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The evaluation of viscous ophthalmic vehicles by slit lamp fluorophotometry in humans

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Summary

Slit lamp fluorophotometry was used to evaluate in humans the precorneal kinetics of viscous eye drops, containing a fluorescent tracer. The viscolysers examined are: dextran, polyvinylalcohol, hydroxypropylmethylcellulose, hydroxypropylcellulose and hydroxyethylcellulose. The ocular retention of the tracer depends on the physicochemical characteristics of the viscous vehicles instilled, firstly on the nature of the polymer added and secondly on its concentration.

Introduction

The instillation of a drug solution into the eye results in an extensive drug loss, primarily by drainage. Only a small amount of the drug will remain in the conjunctival sac to exert a local action or to be absorbed by the eye tissues.

One possible approach to prolong the residence time and to improve the drug bioavailability consists of the addition of water soluble polymers, increasing the viscosity of eye drops (Blaug and Canada, 1965; Hardberger et al., 1975; Trueblood et al., 1975).

Numerous studies have been conducted on rabbits to determine the influence of vehicle characteristics on the ocular retention and the bioavailability of drugs (Krishna and Brow, 1964; Chrai and Robinson, 1974; Patton and Robinson, 1975; Lee et al., 1983; Wilson et al., 1983; Urtti and Salminen, 1985). Considering interspecies differences in blinking rate, physiology of tear flow and drainage, it is uncertain to what extent these results are applicable to humans (Saettone et al., 1982a and b, 1985). In most human studies the influence of two polymers is compared (Waltman and Patrowicz, 1970; Bach et al., 1972; Benedetto et al., 1975; Norn, 1977). Only a few studies on the relative efficacy of several viscolysers have been reported (Saettone et al., 1984, 1985).

The aim of the present work is to examine the influence of the physicochemical properties of different polymeric additives on the precorneal kinetics of viscous solutions containing a fluorescent tracer. A non-invasive method, causing minimal disturbance to normal physiological functions, is chosen. The fluorescence decay of sodium fluo-

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rescein in the precorneal tear film of humans is measured with a slit lamp fluorophotometer. Such information should be useful in the rational design of viscous ophthalmic vehicles for human therapy.

Materials and Methods

Materials

Dextran, henceforth designated as DEX (clinical grade, mol. wt. 78,000) was obtained from Sigma Chemical Company (München, F.R.G.); polyvinylalcohol (PVA) (Polyviol W40/140, mol. wt. 1,000,000) from Wacker Chemie (München, F.R.G.); hydroxypropylmethylcellulose (HPMC) (Celacol 5000 Celanese Ltd.) from Socomer (Brussels, Belgium); hydroxyethylcellulose (HPLC) (Klucel MF, mol. wt. 850,000) from Hercules Chemicals (Brussels, Belgium).

Sodium fluorescein was obtained from Fluka (Buchs, Switzerland). All other chemicals were of analytical grade.

Solution preparation

All preparations were made by adding the required amount of polymer to an aqueous isoosmotic phosphate buffer solution pH 7.4 (Ph. Helv. V.). Sodium fluorescein was added to the vehicles to a final concentration of 0.05% w/w. The solutions were sterilized by autoclaving at 121° C for 20 min.

The composition of the various vehicles tested is indicated in Table 1. The concentrations of the polymers were adjusted to obtain, after sterilization, almost iso-viscous solutions of 7 mPa · s and 25 mPa · s.

Physicochemical measurements

Osmolality. The osmolality of each solution was determined with a vapor pressure osmometer (model 5500, Wescor, Logan, UT, U.S.A.).

Viscosity determination. The viscosity determinations of the sterile polymer solutions were made at 32° C (corneal surface temperature) using a capillary Ostwald viscosimeter (KPG Viskosimeter, Schott Geräte, Mainz, F.R.G.) and a rotary viscosimeter Rheomat 30 (Contraves AG, Zürich, Switzerland) at shear rates ranging from $D = 5$ to 700 s^{-1}.

Surface tension measurement. The surface tension was measured at 22 ± 1.0° C by the Wilhelmy plate method, using a Cahn electrobalance.

Since the equilibrium surface tension of a viscous solution is reached only after several hours, the measurement was performed 20 s after pouring the solution into the Petri dish. This time period is chosen in relation to the blinking dynamics in humans and corresponds to the mean time period elapsing between two blinkings of the volunteers.

Complex formation. The possibility of a complex formation between sodium fluorescein and the polymers was investigated by gel filtration chromatography on Sephadex G10 (Pharmacia, Uppsala, Sweden) column (10 × 150 mm). The column was eluted with phosphate buffer (pH 7.4). The fractions (2 ml) were monitored at 490 nm for sodium fluorescein.

Slit lamp fluorophotometry

Apparatus. The influence of the viscous vehicles on the precorneal kinetics of sodium fluorescein was examined by a slit lamp fluorophotometer. The excitation beam of the slit lamp is projected near the limbus on the conjunctiva at the lateral canthus. The fluorescence of the tear film was detected by the photomultiplier mounted directly onto the eye-piece of the slit lamp. Technical details of the apparatus are described in previous papers (Ludwig and Van Ooteghem, 1986, 1987).

The left ocular of the binocular microscope system of the slit lamp enables the observation of the spreading of the vehicles onto the eye surface.

Instillation procedure and fluorescence monitoring. Five adult volunteers from whom informed consent was obtained, participated in the study, which was carried out under medical supervision. None of the subjects were contact lens wearers or showed any evidence of ocular pathology. The solution (10 µl) is instilled carefully with a sterile Eppendorf pipette in the lower conjunctival sac of the left eye. During the fluorescence monitoring of the tear film the volunteers are allowed to blink freely, as they feel necessary. The fluorescence

decay curve (fluorescence intensity – time curve) is recorded.

A dose volume of 10 μl is chosen, because this volume can be instilled without overflow onto the lids or spillage on the lacrimal lake. Moreover, it was demonstrated in an earlier study that an instillation volume up to 10 μl does not influence the elimination rate (Ludwig and Van Ooteghem, 1987). In this way only the vehicle-mediated effects are studied.

The decay profile recorded after instillation of the phosphate buffer solution and the viscous vehicles obeys fairly well to first order kinetics. The data are subjected to linear regression analysis and the first order rate constant, called tear elimination coefficient (k), is determined for each experiment. The areas under the decay curves (AUC) are calculated using the trapezoidal rule. To determine statistical significance, the Mann–Whitney test and Kruskal–Wallis analysis of variance are used. A probability level of 0.05 or less is accepted as significant.

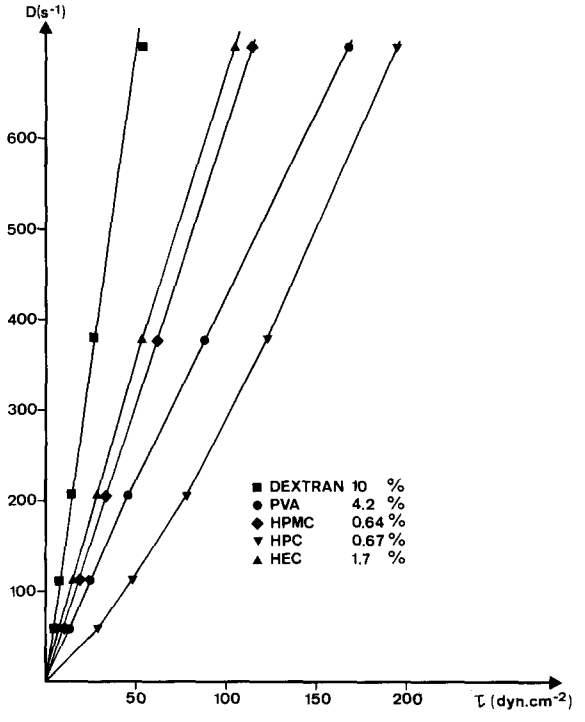

Fig. 1. Rheograms of several vehicles tested.

Results and Discussions

Rheological behaviour of the viscous solutions

As shown in Fig. 1, the rheograms of the polymer solutions under the rate of shear applied show a newtonian behaviour, except the HPC 0.67% w/w solution, which exhibits a slight pseudoplastic behaviour.

The viscosity data reported in Table 1 are the measurements carried out with the capillary viscosimeter, because of the approximate newtonian flow properties of most solutions tested.

Surface tension

The addition of PVA, HPMC and HPC reduces the surface tension of the vehicle. The surface tensions obtained are in the same range as the surface tension of lacrimal fluid (40–46 mN/m) (Miller, 1969, Lin and Brenner, 1982). Dextran exhibits only a slight surface activity. HEC solutions have an intermediate surface tension.

Complex formation

The elution profile shows no binding between sodium fluorescein and any viscolyser, because the tracer is detected at an elution volume twice the void volume. Thus the tracer diffuses freely in the viscous vehicle.

TABLE 1

Characteristics of the viscous vehicles

Composition	Viscosity (mPa·s)	Surface tension (mN/m)	Osmolality (mOsm/kg)
Phosphate buffer sol.	0.98	71.9	280
+ Dextran 5%	2.9	71.4	283
+ Dextran 10%	6.7	71.7	289
+ PVA 1.4%	2.3	44.2	287
+ PVA 2.8%	7.4	43.2	300
+ PVA 4.2%	24.9	43.9	308
+ HMPC 0.36%	6.7	44.5	272
+ HMPC 0.64%	23.7	49.5	282
+ HPC 0.35%	7.5	42.9	269
+ HPC 0.67%	27.4	41.7	290
+ HEC 1.1%	9.0	61.8	278
+ HEC 1.7%	26.5	56.9	286

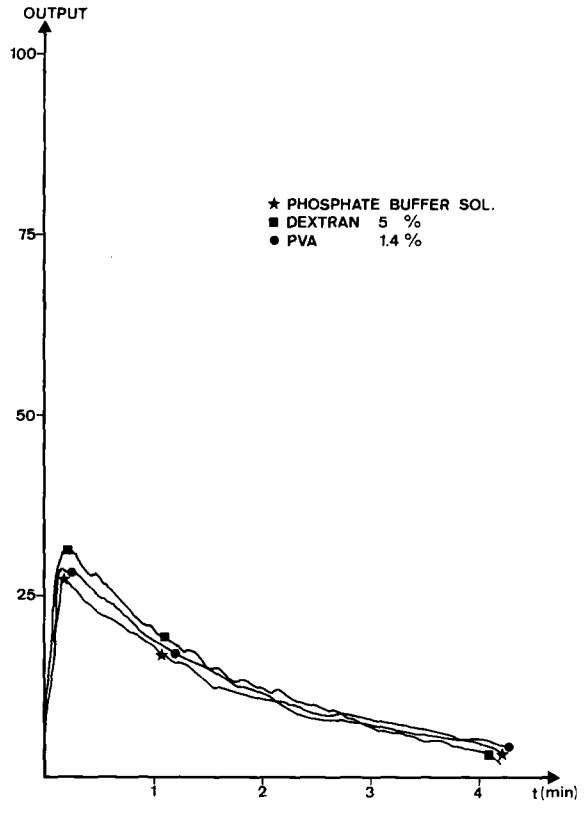

Fig. 2. Fluorescence decay curves (volunteer 1) (solution viscosity of 2.5 mPa·s).

Fluorescence decay curves

The time courses of the fluorescence intensity of 4 min post instillation of phosphate buffer solution and the viscous solutions are displayed in Figs. 2–4. The output of the fluorescence signal is expressed in arbitrary units. Those typical plots originate from experiments with volunteer 1.

The decay curves in Fig. 2 indicate that the rapid fluorescence decay seen after instillation of the phosphate buffer solution is slightly reduced, when the viscosity of the vehicle is increased to 2.5 mPa · s by the addition of 5% dextran or 1.4% PVA. After 4 min still more than 90% of the tracer is lost. Both polymer solutions, which are frequently used as artificial tear solutions in the case of dry eye syndromes, have only a slight effect on the ocular retention in healthy eyes.

The polymer solutions with a viscosity of about 7 mPa · s show a higher fluorescence output compared to the phosphate buffer solution (Fig. 3). Since the fluorescence intensity approximates tracer amount × tear film thickness, the high output value indicates some influence of the polymer vehicles on the precorneal tear film thickness. Moreover the decay curve of the 1.1% HEC solution shows about 30% of the tracer still present 4 min post instillation. This is partly due to the fact that volunteer 1 tolerates HEC much better than PVA, HPMC and HPC, which are eliminated faster by vivid blinking.

As seen in Fig. 4. the instillation of 25 mPa · s solutions HPMC, HPC and especially PVA cause a very high fluorescence signal. But also rapid elimination due to discomfort, blurred vision or lacrimation and vivid blinking is observed. The HEC decay curve shows, however, a lower fluorescence output compared to PVA, HPMC and HPC, but a slower elimination and thus a higher ocular retention.

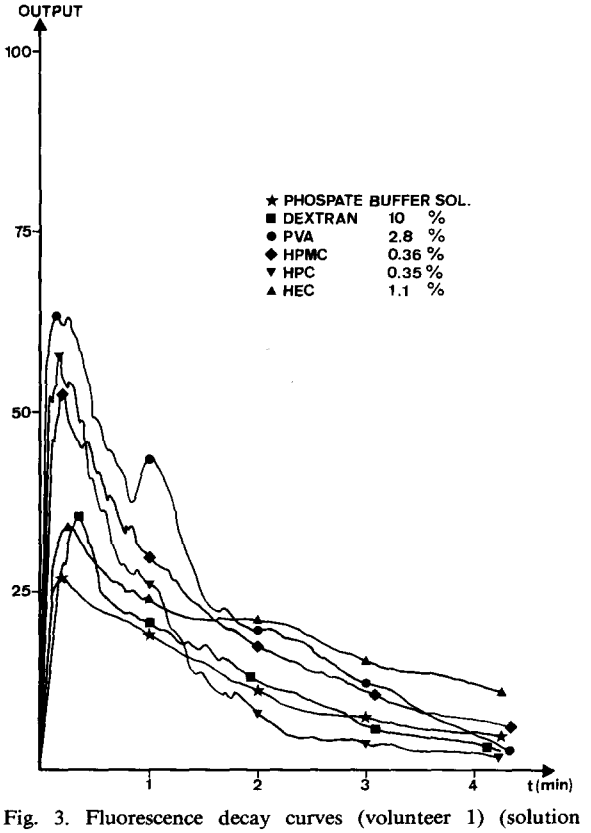

Fig. 3. Fluorescence decay curves (volunteer 1) (solution viscosity of 7 mPa·s).

TABLE 2

The tear elimination coefficient (k) ($10^{-3} \cdot s^{-1}$) and the AUC following instillation of 10 µl of the viscous solutions

Vehicle	Volnt. 1		Volnt. 2		Volnt. 3		Volnt. 4		Volnt. 5	
	k	S.D.	*k*	S.D.	*k*	S.D.	*k*	S.D.	*k*	S.D.
Phosphate buffer sol.	14.17	2.54	8.56	1.21	6.40	1.52	16.06	2.40	15.29	3.90
DEX 5%	13.93	2.58	7.46	1.15	3.40 **	0.89	7.83 **	1.88	16.42	3.04
DEX 10%	15.36	4.22	7.81	1.77	3.03 **	1.11	4.37 **	1.57	7.21 **	2.40
PVA 1.4%	7.40 **	1.38	6.47 *	1.44	5.59	2.86	11.29 **	2.97	16.76	1.51
PVA 2.8%	12.76	3.89	7.50	2.15	3.79 **	1.49	8.89 **	2.46	13.18	3.23
PVA 4.2%	13.87	4.11	6.10 *	1.26	3.05 **	1.48	6.44 **	3.04	13.05	3.99
HPMC 0.36%	14.40	3.79	9.62	2.01	2.00 **	0.75	9.68 **	2.95	18.30	0.82
HPMC 0.64%	11.95	3.24	6.77	2.18	3.04 **	0.43	2.48 **	0.49	11.98	2.95
HPC 0.35%	20.33 **	3.66	8.47	1.96	3.06 **	1.28	5.57 **	1.55	17.35	1.45
HPC 0.67%	15.93	2.84	6.65	2.54	2.81 **	1.11	3.95 **	1.54	16.86	1.54
HEC 1.1%	10.24	3.66	5.36 *	1.35	2.47 **	0.83	2.98 **	1.40	7.47 *	2.84
HEC 1.7%	4.25 **	0.91	5.74 *	1.29	2.61 **	0.81	2.41 **	0.81	4.39 **	1.62
	AUC	S.D.	AUC	S.D.	AUC	S.D.	AUC	S.D.	AUC	S.D.
Phosphate buffer sol.	21.69	8.06	12.64	3.61	18.46	5.54	11.71	2.60	16.49	4.25
DEX 5%	24.40	9.20	16.50	3.60	23.00	7.90	18.60 **	3.40	38.60 **	10.76
DEX 10%	29.70	9.70	17.00	6.00	34.80 *	11.70	34.60 **	14.80	27.75 **	3.86
PVA 1.4%	23.74	4.90	18.86 *	4.78	22.37	8.08	17.72	5.32	25.39 *	2.69
PVA 2.8%	46.05 *	20.50	16.30	3.50	28.00 *	6.80	24.90 *	10.00	22.36	5.17
PVA 4.2%	49.80 **	13.40	11.50	3.40	34.00 *	11.20	36.00 **	15.50	18.37	3.21
HPMC 0.36%	28.68	6.59	9.16	2.56	32.42 *	7.32	18.03 **	1.20	19.30	2.94
HPMC 0.64%	43.34 **	9.54	10.43	5.18	38.09 **	9.31	47.08 **	11.03	29.28 *	11.77
HPC 0.35%	11.73 *	2.31	8.77	2.30	32.66 **	3.84	51.01 **	21.43	16.28	2.16
HPC 0.67%	20.74	3.47	16.45	6.10	67.39 **	24.71	73.50 **	9.19	25.94	10.01
HEC 1.1%	28.60	10.12	8.01 *	2.48	24.78	6.73	28.46 **	15.49	26.92 **	6.76
HEC 1.7%	53.12 *	16.27	9.82	3.43	25.34	8.75	22.94 **	5.90	27.15 *	12.80

*,** Statistically different from phosphate buffer solution at $P < 0.05$ and $P < 0.01$, respectively, by a Mann–Whitney test.

The various polymers tested seem to affect the kinetics somewhat differently. DEX and HPC appear to promote the amount of tracer in the tear film, whereas HEC sustains the presence of fluorescein at the eye surface. Benedetto demonstrated a different mechanism of action of viscolysers in the tear film. PVA increases the film thickness by its water dragging capacity, while HPMC increases the volume of the marginal tear strip (Benedetto et al., 1975).

Tear elimination coefficient and AUC of the decay curve

For each volunteer separately the mean of six *k* values and AUC values of each series of vehicles and the S.D. values are calculated. The summary of the data is presented in Table 2.

The data reported in Table 2 show that the elimination rate is retarded as the polymer concentration is increased. For a 25-fold change in viscosity, there is a 2–6 fold decrease of the tear elimination coefficient *k*. In some cases, however, higher elimination rates with respect to phosphate buffer solutions are observed, when the solution instilled causes irritation or blurred vision. The subjects react by forceful blinking, squeezing the solution out of the conjunctival sac, and accelerating the drainage of the tracer.

The AUC value is determined by the initial fluorescence output just after instillation and by the rate of disappearance of the tracer. Higher AUC values are achieved with increasing polymer concentration. Compared to the phosphate buffer solution, firstly a higher initial fluorescence is measured, indicating an effect of the polymer on the precorneal tear film thickness and secondly the drainage is decreased. The extent of both effects is not the same for each solution.

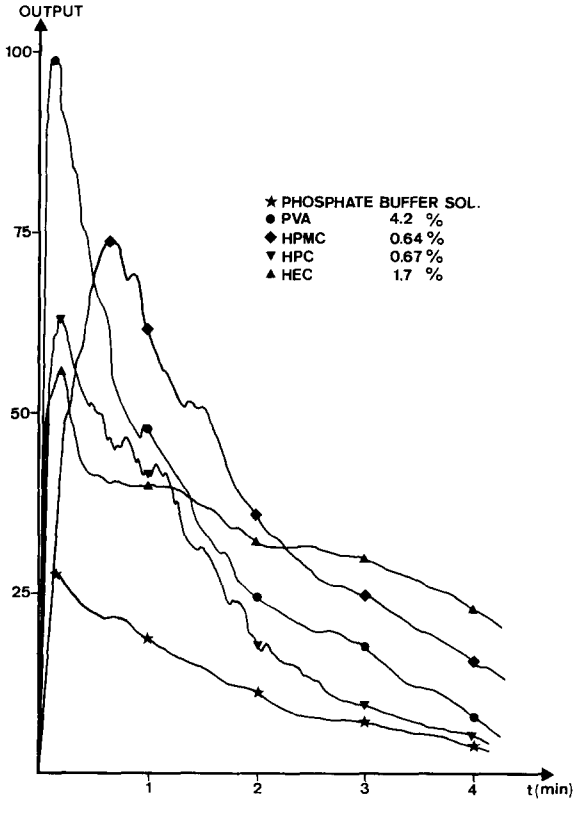

Fig. 4. Fluorescence decay curves (volunteer 1) (solution viscosity of 25 mPa·s).

Nevertheless, in some cases high AUC values are associated with high k values, as seen from subjects 1 and 5. This paradoxical phenomenon is due to an increase of the tear film thickness and consequently the amount of tracer at the eye surface immediately after instillation, but in conjunction with a high blinking rate, induced by discomfort. The gritty sensation of the instilled solution elicits lacrimation, dilutes the dose and promotes drainage.

Based on the k values, HEC seems to be the most effective to decrease the elimination of the tracer from the precorneal area, there being even a 6-fold reduction in the case of subject 4. Based on the AUC values, however, DEX or HPC should be prefered to enhance the amount of sodium fluorescein at the corneal surface. Again a 6-fold increase is noted in the case of subject 4.

The non-parametric statistical analysis reveals that in the case of subjects 3 and 4, the addition of a polymer always prolongs in a significant manner the residence of the tracer in the tear film. It should be mentioned that subjects 3 and 4 have very different blinking frequencies. Under normal conditions, the time elapsing between two blinkings was 20 and 5 seconds, respectively. Besides, the instillation of viscous solution does not change this time period significantly. Subject 4, with the highest blinking rate of all persons participating in this study, seems to be the most sensitive to vehicle viscosity effects.

As far as subjects 1 and 5 are concerned, striking differences in acceptance of the various instilled vehicles are noted.

Influence of the viscosity

The data reported in Table 2 indicate no linear relationship between viscosity and elimination rate of the newtonian solutions. Low viscosity solutions (2.5 mPa · s) cause an important decrease in tear elimination coefficient k over that of the phosphate buffer solution. A further 3.5 fold increase in viscosity from 7 to 25 mPa · s results in a small decrease in k. In the case of the pseudoplastic HPC solutions, k remains even fairly constant.

The effect of increasing the viscosity of the vehicle is also investigated by calculating the ratio of the k values and the AUC values after the instillation of the 7 mPa · s and the 25 mPa · s solution. The results are presented in Table 3.

Table 3 shows that in general the ratio is greater than 1. Thus the most viscous solution is more effective in reducing the elimination rate of the tracer than the 7 mPa · s solution.

A 3.5-fold increase of the viscosity of the vehicle causes less than a two-fold increase of the AUC or decrease of the tear elimination coefficient k. Only in a few cases the k and the AUC ratio are similar.

The removal of the tracer from the precorneal area is influenced by the polymer concentration, but the elimination is not only viscosity-controlled, but presumably also affected by processes such as discomfort, reflex blinking, induced lacrimation, interaction with the tear film. The marked intersubject variations indicate that those processes

TABLE 3

k and AUC ratio following instillation of the 7 mPa·s and 25 mPa·s solutions

	PVA	HPMC	HPC	HEC
k Ratio 7 mPa·s/25 mPa·s				
Subject 1	0.92	1.21	1.28 *	2.41 **
2	1.16	1.42	1.27	0.93
3	1.24	0.66 *	1.09	0.95
4	1.38	3.90 **	1.41 *	1.24
5	1.01	1.53 **	1.03	1.70 *
AUC Ratio 25 mPa·s/7 mPa·s				
Subject 1	1.08	1.51 *	1.77 **	1.86 *
2	0.71 *	1.14	1.88 *	1.23
3	1.21	1.17	2.06	1.02
4	1.45	2.61 **	1.44	0.81
5	0.82	1.52 *	1.59 *	1.01

*,** Statistically significant difference between the 7 mPa·s and the 25 mPa·s solutions, respectively, at $P < 0.01$, using a Mann–Whitney test.

compete in eliminating the tracer. The extent of their influence seems to be very different.

Influence of the nature of the polymer added

The tear elimination coefficient data of isoviscous solutions are subjected to a Kruskal–Wallis analysis of variance (Table 4).

Significant differences measured after instillation of isoviscous solutions indicate that the various polymers used have not the same efficacy to reduce the elimination of the tracer. This could be related to their mol. wt. or to their surface tension characteristics.

Surprisingly, DEX and HEC, which reduce the surface tension of the vehicle only slightly, are the solutions best tolerated by all the subjects. After instillation both vehicles are easily mixed with the lacrimal fluid and do not cause irritation.

TABLE 4

Statistical analysis

Vehicle	Subj. 1	Subj. 2	Subj. 3	Subj. 4	Subj. 5
2.5 mPa·s	$P < 0.01$	N.S.	$P < 0.05$	N.S.	N.S.
7 mPa·s	$P < 0.05$	$P < 0.05$	N.S.	$P < 0.01$	$P < 0.01$
25 mPa·s	$P < 0.01$	N.S.	N.S.	$P < 0.01$	$P < 0.01$

The reduced surface tension of the PVA, HPMC and HPC solutions does not seem to facilitate the mixing of the solution with the resident lacrimal fluid. During the first 15–60 s, irregular fluorescent films with darker spots are seen. After a few blinks an homogeneous film is formed by respreading the viscous solution from the reservoir in the conjunctival sac onto the eye surface. Besides, in the case of HPC solutions their surface tension, being lower than the surface tension of lacrimal fluid, could be the reason for the irritation elicited.

Conclusions

This study demonstrates the relative effectiveness of the various soluble polymers to extend the presence of sodium fluorescein in the tear film and enhance its retention in the conjunctival sac.

A definite influence of the polymer characteristics on the human response to viscous vehicles is apparent from this study. It seems that the preference should be given to the use of viscolysers, which reduce the surface tension of the vehicle only slightly.

The acceptance of a viscous vehicle seems to be related firstly to the nature of the polymer used and secondly to its concentration. The marked individual variations in reaction to the instillation of viscolyser solutions do not facilitate the appropriate formulation of ophthalmic drugs for human therapy.

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