

CARBOPOL 974P IN THE PRESCRIPTION OF DENTAL ANTI-INFLAMMATORY HYDROGELS

JUSTYNA KOŁODZIEJSKA

Department of Drug Form Technology, Applied Pharmacy Faculty
Medical University in Lodz

Summary

The aim of this study was to assess applicative properties of the produced acc. to own prescription dental anti-inflammatory hydrogel with Carbopol 974P. Ketoprofen pharmaceutical availability was tested from hydrogel with Carbopol 974P and to compare – from hydrogels of similar prescription produced on the base of xanthan gum carboxymethylcellulose sodium salt. Very high pharmaceutical availability of ketoprofen was obtained from hydrogel with Carbopol 974P which is related to specific linear crosslinking of polyacrylic acid.

The tests of physicochemical properties of hydrogel with Carbopol 974P demonstrated that it has high pH not creating the risk of demineralisation after its application in oral cavity.

Introduction of zinc chloride into the prescription of hydrogel with Carbopol 974P improves rheological parameters of the preparation i.e. decreases structural viscosity, the value of yield stress and increases extensibility but decreases ketoprofen pharmaceutical availability by about 15%.

Key words: Carbopol 974P, hydrogels, ketoprofen, zinc chloride, pharmaceutical availability, rheology, pH

INTRODUCTION

Polyacrylic acid (carboxypolymethylene, carboxyvinyl polymer, carbomer) known under the trademark Carbopol is a universal adjuvant substance applied in current practical pharmacy and cosmetology. In cosmetology and pharmacy, Carbopols are used for condensing solutions, stabilising suspensions and producing tablets and capsules [1]. Owing to bioadhesive properties they are used in the production of nose, subbucal, intrauterine and intrarectal forms of drugs. Carbopols are used in the prescription of dermatological preparations such as ointments and gels [2-5]. Products with a symbol P, like Carbopol 974P are certified as fit for oral administration and for contact with mucosa.

The aim of this study was to assess applicative properties of the produced acc. to own prescription dental hydrogel with ketoprofen in the composition of which Carbopol 974P was used. The test of pharmaceutical availability of the therapeutic agent contained in the given form of a drug is the most important test that can be performed in *in vitro* conditions. Thus, the assumption of the undertaken studies was to compare pharmaceutical availability of ketoprofen from hydrogels produced on the base of Carbopol 974P and on the base of currently used dental binding substances (xathan gum, carboxymethylcellulose sodium salt) [6-8].

As current clinical studies have demonstrated introduction of zinc compounds into the composition of dental anti-inflammatory preparations appeared to be beneficial. Zinc ions may play a basic role in the control of supragingival plaque formation not affecting at the same time oral cavity biological balance. Citrate, lactate, zinc chloride as well as aspartate and zinc subcarbonate are applied in the prophylaxis and treatment of dental inflammatory conditions. Zinc chloride besides anti-inflammatory activity also demonstrates ability to treat tooth neck hypersensitivity and to prevent unpleasant smell from mouth [9-11].

In this study an attempt has been made to estimate the effect of zinc chloride (ZnCl_2) on physicochemical properties of hydrogel with Carbopol 974P produced acc. to own prescription and on ketoprofen pharmaceutical availability

MATERIAL AND METHODS

Reagents

- ketoprofen, Sigma;
- Carbopol 974P, (C974P), Noveon Inc.;
- trietanolamine (TEA) – Polish Chemical Reagents S.A., POCH, Gliwice;
- xanthan gum, (GK), Sigma;
- carboxymethylcellulose sodium salt, (CMC-Na), Fluka;
- zinc chloride, (ZnCl_2), Aldrich;
- natural iodo-bromo-boron brine “Zabłocka Mgiełka”, Brines Mine and Saltworks, Lokal Serwis Sp. z o.o. Dębowiec;
- Rofam R-15, Chemical Plant „Rokita” in Brzeg Dolny;
- methyl hydroxybenzoate -Nipagin M, Fluka;
- propyl hydroxybenzoate -Nipagin P, Fluka.

Apparatus

- Mutimer et al. apparatus;
- spectrophotometer Nicolet Evolution 300, version 1,0, Spectro-Lab;
- cone-plate digital rheometer DV-III, Brookfield with „Rheocalc for Windows” soft-ware;
- bath thermostat PGW E1, Medingen;
- extensometer with cover plate (carbon fibre of low specific weight);
- pH-meter N5170E with type-ERH-131 electrode, Production Plant of Physicochemical Apparatus Elements, Hydromet Gliwice;
- homogenizer type 302, Precision Engineering, Warsaw;
- analytical balance, Precision Engineering Plant “Radwag”;
- general laboratory balance, Precision Engineering Plant “Radwag”;

Preparation of model prescriptions of dental anti-inflammatory hydrogels

The prescription of model hydrogels of anti-inflammatory activity was worked out for application in oral cavity (tab. 1)

Testing of the kinetics of ketoprofen release from the produced hydrogels [12]

The study of pharmaceutical availability of ketoprofen was carried out by the membrane method using a plastic container (modified apparatus according to Mutimer et al.).

To the apparatus niche 25g of hydrogel was introduced and fastened by a previously prepared dialysing membrane from tomophane (24h exposure in re-distilled water). The rate of the mass exchange process was evaluated by spectrophotometric method by determining the amount of ketoprofen diffusing to the acceptor fluid (re-distilled water) in the same time intervals. The quantity of the released ketoprofen was determined at $\lambda=260$ nm basing on the equation: $y = 0,6411x + 0,0430$ ($p=0,05$ and $r \geq 0,9998$).

Determination of viscosity parameters of the produced hydrogels [13]

Testing of the hydrogels viscosity was performed at 37°C with the cone-plate rheometer connected with a bath thermostat.

Testing of the produced hydrogels extensibility [14]

The determination of the extensibility of hydrogels was performed with an extensometer at $\text{temp.} 25 \pm 0,1^{\circ}\text{C}$.

Testing of the produced hydrogels pH (a_{H^+})

The measurement was carried out by direct immersion of electrode connected with pH-metre in hydrogel samples of the same weigh. The readout of pH was made after 0,5 minute from the electrode immersion moment.

RESULTS AND DISCUSSION

Comparison of the kinetics of ketoprofen release from hydrogels containing xanthan gum, carboxymethylcellulose sodium salt and Carbopol 974P

The course of the process of ketoprofen release from the produced hydrogels is presented in figure 1.

The dependence of the quantity of diffusing ketoprofen in the time function (t) from all the tested hydrogels was described by regression equations: $y = ax + b$ and $\lg(y) = \lg(x) + b$ (logarithmic form of the exponential equation $y = ax^b$). The results are presented in table 2.

The equation of the type $y = ax + b$, after integration, was the basis for calculation of areas P (expressed in conventional units (c.u.)) under ibuprofen release curves. Figure 2 demonstrates the areas under the curves of ketoprofen release from the tested hydrogels.

The highest pharmaceutical availability of the therapeutic agent was obtained *in vitro* for hydrogels with Carbopol 974P. The area under the curve of ketoprofen release from the

hydrogel with Carbopol 974P was 244,65 c.u. (fig. 2) and it is eight-to twelve times higher than the values obtained for the other hydrogels.

Linearly lying hydrated quaternary amino groups form the so called “flow bundle” in the hydrogel structure which causes that the therapeutic agent does not penetrate the created network and it is released from its external surface. Polysaccharides: xanthan gum and carboxymethylcellulose sodium salt are crosslinked through a glycoside bridge. In solution their chain particle assumes disorderly bundled form. In this case diffusion is related only to the therapeutic agent which is found on the outside of the non-flow bundle. However, it is inhibited from the inside of the bundled chain [15].

The assessment of the effect of zinc chloride on physicochemical properties and pharmaceutical availability of ketoprofen from hydrogel produced on Carbopol 974P base

The results of viscosity test

Structural viscosity of the produced preparations was compared at freely selected shear rate (0, 6 and 2,4 l/s on axis x of the flow curve)[16, 17]. The results are presented in table 3. The parameters of Casson’s model determined with Rheocalc for Windows software are demonstrated in the same table. The Casson’s model recommended for description of flow curves of non-linear viscoelastic liquids is described by the following formula:

$$\sqrt{\tau} = \sqrt{\tau_0} + \sqrt{\eta\dot{\gamma}},$$

where: τ – shear stress, τ_0 – yield stress, η – plastic viscosity, $\dot{\gamma}$ – shear rate [18].

Under the effect of zinc chloride there came to the decrease of the value of viscosity and yield stress of hydrogel with Carbopol 974P (tab. 3). The hydrogel containing zinc chloride will remain on the application surface in a shorter period of time and the use of lower pressure results in exceeding the boundary value and the flow of the preparation.

The results of extensibility test

The extensibility curves of hydrogels with Carbopol 974P are presented in figure 3. The course of the dependence between the imposed load and the observed increase of the surface of hydrogel is described with correlation equation of the type $y = ax + b$ and integration method was used to calculate the areas under extensibility curves, expressed in conventional units. The results of the calculations are demonstrated in table 4.

The area under extensibility curve of hydrogel with Carbopol 974P increased under the effect of zinc chloride (fig. 3. tab. 4). Higher extensibility parameters will facilitate spreading of the hydrogel on pathologically changed tissue. This leads to the increase of the area of ketoprofen diffusion from the drug form to the external compartment. These results are convergent with the results of yield stress test (tab. 3).

The results of pH test

The values of pH of hydrogels with Carbopol 974P are compared in fig. 4. According to the recommendations of the Polish Standard established for preparations to be used in the oral cavity, the pH value for these preparations should be within the limits from 5,5 to 10,5 [19]. Regardless of the presence of zinc chloride in the prescription, pH of hydrogels with Carbopol 974P is higher than the critical pH of the enamel (5,5) (fig. 4).

The results of ketoprofen pharmaceutical availability test

Figure 5 demonstrates the kinetics of ketoprofen release from hydrogels with Carbopol 974P. The regression equations describing the rate of ketoprofen release (fig. 5) together with calculated areas under the curves of release are presented in table 5.

Introduction of zinc chloride into the worked out prescription of hydrogel with Carbopol 974P causes the decrease of the quantity of the released ketoprofen by about 15% (tab. 5).

High correlation coefficients of the straight equation of the type $y = ax + b$ prove that the process of ketoprofen diffusion from hydrogels to the dialysis fluid runs according to the kinetics of "0" order. Precise kinetic equations based on the analysis of the diffusion process are usually complex and in many cases resemble the total of exponential functions [20].

CONCLUSION

A vehiculum developed with prescription share of Carbopol 974P is an optimal vehicle for dental anti-inflammatory hydrogel with ketoprofen. Very high pharmaceutical availability of ketoprofen from this hydrogel results from a specific linear cross-linking of polyacrylic acid through quaternary amino groups.

Hydrogels with Carbopol 974P have pH higher than the critical value for enamel (5,5) which does not create the risk of demineralisation when applied in oral cavity.

Introduction of zinc chloride into the prescription of hydrogel with Carbopol 974P improves rheological parameters of the preparation i.e. decreases structural viscosity and the

value of yield stress, increases extensibility but decreases ketoprofen pharmaceutical availability by about 15%. Thus, the estimation of therapeutic effects resulting from the use of zinc chloride in the prescription of a hydrogel of worked out prescription in *in vitro* studies, seems to be of importance.