Consistency of Carbopol 971-P NF gels and influence of soluble and cross-linked PVP

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Abstract

A study is made of the polymerization process of polyacrylic acid, commercially known as Carbopol® 971 NF, assessing its consistency as a function of the degree of neutralization at pH values from 3 to 12, approximately. Percentage concentrations ranging from 0.1 to 1.4% (w/w) were studied. The gels obtained were non-Newtonian, and pseudoplastic. As concentration and pH rise, the consistency of the gels increase to a maximum, which appears between pH 6 and 8, allowing their use as vehicles in bioadhesive formulations for mucosal application. Over the increasing viscosity interval, functions were obtained to indicate the consistency of the gel as a function of pH and concentration. Since the correlation between the theoretical and experimental results is excellent, the equation found can be used to theoretically calculate the working concentration and pH required to secure the necessary consistency for a given vehicle. The addition of soluble polyvinylpyrrolidone (PVP), and cross-linked PVP (PVPP) does not substantially modify the rheological behavior of the gels, thus permitting their addition to usual vehicles. © 2002 Elsevier Science B.V. All rights reserved.

1. Introduction

Carbopol® resins are reticulated polymers of acrylic acid (APHA, 1986), with molecular weights ranging from 2 to 30×10^6, depending on the type of resin involved (Barry, 1983). Although

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they are weak acids ($pK_a > 5$ in most cases), they easily react to form the corresponding salts. Aqueous dispersions of Carbopol exhibit a pH in the range of 2.8–3.2, depending on the concentration of resin employed (Barry, 1983; Hernández et al., 1998).

A molecule of these polymers in the dry powder-state is strongly coiled into a spiral form. When dispersed in water the molecule becomes hydrated and slowly unwinds, generating an in-

crease in viscosity. In order to ensure maximum viscous effects, however, the molecule must unwind completely. There are two mechanisms by which the resin molecule can fully unwind to yield a maximum thickening effect or the best bioadhesive properties. The most common mechanism involves neutralization of the polymer with an appropriate base. Neutralization ionizes the resin, with negative charges along the polymer chain. Repulsion between these charges in turn contributes to unfold the structure, while intertwining of the chains yields a three-dimensional (3-D) matrix. The result is the instantaneous formation of a highly viscous gel (Bremecker et al., 1984; Ünlü et al., 1991, 1992; Dolz et al., 1992; Hernández et al., 1998). The second mechanism consists of adding a hydroxyl donor structure to the resin. The combination of a carboxyl group to one or more hydroxyl groups produces thickening as a result of the formation of hydrogen bonds. This is a time-dependent mechanism, and maximum thickening can result after between 5 min and several hours (Goodrich, 1994). In this case, the system maintains its acid pH. Some commonly used hydroxyl donors are polyols (glycerin, propylene glycol and polyethyleneglycols) or non-ionic surfactants containing five or more ethoxy groups.

Although Carbopol resins undergo polymerization in benzene, the introduction of legislations against toxic waste has led to polymerization in alternative solvents. Such resins may contain very small amounts of a mixture of ethylacetate and cyclohexane as an innocuous cosolvent and solvent, respectively. The resulting gels are highly sensitive to the action of electrolytes; thus, they cannot be associated to either anionic and cationic surfactants or to positively charged ions (Cheng et al., 1985; McNeill and Sadeghi, 1990).

In contrast, the Carbopols remain highly stable in their response to variations in temperature. In this sense, a brief exposure to high temperatures (i.e. sterilization) does not alter the characteristics of the formulation; as a result, they are useful as vehicles of pharmaceutical bioadhesive preparations for application to skin and buccal or gastro-intestinal mucosal membranes (McNeill and Sadeghi, 1990; Singla et al., 2000).

The present study investigates the consistency of Carbopol® 971-P gels at different pH values and concentrations, and their pharmaceutical applicability, both as such and in the presence of soluble and cross-linked polyvinylpyrrolidone (PVP and PVPP, respectively), which may be added to bioadhesive forms in order to modulate drug release characteristics.

2. Materials and methods

The polyacrylic acid polymer employed is commercially known as Carbopol® 971-P NF, and was supplied by Quimidroga S.A. (batch number CC76AAJ021). A 10% (w/w) sodium hydroxide solution was used as neutralizing agent. Bidistilled water was used in all cases. Hydrogels were prepared at concentrations ranging from 0.1 to 1.4% (0.1, 0.3, 0.5, 1.4% (w/w)), at pH values between 3 and 10. A total of 450 g of each hydrogel was prepared as follows: the amount of polymer required to yield 450 g of hydrogel at the desired concentration was added to water under constant stirring at 800 rpm for 45 min. Then, the preparation was sealed, shielded from light and allowed to stand for 24 h to ensure complete humectation of the polymer molecules. Following this storage period, the dispersion was neutralized with the 10% sodium hydroxide solution. Finally, the gel was again stored for 7 days to reach pH equilibrium. Following this period, corresponding pH and viscosity measurements were made. A rotary viscometer equipped with coaxial cylinders (Bohlin Visco 88BV, 25 velocities) was used to determine viscosity at shear rates between 3.28 and 209 s^{-1}.

The hydrogels containing PVP were prepared for a Carbopol concentration of 0.45%, by adding 0.05 and 0.1% of PVP. The hydrogels containing PVPP were prepared for a Carbopol concentration of 0.45%, by adding 0.05 and 0.1% of PVPP. In both cases, the preparation of the gels and the viscosity determinations were made according to the previously described procedure.

3. Results and discussion

3.1. Rheological behavior of the Carbopol® 971-P NF hydrogels

Experimental values of viscosity (η, Pa s) is a function of the shear rate ($\dot{\gamma}$, s^{-1}) are graphically represented in Fig. 1, for a 0.5% (w/w) concentration gel at two pH values without neutralization and at neutral pH. Of note is the decrease in viscosity as the shear rate increases, thus indicating the non-Newtonian, pseudoplastic character of the tested gels, as well as the great difference in viscosity values for the non-neutralized gel (pH 3.0) versus the neutralized formulation (pH 7.0), as will be analyzed below.

The important decrease in viscosity observed with increasing shear rate (at the lower shear rates employed), followed by a less accentuated descent of the curves suggests, a behavior that can be well described by means of an exponential function. This allowed us to employ the Ostwald-De Waele rheological model expressed by Eq. (1), which has been shown to be appropriate in many studies involving different types of hydrogels (Chauveau et al., 1986; McNeill and Sadeghi, 1990; Chu et al., 1991; Herráez et al., 1993; Delegido et al., 1995; Hernández et al., 1998):
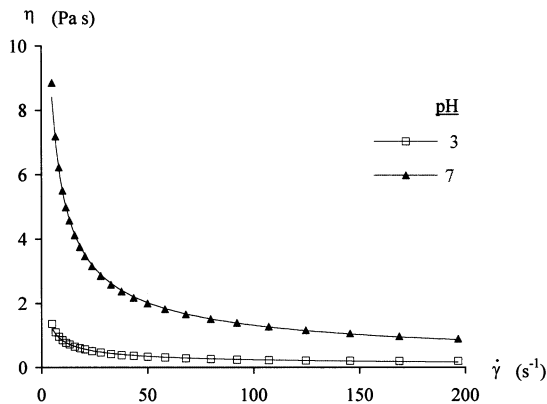
$$\eta = m\dot{\gamma}^{n-1} \tag{1}$$

Table 1
Consistency values and pseudoplasticity indices for Carbopol® 971-P NF hydrogels at a concentration of 0.5% (w/w), at the pH values indicated

pH	m (Pa s^n)	n	r
3	2.902	0.461	0.996
3.7	10.154	0.381	0.999
4.2	15.192	0.376	0.999
4.8	17.641	0.386	0.999
5.4	20.022	0.392	0.999
6.2	21.746	0.389	0.999
7.0	22.764	0.382	0.999
7.4	22.427	0.379	0.999
7.8	22.365	0.381	0.999
10.2	18.680	0.390	0.999
12.3	15.606	0.370	0.999

where m and n are the rheological parameters of the model (m = consistency and n = pseudoplasticity index).

In all cases, the values of m and n were determined using the KaleidaGraph™ fit program. These parameters were subsequently used to objectively establish the modifications produced by the degree of Carbopol neutralization and concentration upon the rheological behavior of the gel.

The values of both parameters, along with the correlation coefficients obtained from the respective fits, are shown (i.e. for a Carbopol concentration of 0.5%) in Table 1. The corresponding plot is given in Fig. 2. Similar point distributions were observed for the remaining concentrations stud-

Fig. 1. Viscosity as a function of shear rate for Carbopol® 971-P NF hydrogels at a concentration of 0.5% (w/w) and the pH values indicated.
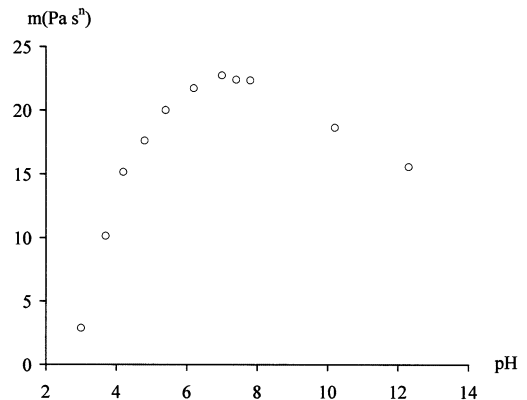

Fig. 2. Consistency as a function of pH for a Carbopol® 971-P NF hydrogel at a concentration of 0.5% (w/w).

ied. A rapid rise in consistency is observed on increasing the pH value, with a maximum at around pH 6; this peak is maintained to about pH 8, after which the consistency is seen to decline.

This behavior can be explained by the molecular structure of the gel. In fact, the polymer chains are initially (i.e. at pH 3) coiled into a spiral form, thus affording a relatively low viscosity. As neutralization progresses, the carboxyl groups of the acrylic acid become ionized, leading to an increasing repulsion of negative charges that causes the molecular structure to unwind, thus inducing a gradual rise in viscosity. The drop in viscosity at pH values above 8 is, in turn, attributable to the increased presence of Na^+ cations from the sodium hydroxide used to achieve neutralization; these cations block the ionized carboxyl groups, thereby reducing the repulsion effect. As a result, the molecules tend to fold, and viscosity decreases.

A valid fit for the up-curve region could be represented by a function of the following general type:

$$m = m_{min} + [m_{max} - m_{min}][1 - e^{-k(pH - pH_i)}] \quad (2)$$

where pH_i and m_{min}, respectively, correspond to the pH and consistency index of the non-neutralized gel. In fact, if $pH = pH_i$, then $m = m_{min}$. The difference $[m_{max} - m_{min}]$ represents the maximum increase in consistency obtained by neutralization of the formulation, i.e. the increment of m induced by neutralization (Δm). Finally, k provides an index, which reflects the rate of increment of m with pH.

Considering that the initial pH of the non-neutralized gel is, in all cases, very close to 3, Eq. (2) can be expressed as follows:

$$m = m_{min} + \Delta m[1 - e^{-k(pH - 3)}] \quad (3)$$

It should be pointed out that for the 0.1% Carbopol concentration, the value of pH_i in Eq. (2) was taken to be 4.1 since, below this value and due to the low viscosity of the gel, it was not possible to conduct viscosity measurements with the system employed.

Table 2 shows the coefficients m_{min}, Δm and k obtained with the different fits corresponding to all the concentrations studied, along with the

Table 2
Values of the coefficients m_{min}, Δm, k and the respective correlation coefficients of the fits corresponding to Eq. (3), at the indicated concentrations

$c\%$	$m = m_{min} + \Delta m[1 - e^{-k(pH - pH_i)}]$			
w/w	m_{min} (Pa s^n)	Δm (Pa s^n)	k	r
0.1	0.476	6.69	0.845	0.994
0.3	0.948	16.26	0.603	0.999
0.5	2.76	21.61	0.660	0.998
0.9	7.91	26.72	0.695	0.998
1.4	12.20	29.81	0.759	0.999

respective correlation coefficients. The values of m as a function of pH, together with the corresponding fits for the up-curve region are shown for all concentrations studied in Fig. 3. As can be seen, the points clearly fit the proposed model.

3.2. Consistency variation with Carbopol concentration: dependence on pH

The above functions were used to calculate m for different pH values at all concentrations studied. The resulting m values are given in Table 3, where the consistency for a hydrogel concentration of 0% has been included (obviously, this figure equals the viscosity of water, a Newtonian fluid, with a value of 0.0009 Pa s^n at 25 °C and 1 atm of pressure) (Raznjevic, 1976).

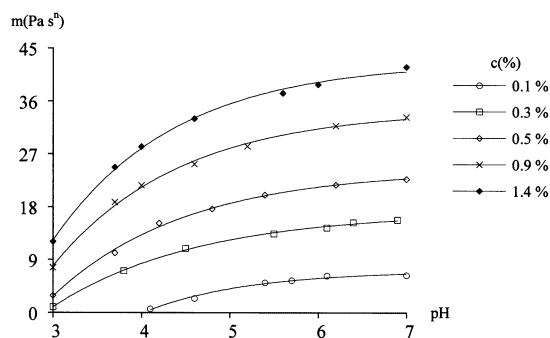The plot of m as a function of concentration for the different pH values selected is given in Fig. 4.

Fig. 3. Consistency as a function of pH for Carbopol® 971-P NF hydrogels at the percentage concentrations indicated (w/w).

Table 3
Carbopol hydrogel consistency values obtained from the equations of Table 2, at the concentrations and pH values indicated

$c\%$	m (Pa s^n)				
w/w	pH				
	3	4	5	6	7
0	0.0009	0.0009	0.0009	0.0009	0.0009
0.1	–	0.476	4.30	5.94	6.64
0.3	0.948	8.31	12.34	14.54	15.75
0.5	2.76	13.20	18.59	21.39	22.83
0.9	7.91	21.29	27.97	31.31	32.97
1.4	12.20	28.07	35.49	38.96	40.58

These point distributions fit an expression of the following type:

$$m = m_{max'}[1 - e^{-k'c}] + m_{min'} \tag{4}$$

where $m_{max'}$ is the asymptotic value towards which m tends at infinite concentration, k' is a parameter related to the rate by which m increases with concentration, and $m_{min'}$ is the m value when the polymer concentration tends to zero, i.e. the viscosity of water. This value can be considered negligible relative to the remaining parameters, and thus Eq. (4) can be simplified to:
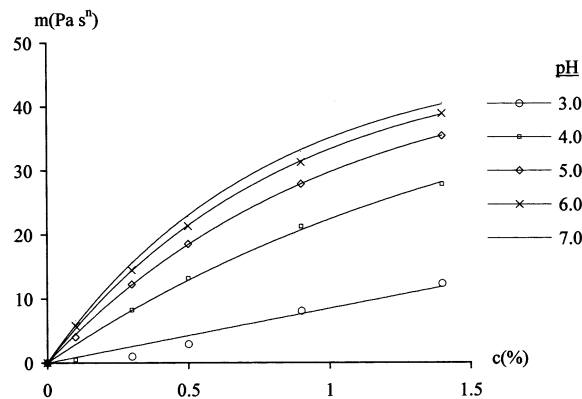
$$m = m_{max'}[1 - e^{-k'c}] \tag{5}$$

Fig. 4. Graphic representation of consistency as a function of concentration, for Carbopol® 971-P NF hydrogels at the pH values indicated.

Table 4
The coefficients $m_{max'}$ and k', with the respective correlation coefficients corresponding to Eq. (5), at the pH values indicated

$m = m_{max'}[1 - e^{-k'c}]$			
pH	$m_{max'}$ (Pa s^n)	k'	r
4	50.16	0.595	0.993
5	46.93	1.01	0.999
6	47.66	1.20	0.999
7	48.08	1.31	0.999

The $m_{max'}$ and k' values obtained for concentrations between 0.1 and 1.4% (w/w), along with the corresponding correlation coefficients for pH values of 4, 5, 6 and 7 are shown in Table 4, in view of the poor correlation coefficient found for pH 3; this is because the points correspond to a linear distribution of the following type (see Fig. 4):

$$m = m_{min} + kc \tag{6}$$

where m_{min} represents the consistency value for a polymer concentration of 0% (i.e. the consistency of water), and k corresponds to the slope of the straight line. This fit provided $m = 0.0009 + 8.32c$, with a correlation coefficient of 0.98. This equation, in turn, allows to the following approximation: $m = 8.32c$. Since the viscosity can not be measured for a 0.1% concentration at pH 3, the correct values are only obtained at concentrations above 0.3%.

For the rest of the pH values considered, $m_{max'}$ was found to be practically independent of pH, since the slight variations in this coefficient with pH were random (Table 4, data column 1); consequently, in practice, we used the mean value, whereby the corresponding dispersion error was:

$$m_{max'} = 48.2 \pm 0.6$$

As regards the k' values, Fig. 5 reflects their dependency upon pH. This dependency could be fitted to a function analogous to Eq. (3), i.e. with an asymptotic value:

$$k' = k'_i + \Delta k'[1 - e^{-a(pH - pH_i)}] \tag{7}$$

where pH_i is the first value corresponding to the validness zone of the equation, and k'_i is the k

value corresponding to this pH (i.e. pH_i 4 and $k'_i = 0.595$); $\Delta k'$ in turn represents the increase in k' produced by the pH rise. The resulting equation is:

$$k' = 0.596 + 0.807[1 - e^{-0.709(pH - 4)}]$$

with a correlation coefficient of 0.9998. If these values are substituted in Eq. (5), we have:

$$m = 48.2[1 - \exp[-(0.596 + 0.807$$
$$(1 - \exp(-(0.704(pH - 4))c]] \qquad (8)$$

which provides the consistency values at any concentration and pH value within the intervals [0.1–1.4% (w/w)] and (4–7), respectively.

Verification of the validity of this expression was made by graphically representing the m values obtained by fitting the experimental viscosity points to the Ostwald model, m_{exp}, as a function of those obtained from Eq. (8), m_{theor}, for the same concentrations and pH values (Fig. 6). The regression straight line and corresponding correlation coefficient are:

$$m_{exp} = -0.191 + 1.001m_{theor} \qquad (r > 0.996)$$

It should be noted that the correlation coefficient is excellent; the intercept and the slope are not statistically different from zero and one, respectively. Consequently, Eq. (8) has been considered to be sufficiently validated.

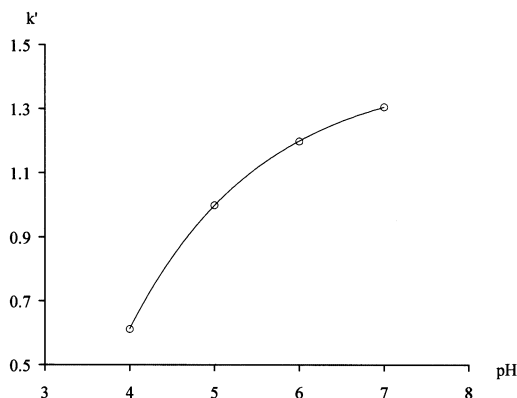### 3.3. Rheological behavior of the Carbopol® 971-P
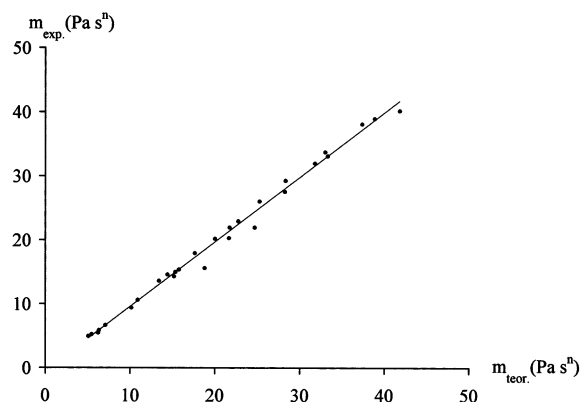
Fig. 5. Graphic representation of k' as a function of pH.

Fig. 6. Consistency values obtained from Eq. (8), m_{theor}, vs. those obtained directly from the Ostwald equation, m_{exp}.

NF hydrogels in presence of PVP and PVPP

The gels obtained in the presence of PVPP showed a non-Newtonian and pseudoplastic rheological behavior, similar to that obtained with the carbomer alone, and which may also be defined by the Ostwald-De Waele model. In Tables 5 and 6, the consistency values (m) and pseudoplasticity indexes (n) for a Carbopol concentration of 0.45%, with 0.05 and 0.1% of PVPP, respectively, are shown. The consistency (m) increases with pH in a way similar to gels prepared with Carbopol alone, and the pseudoplasticity index (n) remains constant; for this reason, the data can be processed by the same type of equations already described.

Table 7 shows the values of the coefficients m_{min}, Δm and k found for both mixtures and for

Table 5
Consistency values and pseudoplasticity indices for Carbopol® 971-P NF hydrogels at a concentration of 0.45% (w/w) with 0.05% of PVPP at the pH values indicated

pH	m (Pa s^n)	n	r
3.0	2.70	0.45	0.991
4.3	14.46	0.37	0.999
5.1	16.42	0.38	0.999
5.6	17.95	0.38	0.999
6.7	20.72	0.38	0.999
7.8	19.06	0.38	0.999

Table 6
Consistency values and pseudoplasticity indices for Carbopol®
971-P NF hydrogels at a concentration of 0.45% (w/w) with
0.1% of PVPP at the pH values indicated

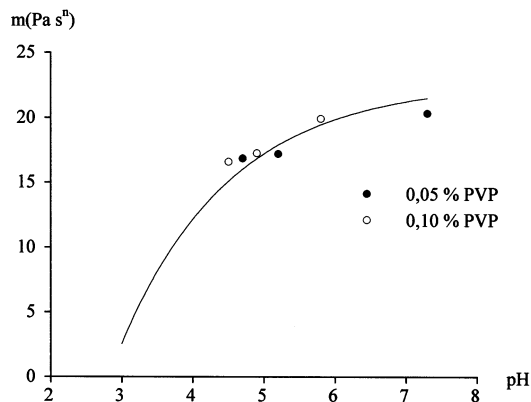| pH	m (Pa s)	n	r
3	3.5	0.38	0.999
4.6	16.94	0.38	0.999
5.0	17.41	0.38	0.999
5.5	18.91	0.38	0.999
6.4	20.09	0.38	0.999

Fig. 7. Consistency curve as a function of pH found for a
Carbopol® 971-P NF hydrogel at a concentration of 0.45%
(w/w) (continuous line) and consistency values of the gels of
Carbopol with PVP 0.05% (●) and 0.1% (○) at the suitable
pH values.

Carbopol alone. As can be observed, the m_{min} valor is somewhat superior to that of the single Carbopol formulations. When they are neutralized, however, the increment in viscosity (Δm) is somewhat inferior to that observed with Carbopol alone, and it decreases when the proportion of PVPP added increases. However, since this decrease is rather unimportant, it is not probable that the gel bioadhesive capacity would be substantially modified (Shin et al., 2000). On the other hand, the consistency at pH 7 was similar in all preparations.

In the case of soluble PVP, when added to Carbopol gels at a pH of under 4.5, coagulation of the gel results. For higher pH values in gels with 0.05 and 0.1% of PVP, the behavior is similar to that of single Carbopol formulations, the pseudoplastic non-Newtonian character being maintained.

In this case, however, it was not possible to establish an equation of asymptotic character relating consistency (m) and pH, since only pH values above 4.5 were available. Notwithstanding, when a curve showing consistency as a function of

pH for a 0.45% Carbopol gel was drawn and the consistency values of the gels of Carbopol with PVP 0.05 and 0.1%, respectively, were located on the graph, they remained near the curve, so that they can be considered equivalent in practice to those of the corresponding single Carbopol gels, as shown in Fig. 7.

3.4. Concluding remarks

Globally, the results obtained indicate that from the rheological perspective, aqueous solutions of Carbopol® 971-P NF behave as expected—i.e. as non-Newtonian pseudoplastic fluids.

The findings also suggest the interest of the polymer as a pharmaceutical excipient, for it can

Table 7
Values of the coefficients m_{min}, Δm and k (with their corresponding correlation coefficients) for hydrogels of 0.45% Carbopol, alone
and with PVPP 0.05 and 0.1%, respectively

$$m = m_{min} + \Delta m[1 - e^{-k(pH - pH_i)}]$$

Carbopol	PVPP	m_{min} (Pa s^n)	Δm	k	r	m (pH 7)
0.45%	–	2.55	20.23	0.645	0.998	21.25
0.45%	0.05%	2.81	19.15	0.650	0.996	20.53
0.45%	0.1%	3.51	17.33	0.879	0.999	20.34

The consistency values (m) for the neutralized gels (pH 7) are indicated (last column).

be used to obtain gels of adequate consistency as a function of the concentration and pH. On the other hand, the working characteristics for obtaining a given consistency can be theoretically calculated from a proposed equation (Eq. (8)).

Gelation occurred at pH 6 and is maintained to pH 8. This is compatible with the physiological range of pH values and consequently, the polymer can be used as a hydrophilic excipient destined for both buccal and cutaneous administration.

We are presently engaged in the preparation and biological evaluation of salbutamol buccal bioadhesive tablets containing Carbopol 971 NF as vehicle, and soluble and/or cross-linked polyvinylpyrrolidone as modulators of the bioavailability rate of the drug.

References

American Pharmaceutical Association, 1986. Handbook of Pharmaceutical Excipients. APHA, Washington, pp. 41–42.

Barry, B.W., 1983. Rheology of dermatological vehicles. In: Dermatological Formulations. Percutaneus Absorption. Marcel Dekker, New York, pp. 351–407.

Bremecker, V.K.D., Strempel, H., Klein, G., 1984. Nitrosamin-free polyacrylate gels: use of new types of bases for neutralization. J. Pharm. Sci. 73, 548–553.

Chauveau, C., Maillols, H., Delonca, H., 1986. Natrosol 250H. Caractérisation et modélisation du comportement rhéologique. Pharm. Acta Helv. 61, 10–11.

Cheng, H.S., Park, H., Kelly, P., Robinson, J.R., 1985. Bioahesive polymers as platforms for oral controlled drug delivery II: synthesis and evaluation of some swelling, water-insoluble bioadhesive polymers. J. Pharm. Sci. 74, 399–405.

Chu, J.S., Chadrasekharan, R., Amidon, G.L., Weiner, N.D., Goldberg, A.H., 1991. Viscometric study of polyacrylic acid systems as mucoadhesive sustained release gels. Pharm. Res. 9, 1408–1412.

Delegido, J., Dolz, M., Hernández, M.J., Pellicer, J., 1995. Pseudoplasticity and thixotropy of different types of starch hydrogels prepared with microcrystalline cellulose-sodium carboximethyl cellulose. J. Disper. Sci. Technol. 3–4, 283–294.

Dolz, M., González, F., Herráez, M., 1992. The influence of neutralizer concentration on the rheological behaviour of Carbopol hydrogel. Pharmazie 47, 351–355.

Goodrich, B.F., Chemical Co., 1994. The proven polymers in pharmaceuticals. Service Bulletin. B.F. Goodrich, Belgium.

Hernández, M.J., Pellicer, J., Delegido, J., Dolz, M., 1998. Rheological characterization of easy to disperse (ETD) Carbopol hydrogels. J. Disper. Sci. Technol. 19, 31–42.

Herráez, J.V., Dolz, M., Sobrino, P., Belda, R., González, F., 1993. Modification of rheological behaviour of cellulose gels with ClNa concentration. Application of Ostwald's model. Pharmazie 48, 359–362.

McNeill, I.C., Sadeghi, M.T., 1990. Thermal stability and degradation mechanisms of poly(acrylic acid) and its salts: Part 1 poly(acrylic acid). Poly. Deg. Stab. 29, 233–246.

Raznjevic, K., 1976. Handbook of Thermodynamic Tables and Charts. Mc Graw-Hill, New York.

Shin, S.C., Kim, J.Y., Oh, I.J., 2000. Mucoadhesive and physicochemical characterization of Carbopol Poloxamer gels containing triamcinolone acetonide. Drug Dev. Ind. Pharm. 26, 307–312.

Singla, A.K., Chawla, M., Singh, A., 2000. Potential applications of carbomer in oral mucoadhesive control drug delivery system: a review. Drug. Dev. Ind. Pharm. 26, 313–324.

Ünlü, N., Ludwig, A., Van Ooteghem, M., Hincal, A., 1991. Formulation of Carbopol 940 ophthalmic vehicles, and in vitro evaluation of the influence of simulated lacrimal fluid on their physico-chemical properties. Pharmazie 46, 784–788.

Ünlü, N., Ludwig, A., Van Ooteghem, M., Hincal, A., 1992. A comparative rheological study on Carbopol viscous solutions and, the evaluation of their suitability as the ophthalmic vehicles and artificial tears. Pharm. Acta Helv. 67, 5–10.