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Polymer effects on ocular bioavailability—the influence of different liquid vehicles on the mydriatic response of tropicamide in humans and in rabbits

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Summary

Five viscous polymeric vehicles containing 0.2% tropicamide were tested for mydriatic activity in humans and in rabbits. The polymers were carboxymethylcellulose (CMC), low molecular weight hydroxypropylcellulose (HPCL), medium molecular weight hydroxypropylcellulose (HPCM), poly(vinylpyrrolidone) (PVP) and poly(vinyl alcohol) (PVA). Their concentrations were adjusted in order to give iso-viscous (70 ± 2 cps) Newtonian solutions (HPCL, PVP, PVA) or pseudoplastic solutions with an apparent viscosity of 70 cps at a rate of shear of 700 s^{-1} (CMC, HPCM).

All vehicles increased the ocular bioavailability of the drug in both species, when compared with a non-viscous solution. However, in humans PVP and PVA were significantly more active with respect to the other polymers. The different activity of the polymeric vehicles in humans could neither be correlated with drug binding, nor with surface or interfacial tension, nor with the rheological behaviour of the solutions (Newtonian vs pseudoplastic). On the basis of experimental evidence, the hypothesis is advanced that some polymers may increase the ocular bioavailability of tropicamide not by viscous effects alone, but also by influencing the spreading characteristics and the thickness of the medication layer over the precorneal area. The reasons for the interspecies differences in activity, presumably residing in different precorneal dynamics of the applied solution, are also discussed.

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Introduction

The addition of suitable polymers to liquid ophthalmic vehicles is a common method for increasing the ocular contact time, and hence the drug bioavailability. This effect, that is generally ascribed to the increased viscosity induced by the presence of the macromolecules, has been widely investigated using different polymers and drugs. However, very few systematic, comparative studies on the relative efficacy of different polymers have been reported, and comparisons of literature data on individual polymers are often hindered by the different experimental techniques used by the various authors.

In a previous investigation (Saettone et al., 1982a) dealing with the effect of four different polymeric iso-viscous vehicles on the miotic effect of pilocarpine, it was shown that poly(vinyl alcohol), PVA, produced both in humans and in rabbits a greater drug bioavailability with respect to the other polymers tested. This finding appeared in contrast with a current assumption, according to which equal viscosities should correspond to equal drug penetration through the cornea. The hypothesis that particular polymers might favour ophthalmic bioavailability by a mechanism not involving viscosity effects alone, but possibly other factors such as, e.g. surface phenomena, was then advanced.

The present investigation represents an extension of the previous one, and was aimed at verifying the effect of five different iso-viscous polymeric vehicles on the activity of tropicamide. It was considered of interest to verify whether the data obtained with pilocarpine could be extended to another drug, possessing different chemical, physicochemical and biological characteristics, and could thus assume a more general scope and validity. A further objective was to gain some insight on the mechanism(s) by which the polymeric additives exert their bioavailability-enhancing action.

Previous reports concerning vehicle effects on the activity of tropicamide are rather contradictory. Mattila et al. (1968) reported that methylcellulose (MC) increased in humans the cycloplegic, but not the mydriatic effect of the drug. Smolen and Schoenwald (1974) failed to find significant effects of three polymeric additives (MC, and two ionogenic polymers) on the mydriatic response of rabbits. Conversely, Minja Lee and Hammarlund (1974) found that hydroxypropylmethylcellulose (HPMC) and a natural gum (guar gum) significantly increased the mydriatic effect of tropicamide in rabbits. Brown and Hanna (1978) reported that 0.1% tropicamide in a MC or HPMC vehicle was as effective a mydriatic in humans as 1.0% tropicamide in a standard vehicle. Previous reports from the present authors (Saettone et al., 1980, 1982b) also pointed to a statistically significant effect of hydroxypropylcellulose on the human mydriatic response to the drug: a similar, but statistically not significant effect was observed in rabbits.

The present investigation was carried out both on humans and on rabbits, also in order to further substantiate the inter-species differences in sensitivity to vehicle-mediated effects, that had been anticipated in previous papers.

Materials and Methods

Ophthalmic vehicles

Tropicamide (Prodotti Roche), m.p. 97–99 °C, was used as received. All preparations were made by adding the specified amount of polymer to an aqueous, isotonic, phosphate-buffered (0.2 M, pH 7.0 Sørensen buffer) 0.2% w/w solution of tropicamide, serving as reference (AS). For the corneal fluorescence studies, 0.1% w/w sodium fluorescein was added to the vehicles. All preparations contained 0.1% w/w methyl *p*-hydroxybenzoate as preservative. The following polymers, at the indicated w/w concentrations, were used: hydroxypropylcellulose, low molecular weight [1] (HPCL), 4.5%; hydroxypropylcellulose, medium molecular weight [2] (HPCM), 1.4%; carboxymethylcellulose [3] (CMC), 1.63%; poly(vinyl alcohol) [4] (PVA), 5.0; poly(vinylpyrrolidone) [5] (PVP), 7.5%.

All preparations were sterilized by autoclaving at 2 bars for 20 min, and were stored in 20-ml sterile plastic dropper bottles.

Biological studies

The human studies were carried out on volunteers of both sexes, aged 18–65 years, free of ocular pathology. Each vehicle was tested on groups of at least 10 subjects, by instilling 50 µl in one eye, the other eye serving as reference. The other experimental details have been described previously (Saettone et al., 1980). Rabbit data were obtained from 1.8–2.5 kg male, preconditioned New Zealand albinos, selected on the basis of their similar response to light intensity, and to the mydriatic activity of tropicamide. Each preparation was tested on groups of at least 10 animals, by instilling 50 µl in one eye, the other eye serving as reference. The experimental procedure suggested by Smolen and Schoenwald (1971) for the assessment of the mydriatic response in rabbits was followed throughout.

The behaviour and retention times of the vehicles in human eyes were assessed by instilling in one eye 50 µl of fluorescein-containing preparations. The corneal area was observed through a slit lamp fitted with a blue filter, and the time during which a fluorescent layer was present over the corneal surface was noted. The spreading characteristics of the vehicles over the cornea were also observed. Each vehicle was tested on both eyes of five different subjects, which were allowed to blink freely during the experiment. All measurements were made by the same operator. A similar test was performed on rabbits, by direct observation of the treated eyes under illumination with a long-wave fluorescent lamp. Each vehicle was tested in both eyes of five different animals; all measurements were made by the same operator.

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[1] Klucel LF, Hercules.
[2] Klucel MF, Hercules.
[3] Blanose CG 7MF, Hercules.
[4] Polyviol W 48/20, Wacker Chemie.
[5] Plasdone K 90, GAF.

Physicochemical measurements

Viscosity determinations on the sterile vehicles were made at 30 °C using a Rheomat 30 rotary viscometer [6].

Studies on tropicamide binding by the polymers were carried out by a dynamic dialysis technique, following essentially a method outlined in a previous paper (Bottari et al., 1975). For the present experiments, a smaller cell (10 ml internal capacity, 12.6 cm^2 membrane area) and cellophane membranes were used. Preliminary experiments demonstrated the impermeability of the membrane to the polymeric materials. For the dialysis experiments, 5.0 ml of 0.2% w/w (approximately 6.8×10^{-3} M) solutions of tropicamide in the polymeric vehicles (without added methyl *p*-hydroxybenzoate) were introduced into the cell, and the drug was allowed to permeate to a receiving solution (200 ml of isotonic, pH 7.0 phosphate buffer) at 30 °C. Samples of the external solution were periodically removed and immediately replaced with an equal amount of prewarmed buffer solution. The removed samples were analyzed spectrophotometrically (256 nm) for tropicamide. Care was taken to maintain adequate sink conditions in the receiving solution during the experiments.

Surface and interfacial tensions (against perhydrosqualene) were determined at 30 °C using a Tensimat n3 tensiometer [7], by the Wilhelmy plate method.

The surface spreading capacity of the polymeric vehicles on glass was determined as indicated by Benedetto et al. (1975), by touching clean, wet glass slides (2 × 2.5 cm, 0.16 mm thick) to the surface of the vehicles (40 μl) contained in a poly(methyl methacrylate) trough of 26 mm by 2 mm, 1.5 mm deep.

Results and Discussion

Biological data

A summary of the biological data (mydriatic activity) obtained with the vehicles under investigation is presented in Table 1. In humans, the polymeric vehicles exhibited in general significantly increased activity parameters, when compared with the non-viscous solution AS. A reduced peak time, together with an increased peak mydriatic intensity (I_{max}), a prolonged duration (with the exception of HPCL), and an increased area under the mydriasis–time curve (AUC) were observed in all cases. The AUC data, which should be considered indicative of the relative ocular bioavailability of the drug from the vehicles, are also presented in graphical form in Fig. 1. An inspection of these data shows that PVA and PVP produced approximately a 3.7-fold AUC increase over AS, while the other polymeric vehicles (CMC, HPCL and HPCM) produced only an approximately two-fold AUC increase over AS. The AUC data for the three latter vehicles were not statistically different from one another. The present results with PVA are in line with previous data, obtained

[6] Contraves A.G.

[7] Prolabo S.A.

TABLE 1

SUMMARY OF HUMAN AND RABBIT ACTIVITY DATA OF TROPICAMIDE IN THE VEHICLES UNDER STUDY

Vehicle	Human				Rabbit			
	Peak time (min)	I_{max} [a] (mm) (±95% CL)	Duration [b] (min) (±95% CL)	AUC [c] (cm^2) (±95% CL)	Peak time (min)	I_{max} [a] (mm) (±95% CL)	Duration [b] (min) (±95% CL)	AUC [c] (cm^2) (±95% CL)
AS	40	2.2 (0.30)	240 (20)	71 (20)	60	1.8 (0.35)	500 (30)	134 (28)
CMC	20	3.1 (0.35)	310 (10)	148 (18)	60	2.4 (0.20)	740 (40)	230 (32)
HPCL	20	4.0 (0.40)	240 (10)	173 (21)	45	2.1 (0.20)	710 (40)	191 (24)
HPCM	30	3.7 (0.30)	300 (20)	156 (36)	60	2.4 (0.10)	700 (30)	204 (26)
PVP	20	4.0 (0.70)	360 (20)	245 (42)	60	2.5 (0.30)	650 (35)	221 (36)
PVA	35	4.4 (0.30)	420 (20)	270 (26)	40	2.5 (0.20)	630 (60)	216 (42)

[a] Peak mydriasis intensity. [b] Time for the pupil to return back to normal; [c] Area under the mydriasis-time curve. AUC data were calculated from graphs where units are $mm \cdot min^{-1}$. On the vertical axis, 5.0 cm corresponded to 1.0 mm of pupil diameter increase; on the horizontal axis 5.0 cm corresponded to 100 min.

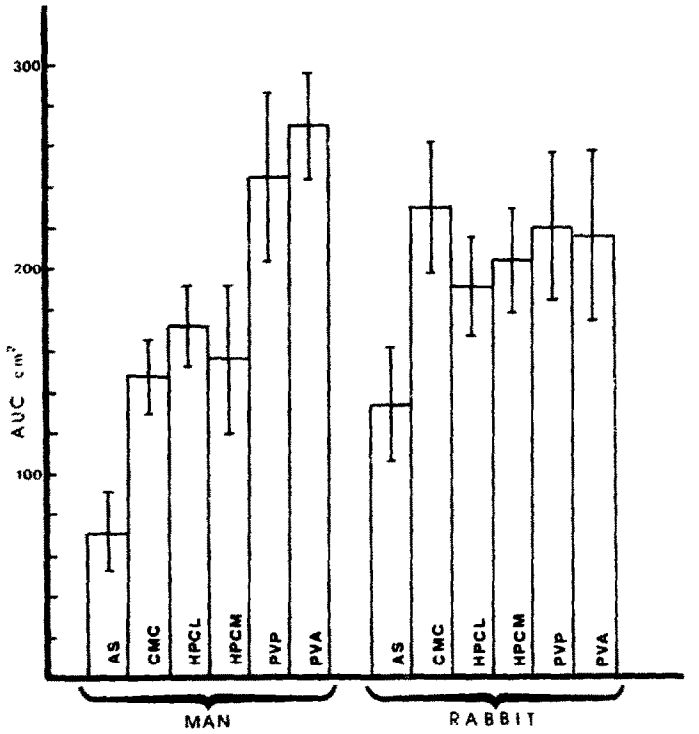

Fig. 1. Areas under the mydriatic response vs time curves (AUC) obtained in humans and in rabbits with the vehicles under study. Vertical lines over bars indicate 95% confidence limits.

with pilocarpine as the test drug (Saettone et al., 1982a). PVP, however, proved a better vehicle for tropicamide than for pilocarpine: with the latter drug this polymer, at the same concentration (6.0% w/w), had shown only a slight, non-significant bioavailability increase over a polymer-free solution.

The rabbit activity data, also reported in Table 1, show that administration of 50 µl of AS resulted in these animals, with respect to humans receiving the same dose of AS, in a delayed peak time, a statistically not different I_{max}, and a doubled duration and AUC value. The delayed peak time possibly depends on a slower absorption rate, caused by the much slower blinking frequency of rabbits with respect to humans (about 4 vs about 550 times/h). As pointed out in the previous papers of this series, blinking may play an important role in periodically recoating the precorneal area with a fresh layer of drug solution, and thus speeding up the absorption process. The increased duration and AUC values, on the other hand, may result from the smaller ocular distribution volume of rabbits with respect to humans, which produces the apparent effect of administration of a larger drug dose. In any case, these data were considered of minor relevance to the present investigation, that was mainly aimed at verifying the relative responses of each species to the effect of polymeric additives.

The polymeric vehicles in rabbits, when compared with AS, had little (in the case of HPCL and PVA) or no influence on the peak time, and a barely significant (or not significant, in the case of HPCL) effect on I_{max}. The duration of the effect was

1.3–1.5 times grater than that produced by AS, and, as said, this parameter was substantially greater in rabbits than in humans. An inspection of the AUC rabbit data (Table 1 and Fig. 1) shows that the polymeric vehicles produced an average 1.6 times bioavailability increase over AS, and were not statistically different from one another. The latter findings about the effect of tropicamide in polymeric viscous vehicles in rabbits parallel those already reported for pilocarpine: in that case also, the AUC values for the miotic effect of the drug in the presence of HPCL, HPCM, PVP and PVA (CMC was not tested) were not statistically different from each other. However, in that case the AUC value produced by PVA was significantly ($P < 0.05$) greater than that shown by AS, while the values of the other vehicles were not statistically different from that of AS.

Retention time and behaviour of the vehicles in the eye

Table 2 shows the results of experiments, in which the retention time and the behaviour of the preparations over the precorneal area were evaluated by monitoring the disappearance of a fluorescent marker. Both in humans and in rabbits, AS showed a very poor mixing behaviour with the tear film: the vehicle collected mainly in the marginal tear strip, producing irregular, small lenses over the corneal surface. CMC and HPCM gave irregular, weakly fluorescent films, while HPCL, PVP and PVA formed uniform films, which, in the case of the latter two vehicles, were highly fluorescent. The strong fluorescence is very probably indicative of a greater film thickness. Retention times were defined as the time elapsed from the instillation of each vehicle into the lower conjunctival sac, to complete disappearance of fluorescence over the precorneal area. It was observed that human blinking during the experiment was instrumental in re-spreading a vehicle layer over the precorneal area, from a reservoir in the marginal tear strip. This factor no doubt accounts for the much longer corneal retention times in humans with respect to rabbits. In both species, but particularly in rabbits, the effective retention time of AS was difficult to assess, since the product, as said, did not form a uniform film over the cornea, but produced tiny spots, or lenses, that in some cases persisted for a long time. In

TABLE 2

RETENTION TIMES (RT) OF THE VEHICLES IN HUMAN AND IN RABBIT EYES

Vehicle	RT [a] (s) (95% CL)		Remarks
	Humans	Rabbits	
AS	260 (67)	–	very poor mixing with tear film
CMC	852 (120)	300 (92)	irregular, weakly fluorescent film
HPCL	590 (62)	310 (75)	uniform, fluorescent film
HPCM	640 (58)	320 (87)	irregular, weakly fluorescent film
PVP	950 (130)	450 (64)	uniform, highly fluorescent film
PVA	1020 (87)	480 (35)	uniform, highly fluorescent film

[a] Time in seconds from the instillation of one drop (50 μl) of vehicle in the lower conjunctival sac to complete disappearance of fluorescence over the precorneal area.

humans, the viscous vehicles showed overall retention times much longer (2–4-fold) with respect to AS; the retention values varied substantially from one vehicle to the other, in spite of quite similar viscosity and/or rheological characteristics. The variations observed in rabbits were much smaller.

Physicochemical data

(a) Viscosity and rheological behaviour of the vehicles. The polymer concentrations were carefully adjusted in order to obtain, when possible, vehicles showing very similar rheological properties: the relevant rheograms are reported in Fig. 2. In the explored rate of shear range (up to 700 s^{-1}), HPCL, PVP and PVA showed a Newtonian behaviour, and a viscosity of 70 ± 2 cps. CMC and HPCM gave pseudoplastic solutions, whose apparent viscosity at 700 s^{-1} was in the same range (ca. 70 cps) of that of the Newtonian vehicles. It was speculated that in human eyes all vehicles might display the same apparent viscosity, in view of the relatively high

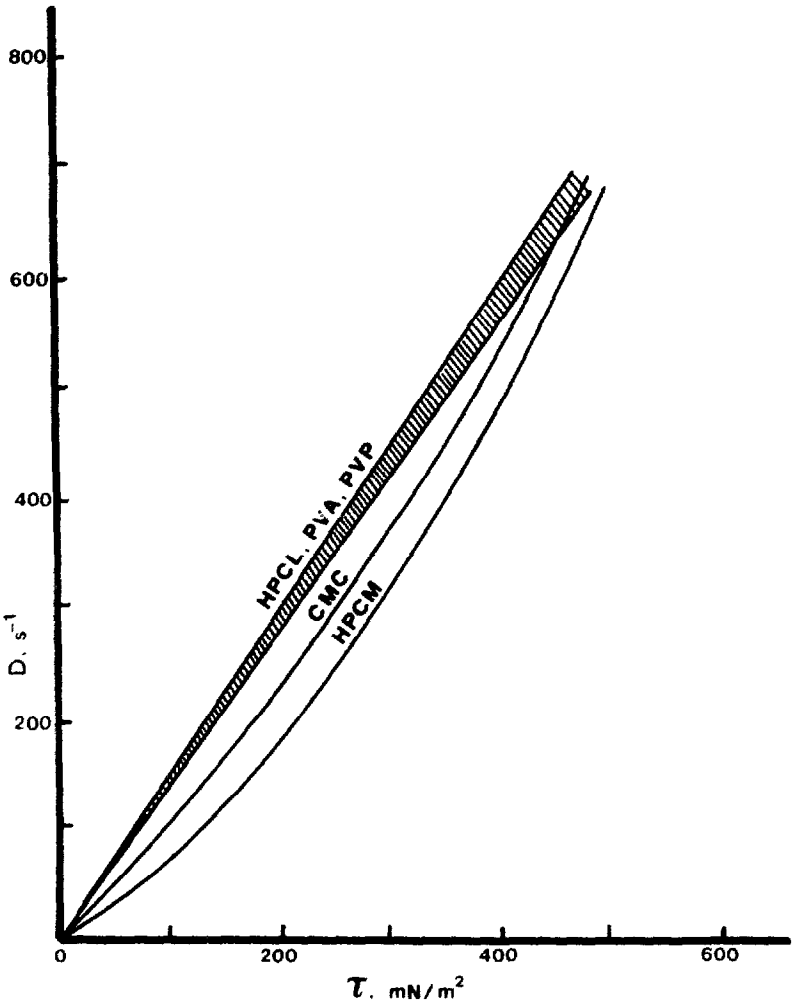

Fig. 2. Rheograms (30 °C) of the vehicles tested in the present study.

rate of shear generated by the upper eyelid movement during blinking (Duke-Elder, 1968).

(b) Tropicamide binding by the polymers. Fig. 3 shows the results of experiments, in which tropicamide in the vehicles under study, at the same initial concentration used for the biological tests, was allowed to permeate through a cellophane membrane under quasi-steady-state conditions. In all cases, linear plots were obtained when log C_i/C_{io}, i.e. the logarithm of the drug fraction remaining inside the permeation cell, was plotted against time. The line corresponding to HPCM was very close to that of HPCL, and was omitted from the graph for clarity. The reported linear plots represented the average of at least three dialysis runs; reproducibility of the experimental runs was quite satisfactory, the values for the slopes corresponding to each polymer not differing from each other by more than 5%. The good linearity of

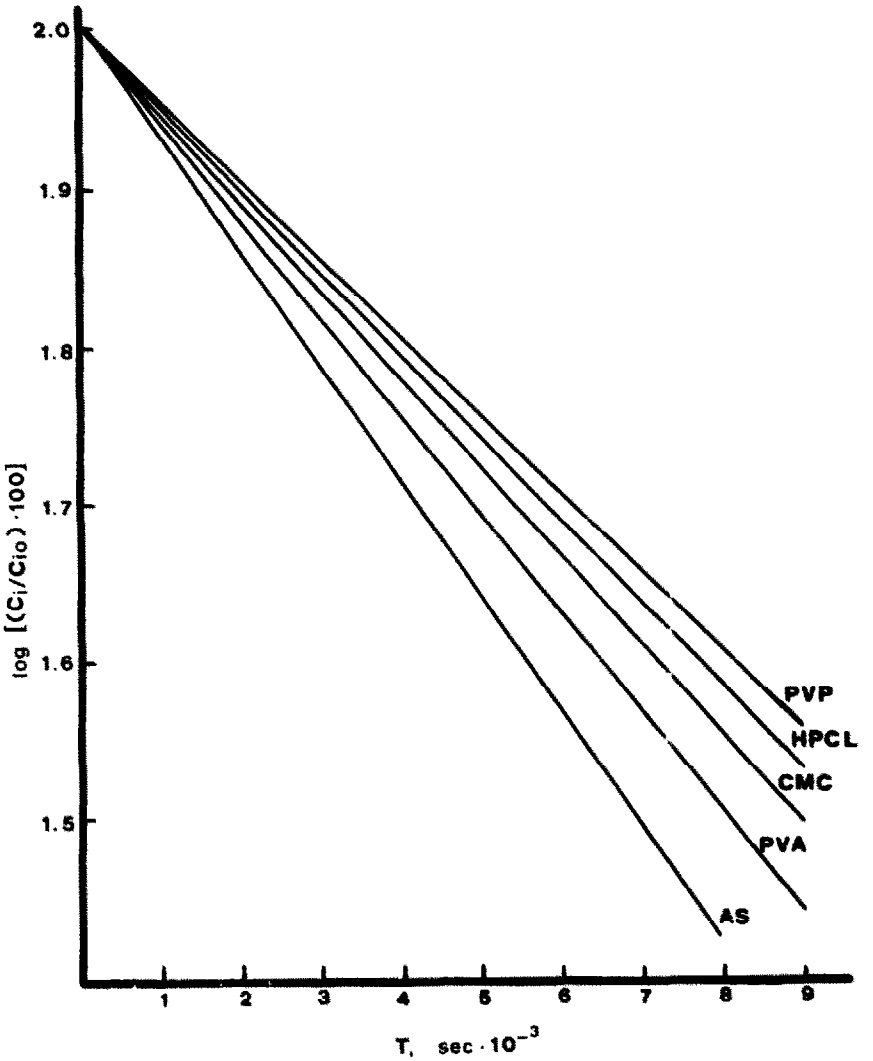

Fig. 3. Plots for the rate of dialysis of tropicamide from the different vehicles. The initial concentration of the drug was in all cases ca. 6.8×10^{-3} mole/liter.

the plots was demonstrated by the correlation coefficients of the linear regressions, which were always in the range 0.92–0.96. As indicated on a theoretical basis in a previous paper (Bottari et al., 1975), such linearity points to a constant C_b/C_f ratio during the permeation run, where C_b and C_f represent the concentrations of macromolecule-bound and of free drug inside the dialysis cell, respectively. It was also shown that the linearity might depend on the low total drug range explored during each dialysis run: similar results were obtained with methyl *p*-hydroxybenzoate at an initial concentration of 2.63×10^{-3} mole/liter, which is not far from the molar concentration of tropicamide in the present experiments (ca. 6.8×10^{-3}). A linear relationship between $\log C_i/C_{io}$ and time is usually no longer observed at higher initial permeant concentration. The ratio of the slope of the plot in the presence of macromolecule, K′, to the slope in its absence, K, is equal to the C_f/C_i

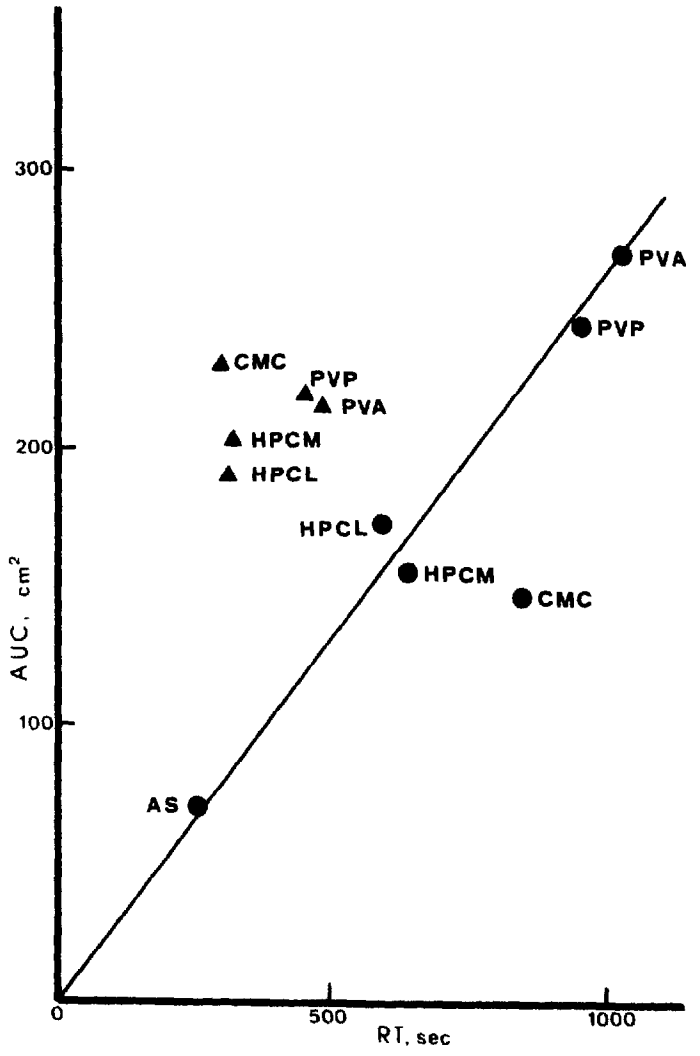

Fig. 4. Plot illustrating the relationship existing, for the vehicles under study, between the AUC value and the preocular retention time (RT). Key: ●, human data; ▲, rabbit data.

TAPLE 3

TROPICAMIDE BINDING BY THE VEHICLES

Vehicle	Tropicamide (% bound)
CMC	23.2
HPCL	28.7
HPCM	31.1
PVP	33.0
PVA	14.9

ratio:

$$K'/K = C_f/C_i \quad (1)$$

where C_f is the concentration of free tropicamide, and C_i is the total drug concentration in the diffusing solution. The percent bound drug in the presence of each macromolecule was calculated using Eqn. 1 from the plots in Fig. 4, considering that $C_b = C_i - C_f$. The values, reported in Table 3, show that all polymers, at the concentrations used for the biological experiments, exert some degree of binding. The least binding capacity (14.9%) was shown by PVA, followed by CMC (23.2%) and by the remaining three vehicles, which bound the drug practically to the same extent (around 30%).

(c) Surface properties of the vehicles. The surface and interfacial (against perhydrosqualene) tensions of the vehicles under investigation are reported in Table 4. All polymer-containing solutions showed a reduced surface tension with respect to AS, the greatest reduction being shown by the cellulose derivatives HPCL and HPCM. With the exception of CMC, the polymer vehicles also lowered the interfacial tension to a greater extent with respect to AS, but the reduction in some cases (PVA, PVP) was very small. An inspection of the data reveals that no definite relationship exists between these surface properties of the vehicles, and their bioavailability-enhancing

TABLE 4

SURFACE, INTERFACIAL TENSIONS AND SPREADING CAPACITY OF THE VEHICLES

Vehicle	γ_l (dine/cm)	$\gamma_{l/s}$ [a] (dine/cm)	Height of rise on glass slide (mm)
AS	60.5	15.7	-
CMC	55.1	22.9	1.9
HPCL	38.8	10.0	1.3
HPCM	39.8	12.4	-
PVP	57.4	13.7	5.5
PVA	45.2	14.5	8.1

[a] Interfacial tension against perhydrosqualene.

action. Thus, the hypothesis (Lemp and Holly, 1970, 1972) that a reduced surface and interfacial tension may per se favour mixing of the solutions with the tear film, and spreading over the corneal surface, is probably to be reconsidered. Indeed, the longest corneal retention times and better spreading capacities, as evidenced by the fluorescence studies, and the greatest drug bioavailability were shown by PVA and PVP, whose surface and interfacial tensions were higher than those of other, less biologically active polymers such as, e.g. HPCL and HPCM.

Benedetto and coworkers (1975) have shown that the capacity of polymer solutions of spreading at the air–tear interface is not directly related to their surface or interfacial tension, but rather to the capacity of the solutions of spreading over a clean glass surface. The same authors described a test, consisting of touching with a clean, wet glass slide the surface of a polymer solution contained in a small trough of approximately 40 μl capacity, and of measuring the rate of rise of the solution over the vertical slide. In experiments with the present vehicles, an almost instantaneous rise of the solutions over the slides was observed, the rate being so fast as to be practically not measurable. The height in mm to which each solution spread on the slide (average of 10 determinations) is reported in Table 4. It can be seen that AS and HPCM did not show any spreading capacity. Of the other polymer solutions, PVA showed the greatest capacity for spreading, followed by PVP, CMC and HPCL. As indicated in the following sections, this vehicle parameter appears to be directly related to the human bioavailability of tropicamide.

Human vs rabbit activity of the polymeric vehicles

The biological data point to substantial inter-species differences in the activity of the present vehicles. The possible reasons for the different biological behaviour of the same medications in human and in rabbit eyes should reside essentially in different precorneal dynamics of the instilled solutions, due to the particular ocular anatomy and physiology of each species. An inspection of Fig. 4, which illustrates the relationship between the preocular retention time of each vehicle and the corresponding AUC value for humans and rabbits is particularly interesting. Fig. 4, which correlates data in Tables 1 and 2, indicates a wide range of human retention times of the different vehicles, and a linear relationship between these values and bioavailability of tropicamide. The data clearly indicate that: (a) iso-viscous, Newtonian vehicles (as e.g. PVA and HPCL) may produce quite different biological results; and (b) the rheological behaviour has apparently a minor relevance to bioavailability, as exemplified by HPCL (Newtonian) and HPCM (pseudoplastic) that show quite similar bioavailability data. Only CMC, a pseudoplastic vehicle, seems to stand slightly out of the correlation line, since a higher bioavailability should correspond to a higher retention time than that actually shown.

The rabbit data, on the contrary, indicate a much narrower range of retention times and AUC values for the different vehicles. This experimental animal, although generically responding to an increased, polymer-induced viscosity, seems incapable of distinguishing, as man does, the effect of different polymeric structures. As anticipated, the main factor held to be responsible for the inter-species differences is probably the blinking activity. As pointed out by Mishima (1965), the fluid in the

human precorneal tear film is stagnant, unless it is mixed by blinking with the fluid in the marginal tear strip. In this way, new tear film (or, if it is the case, new drug solution) is brought to the precorneal area from the marginal strip reservoir, thus neutralizing the evaporative losses of the tear film. In rabbits, however, due to the absence of an efficient blinking activity, a different mechanism is operative. In these animals, the evaporative loss of water in the open eyes is compensated by an osmotic water flow from the aqueous through the cornea. Thus, in humans the ocular physiology cooperates in spreading and in maintaining an ophthalmic medication over the precorneal area, while in rabbits the same mechanism is largely absent, and furthermore, a counter-current of water from the aqueous to the precorneal film may interfere, even if to an unknown and probably small extent, with the absorption of an ophthalmic drug.

Activity differences of the polymeric vehicles in humans

The reported data indicate different bioavailability effects, presumably evidenced and amplified by the human ocular physiology, induced in humans by some of the present polymeric vehicles. Such differences, that are clearly unrelated to viscosity, are difficult to correlate with surface or interfacial tension, or with the drug binding capacity of the polymers. When considering the latter phenomenon, it can be noted that PVP, which, together with PVA, is one of the most active polymers, is endowed with the greatest binding capacity for tropicamide (33%). It can thus be assumed that the remaining free drug is amply sufficient to elicit the pharmacological response.

The effects of polymeric adjuvants in ophthalmic vehicles can perhaps be better understood in the light of the observations of Benedetto and coworkers (1975). According to these authors, since the polymers (as in the present cases) exhibit surface activity, they presumably absorb at the air–tear interface as does meibomian oil. Thus, the surface layer of the precorneal tear film in the presence of polymers probably exists as a mixed film of the two components. Blinking would cause a compression of the film, and the subsequent re-expansion would induce the film to move over the precorneal area, carrying with it a finite amount of drug solution as a result of the viscous drag of the hydrophilic groups of the polymer on the water molecules. The strong interaction of monomolecular or mixed films with a liquid phase, resulting in the carrying of bulk material by films as they spread spontaneously under surface tension gradients, is also an aspect of what is known as the Marangoni effect (Lemp et al., 1970; Adamson, 1982). The differences evidenced by human blinking in the present polymers might possibly depend on two factors: (a) a different spreading capacity, caused by local surface effects; and (b) a different capacity for dragging water, depending on polymer chemistry and conformation in solution. Different spreading capacities were indeed detectable in vivo on visual observation, and are described in Table 2. As is further indicated in Table 4, the polymeric solutions showed different spreading capacities on a wet glass slide, when this was touched to the surface of small (40 μl) solution samples, contained in a trough simulating the marginal strip reservoir. Interestingly, a correlation appears to exist between this parameter and the human bioavailability of tropicamide, as shown

in Fig. 5. As indicated by Benedetto and coworkers (1975), in the spreading process from the trough (or from the tear strip) differences among polymers might emerge, since factors such as energy of adsorption, entanglement and aggregation between polymer chains in the bulk solution may influence either the kinetics of the process and/or the thickness of the dragged water layer.

It should be observed in this context that viscosity effects are also probably operative in vivo, i.e. that the increased resistance to shear-induced flow, operated by the polymer, may be helpful in retaining the medication in the eye by slowing down the drainage rate. Such viscosity effects, superimposed on surface phenomena, may complicate the overall interpretation of the behaviour of a polymeric vehicle in the eye. A tentative assessment of the individual contribution of viscosity and of spreading effects to human bioavailability could be made, assuming that the three less active vehicles, CMC, HPCL and HPCM, were essentially devoid, as it would appear from the data in Tables 2 and 3, of surface spreading activity. In this case,

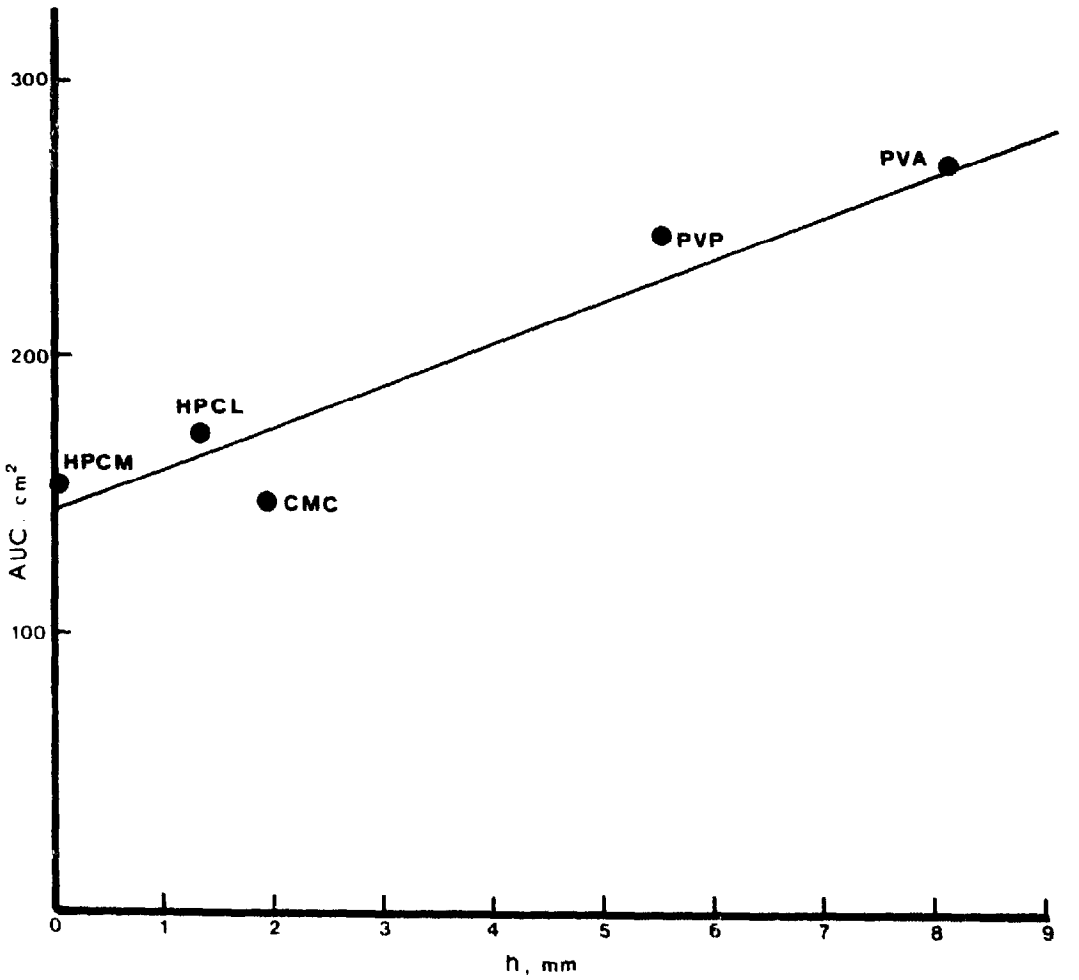

Fig. 5. Plot illustrating the relationship existing, for the vehicles under study, between the human AUC value and the surface spreading capacity (h, height of rise in mm) on wet glass slides.

viscous effects alone would produce roughly a two-fold bioavailability increase (with respect to the non-viscous solution AS), while surface spreading effects (present in PVA and in PVP) would be responsible for a further 1.7-fold AUC increase over the solutions displaying viscous effects alone. These figures, in any case, should be considered only as indicative, and restricted to the present experimental system. Indeed, possible interferences of different drugs with the polymeric solutions and/or pH effects resulting in modification of the spreading phenomena, cannot be discounted. This is exemplified by the observation (Saettone et al., 1982a) that pilocarpine in a pH 5.5 PVP vehicle was much less active in humans than in a PVA vehicle of the same pH and viscosity (73 cps).

In conclusion, the present results appear to indicate that surface spreading phenomena occur in humans, while rabbits would only be sensitive to viscosity effects. This might justify the 'equal viscosity-equal bioavailability' assumptions, derived by earlier workers from experiments in which polymeric ophthalmic drug solutions were tested in rabbits alone. The reported data also clearly emphasize the important contribution to overall human bioavailability of the chemical structure of the polymeric adjuvant, through a direct influence on the shape, thickness and spreading capacity of a medicated liquid film over the precorneal area. It is hoped that further work, now in progress on these peculiar physicochemical properties of polymeric solutions, may shed more light on the dynamics of the interactions of some polymers with the precorneal structures.

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