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An in vitro method simulating drug release from viscous eye drops in rabbit and man

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A method has been developed using a diffusion cell in an attempt to determine the drug release from viscous solutions under conditions simulating the blinking movements in the rabbit and human eye. Diffusion coefficients were determined at rest and at different velocities. For the solutions at rest, corresponding with the conditions at the surface of the rabbit cornea, the diffusion velocity decreases with increasing viscosity. When the solution is moved at a velocity corresponding to that of lachrymal fluid at the surface of the human eye, the influence of viscosity may be neglected.

It has been reported by many authors (Fleming & Merrill 1959; Blaug & Canada 1965; Wang & Hammarlund 1970; Chrai & Robinson 1974; Patton & Robinson 1975; Hardberger et al 1975) that in rabbits an increase in viscosity always prolongs the activity of drugs in eye drops. An enhanced therapeutic response to drugs when applied in viscous vehicles is also reported in man. However, other reports challenge this and conclude that increasing vehicle viscosity does not prolong ocular contact time nor markedly improve drug bioavailability to man. A review of literature concerning the influence of viscosity on prolonged drug activity in man is given in Table 1.

The inconsistency between the results of tests on rabbits and man is apparently due to differences in physiology between the eyes of the two species. On the surface of the rabbit and human eye the precorneal tear film continuously evaporates. It is to be expected that the tear film slightly increases in concentration and that the tonicity also increases. In rabbits this results in an osmotic water flow from the aqueous humour through the cornea to the precorneal tear film (Mishima 1965). The liquid is spread over the surface of the cornea by blinking with a frequency of 4 to 6 times an hour. In man, tear fluid is secreted by the lachrymal glands and distribution of the liquid is accomplished by movement of the lids. The frequency of blinking by man is 600 to 1200 times an hour. Thus there is a substantial difference between rabbit and human eye in frequency of blinking.

In an attempt to verify if the inconsistency of results is due to differences in the physiology of the rabbit and human eye, the release of drugs from viscous solutions has been measured in vitro under conditions simulating the movements of blinking in rabbit and human eyes. A diffusion model has been developed in which the solution can be moved at the same rate as at the eye surface.

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MATERIALS AND METHODS

Drugs: antazoline hydrochloride (B.P.), pilocarpine hydrochloride (B.P.C.). Solutions: distilled water, Menghini phosphate buffer solution pH 6·80 (Menghini 1952). Viscosity increasing agents: methylcellulose (MC Premium 4000 cps, Dow Chemical Company), polyvinyl alcohol (Polyviol W 40/140, Wacker-Chemie). Diffusion membrane: Sartorius Ultrafilter type SM 115 39. Solutions of different viscosities were prepared and the viscosity was measured by the rotational viscosimeter Rheomat-30.

The diffusion cell is composed of two compartments having equal capacities and separated by the membrane (Fig. 1). This has a porosity lower than 50 Å and corresponds nearly to the pore diameter of the corneal epithelium (Maurice 1953). The diffusion cell can be rotated at different speeds. The velocity of the solution in the diffusion cell depends on the rotation speed of the motor and the distance between the axis and the position of the liquid in the cell. At each rotation the molecules in the cell cover a distance of 10·1 to 21·4 cm depending on their position. Based on these values the solution velocities can be calculated for the different motor speeds. The solution velocity on the eye surface can be calculated considering the velocity of the blinking movement; in a normal blink the upper lid covers a distance of 1 cm at a velocity of 0·05 s for lowering

Table 1. Review of literature concerning the influence of viscosity of eye drops on prolonged drug activity in man.

Viscosity increasing agent	Drug	Prolonged activity[4]
Mueller & Deardorff 1956		
MC[1] 4000 cps 0·1%	homatropine	—
MC 4000 cps 1·0%	homatropine	+
Haas & Merrill 1962		
MC 0·5%	pilocarpine	?
Mattila et al 1968		
MC 4000 cps	tropicamide	—
MC	phenylephrine	—
MC 4000 cps	pilocarpine	—
MC 4000 cps	physostigmine	—
Linn & Jones 1968		
HPMC[2] 4000 cps 0·25%	fluorescein	⊕
HPMC 4000 cps 2·5%	fluorescein	⊕
PVA[3] 1·4%	fluorescein	○
Waltman & Patrowicz 1970		
HPMC 4000 cps 0·5%	fluorescein	+
PVA 1·4%	fluorescein	—
Adler et al 1971		
MC 2500 cps	fluorescein	?
PVA	fluorescein	?
Hardberger et al 1975		
MC 1%	radioactive	⊖
PVA 1·4%	!echnetium	⊕
Trueblood & Rossomondo 1975		
HPMC 0·5%	radioactive	⊕
PVA 1·4%	technetium	⊕

[1]MC = methylcellulose.
[2]HPMC = hydroxypropyl methylcellulose.
[3]PVA = polyvinyl alcohol.
[4]Prolonged activity = +: increased penetration through the cornea. —: no increased penetration through the cornea. ?: results unconvincing. ⊕: increased contact time on the surface of the cornea. ⊖: no increased contact time on the surface of the cornea.

and 0·20 s for raising of the lid (Duke-Elder 1968). These values also give a mean velocity of 12·5 cm s^{-1}. A comparison of the solution velocity in the diffusion cell and at the eye surface shows that the velocities (cm s^{-1}) in the diffusion cell were at 1 rev min^{-1} 0·2–0·4; 3 rev min^{-1} 0·5–1·1; at 6 rev min^{-1} 1·0–2·2 and at 36 rev min^{-1} 6·0–12·8 cms^{-1},

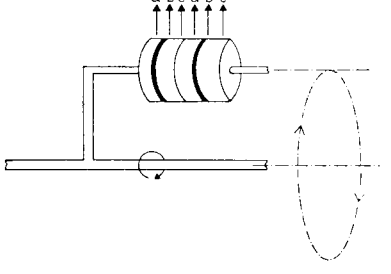

FIG. 1. The apparatus: a donor compartment, b membrane, c receptor compartment.

while at the eye surface the mean velocity of closing the lids (20) and opening the lids (5) was 12·5 cm s^{-1}. It appears that a rotation of 36 rev min^{-1} corresponds to the solution velocity on the eye surface.

The donor compartment contains 1% antazoline hydrochloride or pilocarpine hydrochloride with increasing concentrations of methylcellulose or polyvinyl alcohol. The receptor compartment contains distilled water—for antazoline hydorchloride—or a buffer solution pH 6·80—for pilocarpine hydrochloride.

At different times the diffused quantities are assayed spectrophotometrically at 242 nm for antazoline hydrochloride and at 215 nm for pilocarpine hydrochloride. The experiments are carried out at 33 ± 0·1° C, which is the temperature at the corneal epithelium of rabbits and man (Mishima & Maurice 1961; Mattheus 1961).

RESULTS AND DISCUSSION

The diffusional process takes place in quasi-steady state conditions and the diffusion coefficient is calculated by equations described by Lueck et al (1957).

Influence of rotation

The diffusion coefficients, registered at several speeds for antazoline hydrochloride and pilocarpine hydrochloride in aqueous solution and viscous solutions of 4% polyvinyl alcohol or 0·6% methylcellulose both having the same viscosity, show the effect of movement on diffusion (Fig. 2).

At rest, corresponding with the conditions at the surface of the rabbit cornea, a slower drug diffusion was noted by viscous solutions compared with aqueous solutions.

When rotated, a significant increase of diffusion velocity was noted from 3 rev min^{-1}. The lower values of diffusion coefficients obtained with polyvinyl alcohol solutions compared with methylcellulose solutions could be due to the Newtonian properties of polyvinylalcohol solutions and the pseudoplastic character of methylcellulose solutions. At 36 rev min^{-1}, corresponding to the velocity of the solution on the human eye surface, diffusion was the same for the viscous and aqueous solutions. It could be supposed that in this case diffusion is principally influenced by the kinetic energy conferred on the molecules by the effect of rotation. This energy exceeds the influence of viscosity.

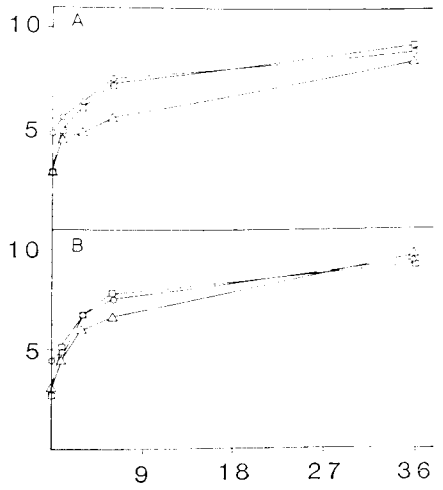

FIG. 2. Influence of the movement rev min^{-1} (abscissa) on the diffusion coefficients, m^2 s $\times$ 10^{-3} (ordinate). A, antazoline hydrochloride, B, pilocarpine hydrochloride, ○ aqueous solution, □ 0·6% methylcellulose solution and △ 4·0% polyvinyl alcohol solution.

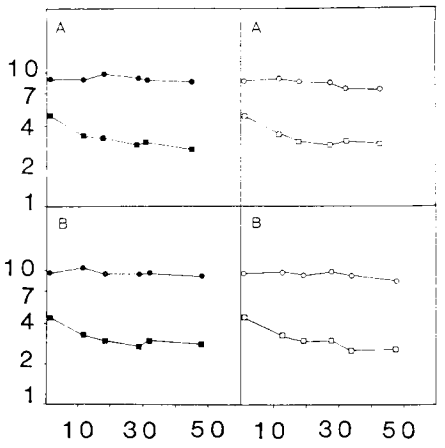

FIG. 3. The effect of viscosity (cP: abscissa) on the diffusion coefficients ($m^2 s^{-1}$ $\times$ 10^{-3}: ordinate). A, antazoline hydrochloride, B, pilocarpine hydrochloride. Solid symbols: methylcellulose; open symbols: polyvinyl alcohol. Circles 36, squares 0, rev min^{-1}.

Influence of viscosity

The diffusion velocities through the membrane of drugs in solutions with increasing viscosities were measured at rest and at 36 rev min^{-1} (Fig. 3).

For solutions at rest the diffusion velocity diminished significantly with increase in viscosity. The decrease was more pronounced for the low viscosity values and could be attributed to the viscosity of the solution in itself. At higher viscosities the diffuion coefficients did not decrease markedly. Here the viscosity of the solution in itself has not been assumed to be responsible for a slower diffusion. A film of molecules of the viscous solution on the membrane side would form a barrier to the passage of the drugs (Meares 1976). The film is destroyed when the diffusion cell is rotated.

When the solutions were moving, a very low decrease in diffusion velocity was noted with increasing viscosity. This could be explained by a transfer of kinetic energy to the molecules of the solution.

From this study it can be concluded that for the solutions at rest the diffusion coefficients decrease with increasing viscosity but when the solution is moved at a velocity corresponding to the velocity of lachrymal fluid at the surface of the human eye, the influence of viscosity may be neglected.

The difference in blinking frequency between rabbits and man provides an explanation for the contradictory results described in the literature. However, the experiments are carried out in in vitro conditions, and an extrapolation from the in vitro to the in vivo situation could be erroneous if some factors such as increase of the blink-rate due to discomfort and/or blurring of vision with viscous solutions are not considered. An increased blink-rate might increase the rate of mechanical elimination of drops and affect the absorption of the drug.

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