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In vitro release study of betamethasone and phenylephrine hydrochloride from ophthalmic preparations

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Summary

The in vitro release of betamethasone and phenylephrine hydrochloride from ophthalmic solutions and gels was investigated. Linearization of release data of either drug or their combination was attempted according to zero-order, first-order and diffusion kinetics. The data obtained are directly in favour of a first-order mechanism both for betamethasone and phenylephrine hydrochloride and they show that the mechanism of drug release from solutions containing viscolizers or from hydrogels is independent of the nature of the drug in terms of its water solubility or ionization. The type of polymer or the increase in viscosity of the ophthalmic preparation do not indicate the release mechanism to any significant extent. The release rate constants of phenylephrine hydrochloride are consistently higher than those of betamethasone. The preparation based on carbomer is the only exception to this. The release rate constant of the drug is highly dependent on the viscosity of the ophthalmic solution. Below the critical viscosity of 5 cp a considerable lowering of the release rate constant takes place. In ophthalmic gel the release rate constant of either drug shows a very low dependency on the basic viscosity of the gel.

Introduction

Ophthalmic medications are usually introduced into the eye by placing them in contact with conjunctiva and cornea. Of the ophthalmic medications, eye drops still represent the major form and method of administration for topical ocular route. Other forms of ophthalmic medications which are being used to a lesser extent are the semisolid preparations. The hydrogel drug delivery systems have been investigated for their suitability as ophthalmic application (Hecht et al., 1979; Chrai et al., 1973).

Some of the most important physicochemical properties of aqueous ophthalmic preparations that influence corneal penetration are: (a) pH; (b) isotonicity; (c) surface tension; (d) viscosity; (e) miscibility with secretions of the eye; (f) relative affinity which the drug exhibits between vehicle and tissue fluids of the eye; and (g) the water–lipid solubility partition coefficient of the drug. Of these physicochemical properties, the viscosity and its biopharmaceutical impact on the in vivo performance of ophthalmic preparations have not yet been fully explored.

One of the tools resorted to, in the last few

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decades, for the minimization of drug loss in the precorneal area is the addition of a viscolizer to liquid ophthalmic preparations. Patton and Robinson (1975) reported that the rate of drainage loss for PVA solutions was found to compare favourably to methylcellulose solutions of similar viscosity.

The effect of viscolizers on ocular drug bioavailability has been investigated most extensively with pilocarpine. For example, Chrai and Robinson (1974) demonstrated in albino rabbits that instillation of pilocarpine nitrate solutions of increasing viscosity — using methylcellulose — resulted in higher aqueous humor drug concentration. However, the magnitude of the increase in aqueous humor drug concentration was found to be small over a 100-fold change in solution viscosity. The effect was more pronounced in the lower viscosity range, viz. 1- ~ 15 cp.

A major side-effect of steroids in ocular therapy is their ability to elevate intraocular pressure (IOP) and even to induce, in susceptible individuals, an intractable glaucoma (Akers et al., 1977). It is therefore of interest to note that of the drugs which are commonly used in ophthalmology, phenylephrine hydrochloride has been recently reported to inhibit rapidly the elevation of the IOP in the rabbit eye (Conquet and Vareilles, 1978).

The purpose of this work was to study the dependency of the drug-releasing properties of the solution on viscosity. The drugs tested were the corticosteroid betamethasone, and the co-drug, phenylephrine hydrochloride, in ophthalmic solutions and gels. Non-viscous solution of the drugs was used as a control. The viscolizers were: two grades of phenvinyl alcohol (low and high molecular weight), methylcellulose and methylhydroxyethylcellulose (tylose). The gels were based on methylcellulose, carbomer 934 and polyethylene glycols.

Experimental

Materials

Betamethasone (Schering), phenylephrine hydrochloride (Siegfried), methylcellulose 450 (BDH), methylhydroxyethylcellulose (Tylose 4000, Hoechst), polyvinyl alcohol (PVA) 14,000 and 72,000 (BDH), carboxyvinyl polymer (Carbomer 934; B.F. Goodrich Chemicals). Polyethylene glycols 300, 400, 600, 1500, 2000 and 4000 were all of pharmaceutical grade. 2,3,5-triphenyltetrazolium chloride (BDH); glacial acetic acid, sodium hydroxide, benzalkonium chloride, sodium metabisulfite, sodium edetate, mono- and dibasic sodium phosphate, sodium chloride and potassium hydroxide were all of pharmaceutical grade.

Apparatus

pH-meter Titrimeter Type U9N (Tacussel), Ferranti Shirley cone and plate rotational viscometer (Ferranti, Manchester, U.K.), spectrophotometer (Shimadzu, Japan); Laminar, air-flow hood, model NB 48 INOX Gelaire class 100, Gelman Instruments, Semipermeable Fischer Cellulose membrane 30/32 (Fischer Scientific, London, U.K.).

Procedures

Preparation of ophthalmic solutions

Ophthalmic solutions containing 0.05% w/w betamethasone and/or 2.5% w/v phenylephrine-HCl were prepared according to the following procedure.

The polymers in question were dissolved in isotonic phosphate buffer solution (pH 6.8). Betamethasone was dissolved in the least amount (1% of the ophthalmic solution) of polyethylene glycol 400. Solutions of betamethasone and phenylephrine hydrochloride (the latter in buffer) were mixed with the isotonic buffer solution, benzalkonium chloride (1 : 10,000) was added as preservative; sodium metabisulfite (0.5%) and disodium edetate (0.3%) were added as stabilizers. The pH of the solution was adjusted to $= 6 \pm 0.2$. The solutions were then completed to volume and filled under aseptic conditions in neutral glass vials, which were then kept in boiling water for a period of 30 min.

The concentration ranges of the polymer were: 0.25–1%, 0.125–0.5%, 1–3% and 0.5–2% w/v for methylcellulose, methylhydroxyethylcellulose, polyvinyl alcohol 14,000 and polyvinyl alcohol 72,000, respectively.

Preparation of ophthalmic gels

The gels contained the same concentrations of drugs, preservative and stabilizers 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) containing the stabilizers and preservative. The solution of betamethasone or phenylephrine-HCl 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 solution was complete; the stabilizers and preservative were then dissolved. The solution was then neutralized with sodium hydroxide (400 mg NaOH/1 g carbomer). The solutions of the drugs were then added to the gel with gentle mixing.

Polyethylene glycol gels (PEG)

Phenylephrine-HCl, preservative and stabilizers were 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.

Two polyethylene glycol bases were used, viz. PEG I and PEG II. 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 PEG 400 (52.1%), PEG 600 (18.5%), PEG 1500 (9%), PEG 2000 (6.7%) and PEG 4000 (3.7%) (Habib et al., 1985).

Investigation of the rheology of ophthalmic preparations

The viscosity of the ophthalmic preparations, solutions or gels, was determined using the Ferranti Shirley cone and plate rotational viscometer at $33 \pm 0.1°C$.

The viscosity was calculated at two limiting levels of shear dictated by the physiology of blinking in the rabbit eye. Since the rate of blinking has been shown by Melis-Decerf and Van Octeghem (1979) to be very low in the rabbit ($4 \text{ times} \cdot h^{-1}$), the lower level of shear was a value near to zero ($\simeq 0$), to represent the non-blinking condition, and this was represented by the basic viscosity. The upper limit of shear was a rate similar to that calculated for the 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

TABLE 1

VISCOSITIES OF OPHTHALMIC PREPARATIONS OF DIFFERENT SHEARING RATES ACCORDING TO STEIGER-TRIPPI'S EQUATION

Polymer type and concentration		c	n_0	n_1	n_2
Ophthalmic solutions					
Methyl cellulose	0.5%	11.28	0.08	0.08	–
Methyl cellulose	1.0%	4.66	0.21	0.19	–
Tylose	0.5%	6.30	0.16	0.13	–
Ophthalmic gels					
Methyl cellulose		0.01	193.08	–	65.62
Carbomer		0.01	175.44	–	81.30
PEG I		0.07	14.04	–	14.04
PEG II		0.02	40.32	–	41.32

n_0 and n_1 are the viscosities (in poise) at $D \simeq 0$ and 4500 s^{-1}. n_2 is the viscosity at the highest shearing rate of gel (i.e. at $D = 94.2 \text{ s}^{-1}$). c is a constant (reciprocal of viscosity) determined from Steiger-Trippi's Equation.

system under investigation, was looked at among the equations available for characterization of non-Newtonian flow. Steiger-Trippi's equation seemed to fullfil the above-mentioned requirements (Steiger-Trippi and Ory, 1961).

$$D = a\tau^3 + C\tau$$

where D = rate of shear, τ = shearing stress, a and c are constants calculated from the following equations:

$$a = \frac{\tau_1 D_2 - \tau_2 D_1}{\tau_1 \tau_2^3 - \tau_2 \tau_1^3}$$

$$c = \frac{D_1}{\tau_1} - a\tau_1^2$$

$$\eta = \frac{\tau i}{D_i}$$

where D_i is the shearing rate (s^{-1}) obtained with a velocity V_i; τ_i is the shearing stress (dyne/cm^2) produced at a shearing rate D_i; D_1, τ_1 and D_2 τ_2 are values of shearing rates and shearing stresses, obtained from the flow curve at low (V_1) and high (V_2) velocities, respectively; c is the reciprocal of basic viscosity (η_0) which is the viscosity at infinitely small rate of shear (tending to zero) — by the equation:

$$\eta_0 = \frac{1}{c}$$

The data of the viscosity of the opthalmic solutions and gels are presented in Table 1.

Determination of the in vitro release of betamethasone and / or phenylephrine hydrochloride from ophthalmic preparations

The release of the drug from ophthalmic preparations, solutions or gels, was carried out using the dialysis method (Attia et al., 1981). Samples each of 5 ml (for betamethasone) or 1 ml (for phenylephrine-HCl) were withdrawn from the beaker at 0.5, 1, 2, 3, 4, 5 and 6 h intervals. Each sample withdrawn was replaced by an equal volume of distilled water to maintain a constant volume.

Determination of betamethasone in the dialysate

The amount of drug released was determined by the tetrazolium reaction (B.P. 1963). The intensity of the colors of the samples was measured at 485 nm.

Determination of phenylephrine hydrochloride in the dialysate

Samples of the dialysate were measured spectrophotometrically at 273 nm, after appropriate dilution.

Results and Discussion

The in vitro release of betamethasone and phenylephrine hydrochloride from ophthalmic solutions and gels was investigated at 35°C.

Mechanism of drug release

Linearization of release data of either drug or their combination was attempted according to zero-order, first-order and diffusion kinetics. Preference of a certain mechanism was based on the correlation coefficient and the coefficient of variation percent for the parameters involved. Further weighting of the mechanisms was based on the duration of the time lag, if any, preference being made for the mechanism involving no or a shorter lag time, such an approach has been already suggested by Samuelove et al. (1979).

The results of the mathematical treatments of the release data are presented in Table 2 for betamethasone and Table 3 for phenylephrine hydrochloride.

The data are directly in favour of a first-order mechanism both for betamethasone and phenylephrine hydrochloride.

The mathematical treatments of the release data of either drug in presence of the other are presented in Tables 2 and 5. Here also the data are supportive of a first-order mechanism.

Tables 2–5 demonstrate the first-order release kinetics of the individual drugs as well as their combination in different ophthalmic vehicles.

The data presented show that the mechanism of drug release from solutions containing viscolizers or from hydrogels is independent of the nature of

TABLE 2

MATHEMATICAL TREATMENTS OF THE RELEASE DATA ACCORDING TO ZERO-ORDER, FIRST-ORDER AND DIFFUSION MECHANISMS FOR BETAMETHASONE IN BETAMETHASONE OPHTHALMIC PREPARATIONS

Polymer type and concentration	Zero-order	First-order		Diffusion		
	r	*r*	Lag time (h)	*r*	Lag time (h)	Slope of log Q vs log t
Ophthalmic solutions						
Non-viscous	0.953	0.997	1.44	0.981	141.0	0.681
PVA14 1%	0.973	0.997	1.66	0.996	90.9	0.630
PVA14 2%	0.984	0.998	1.19	0.999	398.3	0.817
PVA14 3%	0.985	0.999	1.06	0.999	519.2	0.944
PVA72 0.5%	0.973	0.999	2.03	0.995	26.1	0.523
PVA72 1%	0.976	0.999	1.31	0.997	96.1	0.864
PVA72 2%	0.977	0.997	0.12	0.998	91.9	0.690
MC 0.25%	0.977	0.999	1.29	0.997	110.3	0.621
MC 0.5%	0.979	0.997	0.77	0.988	109.6	0.724
MC 1%	0.992	0.999	1.03	0.998	182.2	0.772
0.125% Tylose	0.985	0.999	1.06	0.999	527.1	0.948
0.25% Tylose	0.991	0.999	1.12	0.999	164.9	0.737
0.5% Tylose	0.993	0.998	1.01	0.998	193.8	0.796
Ophthalmic gels						
MC	0.995	0.996	0.88	0.998	636.8	1.101
Carbomer	0.997	0.998	1.03	0.997	278.8	0.836
PEG I	0.994	0.997	1.38	0.998	34.5	0.560
PEG II	0.981	0.996	1.50	0.996	61.3	0.428

r = Correlation co-efficient; Q = Total amount of drug released; L = Time of drug released. Lag time is the extrapolation of the steady-state slope to the time-axis of the release plots.

TABLE 3

MATHEMATICAL TREATMENTS OF THE RELEASE DATA ACCORDING TO ZERO-ORDER, FIRST-ORDER AND DIFFUSION MECHANISMS FOR PHENYLEPHRINE-HCl IN PHENYLEPHRINE-HCl OPHTHALMIC PREPARATIONS

Polymer type and concentration	Zero-order	First-order		Diffusion		
	r	*r*	Lag time (h)	*r*	Lag time (h)	Slope of log Q vs log t
Ophthalmic solutions						
Non-viscous	0.931	0.997	1.48	0.976	86.21	0.667
PVA14 1%	0.934	0.998	1.52	0.977	10.30	0.541
PVA14 2%	0.936	0.997	1.49	0.978	1.24	0.563
PVA14 3%	0.940	0.996	1.46	0.980	0.26	0.582
PVA72 0.5%	0.947	0.998	1.56	0.982	74.61	0.471
PVA72 1%	0.943	0.997	1.53	0.981	28.51	0.503
PVA72 2%	0.973	0.998	1.47	0.997	10.95	0.482
MC 0.25%	0.982	0.997	1.38	0.997	26.39	0.530
MC 0.5%	0.984	0.998	1.27	0.998	91.66	0.643
MC 1%	0.987	0.998	1.32	0.999	17.82	0.567
0.125% Tylose	0.959	0.997	1.52	0.988	17.25	0.505
0.25% Tylose	0.959	0.997	1.58	0.991	28.69	0.490
0.5% Tylose	0.989	0.995	1.23	0.998	90.21	0.651
Ophthalmic gels						
MC	0.992	0.996	1.41	0.998	4.19	0.522
Carbomer	0.993	0.989	1.17	0.981	4.51	0.440
PEG I	0.978	0.999	1.34	0.996	377.3	0.770
PEG II	0.987	0.998	1.46	0.997	61.47	0.586

TABLE 4

MATHEMATICAL TREATMENTS OF THE RELEASE DATA ACCORDING TO ZERO-ORDER, FIRST-ORDER AND DIFFUSION MECHANISMS FOR BETAMETHASONE IN BETAMETHASONE AND PHENYLEPHRINE-HCl OPHTHALMIC PREPARATION

Polymer type and concentration	Zero-order	First-order		Diffusion		
	r	*r*	Lag time (h)	*r*	Lag time (h)	Slope of log Q vs log t
Ophthalmic solutions						
Non-viscous	0.971	0.999	1.36	0.993	255	0.713
PVA14 1%	0.974	0.998	1.34	0.996	182.6	0.692
PVA14 2%	0.984	0.998	1.14	0.999	485.2	0.875
PVA14 3%	0.991	0.998	1.01	0.998	614.8	0.967
PVA72 0.5%	0.972	0.999	1.41	0.995	40.1	0.591
PVA72 1%	0.980	0.998	1.05	0.998	143.4	0.701
PVA72 2%	0.975	0.998	1.21	0.999	100.5	0.677
MC 0.25%	0.971	0.997	1.21	0.995	164.6	0.755
MC 0.5%	0.996	0.998	1.03	0.996	211.5	0.779
MC 1%	0.997	0.995	1.19	0.985	226.8	0.800
0.125% Tylose	0.990	0.998	1.01	0.998	390.8	0.964
0.25% Tylose	0.991	0.999	1.10	0.999	167.8	0.746
0.5% Tylose	0.995	0.995	0.94	0.992	257.6	0.848
Ophthalmic gels						
MC	0.997	0.997	0.39	0.993	873.9	1.648
Carbomer	0.994	0.997	0.29	0.995	199.3	0.792
PEG I	0.997	0.997	0.77	0.995	1057.8	1.273
PEG II	0.993	0.997	1.09	0.997	431.3	0.871

TABLE 5

MATHEMATICAL TREATMENTS OF THE RELEASE DATA ACCORDING TO ZERO-ORDER, FIRST-ORDER AND DIFFUSION MECHANISMS FOR PHENYLEPHRINE-HCl IN PHENYLEPHRINE-HCl AND BETAMETHASONE OPHTHALMIC PREPARATIONS

Polymer type and concentration	Zero-order	First-order		Diffusion		
	r	*r*	Lag time (h)	*r*	Lag time (h)	Slope of log Q vs log t
Ophthalmic solutions						
Non-viscous	0.983	0.999	1.47	0.997	46.84	0.590
PVA14 1%	0.943	0.996	1.51	0.982	16.83	0.534
PVA14 2%	0.943	0.996	1.52	0.981	25.56	0.525
PVA14 3%	0.944	0.995	1.50	0.983	18.55	0.532
PVA72 0.5%	0.949	0.999	1.48	0.986	0.87	0.587
PVA72 1%	0.944	0.997	1.46	0.983	1.59	0.606
PVA72 2%	0.983	0.998	1.41	0.997	1.36	0.520
MC 0.25%	0.979	0.998	1.32	0.998	56.48	0.623
MC 0.5%	0.981	0.998	1.25	0.997	107.40	0.670
MC 1%	0.988	0.998	1.28	0.999	37.83	0.592
0.125% Tylose	0.955	0.998	1.41	0.989	16.28	0.630
0.25% Tylose	0.963	0.997	1.40	0.993	6.11	0.590
0.5% Tylose	0.990	0.997	1.19	0.997	124.76	0.685
Ophthalmic gels						
MC	0.995	0.997	1.35	0.997	29.32	0.560
Carbomer	0.996	0.995	0.83	0.985	66.28	0.747
PEG I	0.975	0.999	1.50	0.994	12.49	0.561
PEG II	0.980	0.999	1.26	0.997	560.80	0.869

TABLE 6

FIRST-ORDER RELEASE CONSTANTS (k in h^{-1}) AND HALF-LIVES ($t_{1/2}$ in h) FOR BETAMETHASONE IN OPHTHALMIC PREPARATIONS

Polymer type and concentration	in betamethasone preparations		in betamethasone and phenylephrine-HCl preparations	
	k (h^{-1})	$t_{1/2}$ (h)	k (h^{-1})	$t_{1/2}$ (h)
Ophthalmic solutions				
Non-viscous	0.829	0.84	0.573	1.21
1% PVA14	0.408	1.70	0.406	1.71
2% PVA14	0.319	2.17	0.322	2.15
3% PVA14	0.274	2.53	0.258	2.69
0.5% PVA72	0.359	1.93	0.350	1.98
1% PVA72	0.281	2.50	0.264	2.63
2% PVA72	0.190	3.66	0.186	3.72
0.25% MC	0.264	2.63	0.226	3.06
0.5% MC	0.169	4.11	0.152	4.55
1% MC	0.143	4.83	0.123	5.65
0.125% Tylose	0.264	2.63	0.265	2.62
0.25% Tylose	0.169	4.1	0.165	4.21
0.5% Tylose	0.143	4.85	0.139	4.99
Ophthalmic gels				
MC	0.136	5.08	0.112	6.17
Carbomer	0.117	5.92	0.099	6.97
PEG I	0.184	3.76	0.159	4.35
PEG II	0.161	4.31	0.155	4.46

TABLE 7

FIRST-ORDER RELEASE RATE CONSTANTS (k in h^{-1}) AND HALF-LIVES ($t_{1/2}$ in h) FOR PHENYEPHRINE-HCl OPHTHALMIC PREPARATIONS

Polymer type and concentration	Phenylephrine-HCl preparations		Phenylephrine-HCl and betamethasone preparation	
	k (h^{-1})	$t_{1/2}$ (h)	k (h^{-1})	$t_{1/2}$ (h)
Ophthalmic solutions				
Non-viscous	0.919	0.75	0.685	1.01
1% PVA14	0.467	1.48	0.383	1.81
2% PVA14	0.401	1.73	0.368	1.88
3% PVA14	0.371	1.87	0.342	2.03
0.5% PVA72	0.428	1.62	0.429	1.62
1% PVA72	0.396	1.75	0.382	1.82
2% PVA72	0.264	2.63	0.246	2.82
0.25% MC	0.273	2.54	0.246	2.81
0.5% MC	0.225	3.10	0.215	3.21
1% MC	0.194	3.57	0.181	3.82
0.125% Tylose	0.389	1.78	0.332	2.09
0.25% Tylose	0.287	2.42	0.270	2.57
0.5% Tylose	0.192	3.62	0.186	3.73
Ophthalmic gels				
MC	0.169	4.11	0.155	4.47
Carbomer	0.053	13.13	0.053	13.20
PEG I	0.299	2.32	0.307	2.26
PEG II	0.292	2.38	0.276	2.51

the drug in terms of its water solubility or ionization. Donbrow and Friedman (1975) and Sciarra and Gidwani (1972) came to a similar conclusion for drugs incorporated into polymer-based films.

The present results also indicate that this mechanism is reproducible for all systems investigated.

Apparently, the type of polymer or the increase in viscosity of the ophthalmic preparation do not dictate the release mechanism to any significant extent.

Release rate of betamethasone and phenylephrine hydrochloride

The release rate constants and the release half-times of betamethasone, phenylephrine hydrochloride individually or in combination are presented in Tables 6 and 7.

It is obvious that the release rate constants of phenylephrine hydrochloride are consistently higher than those of betamethasone. The preparation based on carbomer is the only exception.

The tables also reveal a tendency of the release rate constant of a drug to be suppressed by the presence of the other. However, in most instances, the effect is minimal involving not more than a 10% decrease in the release rate constant.

In gel systems, phenylephrine hydrochloride seems to suppress the release rate constant of betamethasone to an extent greater than that of the latter towards the former.

Dependency of the release rate constant of the drug on the viscosity of the ophthalmic solution

Figs. 1 and 2 depict the dependency of the first-order release rate constant of betamethasone, phenylephrine hydrochloride individually or in combination on the viscosity of the ophthalmic solution.

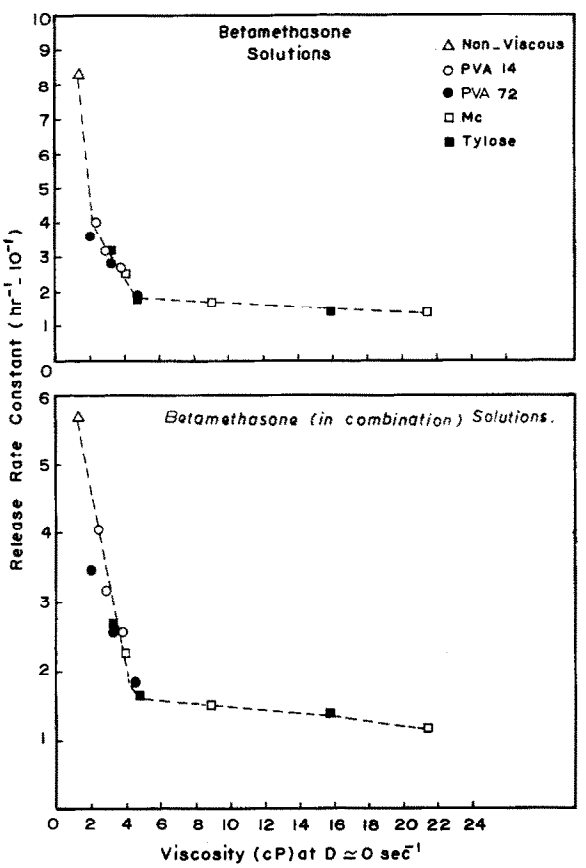

Fig. 1. Effect of the viscosity of ophthalmic solutions of betamethasone on the release rate constant of the drug.

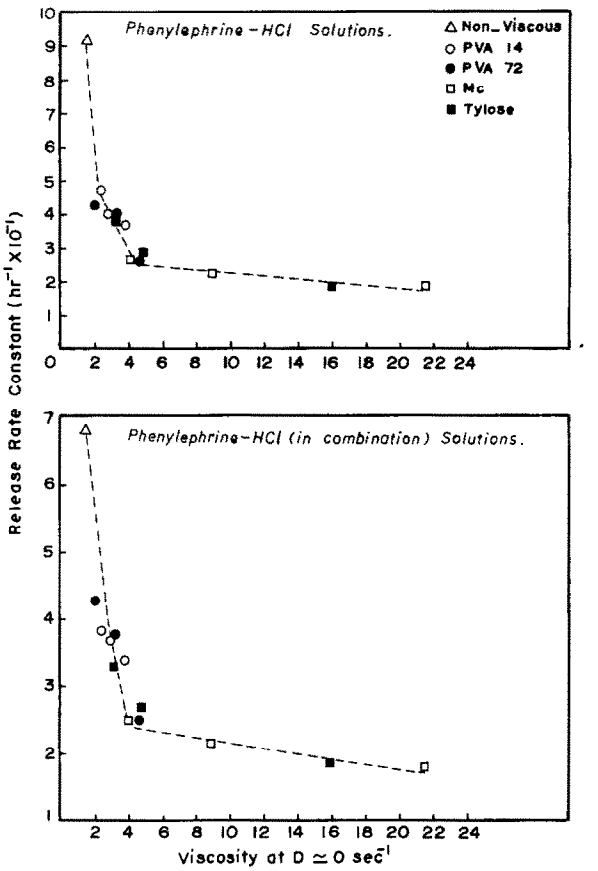

Fig. 2. Effect of the viscosity of ophthalmic solutions of phenylephrine-HCl on the release rate constant of the drug.

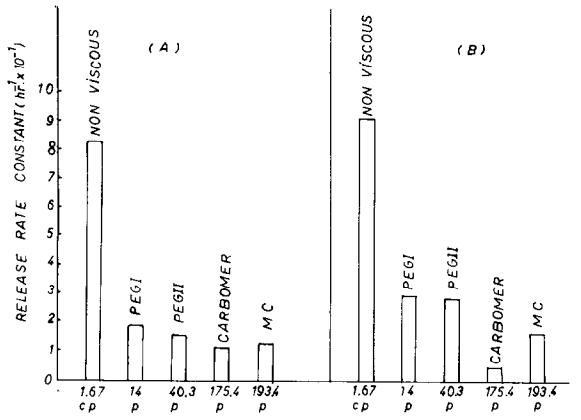

Fig. 3. Effect of viscosity of ophthalmic gels of betamethasone (A) and phenylephrine-HCl (B) on the release rate constant of the drug.

The first-order release rate constant of betamethasone or phenylephrine hydrochloride was found to be dictated by the viscosity of the ophthalmic solution. The release rate constant decreases rapidly in the viscosity range below 5 cp ($D \simeq 0\ s^{-1}$); beyond this viscosity range the release rate constant decreases only slightly. This finding is reproducible both for betamethasone and phenylephrine hydrochloride. Melis-Decerf and Van Octeghem reported data on pilocarpine-HCl and antazoline-HCl which are in line with the present findings (Figs. 1 and 2).

Dependency of the release rate constant of the drug on the viscosity of ophthalmic gel

The dependency of the release rate constant of the drug on the basic viscosity of the ophthalmic gel is presented in Fig. 3 for betamethasone and phenylephrine hydrochloride.

It is apparent that the release rate constant of either drug shows a very low dependency on the basic viscosity of the gel. A vast increase of viscosity (from 1500 to 2000 cP) does not bring about more than a minimal decrease in the release rate constant.

Comparison of the release rate data for ophthalmic solutions and gels reveals that the release rate constants of the drug in the gel systems do not differ to any marked extent from those in ophthalmic solutions having a basic viscosity just exceeding 5 cP.

Additional work is necessary to provide an answer to some unresolved questions; for example, how does the viscosity of these ophthalmic preparations influence the in vivo performance of the drug (under investigation); and how far does the in vitro release correlate to the in vivo performance of the drug?

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