The following hydrogels were produced:
– with xanthan gum (XG),
– with xanthan gum (XG) and guar gum (GG) in the ratio 9:1,
– with carboxymethylcellulose sodium salt (CMC-Na),
– with hydroxyethylcellulose (HEC),
– with carboxymethylcellulose sodium salt (CMC-Na) and hydroxyethylcellulose (HEC) in the ratio 1:1.

Determination of model hydrogels pH (a_{H^+}) (10)

The measurement was performed through direct immersion of ERH-131 electrode connected with pH-meter N5 170 E (Production Plant of Physicochemical Apparatus Elements, Hydromet Gliwice, Poland) in hydrogel samples of the same weight. The pH value was read 0.5 min after the electrode immersion.

Testing the kinetics of therapeutic agent (ketoprofen) penetration from model hydrogels to dialysis fluid

Testing ketoprofen pharmaceutical availability was performed by membrane method with a plastic container (modified Mutimer et al. apparatus). The niche of the apparatus was filled with 25 g of hydrogel fixed with earlier prepared tomofan dialysis membrane (24 h exposure in double distilled water). The rate of mass exchange was investigated with spectrophotometric method (Nicolet Evolution 300 spectrophotometer, version 1.0, Spectro-Lab, England) by determination of quantity of ketoprofen diffusing into the dialysis fluid (double distilled water) at equal time intervals. Approximation equation at $p = 0.05$ and $r \geq 0.9998$: $A = 0.6411\ c + 0.0430$, with which the dependence between absorbance (A) and therapeutic agent concentration (c) was described, transformed to the form: $c = A - 0.0430/0.6411$ enabled to determine the amount of ketoprofen diffusing through the phase boundary in the time function t (min).

Determination of viscosity parameters of the tested hydrogels (11, 12)

Viscosity determinations of hydrogels were performed at 37°C with cone-plate digital rheometer (Brookfield, DV-III, version 3.0, USA) connected with bath thermostat PGW E-1 (Medingen, Germany).

Extensibility tests of model hydrogels (13)

The determination of model hydrogels extensibility was performed with an extensometer at 25 ± 0.1°C.

Determination of the rate of water loss from model hydrogels (14)

The determination of the rate of water loss was performed from the surface of glass plates (Petri dish) of 58 mm diameter, which were covered with uniform layer of hydrogel. The plates were placed in a thermostat at 37 ± 0.1°C with gravitational air circulation and the sample mass was determined after every 15 min.

RESULTS AND DISCUSSION

Estimation of model hydrogels pH and ketoprofen pharmaceutical availability

Hydrogels with CMC-Na demonstrated the highest pH (a_{H^+}). The value of pH of the preparation containing only CMC-Na was 5.23, whereas of that containing CMC-Na and HEC – 5.04. The values obtained for other hydrogels were < 5.

Forming a system of defined pH, the prescription components of hydrogels affect the degree of ketoprofen dissociation and thus the process of its release. Taking into account that ketoprofen pK_a is 5.94, it may be anticipated that the process of mass exchange on the phase boundary will be most effective from hydrogels with CMC-Na and with CMC-Na and HEC (15). In the case of hydrogels of pH (a_{H^+}) ≤ 4.75, a decrease of the degree of equilibrium dissociation of ketoprofen would cause a decrease of

the quantity of ionized molecules and thus, a decrease of pharmaceutical availability of the therapeutic agent.

Figure 1 demonstrates an example of the kinetics of ketoprofen release (with standard deviations) from hydrogel with xanthan gum.

The results which were an arithmetical mean of three measurements were subjected to statistical analysis with Statistica 5.1 G (Windows 97) and regression was determined with the method of the least squares. The determined types of regression equation at the level of significance p = 0.05, had high values of correlation coefficients ($r > 0.9507$ at r_{max} + 9931 for n = 10) proving strict correlation between the analyzed variables.

The dependence of the quantity of ketoprofen diffusing in time function (t) from all the tested hydrogels was described with regression equations: $y = a + bx$ and $\lg(y) = a\lg(x) + b$ (logarithmic form of an exponential equation $y = ax^b$). The equation of the type $y = a + bx$, after integration, was the base for calculating the areas P (expressed in conventional units (c.u.)) under ketoprofen release curves. Results of the calculations are presented in Table 1.

The largest areas under ketoprofen release curves were obtained for hydrogels with the highest pH (a_{H^+}) (> 5), that is for the system with CMC-Na and with CMC-Na + HEC.

Considering the above results, attention should be paid to the fact that in a definite equilibrium ketoprofen sodium salts can be formed which results from high content of sodium chloride in saline. High effectiveness of the release of therapeutic agent from hydrogels containing CMC-Na may be associated with compatibility of sodium ion (Na^+) derived from carboxymethylcellulose with ketoprofen sodium salt. In this case, high electrophoretic mobility of sodium ion (Na^+) and the salt formed with its share will affect the quantitative course of the process of mass exchange on phase boundary.

High coefficients of line correlation equation of the type $y = ax + b$ prove that the process of ketoprofen diffusion from hydrogels to the external compartment is in accordance with zero-order kinetics. Precise kinetic equations based on the analysis of the process of diffusion are usually quite complex and in a majority of cases are the sum of exponential functions (16).

Estimation of model hydrogels rheological properties

Viscosity measurements enabled to determine flow curves (the dependence of shear stress on shear rate) of the produced systems, which is presented in Figure 2.

All the tested systems are viscoelastic liquids having experimentally determined yield stress. It is the value of shear stress below which the system behaves like an elastic solid body. Having reached a certain threshold shear stress, the structure of the

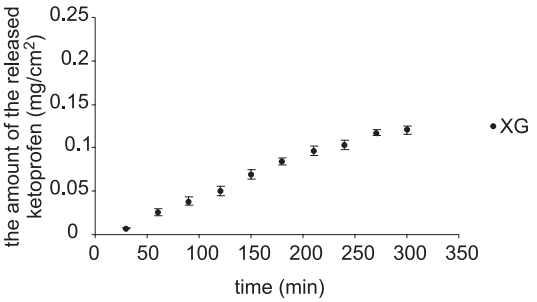

Figure 1. Kinetics of ketoprofen release from model hydrogel produced on the base of xanthan gum.

Table 1. Regression equations describing the rate of ketoprofen release from model hydrogels to dialysis fluid.

Name of model preparation	Type of equation	Correlation equation coefficient		Correlation coefficient	Area (c.u)
		a	b	r	
XG	$y = ax + b$ $\lg(y) = a\lg(x) + b$	$4.3118 \cdot 10^{-4}$ 1.1766	$0.6001 \cdot 10^{-4}$ -3.7621	0.9929 0.9888	19.21
GK+GG	$y = ax + b$ $\lg(y) = a\lg(x) + b$	$4.6440 \cdot 10^{-4}$ 1.2815	$-30.1067 \cdot 10^{-4}$ -3.9877	0.9929 0.9862	19.88
CMC-Na	$y = ax + b$ $\lg(y) = a\lg(x) + b$	$7.6127 \cdot 10^{-4}$ 1.3656	$-199.6000 \cdot 10^{-4}$ -4.0298	0.9915 0.9800	28.53
HEC	$y = ax + b$ $\lg(y) = a\lg(x) + b$	$3.3066 \cdot 10^{-4}$ 0.9635	$56.7340 \cdot 10^{-4}$ -3.3521	0.9898 0.9635	16.26
CMC-Na +HEC	$y = ax + b$ $\lg(y) = a\lg(x) + b$	$3.0339 \cdot 10^{-4}$ 0.5618	$376.00 \cdot 10^{-4}$ -2.2843	0.9560 0.9874	23.67

Table 2. Parameters of Casson's model determined for model hydrogels produced on different vehicles.

Name of model preparation	Plastic viscosity (mPa·s)	Yield stress (N/m^2)	Confidence of fit (%)
XG	3238	33.7	95.9
XG+GG	2903	32.1	94.7
CMC-Na	1858	43.8	86.1
HEC	7639	1.6	92.0
CMC-Na +HEC	6851	10.2	91.6

system is rapidly and totally destroyed and it starts to flow like viscous liquid (17, 18).

Yield stress was determined by describing shear stress – shear rate dependence in the form of a flow curve by Casson's mathematical model (using Rheocalc for Windows program) (Table 2). It is a rheological model recommended for the description of flow curves of non-linear viscoelastic liquids (19).

Low values of yield stress were noted for model drug forms with hydroxyethylcellulose. Slight pressure caused exceeding of the threshold value and flow of the system, which allowed to predict that these preparations would not stay long on the surface of their application. *In vivo* hydrogels with HEC spread easily on the pathologically changed tissue, which contributed to the increase of the area of therapeutic agents diffusion (ketoprofen, therapeutic salts) and caused the increase of their pharmaceutical availability.

The highest value of yield stress was observed for a model hydrogel with carboxymethylcellulose sodium salt, which proved very condensed contact of dispersed molecules and rigid structure of the formed system. Also a preparation, the prescription of which was based on xanthan gum, required high value of shear stress destroying the hydrogel structure. After introduction of guar gum (0.3 g at the cost of xanthan gum) into the hydrogel composition, the value of yield stress slightly decreased.

Yield stress determines the force the use of which starts an increase of the preparation surface. The results of the extensibility test provide information on the changes of the system area after exceeding yield stress.

Extensibility (or spreadness) is the measure of preparation ability to increase its surface under the influence of pressure (20). The applicative value of the preparations of high extensibility is associated with the fact that they spread easily on pathologically changed tissue. The above leads not only to the increase of the area of therapeutic agents diffusion but also causes that the process of hydrogel application on the inflamed mucosa is the easiest and the least painful.

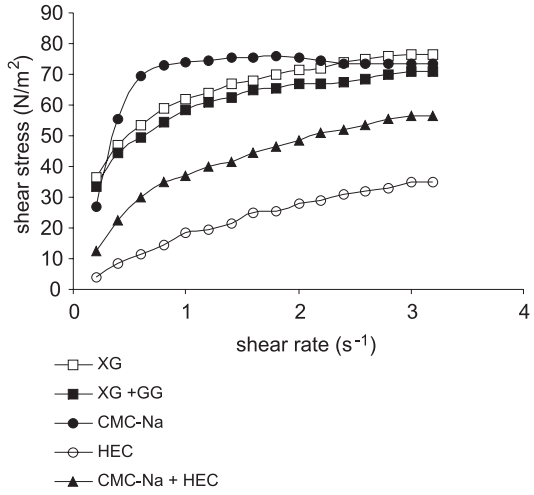

Figure 2. Flow curves of model hydrogels.

Figure 3 presents an example of the extensibility curve obtained for hydrogel with xanthan gum.

The course of dependences between the surface of model dental hydrogels and the value of the imposed load is described with regression equation of the type $y = ax + b$, at the level of significance $p = 0.05$. Parameters "a" and "b" of this equation are used to calculate, with integration method, areas (P) under extensibility curves, expressed in conventional units [c.u.]. The results of the calculations are presented in Table 3.

In the group of the produced preparations, hydrogels with HEC demonstrate the highest extensibility. Introduction of CMC-Na into the prescription including HEC contributes to the decrease of extensibility parameters. Hydrogel with XG demonstrates the lowest extensibility under the imposed load.

Table 3. The coefficients of regression equation of the type y = ax + b describing extensibility of model hydrogels and the values of areas under extensibility curves.

Name of model preparation	Correlation equation coefficient		Correlation coefficient	Area (c.u.)
	a	b	r	
XG	0.1002	7.6307	0.9837	3718
XG+GG	0.1346	10.539	0.9798	5122
CMC-Na	0.1003	14.105	0.9702	5067
HEC	0.1554	28.001	0.9140	9080
CMC-Na +HEC	0.1154	22.076	0.9291	6999

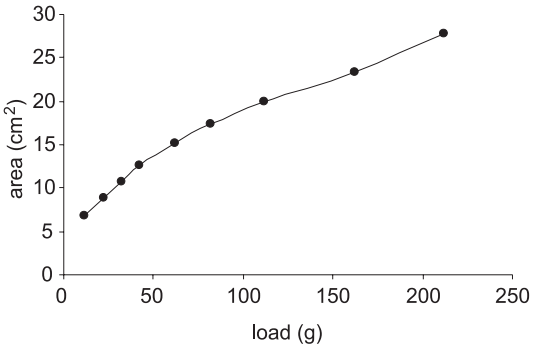

Figure 3. The course of the dependence between the imposed load and the observed increase of the surface of hydrogel with xanthan gum.

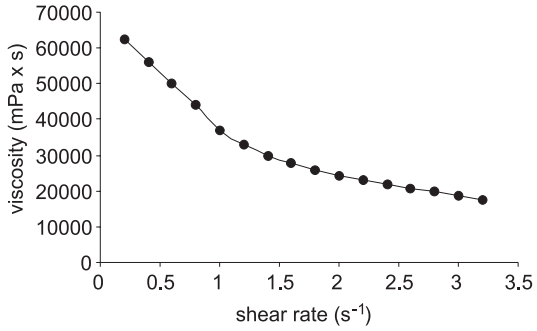

Figure 4. Viscosity curve of model hydrogel with CMC-Na+HEC.

Rheometric tests enabled to determine the dependence of the investigated hydrogels on the shear rate applied in the course of the experiment. An example of the viscosity curve obtained for hydrogel with CMC-Na + HEC is presented in Figure 4.

Structural viscosity of model preparations was compared at two freely selected shear rates (0,6 and 2.4 s^{-1} on axis x of the curve). The results are presented in Table 4.

Hydrogel, vehicle of which contained only HEC had the lowest value of viscosity. Introduction of HEC into the prescription of a hydrogel with CMC-Na caused a decrease of the system viscosity. Preparations with natural gums and with CMC-Na demonstrated the highest viscosity. Introduction of GG into the prescription of hydrogel with XG decreased its viscosity. The above dependences were also observed at all shear rates (Table 4).

The results of the tests of the kinetics of water loss from the produced systems provide information on the changes of viscosity of hydrogel preparations during their exposure on pathologically changed tissue (14). Figure 5 presents an example of the curve of water loss obtained for model hydrogel with HEC.

The course of the dependence between mass loss (%) of the tested hydrogels and time is described, at the level of significance p = 0.05, by a regression equation of the type y = ax + b. Parameters a and b of the equation are used to calculate, with integration method, areas P under the curves of the rate of water loss by the produced preparation, expressed in conventional units [c.u.]. The results of the calculations are presented in Table 5.

The tendencies of model hydrogels produced on the base of natural gums to water loss are comparable. Model hydrogels with HEC lost the least amount of water in the course of exposure of samples at human body temperature (37°C). It may be expected that during application of hydrogels with HEC on the surface of oral cavity tissues, these preparations will not change basically the viscosity parameters. The diffusion coefficient of therapeutic agents from hydrogels containing HEC will be on similar level during the whole time of application, which results from Einstein-Smoluchowski equation ($D = kt/6\pi r\eta$).

Table 4. Viscosity parameters of model hydrogels determined at selected shear rates.

Name of model preparation	Shear rate 0.6 s^{-1}		Shear rate 2.4 s^{-1}	
	shear stress (N/m^2)	viscosity (mPa·s)	shear stress (N/m^2)	viscosity (mPa·s)
XG	57.7	89460	73.8	30731
XG+GG	49.5	82502	69.0	28743
CMC-Na	69.6	115967	73.6	30648
HEC	11.7	19549	30.8	12839
CMC-Na +HEC	30.0	50031	52.1	21702

Table 5. Parameters of regression equation of the type y = ax + b describing the rate of water loss by model preparations together with calculated areas under the curves of water loss.

Name of model preparation	Correlation equation coefficient		Correlation coefficient	Area (c.u.)
	a	b	r	
XG	0.0364	0.1780	0.9999	429.44
XG+GG	0.0361	0.0279	0.9998	405.83
CMC-Na	0.0324	0.4372	0.9995	419.88
HEC	0.0319	0.0735	0.9999	365.21
CMC-Na +HEC	0.0346	0.0187	0.9961	382.83

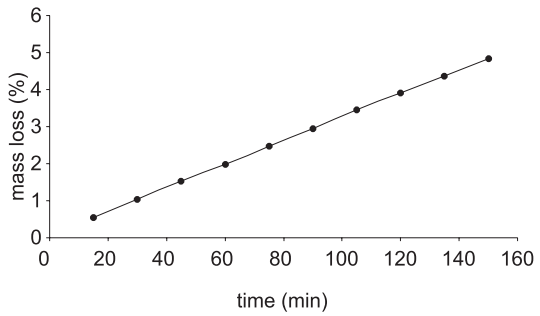

Figure 5. Kinetics of water loss by model hydrogel with HEC.

CONCLUSIONS

Prescription components of model hydrogels, forming systems of definite pH, affected the degree of ketoprofen dissociation and the process of its release. Ketoprofen pharmaceutical availability was the highest from preparations with carboxymethylcellulose sodium salt (hydrogel CMC-Na and CMC-Na + HEC) of pH > 5. The process of therapeutic agent diffusion was in accordance with the zero-order kinetics.

Model systems produced on the base of hydroxyethylcellulose (hydrogel HEC and CMC-Na + HEC) demonstrated expected rheological properties (low value of yield stress and structural viscosity, insignificant water loss at 37°C and good extensibility).

The most beneficial results of the tests were obtained for a model form of a dental drug with cellulose derivatives (CMC-Na + HEC) which were introduced into the vehicle prescription in the quantitative ratio 1:1 (1.5 g + 1.5 g). It is a system demonstrating not only high pharmaceutical availability of ketoprofen but also appropriate applicative properties resulting from the obtained rheological parameters.

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