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Activity of ophthalmic gels of betamethasone and phenylephrine hydrochloride in the rabbit's eye

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Summary

Four gel systems were considered to represent a differential in viscosity covering the range from ~ 15–200 P ($D \simeq 0\ s^{-1}$). The gel systems were based on methylcellulose (MC), carbomer and polyethylene glycols (PEG) (two gels). The effect of different gel formulations on the activity of betamethasone (increase in the intraocular pressure: IOP) and phenylephrine hydrochloride (decrease in IOP and increase in pupil diameter) was investigated. The parameters that have been utilized to assess the performance of preparations of the two drugs were the area under (AUC) or above the curve (AAC), the maximum response (MR) time of maximum response (TMR), and duration of activity (DA). In the case of betamethasone, it was found that a 14-fold increase in viscosity ($D \simeq 0\ s^{-1}$) brought about a decrease in the AUC of only 10%. With phenylephrine hydrochloride the AAC (in both drug actions (IOP) or pupil diameter) is independent of the viscosity of the ophthalmic gel over the range of ~ 15–200 P ($D \simeq 0\ s^{-2}$)

Introduction

In view of the numerous disadvantages of the classical petrolatum-based ointments (Havener, 1970; Saettone et al., 1984), hydrogel drug delivery systems have been investigated with regard to their suitability for ophthalmic application (Doelker and Buri, 1972; Miller and Donovan, 1982; Habib et al., 1985).

Although many of the viscolizers used reduce the surface tension significantly, their effect on ocular drug bio-availability has been found to correlate to their viscosity-imparting properties rather than to their surface activity (Muller and Deardorff, 1956).

As an example of ophthalmic gels (carbopol 940) of pilocarpine hydrochloride, Schoenwald et al. (1978) were able to demonstrate in albino rabbits, that the duration of miosis was, to a certain extent, dependent on the plastic yield value of the gel. Gels with yield values greater than 11,000 dyne $\cdot$ cm^{-2} gave rise to longer miosis compared to gels with yield values lower than 11,000 dyne $\cdot$ cm^{-2}.

As an example of poloxamer 407 gels of pilocarpine nitrate, Miller and Donovan (1982) were able to demonstrate in albino rabbits that the gel formulation enhanced the activity of pilocarpine when compared to the aqueous solution. However,

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the effect obtained was similar in magnitude to that observed with viscous solutions.

Habib and Attia (1984) demonstrated, in the rabbit eye that adrenaline bitartrate produced greater mydriasis and a lowering of intraocular pressure (IOP) in a hydrogel base (carbopol 934 or poloxamer 407) when compared to a similarly dosed simple aqueous solutions of the drug.

The aim of this present work was to elucidate the influence of the gel-state on the drug bioavailability. The drugs under investigation are the anti-inflammatory corticosteroid, betamethasone, and the co-drug, phenylephrine hydrochloride, which is used to compensate the elevation in the IOP caused by betamethasone. Measurement of both IOP and pupil diameter was carried out. The investigated gels were based on methylcellulose, carboxyvinyl polymer (carbomer 934) and two types of polyethylene glycol (PEG I and II).

Experimental

Materials

Betamethasone (Schering), phenylephrine hydrochloride (Siegfried), carboxyvinylpolymer (carbomer 934, B.F. Goodrich Chemical Co.), methylcellulose 450 (BDH), polyethylene glycols 300, 400, 600, 1500, 2000 and 4000, all of pharmaceutical grade.

Methods

Preparation of ophthalmic gels. Ophthalmic gels containing 0.05% w/v betamethasone and/or 2.5% w/v phenylephrine hydrochloride — the gels contained the same concentrations of drugs, used in ophthalmic solutions.

Methylcellulose ophthalmic gel (MC). A 5% w/v polymer powder was dissolved in hot isotonic phosphate buffer solution (pH 6.8). The solution of betamethasone (0.05% w/v) or phenylephrine hydrochloride was added with gentle mixing.

Carbomer ophthalmic gel. A 2% w/v of polymer powder was first dispersed in cold freshly distilled water with the aid of a high speed stirrer, until complete solution. The solution was neutralized with sodium hydroxide (400 mg NaOH/1 g carbomer). The solutions of the drugs were then added with gentle mixing.

Polyethylene glycol gels (PEG I and II). Phenylephrine hydrochloride was dissolved in 10 parts of isotonic phosphate buffer solution (pH 6.8). Betamethasone was dissolved in the molten polyethylene glycol bases (90 parts). The aqueous solution was gradually incorporated into the molten bases with continuous and gentle stirring to congeal. The composition of PEG I was PEG 300, PEG 1500 and isotonic phosphate buffer in the ratio 9:9:2. The composition of PEG II was: PEG400 (52.11%), PEG 600 (18.54%), PEG 1500 (9%), PEG 2000 (6.66%) and PEG 4000 (3.69%) (Habib et al., 1985).

Investigating of rheology of ophthalmic gels. The viscosity of ophthalmic gels was determined using the Ferranti Shirley cone and plate rotational viscometer at 33 + 0.1°C. The viscosity was calculated at two limiting levels of shear dictated by the physiology of blinking in the eye of rabbit. Since the blinking rate has been shown by Melis-Decerf et al. (1979) to be very low in the rabbit (5 times $\cdot h^{-1}$), the lower level of shear was a value near to zero ($\simeq 0$), to represent the non-blinking condition: this was represented by the basic viscosity. The upper limit of shear was a rate similar to that calculated for human eye during blinking (Khalil, 1981); a value of 4500 s^{-1} was taken. An ideal equation giving an indication of the viscosity of the system at negligible rates of shear, and allowing the calculation of the apparent viscosity at any particular shearing rate, together with the characterization of the flow pattern of the system under investigation was looked at among the equations available for characterization of non-Newtonian flow. Steiger–Trippi's equation seemed to fulfill the above-mentioned requirements. Other details were described by Kassem et al. (1986).

Measurement of IOP and pupil diameter.

Albino rabbits of 1.5–2.0 kg receiving green fodder and drinking water ad lib were used. Isotonic xylocaine solution (1% w/v was dropped into the rabbit's eye to anaesthetize the cornea. It was proved experimentally that xylocaine had no effect on pupil diameter or IOP of the eye. In all cases topical doses each of 0.1 mg of ophthalmic

gels were applied. The dose was placed in the lower conjunctival sac. Non-medicated formulations were applied to the opposite eye which served as control. Each formulation was tested in each of six rabbits kept in a room with standardized illumination. The assigned formulation was applied to the right eye, while the control solution (the same gel formulation without drug) was applied to the left eye. Before and after application of both control and test formulations, the pupil diameter in mm and the IOP in mm Hg) of both eyes were measured using Haab's pupillometer and Maclocof tonometer, respectively, every hour. The parameters of activity of both drugs are: area under (or above) the curve (AUC), maximum response (MR), time of maximum response (TMR), and duration of drug action (DA).

Results and discussion

To investigate the activity of either betamethasone or phenylephrine hydrochloride in highly viscous systems, it was necessary to consider four gel systems which represented a differential in viscosity covering the range from ~ 15 to ~ 200 P ($D \simeq 0\ s^{-1}$). This range of viscosity is about 100–200 times that considered in the study of the ophthalmic solutions by Kassem et al. (1985).

Betamethasone

The time course of the IOP of the rabbit's eye in response to betamethasone is presented in fig. 1 for the different gel systems. It is evident that the time course of the IOP differs to a certain extent from one gel to the other according to the viscosity of each gel.

Area under IOP / time curve in relation to viscosity of ophthalmic gel

Table 1 depicts the independence of the AUC, over a 6 h period, of the viscosity of the gel in the range of ~ 15 to ~ 200 P at $D \simeq 0\ s^{-1}$ and ~ 11 to ~ 81 P at $D = 94.2\ s^{-1}$. A 14-fold increase in viscosity ($D \simeq 0\ s^{-1}$) brings about a decrease in the AUC of only 10%.

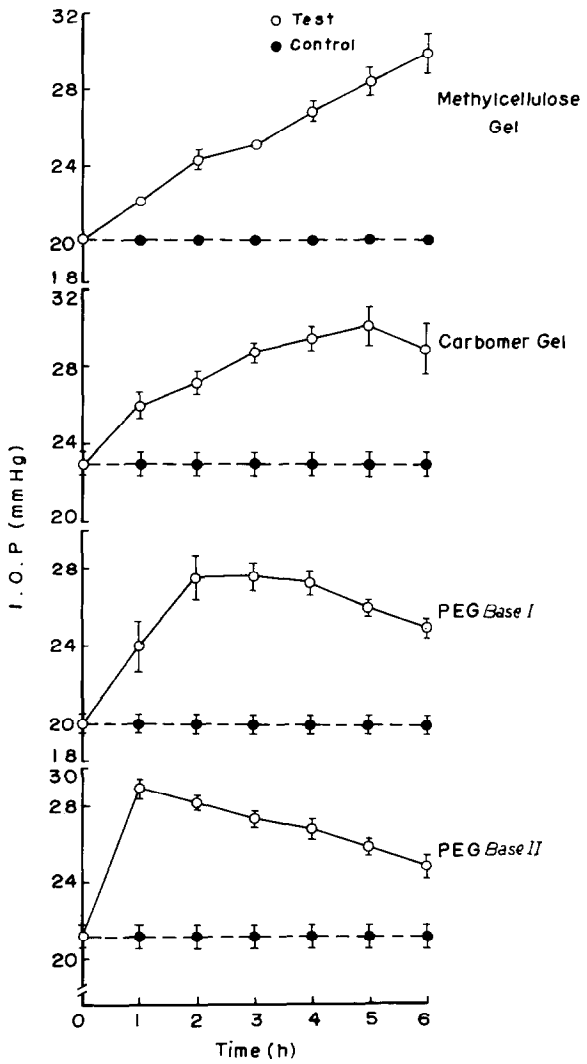

Fig. 1. Intraocular pressure (in mm Hg) of rabbit's eye post-instillation of 0.05% w/v betamethasone ophthalmic gels.

Table 2 reveals that the observed differences are not only minor but are also statistically insignificant.

If the AUC is considered as an indicator of the amount of drug absorbed, it would be obvious that gel-viscosity, in the range ~ 15 to ~ 200 P ($D \simeq 0\ s^{-1}$) has no significant effect on that amount.

Maximum response in relation to viscosity of ophthalmic gel

Table 1 illustrates the relation between the

TABLE 1

COMPARISON OF AUC, MR, TMR AND DA TO THE VISCOSITY OF OPHTHALMIC GELS OF BETAMETHASONE IN GROUPS OF 6 RABBITS (ONE EYE TEST, ONE EYE CONTROL)

Gel Type	Viscosity (p)		Parameters of activity			
	$D \simeq 0$ (s^{-1})	$D = 94.2$ (s^{-1})	Area under ** curve (mm Hg · h)	Maximum response (mm Hg)	Duration of action (h)	Time of maximum response (h)
Methylcellulose	193.8	65.62	30.54(2.6) *	9.75(0.8)	6	5.83(0.17)
Carbomer	175.4	8.13	29.75(3.3)	7.83(0.74)	6	3.83(0.4)
PEG Base I	14.04	11.22	34.54(2.6)	8.08(0.6)	6	2.33(0.42)
PEG Base II	40.32	16.33	33.71(3.1)	7.92(1.04)	6	1.5 (0.5)

* The values in parentheses in this table and subsequent ones represent the standard error of the mean.
**In excess to the corresponding control gels (i.e. without drug).

maximum response (observed over 6 h) to betamethasone gels and the viscosity of the gels throughout the range ~ 15 to ~ 200 P ($D \simeq 0$ s^{-1}) or ~ 11 to ~ 81 P ($D = 94.2$ s^{-1}).

It is obvious that the maximum response to betamethasone gels (Table 1) does not depend on the viscosity of these gels throughout the investigated viscosity range which is rather wide.

From the statistical point of view, Table 2 demonstrates that gels of very different viscosities do not bring about any significant differences with regard to intensity of drug action.

Time of maximum response in relation to viscosity of ophthalmic gel

Table 1 illustrates the relationship between the TMR to betamethasone gels and the viscosity of the gels.

The table demonstrates that the time of maximum response is dependent on the viscosity of the ophthalmic gel. As the viscosity increases 13-fold (from ~ 15 to ~ 200 P, $D \simeq 0$ s^{-1}) the time of maximum response increases 1.5-fold.

Statistical analysis of the data (Table 2) reveals that the differences in the viscosities of the gel are reflected in significant differences in the TMR. The only exceptional case is the difference between the two polyethylene glycol gels, PEG I and PEG II.

If the TMR is truely a function of gel-viscosity, it may be postulated that the viscosity data at $D \simeq 0$ s^{-1} reflect the situation under the in vivo conditions better than the viscosity data at $D \simeq 94.2$ s^{-1}. This assumption is based on the comparison of the rank order of the gels in terms of their viscosities and in terms of their effect on the TMR. At $D \simeq 0$ s^{-1}, there is a better compliance of the rank order based on the 2 parameters, viz. viscosity and TMR.

TABLE 2

SIGNIFICANCE LEVEL (VALUE OF *P*) OF DIFFERENCES BETWEEN MEAN VALUES OF THE PARAMETERS OF ACTIVITY FOR OPHTHALMIC GELS OF BETAMETHASONE

Pairs of comparison	Parameters of activity			
	AUC (mm Hg · h)	MR (mm Hg)	DA (h)	TMR (h)
Methylcellulose with carbomer	0.1	0.1	0.1	0.01
Methylcellulose with PEG Base I	0.1	0.1	0.1	0.01
Methylcellulose with PEG Base II	0.1	0.1	0.1	0.01
Carbomer with PEG Base I	0.1	0.1	0.1	0.05
Carbomer with PEG Base II	0.1	0.1	0.1	0.05
PEG Base I with PEG Base II	0.1	0.1	0.1	0.1

Duration of activity in relation to viscosity of ophthalmic gels

The time course of the IOP curves presented under this title reveals that the effect of betamethasone in the gel form is not terminated throughout the experimental observation period of 6 h. In view of this it is not possible to discuss this factor. The experiment should have been followed for longer than 6 h.

Phenylephrine hydrochloride

Thé time course of the IOP and pupil diameter of the rabbit's eye following the ophthalmic application of different gel systems are presented in Fig. 2 and 3, respectively.

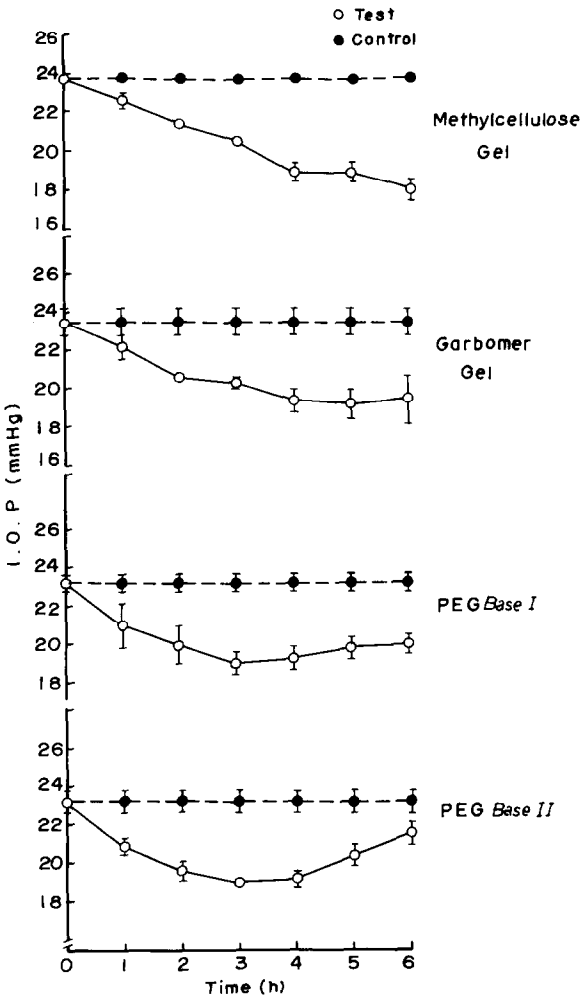

Fig. 2. Intraocular pressure (in mm Hg) of rabbit's eye post-instillation of 2.5% w/v phenylephrine hydrochloride ophthalmic gels.

It is obvious that there is some difference between the curve depending on the gel system.

It is also evident that the IOP curves presented here differ from those described under the solutions (studied by the same authors; Kassem, et al., 1985) in that the IOP does not revert back to the initial value as fast as the case observed for the solutions. Chrai and Robinson (1974) as well as Patton and Robinson (1975) related the viscosity of ophthalmic solution to the drainage rate and came to the conclusion that viscosities in the ranges of 15–20 cp and 12–15 cp, respectively, may represent optimum values for enhancing ophthalmic drug effect.

Area above IOP / time curve in relation to viscosity of ophthalmic gel

Table 3 illustrates the area above the IOP/time curve in relation to the viscosity of the ophthalmic gel. It is obvious that the area above the curve is independent of the viscosity of the ophthalmic gel over the range of ~ 15 to ~ 100 P ($D \simeq 0\ s^{-1}$). The minor differences between the AAC for the different gels are statistically insignificant (Table 4).

Area under the pupil diameter / time curve in relation to viscosity of ophthalmic gel

Table 3 shows the area under the pupil diameter time curve in relation to the viscosity of the different gels over the range ~ 15 to ~ 200 P ($D \simeq 0\ s^{-1}$) or ~ 11 to ~ 81 P ($D = 94.2\ s^{-1}$).

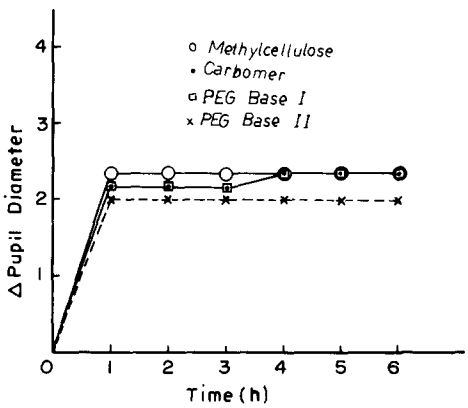

Fig. 3. Pupil diameter (in mm) of rabbit's eye post-instillation of 2.5% w/v phenylephrine hydrochloride ophthalmic gels.

TABLE 3

COMPARISON OF AAC, MR, DA AND TMR (FOR INTRAOCULAR PRESSURE AND PUPIL DIAMETER) TO THE VISCOSITY OF OPHTHALMIC GELS OF PHENYLEPHRINE HYDROCHLORIDE IN GROUPS OF 6 RABBITS (ONE EYE TEST, ONE EYE CONTROL)

Gel Type	Viscosity (P)		Parameters of activity (for IOP)			
	D = 0 (s^{-1})	D = 94.2 (s^{-1})	AAC (mm Hg · h)	MR (mm Hg)	DA (h)	TMR (h)
Methylcellulose	193.8	65.6	18.8(3.3)	5.5(0.93)	6	5.2(0.54)
Carbomer	175.4	81.3	18.2(2.2)	5.2(0.38)	6	4.3(0.8)
PEG Base I	14.0	11.2	18.6(1.9)	4.4(0.37)	6	3.8(0.17)
PEG Base II	40.3	16.3	17.8(3.0)	4.6(0.64)	6	2.8(0.4)
			Parameter of activity (for pupil diameter)			
			AUC (mm · h)	MR (mm)	DA (h)	TMR (h)
Methylcellulose	193.8	65.6	12.8(1.2)	2.3(0.21)	6	1.0
Carbomer	175.4	81.3	12.3(0.9)	2.3(0.21)	6	1.5(0.5)
PEG Base I	14.0	11.2	12.3(0.9)	2.3(0.2)	6	1.5(0.5)
PEG Base II	40.3	16.3	11.0	2.0	6	1.0

Also here, only minor differences are observed for the AUC throughout the viscosity range investigated. The AUC is independent of the gel viscosity.

Statistical analysis of the differences reveals their insignificance (Table 4).

Maximum response in terms of IOP in relation to viscosity of ophthalmic gel

The maximum response (IOP) to phenylephrine hydrochloride is presented in Table 3 as a function of the viscosity of the gel system applied to the rabbit's eye.

TABLE 4

SIGNIFICANCE LEVEL (VALUE OF *P*) OF DIFFERENCES BETWEEN THE MEAN PARAMETERS OF ACTIVITY (FOR INTRAOCULAR PRESSURE AND PUPIL DIAMETER) FOR OPHTHALMIC GELS OF PHENYLEPHRINE HYDROCHLORIDE

Pairs of comparison	Parameters of activity (for IOP)			
	AAC (mm Hg · h)	MR (mm Hg)	DA (h)	TMR (h)
Methylcellulose with Carbomer	0.1	0.1	0.1	0.1
Methylcellulose with PEG Base I	0.1	0.05	0.1	0.01
Methylcellulose with PEG Base II	0.1	0.1	0.1	0.01
Carbomer with PEG Base I	0.1	0.01	0.1	0.1
Carbomer with PEG Base II	0.1	0.1	0.1	0.1
PEG Base I with PEG Base II	0.1	0.1	0.1	0.1
	Parameters of activity (for pupil diameter)			
	AUC (mm · h)	MR (mm)	DA (h)	TMR (h)
Methylcellulose with carbomer	0.1	0.1	0.1	0.1
Methylcellulose with PEG Base I	0.1	0.1	0.1	0.1
Methylcellulose with PEG Base II	0.1	0.1	0.1	0.1
Carbomer with PEG Base I	0.1	0.1	0.1	0.1
Carbomer with PEG Base II	0.1	0.1	0.1	0.1
PEG Base I with PEG Base II	0.1	0.1	0.1	0.1

The table shows not more than a slight increase in the maximum response throughout the whole viscosity range investigated. The increase observed is statistically significant only for gels of very different viscosities, viz. below 25 P and above 150 P ($D \simeq 0\ s^{-1}$) as depicted by Table 4.

Maximum pupillary response in relation to viscosity of ophthalmic gel

Table 3 demonstrates the dependency of the maximum pupillary response on the viscosity of the gel.

It is obvious that the maximum pupillary response is independent of the viscosity of the gel. Any minor differences observed are found to be statistically insignificant (Table 4).

Time of maximum response in terms of IOP in relation to viscosity of ophthalmic gel

The dependency of the time of maximum response on the viscosity of phenylephrine hydrochloride gels is presented in Table 3.

It is obvious that the TMR increases with increasing viscosity of the gel. The increase in the TMR is statistically significant (Table 4) only for gels of very different viscosities, viz. 50 and 200 P ($D \simeq 0\ s^{-1}$).

If the TMR is truly dependent on the viscosity of the gel it would be plausible that a rate of shear approaching $0\ s^{-1}$ reflects the situation in the rabbit eye much better than a rate of shear of $95\ s^{-1}$ because the viscosity has been determined at well defined conditions of shear and the shear rate is very close to zero to exclude time-dependent effects in the rheology of the system.

This hypothesis is based on the rank order of the gel in terms of their influence on the TMR and their viscosities at the above-mentioned rates of shear. It is evident that the best correlation between the 2 parameters would be given for viscosities measured at $D \simeq 0\ s^{-1}$.

Time of maximum pupillary response in relation to viscosity of ophthalmic gel

Table 3 illustrates the relationship between gel-viscosity and the time of maximum pupillary response. It is obvious that this relation is not a straight forward one.

Statistical analysis of the data (Table 4) reveals that all differences observed are insignificant.

Duration of activity in relation to viscosity of ophthalmic gel

Both the intraocular pressure/time and the pupil diameter/time curves presented above reveal that the duration of activity extends throughout the experimental observation period. In view of this, assessment of the title parameter necessitates observation periods longer than 6 h. The present findings indicate the following results.

(a) The effect of the drug, whether water-soluble (phenylephrine hydrochloride) or lipid-soluble (betamethasone) is dictated to a great extent by the viscosity of the system or is totally independent of the viscosity of the system depending on the viscosity range under consideration.

(b) The viscosity of the system dictates the in vivo performance of the drug only within a very narrow and low viscosity range extending up to about 4–5 cp. Throughout this range, increasing the viscosity provides a powerful tool to promote drug effect in terms of AUC (or AAC) as a measure of the amount of drug absorbed, in terms of maximum response and duration of drug action.

(c) The in vivo performance of the drug shows much less dependency on the viscosity of ophthalmic systems in the range beyond 4–5 cp and is almost independent beyond ~ 20 cp and up to values of about ~ 10,000 cp. Throughout this vast range, the parameters of drug effect (i.e. AUC or AAC, MR and DA) do not undergo any pronounced change.

These findings demonstrate that liquid ophthalmic preparations of low viscosity are equivalent to ophthalmic gels. In other words, the use of gel systems instead of liquid ophthalmic preparations containing a viscolizer with the objective of increasing intensity of drug action or amount of drug absorbed is totally unjustified.

(d) The parameters of drug effect responding most to increase of viscosity in the range below 4–5 cp are the AUC (or AAC) and the duration of drug action. The intensity of drug effect responds to the increase in viscosity to a lower extent.

(e) For a water-soluble drug (phenylephrine

hydrochloride), the dependency of drug effect on viscosity is less pronounced than that for a lipid-soluble drug (betamethasone). This is valid for all parameters of drug effect, namely AUC (or AAC), MR and DA.

According to Muller and Deardorff (1956), the effect of viscolizers in enhancing ophthalmic drug effect is due to the suppression of reflux lacrimation. While Adler et al. (1971) noticed that viscolizers produce no thickening of the precorneal tear film. Furthermore, they found no prolongation of drug solution of the tear film with drops. However, discussion of the findings obtained suggests that drug loss is primarily controlled by the release rate constant of the drug in the drug reservoir (i.e. the viscous ophthalmic solution or gel) in the cul de sac and that the drug reservoir remains for a certain time without major dilution by physiological fluids. The loss of this stage takes place mainly with regard to the drug rather than to the viscous solution of the drug. The drug leaving the reservoir is transported to the precorneal tear film where loss of drug solution takes place via drainage and is controlled by the drainage rate constant at this stage. Implicit in the explanation is that drug loss via drainage is of secondary importance since the amount of drug lost via drainage would be primarily controlled by the amount of drug lost from the reservoir. The data from the present study reveal that a levelling-off of drug effect with increasing viscosity of the ophthalmic solution takes place at a viscosity much lower than that found for the levelling-off of drainage rate constant with increasing viscosity. The former takes place at about 4 cp while the latter at about 15 cp. The finding of Adler et al. (1971) that viscous solutions do not increase the viscosity of the precorneal film provides further support. According to the explanation presented in this present study, the effect of viscolizers is primarily correlated to their influence in suppressing the mass transport of the drug from the viscous solution rather than to their influence in suppressing the drainage rate.

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