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# In vivo performance of [$^3$H]dexamethasone ophthalmic film delivery systems in the rabbit eye

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## Summary

The disposition of dexamethasone in different eye tissues was investigated following the application of an ophthalmic suspension and ocular inerts. The disposition in the corneal tissue, which was rather poor relative to the conjunctiva and iris-ciliary body in the case of the suspensions, was markedly enhanced through application of the drug in a film delivery system. Eudragit and cellulose acetate phthalate-based films enhance the disposition of the drug in the aqueous humor at specific time intervals. It is apparent from the results that ophthalmic film delivery systems may target the drug to the eye tissues in which the drug is otherwise poorly available. Ophthalmic film delivery systems, in general, bring about a considerable increase in extent of drug absorption compared to the suspension dosage form. In the present study they brought about an increase in peak dexamethasone concentration.

## Introduction

The biologic activity responsible for therapeutic effect is influenced by the mode of action, the distribution and duration of contact of the drug with ocular tissues, biochemical and physical interactions between the drug and the tissues, and the site of action of the drug. Drug characteristics that influence biologic activity include solubility characteristics, concentration of the active agent viscosity and additives. The amount of drug that penetrates through the cornea increases as the concentration of the active ingredient increases.

Lee et al. (1983) used benzalkonium chloride and microcrystalline collagen to enhance drug activity. These agents increase the amount of material which penetrates the anterior chamber and is available for biological activity. Highest concentrations of topically administered corticosteroid in the eye are in the cornea and conjunctiva; however, all parts of the eye contain some of the preparation. Steroids, also occur in the aqueous humor after topical instillation. Penetration of corticosteroids is determined by both differential solubility characteristics of the drug and tissue factors. Stratford et al. (1983) investigated the ocular disposition of epinephrine and inulin in the albino rabbit following their encapsulation in multilamellar liposomes. They found that epinephrine absorption was reduced by 50% whereas inulin absorption was increased 10

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times. Lee et al. (1982) studied the disposition of pilocarpine in the pigmented rabbit eye following instillation of different concentrations of pilocarpine solutions. They found that the most striking difference in the behaviour of pilocarpine in pigmented and albino rabbits is the accumulation of drug in the iris-ciliary body of the pigmented rabbit.

The aim of this work is investigation of the in vivo performance of the ophthalmic film delivery system housing the anti-inflammatory compound, dexamethasone, representing that class of steroids.

## Experimental

*Materials*

Eudragit $RL_{100}$ and RSPM (obtained from Rohm and Haas G.m.b.H. Pharma Darmstadt, F.R.G.); polyvinyl achohol (14000) BDH; Gelatin, BDH; polyvinylpyrrolidone (k 90) Poole, U.K.; hydroxypropyl cellulose (4000), BDH; methylcellulose (MH20), Hoechst; cholesterol, BDH; benzalkonium chloride, BDH; Tween 20, Merck; Span 20, Roth; polyethylene glycol 400, BDH; polypropylene glycol 2000, 1020, Roth; triacetin, Merck; glycerin, El-NASR; dibutylphthalate, BDH. Male albino rabbits weight varied between 1.8–2.8 kg.

*Solvents*

Isopropanol; acetone; ethylalcohol, all are analytical grade (ADWIC).

*Radioactive material*

[1,2(n)-$^3$H]-Dexamethasone with specific activity of (26 Ci/mmol), Amersham.

| Scintillation liquid | Prepared as follows |
|---|---|
| Triton X-100 | 300 ml Fisons |
| Toluene | 700 ml (Scintillation Grade) for high counting efficiency |
| Popop | 0.2 g (Amersham/Searle) |
| PPo | 3.0 g (Scintillation Grade) |
| Glacial acetic acid 7 ml | |

*Equipment*

Liquid scintillation counters, a Beckman LK 700 counter; quench correction was made by external standardization; Micro-selecta pette pipette type 10, 20, 25, 30 microliter (Clay Adams), siliconized for micropipetting; automatic pipette 1 ml (p. 1000), Gilson (France); Scintillation vials.

*Procedures*

*Preparation of base films.* Solutions of the composition described in Table 1 were prepared. The solutions were filtered through a sintered glass ($G_3$). A volume of 15 ml of the clear filtrate was transferred into the dust-free circular PTFE mold. The mold was covered with an inverted funnel (stem orifice diameter 5.7 mm) to control solvent evaporation and placed on a level surface in a laminar flow hood (Microflow laminar air flow station), with an air speed of 0.5 $m \cdot s^{-1}$. Solvent was permitted to evaporate for 24–48 h at ambient temperature before transfer of the formed film to a desiccator containing silica gel, where it was stored for a further 24 h before use. The films were subjected to evaluation within one week of their preparation.

*Preparation of [$^3$H]dexamethasone suspension.* A 0.1% suspension of dexamethasone was prepared according to the following procedure. In a very small mortar, 10 mg of dexamethasone was placed, and the least amount of ethyl-alcohol added to dissolve the dexamethasone. The required volume of radioactive dexamethasone ethanolic solution (25 $\mu$l) was pipetted, mixed thoroughly and as much as possible of ethyl alcohol allowed to evaporate without precipitating the dexamethasone. By portion-wise trituration, 0.5% tylose solution in water was added to the required volume (10 ml). The initial activity of a dose (60 $\mu$l) of the suspension was determined using a scintillation counter.

*Application of suspension and ocular inserts.* Male albino rabbits weighing 1.8–2.0 kg were used throughout the study. Unanaesthetized rabbits were placed into wooden restraining boxes in a normal upright posture. A single 60 $\mu$l dose of the suspension was instilled, using a micropipette inside the center of the lower cul-de-sac, care being taken not to irritate the eye or to touch the corneal surface. The lower lid was gently moved across the cornea to spread the dose evenly and was then released. During instillation, the lower

TABLE 1

*Formulation of film delivery systems from different polymers*

In parentheses the weights are given

| Formula number | Polymer (g) | Plasticizer (g) | Solvent to 100 ml |
|---|---|---|---|
| (1) | Gelatin (1) | Glycerin (20) | distilled water |
| (2) | Polyvinylalcohol (1) Luviskol (K 90) (0.25) | Polyethylene glycol 400 (20) | distilled water/isopropanol (2 : 1) |
| (3) | Hydroxypropyl cellulose (1) | Propylene glycol 1020 (20) | isopropanol |
| (4) | Ethylcellulose (1) | Polyethylene glycol 400 (20) | isopropanol |
| (5) | Cellulose acetate(1) phthalate (1) | Polyethylene glycol 400 | acetone/isopropanol (4 : 1) |
| (6) | Eudragit RL100/RS100 (1) | Polyethylene glycol 400 (20) | acetone/isopropanol (4 : 1) |
| (7) | Eudragit RSPM (1) | Polyethylene glycol 400 (20) | acetone/isopropanol (4 : 1) |
| (8) | Eudragit E (1) | Polyethylene glycol 400 (20) | isopropanol |

eyelid was pulled slightly away from the globe but was returned to its normal position immediately after instillation. The same procedure adopted in the application of suspension was for introducing the ocular inserts into the rabbit eye. No other manipulative techniques were used to distribute the formulation in the precorneal area. The normal eye movement was maintained. The 60 $\mu$l dose of the suspension was equivalent to one disc in terms of dexamethasone content and radioactivity. The radioactivity was so adjusted as to evoke sufficient activity in the different tissues of the eye.

*Separation of eye tissues.* The rabbits were killed with an overdose of pentobarbital sodium injected into a marginal ear vein. Following killing of the rabbit and separation of its conjunctival surface, a single incision was made with a scalpel at the corneal margin and the entire cornea was excised. The whole cornea and conjunctiva surfaces were thoroughly rinsed with normal saline and blotted with tissue in order to remove any residual radioactivity. The anterior segment tissues – conjunctiva, aqueous humor, cornea and iris – ciliary body were obtained in that order. The surgical procedures on each eye were completed within 5 min of sacrificing the rabbit so that any errors due to redistribution of drug during the time required to obtain ocular tissue samples were minimized. Each individual tissue was transferred into a scintillation vial and the wet weight of tissue was determined using an analytical balance.

*Determination of radioactive dexamethasone in ocular tissues.* 1 ml of tissue solubilizer (NCS) diluted with an equal volume of isopropanol was added to the tissue. The vials were then kept at 40–50 °C for 2 h to allow complete solubilization of tissue. The vials were then allowed to cool down to room temperature for half-an-hour, 0.5 ml hydrogen peroxide solution (33%) was then added to each vial. Only the iris-ciliary body required 1 ml to achieve complete decolorization. The solutions were allowed to stand at room temperature for half-an-hour with occasional swirling. The vials were then incubated at 50 °C for 1 h to remove excess hydrogen peroxide. A small amount of ascorbic acid, serving as a reducing agent, was added to each vial to remove any residual hydrogen peroxide. 10 ml of the scintillation cocktail was added to each vial which were stoppered, shaken and kept in the dark for 24 h prior to counting in a liquid scintillation counter. After correcting for background and quenching effects, the data in counts per minute (cpm) were converted to disintegrations per minute (dpm).

## Results and Discussion

The disposition of dexamethasone in the different eye tissues was investigated following the application of an ophthalmic suspension (60 $\mu$l) to the pigmented eye of rabbit. The disposition pat-

TABLE 2

*Mean concentrations of dexamethasone radioactivity (dpm/g tissue $\times 10^{-2}$) in the tissues of the anterior segment rabbit eye (4 eyes) following application of suspension and ocular inserts*

In parentheses are given the values of S.E. $\times 10^{-2}$.

| Time (h) | Conjunctiva | | Cornea | | Iris-ciliary body | | Aqueous humor | |
|---|---|---|---|---|---|---|---|---|
| *Suspension* | | | | | | | | |
| 0.5 | 31.5 | (7.2) | 8.95 | (3.1) | 2.47 | (1.0) | 1.74 | (0.8) |
| 1.0 | 23.8 | (5.1) | 5.95 | (1.9) | 22.7 | (7.1) | 1.84 | (0.5) |
| 2.0 | 23.3 | (5.4) | 4.0 | (0.7) | 25.5 | (4.7) | 3.1 | (0.7) |
| 3.0 | 20.0 | (6.6) | 3.9 | (0.3) | 15.0 | (3.1) | 1.1 | (0.1) |
| 4.0 | 13.2 | (1.5) | 3.3 | (0.6) | 11.8 | (3.9) | 0.8 | (0.2) |
| 5.0 | 8.4 | (3.1) | 2.6 | (0.4) | 8.3 | (3.3) | 0.8 | (0.1) |
| *PVA-cholesterol insert* | | | | | | | | |
| 0.5 | 631.0 | (43.5) | 354.7 | (72.9) | 18.4 | (3.6) | 10.8 | (1.2) |
| 1.0 | 1474.1 | (52.1) | 852.6 | (57.5) | 76.9 | (8.3) | 61.2 | (4.2) |
| 2.0 | 206.4 | (39.7) | 334.9 | (20.9) | 50.8 | (3.4) | 36.3 | (9.9) |
| 3.0 | 140.0 | (13.2) | 296.2 | (60.1) | 30.0 | (0.7) | 28.1 | (1.0) |
| 4.0 | 59.8 | (1.1) | 243.7 | (6.8) | 27.1 | (3.5) | 17.0 | (1.0) |
| 5.0 | 26.7 | (0.2) | 189.4 | (27.3) | 20.2 | (2.8) | 14.8 | (2.0) |
| *Gelatin insert* | | | | | | | | |
| 0.5 | 106.2 | (49.3) | 75.0 | (20.4) | 18.6 | (4.3) | 11.1 | (2.6) |
| 1.0 | 558.6 | (30.0) | 115.5 | (47.6) | 38.9 | (16.1) | 11.2 | (1.9) |
| 3.0 | 40.1 | (14.7) | 27.7 | (10.7) | 28.8 | (4.1) | 6.1 | (1.5) |
| 4.0 | 34.4 | (6.6) | 14.6 | (1.0) | 19.2 | (3.5) | 4.3 | (2.1) |
| 5.0 | 12.2 | (0.8) | 9.7 | (1.2) | 16.3 | (4.1) | 1.9 | (0.9) |
| *Hydroxypropyl cellulose insert* | | | | | | | | |
| 0.5 | 549.2 | (37.3) | 125.1 | (8.4) | 46.2 | (5.3) | 7.6 | (1.2) |
| 1.0 | 459.3 | (30.6) | 238.7 | (12.8) | 58.5 | (16.9) | 4.3 | (1.2) |
| 2.0 | 266.3 | (11.7) | 548.2 | (10.4) | 450.3 | (7.8) | 3.9 | (0.8) |
| 3.0 | 64.9 | (26.2) | 159.1 | (31.9) | 20.6 | (0.9) | 4.0 | (0.9) |
| 4.0 | 27.4 | (11.1) | 140.8 | (51.3) | 19.1 | (2.0) | 3.5 | (1.1) |
| 5.0 | 11.3 | (3.6) | 11.8 | (0.7) | 12.1 | (1.1) | 0.9 | (0.1) |
| *Cellulose acetate phthalate insert* | | | | | | | | |
| 0.5 | 66.6 | (1.8) | 101.6 | (72.0) | 58.5 | (5.0) | 4.1 | (0.7) |
| 1.0 | 36.5 | (0.7) | 40.0 | (3.2) | 139.9 | (0.2) | 13.2 | (0.3) |
| 2.0 | 81.5 | (0.8) | 45.0 | (4.9) | 59.8 | (0.4) | 13.0 | (0.6) |
| 3.0 | 87.4 | (4.3) | 26.1 | (1.0) | 27.9 | (2.4) | 3.6 | (0.2) |
| 4.0 | 27.3 | (1.2) | 10.9 | (0.6) | 15.8 | (0.5) | 2.5 | (0.7) |
| 5.0 | 6.7 | (0.3) | 8.0 | (0.0) | 6.2 | (0.1) | 0.9 | (0.0) |
| *PVA-benzalkonium chloride insert* | | | | | | | | |
| 0.5 | 857.1 | (44.0) | 209.8 | (57.3) | 42.9 | (7.8) | 9.7 | (1.3) |
| 1.0 | 479.2 | (175.6) | 270.1 | (60.0) | 87.3 | (18.0) | 10.2 | (1.1) |
| 2.0 | 295.1 | (78.7) | 123.3 | (39.9) | 65.6 | (25.0) | 26.7 | (6.1) |
| 3.0 | 67.0 | (9.7) | 54.8 | (11.0) | 20.1 | (6.1) | 4.2 | (1.5) |
| 4.0 | 47.1 | (2.0) | 12.8 | (2.0) | 15.9 | (2.3) | 2.9 | (0.8) |
| 5.0 | 17.3 | (1.9) | 9.0 | (0.6) | 11.8 | (0.8) | 2.0 | (0.3) |

Table 2 (continued)

| Time (h) | Conjunctiva | | Cornea | | Iris-ciliary body | | Aqueous humor | |
|---|---|---|---|---|---|---|---|---|
| *Eudragit RSPM insert* | | | | | | | | |
| 0.5 | 158.8 | (25.7) | 63.4 | (7.5) | 66.7 | (15.1) | 6.5 | (0.7) |
| 1.0 | 280.3 | (37.2) | 67.2 | (7.1) | 79.8 | (12.1) | 9.4 | (1.4) |
| 2.0 | 209.0 | (18.1) | 98.1 | (8.2) | 77.4 | (18.2) | 9.4 | (2.1) |
| 3.0 | 165.7 | (15.7) | 133.0 | (10.5) | 23.4 | (5.9) | 17.4 | (5.7) |
| 4.0 | 102.7 | (7.3) | 70.0 | (14.2) | 13.1 | (2.2) | 13.7 | (3.8) |
| 5.0 | 17.8 | (3.4) | 17.5 | (4.1) | 12.1 | (1.9) | 6.0 | (1.9) |
| *Eudragit RL/RS100 insert* | | | | | | | | |
| 0.5 | 106.2 | (24.9) | 62.7 | (21.6) | 18.9 | (3.5) | 7.1 | (0.4) |
| 1.0 | 88.1 | (9.7) | 45.4 | (7.2) | 15.8 | (0.5) | 18.7 | (3.9) |
| 2.0 | 87.3 | (6.1) | 57.3 | (18.5) | 96.5 | (14.2) | 18.5 | (5.8) |
| 3.0 | 79.9 | (25.6) | 63.0 | (25.7) | 239.8 | (32.3) | 11.0 | (2.8) |
| 4.0 | 30.3 | (2.5) | 20.6 | (0.9) | 99.1 | (8.5) | 6.8 | (0.3) |
| 5.0 | 14.4 | (0.3) | 6.5 | (1.8) | 65.7 | (5.2) | 2.0 | (0.8) |
| *Eudragit E insert* | | | | | | | | |
| 0.5 | 13.5 | (2.2) | 4.7 | (0.3) | 3.8 | (0.6) | 0.6 | (0.1) |
| 1.0 | 9.1 | (1.3) | 6.3 | (0.7) | 5.8 | (0.8) | 1.6 | (0.2) |
| 2.0 | 13.5 | (3.1) | 5.3 | (0.4) | 2.7 | (0.2) | 0.9 | (0.2) |
| 3.0 | 12.1 | (2.7) | 11.8 | (0.6) | 4.4 | (0.4) | 1.3 | (0.4) |
| 4.0 | 8.8 | (0.3) | 4.1 | (0.2) | 9.9 | (0.9) | 1.2 | (0.3) |
| 5.0 | 1.6 | (0.3) | 2.1 | (0.3) | 2.8 | (0.3) | 1.0 | (0.02) |
| *Ethyl cellulose insert* | | | | | | | | |
| 0.5 | 141.1 | (94.3) | 18.6 | (5.5) | 8.3 | (2.2) | 1.5 | (0.7) |
| 1.0 | 76.1 | (27.0) | 10.6 | (3.4) | 17.9 | (4.5) | 3.7 | (1.7) |
| 2.0 | 44.5 | (9.1) | 10.0 | (0.6) | 17.1 | (6.4) | 3.1 | (1.1) |
| 3.0 | 17.3 | (3.6) | 5.6 | (1.0) | 11.2 | (3.7) | 2.9 | (1.1) |
| 4.0 | 13.6 | (3.1) | 4.7 | (1.0) | 7.2 | (1.7) | 1.5 | (0.5) |
| 5.0 | 9.4 | (1.6) | 1.9 | (0.2) | 2.3 | (0.7) | 0.7 | (0.1) |
| *Gelatin-formaldehyde insert* | | | | | | | | |
| 0.5 | 161.8 | (30.7) | 98.5 | (7.6) | 21.9 | (2.1) | 3.5 | (1.0) |
| 1.0 | 222.8 | (41.6) | 214.0 | (10.3) | 69.9 | (5.4) | 7.3 | (1.2) |
| 2.0 | 150.5 | (11.9) | 75.5 | (12.6) | 163.0 | (5.7) | 14.6 | (3.4) |
| 3.0 | 117.4 | (20.7) | 42.1 | (4.9) | 54.5 | (11.1) | 23.0 | (4.6) |
| 4.0 | 48.3 | (15.1) | 26.7 | (1.2) | 20.6 | (2.2) | 5.8 | (0.4) |

tern in the eye tissues was followed as a function of time over a period of 5 h.

Table 2 shows the disposition of dexamethasone in the tissues of the anterior segment of the eye following application of suspension and ocular inserts. It is obvious that conjuntiva is the tissue which is most highly enriched with dexamethasone, maximum disposition is observed in this tissue already half-an-hour post-drug application. The concentration in the iris-ciliary body increases rapidly with 1 h post-drug application and approaches that in the conjunctiva. At subsequent

time intervals, the concentrations in these tissues are very similar and the differences in concentrations are statistically insignificant so that the concentrations in these tissues may be considered equal beyond half-an-hour post-drug application.

The disposition of dexamethasone in the cornea is found to be much lower than that in the conjunctiva (or iris–ciliary body). The corneal concentrations of the drug do not exceed 0.25–0.33, the corresponding concentrations in the conjunctiva at any time interval. Beyond half-an-hour post-drug application, the corneal concentrations of dexamethasone relate to those in the iris-ciliary body (at a ratio of 1 : 4 to 1 : 3).

The disposition of the drug in the aqueous humor is found to be very weak. Generally, the concentrations of dexamethasone in the aqueous humor are about 1/10 those in the conjunctiva.

The high disposition of dexamethasone in the conjunctival tissue, a tissue rich in protein content may be interpreted in terms of protein binding, since dexamethasone is known to be strongly bound to proteins.

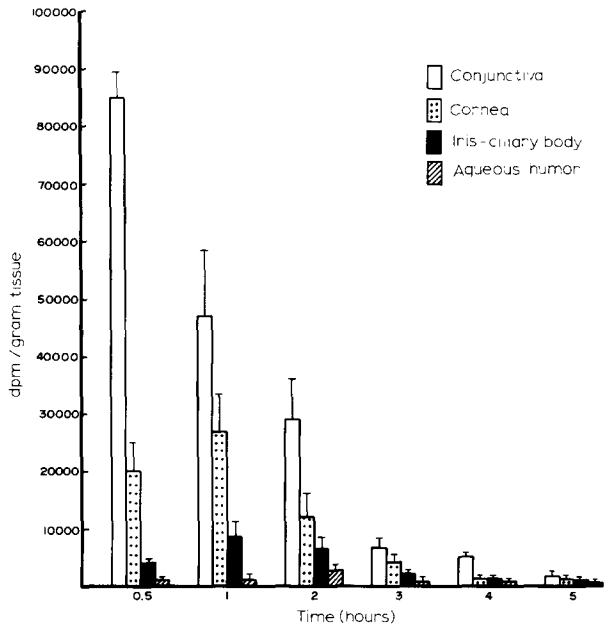


Fig. 1. Disposition of dexamethasone in ocular tissues following application of ophthalmic film delivery system (polyvinyl alcohol/benzalkonium chloride).

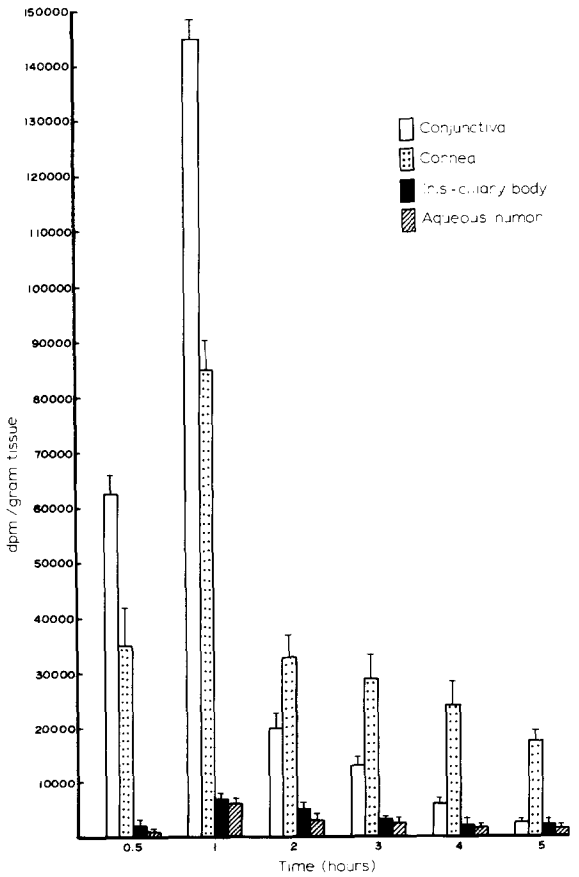


Fig. 2. Disposition of dexamethasone in ocular tissues following application of ophthalmic film delivery system (polyvinyl alcohol/cholesterol).

The disposition of dexamethasone in ocular tissues was investigated following the application of the drug in ophthalmic film delivery systems to find out whether such a delivery system would have an influence on the disposition pattern of the drug or not. Film delivery systems considering different base polymers and surfactant were investigated; these are: PVA/cholesterol; PVA/benzalkonium chloride; gelatin; gelatin/formaldehyde; hydroxypropyl cellulose; ethyl cellulose; Eudragit E; Eudragit RSPM; Eudragit RL/RS100; cellulose acetate phthalate; -based films. The results are presented in the bar charts, presented in Figs. 1–8. Comparison of these figures with Table 2 representing the suspension dosage form shows that film delivery systems, irrespective

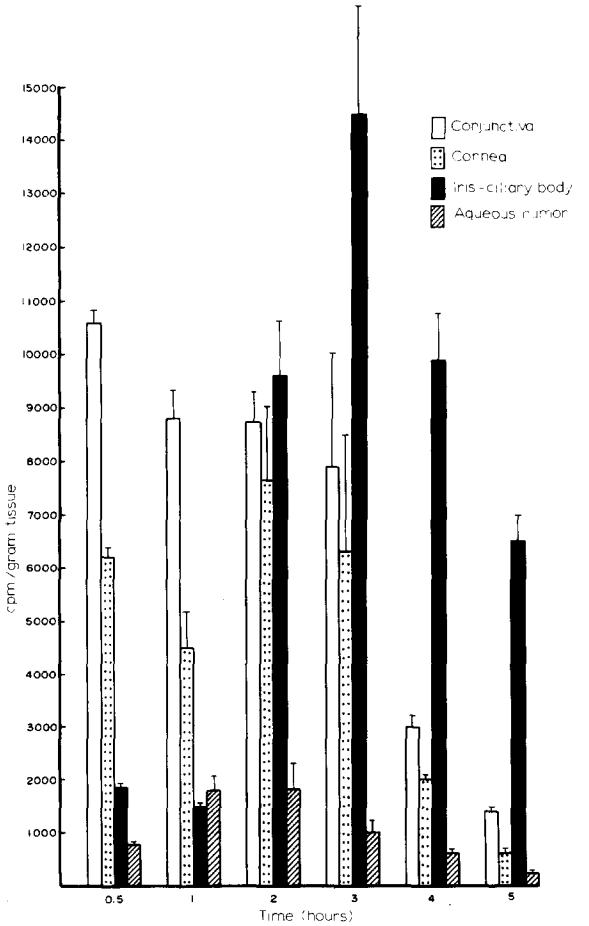


Fig. 3. Disposition of dexamethasone in ocular tissues following application of ophthalmic film delivery system (Eudragit RL/RS 100).

of their composition, bring about an increase in the corneal concentration of the drug. This effect was consistent for almost all ophthalmic film delivery systems and appears to be associated with this type of dosage form. The disposition of dexamethasone in the corneal tissue, which was rather poor relative to the conjunctiva and iris–ciliary body in the case of the suspensions, was markedly enhanced through application of the drug in a film delivery system.

Also some of the Eudragit-based films, especially Eduragit RSPM and Eudragit RL/RS 100, as well as the cellulose acetate phthalate-based film bring about an enhancement in the disposition of the drug in the aqueous humor at specific time intervals in comparison with suspension (Table 2).

These findings demonstrate that ophthalmic film delivery systems are capable of influencing the deposition pattern of dexamethasone in the different eye tissues.

This phenomenon, which the present work illustrates for the first time, points to the potential usefulness of dosage form design in influencing not only drug bioavailability but also drug deposition. It is apparent from the results presented that ophthalmic film delivery systems may function as drug targeting agents, targeting the drug to the eye tissues in which the drug is otherwise poorly available.

Lee et al. (1983) considered the ocular deposition of sodium cromoglycate in the albino rabbit by applying the drug in aqueous solution with and without viscolizer and 3 different ointment bases.

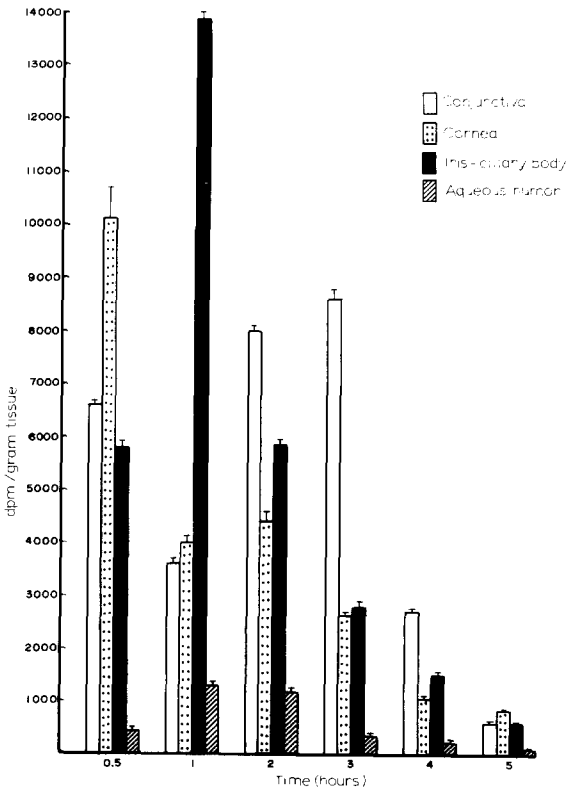


Fig. 4. Disposition of dexamethasone in ocular tissues following application of ophthalmic film delivery system (cellulose acetate phthalate).

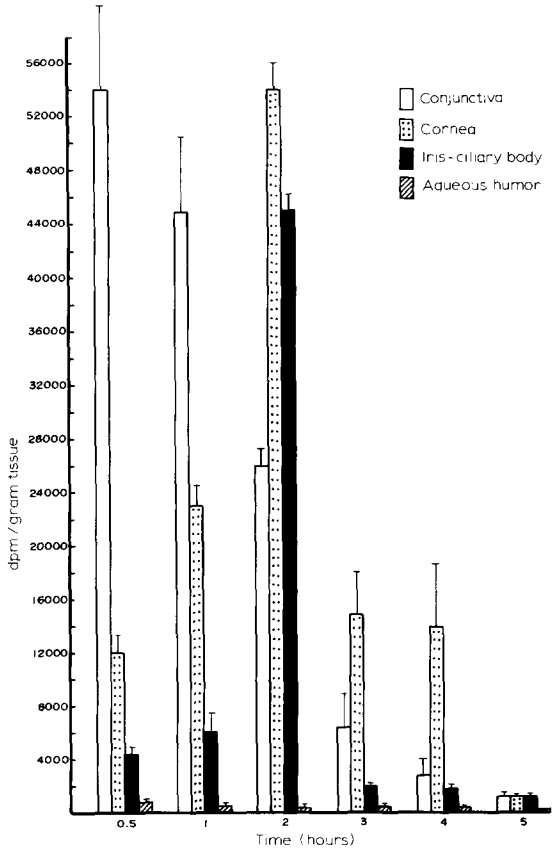


Fig. 5. Disposition of dexamethasone in ocular tissues following application of ophthalmic film delivery system (hydroxypropyl cellulose).

They reported quantitative differences in the drug concentrations in the different eye tissues dependent on the preparation applied to the eye; the change of the dosage form from a liquid to a semisolid (ointment) did not bring about any change in the pattern of deposition of sodium cromoglycate in the eye tissues. This would indicate that the targeting effect may be dosage form-specific. Lee et al. (1983) demonstrated the failure of ointment dosage form to bring about such an effect; the present investigation, on the other hand, clearly showed the capability of ophthalmic delivery systems to induce such an effect.

Since the targeting effect of film delivery systems may have practical implications with regard to ophthalmic drug therapy, it is recommended that more drug examples be investigated to further substantiate the findings presented here.

The result that the effect of the ophthalmic drug delivery system may be so dramatic as to influence the deposition pattern of the drug in ocular tissues is rather unique. This phenomenon may, however, be understood in the light of the unique property of the eye with regard to the relative deficiency of the physiological transport organ, and the transportation network, namely, the plasma and the circulatory system, respectively. This deficiency brings about a situation which is very different to that given for systemic drug therapy.

Ophthalmic drug bioavailability was assessed by two parameters, namely, extent and rate of drug absorption.

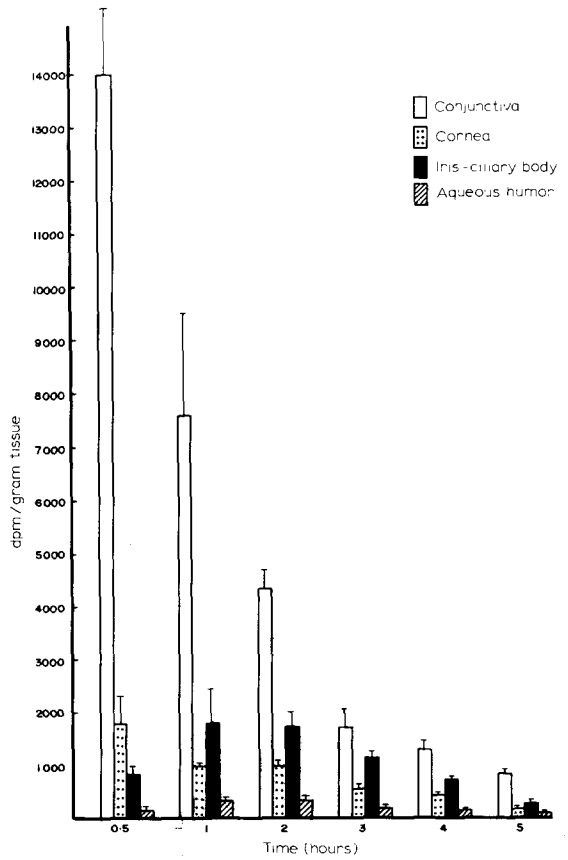


Fig. 6. Disposition of dexamethasone in ocular tissues following application of ophthalmic film delivery system (ethyl cellulose).

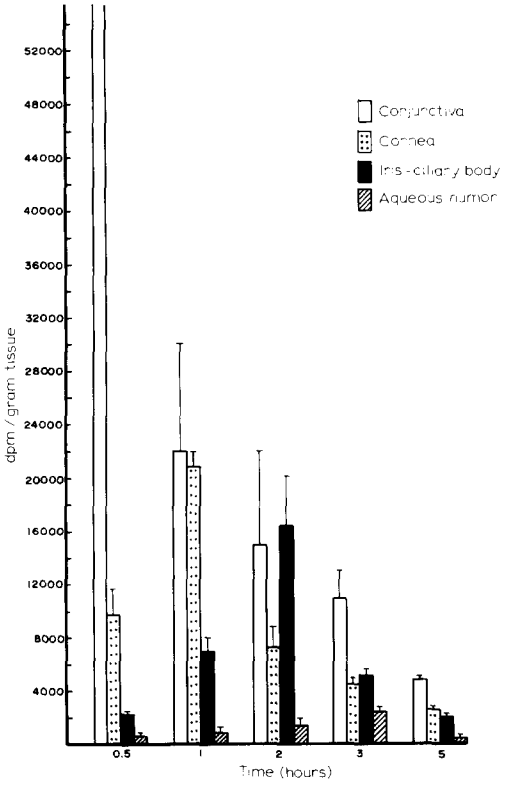


Fig. 7. Disposition of dexamethasone in ocular tissues following application of ophthalmic film delivery system (gelatin/formalin).

The extent of dexamethasone absorption was assessed by the area under the concentration–time curve for the anterior segment of the eye tissues.

Table 3 shows the values of the *AUC* for the tissues of the anterior segment following the application of dexamethasone as suspension or in an ophthalmic film delivery system. The data show that the ophthalmic film delivery systems, in general, bring about a considerable increase in the degree of drug absorption compared to the suspension dosage form. The enhancement of total drug bioavailability takes place to a different extent depending on the nature of the base polymer and additive. This increase may be as high as 32-fold in the case of PVA/cholesterol-based films or 24-fold in the case of HPC-based films. The increase in extent of drug absorption may be less pronounced as in the case for ethyl cellulose-based film (~ 3-fold) and Eudragit RL/RS.100 (~ 7-fold).

The different film delivery systems may be arranged in terms of their effect on enhancing the bioavailability of dexamethasone in the total eye tissues in the following order: PVA/cholesterol > hydroxypropyl cellulose > PVA/ benzalkonium chloride > gelatin > cellulose acetate phthalate > gelatin/ formaldehyde > Eudragit RL/RS.100 > ethylcellulose (Eudragit Rspm, Eudragit E).

The differences between these films and the suspension with regard to the total area under the curve are statistically significant ($P = 0.001$ in 3 cases, $P = 0.01$ in 3 cases, $P = 0.05$ in 2 cases) as shown in Table 4.

In the case of gelatin or ethyl cellulose-based films, however, the differences from the suspension are statistically insignificant. On the basis of the significance test, the above-mentioned rank order reduces to: polyvinyl alcohol/cholesterol

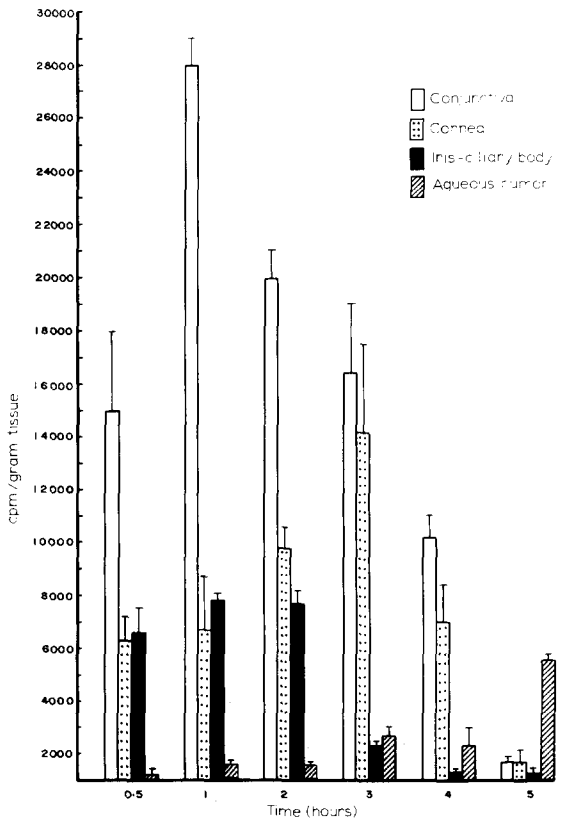


Fig. 8. Disposition of dexamethasone in ocular tissues following application of ophthalmic film delivery system (Eudragit RSPM).

TABLE 3

*AUC for dexamethasone concentration following application of dexamethasone as suspension and in an ophthalmic delivery system*

In parentheses are given the values of S.E.

| Preparation | *AUC* ((dpm/g tissue) · h) | | | | |
|---|---|---|---|---|---|
| | Conjunctiva | Cornea | Iris-ciliary body | Aqueous humor | Anterior segment |
| Suspension | 11,125 (1018) * | 2513 (368) | 6694 (573) | 1658 (607) | 2730 (158) |
| Polyvinyl alcohol/cholesterol | 196,482 (5219) | 187,145 (4219) | 18,291 (494) | 14,346 (956) | 88,605 (2060) |
| Polyvinyl alcohol/ benzalkonium chloride | 167,816 (4617) | 44,855 (5686) | 14,497 (2926) | 4418 (1099) | 36,865 (8907) |
| Gelatin | 30,891 (7617) | 14,735 (4481) | 9031 (4087) | 4497 (1317) | 33,084 (19,942) |
| Eudragit RL/RS100 | 33,453 (2724) | 21,554 (814) | 51,883 (3508) | 6360 (1134) | 19,864 (1967) |
| Eudragit RSPM | 72,503 (1317) | 36,597 (9031) | 21,136 (201) | 9072 (242) | 1936 (1058) |
| Gelatin/formalin | 58,651 (4302) | 39,136 (2109) | 42,107 (502) | 6924 (651) | 23,691 (1827) |
| Cellulose acetate phthalate | 26,016 (252) | 16,667 (1570) | 23,274 (771) | 3141 (163) | 9742 (339) |
| Hydroxy propyl cellulose | 107,948 (5549) | 9689 (229) | 7709 (988) | 1824 (113) | 66,812 (14,398) |
| Ethyl cellulose | 20,793 (3540) | 3468 (19) | 4833 (1097) | 1424 (433) | 7763 (4003) |
| Eudragit E | 4885 (97) | 3081 (153) | 2551 (162) | 668 (122) | 1560 (216) |

TABLE 4

*Significance of differences between ophthalmic film delivery systems and suspensions with regard to AUC for dexamethosane*

| Comparison | Conjunctiva | | Cornea | | Iris-ciliary body | | Aqueous humor | | Anterior segment | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *t* | *P* | *t* | *P* | *t* | *P* | *t* | *P* | *t* | *P* |
| Suspension and polyvinylalcohol/ cholesterol | 32 | 0.001 | 43 | 0.001 | 15 | 0.001 | 11 | 0.001 | 3.7 | 0.001 |
| Suspension and polyvinylalcohol/ benzalkonium chloride | 33 | 0.001 | 7.4 | 0.001 | 2.6 | 0.05 | 2.2 | 0.1 | 3.8 | 0.01 |
| Suspension and gelatin | 2.6 | 0.05 | 2.7 | 0.05 | 0.6 | (i) | 1.9 | 0.2 | 1.5 | 0.2 |
| Suspension and gelatin/formalin | 10.7 | 0.001 | 17 | 0.001 | 46 | 0.001 | 5.9 | 0.01 | 11 | 0.001 |
| Suspension and hydroxy-propylcellulose | 17 | 0.001 | 16.5 | 0.001 | 0.9 | (i) | 0.26 | (i) | 4.5 | 0.01 |
| Suspension and ethylcellulose | 2.6 | 0.05 | 2.6 | 0.05 | 1.5 | (i) | 0.3 | (i) | 1.25 | 0.3 |
| Suspension and Eudragit E | 6 | 0.001 | 1.4 | 0.1 | 6.95 | 0.001 | 1.6 | 0.2 | 4.4 | 0.01 |
| Suspension and Eudragit RL/RS100 | 7.76 | 0.001 | 21.31 | 0.001 | 12.71 | 0.001 | 3.65 | 0.05 | 8.7 | 0.001 |
| Suspension and Eudragit RSPM | 36 | 0.001 | 3.7 | 0.01 | 23 | 0.001 | 11.3 | 0.001 | 0.7 | 0.05 |
| Suspension and cellulose acetate phthalate | 14.1 | 0.001 | 8.77 | 0.001 | 17.2 | 0.001 | 2.35 | 0.1 | 2.74 | 0.05 |

TABLE 5

*Maximum concentration of dexamethasone in different ocular tissues following application of suspension or ocular inserts*

In parentheses are given the values of S.E.

| Formula | Maximum conc. of dexamethasone (dpm/g tissue) in | | | | |
|---|---|---|---|---|---|
| | Conjunctiva | Cornea | Iris-ciliary body | Aqueous humor | Anterior segment |
| Suspension | 3153 | 895 | 2273 | 184 | 765 |
| | (1452) | (311) | (717) | (54) | (382) |
| Polyvinyl alcohol/cholesterol | 147,407 | 85,257 | 7686 | 6118 | 48,912 |
| | (5207) | (5745) | (829) | (417) | (1781) |
| Polyvinyl alcohol/Benzalkonium chloride | 85,706 | 27,009 | 8730 | 2667 | 14,927 |
| | (4395) | (5999) | (1798) | (612) | (7463) |
| Gelatin | 10,624 | 20,274 | 4159 | 1369 | 7898 |
| | (4932) | (4762) | (1472) | (725) | (3601) |
| Gelatin/formalin | 22,275 | 21,396 | 16,300 | 1458 | 11,001 |
| | (9992) | (281) | (33) | (24) | (2278) |
| Hydroxypropyl cellulose | 54,927 | 12,513 | 4622 | 758 | 17,999 |
| | (3730) | (840) | (533) | (118) | (8709) |
| Ethyl cellulose | 14,112 | 1826 | 1794 | 369 | 2443 |
| | (9434) | (548) | (446) | (171) | (1221) |
| Eudragit RL/RS100 | 10,621 | 5304 | 23,975 | 1874 | 5282 |
| | (2489) | (2565) | (3230) | (397) | (822) |
| Cellulose acetate phthalate | 8737 | 10,156 | 13,985 | 1321 | 3758 |
| | (430) | (7202) | (20) | (34) | (536) |
| Eudragit E | 1348 | 1175 | 990 | 155 | 574 |
| | (188) | (48) | (80) | (43) | (103) |
| Eudragit RSPM | 28,028 | 13,299 | 7984 | 5593 | 4644 |
| | (6607) | (3937) | (140) | (148) | (731) |

> hydroxypropyl cellulose > polyvinyl alcohol/ benzalkonium chloride > cellulose acetate phthalate > gelatin/ formaldehyde > Eudragit RL/ RS.100.

In only 2 cases did the ophthalmic film drug delivery system bring about a suppression of drug bioavailability into the anterior segment. This took place with Eudragit E and Eudragit RSPM based films (Table 3).

The peak concentration of dexamethasone was taken as an indication of the absorption rate into the eye tissues. The peak dexamethasone concentrations in the anterior segment of the eye, post application of dexamethasone in suspension form or incorporated in an ophthalmic film delivery system are presented in Table 5. The data demonstrate that, with the exception of the Eudragit E-based film, the ophthalmic film delivery systems bring about an increase in peak dexamethasone concentration. This increase in highly dependent on the composition of the ophthalmic film delivery system. The increase is 64-fold at maximum and may be as low as 3-fold at minimum.

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