Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 26 issue 3, 2016, pp.317- 321

QUALITATIVE ASSESSMENT OF SOME HYDROGELS CONTAINING KETOPROFEN

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ABSTRACT: This paper is a complex biopharmaceutical study that analyses the formulation of some hydrogels intended for cutaneous use, which favour a rapid release of the active substance from the designed vehicles onto and through the skin surface. The influence of the gel-forming polymer type on the main quality parameters of hydrogels with ketoprofen was assessed. Through the experiments conducted the organoleptic control, pH determination, drug content and spreadability were carried out for the formulations. A study of the rheological properties characteristic for the designed hydrophilic gels was also performed and the relation between their flow properties and both the structure and composition was further analyzed. This characterization contributes to the design evaluation and the optimization of semisolid pharmaceutical systems, in order to be used for specific purposes.

Key words: carbomer 940, hydroxyethylcellulose, ketoprofen, hydrogel

INTRODUCTION:

The symptomatological treatment of pain represents administering antalgic medicine, which is selected depending on the cause which produces the pain. The purpose of administering a pharmaceutical form in the treatment of pain in the inflammatory diseases is to provide a sufficient dose of active ingredient to the location of the inflammation, which should thus be able to manifest its therapeutic effect in due time and for a prolonged period of time, so that the interval between the administrations is correct and to avoid the possible side effects. Oral administration of the conventional forms with non-steroid anti-inflammatories (NSAIDs) can develop a series of side effects due to the gastric irritability which they induce. The topic administration of NSAIDs offers attractive ways to reduce adverse reactions by maximizing local release of the active ingredient with the minimisation of its systemic release (Kumar et al., 2005). The pharmaceutical systems for topic administration, must be formulated, made and conditioned in order to ensure more their qualities regarding bioavailability, physical and chemical stability and the absence of microbial contamination, rather than the cosmetic criteria (Hoare et al., 2008).

Hydrogels are tridimensional polymericnetworks of hydrophil polymers, which contain a high quantity of water. They can be likened with a massive macromolecule, which has sthe capacity to integrate high quantities of water/watery solutions. Generally, the water quantity represents more than 20% of the hydrogel's total weight. The necessity of improving the physio-chemical, biological and mechanic properties of the hydrogel has led to the diversification of the selection of neutral monomers or carriers of electrical loads (anions, cations), as well as groups susceptible to reticulate in order to obtain these (Barry, 2002; Popovici et al., 2008). Individualizing hydrogels from other biomaterials is done through the following characteristics: they have an own volume and form; in general, they are transparent (colourless or with colour); under the action of heat a massive loss of mass takes place accompanied by a powerful contraction of the volume; under reduced mechanical demand they have a visible elastic behaviour; under volume compression efforts there is a contraction of the volume and an increase in density (Popovici et al., 2008; Rathapon et al., 2005; Suhaime et al., 2012).

In the last years, there is a special interest for the use of carbopoles as excipients in various pharmaceutical formulations. Carbopoles can offer some desirable characteristics for a topic formulation: adequate viscosity in low values of the polymer concentration, suspension of substances, increase of density and reduced tixotropy, as well as clarity of product, which offers practical and aesthetic reasons to prefer carbopole formulations (Rathapon et al., 2005; Suhaime et al., 2012; Orţan et al., 2011).

Ketoprofen is a non-steroid anti-inflammatory which falls in the category of minor anti-inflammatories. It can be administered orally, parenterally, rectal, as well as local through the medium of topic formulations. The plasmatic halving time is short, of approximately two hours. It presents the side effects characteristic of the NSAIDs class. The products dedicated tp topic administration offer attractive ways to reduce side effects by maximizing local release of the active ingredient with minimizing its systemic release (Rençber et al., 2009; Oliveira et al., 2012; Nikumbh et al., 2015).

MATERIALS AND METHODS:

Materials

Ketoprofen (Sigma Aldrich)
Etanol (Merck, Germany)
Sodic carboximetilcelulosis, NACMC(Fluka)
Carbomer 940 (Alpha Farm Belgium)
Glycerol (Tunic)
Sodium hydroxid(Merck, Germany)

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Trietanolamine(Tunic)
Distillated water
Composition of projected hydrogels

The pharmaceutical systems used in this study have been represented by 2 hydrogels containing ketoprofen with different compositions of the release base and with a constant composition in medicated substance.

1. **Experimental gel G1** contains: 2.5 g ketoprofen, 3 g sodic carboximetilcelulosis, 15 g ethanol, 8 g glycerol, distillated water q.s ad 100 g. The neutralisation has been preformed using a solution of NaOH of 1M concentration.

2. **Experimental gel G2** contains: 2.5 g ketoprofen, 1 g carbomer 940, 15 g ethanol, 8 g glycerol, 0.4 g trietanolamine, disttillated water q.s. ad 100g.

Mehtods
Quality control of experimental gels

In order to evaluate the quality, stability and efficiency of the experimental gels, a series of determinations recommended for such topical formulations has been carried out.

a) Examination of macroscopic characteristics represents the first approximation of their quality. The assessment of the visual macroscopic characteristics (aspect, consistency, homogeneity), olfactory (smell) and tactile, has been performed according to the regulations F.R. X (***FRX, 1993). The alterations observed in these characteristics are possible indicators of a degradation due to various reasons (oxidation, pH variations).

b) pH of the experimental gels has been determined through the potentiometric method (according to the regulations F.R. X) using a digital portable pH-metre (Corning 430, Cole Parmer), after these have been previously properly processed. Thus, 20 mL water at 37±1ºC have been brought over 5g gelwhile being shaken continuously for 5 min. The shaking has been maintained for 2 min., the formulation has been cooled down, has been filtered and then the pH value has been determined.

c) Rheological analysis of the experimental hydrogels has been performed using a rational viscosity meter (MultiVisc - Rheometer, Fungilab), equipped with a TR 10 standard probe. The determinations have been performed at two working temperatures, and the rheological experiments ran in a random order to ensure the objectivity of the study and the data acquisition.

The operational conditions for running the rheological experiments, maintained constant during the execution of all rheological experiments have been the following:

- Work temperature: $23^o \pm 0.1^oC$ adequate to the temperature in which hydrogels should be kept (room temperature), meaning $37^o \pm 0.1^oC$;
- In order to ensure a thermic and mechanic balance and in order to ensure that the results are reproducible, each gel has been left in a state of rest for 10 min in the thermostat pot in which the rheological determinations have been conducted, before commencing the experiment;
- The rheological experiments have been performed while increasing the rotation speed from a minimum 0.3 rpm to faster speeds of 60 rpm, respectively by decreasing its speed from 60 to 1.5 rpm. The time intervals between the determinations and the duration of each measurement have been 10 s.

d) The exhibition capacity of the hydrogels has been determined through the method Ojeda-Arbussa (Popovici et al., 2008). Two identical, square, glass plates have been used. The inferior plate has a circle in its middle inside which 1g of gel has been placed. The second plate is placed in the central area of weight, varying between 50 and 500g. All the determinations have been performed three times, at 25°C.

e) Determination of content in the active ingredient has been made spectrophotometrically, after processing adequately the gels. Thus, 1g of gel, brought quantitatively in a graded balloon of 50 mL, has been dissolved in ethanol. 1 mL of this solution has been diluted accordingly and analysed spectrophotometrically using a spectrometer Jasco V-550, at a wave length λ=254 nm. All the determinations have been performed in comparison with the control probe, which has been prepared identically using the gel without ketoprofen.

RESULTS AND DISCUSSIONS:

a). Examination of the macroscopic characteristics

Experimental gels are homogenous, yellow colour (G1), translucent, no particular smell, consistent, the gelification being firm. It is noticed that gel G1 has a lowered consistency.

b). pH of experimental gels

It is noticed that the pH of the experimental gels (Table 1) falls within the limits imposed by FR X, the carbopol gel having a value closer to the pH of the skin compared to the one made of sodic carboximetilcelulosis.

Table 1.
pH values and percentage of active ingredients in the experimental formulations

Gel code	pH	Active ingredient (%)
G1	6.55±0.13	96.83±0.63
G2	5.80±0.07	98.45±0.45

c). Rheological analysis

The rheological patterns recorded at both work temperatures for the designed hydrogels were represented as viscosity versus shear rate (Fig. 1a-b and Fig 2 a-b).

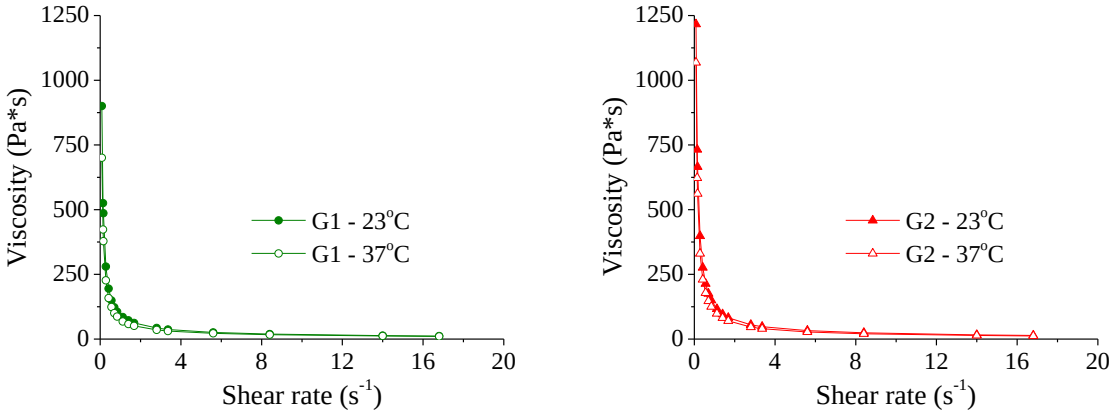


Fig. 1: Flow profiles viscosity as a function of shear rate for the hydrogel: a) G1; b) G2 tested at 23°C and 37°C

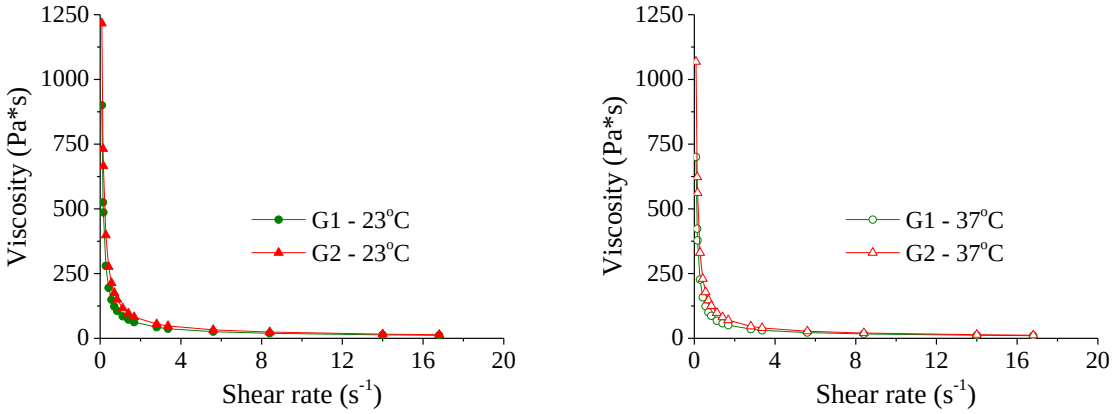


Fig. 2: Flow profiles viscosity as a function of shear rate for the hydrogels G1 and G2 tested at: a) 23°C;b) 37°C

As can be seen in Fig. 1 and Fig. 2 for all the hydrogels the viscosity decreased with the shear rate increase for both temperatures. This behaviour is characteristic for the non-Newtonian pseudoplastic formulations.

The Power law model (eq. 1) was used to quantify the relation between viscosity and shear rate:

$\eta = m \cdot \dot{\gamma}^{-n}$ (1) where, m and n are rheological parameters correlated with the hydrogels composition (Ghica et al., 2016) and determined through the linearization of eq. (1) by double logarithmic method. "m" parameter is associated with the viscosity obtained for the shear rate of $1 \cdot s^{-1}$. The values obtained for these parameters as well as the value of the determination coefficients R^2 are given in Table 2.

Table 2:

The m and n parameters values and the determination coefficients characteristics for the Power law model applied to the designed hydrogels analyzed at 23°C and 37°C

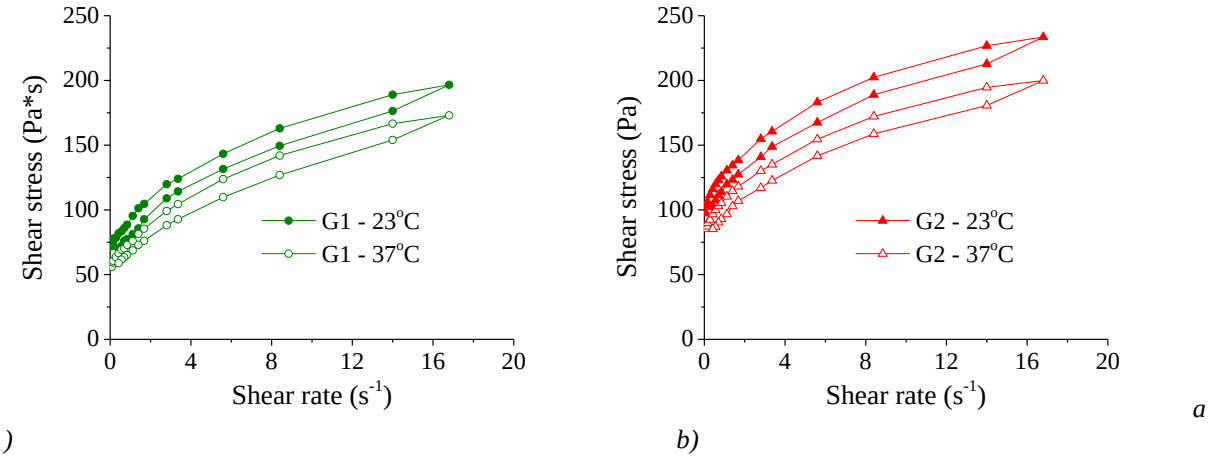
Hydrogel	Temperature - 23°C			Temperature - 37°C		
	m	n	R^2	m	n	R^2
G1	90.132	0.909	0.9992	74.758	0.884	0.9996
G2	129.093	0.887	0.9998	104.607	0.917	0.9996

The values of R^2 higher than 0.999 indicated that the experimental data fitted very well the above rheological model.

The values of "m" parameter is strongly influenced both by the work temperature and type of gel-forming polymer (NaCMC and carbomer

940). Thus, the increase of the temperature led to a decrease of "m" parameter of about 17-19%. A higher value for this parameter was recorded for the hydrogel formulated with carbomer 940 in comparison with the one obtained with NaCMC at both temperatures.

For the evaluation of the hydrogels thixotropy the up and down curves shear stress as a function of shear rate were built. In Fig. 3 a-b are presented the up and down rheological profiles for hydrogel G1 and G2 tested at 23°C and 37°C.



a) *b)*

Fig. 3: Up and down rheograms for hydrogel: a) G1 tested at 37 °C; b) G2 tested at 23 °C

From Fig. 3 a-b it can be noticed that for the same shear rate value, a lower shear stress corresponds for the down curve compared to the up curve, recordingthe hysteresis thixotropy area (Ghica et al., 2016; Ghica et al., 2012). During the shearing the system destructuration takes place, the viscosity decreases, followed by the recovery of the initial structure after a shorter or longer rest period (Orţan et al., 2011; Rençber et al., 2009; Oliveira et al., 2012; Nikumbh et al., 2015; ***FR X, 1993; Ghica et al., 2016)

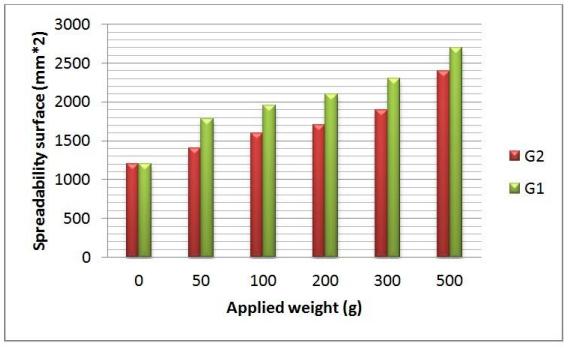


Fig. 4.: The influence of gel-forming polymers on spreadability

e). Determining content in active ingredient

The ketoprofen quantity found in the gels is in accordance with the specifications of the pharmacopeia regarding the content of active ingredients (Table 1). The results show a uniform distribution of the ketoprofen in the tested formulations.

CONCLUSIONS

We proposed for topical administration of ketoprofen, two formulations using the gel-forming polymers - sodium carboxymethylcellulose and

d). Capacity of exhibition

The capacity of exhibition has been evaluated in comparison for gels with ketoprofen and, respectively, a base without active ingredient.The results have not been significantly differentfor the gel containing ketoprofen and the base out of which it is made of. Fig. 4 presents as comparison the data obtained experientially for the two analysed gels. It is to be highlighted that the gel G1 has a spreading surface bigger than that of gel G2, which could have been foreseeable considering the results of the rheological analysis.

Carbopol 940. The pH was near to pH of the skin which revealed nonirritating nature of the formulation. The drug content determination showed that drug loss during formulation occurred within the admissible limits. By examining the obtained rheograms, it is ascertained that the tested hydrogels showed a pseudoplastic and thixotropic non – newtonian behavior for both temperatures (23°C and 37°C). The pseudoplastic feature is demonstrated by the viscosity decrease when the shear tension increases; while the thixotropic feature is demonstrated by the fact that, for the same shear speed, the points shown by the return curves are corresponding to shear tensions lower than on the direct curves. At the same shear speed, it is shown that the viscosity is smaller at 37°

Celsius than for 23^{o} C, which shows that at 37 degrees the gel becomes less viscous and, so, the release of the active principle incorporated into the hydrogel is favored. This rheological behavior allows an appropriate display when cutaneously administered. The viscosity and spreadability suitable which ensures that the developed system will not flow by itself and the application to inflamed skin is more comfortable and it spreads easily.

The adequate viscosity, the efficient suspension of the active substance, the low thixotropy, as well as the product clarity are the reasons for which, out of practical and aesthetic considerations, we recommend the formulation based on carbopol.

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