*Br. J. clin. Pharmac.* (1992), **33**, 603–609

# Scintigraphic studies on the corneal residence of a New Ophthalmic Delivery System (NODS): rate of clearance of a soluble marker in relation to duration of pharmacological action of pilocarpine

J. L. GREAVES[1], C. G. WILSON[2], A. T. BIRMINGHAM[1], M. C. RICHARDSON[3] & P. H. BENTLEY[3]
[1]Department of Physiology and Pharmacology, Medical School, Queen's Medical Centre, Nottingham NG7 2UH, [2]Department of Pharmaceutical Sciences, University of Strathclyde, Royal College, 204 George Street, Glasgow G1 1XW and [3]Smith & Nephew Research Ltd, Gilston Park, Harlow, Essex CM20 2RQ

1 A gamma scintigraphic study has been carried out on the precorneal residence and pharmacodynamic action of a radiolabelled New Ophthalmic Delivery System (NODS) containing pilocarpine nitrate in 12 healthy volunteers.
2 The NODS was radiolabelled with the soluble marker technetium-99m labelled diethylenetriaminepentaacetic acid, to mark the release characteristics of soluble drugs contained within the matrix.
3 The relationship between the precorneal residence time of the marker and the duration of drug effect on intraocular pressure and pupil diameter was monitored. Results obtained following administration of the NODS were compared with those obtained after administration of a 25 μl drop of a 2% w/v pilocarpine nitrate solution. Each formulation was administered to one eye only, the other eye acting as a control.
4 Dissolution of the radiolabel from the NODS *in vivo* showed considerable intersubject variation with half-times of dissolution ranging from 46 s to 833 s (mean ± s.d. −280 ± 217 s), the mean (± s.d.) half-time of clearance of the radiolabel from the NODS and corneal region of interest was 406 ± 214 s whereas the radiolabelled solution had a mean (± s.d.) ocular surface residence time of 2.9 ± 1.5 s.
5 Pupil diameter and intraocular pressure were measured for 5 h post-administration of the NODS and the solution. After both treatments pupil diameter was significantly constricted in the test eye when compared with the control eye ($P < 0.001$; Student's paired *t*-test). Pupil diameter was constricted by 52% after administration of the NODS and by 35% after administration of the solution.
6 Intraocular pressure was significantly reduced in the test eye compared with the control eye after administration of the NODS ($P < 0.05$) but not after administration of the solution.
7 There were no apparent differences in degree of pharmacological action of pilocarpine between subjects with longer half-times of NODS dissolution and those with shorter half-times, indicating that drug diffusion from the matrix was not rate-limiting for the magnitude of the pharmacological effect.

**Keywords** pilocarpine ophthalmic drug delivery gamma scintigraphy ophthalmic inserts intraocular pressure pupil diameter

## Introduction

Pilocarpine is usually administered in aqueous solution as eyedrops, but problems with acceptance and compliance may occur because of its short duration of action and the side-effects associated with topical administration of this drug, namely headache and reduced visual acuity. Alternative systems have been evaluated for the delivery

Correspondence: Ms J. L. Greaves, Department of Physiology and Pharmacology, Medical School, Queen's Medical Centre, Nottingham NG7 2UH

of pilocarpine, including the use of soft contact lenses and the Ocusert® (Alza, Palo Alto, CA, USA). The Ocusert® was designed to release either 20 or 40 μg $h^{-1}$ of pilocarpine for 7 days while under the patient's eyelid (Shell & Baker, 1974). Recently, a New Ophthalmic Delivery System (NODS) has been designed which delivers a precise amount of drug to the eye (Bentley, 1990), and has the advantage of increased ocular retention and bioavailability, thus allowing the use of lower administered doses with a consequent lessening of unwanted side-effects.

Ocular drug bioavailability following topical administration is dependent on the precorneal residence time (Patton & Robinson, 1979). In a study comparing the corneal residence of the NODS radiolabelled by incorporation of the non-soluble marker technetium-99m sulphur colloid in man the system was found to have a mean half-time of clearance of 9 min although the data from individual subjects showed marked differences with half-times between 2 and 24 min (Fitzgerald *et al.*, 1992). The differences were thought to reflect the induced lacrimation potential in naive users which could affect the response to incorporated drugs.

Kelly and co-workers (1989) have compared the magnitude of the miotic and the light reflex responses to NODS containing 40, 80, and 170 μg pilocarpine nitrate with a single 2% Minims® eyedrop (518 μg) in healthy volunteers. Dosage comparisons of drug responses were obtained and it was found that one eyedrop had the equivalent dose response to 67 ± 11 μg pilocarpine from a NODS formulation, suggesting an eight-fold greater bioavailability from NODS than from a conventional eyedrop.

In the present study the aim was to follow the behaviour of a soluble drug in the system. The NODS was radiolabelled with technetium-99m diethylenetriaminepentaacetic acid ($^{99}Tc^m$-DTPA) a soluble marker which marks the release characteristics of pilocarpine contained within the matrix. The relationship between the corneal residence time of the marker and the duration of pharmacological action of pilocarpine was investigated. Each NODS was cast to contain about 67 μg pilocarpine nitrate, that is to have dose-equivalence to one 25 μl drop 2% w/v pilocarpine nitrate solution (500 μg) (Kelly *et al.*, 1989). The duration of pharmacological action of the drug was monitored by measuring changes in pupil diameter using a video camera and intraocular pressure using a non-contact tonometer. The data from the NODS administration were compared with the changes after topical administration of 25 μl 2% w/v pilocarpine nitrate solution.

## Methods

### *Preparation of the NODS*

The pilocarpine nitrate/PVA casting solutions (pH 7.0) were prepared by Smith & Nephew Research Limited. The polyvinyl alcohol used in the preparation of NODS is a highly soluble form of the polymer (Gohsenol GH-17) with a median molecular weight of 98,000 and a 87–89 mol% degree of hydrolysis. The casting solutions were prepared at a concentration of 2.58% w/w to allow for dilution of the formulation to 2% w/w with the radioactive marker. The casting of the NODS film was carried out in a Class 1 clean room in the Department of Medical Physics, Medical School, Queen's Medical Centre, Nottingham.

The concentrated solution (4 g) was weighed into a sterile 20 ml beaker and 1.16 ml of Tc-99m diethylenetriaminepentaacetic acid ($^{99}Tc^m$-DTPA specific activity approximately 1000 MBq) was added and mixed to give a final concentration of 2% w/w. A stainless steel hand-spreader was used to cast a PVA/pilocarpine nitrate film (slit width of spreader 8/1000″ (2.032 mm)) onto a Melinex backing strip. The Melinex was sufficiently hydrophobic to allow easy removal of the dried film. A film approximately 35 cm long and 8 cm wide was cast by pulling the hand-spreader containing the casting solution over the Melinex backing strip as slowly and as evenly as possible. The film was left to dry in a ventilation cupboard in the Clean Room for approximately 1 h, and then cut into 25 $mm^2$ sections using a sharp scalpel. The NODS were then stored in a sterile petri dish until required.

The cast film not required for the study was left for the isotope to decay to background activity and then analysed for pilocarpine nitrate by Smith & Nephew Research Ltd.

### *Preparation of the radiolabelled pilocarpine nitrate solution*

Pilocarpine nitrate solution (4 ml 2.5% w/v) (Smith & Nephew Research Ltd) was diluted to 2% w/v by adding 1 ml Tc-99m DTPA (200 MBq) to give a dose of 1 MBq $^{99}Tc^m$ per 25 μl dose at the time of administration.

### In vitro *release of the soluble marker and pilocarpine nitrate from the NODS*

Previous studies have followed the disintegration of the matrix (or release of a poorly soluble drug) by incorporation of technetium-99m sulphur colloid into the PVA slab (Fitzgerald *et al.*, 1992). *In vitro* studies established that the release of this colloidal marker would not follow the release of a soluble drug and therefore the Tc-99m DTPA marker was chosen for the present study. An *in vitro* dissolution test was used to confirm the comparative release rates of the Tc-99m DTPA and the pilocarpine nitrate from the films. The release of the drug and the radiolabel from the film were assessed separately.

*Release of the radiolabel from the PVA film* A PVA film was cast without any incorporated pilocarpine nitrate. A section of the radiolabelled PVA film 25 mm × 10 mm (equivalent to ten NODS), was cut from the dried film and removed from the Melinex backing sheet. The film was enclosed in a fine gauze and placed in a beaker containing 100 ml artificial tear solution consisting of sodium bicarbonate (2 g $l^{-1}$), sodium chloride (6.7 g $l^{-1}$) and calcium chloride (0.064 g $l^{-1}$) at 34° C and pH 7.4 and stirred at 50 rev $min^{-1}$. The release of the radiolabel from the film was monitored using a pencil gamma

probe. The pencil probe (John Caunt Scientific Ltd, Oxford, UK) operates on a similar principle to the gamma camera. A thallium doped sodium iodide crystal coupled to a photomultiplier tube acts as a detector, the probe detector was interfaced to an Apple Macintosh® microcomputer via a scintillation interface, which encoded the count rate in ASCII form to a communication package (Red Ryder® V10.3). The probe was encased in a lead collimator with an aperture of 3 mm in order to count only the radioactivity released into the dissolution solution and to prevent detection of the NODS film enclosed within the gauze. The release of the radioactivity into the dissolution solution was monitored for 10 min using 5 s counting periods. The data acquired in the communications package were transferred to a spread-sheeting program (Microsoft Excel V2.2), normalised and plotted. Ninety percent of the radiolabel was released from the PVA film in the first minute of dissolution.

*Release of the drug from the PVA film* A PVA/pilocarpine nitrate film was cast without the addition of any radiolabel. The casting solution was diluted to 2.0% w/w with sterile water. The dissolution experiment was set up as for the radiolabel release. Two hundred microlitre samples of the dissolution solution were taken at 0 and 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 180, 240, and 520 s after the introduction of the NODS film enclosed in gauze to the dissolution vessel and replaced with 200 μl artificial tear solution at 34° C. The dissolution was repeated four times. The samples were analysed for pilocarpine nitrate content by high pressure liquid chromatography based on peak height ratio measurement using 8-hydroxyquinoline as the internal standard (Smith & Nephew Method 193). Five standards containing pilocarpine nitrate and 8-hydroxyquinoline, were prepared and run on the day of the assay.

Samples of 20 μl were injected onto a 100 mm × 4 mm i.d. stainless steel column containing Lichrosorb Si-60 using h.p.l.c. grade methanol as the mobile phase at a flow rate of 1.0 ml $min^{-1}$. The h.p.l.c. equipment consisted of a Beckman Altex 110A pump with a manual Rheodyne injection valve with a 20 μl loop. The absorption was monitored at 220 nm using a Perkin-Elmer spectrophotometer (LC-55). Peak heights were recorded on a Servoscribe recorder.

*Protocol*

Twelve healthy volunteers (eight males and four females, aged 19–20 years) took part in the study on two occasions separated by at least 1 week, starting at noon on each occasion to minimise any diurnal variations in the physiological parameters measured. The subjects were asked to complete a medical questionnaire before inclusion into the study. Subjects with a history of significant eye infections, or any disease likely to lead to alteration of the tear film or drainage dynamics were excluded from the study as were contact lens wearers. Subjects with dark irides were also excluded from the study due to difficulties in the measurement of pupil diameter.

The study was approved by the University of Nottingham Medical School Ethics Committee, and was carried out in accordance with the Declaration of Helsinki (1984). A certificate to administer radioisotopes to healthy volunteer subjects was obtained from the Department of Health (ARSAC certificate RPC-253-17(3)), and all subjects signed a consent form to participate in the study prior to the commencement of the study. During the course of the study each subject received 2 MBq Tc-99m DTPA which gave a total radiation exposure of 0.06 mSv. The subjects did not drink any caffeinated drinks on the study days.

*Gamma scintigraphy*

On the study day the subjects arrived at 12.00 h and baseline measurements of intraocular pressure and pupil diameter were recorded. The subject was then seated in front of the gamma camera (IGE Maxicamera 11 (I.G.E., Slough, UK)) fitted with a 5 mm pinhole collimator, views were acquired using a 20% energy window centred on the 141 keV photopeak of $^{99}Tc^{m}$. The subject's head was supported on an ophthalmic table to position the eye 5 cm from the aperture of the collimator. The PVA gel insert (25 $mm^2$ square) was placed in the lower fornix of the right eye with sterile forceps or 25 μl of the 2% w/v radiolabelled pilocarpine nitrate solution was instilled into the lower fornix of the right eye using a Gilson pipette fitted with a sterile disposable tip. Clearance was followed for 10 min using dynamic imaging (36 × 5 s frames) (42 × 10 s frames). One hundred and twenty second static images were then recorded approximately every 20 min until the formulation had cleared from the eye. The images were stored in a 64 × 64 pixel matrix using a dedicated Nuclear Diagnostics computer system (Gravesend, Kent, UK).

*Pupil diameter*

Pupil diameter was measured approximately every 30 min for 5 h post-dose using a video camera fitted with a macro lens (Sony V8 Pro-CDD-V100E) and television monitor. The subject sat with the head supported on the ophthamic table and a video recording of 1 min duration was made of the study eye and the control eye. A small adhesive paper spot of known diameter was placed on the skin directly below the eye during these measurements to ascertain the magnification of the video image.

*Intraocular pressure*

Intraocular pressure was measured in the test and control eye approximately every hour for 5 h post-dose using a Reichert non-contact tonometer (Cambridge Instruments, Inc., New York) (Grolman, 1972; Shields, 1980). The instrument was supplied fully calibrated but a calibration check of the pneumatic-electronic network was carried out between each reading as per instrument instruction manual.

Two readings were recorded for each eye. Although three readings are normally made in clinical practice, two readings were considered sufficient in the current study due to the relatively large number of readings required from each subject over the study period.

Subjects remained in a room which had controlled lighting (no windows) and temperature during the course

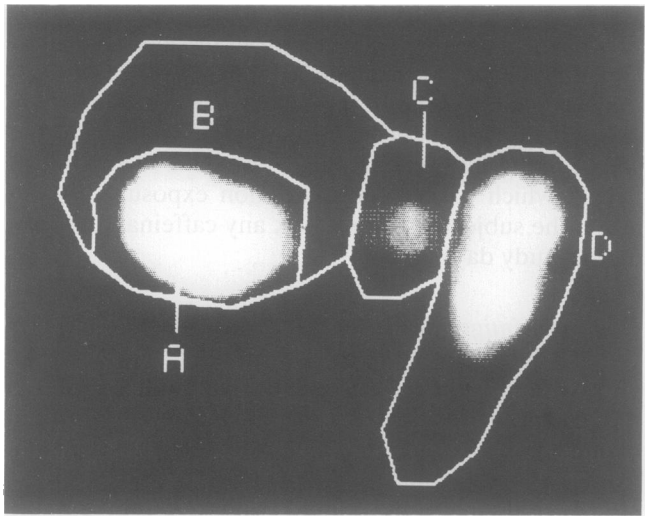


**Figure 1** Regions of interest constructed on the summed gamma camera image.
(A–NODS, B–Corneal surface, C–Inner canthus and D–nasolacrimal duct).

of the study in order to minimise variation due to external factors.

*Data analysis*

*Gamma scintigraphy* Individual dynamic gamma camera images were summed to produce an overall picture of label distribution. The data were analysed by creating regions of interest (ROIs) around the whole eye, cornea, inner canthus, nasolacrimal duct and NODS insert (Figure 1). A further ROI was drawn for background activity correction. The count rates from the regions of interest were corrected for background activity and decay of the isotope. The data from the regions of interest were normalised to the count rate in the whole eye in the first frame. The half-times of clearance of the radiolabel released from the NODS onto the corneal surface, NODS dissolution and clearance of the solution from the corneal surface were determined for each subject. The half-times were compared using Student's paired *t*-test.

The area-under-curve of the clearance of the radiolabel from the corneal ROI after administration in the solution or after release from the NODS was determined for each subject and the data compared using Student's paired *t*-test.

The NODS used in the study were cast on two separate occasions, five subjects received NODS from the first cast and seven subjects from the second cast. Corneal residence of the marker administered in the NODS was compared between the two groups using a 1-way analysis of variance.

*Pupil diameter* The video was played back on a television monitor and two measurements of pupil diameter and adhesive spot for each eye were made from the screen for each time point. The data were corrected for the magnification effect of the camera.

The change in pupil diameter from the baseline reading was determined over the 5 h study period. The area-under-effect curve (AUEC(0,5 h)) values were determined for both eyes in each subject and the data compared using Student's paired *t*-test. The maximal pupil constriction achieved in each subject after the two treatments was also determined both in the test eye and the control eye and the data were compared using Student's paired *t*-test.

*Intraocular pressure* The two readings from each eye were averaged and plots made of intraocular pressure *vs* time from dosing.

The change in IOP from the baseline reading was determined over the 5 h study period. The area-under-effect-curve (AUEC(0,5 h)) values were determined for both eyes in each subject and the data compared using Student's paired *t*-test. The maximal change in IOP achieved in each subject after the two treatments was also determined both in the test eye and the control eye and the data were compared using Student's paired *t*-test.

## Results

In vitro *dissolution test*

Approximately 97% of the pilocarpine nitrate was released from the NODS within the first minute. A plot of mean percentage release of the pilocarpine nitrate and the radiolabel from the film is shown in Figure 2.

*Gamma scintigraphy*

Plots of the mean clearance (± s.e. mean) of the radiolabel from the corneal surface after administration in the NODS and solution are shown in Figures 3a and 3b respectively. A plot of mean (± s.e. mean) dissolution of the radiolabel from the NODS (release of radiolabel from the NODS) *in vivo* is shown in Figure 4. The half-times of clearance of the radiolabel released from the NODS onto the corneal surface, NODS dissolution and clearance of the solution from the corneal surface are summarised in Table 1.

Dissolution of the radiolabel from the NODS *in vivo* showed considerable intersubject variation with half-

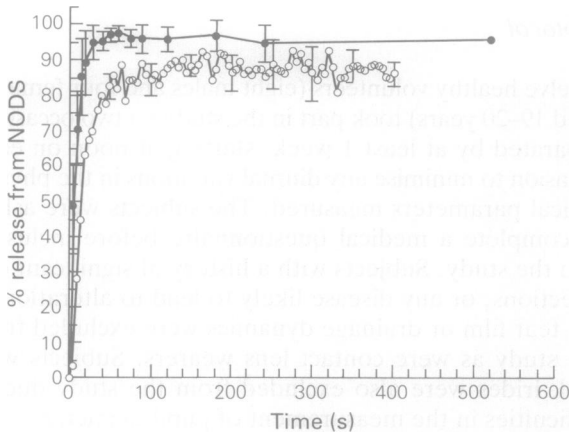


**Figure 2** *In vitro* release of pilocarpine nitrate (●, $n = 4$) and radioactive marker (Tc-99m DTPA, ○, $n = 5$) from NODS (mean ± representative s.d.).

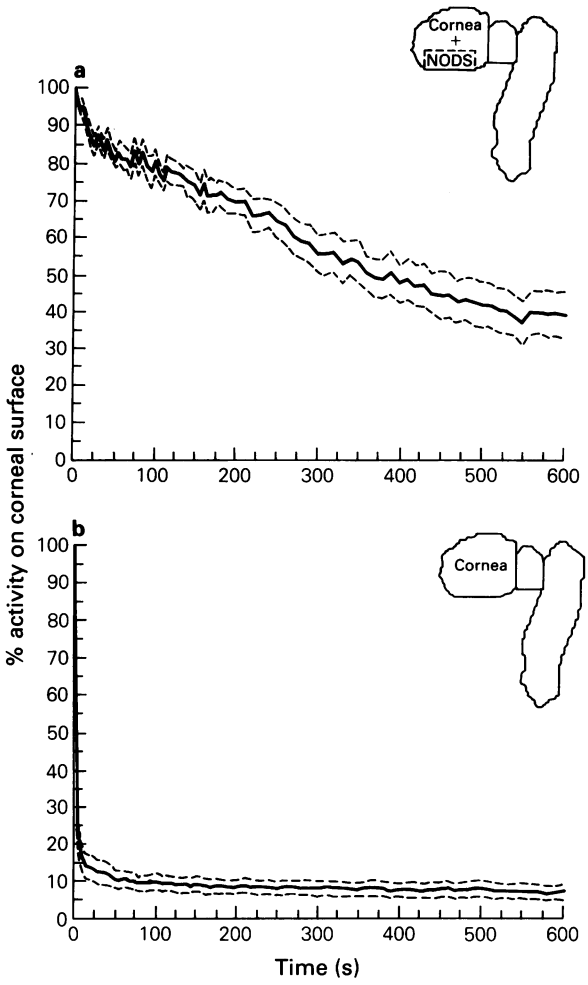


**Figure 3** a) Precorneal residence of the radioactive marker after administration in a NODS (mean ± s.e. mean, $n = 12$). b) Precorneal residence of the radioactive marker after administration in solution (mean ± s.e. mean, $n = 12$).

times of dissolution ranging from 46 s to 833 s (mean ± s.d. 280 ± 217 s), the mean (± s.d.) half-time of clearance of the radiolabel from the NODS and corneal ROI was 406 ± 214 s, whereas the radiolabelled solution had a mean (± s.d.) ocular surface residence time of 2.9

**Table 1** Time (s) for 50% of the radiolabel (Tc-99m DTPA) to be cleared from the ocular surface after administration in a NODS and a solution

| | *Half-time (s)* | | |
|---|---|---|---|
| *Subject* | *NODS dissolution* in vivo | *NODS + corneal ROI* | *2% w/v pilocarpine solution* |
| 1 | 230 | 345 | 2 |
| 2 | 46 | 139 | 2 |
| 3 | 833 | 860 | 4 |
| 4 | 427 | 375 | 3 |
| 5 | 425 | 680 | 2 |
| 6 | 244 | 290 | 2 |
| 7 | 160 | 208 | 2 |
| 8 | 78 | 245 | 2 |
| 9 | 402 | 625 | 3 |
| 10 | 98 | 407 | 7 |
| 11 | 217 | 266 | 2 |
| 12 | 205 | 427 | 4 |
| Mean | 280.4 | 405.6 | 2.9 |
| s.d. | 217.4 | 214.0 | 1.5 |
| s.e. mean | 65.5 | 64.5 | 0.5 |

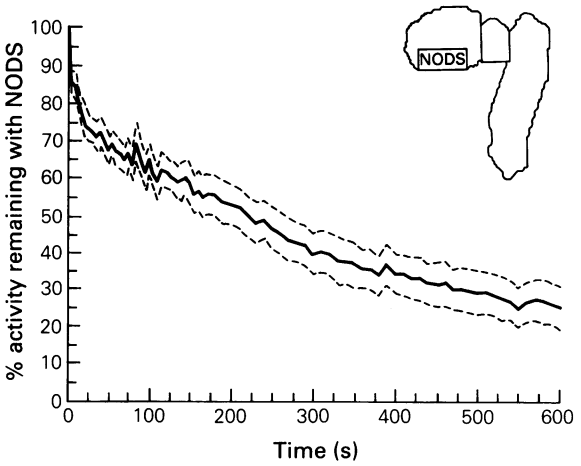


**Figure 4** *In vivo* dissolution of the radioactive marker from the NODS (mean ± s.e. mean, $n = 12$).

± 1.5 s. The radiolabel remained on the corneal surface significantly longer when delivered by a NODS formulation than when delivered in solution ($P < 0.001$; paired $t$-test). The mean (± s.d.) area-under-curve of the clearance of the radiolabel from the corneal ROI after administration in the 2% w/v pilocarpine nitrate solution or after release from the NODS were 5309.8 ± 4041.1% remaining s and 9710.6 ± 4912.0% remaining s, respectively. The marker remained on the corneal surface significantly longer after administration in a NODS than after administration in a solution ($P < 0.05$; paired $t$-test).

Corneal residence of the marker administered in the NODS was compared between the two groups. There was no significant difference in residence times between the two groups of subjects receiving the NODS from the different castings.

*Pupil diameter*

Figure 5 shows the mean (± s.e. mean) change in pupil diameter in the test eye from the baseline value after administration of pilocarpine nitrate in solution and in a NODS. The area-under-effect-curve data (0,5 h) (AUEC(0,5 h)) values are presented in Table 2.

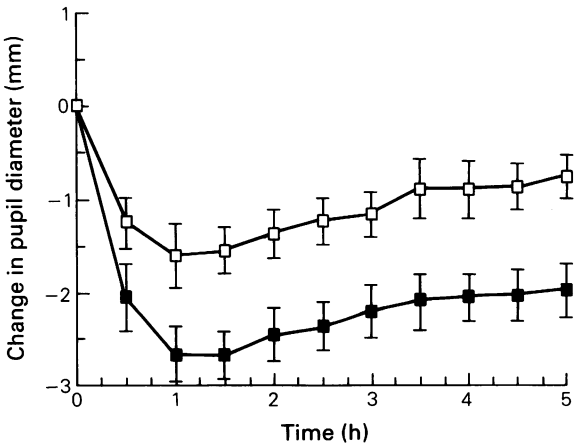


**Figure 5** Changes in pupil diameter in the test eye after administration of pilocarpine nitrate in a solution (□) and a NODS (■) (mean ± s.e. mean, $n = 12$).

**Table 2** AUEC(0,5 h) values (mm h) for pupil diameter data after dosing with 2% w/v pilocarpine nitrate solution and a pilocarpine NODS

| | *AUEC (mm h)* | | | |
|---|---|---|---|---|
| | *Solution* | | *NODS* | |
| *Subject* | *Test eye* | *Control eye* | *Test eye* | *Control eye* |
| 1 | −4.44 | 3.35 | −14.04 | 5.74 |
| 2 | −5.92 | 1.77 | −8.26 | −0.63 |
| 3 | −9.65 | −3.06 | −7.07 | 4.57 |
| 4 | −5.88 | 1.09 | −2.70 | −0.04 |
| 5 | −2.18 | 5.75 | −13.06 | 0.13 |
| 6 | −13.34 | −1.14 | −4.11 | 6.47 |
| 7 | 3.67 | 3.10 | −10.11 | 0.37 |
| 8 | −4.50 | −1.18 | −10.56 | 0.36 |
| 9 | −6.16 | 0.88 | −11.56 | 1.03 |
| 10 | −7.08 | 2.03 | −18.63 | −4.41 |
| 11 | −4.52 | 6.02 | −10.56 | −0.46 |
| 12 | −6.07 | 3.60 | −12.94 | −7.23 |
| Mean | −5.51 | 1.85 | −10.30 | 0.49 |
| s.d. | 4.05 | 2.75 | 4.37 | 3.89 |
| s.e. mean | 1.22 | 0.83 | 1.32 | 1.17 |

Comparing AUEC(0,5 h) for the pupil diameter, the NODS formulation significantly decreased pupil diameter in the test eye compared with the control eye ($P < 0.001$; paired $t$-test). Pupil diameter was also significantly reduced in the test eye after dosing with the pilocarpine nitrate solution when compared with the control eye ($P < 0.001$; paired $t$-test) and between the test eye after NODS administration and the test eye after dosing with the pilocarpine solution ($P < 0.05$; paired $t$-test). There was no significant difference in pupil diameter between the control eye after NODS administration and the control eye after dosing with the pilocarpine solution.

Maximal pupil constriction was compared after the two treatments, the mean (± s.d.) constriction after administration of the pilocarpine in the NODS was 2.87 ± 0.89 mm in the test eye, 0.73 ± 0.73 mm in the control eye and after administration in the solution 1.8 ± 0.95 mm in the test eye and 0.41 ± 0.63 mm in the control eye. The maximal pupil constriction was significantly greater in the NODS treated eye than in the solution treated eye ($P < 0.01$; paired $t$-test). There was no difference in the change in pupil diameter between the NODS control eye and the solution control eye.

*Intraocular pressure*

Figure 6 shows the mean (± s.e. mean) change in IOP in the test eye from the baseline value after administration of pilocarpine nitrate in solution and in a NODS. The area-under-effect-curve data (0,5 h) (AUEC(0,5 h)) values are presented in Table 3.

Comparing AUEC(0,5 h) for the IOP, the NODS formulation significantly decreased IOP in the test eye compared with the control eye ($P < 0.05$; paired $t$-test). Intraocular pressure was also reduced in the test eye after dosing with pilocarpine solution however, the change in IOP was not significantly different from the change in IOP in the control eye. There was no significant change in IOP between the solution test eye and the NODS test eye or between the control eye after the two treatments.

The mean maximal change (± s.d.) in IOP after

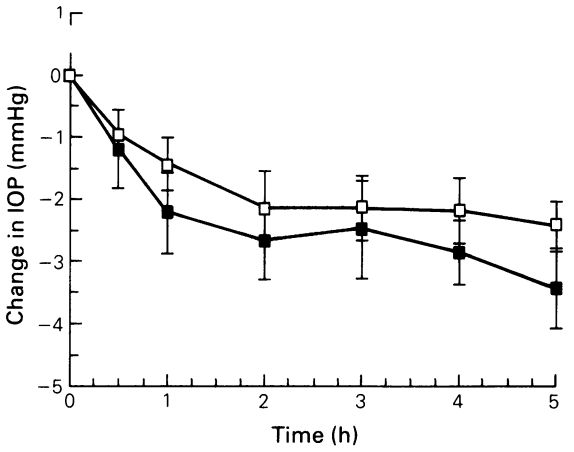


**Figure 6** Changes in intraocular pressure in the test eye after administration of pilocarpine nitrate in a solution (□) and a NODS (■) (mean ± s.e. mean, $n = 12$).

**Table 3** AUEC(0,5 h) values (mm Hg h) for intraocular pressure data after dosing with 2% w/v pilocarpine nitrate solution and a pilocarpine NODS

| | *AUEC (mm Hg h)* | | | |
|---|---|---|---|---|
| | *Solution* | | *NODS* | |
| *Subject* | *Test eye* | *Control eye* | *Test eye* | *Control eye* |
| 1 | −9.45 | −5.81 | −12.03 | 4.56 |
| 2 | −6.61 | 0.01 | −25.23 | −10.56 |
| 3 | −12.93 | −9.19 | −10.09 | −8.19 |
| 4 | −20.03 | −4.09 | 2.42 | −7.30 |
| 5 | −11.80 | −9.76 | −16.98 | −5.25 |
| 6 | −11.94 | −11.99 | −6.88 | −10.02 |
| 7 | 4.28 | −10.71 | −4.45 | 0.71 |
| 8 | −11.93 | −6.60 | −5.29 | 5.50 |
| 9 | −8.10 | −4.26 | −10.78 | −10.23 |
| 10 | −15.19 | −5.05 | −22.96 | −13.50 |
| 11 | −4.57 | −12.35 | −23.70 | −6.40 |
| 12 | −1.67 | −3.58 | −6.83 | −1.75 |
| Mean | −9.16 | −6.95 | −11.90 | −5.20 |
| s.d. | 6.44 | 3.84 | 8.66 | 6.16 |
| s.e. mean | 1.94 | 1.16 | 2.61 | 1.86 |

administration of the pilocarpine in the NODS was 3.29 ± 1.68 mm Hg in the test eye and 1.83 ± 0.96 mm Hg in the control eye and after administration in the solution 2.67 ± 1.57 mm Hg in the test eye and 2.63 ± 1.19 mm Hg in the control eye. Intraocular pressure was significantly lowered in the test eye compared with the control eye after administration of the NODS preparation ($P < 0.05$; paired $t$-test); but not after administration of the solution. There was no significant difference in the maximum change in IOP in the test eye after pilocarpine administration in the two preparations.

*Side-effects*

Intense miosis in the test eye was noted in all twelve subjects who experienced a slight eye ache/browache above the test eye after administration of the pilocarpine nitrate in a NODS. The effect lasted 15–45 min post-dose but was not severe enough to require any medication. Seven of the twelve subjects experienced a very slight transient browache after administration of the 2% w/v pilocarpine nitrate solution. All of the subjects in this

study tolerated the NODS very well, with only a transient foreign body sensation at the time of administration.

## Discussion

The rapid release (or burst effect) of the pilocarpine seen in the *in vitro* dissolution test is characteristic of drug release from slab systems in perfect sink conditions (Hadgraft, 1979). The drug release was slightly faster than the release of the radiolabel and therefore *in vivo* dissolution rate as measured using the radiolabel will tend to over-estimate the true residence time of the drug. However, the large intersubject variation in *in vivo* dissolution rates should allow pharmacodynamic effects due to these differences to become apparent.

The radiolabel Tc-99m DTPA diffused rapidly from the PVA film (406 ± 214 s) in a similar time to the Tc-99m sulphur colloid (549 ± 149 s) used in the study by Fitzgerald and co-workers (1992). The PVA film was exhausted of both the soluble and insoluble marker before complete disintegration of the matrix, inferring that any incorporated drug would rapidly be released from the system in a similar manner, accounting for the rapid onset and degree of miosis experienced by all subjects treated with the NODS.

The PVA/pilocarpine nitrate films used in the study were found to contain 63 μg pilocarpine nitrate (10.9% w/w cast at 20 gsm;) and 30 μg pilocarpine nitrate (9.93% w/w cast at 12 gsm;). The pilocarpine delivered in the NODS produced from both these films significantly decreased intraocular pressure in the test eye compared with the control eye, an effect which was not observed after delivery of pilocarpine as a solution. This is the first time that the NODS containing pilocarpine has been reported to produce a lowering of intraocular pressure in normotensive individuals. Pilocarpine delivered in the NODS also produced a greater decrease in pupil diameter than when delivered in the solution, with decreases of 52% and 35%, respectively.

Kelly and co-workers (1989) found that a NODS containing 67 ± 11 μg pilocarpine nitrate had equivalent effect to one 30 μl eyedrop of 2% w/v pilocarpine nitrate solution (517 μg pilocarpine nitrate). Since both of the films used in this study were found to contain less than 67 μg pilocarpine nitrate per NODS, the results of the present study suggest that the bioavailability of pilocarpine from a NODS is greater than eight-fold higher compared with a solution.

Clearly the amount of drug delivered by the NODS could be reduced further for equivalence to a drop, with a proportionately reduced risk of systemic side-effects to the subject. There was no apparent relationship between the length of precorneal residence time of the pilocarpine delivered by the NODS to the ocular surface and the degree of pupil constriction or reduction in intraocular pressure.

The anhydrous nature of the system offers advantages for drugs which have poor aqueous stability and, therefore, cannot be easily formulated into standard drops without significant loss of drug. Thus pilocarpine can be formulated in PVA at neutral pH without significant decomposition on ageing up to 1 year at 20° C (Bentley, 1990). In contrast, pilocarpine in solution is normally formulated as a salt with pHs of about 4.5. At pH 7 decomposition in the solution would be expected to be significant over a few days (Yoshioka *et al.*, 1986).

The authors would like to thank Mr Fraser Harvie and Mrs Fiona Sandbank for their help and advice in the preparation of the New Ophthalmic Delivery System and Ms Elaine Blackshaw for her technical assistance in the running of this study.

NODS and MINIMS are trade marks of Smith & Nephew Pharmaceuticals Limited.

## References

Bentley, P. H. (1990). A new ophthalmic delivery system (NODS). *9th Pharmaceutical Technology Conference*, Holland.

Fitzgerald, P., Wilson, C. G., Greaves, J. L., Frier, M., Hollingsbee, D., Gilbert, D. & Richardson, M. C. (1992). Scintigraphic assessment of the precorneal residence of a New Ophthalmic Delivery System (NODS) in man. *Int. J. Pharm.*, (in press).

Grolman, B. (1972). A new tonometer system. *Am. J. Optom. Physiol. Opt.*, **49**, 646–660.

Hadgraft, J. (1979). Calculations of drug release rates from controlled release devices. The slab. *Int. J. Pharm.*, **2**, 177–194.

Kelly, J.A., Molyneux, P.D., Smith, S.A. & Smith, S.E. (1989). Relative bioavailability of pilocarpine from a novel ophthalmic delivery system and conventional eyedrop formulations. *Br. J. Ophthalmol.*, **73**, 360–362.

Patton, T. F. & Robinson, J. R. (1979). Ocular evaluation of polyvinyl alcohol vehicle in rabbits. *J. pharm. Sci.*, **64**, 1312–1315.

Shell, J. W. & Baker, R. W. (1974). Diffusional systems for controlled release of drugs to the eye. *Ann. Ophthalmol.*, **6**, 1037–1047.

Shields, M. B. (1980). The non-contact tonometer. Its value and limitations. *Surv. Ophthalmol.*, **24**, 211–219.

Yoshioka, S., Aso, Y., Shibazaki, T. & Uchiyama, M. (1986). Stability of pilocarpine ophthalmic formulations. *Chem. Pharm. Bull.*, **34**, 4280–4286.

*(Received 22 October 1991, accepted 31 January 1992)*