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Formulation and quality evaluation of some hydrogels containing piroxicam 1% or meloxicam 0,5%

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Abstract

The aim of the present work was the formulation, preparation and quality control of hydrogels containing piroxicam 1% and meloxicam 0,5% respectively, used for topical application with analgesic and anti-inflammatory effect.

As substances which are slightly soluble in water, piroxicam and meloxicam were solubilised in the hydrogel vehicle either by cosolvation (using polyethylene glycol 400 mixed with ethanol or glycerol as cosolvents) or by complexation with cyclodextrins (β-cyclodextrin and 2OH-β-cyclodextrin).

The quality control of the obtained hydrogels included: the examination of macroscopic characteristics (appearance, consistency, homogeneity, smell, tactile features), the pH determination and the rheological analysis (determination of flow behaviour and viscosity, as well as determination of consistency).

The quality control of hydrogels with piroxicam 1% or meloxicam 0.5% shows that the presence of these solubilisants in the formulations under study does not affect the characteristics of the preparations, which followed the requirements of the pharmacopoeia.

Keywords: hydrogels, piroxicam, meloxicam, cosolvents, rheological, consistency.

1. Introduction

Hydrogels contain a high percentage of water (80-95%), and are obtained by the hydration and swelling of macromolecular substances in water; they are physiologically inert, siccative and form a film after application on the skin. They are easily washable and are therefore recommended in the treatment of hairy surfaces, mucous membranes and lesioned or sicked integuments [4, 9, 11].

They are compatible with the majority of active substances, as their pH can easily be adjusted by buffering. Their viscosity depends to a very small extent on temperature.

Hydrogels are thixotropic products, which in time, undergo a release of water from the composition of the gel as a result of network contraction and increase in crystal formations [4, 5, 10].

Hydrogel formulation includes a gel-forming agent, an agent for maintaining humidity, a preservative agent and a vehicle.

Carbomers, also known as polyacrylic acids or carboxyvinyl polymers and most frequently sold under the name Carbopol, are synthetic polymers of the acrylic acid, cross-linked with allylsucrose or

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with allyl ethers of the pentaerythritol; they have anionic character, high molecular mass between 7 • 105 – 4 • 109 and they contain 56-68% carboxyl groups. Currently, there are available many types of carbomers, which differ in molecular mass, degree of reticulation, structure and residual solvent (e.g. 934NF, 940NF, 980NF, EDT 2050).

Carbomers in pharmaceutical use appear as white, very fine, very light, acid powders with weak specific smell; they are hygroscopic.Carbopol hydrogels are obtained by neutralising the slightly viscous dispersions with alcaline hydroxide solutions (sodium hydroxide 0,4g/1g carbopol) or amine solutions (triethanolamine 0,75g/1g carbopol). Maximum viscosity is obtained at pH = 6 – 11. This viscosity is considerably reduced at a pH below 3 and above 12, as well as in the presence of strong electrolytes or light and is increased in the presence of 10-25% alcohol or 5-15% glycerol, propylene glycol. The carbomer depolymerisation can be avoided either by storing the hydrogels protected from light, in properly closed recipients, or by adding antioxidants.

The homogenous aqueous dispersions of Carbopol are obtained by slowly introducing the powder into water under continuous agitation, as the carbopols, due to their strongly hydrophilic character, tend to form agglomerations which are difficult to disperse later. After obtaining the acid dispersion, it is left to rest at room temperature for about 30 minutes, in order to finalise the process of imbibition of the polymer and elimination of the air possibly incorporated (air elimination is extremely difficult after neutralisation and gelification). Further, the Carbopol dispersion is neutralised with a dilute alkaline solution (e.g. ammonium hydroxide 28% solution or sodium hydroxide 10% solution or triethanolamine 50% solution), added gradually and under slow agitation, until the dispersion is transformed into a transparent mass more or less viscous. Maximum viscosity is generally obtained at pH=7.

Medical hydrogels based on Carbopol are non-greasy, easily washable, and stable; they quickly release the incorporated active substances and are well tolerated by the skin [5, 7, 8, 9]. Oxicams are recognized for their anti-inflammatory and analgesic properties after oral administration, but because of adverse reactions which are manifest at gastric level, topical administration is preferred in order to obtain the same benefits without adverse reactions.

The experimental part of this work studied the formulation, preparation and quality control of hydrogels containing piroxicam and meloxicam in concentration of 1% and 0,5% respectively, used for topical application for analgesic and anti-inflammatory purpose [1, 2, 6, 12].

2. Materials and method

The following materials were used: piroxicam (Terapia Cluj, Romania) and meloxicam (LaborMed Pharma, Cluj, Romania) as active substances; β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin (CycloLab, Hungary), polyethylene glycol 400 (PEG 400, BASF Chem Trade GmbH, Germany), ethanol (Chimopar Bucharest, Romania) and glycerol (Chimopar Bucharest, Romania) as solubilisants; Carbopol 940 NF (Noveon, USA) as gel-forming substance; triethanolamine (TEA, Merck) as neutralizing agent for carbomer; preservative solution (F.R.X) as vehicle.

Preparation of hydrogels with piroxicam and with meloxicam

Four hydrogels with piroxicam 1% (P1-P4 formulations) and four hydrogels with meloxicam 0,5% (M1-M4 formulations) were prepared, using mixtures of cosolvents PEG 400-ethanol or PEG 400-glycerol in proportion of 1:1, alone or in association with β-cyclodextrin or 2OH-β-cyclodextrin for the solubilisation of the two oxicams (table 1) (3).

The carbomer powder was added slowly, in small portions and under moderate agitation (1000±50 rot/min, the lower impeller being immersed about 1/4 liquid depth off the bottom) to 45 g preservative solution heated at 40°- 50°C, ensuring that loose aggregates of powder are broken up; after that, the stirring at 1000 ± 50 r/min was continued for 15 min, then the stirrer was removed.

The homogenous acid dispersion obtained was left to rest at room temperature for 30 minutes, then it was neutralized with TEA dilute solution (1,5 g TEA mixed with 4 g preservative solution), added gradually and under soft agitation (300±25 rot/min). The piroxicam/meloxicam solution was prepared by drug dissolution into a mixture of PEG 400-ethanol or PEG 400-glycerol, associated or not with cyclodextrin.

Table 1. Composition of hydrogels with piroxicam 1% and with meloxicam 0,5%.

Components	Quantity (g)							
	P1	**P2**	**P3**	**P4**	**M1**	**M2**	**M3**	**M4**
Piroxicam	1,00	1,00	1,00	1,00	-	-	-	-
Meloxicam	-	-	-	-	0,50	0,50	0,50	0,50
Carbopol 940NF	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00
Poliethyleneglycol 400	20,00	20,00	20,00	20,00	20,00	20,00	20,00	20,00
Ethyl alcohol	20,00	-	20,00	-	20,0	-	20,0	-
Glycerol	-	20,00	-	20,00	-	20,00	-	20,00
β-cyclodextrin	-	-	3,42	3,42	-	-	-	-
2OH-β-cyclodextrin	-	-	-	-	-	-	3,35	3,35
Triethanolamine	3,20	3,20	3,20	3,20	3,20	3,20	3,20	3,20
Preservative solution	54,80	54,80	51,38	51,38	55,30	55,30	51,95	51,95

Table 2. Organoleptic properties of hydrogels with piroxicam 1% and with meloxicam 0,5%

Code formulation	Apearance	Colour	Odor
P1	Homogenous translucent	yellow	slight characteristic and ethanol odor
P2	Homogenous translucent	yellow	slight characteristic odor
P3	Homogenous opalescent	yellow	slight characteristic and ethanol odor
P4	Homogenous opalescent	yellow	slight characteristic odor
M1	Homogenous translucent	yellow	slight characteristic and ethanol odor
M2	Homogenous translucent	yellow	slight characteristic odor
M3	Homogenous translucent	yellow	slight characteristic and ethanol odor
M4	Homogenous translucent	yellow	slight characteristic odor

Table 3. Equations and squares of the correlation coefficients of lines calculated by regression analysis for viscosity curves of hydrogels with piroxicam 1% and meloxicam 0,5% (negative values indicate the decrease of viscosity).

Code formulation	Equation	Square of the linear correlation coefficient (r^2)
P1	y = -1.2603x + 5.6574	0,9978
P2	y = -1.2966x + 5.9187	0,9982
P3	y = -1.2776x + 5.6576	0,9976
P4	y = -1.3095x + 5.9364	0,9979
M1	y = -1.2422x + 5.8043	0,9993
M2	y = -1.2732x + 6.1089	0,9990
M3	y = -1.2877x + 5.9901	0,9986
M4	y = -1.3106x + 6.3026	0,9982

Finally, the piroxicam/meloxicam solution was incorporated into carbomer hydrogel, then the preparation was filled up to 100 g with preservative solution.

The quality evaluation of the hydrogels obtained was carried out through the following tests:

- Macroscopic examination: aspect, homogeneity, colour, smell according to F.R. X guidelines;
- Determination of pH: potentiometrically, using a Sension, Hach portable pH-metre;
- Determination of rheological characteristics (flow, viscosity): according to F.R. X and Ph. Eur. VI, using a Brookfield DV-I+ rotational viscometer;
- Determination of consistency by measuring the spreadability, using the Pozo Ojeda-Sune Arbussa extensometer.

All measurements were carried out in triplicate.

3.Results and discussions

The macroscopic examination of the obtained hydrogels (table 2) showed that all the formulations are in accordance with F.R. X guidelines.

Determination of pH

By further analysing the results obtained after determining the pH of hydrogels (figure 1), we concluded that the pH of hydrogels with meloxicam 0,5% (M2-M4 formulations) is slightly higher than that of those with piroxicam 1% (P2-P4 formulations), but in all cases the value of the pH is within the limits imposed by the F.R. X (4,5 - 8,5) [13].

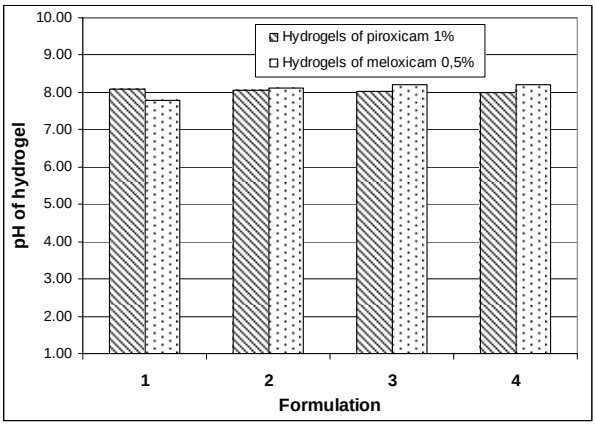


Figure 1. pH variation of hydrogels with piroxicam 1% and with meloxicam 0,5%.

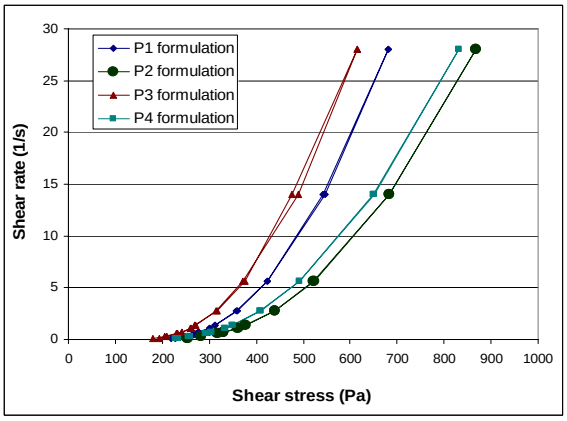
Determination of rheological characteristics

Determination of rheological behaviour and viscosity of hydrogels are very important, as these provide information concerning the microstructure of hydrogels and highlights the influence of the procedure and preparation conditions on their quality.

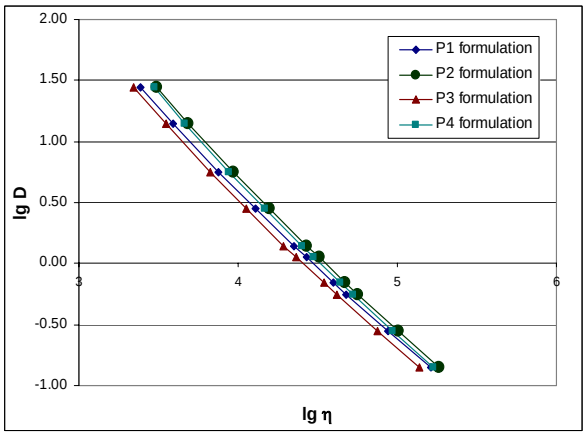
Based on the obtained data, the flow curves were drawn and the viscosity curves of the hydrogels we studied were linearized (figures 2 and 3, table 3).

It can be observed that the analyzed hydrogels showed plastic behaviour. Generally, the viscosity of hydrogels with piroxicam was lower than that of hydrogels with meloxicam; the hydrogels prepared with glycerol were more viscous both in the case of piroxicam and meloxicam.

The values of r^2 indicated in table III confirm the good fitting of viscosity data with a straight line and respectively, the linear relationship between all hydrogels apparent viscosities and share rate.



(a)



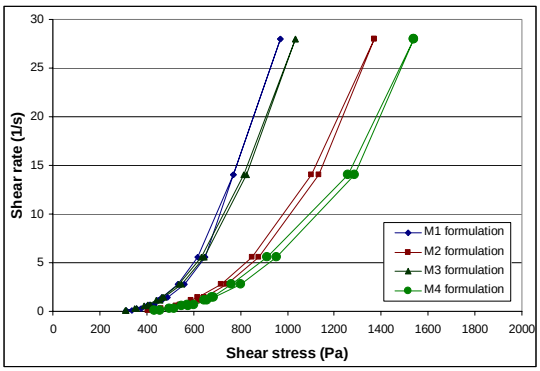
(b)

Figure 2. Flow curves (a) and linearization of viscosity curves (b) of hydrogels with piroxicam 1%.

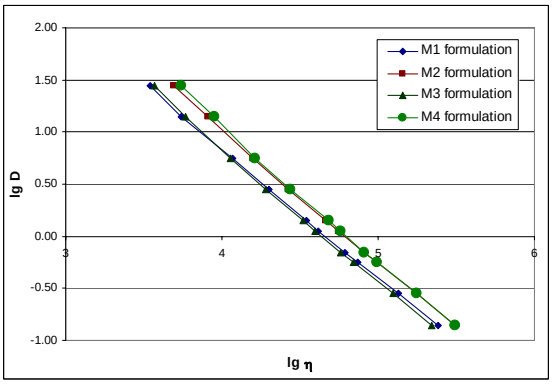
Determination of hydrogels consistency

Is a test specific to semisolid preparations, which highlights their other rheological characteristics (e.g. rigidity, toughness, plasticity etc.).

Determining the plasticity (spreadability) provides information regarding the easiness of semisolid preparation to apply on the skin or mucous membranes. Using the values of spreading area, the extensometric curves of analyzed hydrogels were obtained (figure 4).

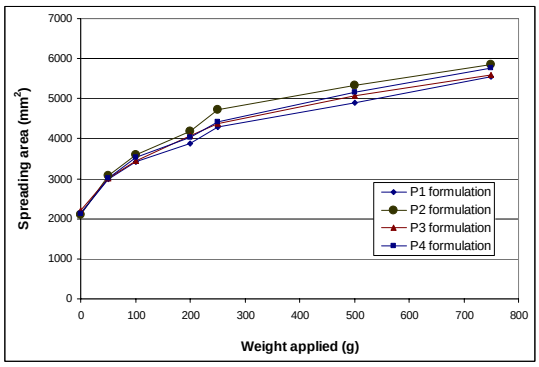


(a)

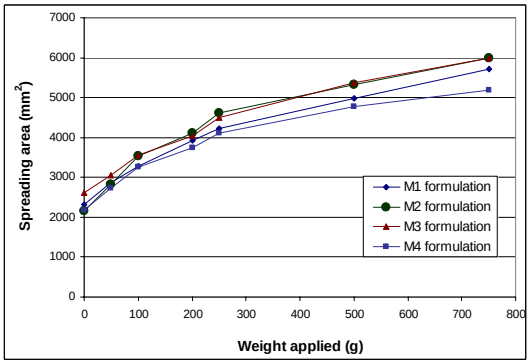


(b)

Figure 3. Flow curves (a) and linearization of viscosity curves (b) of hydrogels with meloxicam 0,5%



(a)



(b)

Figure 4. Extensometric curves of hydrogels with piroxicam 1% (a) and with meloxicam 0,5% (b).

The high values of the spreading areas and the shape of the extensometric curves showed the right consistency and the good spreadability of all analyzed hydrogels.

Conclusions

The mixtures of cosolvents polyethylene glycol 400-ethanol 1:1 and polyethylene glycol 400-glycerol 1:1, as well as β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin can be used as solubilisants for piroxicam and meloxicam, nonsteroidal anti-inflammatory substances which are slightly soluble in water. These solubilisants ensure the maintenance in dissolved state of the piroxicam in concentration of 1% and of the meloxicam in concentration of 0,5% in cutaneous hydrogels based on Carbopol 940NF.

The quality control of hydrogels with piroxicam 1% and with meloxicam 0,5% shows that the presence of these solubilisants in the studied formulations does not affect the characteristics of the preparations, which were in accordance with the requirements of the pharmacopeia.

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