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Research paper

Polyacrylic acid/polyvinylpyrrolidone bipolymeric systems. I. Rheological and mucoadhesive properties of formulations potentially useful for the treatment of dry-eye-syndrome

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Abstract

For the treatment of dry-eye-syndrome preparations containing polymers as active agents are used. Polyacrylic acid (PAA) is a well known mucoadhesive polymer. For ocular use, however, the very high viscous gel systems can cause irritation post application which can result in a low patient compliance. In this study we have shown that it is possible to formulate PAA based low viscous formulations with polyvinylpyrrolidone (PVP) as 2nd polymer. The survey of the systems for the parameters microviscosity with polarization and oscillatory rheology shows that the 2nd polymer influences the structure of the PAA gel framework that causes the significant decrease in apparent viscosity of the combination. The mucoadhesion and rheological characteristics were determined by means of rheological methods. The acquired results, low viscosity and a high mucoadhesion index in comparison with the monopolymer PAA preparation and with two PAA containing commercial artificial tear preparations, Vidisic® and Thilo Tears®, led to the conclusion that the combination of the two polymers, PAA and PVP, could be advantageous for the treatment of the dry eye.

Keywords: Polyacrylic acid; Polyvinylpyrrolidone; Dry-eye-syndrome; Ocular; Mucoadhesion; Rheology

1. Introduction

For the treatment of dry-eye-syndrome usually formulations with soluble polymers to increase viscosity are used. The polymers may differ in their concentrations, in order to increase the duration of the effect.

Because of the excellent adhesive behaviour of the polymer [1,2] and especially its high capacity to restrain water, dosage forms containing polyacrylic acid seem to be suitable for teardrop substitute solutions.

These positive characteristics are diminished by the disadvantage that polyacrylic acid builds high viscose gels in usual concentrations (about 0.2%) and physiological pH-values. The application of such high viscous gel systems causes irritation of the eye usually resulting in a reduced patient compliance [3] and makes the application of such formulations more difficult than with preparations capable of forming drops.

We know from earlier studies [4] that it should be possible to formulate stable dosage forms on the base of polyacrylic acid containing another polymer. The objective of this study was to formulate bipolymeric dosage forms in order to get liquid preparations with concentrations of polyacrylic acid between 0.1 and 0.2% and polyvinylpyrrolidone as 2nd polymer. Examinations of the influence of the 2nd polymer on the macroviscosity, microviscosity and mucoadhesion were carried out.

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2. Experimental

2.1. Materials

Thilo Tears® (Alcon Thilo, Germany), Vidisic® (Dr. Mann Pharma, Germany), Carbopol®980 (PAA) (B.F. Goodrich, USA), Kollidon®25 (PVP) (BASF, Germany), sodium hydroxide, mannitol (E. Merck, Germany), disodium edetate (EDTA) (Berlin Chemie, Germany) and Mucin Type II (Sigma, St. Louis, MO, USA) were used as supplied.

Acenaphthylene labelled samples of polyacrylic acid (ACE-PAA) were synthesized as described by Soutar et al. [5].

2.2. Methods

2.2.1. Preparation of polyacrylic acid/polyvinylpyrrolidone formulations

To guarantee a full hydration of the PAA-polymer, a dispersion containing 2% PAA was prepared by stirring for 24 h at room temperature. PVP was dissolved in water. At a temperature of 30°C the PAA dispersion and the solution of PVP were united while stirring. The resulting opalescent suspension was stirred for 1 h at the same temperature and then sodium hydroxide solution (10%) was added resulting in clear preparations. All formulations were made isotonic with mannitol and stabilized with 0.01% EDTA. After 24 h storage time the measurements were performed.

2.2.2. Rheological methods

The apparent viscosity was determined by shear rate experiments using the Rheolab®MC 100 universal measuring drive system and the concentric cylinders double gap measuring system MS-Z1 DIN (Physica, Germany).

The rheological properties of the preparations with oscillatory rheology were evaluated using the measuring system described above. The viscoelastic region was determined by deformation sweep from 0.01 to 1.0 at a frequency of 1 Hz. A deformation of 0.1 was chosen for the frequency sweep analysis. The oscillatory measurements were performed over an angular frequency range of 0.1 to 10 s^{-1}. The time before each measurement was 10 min and the sample volume 17 cm^3.

Mucoadhesion was determined using a simple rheological method described from Hassan and Gallo [6]. The measurements were performed using the Rheolab®MC 100 universal measuring drive system and the concentric cylinders double gap measuring system MS-Z1 DIN.

Dried mucin was hydrated with acetate buffer (pH 6.0) by stirring for 12 h at room temperature yielding a dispersion of 20% (w/w). Fifteen grams of this dispersion were mixed for 20 min with 5 g of each test preparation before measurement. The final concentration of mucin was 15% (w/w). Viscosities of the test preparation/mucin systems (η_t) and that of 15% (w/w) mucin dispersion (η_m) were measured at 32°C at the shear rates D of 12.5, 25, 50 and 100 s^{-1}. The viscosities of the test preparation/acetate buffer systems (η_p) were determined in the same way. Viscometric measurements were performed for 1 min after exactly 3 min of application of the shear force. The viscosity component due to bioadhesion η_b can be obtained by the empirical equation, $\eta_b = \eta_t - \eta_m - \eta_p$. The mucoadhesion index M [Pa] was calculated using the shear rate D [s^{-1}] and the viscosity component η_b [mPas] according to the equation $M = \eta_b * D$.

2.2.3. Fluorescent polarization

The microviscosity was determined by fluorescent polarization using an LS 50 B (Perkin Elmer, UK). Excitation was performed at 295 nm; the emission was detected at 337 nm. As the fluorescent sample the ACE-PAA copolymer, synthesized as described [5], was used.

There are two reasons for using this labelled polymer instead of sodium fluorescein, for example; firstly the most fluorophores have no, or only a low affinity for PAA and so the polarization characteristics of the polymer cannot be detected. Secondly the addition of a molecule such as sodium fluorescein resulted in a significant decrease in viscosity of the aqueous formulation [7]. Therefore, it can be assumed that the additional molecule has an influence on the microviscosity of the preparation and the values measured did not represent the polarization characteristics of the bipolymeric system. Using the ACE-PAA copolymer no influence on the microviscosity of the formulations was to be expected.

3. Results and discussion

A possible method for indirect measurement of the microviscosity is fluorescence spectroscopy with polarized light at steady-state conditions. If a fluorescent sample is illuminated by plane polarized light under steady-state conditions the polarization degree [8] is defined as:

$$P = \frac{I_V - I_H}{I_V + I_H} \quad (1)$$

where I_V and I_H are the intensities of the fluorescence measured through vertical and horizontal polarizers when vertically polarized excitation light is used. The higher the value of P, the smaller the motion of the fluorophore during its fluorescent lifetime. Therefore the polarization determined by Eq. (1) can be related to the microviscosity: polarization $P \sim$ microviscosity η_M.

Fig. 1 shows the results of the rheological controlled shear rate measurements and polarization study of 0.2% PAA solutions with variable concentrations of PVP.

As can be seen, the apparent viscosity η_{D100} determined at a shear rate of 100 s^{-1} shows a minimum at a PVP concentration of 6%. The polarization curve shows a maximum at

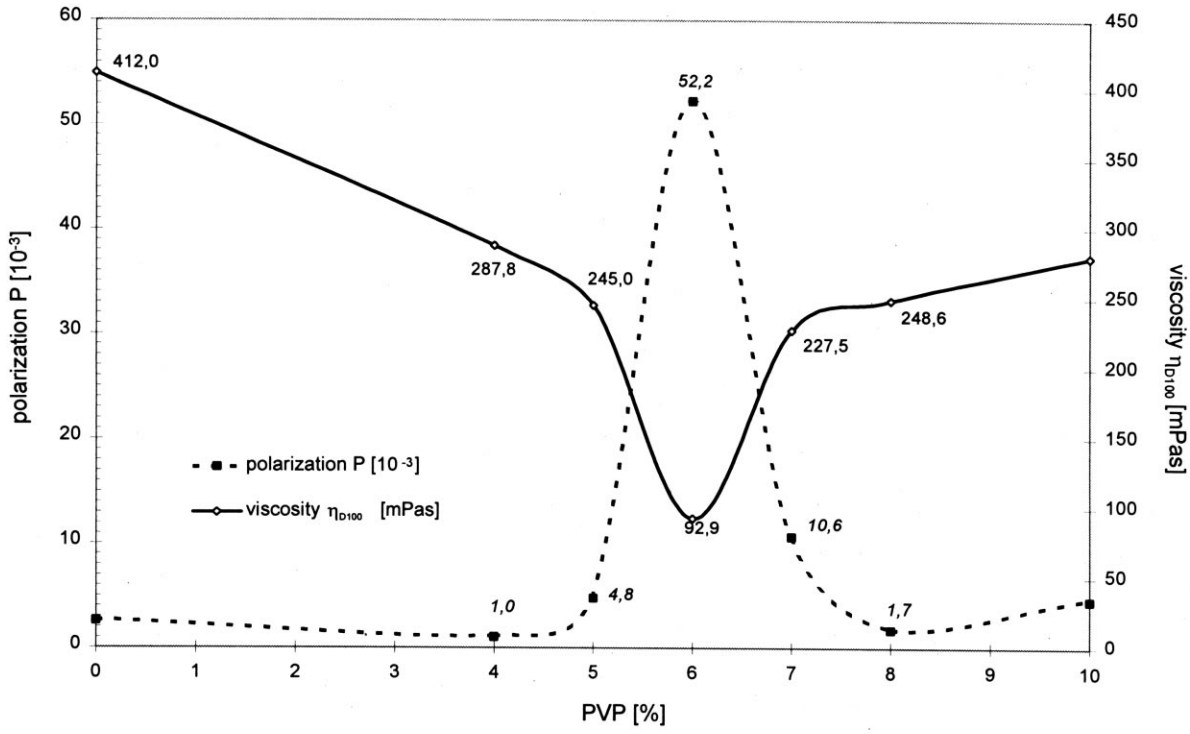

Fig. 1. Polarization P and viscosity η_{D100} of bipolymeric systems with 0.2% PAA in dependency on PVP concentration.

the same concentration. As already reported [9], PAA forms complexes with PVP that are insoluble in acid but readily soluble in alkaline medium. The results obtained led to the conclusion that this complex destroys the PAA sol framework. It is generally excepted that neutralized PAA solutions form gel frameworks of many hydrated, loosely coiled macromolecules. If the coiled form of the PAA was assumed, the 2nd polymer PVP would cause a partial dehydration and consequently a transition from loosely to compact coiled form. The partial dehydration leads to an increase in the bulk water phase. The apparent viscosity decreases, and where the mobility of the polymer chain in the compact coiled macromolecules decreases the microviscosity increases simultaneously. This phenomenon depends, as can be seen, on the PAA/PVP relation. After exceeding the optimal PVP concentration, the effect is not obtainable. For further investigations four preparations were selected, the 0.1 and 0.2% PAA solutions and, because of their low apparent viscosity, the corresponding bipolymeric systems containing 6% PVP. The compositions and abbreviations used in the following text are shown in Table 1.

A second possibility to characterize the sol framework of PAA solutions and PAA/PVP bipolymeric systems is oscillatory rheology. The parameters characterizing the rheological behaviour of the 002-preparation and the 602-bipolymeric formulation are the elastic modulus G′ and the loss tangent (tan δ). The elastic modulus reflects the solid-like component of the viscoelastic behaviour of the preparation and it is a means to determine the stored and recovered energy per cycle of deformation. Additionally, the loss tangent (tan δ) is a useful parameter to describe the viscoelastic nature of semisolids and polymer solutions. It is a measure of lost and stored energy during oscillatory rheological measurement. A higher value for tan δ indicates a lower degree of elasticity of the sample. The values of G′ and loss tan δ for the two preparations in an angular frequency range of 0.1 to 10 s^{-1} are shown in Fig. 2.

It can be seen (Fig. 2) that the 002-preparation forms a more elastic sol network than the combination of the two polymers. The less flexible network of the combination could be caused by the postulated interaction between the functional groups of the two polymers. It can be assumed that the complexation of PAA and PVP leads to a higher cross-link-like density which affects the chain segment mobility of the PAA-polymer, followed by a less elastic polymer framework.

The tan δ values shown in Fig. 2 illustrate distinct differences between the gel structures of the 002- and 602-for-

Table 1

Abbreviations (used in text) and composition of monopolymer PAA formulations and bipolymeric PAA/PVP preparations

Abbreviation	001	002	601	602
PAA [%]	0.1	0.2	0.1	0.2
PVP [%]	None	None	6.0	6.0
Viscosity η_{D100} [mPAS]	73.9	412.0	18.8	92.9
pH value		5.5–5.8		

All formulations are isotonic (mannitol) and contain 0.01% NaEDTA.

mulations. In case of the 002-preparation the tan δ value indicates a prevalence of viscous over elastic nature. The addition of PVP causes an absolute reduction of elasticity, represented by a lower G′ value. A prevalence of elastic over viscous nature, indicated by a tan δ value <1.0 is thought to be advantageous for mucoadhesive systems [10].

Regarding tear film stability and physiological compatibility, the viscosities of the preparations are of interest. First of all, a higher viscosity compared with natural tears is one prerequisite for artificial tears [11]. On the other hand, the viscosity should not be higher then 30 mPas because of an unpleasant feeling for the patients [12]. Also the use of Newtonian or weak pseudoplastic preparations should be preferred [13].

The shear rate on the cornea may differ considerably. While the eyes are open, the shear rate only depends on the gravitation and can assumed to be $D \approx 1\ s^{-1}$. While blinking the shear rate can be calculated from the tear film thickness, 7–8 μm [14], and the blinking speed, 10 cm s^{-1} [13]. Therefore, the shear rate is approximately 10 000 s^{-1}. Other authors reported a 'blink' shear rate of about 40 000 s^{-1} [15].

The apparent viscosities of the four formulations determined by controlled shear rate experiments in a range between $D = 100$ to 3000 s^{-1} are shown in Fig. 3. The strong decrease in the apparent viscosity caused by the addition of PVP to the PAA system can be seen here. With the measured values of shear stress τ [Pa] in dependence on shear rate D [s^{-1}], the apparent viscosity η_A [mPas] for $D = 1$ and 10 000 s^{-1} and the fluidity index N were calculated according to the Ostwald model for pseudoplastic substances:

$$\tau = K \times D^N \text{ or rather } \eta_A = K \times D^{(N-1)}$$

$$\text{with } K = \eta_a \text{ for } D = 1\ s^{-1} \quad (2)$$

These are presented with the measured apparent viscosities for $D = 100$ and 2000 s^{-1} in Table 2. Additionally, the viscosities of two PAA based commercial tear substitutes, Thilo Tears® and Vidisic®, are shown.

It can be seen that the calculated viscosities of the bipolymeric preparations at a shear rate of 10 000 s^{-1} are higher than that of natural tear fluid of about 1.3–5.9 mPas [16], but lower than 30 mPas. On the other hand, the values for $D = 1\ s^{-1}$, especially for the formulations containing 0.2% PAA, are relatively high. The values for the exponent N are calculated from log-log-plots of τ vs. D and are a measure for the pseudoplastic flow behaviour. These indicate that the two bipolymeric preparations show less distinct pseudoplastic flow character than the comparable PAA preparations.

It also can be seen that the viscosities of the two commercial products are distinctively higher than those of the bipolymeric formulations. The application of the two preparations is not as easy as the application of liquid formulations and the extremely high calculated viscosities for $D = 1\ s^{-1}$ could cause irritation after application. The values for the fluidity index N indicate that the commercial preparations, Thilo Tears® and Vidisic®, have a marked pseudoplastic flow behaviour.

From these rheological results it can be concluded that the bipolymeric formulations would have a prolonged contact time at the application site of the cornea. Irritation while blinking is not expected because of the relatively low cal-

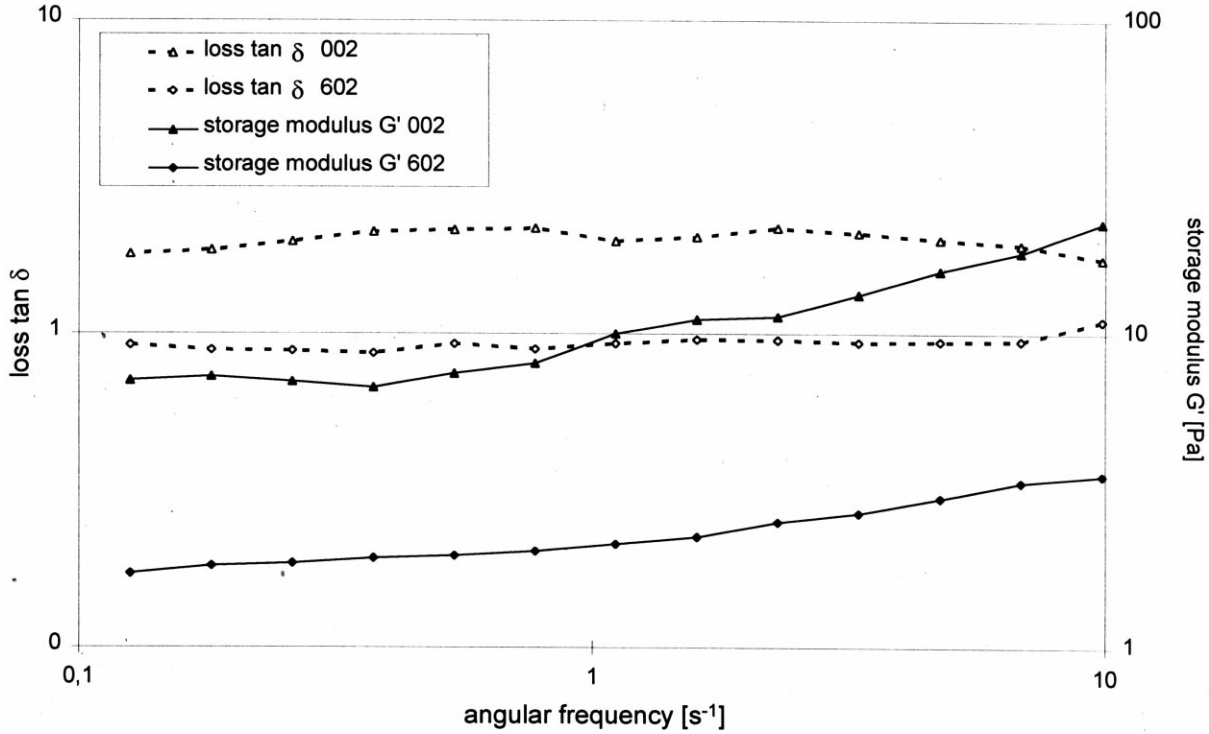

Fig. 2. Loss tan δ and storage modulus of the PAA-formulation 002 and the bipolymeric formulation 602 in dependency on the angular frequency.

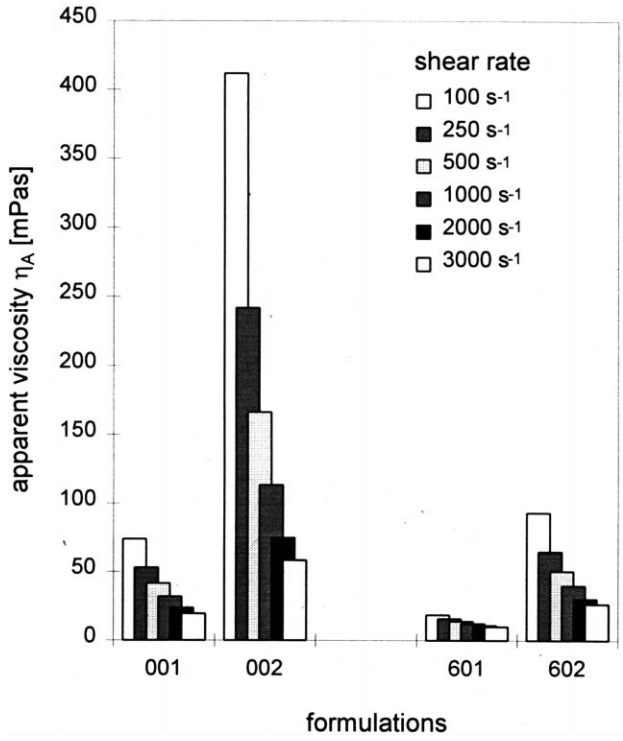

Fig. 3. Apparent viscosities of the PAA-formulations 001 and 002 and the bipolymeric formulations 601 and 602 in dependency on the applied shear rate D [s^{-1}].

culated 'blink' viscosities for $D = 10\,000\ s^{-1}$ (<30 mPas). In addition, the reduced apparent viscosities of the bipolymeric systems in comparison to the monopolymeric PAA and the two commercial preparations lead to liquid formulations and a less distinct pseudoplastic flow character, which is preferable for aqueous artificial tears [13].

The mucoadhesive phenomenon plays a dominant role as far as the contact time of aqueous tear substitutes in the precorneal area is concerned. The results of mucoadhesion measurements with the rheological method described by Hassan and Gallo [6] are presented in Table 3. In addition to the four preparations described above and the commercial artificial tears, Thilo Tear® and Vidisic®, a solution of 6% PVP (600) was measured.

As expected, it can be seen from these results that the mucoadhesion index depends both on the type and the concentration of the polymer. In polymer concentrations used in commercial artificial tears [17] and also in our bipolymeric formulations there is a linear dependence of the mucoadhesion index on the concentration of the polymer. From the results presented (Table 3) and additional investigations using other concentrations of the two polymers [18], the reported rank order of the mucoadhesive properties of the two polymers at the same concentration can be confirmed [19].

As reported earlier [20], some preservatives have an increasing influence on the mucoadhesion index. This effect can be seen (Table 3) when comparing the mucoadhesion index of the formulation 002 with the index of the product Vidisic®. Both formulations contain 0.2% PAA. Vidisic® also contains cetrimide, a cationic preservative. The addition of this cationic preservative causes a slight increase in the mucoadhesion index of the product Vidisic® (1.84 Pa) compared with the monopolymeric 0.2% PAA solution 002 (1.62 Pa).

A combination of PAA with PVP leads to a higher mucoadhesion index than can be calculated from the monopolymeric solutions, and to a higher index compared with the commercial products, Thilo Tears® and Vidisic®, containing preservatives. It can be assumed that the disintegration of the PAA sol framework in combination with the PVP polymer leading to a dehydration of some polymeric acid groups could be the reason for this effect. The dehydrated acid groups of the PAA molecule can easily interact with the glycoproteins of the mucin. For the dehydrated functional groups the interaction might be more simple than for the hydrated functional groups. This resulted in an extended intermolecular network between the combined macromolecules and mucin leading to an increase in the mucoadhesion index.

4. Conclusion

This study has shown that it is possible to prepare clear, liquid formulations containing PAA and PVP as an additional 2nd polymer. The combination of the two polymers leads to bipolymeric systems with lower apparent viscosities and higher mucoadhesive indices compared with the

Table 2
Fluidity index N, calculated and measured viscosities of the tested formulations

Formulation	Viscosity η_A [mPas]				Fluidity index
	[a]$D = 1\ s^{-1}$	$D = 100\ s^{-1}$	$D = 2000\ s^{-1}$	[a]$D = 10000\ s^{-1}$	N
001	449.5	73.9	23.7	12.7	0.6127
002	5723.7	412.0	74.7	29.8	0.4291
601	43.8	18.8	10.8	8.1	0.8161
602	503.1	92.9	30.2	16.8	0.6309
Thilo Tears®	13455.0	855.4	135.5	52.4	0.3976
Vidisic®	23046.0	1140.3	172.4	57.0	0.3487

[a]Calculated.

Table 3

Mucoadhesion index *M* of monopolymeric and bipolymeric formulations and of two commercial tear substitutes

Formulation	Mucoadhesion index [Pa]
001	0.72
002	1.62
600	2.76
601	3.84
602	4.44
Thilo Tears®	2.75
Vidisic®	1.84

monopolymeric PAA formulations. Especially for the treatment of dry-eye-syndrome the variation of these two parameters could be advantageous for the application as tear drops, the subjective pleasant feeling of the patient and objectively prolonged duration of the desired effect.

Probably the postulated forming of a PAA-complex with PVP, the 2nd polymer, might be used to incorporate hydrophilic and lipophilic drugs to prolong their release. In vitro and in vivo investigations using pilocarpine have been reported in [18].

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