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Scintigraphic assessment of the precorneal residence of a new ophthalmic delivery system (NODS) in man

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Summary

The release of ^{99m}Tc-labeled sodium pertechnetate and sulphur colloid from polyvinyl alcohol films for ophthalmic administration (new ophthalmic delivery system – NODS) has been studied in vitro and in vivo. ^{99m}Tc-labeled sulphur colloid was selected as the marker for incorporation into the device to monitor dissolution on the cornea by gamma scintigraphy, in both rabbit and man. Clearance of the device followed mono-exponential kinetics with a mean half-time (±SD) of precorneal residence in man of 9.2 ± 7.4 min, demonstrating the potential of the formulation for sustained drug delivery.

Introduction

Ocular drug bioavailability following ophthalmic administration is critically dependent on the precorneal residence time, which provides the rationale for the employment of viscosity-enhancing polymers such as polyvinyl alcohol or hydroxypropylmethylcellulose to sustain drug action. The administration, of viscous solutions, although widely used and convenient for the patient, does suffer from certain disadvantages, as summarized by Dumortier and coworkers (1989):

(1) The duration of action is limited by the dilution and then rapid elimination in tears.
(2) The tear film concentration shows oscillations based on the frequency of application of the formulations, with periods of overdosing and under-dosing.
(3) In certain pathologies, such as keratoconjunctivitis sicca, the utilization of preservatives may be contraindicated due to hypersensitivity to these compounds associated with insufficiency of tear flow.

Generally, viscolysing polymers do not markedly sustain the ocular contact time in man

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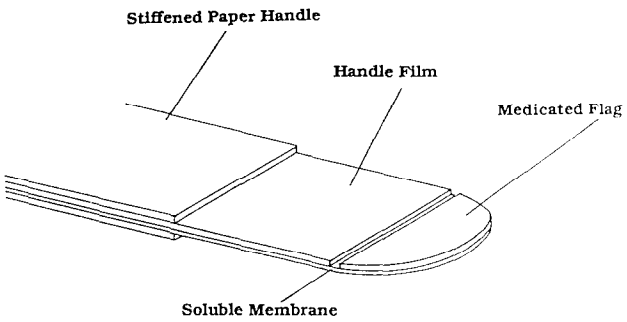

Fig. 1. The new ophthalmic delivery system (NODS).

(Zaki et al., 1986) and it is necessary to employ ointments, gelling vehicles or non-erodible matrices to sustain the release of water-soluble drugs over prolonged time periods. Recently, a new ophthalmic delivery system based on a PVA film has been introduced for use in man (NODS, Smith & Nephew Pharmaceuticals Ltd) which can achieve an 8-fold increase in bioavailability for pilocarpine compared to eyedrop formulations (Kelly et al., 1989).

The new ophthalmic delivery system (NODS) is designed to deliver precise amounts of drugs to the eye within a water-soluble drug-loaded film, providing an accurate, reproducible dose in an easily administered, preservative free form. The device consists of a water soluble drug loaded film approx. 25 μm thick with an area of 20 mm^2 and weight of 0.5 mg. The film is attached to a stiffened paper handle via a soluble membrane approx. 0.7 mm in length (Fig. 1). The unit is applied by drawing down the lower eyelid and touching the film onto the surface of the lower conjunctival sac. On contact with the moist eye, the membrane quickly hydrates and the film detaches from the handle into the cul-de-sac.

In the present study, the precorneal retention of this soluble polyvinyl alcohol matrix has been studied in man using the technique of gamma scintigraphy. This was facilitated by the incorporation of ^{99m}Tc-labelled sulphur colloid during manufacture of the film, a short time prior to administration. This label was selected as a marker of matrix dissolution. Prior to the human studies, a full evaluation was carried out in rabbits to assess the behaviour of the delivery system in vivo.

Materials and Methods

Preparation of the PVA delivery system

A highly soluble form of polyvinyl alcohol was used in this study (Gohsenol GH-17) which had a

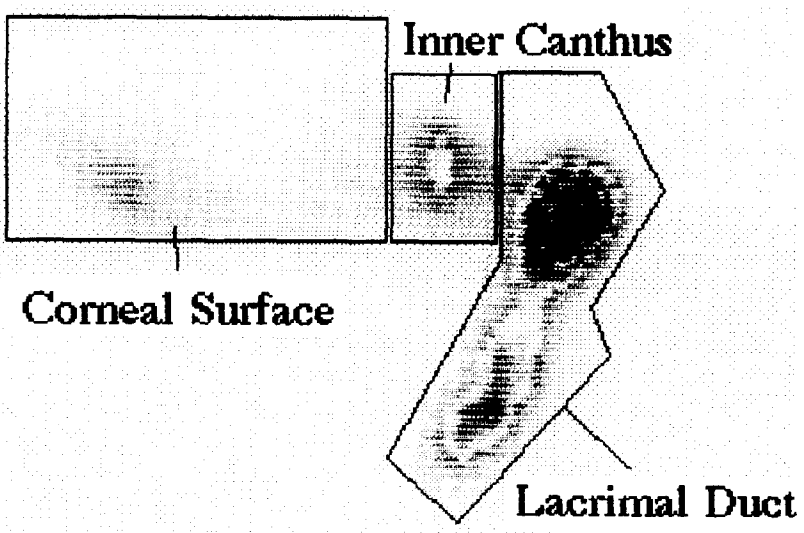

Fig. 2. Regions of interest (ROIs) constructed on the summed gamma camera image.

median molecular weight of 98 000 with an 87–89 mol% degree of hydrolysis. A sterile concentrated (15 g/90 ml) solution of polyvinyl alcohol was prepared in filtered distilled water by dispersing the powder in cold water (4°C), followed by heating to 80°C and overnight stirring. 0.8 g of the concentrated solution was weighed into a clean 20 ml vial and 0.2 ml of sodium [^{99m}Tc]pertechnetate or ^{99m}Tc-labelled sulphur colloid (specific activity approx. 2000 MBq) was added and mixed in using a fine glass rod.

A stainless-steel hand-spreader was used to form a polyvinyl alcohol film approx. 25 μm thick supported on a melinex backing strip (100 μm thick, 30 × 5 cm). The melinex was sufficiently hydrophobic to allow easy removal of the dried film. A wet film (width, 5 mm; length, 20 cm) was spread by pulling the melinex strip through the slit in the spreader as slowly and as evenly as possible. The film was dried in an oven at 70°C for 15 min and then cut into 25-mm^2 sections using a sharp scalpel. 10 individual sections were weighed and counted in a gamma well-counter to determine the average weight and activity per section.

On the day of preparation, each section weighed 1 ± 0.2 mg and contained 2 ± 0.6 MBq of activity.

Determination of label integrity

In order to monitor the dissolution and distribution of PVA films in vivo, the isotope employed must remain associated with the film and not diffuse rapidly from the matrix immediately after instillation. An in vitro test was therefore designed to assess the rate of diffusion of two potential labelling systems, sodium [^{99m}Tc]pertechnetate solution and ^{99m}Tc labelled sulphur colloid. The GH-17 polymer is very soluble and dissolves rapidly on contact with water, therefore, the release of ^{99m}Tc from this polymer was compared to the release rate from a cold water insoluble form of PVA (N-300 grade, 99–100 mol% hydrolysed). The insoluble system would indicate whether the isotope was diffusing at a faster rate than the film was dissolving, or if the label remained associated with the film during dissolution.

GH-17 or N-300 films were spread on a melinex strip with a uniform thickness of approx. 50 μm and dried at 70°C for 60 min. Each type of film contained either sodium [^{99m}Tc]pertechnetate or ^{99m}Tc-labelled sulphur colloid. Several 3 × 5 cm sections were cut from the cast films and each section placed in a dissolution apparatus (Erweka DT-D6) containing 900 ml distilled water at 33–34°C. The films were submerged in the dissolu-

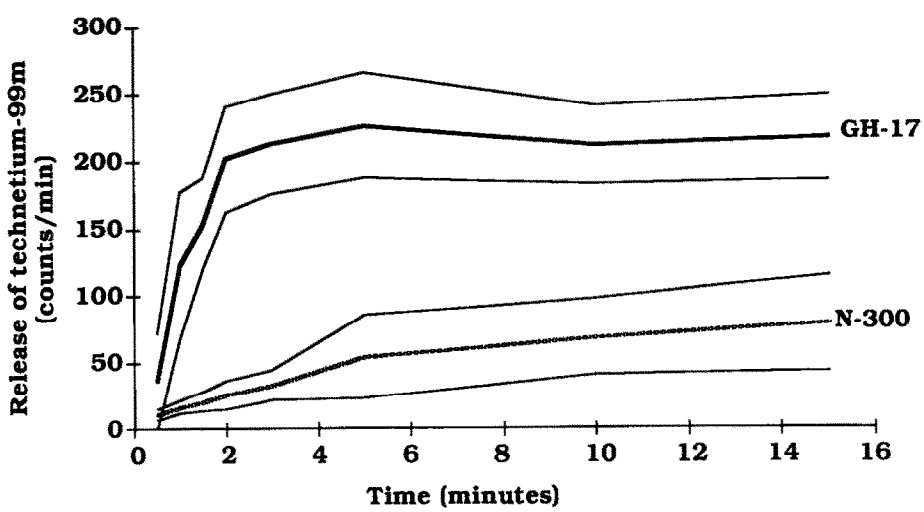

Fig. 3. Release of ^{99m}Tc-labelled sulphur colloid from N-300 and GH 17 PVA films at 33°C (mean ± SE, n = 4).

tion medium using wire meshes, and a rotating paddle (60 rpm) was positioned 2 cm above the mesh to reduce stagnant layer formation. 1.0-ml samples were removed at regular intervals over a period of 30 min and the volume replaced with warm distilled water. The samples were assayed using a gamma scintillation well-counter at an energy window of 120–140 keV. Corrections were made for background radiation. Four determinations were made for each polymer type and each labelling system.

Protocol

Animal studies

Preparations radiolabelled with sodium [^{99m}Tc]pertechnetate and ^{99m}Tc-labelled sulphur colloid were tested in a group of six New Zealand white rabbits (weight range 2.5–4.5 kg). The animals were positioned to ensure that the test eye was 5 cm from a pinhole collimator fitted with a 3 mm aperture: this ensures that the image is contained within the central 50% of the field of view. The PVA film, labelled by incorporation of sodium [^{99m}Tc]pertechnetate, was then placed on the test eye and the eye closed and opened once by gentle manipulation of the lid. A series of 15 s frames were then taken over a 13 min period and stored on the computer for later analysis. 3 days later the experiment was repeated in the same eye using the same material incorporating ^{99m}Tc-labelled sulphur colloid.

Volunteer studies

10 healthy male and female volunteers, age range 20–38 years, with no evidence of eye infection or nasal pathology participated in the study. The study was approved by the University of Nottingham Medical School Ethical Committee and an ARSAC licence for administration of radioactive substances obtained from the D.H.S.S. The protocol was explained to each subject and written consent to participate in the trial obtained. Subjects were acclimatised to the room conditions for 30 min prior to the study and none of the subjects wore eye cosmetics on the day of the trial.

Each subject was seated in front of the gamma camera with the test eye positioned at a distance of 5 cm from the pinhole collimator, and the head was supported on a modified ophthalmic table. The subject was then instructed to remain in this position throughout the imaging period.

The radiolabelled PVA film was placed in the eye by gently pulling down the lower eyelid and inserting it into the cul-de-sac with sterile forceps. A series of dynamic images of 15 s duration were then acquired for 15.5 min (62 frames).

Data analysis

From the summed gamma camera image, three regions of interest (ROIs) were discriminated as described previously by Zaki et al., (1984), viz., the cornea, the inner canthus and the nasolacrimal duct (Fig. 2). For some subjects only the first two ROIs could be constructed. The counts in each region were corrected for background activity and decay of the radioisotope. Data were normalised and curves of the mean corneal clearance constructed.

Results

Release rates of two labelling systems impregnated into soluble and insoluble PVA films

The GH-17 films rapidly disintegrated and dissolved on contact with the dissolution medium whereas the N-300 films softened due to penetration of aqueous medium into the polymer matrix,

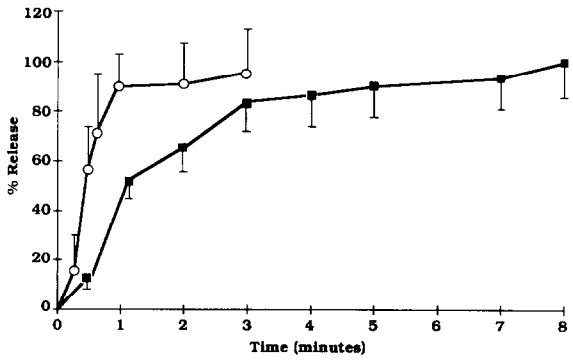

Fig. 4. Release of ^{99m}Tc-labelled sulphur colloid (■) or sodium [^{99m}Tc]pertechnetate (○) from Gohsenol GH-17 at 33°C (mean ± SE, $n = 4$).

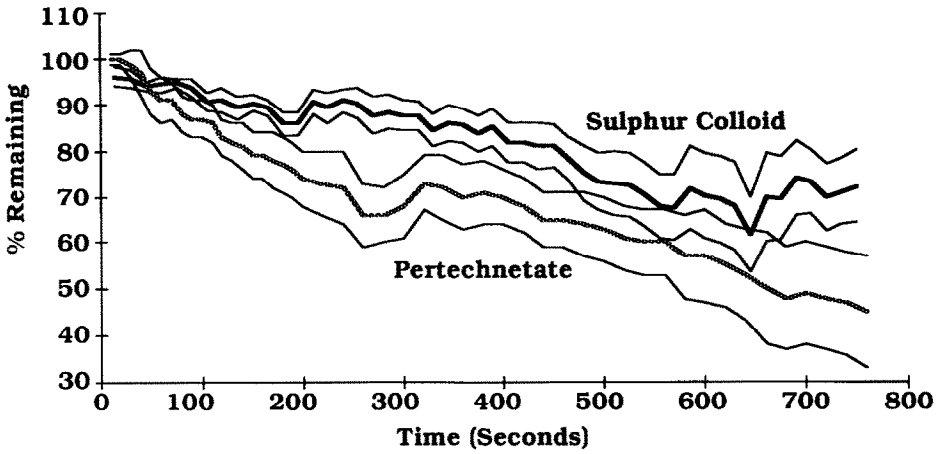

Fig. 5. Precorneal clearance of Gohsenol GH-17 film in the rabbit labelled with sodium [^{99m}Tc]pertechnetate or ^{99m}Tc-labelled sulphur colloid (mean ± SE, $n = 6$ animals per group).

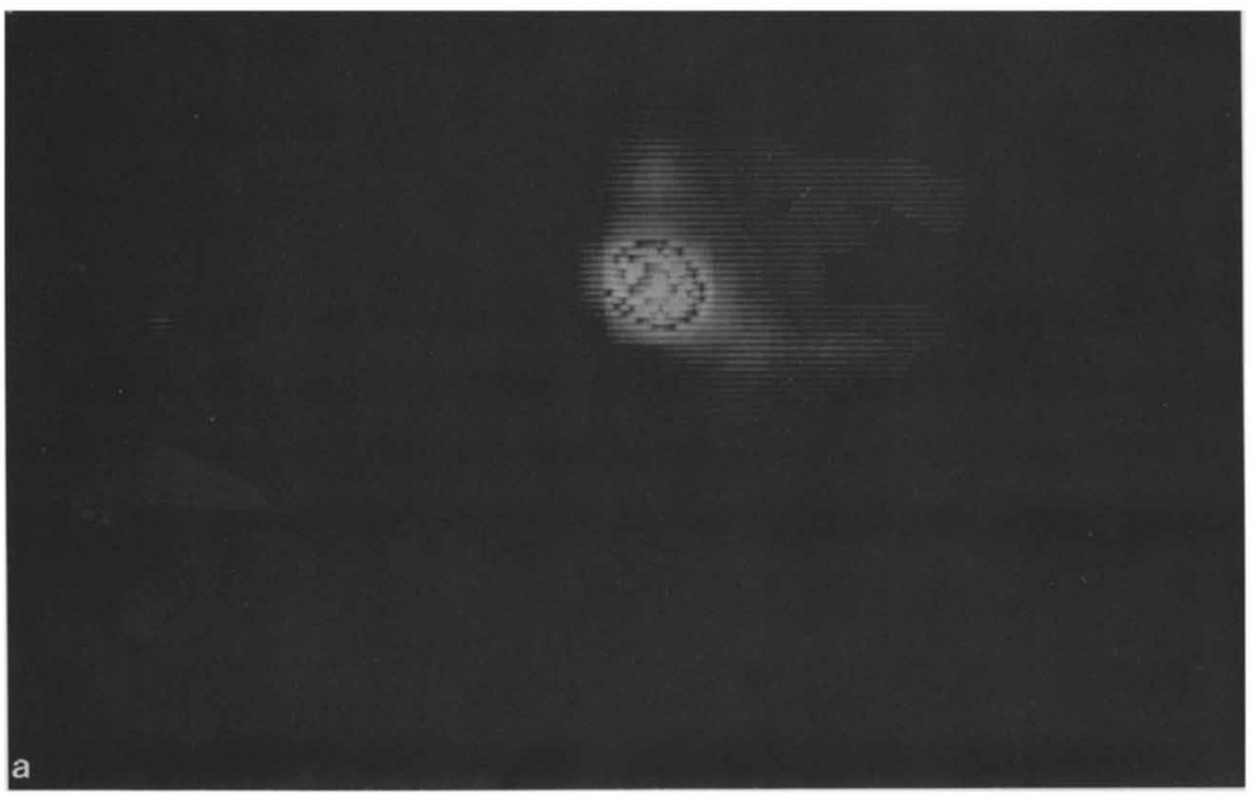

Fig. 6. Scintigraphic images following administration of a NODS system labelled with ^{99m}Tc-labelled sulphur colloid in man. (a) 15–75 s post-administration; (b) 385–450 s post-administration; (c) 765–825 s post-administration.

but remained intact throughout the experiment. The release profile is illustrated in Fig. 3. The apparent diffusion coefficient, D, was determined from the gradient of the amount of activity released against the half-time profile. The ^{99m}Tc-sulphur colloid showed planar diffusion characteristics when impregnated into the N-300 film with an apparent diffusion coefficient determined graphically of 6.04×10^{-15} m^2 s^{-1}. Since the ^{99m}Tc-sulphur colloid remains associated with the N-300 polymer matrix, it can be inferred that this label will also follow the disintegration of the GH-17 material. As may be noted from Fig. 4, the release of sodium [^{99m}Tc]pertechnetate from the GH-17 film was rapid and complete by 1 min. This burst effect is characteristic of drug release from a slab system in perfect sink conditions (Hadgraft, 1979).

Animal studies

Fig. 5 shows the clearance of sodium [^{99m}Tc]pertechnetate and ^{99m}Tc-labelled sulphur colloid administered in the Gohsenol GH-17 film to the rabbit eye. Both materials were cleared from the eye in an exponential fashion, with a first-order clearance rate constant of 0.06 ± 0.02 min^{-1} for the pertechnetate label (corresponding to a T_{50} of 12 min) and 0.03 ± 0.01 min^{-1} for the technetium sulphur colloid (T_{50} of 22 min). The clearance of a saline eyedrop, containing sodium [^{99m}Tc]pertechnetate, in the same group of animals had a mean half-life of 18 ± 4 s.

Volunteer studies

Typical scintigraphic images following the behaviour of the NODS matrix are shown in Fig. 6. Following insertion into the lower cul-de-sac, the

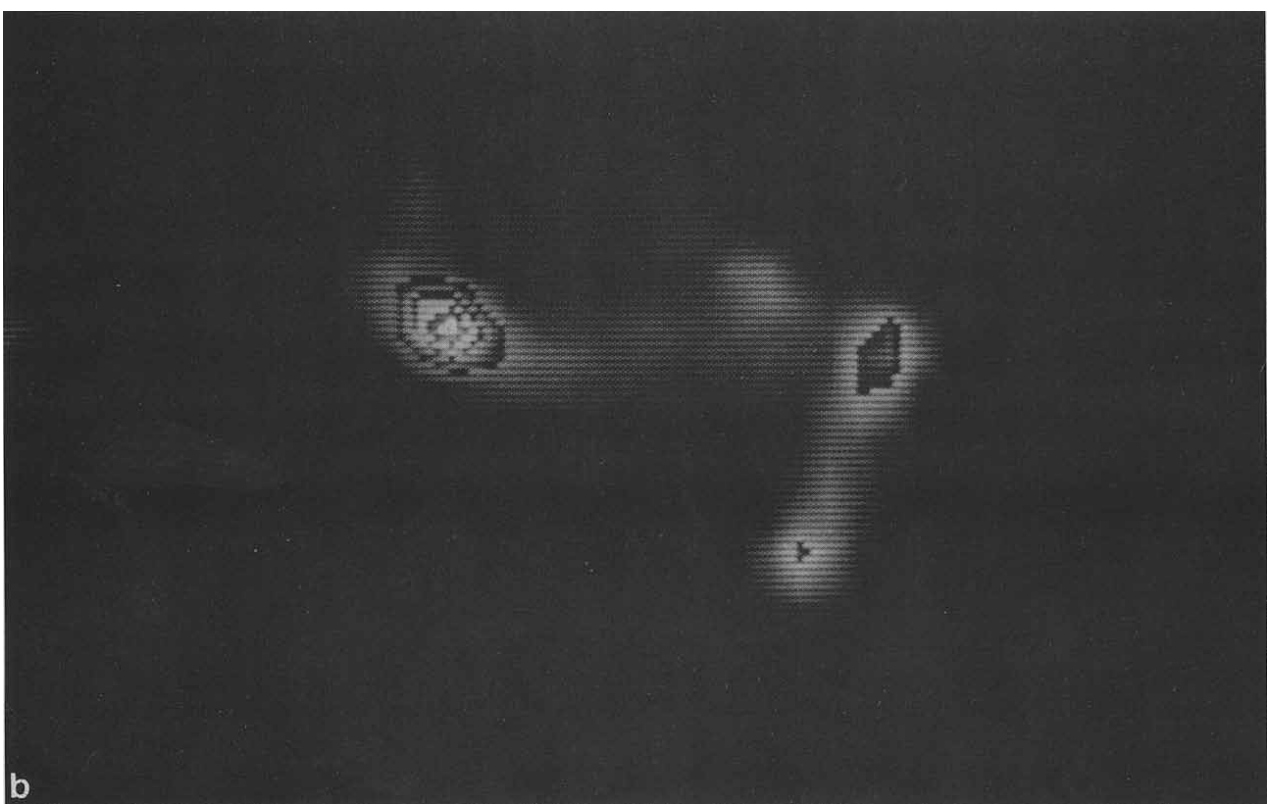

Fig. 6. (continued).

PVA film was observed to soften during the first minute (Fig. 6a) and by 2 min, released activity was observed in the lower tear margin and nasolacrimal sac. At approx. 7 min post-administration, considerable dissolution had taken place and drainage into the nasolacrimal duct was observed (Fig. 6b). In the last few frames illustrated in Fig. 6c, the polymer film had completely dissolved and the majority of the material was in the nasolacrimal drainage apparatus (13 min after administration).

The mean data for the corneal ROI are shown in Fig. 7. The mean curve showed a mono-exponential clearance with a mean half-time of 9.2 ± 7.0 min. Data from individual subjects showed marked differences in rate of clearance with half-times between 2 and 24 min (Table 1).

Discussion

The polyvinyl alcohol ophthalmic insert was observed to dissolve rapidly in the tear film. The insert was well tolerated and foreign body sensation disappeared within 30 s of application. In vitro studies and the investigation of the behaviour of the two radiolabels sodium [^{99m}Tc]pertechnetate and ^{99m}Tc-labelled sulphur colloid in the rabbit indicate that small soluble molecules diffuse rapidly from the GH-17 film. Scintigraphic data obtained following administration of eyedrops to man have shown that greater than 75% of the dose is eliminated from the eye within the first minute post-instillation (Zaki et al., 1986). A prolongation of contact time with the corneal surface mediated by polymers should therefore

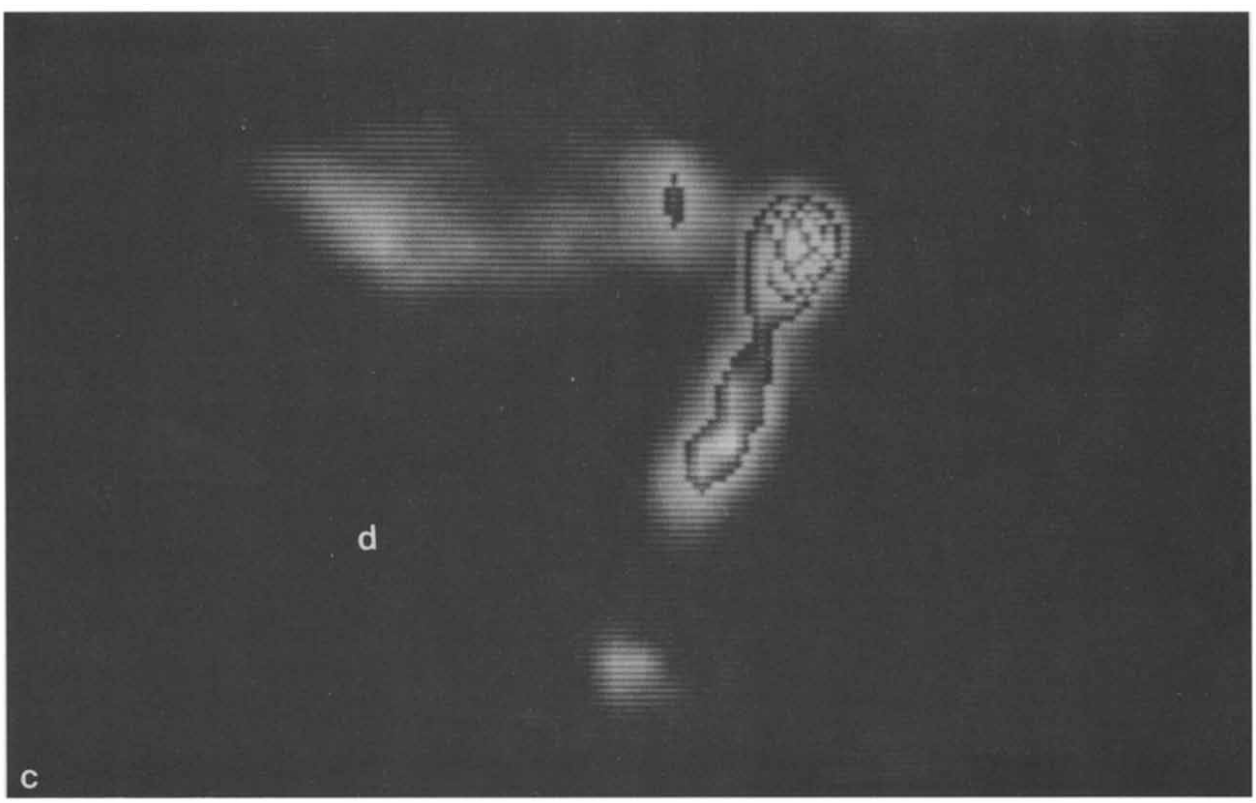

Fig. 6. (continued).

TABLE 1

Intersubject variation in half-times of clearance of the NODS in man

Subject No.	Half-time (min)
1	12.0
2	4.1
3	5.0
4	16.0
5	24.5
6	15.2
7	4.6
8	4.5
9	3.9
10	1.7
Mean	9.2
SD	7.4

increase the bioavailability of drugs applied topically and alter the pharmacodynamic response. Grass and colleagues (1984) have shown a linear correlation between time of 50% drug release from the polymer and the time required to attain 90% of maximum pupillary constriction in the rabbit following application of a PVA gel slab containing pilocarpine nitrate. Studies by Kelly and co-workers (1989) have demonstrated that the pupillary response to 67 μg pilocarpine nitrate delivered in a NODS formulation is equivalent to 518 μg of drug delivered as a conventional eyedrop formulation, i.e., one drop of a 2% w/v solution.

A marked difference between rabbit and man in the rate of clearance of the insert was noted. Hydration on the rabbit eye was noted to be slower, presumably because the rabbit does not demonstrate reflex lacrimation on insertion of the device. Pierce and co-workers (1985) have estimated lacrimation kinetics in both man and rabbit using a novel Schirmer test, in which the time to wet a filter paper strip is measured but the eye is not anaesthetised. This could be regarded as an

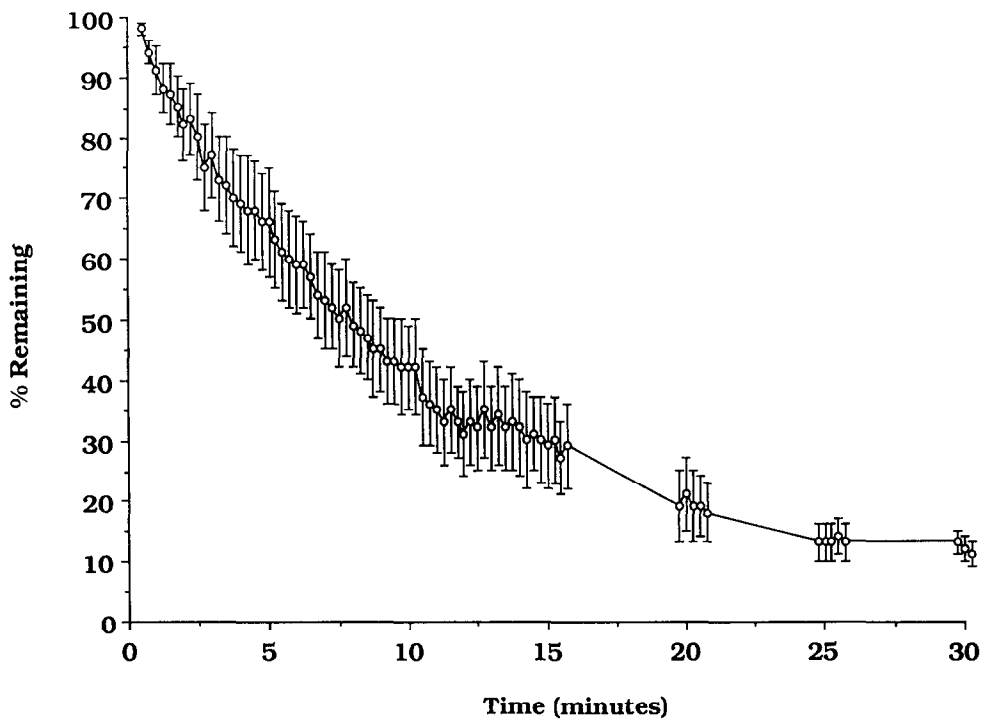

Fig. 7. Clearance of ^{99m}Tc-labelled sulphur colloid from the corneal region of interest of man after administration in a NODS (mean ± SE, n = 10).

analogous situation to insertion of the non-hydrated matrix. The initial tear secretion rate was 7.83 μl min^{-1} in rabbit and 17.7 μl min^{-1} in man. At the end of the test the average tear secretion rate was similar for both man and rabbit (1.78 μl min^{-1} in the rabbit and 2.30 μl min^{-1} in man).

The dissolution behaviour of the markers in the PVA film in man showed great variability, with half-times between 1.7 and 24 min. These extreme differences reflect the induced lacrimation potential in naive users which might affect the response to the incorporated drugs. In man, the degree of induced lacrimation can vary widely with initial rates of secretion between 4.6 and 362 (median 12.7) μl min^{-1} (Holly et al., 1986).

The observed differences in dissolution and clearance from the ocular surface between subjects have led us to progress to further studies to examine the relative bioavailability of pilocarpine nitrate delivered to the eye in a new ophthalmic delivery system (NODS) and a conventional eyedrop formulation and to correlate the pharmacodynamic response and rate of clearance of entrapped marker in man.

Acknowledgement

NODS is a trademark of Smith & Nephew Pharmaceuticals Limited.

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