

RELEASE STUDY OF DICLOFENAC FROM NEW CARBOMER GELS

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ABSTRACT

Carbopol gels were prepared using a traditional polymer with mucoadhesive properties (974P). A new Carbomer derivative Ultrez 21 was also evaluated. Mineral oil, as occlusive ingredient, glycerol as humectant and ethanol were included in all the compositions. The feasibility of preparing these formulations with or without a bioadhesive polymer (Polycarbophil AA-1) and a second oil phase with enhancer activity (Miglyol 840) was evaluated. Further characterization including physical stability during a year was carried out. *In vitro* release behaviour of diclofenac sodium in Franz diffusion cell was evaluated with some selected formulations using an ethanol-water (50 % w/w) solution as receptor medium. Addition of Polycarbophil AA-1 increased formulation viscosity and decreased drug release. These types of topical dosage forms could give sustained delivery of drug onto the skin, could tolerate the incorporation of an enhancer, a humectant and an occlusive phase, so they are interesting promises to improve skin absorption of nonsteroidal anti-inflammatory drugs and to prevent side effects associated.

Keywords: Carbopol, diclofenac sodium, topical administration, transdermal delivery.

INTRODUCTION

Because of its highly organized structure, the stratum corneum (SC) is the major permeability barrier to external materials, and is regarded as the limiting factor in the penetration of therapeutic agents through the skin (Foldvari 2000; Levin 2005; Müller *et al.* 2003; Welin-Berger 2002; Lawrence 1997); however percutaneous absorption is an increasing interesting area in semisolid formulations. Lipid-based delivery systems have gained recognition as potential particulate carriers for topical drugs. The initial intent was to develop new delivery systems for the topical application of drugs in order to improve bioavailability, increase residence time of the drug within the skin and decrease systemic and local toxicity.

The therapeutic efficacy of a topically applied drug depends on its ability to penetrate the skin and to be accumulated in the deeper layers of the skin. The extent of this absorption varies depending on the physicochemical properties of the penetrant and its formulation. The vehicle composition can affect both drug release and skin permeability properties (Csóka *et al* 2005; Bonina *et al* 1994).

Moreover, for the development of effective topical dosage forms, it is necessary not only to have reproducible, physical stable and well-characterized formulations but it is also important to determine the diffusion properties of the drug in the semisolid vehicles. Because of that,

carbomers that are the most traditional base of topical preparations are still interesting for go on researching (Taş *et al* 2004; Barreiro-Iglesias *et al* 2001). They are polymers of acrylic acid and form hydrogel in water or alkaline solution, due to hydration of the carboxyl groups (Muramatsu *et al* 2000; Macedo *et al* 1993).

The Noveon® series of products is generically known as "Polycarbophil". Specifically, Polycarbophil AA-1, the selected for this study is a homopolymer of acrylic acid crosslinked with divinyl glycol. For bioadhesive applications, Noveon AA-1 polycarbophil has been extensively formulated in a variety of drug delivery systems for mucous membranes.

Diclofenac has been extensively assayed for topical applications; a study dealing with the relationship between different colloidal structures (liposomal dispersions, microemulsions, lamellar liquid crystals) and their delivery of diclofenac diethylamine is interesting (Kriwet 1995).

Percutaneous drug absorption is described by Fick's first law of diffusion and one of the attempts made to manipulate the drug delivery through the skin was the use of enhancers. Fatty acids derivatives, one of the most studied enhancers, increase fluidity of the intercellular lipids and it was also observed that shorter chain (C10-12) and branched or unsaturated chain ones are more effective than the others that have longer saturated chain (Foldvari 2000).

Miglyol 840, the selected enhancer in this work, is a propylene glycol diester of saturated vegetable fatty acids

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with chain lengths of C8 and C10 and emollient properties. In addition, it is a non-occlusive oil component with excellent spreadability, penetration-enhancing lipid bases and it is a fat component, readily miscible with natural oils and surfactants (EP, 2002).

Finally, there are reasons in literature that encourage *in vitro* release studies of diclofenac sodium using pH media of above 6.5; firstly because of its pH dependence of solubility and on the other hand, the intramolecular cyclation suffered by the molecule under acidic conditions which causes the salt to become inactivated (Palomo *et al* 1999).

The aim of this work was to evaluate the feasibility of preparation and the behavior of formulations with components such as an enhancer and a bioadhesive polymer to different gels based on traditional and new carbomers.

EXPERIMENTAL

Instrument

Viscometer (Brookfield Rotational Digital Viscometer), stability chamber (WEISS 240 T-Karl Giessen, Germany), Franz type glass diffusion cell, UV spectrophotometer (CARY [1E] UV-Visible Spectrophotometer Varian, USA), pH meter (ALTRONIX® TPA-III, USA) were used.

Materials

The following materials were used as received: Carbopol 974 P NF, Ultrez 21 and Polycarbophil AA-1 (Noveon Inc's Pharmaceutical, Argentina), mineral oil (Castrol Whitmor, UK), Miglyol®840 (SASOL, Germany), glycerol (Sigma, USA), cellulose nitrate membrane (0.65 µm) (Sartorius-Membranfilter, Germany), Diclofenac sodium (Hoechst Roussel Pharmaceuticals).

Procedure

Preparation of gels:

The manufacturing process to prepare the gels was the following: 1) Dissolution of diclofenac sodium in aqueous phase containing ethanol and glycerol; 2) addition of Carbomer or a mix of Carbomer and Polycarbophil AA-1 through a mess on the vortex formed by agitation of the aqueous phase with continuous stirring until total homogenization occurred; 3) addition of oil phase (mineral oil and Miglyol 840) to the preparation of point

2; 4) Neutralization of the prepared gels using a NaOH 0.1 mol.L⁻¹ solution.

The following composition was common for all the prepared formulations: Diclofenac sodium 1.00 g, ethanol 6.40 g, glycerol 12.90 g, mineral oil 4.20 g, distilled water to 100.00 g and NaOH to neutralization.

A distinctive component of each composition is summarized in table 1.

The feasibility of preparation of these formulations was studied with different bases. The compositions based on Carbopol 974 P, a mucosal adhesive grade polymer, and Ultrez 21, a new carbomer derivative, were chosen for further investigation.

Viscosity measurements:

Samples of gels were allowed to settle over 30 minutes at the assay temperature (25 ± 1°C) before the measurements were taken at 10 rpm. Each reading was the average of three determinations.

In vitro diffusion studies:

Franz diffusion cells with a receiver compartment volume of 15 mL and effective diffusion area of 2.84 cm² were used to evaluate drug delivery characteristics from the eight selected compositions. A cellulose nitrate membrane (0.65 µm) was used. The receptor phase (ethanol 50 %, w/w) was continuously stirred and kept at a temperature of 32 ± 0.5°C during the experiments. One gram of gel formulation was placed in the donor compartment. At appropriate time, 1 mL of the sample was withdrawn from the receiver compartment and the same amount of fresh solution was added to keep the volume constant. Each experiment was run in three independent cells. The samples were analyzed spectrophotometrically at a wavelength of 276 nm and the concentration of diclofenac sodium in each sample was determined from a standard curve (4-24 µg. mL⁻¹). Each data point represented the average of three determinations. *In vitro* release studies were recorded for a four hour period. Previous solubility tests were made so as to ensure sink conditions for drug dissolution in the donor medium.

Data analysis:

The cumulative amount of diclofenac sodium permeated expressed in % was plotted for each one of the eight studied compositions. The cumulative amount of drug

Table 1: Compositions of the formulations (% , w/w)

Batch	C	CP	CM	CPM	U	UP	UM	UPM
Carbopol 974	1	1	1	1	-	-	-	-
Ultrez 21	-	-	-	-	1	1	1	1
Polycarbophil AA-1	-	2	-	2	-	2	-	2
Miglyol 840	-	-	1	1	-	-	1	1

released of cellulose membrane at the end of the four hour period was compared through analysis of variance.

Physical characteristics evaluation:

Three physical characteristics of the selected compositions were evaluated after a year of storage at 25°C/60% RH $\pm$ 5 %. They were: change of colour, visible changes such as inhomogeneous appearance or phase separation and appearance of unpleasant smell.

RESULTS AND DISCUSSION

pH measurements

Table 2 summarizes the pH values obtained in each prepared gel. The maximum difference between all the preparations is 0.36 units and it is shown between the composition based on Carbopol 974 with Miglyol 840 (pH = 7.56) and the one based on Ultrez 21 containing Polycarbophil AA-1(7.20).

This little difference is an important fact, because it is well-known the influence that pH has got on carbomer gel structure. In one of the most recent work in this area, Bonacucina et al, state that the rate of drug release is influenced by the pH value of the dissolution medium since it determines the percentage of ionized Carbopol acidic groups at the interface medium. So, it is remarkable that this parameter can be kept out of analysis in the present work.

Table 2: pH values of the formulations measured after preparation

Code	pH
C	7.37 $\pm$ 0.12
CP	7.47 $\pm$ 0.02
CM	7.56 $\pm$ 0.04
CPM	7.52 $\pm$ 0.02
U	7.42 $\pm$ 0.05
UP	7.20 $\pm$ 0.05
UM	7.33 $\pm$ 0.02
UPM	7.23 $\pm$ 0.10

Viscosity measurements

Table 3 exhibits the viscosity of each one of the prepared formulations. It is necessary to point out that no composition showed thixotropy behaviour.

For the compositions that had Miglyol 840 as addition, the lowest viscosity was observed for the gel based on Carbopol 974.

The aggregate of Polycarbophil AA-1 to Carbopol 974 and Ultrez 21 increased their viscosities more than 2 and 3-fold respectively; the obtained formulations, CP and UP showed similar viscosity values between them.

The formulations that had included in their composition both the enhancer and the bioadhesive polymer showed the highest viscosities, greater than the formulations which included only Polycarbophil AA-1. The values of viscosity presented by the four carbomer polymers were not significantly different.

In reference with the literature, it is known that Carbomer 974 gives gels with a greatest elastic character. Usually, the release rate of a drug from a semisolid matrix is inversely proportional to its solid character; however previous studies (Lochhead 1989) have already demonstrated that higher viscosity gels made by Carbopol 974 showed a non-homogeneous viscosity with regions characterised by a very high macroviscosity and regions of water-thin microviscosities. Due to these differences Carbopol 974 in water shows the most rigid gel microparticles when fully hydrated and channels are present in the gel structure, the presence of these channels gives rise to a faster drug release rate for this polymer (Bonacucina 2006).

So, it is interesting indeed to analyse the drug delivery behaviour showed by the formulations of the present work. It is also necessary to remark that the addition of Polycarbophil to Carbopol 974 and Ultrez 21, with or without the enhancer, gives formulations with similar rheological behaviour, because of this, the analysis of drug delivery becomes in an easier issue.

Table 3: Viscosity values of the formulations measured after preparation

Code	Viscosity $\pm$ SD (mPa.s)
C	50 $\pm$ 2
CP	172 $\pm$ 8
CM	46 $\pm$ 2
CPM	249 $\pm$ 12
U	70 $\pm$ 3
UP	174 $\pm$ 7
UM	72 $\pm$ 3
UPM	245 $\pm$ 9

(SD: standard deviation, n = 3).

Drug release studies

The results of *in vitro* drug release studies are presented in fig. 1. Initially, the amount of drug released from both polymers used in single compositions was not significant different. Carbopol 974 samples released an amount of near 30%; while Ultrez 21 samples deliver a slightly higher amount, near to the 40% of drug for the studied period of time. The aggregate of Miglyol to both bases did not cause any significant difference although the gel based on Ultrez 21 released a slightly greater amount of drug and the one based on Carbopol 974 released a lower amount when were compared with the respective base used in single form.

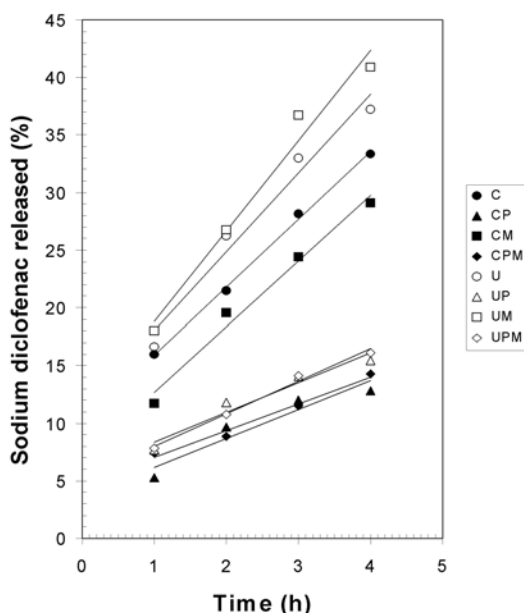


Fig. 1: Results of *in vitro* release of sodium diclofenac.

When formulations were added with Polycarbophil AA-1 drug delivery decreased significantly for both carbomers, although it was very similar among them.

The addition of the bioadhesive polymer made delivery failed to less than half if it is compared with the gels of single base or the ones that contained only the enhancer. The formulations with enhancer and bioadhesive also showed an amount of released drug substantially smaller.

The gels obtained after the addition of Polycarbophil to Carbopol 974 or Ultrez 21 have a good ability to control drug release. After 240 min, about 15% of the diclofenac is released for Ultrez 21 with Polycarbophil AA-1 or with bioadhesive and enhancer. For Carbopol 974, about 12% of the active compound is released at the same time.

Significant changes of viscosity between the compositions based on different single polymers were not observed, either when formulations contained the enhancer selected for this work, Miglyol 840. However, an important increase in the value of viscosity with the aggregate of the bioadhesive polymer Polycarbophil AA-1, with or

without the addition of enhancer was observed. The drug delivery decreased with the viscosity of the formulations (fig. 2).

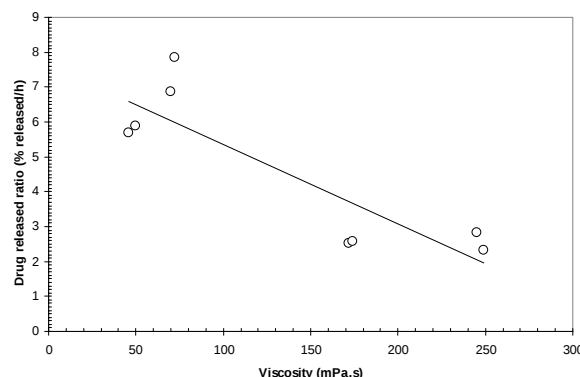


Fig. 2: Dependence of the drug released ratio vs. the viscosity of the formulations.

Physical characteristics

A stability study of the formulations regarding physical changes such as colour, homogeneity of phases and odour was carried out during one year at a temperature of 25°C/60% RH $\pm$ 5%RH. The results are presented in table 4.

Carbopol 974 used as single base showed oil phase separation; the same carbomer also presented phase separation when was added with the enhancer, but no other changes was registered. The other two studied compositions based on this polymer and that included Polycarbophil AA-1 changed their colour slightly, but no other sign of instability was observed. According with these data the bioadhesive polymer could act as a stabilizer for the addition of oil phases.

Related with Ultrez 21, it is remarkable that the adding of enhancer and/or bioadhesive polymer did not alter the homogeneity of the systems; apparently the inclusion of Polycarbophil AA-1 seems to be responsible of the change of colour as result in the detailed analysis behaviour of compositions UPM and UP. Ultrez 21 added with Miglyol did not show any significant change in the evaluated parameters.

Table 4: Summary of physical characteristics of formulations after a year of storage (25°C/60% RH $\pm$ 5 % RH)

Code	Visual changes	Change of colour	Appearance of unpleasant smell
C	Oil phase separation	–	–
CP	–	+	–
CM	Oil phase separation	–	–
CPM	–	+	–
U	–	–	–
UP	–	+	–
UM	–	–	–
UPM	–	+	–

It seems that Polycarbophil AA-1 could act as stabilizer for the addition of oil phases to Carbopol 974. On the other hand, the use of Ultrez 21 resolved the problem of the separation of phases, although compositions based on this Carbomer and added with the bioadhesive polymer showed change of colour; it could be that the chosen excipients were not adequate for the compositions, so a more exhaustive study must be followed to understand this phenomenon better.

CONCLUSIONS

It is feasible to aggregate an enhancer and/or a bioadhesive polymer to gels based on traditional or new type of carbopol polymers recommended for mucosa or topical use. These formulations include in their composition an oil phase with occlusive property, a humectant and also ethanol. So, novel compositions for topical use with pharmaceutically acceptable excipients and within concentrations allowed for the route have been obtained. It is remarkable, that the addition of these other excipients able Carbopol 974 gels to give a sustained and controlled drug delivery, changing, in this way the typical behaviour of this polymer single formulations.

Formulations' viscosity is in inverse relationship with the amount of released drug, this observation is according with a vast previous literature. The additional possibility to incorporate a transdermal enhancer and a polymer with bioadhesive capacities make them very interesting for a number of different types of drugs. As the final pH for all these formulations was similar, it is possible to design topical drug delivery systems based in the ones showed in the present work.

These types of gels would be interesting candidates in the attempt to improve transdermal drug absorption for NSAIDs for instance; more time-residence could be achieved, sustained drug delivery is possible and physical stability characteristics are promising; three important factors for topical drug delivery development.

It is also possible to apply these types of formulations for the topical delivery of drugs that present problems of skin irritation at the recommended dose like benzoyl peroxide.

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