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The break-up time of artificial pre-ocular films on the rabbit cornea

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The usual treatment for dry-eye diseases is frequent application of artificial 'tears' (Jones & Coop, 1965; Wright, 1971; Lemp, 1973). These normally consist of buffered isotonic solutions of hydrophilic polymers which bear scant resemblance to the natural pre-ocular film. Lemp, Dohlman & others (1971) have found that the break-up time (BUT) of the natural film in the absence of blinking is shorter in some human dry-eye diseases than in normals and the increase in this interval has been used as a criterion of the efficacy of artificial tears (Lemp, Goldberg and Roddy, 1975). The rabbit corneal surface resembles that of the human in a number of respects (Ehlers, 1970) and although differing in others it is likely that solutions forming stable pre-ocular films in the rabbit would have properties of value in the formulation of artificial tears for man. Blinking and pathological corneal changes might affect the performance of a given solution in the clinic, but for comparison of different solutions the rabbit is probably an adequate model. This report, then, describes the BUT of films formed on the corneas of anaesthetized rabbits with solutions of hydrophilic polymers and with commercial artificial tears.

Experiments were conducted in a darkened air-conditioned room. Male rabbits (3·5–5·5 kg) were anaesthetised with chlorpromazine (May and Baker) 25 mg kg^{-1} intramuscularly plus pentobarbitone sodium (Nembutal Veterinary, Abbot) 25–30 mg kg^{-1} intravenously. Each animal was wrapped in a homeothermic blanket (Electrophysiological Instruments) and placed prone in an aluminium holder in front of a slit-lamp biomicroscope. One eye was held open with a speculum. The image of a white grid against a black background was projected on to the cornea using a mirror galvanometer projector (Type 4754, Tinsley) and its reflection was viewed with the biomicroscope. As long as the pre-ocular film was intact the image was clearly seen, but as the film disintegrated the image broke up. It was found that the BUT was highly reproducible. The solution for test was applied liberally to the cornea and the film breakup awaited, whereupon 50 μl was carefully applied over the cornea with a micropipette and the BUT of the resultant film observed. Each solution was tested on one eye of three or four rabbits. The polymers investigated were hydroxyethylcellulose (Natrosol 250 M, Hercules Powder Co.), hydroxypropylmethylcellulose (Methofas PM 4500, ICI), polyvinylalcohols (Gohsenol N300, GL05 and GH17, Nippon Gohsei), polyethyleneoxide (Polyox WSR-301, Union Carbide) and methylcellulose (Celacol M450GP, British Celanese), each dissolved in distilled water.

In concentrations where the polymer solutions were mobile liquids there was, in all cases, a good approximation to a straight line relation between BUT and concentration. In addition, a measurement of viscosity of the polymer solutions was made with a Brookfield viscometer. Solutions were maintained at 25° and the determinations performed with spindle 2 at 30 rev min^{-1}. The results indicate that BUT increased more for a given increase in viscosity with solutions containing low concentrations of polymer than with solutions containing high concentrations. Since some of the solutions would be non-Newtonian, interpretation of these results is difficult. However, in Table 1 are mean BUT values corresponding to several viscosities for each polymer,

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Table 1. *Pre-ocular film mean break-up time related to solution viscosity for several polymers. Results of experiments on one eye of each of four rabbits.*

Viscosity mPa s	Pre-ocular film mean break-up time(s) ± s.e.m.						
	Hydroxyethyl-cellulose	Hydroxypropyl-methylcellulose	Polyethylene-oxide	Polyvinyl alcohol GH-17	Polyvinyl-alcohol N-300	Polyvinyl-alcohol GL-05	Methyl-cellulose
10	33·3 ± 0·7	31·0 ± 3·3	48·8 ± 4·5	36·3 ± 0·9	57·5 ± 6·3	50·4 ± 2·4	38·8 ± 1·3
15	63·3 ± 2·4	51·5 ± 5·7	66·0 ± 5·5	54·0 ± 4·2	73·2 ± 8·3	73·9 ± 5·3	62·0 ± 5·2
25	92·0 ± 1·2	73·7 ± 6·5	88·3 ± 5·7	83·0 ± 8·6	96·7 ± 13·2	108·0 ± 7·1	111·5 ± 7·1
50	121·0 ± 5·9	107·7 ± 6·9	130·8 ± 8·9	131·8 ± 10·4	134·3 ± 27·3	—	132·0 ± 14·6
75	139·3 ± 8·5	130·0 ± 7·5	157·3 ± 11·9	168·8 ± 7·1	151·5 ± 38·3	—	140·0 ± 13·9
100	153·0 ± 9·8	147·8 ± 7·8	161·7 ± 12·4	194·8 ± 4·1	—	—	145·3 ± 13·4
150	173·5 ± 9·8	176·0 ± 8·9	190·3 ± 12·1	235·3 ± 5·3	—	—	—
200	190·3 ± 9·5	193·5 ± 10·6	218·7 ± 13·3	257·0 ± 10·2	—	—	—

derived from the BUT-viscosity curves for individual rabbits. It is apparent that none of the polymers offers outstanding BUT at a viscosity acceptable for artificial tears. The six commercial artificial tears tested gave BUT values ranging from 64·5 s (s.e.m. 7·7) to 113·6 s (s.e.m. 18·4).

Drainage and dilution by tear secretion, even when diminished in pathological states, may be expected to reduce the concentration of exogenously applied polymer solutions quite rapidly, and it is concluded that materials capable of producing more stable artificial pre-ocular films should be sought.

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Influence of stomach emptying rate on tissue radioactivity after [^{14}C]imipramine in the rat

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As large as 36-fold differences in steady state plasma concentrations of tricyclic antidepressant compounds have been reported in patients given the same oral dosing regimen (Hammer & Sjöqvist, 1967). Several pharmacokinetic factors have been postulated to contribute to these differences. These include individual variation in liver metabolism (Hammer & Sjöqvist, 1967; Alexanderson & Borga, 1973), plasma protein binding (Alexanderson & Borga, 1972; Glassman, Hurwic & Perel, 1973) and first pass metabolism (Gram & Christiansen, 1975). Most investigators, however, have assumed individual variation in gastrointestinal absorption to be unimportant (Haydu, Dhrymiotis & Quinn, 1962; Kragh-Sørensen, Hansen & others, 1974).

An opportunity to test the relative importance of individual variation in metabolism or absorption on tissue concentrations of imipramine (with its metabolites) was provided from data obtained in a study concerning the effects of tranquillizers on [^{14}C]imipramine pharmacokinetics (Beaubien, Mathieu & Coldwell, 1975). One of the experiments utilized non-anaesthetized male Wistar rats with bile fistulas and which were orally administered either thioridazine (16 mg kg^{-1}), diazepam (10 mg kg^{-1}) or 0·25% (w/v) gum tragacanth solution (controls) 40 min before [^{14}C]imipramine; dosing volumes were 5 ml kg^{-1} in each instance. The animals were decapitated 90 min after [^{14}C]imipramine dosing. Although thioridazine reduced the biliary elimination of radioactivity as a result of inhibition of stomach emptying, diazepam had no measurable effect on imipramine pharmacokinetics except perhaps to slightly enhance the intestinal absorption of radioactive drug. Because the rate limiting step in gastrointestinal absorption of radioactivity was the velocity of stomach emptying rather than intestinal absorption rate (see below), the diazepam-pretreated animals (n = 5) were grouped with the controls (n = 5) in testing for a mechanism which caused variation between individuals in tissue concentrations of radioactivity.

Correlation coefficients were obtained between tissue concentrations of ^{14}C and the amount of radioactivity contained at absorption sites or in excreta 90 min after [^{14}C]imipramine administration. It was reasoned that a significant negative correlation should result between tissue radioactivity concentrations and the total amount of ^{14}C label in either absorption or elimination pools if the rate constants from or to these pools exerted a strong controlling influence. A significant positive correlation would indicate that both tissue and pool radioactivity concentrations were controlled by the same mechanism.

Table 1 shows that at 90 min after [^{14}C]imipramine dosing a positive correlation existed between radioactivity in the bile and urine. A weak positive correlation also existed between bile and tissue radioactivity although this was statistically insignificant. The fact that a negative correlation of tissue radioactivity with that of bile did not occur indicates that individual variation in biliary elimination of imipramine and its metabolites played only a minor role in causing differences in tissue concentrations of radioactivity within the 90 min time period. This is remarkable in that 57·0 ± 2·79% (mean ± s.e.) of all the absorbed radioactivity (calculated as the sum of ^{14}C in all the tissues, bile and urine) was recovered in the bile by this time. Biliary excretion was

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