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Rheological evaluation and ocular contact time of some carbomer gels for ophthalmic use

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Abstract

The poor uptake of many ophthalmic drugs is mainly due to the rapid elimination process by tear turnover. A prolonged precorneal residence time would result in higher absorption and, for some drugs, a prolonged duration of their therapeutic effect. It is known that gels are retained better in the eye than ordinary solutions but relatively little is known about the importance of the rheological properties of gels for their retention. In this study the ocular residence time of carbomer gels have been monitored in humans and the gels were also rheologically characterised. The contact time of Carbopol 974P and Carbopol 1342NF was concentration dependent and was approximately 2–2.5 h for a 2% gel. There was a good correlation of the human contact time and the elastic properties of the gels. The miotic response from gels with pilocarpine nitrate was monitored in rabbits and the area under the curves (AUCs') were calculated. The relative AUCs were 1.5–2.1 for the gel preparations relative to a solution. No concentration dependence was seen and there was no significant difference in AUC between the different carbomers. The ocular contact time of the gels were much less in rabbits than those obtained in humans.

Keywords: Ocular residence time; Carbopol 974P; Carbopol 1342NF; Noveon AA1; Bioavailability; Area under the curve (AUC); Rheology; Gel; Carbomer; Pilocarpine

1. Introduction

Conventional eye drops, for example pilocarpine, that is used for treatment of glaucoma, have low bioavailability. Only about 2–3% of the drug is absorbed through the cornea. (Asseff et al., 1973; Lee, 1992) The low bioavailability is partly due to the rapid elimination by tear turnover resulting in a contact time of only about 5 min on the cornea. Another reason for the low bioavailability is the slow diffusion of water soluble drugs through the cornea (Shell, 1982; Grass and Robinson, 1984; Shell, 1985; Robinson, 1989).

Increased contact time is not only important for increasing the amount of drug entering through the cornea. In therapies intended for precorneal diseases, e.g. infections and inflammations, the

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contact time might be decisive for the successful outcome of the treatment.

If the contact time is increased for a water soluble drug, an increased bioavailability is observed (Grass and Robinson, 1984). Inserts can provide almost unlimited contact time and hold constant dosage level during this time. On the other hand they may be expelled from the eye and can be difficult to put in and take out by older patients. More common methods to prolong ocular residence times for drugs are viscosity enhancement with polymers or by using suspensions and ointments which retain drugs in the eye much better than solutions. (Hardberger et al., 1975; Sieg and Robinson, 1975; Massey et al., 1976; March et al., 1982).

The variations in contact times and bioavailabilities between different vehicles may also depend on deviations from isotonicity and physiological pH. Large deviations may result in excessive lacrimation washing away the drug (Sieg and Robinson, 1975).

As mentioned above, polymers are frequently used in ophthalmic formulations. Some of them contain chemical groups which may specifically bind to mucus. Mucoadhesive properties of polymers might therefore influence contact times of vehicles. In this study we present ocular contact times of gels made from crosslinked copolymers of acrylic acid, carbomers, that are known to be mucoadhesive. (Duchene et al., 1988; Smart, 1991). The carbomer gels are frequently used in pharmaceutical formulations.

The relationship between the contact time and the rheology is easily understood for viscosity enhanced ophthalmic solutions. During blinking the shearing force on the preparation is large. If the viscosity at high shear rate is too high this will result in irritation. If, on the other hand, the viscosity is too low it will give rise to increased drainage. To decrease the drainage between blinks the viscosity at low shear should be high. The rheological properties of a gel are most likely of importance for the ocular contact time but the same reasoning as for viscosity enhanced eye drops may not be relevant. For a solution the viscosity at different shear is the important rheological parameter. For a gel that is put under the lower eyelid the gel may not be subject to a shearing action. The rheological properties of a gel is characterised by its viscoelastic properties that is measured at low shear in an oscillating experiment. How well the gel stays in the eye is most likely dependent on, not only the mucoadhesive properties of the gel, but also the bulk rheological properties of the gel, i.e. how well the gel is held together in situ.

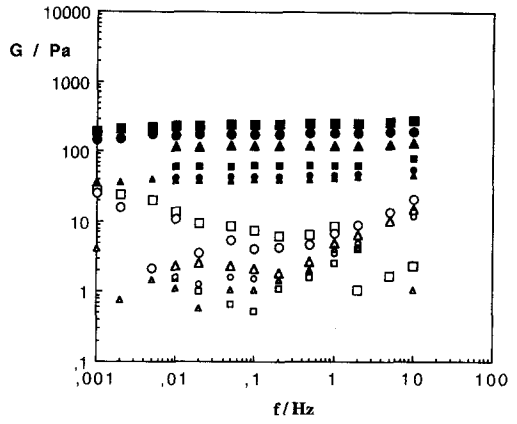

Fig. 1. Effect of concentration of Carbopol 1342 containing glycerol at 25°C, elasticity modulus (G'), filled symbols, and viscosity modulus (G''), unfilled symbols, as a function of frequency. Concentration: ■ 2.0%, ● 1.5%, ▲ 1.0%, ■ 0.5%, ● 0.3%, ▲ 0.2%.

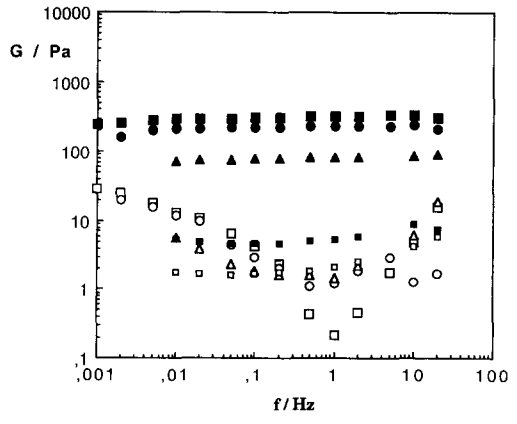

Fig. 2. Effect of concentration of Carbopol 1342 containing sodium chloride at 25°C, elasticity modulus (G'), filled symbols, and viscosity modulus (G''), unfilled symbols, as a function of frequency. Concentration: ■ 2.0%, ● 1.5%, ▲ 1.0%, ■ 0.5%.

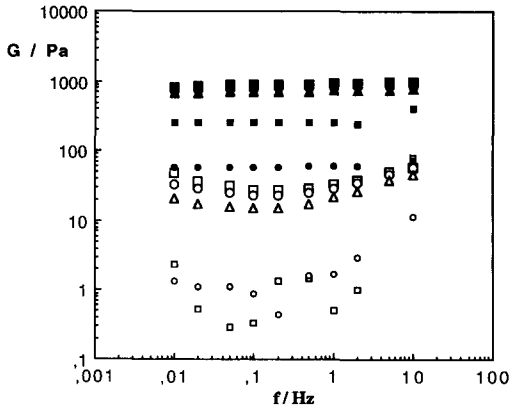

Fig. 3. Effect of concentration of Carbopol 974 containing glycerol at 25°C, elasticity modulus (G'), filled symbols, and viscosity modulus (G''), unfilled symbols, as a function of frequency. Concentration: ■ 2.0%, ● 1.5%, ▲ 1.0%, ■ 0.5%, ● 0.3%.

Rheology, in combination with dielectric spectroscopy, has proven to be an interesting tool in order to understand and predict the release of drugs from gels (Craig et al., 1994). In this paper we have sought a relationship between the rheology and the ocular contact times of carbomer gels. The study of ocular contact time was made on human volunteers. In a rabbit study we have followed the miotic response and calculated area under the curves (AUCs) after administering pilocarpine nitrate in carbomer gels.

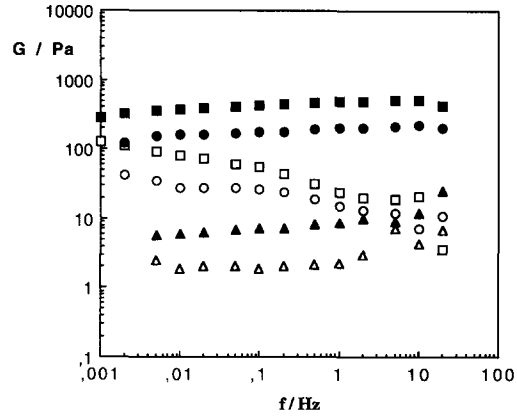

Fig. 4. Effect of concentration of Carbopol 974 containing sodium chloride at 25°C, elasticity modulus (G'), filled symbols, and viscosity modulus (G''), unfilled symbols, as a function of frequency. Concentration: ■ 2.0%, ● 1.5%, ▲ 1.0%.

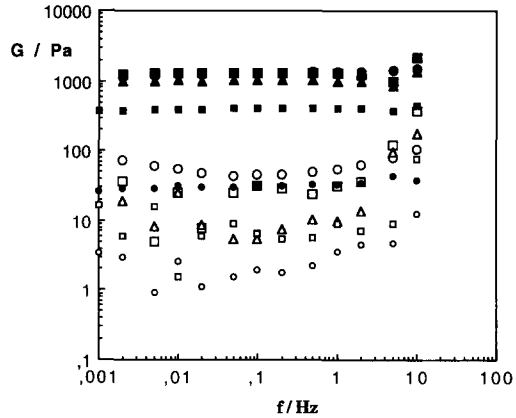

Fig. 5. Effect of concentration of Noveon AA1 containing glycerol at 25°C, elasticity modulus (G'), filled symbols, and viscosity modulus (G''), unfilled symbols, as a function of frequency. Concentration: ■ 2.0%, ● 1.5%, ▲ 1.0%, ■ 0.5%, ● 0.3%.

2. Materials and methods

2.1. Materials

Carbopol 974P, Carbopol 1342NF and Noveon AA1 were a kind gift from BF Goodrich. Pilocarpine nitrate was purchased from Sigma. All other chemicals were of pharmaceutical grade.

2.2. Methods

2.2.1. Preparation of gels

A standard solvent was made containing benzalkonium chloride 0.01% (w/v), EDTA 0.05% (w/v) and glycerol 3% (w/v). For some of the solutions which were for the rheological studies 0.9% NaCl (w/v) was added instead of glycerol. The gel with the highest concentration of carbomer (2% w/v) was prepared using this solvent. The carbomers were neutralized by the addition of NaOH until a pH of 7.4 was reached. The gel was allowed to swell while stirring for 1 day before any further dilutions were made. Lower concentrations of the gel were made by dilution using the standard solvent.

Table 1
Elacticity modulus for the gels at 25°C, concentration and frequency dependence

Sample	Frequency (Hz)	c = 0.2%	c = 0.3%	c = 0.5%	c = 1.0%	c = 1.5%	c = 2.0%
C1342NF	0.01	38.7 (40.0)	41.0 (43.5)	60.5 (62.4)	115 (117)	168 (163)	229 (225)
Glycerol	0.1	39.2 (41.1)	43.4 (45.7)	62.1 (64.7)	119 (122)	177 (178)	245 (243)
	1	42.2 (44.3)	45.9 (48.3)	63.9 (66.6)	123 (125)	183 (185)	251 (254)
C1342NF	0.01		a	5.50	72.0	210	290
NaCl	0.1		a	4.70	79.0	220	310
	1		a	5.40	83.0	230	320
C974P	0.01		56.9 (57.6)	254 (252)	673 (687)	744 (756)	834 (851)
Glycerol	0.1		58.4 (59.5)	258 (268)	701 (723)	787 (817)	886 (924)
	1		60.2 (62.0)	256 (269)	730 (755)	823 (856)	927 (969)
C974P	0.01			a	5.90	160	370
NaCl	0.1			a	7.10	180	430
	1			a	8.50	200	480
NAA1	0.01		31.1 (34.7)	383 (418)	1030 (1050)	1220 (1250)	1300 (1320)
	0.1		31.5 (35.2)	401 (409)	1020 (1070)	1280 (1330)	1290 (1390)
	1		33.2 (38.3)	412 (416)	1000 (1080)	1350 (1400)	1270 (1380)

Values given in paranthesis refer to 35°C.
a, not measurable.

Table 2
Viscous modulus for the gels at 25°C, concentration and frequency dependence

Sample	Frequency (Hz)	c = 0.2%	c = 0.3%	c = 0.5%	c = 1.0%	c = 1.5%	c = 2.0%
C1342NF	0.01	1.11 (0.68)	1.63 (2.89)	1.57 (2.63)	2.33 (3.75)	10.7 (13.3)	13.4 (21.9)
Glycerol	0.1	1.07 (0.93)	1.54 (1.69)	0.52 (1.10)	2.11 (2.98)	4.1 (6.1)	7.4 (10.2)
	1	4.01 (1.45)	3.49 (3.13)	2.52 (2.76)	5.00 (3.78)	6.8 (7.6)	8.7 (8.9)
C1342NF	0.01		a	1.80	5.70	12.0	13.0
NaCl	0.1		a	1.70	1.90	3.0	4.30
	1		a	2.10	1.50	1.20	0.22
C974P	0.01		1.33 (2.04)	2.31 (10.3)	20.6 (27.9)	33.9 (69.3)	48.3 (90.9)
Glycerol	0.1		0.89 (1.56)	0.33 (0.64)	14.9 (19.2)	23.1 (32.7)	27.4 (39.1)
	1		1.70 (2.10)	0.51 (0.38)	21.7 (21.9)	28.8 (34.5)	32.8 (39.1)
C974P	0.01			a	1.90	28.0	80.0
NaCl	0.1			a	1.90	26.0	54.0
	1			a	2.20	15.0	24.0
NAA1	0.01		2.59 (0.85)	1.52 (3.77)	25.5 (26.2)	55.7 (96.3)	25.3 (29.3)
	0.1		1.98 (2.03)	6.45 (10.9)	5.35 (8.48)	45.1 (57.4)	31.5 (3.85)
	1		3.49 (2.62)	8.89 (9.32)	10.0 (1.76)	54.2 (60.6)	31.5 (19.9)

Values given in paranthesis refer to 35°C.
a, not measurable.

Sodium fluorescein was added to some gels before studying ocular contact time.

The gels that were used for the bioavailability experiments on rabbits contained 1% pilocarpine nitrate. A pilocarpine solution without gel in the standard solvent was prepared as a reference.

2.2.2. Rheology

The rheological properties were studied using a Bohlin VOR rheometer (Bohlin, Lund, Sweden). The rheometer is of the couette type. The measuring system used were concentric cylinders C14. The sample volume was about 2.5 ml. Silicone oil was added to the surface of the sample to prevent evaporation of solvent. The measurements were made at room temperature, 25.0°C, and at 35.0°C, the temperature in the conjunctival sac of the eye.

Strain sweep measurements were made for all samples to determine the maximum strain amplitude for the gel. Above a certain strain amplitude the three dimensional network of the gel is destroyed. Thus, measurements above this level do not measure the physical properties relevant for a gel at rest under the lower eyelid. All further measurements of rheological properties were made within the linear region, i.e. below this maximum strain.

In oscillation experiments the response in stress of a gel to a sinusoidally varying strain is monitored as a function of time. The shear strain, the stress and the phase angle are determined in the measurement, the parameters obtained are the complex modulus, G*, and the phase angle, δ. The elastic modulus (G′), the viscous modulus (G″) and the dynamic viscosity (η') are calculated by:

$$G' = G^* \cos(\delta)$$

$$G'' = G^* \sin(\delta)$$

$$\eta' = G''/\omega$$

where ω is the angular frequency.

Since gels by definition have a very low phase angle, a small error in the determination of the phase angle will result in a relative error in G″ that is comparatively large.

From oscillation measurements, the elasticity modulus G′ and the viscosity modulus G″ (storage modulus and loss modulus) were determined, for frequencies between 0.01 and 20 Hz. A gel is defined in rheological terms as a preparation where the G′ and G″ are frequency independent and the phase angle δ ($\tan\delta = G''/G'$) is low at all frequencies. This is in contrast to concentrated solutions where there is a frequency dependence of G′ and G″ and the phase angle can vary from a low to a high value when changing the frequency.

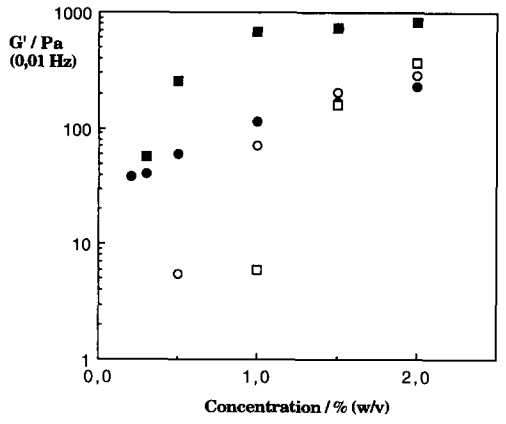

Fig. 6. Concentration dependence of the elasticity modulus at 0.01 Hz for Carbopol 974 P and 1342NF preparations with glycerol or sodium chloride ■ 974, glycerol, □ 974, NaCl, ● 1342, glycerol, ○ 1342, NaCl.

2.2.3. Ocular contact time

The contact times of the gels were measured in the eye of a human volunteer. Twenty-five microlitres of the gel was placed under the lower eyelid and the presence of the gel was detected using a slit lamp. Fluorescein was used as a marker to facilitate the observation of the gels. Ocular inspection were performed at selected time intervals. When 10% or less of the gel remained in the eye the gel was considered as having been drained away.

2.2.4. Bioavailability

The bioavailability of pilocarpine was estimated by monitoring the miosis on albino rabbits. Twenty-five microlitres of the preparation was put under the lower eyelid of the rabbit. For each gel, data were collected from six albino rabbits in which the left eye was given a placebo solution

Table 3
Viscosity (mPa) of the different gels at 25°C

Frequency (Hz)	Concentration (%)	C1342NF glycerol	C1342NF NaCl	C974P glycerol	C974P NaCl	Noveon™
0.01	2.0	3650	4590	13300	6050	20600
0.01	1.5	2680	3300	11900	2550	19500
0.01	1.0	1840	1140	10700	98	16400
0.01	0.5	964	91	4040	a	6090
0.01	0.3	653		906		497
5	2.0	8	10	30	16	31
5	1.5	6	7	27	7	45
5	1.0	4	3	24	0.4	27
5	0.5	0.7	0.3	0.7	a	11
5	0.3	0.7		0.7		1

a not measurable.

Table 4
Contact time and irritation

Polymer concentration (%)	Contact time/min		Irritation	
	C974P	C1342NF	C974P	C1342NF
0.1	7	5	0	0
0.2	7	10	a	0
0.3	30	12	a	0
0.5	30	70	a	0
1.0	70	135	0	0
1.5	105	150	0	0
2.0	120	150	0	0

a, irritation noticed.

and the right eye received a gel containing pilocarpine. The change in pupillary diameter was recorded as a function of time. The AUC was calculated for the first 4.5 h.

3. Results and discussion

3.1. Rheology

The polymer concentration were varied between 0.2 and 2% for the different carbomers. All the gels had a higher elasticity modulus (G′) than viscosity modulus (G″) and the frequency dependence was very small (Figs. 1–5) irrespective of the concentration. This is typical rheological behaviour for a gel. A higher concentration resulted in a higher G′ and a higher G″ as was to be expected. The relative error of the viscous modulus (G″) was much larger due to the low phase angle which explains the larger scatter of G″ values compared to the G′ in the figures.

The rheological results presented in the figures were obtained at 25.0°C but measurements were also made at 35°C for some of the gels (see Tables 1 and 2). The difference in results between the two temperatures represents both the error in the measurements and a very small temperature dependence.

The elasticity modulus for Carbopol 1342 increased with increasing concentration, the viscous modulus was also concentration dependent, but to a lesser extent. When sodium chloride was used instead of glycerol the concentration dependence

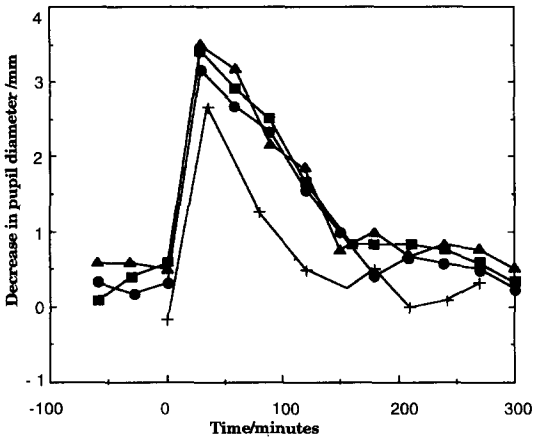

Fig. 7. Effect of the different gels. Decrease in pupil diameter. Concentration of Pilocarpine is 1.0%. ■ Noveon AA1, ● Carbopol 1342, ▲ Carbopol 974, + without gel.

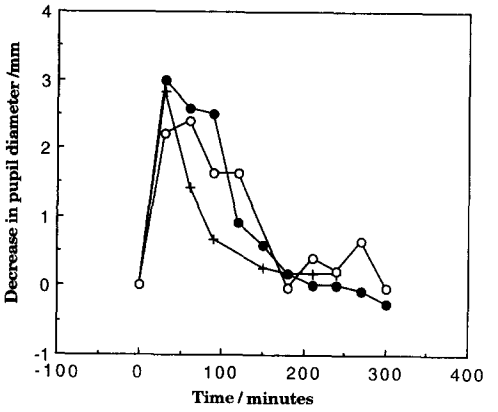

Fig. 8. Effect of concentration of Carbopol 1342. Decrease in pupil diameter. Concentration of Pilocarpine is 1.0%. Concentration of Carbopol: ● 0.5%, ○ 1.5%, + 0%.

of the elasticity modulus was more pronounced, but the difference between the highest concentrations were small (Fig. 2). The viscous modulus was relatively similar when using glycerol or sodium chloride (compare Figs. 1 and 2).

For Carbopol 974 the concentration dependence of G′ and G″ diminished above a certain concentration (see Fig. 3), i.e. the elasticity of the gel did not gain on an increased concentration above 1%. The elasticity was higher than for Carbopol 1342. When sodium chloride was used, the elasticity modulus was much lower and had a more pronounced concentration dependence even at higher concentrations (Fig. 4). The concentration dependence of the elasticity modulus of the Carbopols is shown in Fig. 6. Carbopol 974P is more sensitive for salts at all concentrations but for Carbopol 1342 the effect of salt is only seen for concentrations below 1%.

Table 5
Relative bioavailability of gels containing 1% pilocarpine

Preparation	Relative AUC
Without gel	1.0
Carbopol 1342NF (0.5%)	1.8
Carbopol 1342NF (1.5%)	1.5
Noveon™ (0.5%)	2.0
Carbopol 974P (0.5%)	2.1

The elasticity of Noveon AA1 was concentration dependent only for the lowest concentrations (see Fig. 5). However, due to the scatter in the viscosity modulus data it is difficult to be certain about its concentration dependence. Also the elasticity modulus for Noveon was higher than for Carbopol 1342, and approximately the same as for Carbopol 974 without salt.

During viscosity measurements made under continuous shear, the gel structure will be destroyed and the results will not describe the gel state. The viscosity can, however, also be calculated from dynamic (oscillating) measurements (Cox and Merz, 1958) where the structure of the gel will be intact.

The viscosity of the gels, both at high and at low frequency, see Table 3, showed the same concentration dependence as the elasticity and the viscosity modulus. A higher concentration of the gel resulted in a higher viscosity, but the concentration dependence for Carbopol 974 with glycerol and Noveon AA1 is very small above 1%.

3.2. Contact time

The contact time was studied for Carbopol 974P and Carbopol 1342NF. A higher concentration gives a longer contact time (see Table 4). This can be compared with the rheological results

where preparations with concentration higher than 0.5% become more elastic and hence less susceptible to deformation which increases the probability of the gel stays in place under the lower eyelid. It is important that the gel stays in place under the eyelid because gel on the cornea will lead to blurred vision and increased blinking, with consequently shorter contact times.

There was a concentration dependence of the contact time for Carbopol 974P although this is not the case for the rheological properties above 1% when using glycerol. This can be explained by the dilution of the gel in the eye with tear fluid and the larger sensitivity to salt leading to a more pronounced concentration dependence as compared to Carbopol 1342.

Contact times obtained for C974P and C1342NF correlate well with the rheological properties in solutions containing salt. The elasticity modulus of C974P is more concentration dependent than Carbopol 1342NF; the elasticity of the highest concentrations were almost equal for C974P and C1342NF (compare Fig. 6 and Table 4).

Some concentrations of Carbopol 974P were irritating to the eye giving a burning sensation and the eyes became somewhat red. It was interesting to note that no irritation was found for concentrations above 0.5%. Comparing with rheological data shows that approximately at this concentration the elasticity increases drastically for preparations containing glycerol. For preparations containing salt, a concentration of 0.5% or less resulted in solutions with elasticities too low to be measurable. The lack of irritation at higher concentrations could be due to the increased elasticity since the gel holds together better and therefore does not flow out as easily onto the sensitive cornea. Thus, with an increased elasticity, two positive effects have been achieved, namely a longer contact time and elimination of irritation.

3.3. Bioavailability studies

The pupillary diameter was studied for a reference solution of pilocarpine and pilocarpine preparations containing all three gels at a concentration of 0.5%. The results are shown in Fig. 7 and Table 5. All the three gels gave an increased bioavailability as compared to the pilocarpine solution, and there is no difference in bioavailability between the different gels.

In order to see the concentration dependence two concentrations were studied using C1342NF. The results are given in Fig. 8 and Table 5. A higher concentration does not give an increased bioavailability as could be expected from the contact time measurements. If anything, the AUC was somewhat lower for the higher concentration of C1342NF. There are two possible explanations for this. Firstly, the pilocarpine nitrate may diffuse out of the gel very quickly and therefore one would not be able to detect the difference in contact times for the vehicle from bioavailability studies. The diffusional hindrance of a gel at 0.5% will not be very different from a gel at 1.5% for such a small molecule as pilocarpine nitrate. Another explanation for this may be the difference in anatomy of the eye between humans and rabbits. A difference in the behaviour between the two species was seen during the experiments. In the rabbit eye, the gel became spread out over the eye and was rapidly drained off, in contrast to the human eye where the gel stayed in place under the lower eyelid and displayed a gradual decrease in volume. This effect resulted in much shorter contact times for the rabbits as compared to humans. This observation shows that caution must be observed when comparing preparations of different physical form based on rabbit data for predicting the effects of various vehicles in humans.

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