Drug Development and Industrial Pharmacy, 24(4), 337-343 (1998)

RESEARCH PAPER

Possibilities of Conveying a Cationic Drug in Carbomer Hydrogels

Nicola Realdon, Enrico Ragazzi,* Marisa Dal Zotto, and Gabriella Dalla Fini

Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Padua, Padua, Italy

ABSTRACT

A drug with cationic characteristics such as procaine can be conveyed in a Carbomer hydrogel in two different ways: (i) in the form of salt in solution in the aqueous phase, and (ii) in the base form salified with the same polymer. Introduction of the drug into the hydrogel with different concentrations of polymer produced, in both cases, a reduction in viscosity in relation to drug concentration. The gels with procaine salified with the polymer showed greater viscosity.

The drug release rate, in general, diminished with the increase in polymer concentration. Nevertheless, when this concentration was maintained, there was no variation in release rate when the viscosity produced as a consequence of drug concentration was changed. Gels with procaine salified with the carboxyvinylic polymer had a faster release rate than those with procaine in the hydrochloride form dissolved in the aqueous phase. These results have also been confirmed by a simulated absorption test.

INTRODUCTION

Over the last decade hydrogels formed from natural, semisynthetic, or synthetic polymers have been confirmed as vehicles for different types of pharmaceutical applications. They have good viscosity, satisfactory bioadhesion, and are without irritating or sensitizing actions (1–4). These hydrogels, which are able to convey various types of drugs, have been used rectally in the form of microenemas or in ophthalmic applications such as collyrium, which because of their viscosity permit the drug to have prolonged contact with the eye surface (5–7).

Carboxyvinylic polymers are currently among the most commonly used viscosizing substances. In the free-acid state they are able to swell in contact with water

*To whom correspondence should be addressed. Dipartimento di Scienze Farmaceutiche, Università di Padova, Via F. Marzolo, 5, I-35131, Padova, Italy. Fax: +39 49 8275338/66. e-mail: realdon@pdfar3.dsfarm.unipd.it

producing opalescent dispersion of low viscosity. When salified with bases of different structures, they produce transparent gels of high viscosity even at low concentrations. Their rheological characteristics are conditioned by the type and quantity of the organic or inorganic base used for salification. The maximum viscosity is reached in a range of pH values around neutrality (1,8,9).

Substances which can act on the ionization of the salified carboxylic groups or the level of hydration of the macromolecules (electrolytes, alcohols, polyalcohols) can cause a drop in viscosity of the gels (9–11) until flocculation of the polymer itself occurs.

Early trials in conveying drugs of a different nature have indicated that they may produce the same effects. Cationic drugs can be conveyed in polyacrylate gels in two different forms: in the state of salt in solution in the aqueous vehicle of the gel, or in the base form with which the polymer itself is salified, totally or partially substituting the usual bases to produce the gel.

In this study it was therefore decided to ascertain the effect that the two different methods of vehicling and concentration of a typical cationic drug, procaine, could have on the rheological characteristics of polyacrylate gels and drug availability.

MATERIALS AND METHODS

Materials

The following materials were used to obtain the gels: Carbopol 934 (B. F. Goodrich Co., Cleveland, OH); ethanol, sodium hydroxide (Carlo Erba, Milan, Italy); glycerine, procaine (ACEF, Fiorenzuola D'Arda, Italy); and procaine hydrochloride (Hoechst AG, Frankfurt, Germany).

Gel Preparation

Two series of Carbopol 934 gels in the three concentrations of 1, 2, and 3% (p/p) were prepared. In the first series the procaine was conveyed in the form of hydrochloride in solution in the aqueous phase; in the second series the procaine itself was used as salifying base for the carboxylic groups.

In both series the drug was introduced in the following concentrations: in the 1% gels, 37.5 and 75 mM; in the 2% gels, 37.5, 75, 112.5, and 150 mM; in the 3% gels, 37.5, 75, 112.5, 150, 187.5, and 225 mM. When procaine is used as a base for salifying the carboxyvinylic polymer the quantity of drug conveyed is necessarily limited by the quantity required for the saturation of the polymer at the established concentrations. If, instead, procaine is used in the hydrochloride form (soluble in the aqueous phase of the gels, with the polymer salified by the sodium hydroxide), the quantity of drug conveyed is not limited. However, both series used procaine concentrations compatible with the quantity salifiable by the polymer to be able to give the comparable results between the two means of vehicling tested.

Gels with Procaine Hydrochloride

The required quantity of Carbopol 934 was suspended in half the quantity of water and left to hydrate for 20 hr at room temperature. The required quantity of sodium hydroxide solution 10% (p/v) to salify the polymer (pH 7–7.5) was added while it was in a vacuum and stirred constantly. Then the quantity of 1 M procaine hydrochloride solution needed to reach the desired concentration, followed by a quantity of ethanol to give the finished gel a concentration of 5%, and the amount of water necessary to reach the required weight of the preparation were added.

Gels with Procaine Salifying the Polymer

The required quantity of Carbopol 934 was left to hydrate for 20 hr in half the water available at room temperature. In a vacuum and while being constantly stirred, the established quantity of base procaine dissolved in a volume of ethanol equal to 5% (p/p) of the final weight of the gel was then added, followed by the quantity of 10% sodium hydroxide solution necessary for the complete saturation of the polymer (pH 7–7.5). To complete the preparation, the quantity of water required to reach the given weight of the gel was then added.

Determination of the Rheological Characteristics

The RV12 rotational viscometer (Haake, Karlsruhe, Germany) was used with a PG142 programmer, using the SVI and PKI 1° measuring systems operating at a temperature of 20°C.

Determination of In Vitro Drug Release (12)

Gel samples were placed in cells 70 mm in diameter and 2 mm deep in the center of Perspex dishes (110 mm in diameter, 7 mm thick). The surfaces of the gels were

leveled with a spatula and the samples were weighed. A dialysis membrane (Visking), 90 mm in diameter, was soaked in water for 20 hr, and patted with filter paper, then placed on the surface of the gel sample; care was taken to avoid air bubbles between gel and membrane. A rubber O-ring (96 mm in diameter) was placed on top and the membrane, fixed with a Perspex ring (external diameter 110 mm, internal diameter 70 mm, 7 mm thick), and attached with stainless steel screws. The cells were then placed, with the membrane upward, in 2-liter beakers containing 1 liter of phosphate buffer 1/15 M, pH 7.4, thermostated at 37 ± 0.5°C and stirred constantly at 60 rpm by a blade stirrer. At 15-min intervals, 2-ml samples of the diffusion fluid were collected and replaced with 2 ml of buffer at 37°C. After dilution the amount of procaine was measured spectrophotometrically at 288 nm. The test was performed in six parallel cells.

The percentages of drugs released from gels showed a linear relationship with the square root of time (correlation coefficient > 0.998). The release rates (V) of the drug were therefore expressed by the equation $V = Q/\sqrt{t}$ following Higuchi's model (13), where Q is the amount of drug released from gel sample at time t.

In Vitro Simulated Drug Absorption (12)

The procedure described in the drug release test was followed, except that a coupled membrane was used (14). A cellulose mixed ester membrane (Millipore HAWP09000, type HA, 90 mm diameter) was soaked by immersion for 1 hr in isopropylmiristate and wiped between two disks of filter paper. A second cellulose acetate dialysis membrane (Visking, 90 mm in diameter), soaked for 20 hr in water, was superimposed and made to adhere well by a rubber roller. The coupled membrane was placed with the cellulose membrane side in contact with the gel sample.

RESULTS AND DISCUSSION

A cationic drug, procaine, showed that it could be vehicled in a polyacrylate gel in two different ways: in the form of salt (hydrochloride) in solution in the aqueous phase and in the base form salified to the polymer.

According to the concentrations of both polymer and drug, the two different methods of vehicling showed not only significant variations in rheological characteristics of the gels, but also in drug availability.

Dispersing Procaine in the Form of Hydrochloride in Solution in the Aqueous Phase of Gels

The viscosity of the hydrogels at each of the three concentrations of Carbopol 934 tested was influenced significantly by drug concentration. As shown in Table 1, with increasing concentrations of procaine hydrochloride, a progressive reduction in gel viscosity was observed which was even more marked with a lesser polymer concentration. In fact at 1% Carbopol, the introduction of a 37.5 mM concentration of procaine hyrochloride (equal to 1% p/p) caused a 20% drop in viscosity compared with its initial values. In the 2% polymer gel, viscosity diminished by almost 20%, at the same concentration of the drug, while in the 3% gel there was, instead, an increase in viscosity of 7%. The progressive reduction in viscosity of all gels as drug concentration increased was even more marked with a lesser polymer concentration.

Carbopol gels at the same concentrations showed similar behavior with the introduction of an electrolyte such as sodium chloride (Table 2). The effect produced by the procaine hydrochloride in solution in the aqueous phase of the gels could therefore be attributed to the influence that an electrolyte, in general, could have on the ionization level of the polymer carboxylic groups, on the level of hydration, and on the type of intermolecular bonds that can be formed. The different structure that the macromolecules assume and the different intermolecular bonds formed necessarily influence the conformation of the internal structure of the gels which is responsible for their rheological behavior.

Table 1

Relative Viscosity (D = 100 sec^{-1}) at 20°C of Carbopol 934 Hydrogels Containing Different Concentrations of Procaine Hydrochloride in Solution in the Aqueous Phase

Procaine Hydrochloride Concentration (mM)	Viscosity (Pa · sec) of Gels at Polymer Concentrations of		
	1%	2%	3%
0	5.22	6.90	9.38
37.5	1.17	5.65	10.04
75.0	0.59	4.10	9.45
112.5		2.86	8.38
150.0		1.96	6.58
187.5			4.79
225.0			4.45

Table 2

Relative Viscosity (D = 100 sec^{-1}) at 20°C of Carbopol 934 Hydrogels Containing Different Concentrations of Sodium Chloride

Sodium Chloride (mM/l)	Viscosity (Pa · sec) of Gels at Polymer Concentrations of 1%	2%	3%
0	5.22	6.90	9.38
50	3.90	6.39	8.43
100	2.93	5.32	7.63
150	2.40	4.70	6.65
200	1.95	4.35	6.30

At the same drug concentrations the release rate is conditioned by the concentration of the polymer, in strict relation with the gel viscosity. The lower the release rate, the greater the polymer concentration and therefore the more compact the network structure of the gel and the higher its viscosity (Fig. 1). On the other hand, with an increase in procaine hydrochloride concentration the gels with 1 and 2% Carbopol showed a reduction in release rate. In the 3% gel the release rate appeared almost constant and was independent of the significant variation in viscosity and different drug concentrations.

Dispersing Procaine as a Salifying Base of the Polymer

When procaine was used as a base to salify the polymer in partial or total substitution of the sodium hydroxide, the gels obtained were equally limpid and had greater viscosity with the same concentration of both polymer and drug (Table 3). For the 1% Carbopol 934 gel with a 37.5 mM concentration of procaine as partial substitution of the base required for polymer saturation, the drop in viscosity was only 7%; for the 75 mM concentration, with total substitution of the sodium hydroxide, the viscosity decreased by 25%. The gels with 2 and 3% polymer, conversely, showed a slight increase in viscosity, (up to 9% for the first and 20% for the second), followed by a successive reduction that did not go below 15–20% of the viscosity of gels without procaine. This can be attributed to the different structure assumed by the macromolecules of the polymer when salified with different bases.

Although the procaine is involved in salifying the polymer, its release rate is satisfactory (Fig. 2). Also in this case the release rate diminishes with increasing Carbopol concentration as a result of the greater compactness of the network around the system. With increasing concentrations of procaine salifying the polymer, the release rate underwent a progressive reduction

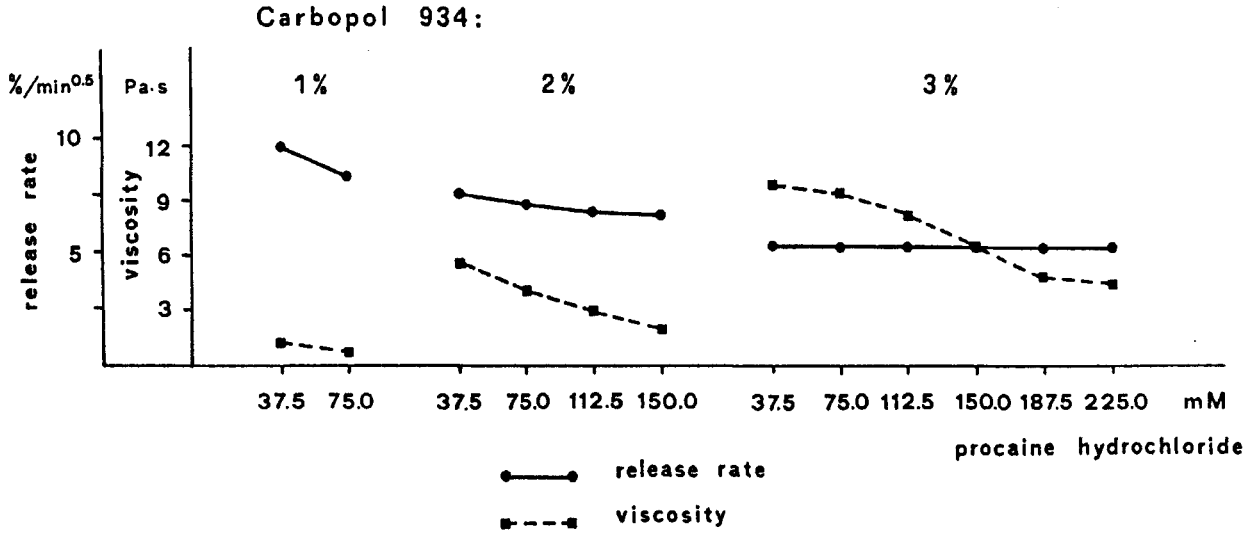

Figure 1. Release rate constants of procaine from Carbopol 934 gels containing different concentrations of procaine hydrochloride in solution in the aqueous phase compared with the relative viscosity (D = 100 sec^{-1}).

Table 3

Relative Viscosity (D = 100 sec^{-1}) at 20°C of Carbopol 934 Hydrogels Containing Different Concentrations of Procaine Salified with the Polymer

Procaine Concentration (mM)	Viscosity (Pa · sec) of Gels at Polymer Concentrations of 1%	2%	3%
0	5.22	6.90	9.38
37.5	4.85	7.18	10.98
75.0	3.91	7.52	11.25
112.5		6.90	10.58
150.0		5.65	9.72
187.5			8.98
225.0			7.85

which cannot be correlated to the pattern of gel viscosity.

At the same concentrations of polymer and drug, the release rate of a cationic drug such as procaine appeared to be generally higher when used to salify the polymer compared with when found in solution such as salt in the aqueous phase of the gel (Fig. 3), despite the significant differences in gel viscosity at the same concentrations of both drug and polymer. In fact if the viscosity, and therefore conformation of the internal network of the system, influenced the speed of drug diffusion, in the case of procaine vehicled as hyrochloride (in which gels have less viscosity), it would be necessary to have a rate of diffusion, and therefore release, which is higher than when the same procaine was salified with the polymer.

This behavior could not be attributed solely to a physical mechanism and therefore the intervention of a chemical mechanism was hypothesized.

In the release test through a porous membrane the hydrogel sample was mechanically separated from the accepting aqueous phase, but was in direct contact with it through the pores of the membrane filled by capillary action with the same aqueous phase. This type of test is currently used to check drug availability from an ointment in relation to the speed at which it leaves the excipient and comes into contact with the cutaneous compartment through which it is absorbed.

Because of the accepting aqueous phase consisting of pH 7.4 phosphate buffer, in the used model, the greater release of procaine from the gel in which it was salified with the polymer could be attributed to an ionic exchange between hydrogel and buffer solution through the pores of the interposing membrane (15). In fact sodium and potassium ions from the buffer solution could be diffused in the hydrogel sample and be ex-

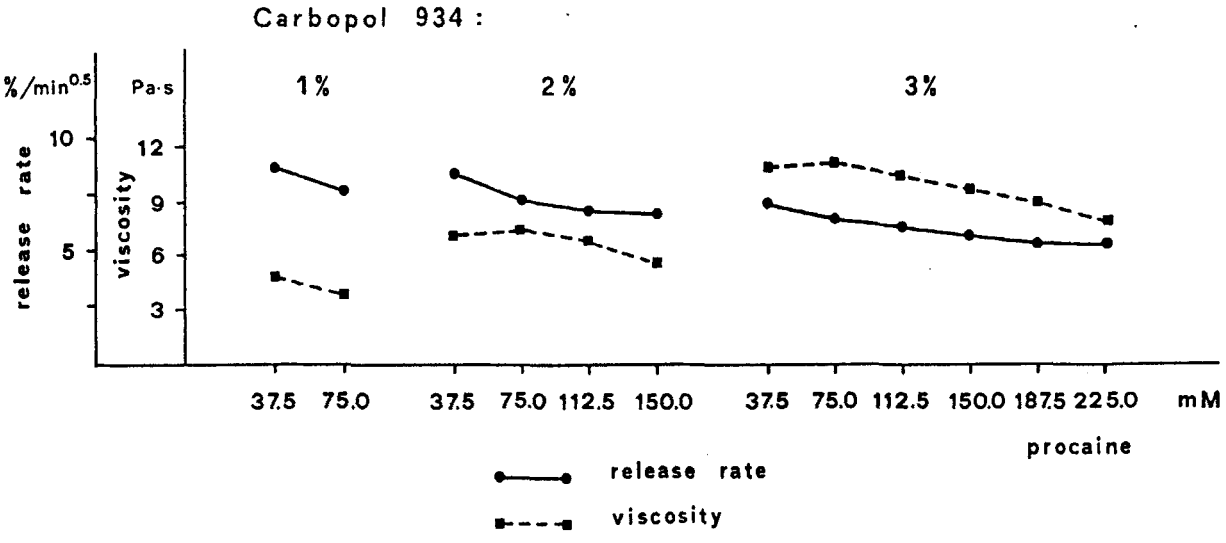

Figure 2. Release rate constants of procaine from Carbopol 934 gels containing different concentrations of drug salified with the polymer compared with relative viscosity (D = 100 sec^{-1}).

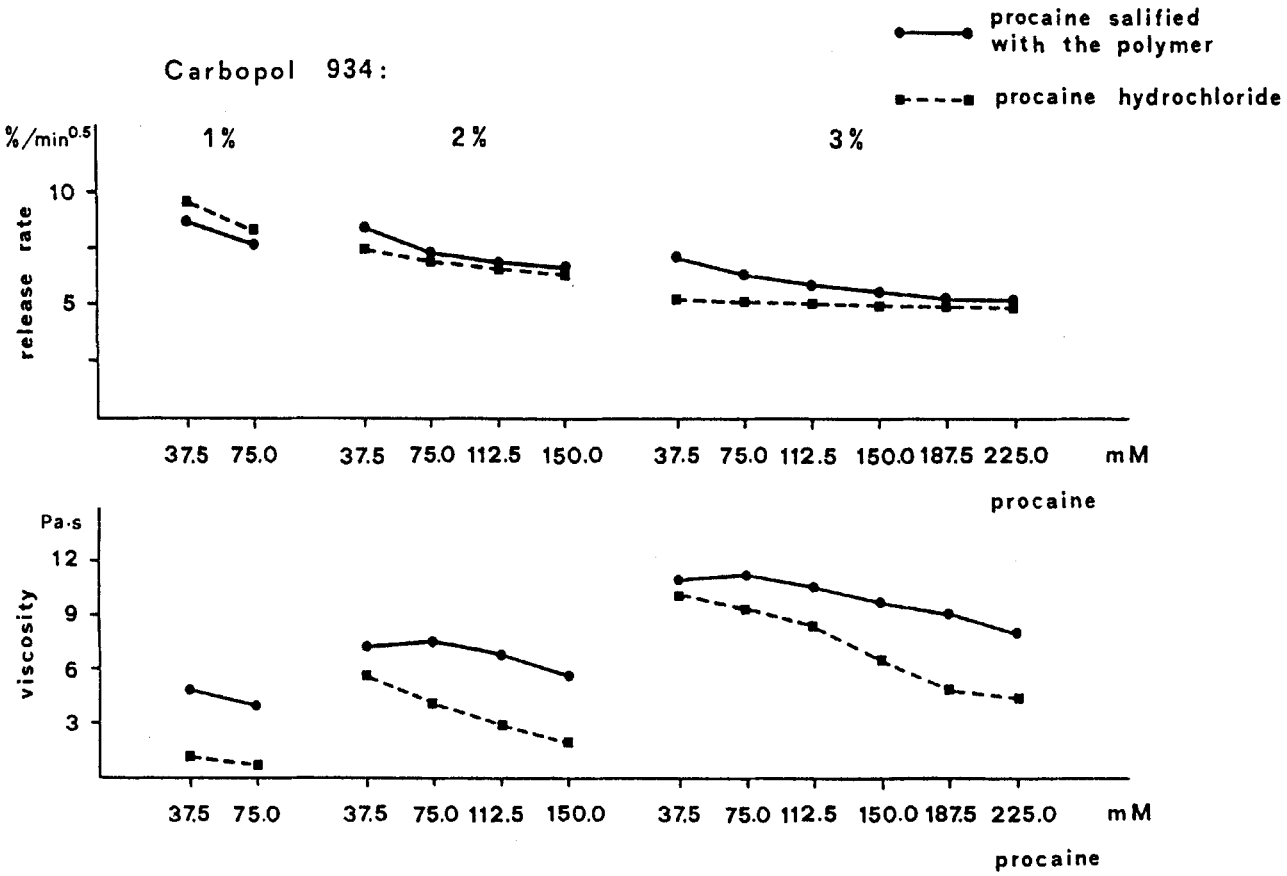

Figure 3. Pattern of procaine release rate from Carbopol 934 gels vehicled in different concentrations in the two test conditions compared with relative viscosity pattern (D = 100 sec^{-1}).

changed with the procaine salifying the polymer carboxylic groups, in turn diffusing into the adjacent aqueous phase as a function of the concentration gradient. This could explain the greater release rate shown by procaine, compared with when it is found in solution in the gel in the ionic state.

With the aim of avoiding direct contact of the gels with the aqueous phase of the cutaneous compartment model as mentioned above,a porous membrane of cellulose acetate was substituted with a membrane of cellulose nitrate and acetate saturated with a lipid phase such as isopropyl myristate, frequently used to simulate a cutaneous barrier (16–19). This model permits the cutaneous barrier to be simulated. The drug is made available to a plasma compartment by diffusion from the ointment to the lipid phase by saturating the membrane and from there to the aqueous phase which simulates the plasma compartment. With this model the possibility of an ionic exchange between the two phases as mentioned above would be avoided in that they are separated by the lipid barrier that saturates the membrane.

Carbopol 934 hydrogels were tested with this simulated absorption model in three concentrations of 1, 2, and 3% p/p and with two different concentrations of procaine, 75 and 150 mM, vehicled in the two different test conditions.

The simulated absorption curves obtained, compared in Fig. 4, confirmed how the availability of a drug with the characteristics of procaine from a hydrogel of carboxylic groups of the polymer itself, excluding an ionic exchange mechanism with the accepting phase.

The good availability of procaine in the simulated absorption test, both in solution as hydrochloride in the aqueous phase of the gel and as salified with the polymer, suggests how in both cases, given the K_b value, by a hydrolytic phenomenon it is in part dispersed in the hydrogel as a nondissociated base. In this way, procaine is in a sufficiently lipophilic form to be able to diffuse

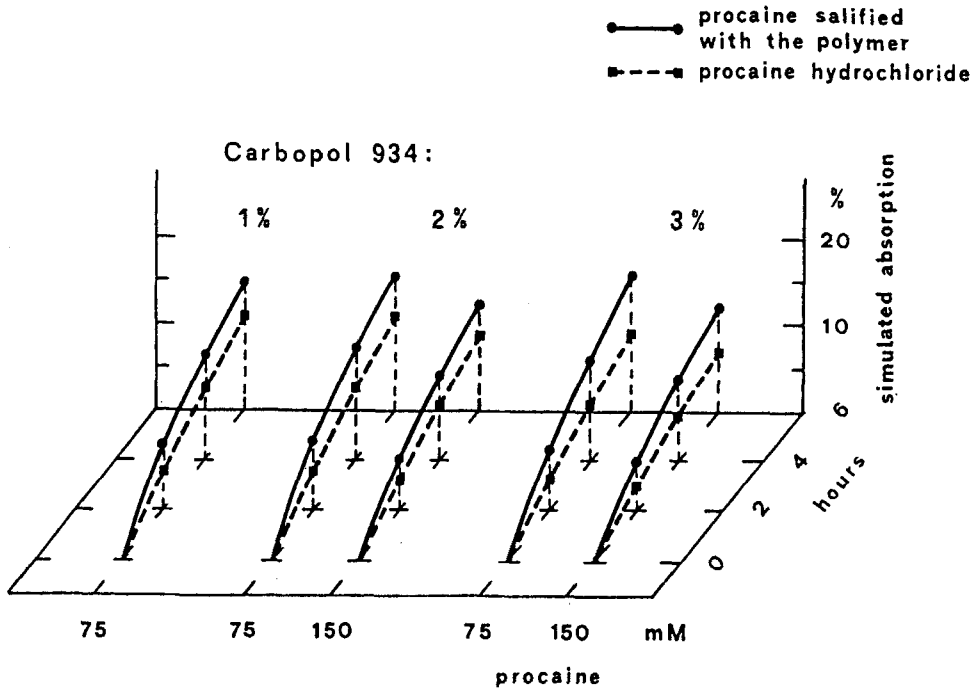

Figure 4. Simulated absorption curves of Carbopol 934 gels with procaine vehicled in different concentrations in the two test conditions.

into the lipid phase of the cutaneous barrier that simulates the cutaneous membrane and then transfer into the accepting plasma phase. Such a phenomenon is accentuated when the drug is salified with the polymer.

REFERENCES

1. A. G. Perotti, Farmaco, pr. ed. 25 (1970).
2. K. Park and J. R. Robinson, Int. J. Pharm., 19, 107 (1984).
3. K. Park and J. R. Robinson, Pharm. Res., 4, 457 (1987).
4. J. D. Smart, I. W. Kellaway, and H. E. Worthington, J. Pharm. Pharmacol., 36, 295 (1984).
5. A. Ludwing, N. Unlu, M. Van Oothnghen, Int. J. Pharm., 61, 15 (1990).
6. N. Unlu, A. Ludwing, M. Van Oothnghen, and A. Hincal, Pharmazie, 46, 784 (1991).
7. N. Unlu, A. Ludwing, M. Van Oothnghen, and A. Hincal, Pharm. Acta Helv., 67, 5 (1992).
8. K. D. Bremecker, Pharm. Ind., 51, 199 (1991).
9. J. Plaizier-Vercammen and M. Delecluyse, Pharmazie, 46, 646 (1991).
10. S. Ishikawa, M. Koba Yashi, and M. Samejima, Chem. Pharm. Bull., 36, 2118 (1988).
11. V. I. Erős, R. Diszl, and I. Aponyi, Pharm. Ind., 52, 511 (1990).
12. N. Realdon, Eug. Ragazzi, M. Dal Zotto, and Enr. Ragazzi, Pharmazie, 51, 113 (1996).
13. W. I. Higuchi, J. Pharm. Sci., 51, 802 (1962).
14. H. Loth and A. Holla-Beninger, Pharm. Ind., 40, 256 (1978).
15. M. N. Mutimer, C. Riffkin, J. A. Hill, M. E. Glickman, and D. N. Cyr, J. Am. Pharm. Assoc. Sc. Ed., 45, 212 (1956).
16. C. L. Gummer, R. S. Hinz, and H. I. Maibach, Int. J. Pharm., 40, 101 (1987).
17. J. Hadgraft and G. Ridout, Int. J. Pharm., 39, 149 (1987).
18. J. Hadgraft and G. Ridout, Int. J. Pharm., 42, 97 (1988).
19. G. P. Gree, J. Hadgraft, and M. Wolff, Int. J. Pharm., 55, 265 (1989).