A NEW APPROACH FOR COMPOUNDING GELS CONTAINING A NON – STEROIDAL INFLAMMATORY DRUG

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INTRODUCTION

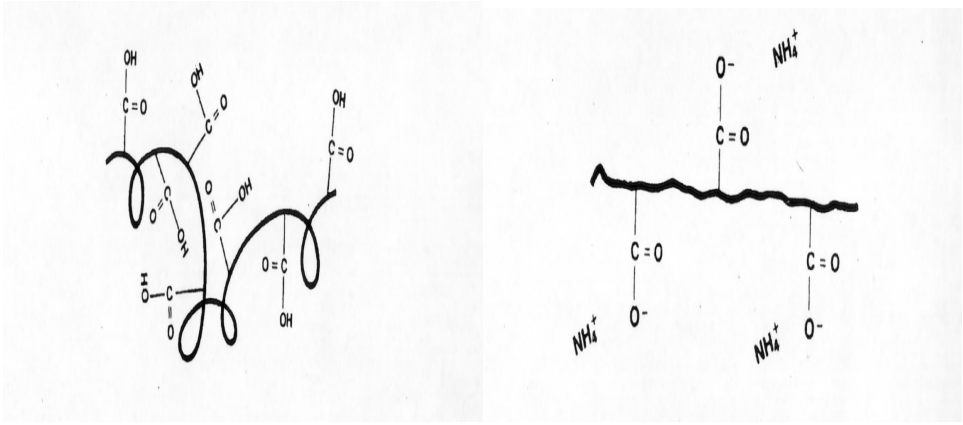
Improving the control of arthritic pain in elderly patients is becoming increasingly important. Gels containing active ingredients with an antiphlogistic activity belong to the group of regularly compounded preparations as non-steroidal anti-inflammatory drugs (NSAID's) can cause gastrointestinal irritation when taken over longer periods. The most common actives prescribed are: flufenamic acid, ibuprofen and ketoprofen. The first is not available as a gel among the pharmaceutical products marketed in Belgium but a series of brand gel products contain ibuprofen or ketoprofen as e.g. Ibutop, Nurofen and Fastum gel.

Besides these three molecules other derivatives of arylpropionic acid are used topically as: nimesulfide, niflumic acid and piroxicam. All compounds of this class are poorly water soluble, but good soluble in ethanol, isopropanol, acetone, ether and chloroform. They are weak acids with a pKa between 4 and 5.

PREPARATION OF GELS CONTAINING DERIVATIVES OF ARYLPROPIONIC ACID

Carbomers (Carbopol) are the polymers, which are very frequently used for the formulation of hydrophilic gels, because of their excellent cosmetic properties. Accordingly many formularies as for example the new Formulaire Thérapeutique Magistrale (FTM) (2) publishes the composition of a carbomer gel. But if, as in the case of the derivatives of arylpropionic acid derivatives, the objective is a transparent gel the hydrophilic carbomer gel of FTM is not appropriate. A hydro-alcoholic gel will be required. Indeed the NSAID's have a good solubility in alcohols. But very few polymers are compatible with a high alcohol concentration. This is the case for carbomers and hydroxypropyl cellulose (Klucel). However due to the stickiness of its gels hydroxypropyl cellulose is considered less interesting for a topical product.

Besides these solubility problems other problems will arise during compounding, because of the acid character of these derivates of arylpropionic acid, which have a pKa between 4 and 5. When adding base, the carboxylic function, which is present in their chemical structure, will compete with the carboxylic groups of carbomer, which need to be converted in their salt form in order to unfold maximally.



a b

Figure 1 Schematic representation of Carbopol in its non-neutralized (a) and neutralized form (b) (3)

Choice of the polymer

A study of the compositions of a series of gels containing a NSAID learns that three polymers were chosen for their formulation: hydroxyethyl cellulose, hydroxypropyl cellulose and carbomer. The choice of the polymer will determine the concentration of alcohol in the finished product. Indeed hydroxyethyl cellulose supports a maximal concentration of 30 % alcohol while hydroxypropyl cellulose and carbomer are compatible with very high concentrations of ethanol or isopropanol.

Examples of brand gels containing a NSAID

1. Ibuprofen Teva 5 % gel

   Composition:
   Ibuprofen 5 g, isopropyl alcohol 5 g , hydroxethyl cellulose 1,8 g , sodium hydroxide 1g , benzyl alcohol 5 g and water ad 100 g

2. Ibutop

   Composition:
   Ibuprofen 5 g, isopropyl alcohol, 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolan, poloxamer 407, triglycerides, water, lavender and orange blossom essential oil.

3. Nurofen gel

   Composition:
   Ibuprofen 5 g, isopropyl alcohol, hydroxyethyl cellulose, sodium hydroxide, benzyl alcohol and water ad 100 g

4. Fastum gel

   Composition:
   Ketoprofen 2,5g, carbomer 940, ethanol, lavender essential oil, diethanolamine and water

5. Feldene gel

   Composition:
   Piroxicam 0,5 g , carbomer 980, propylene glycol, ethanol, benzyl alcohol, diisopropanolamine, hydroxy ethylcellulose and water ad 100 g

6. Niflugel :

   Composition:
   Nifluminic acid 2,5 g , diisopropanolamine , carboxymethylen , ethanol 95 ° and water ad 100 g

7. Piroxicam 1 % alcoholic gel

   Composition:
   Piroxicam 1 g, hydroxypropyl cellulose 1.75 g, propylene glycol 5 ml, polysorbate 80 2 ml, isopropyl alcohol 70 % ad 100 ml

Analysis of the compositions

In this series Ibutop is more or less an outsider. Indeed this gel is not a classic hydrophilic polymeric gel but a micro-emulsion based on poloxamer, which is a surfactant with the chemical structure of a copolymer of ethylene – and propylene oxide. Poloxamer (Lutrol) is not sold by all suppliers of pharmaceutical ingredients and therefore this formulation was not taken into consideration for this article.

In all other formulations of the listed examples the three already mentioned polymers are found. Composition n°1 and probably also n°3 contain an amount of sodium hydroxide sufficient to convert 5 g ibuprofen into its salt. This transformation contradicts the general rule that a non-ionized molecule permeates better through the epidermis than its ionized form. One could increase the concentration of isopropyl alcohol in this formulation in order to dissolve a fraction of the quantity of ibuprofen present and then convert the rest to the water soluble sodium salt.
Compositions 4, 5 and 6 use carbomer, which is compatible with high alcohol concentrations. This means that a large amount of alcohol can be expected in order to dissolve the NSAID and to obtain a transparent gel with a good penetration into the skin. So in these cases base is added not to dissolve the NSAID but to give a good consistency to the gel. However one should take into account the competition for the base in between the polymer and the active ingredient. As a result the amount of base added is critical. On the one hand a sufficient number of carboxylic groups of carbomer should be ionized in order to give it the opportunity to unroll and on the other hand it is advisable not to convert a too large quantity of NSAID into its ionized form. In general these gels contain a larger amount of carbomer than usual (4).

Surprising is also the nature of the base used in these three formulations. This is due to the insolubility in alcohol of the polymer salts obtained after neutralization with sodium hydroxide or trometamol. Therefore typical organic bases must be used as diethanolamine and diisopropanolamine. However they are not easily accessible to the pharmacist through which his possibilities become limited.

This is the reason why hydroxypropyl cellulose has been used occasionally as a gelling agent as in composition 7 and in a composition for a flufenamic acid gel published recently (5). Hydroxypropyl cellulose contains no ionizable groups and as consequence the problems given by the incompatibility between an acidic drug and carbomer do not appear. But the patient complains very often of the stickiness and slow penetration into the skin of hydroxypropyl cellulose gels.

Anhydrous gels

The exception on the general rule carbomers require neutralization with base in order to obtain an adequate consistency is known since long. Molecules, which contain a sufficient number of hydroxyl groups as poly ethoxy and hydroxyl solvents, are also capable to initiate swelling and gel formation (Figure 2).

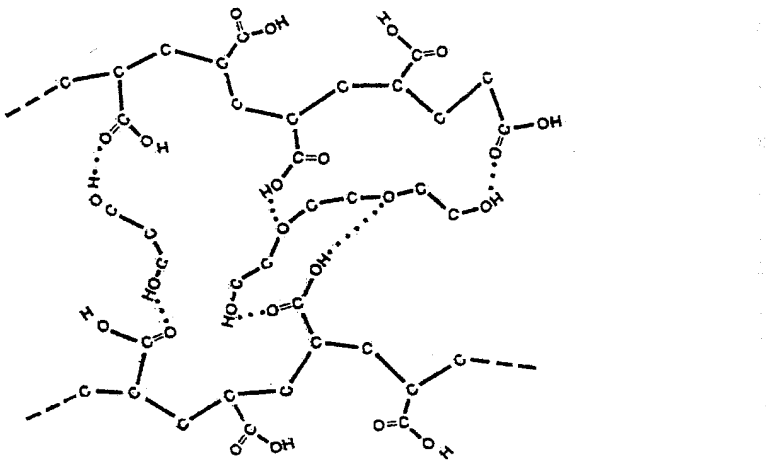


Figure 2 Schematic representation of the formation hydrogen bounds with Carbopol (3)

Already in 1972 Lang (6) formulated anhydrous gels without the addition of any alkaline substance for the preparation of shampoos and hair styling gels. But this approach remained rarely utilized in practice. The literature makes reference of a few rather theoretical studies on gels (7,8,9) including also anhydrous gels.

To achieve a maximal swelling the carbomer powder must be brought into contact with the semi-polar solvent during a sufficiently long period of time. The duration of this period depends on the viscosity and the chemical properties of the solvent. Normally it lasts 30 minutes up to 3 hours. Heating can shorten this period. The viscosity obtained depends also on the frequency of the hydroxyl groups in the chemical structure of the solvent (3). The stability of the viscosity of the anhydrous gels is comparable with those obtained by neutralization.

Lubrizol (3), the manufacturer of Carbopol, recommends the use of carbomer gels obtained without neutralization when addition of base is problematic. The main advantage is their acidic pH, as far as a pH is applicable in such a medium. A weak acidic pH is ideal for NSAID's.

Lubrizol proposes the following formulations:

a. for cosmetic applications :

1. hair gel : water 70 g, methylcellosolve (2-methoxyethanol) 30 g, Carbopol 980 2,5g
2. hydrogene peroxide gel : perhydrol 6 g, Carbitol (monoethyl ether ou diethylene glycol) 50 g, water 50 g, Carbopol 981 3 g
3. Shampoo: sodium laurylsulphate 2 g, Brij 30 (POE (4) laurylether) 10 g, water 90 g, Carbopol 981 2 g

b. for pharmaceutical applications :

1. Gel n° 1 : Carbopol 980 or 981 1 to 2 g, propylene glycol ad 100 g
2. Gel n° 2 : Carbopol 980 or 981 2 g, glycerine ad 100g
3. Gel n° 3 : Carbopol 981 2 g, PEG 600 ad 100g

Anhydrous gel containing flufenamic acid and ibuprofen

Problems encountered when neutralizing a carbomer gel in presence of an acidic active ingredient were submitted to the question box (4) very regularly. In order to find a sound solution we decided to try the use of an anhydrous carbomer gel as an excipient for flufenamic acid and ibuprofen. In a series of preliminary experiments the concentrations of the components were optimized and finally the following formulation was found satisfactory for compounding practice:

R/	propylene glycol	12 g
	carbomer 980	3 g
	ethanol denatured with ether ad	100 g

Propylene glycol can be replaced by glycerol. If the viscosity is found too low, the concentration of propylene glycol or glycerol may be increased.

Preparation of the anhydrous carbomer gel

Tare a beaker with a volume of 150 to 200 ml and place a rod for magnetic stirring on the bottom of the beaker. Weigh 12 g propylene glycol and 42 g ethanol denatured with ether, mix and sprinkle slowly 3 g carbomer 980 while stirring intensively. Continue stirring during 10 minutes at lower speed. Remove the rod and cover the beaker.
Place the beaker in the freezer during 2 hours. After this period fill up to 100 g with denatured ethanol and transfer the covered beaker for one night in the freezer. Take the beaker out of the freezer and store the gel in a hermetically closed jar at room temperature.

Composition and method of preparation of a 3 % flufenamic acid and a 5 % 'ibuprofèn gel

For the local treatment of some inflammations as: arthritis or peri-arthritis or painful traumas, a gel containing either flufenamic acid or ibuprofen can be prescribed. They give the great advantage that their pharmacological action is limited to the area of application.

Composition

R/ flufenamic acid 3 g or ibuprofen 5 g
anhydrous carbomer gel ad 100 g

Method of preparation

Weigh in a beaker respectively 97 g anhydrous gel for the flufenamic acid gel or 95 g for the ibuprofen gel. Sprinkle slowly respectively 3 g flufenamic acid or 5 g ibuprofen on top of the gel and mix till the powder is dissolved. Transfer the gel in an aluminum ointment tube and store at room temperature.

SUMMARY

This article describes the problems encountered during the preparation of hydrophilic gels containing an acidic active ingredient. The analysis of the compositions of several topical pharmaceutical products containing a NSAID reveals that preference is given to carbomer as gelling agent. In order to avoid the difficulties encountered during neutralization of a hydro-alcoholic gel due to the presence of an acidic compound, an anhydrous carbomer gel is preferred as excipient for flufenamic acid and ibuprofen gels. The use of this excipient will without doubt not remain limited to these two API's, as the anhydrous carbomer gel can be suitable for many other drug products.

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