INVFSTIGATION OF THE SUSTAINED RELEASE OF PILOCARPINE FROM POLY-HEMA MATERIAL IN SUSPENSION FORM

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Introduction

A common approach to reduce (i) the incidence and severity of local and any systemic side effects, (ii) the difficulty of administration, and (iii) the number of applications per day of pilocarpine eyedrops, the conventional treatment of chronic glaucoma, has been to sustain the delivery of the drug to the eye (Chandrasekaran et al., 1978). Phillips and Stone (1990) state that a low water content lens, such as one made from poly-hydroxyethylmethacrylate (HEMA) material, controls intraocular pressure well for up to 12 hours of wear. However, clinical experience, mainly with the Pilocarpine Ocusert^{R}, has shown that solid dosage forms suffer from problems of insertion, retention and discomfort, particularly in elderly patients (Salminen 1987; Conn and Langer, 1984). It has in fact been suggested that a critical element in achieving successful commercial use of sustained release systems would be to formulate them in eyedrop rather than insert form (Conn and Wise, 1984). For this reason, tests were carried out to investigate the possibility of using an aqueous suspension of pilocarpine-loaded poly-HEMA material as an alternative to a lens in sustaining the release of pilocarpine.

Rationale for Experimental Work

Discs (taken to represent lenses) and entities (taken to represent suspensions) in the form of particles (of approximately the same thickness as discs), scrapings and finely-cut (f.c.) scrapings, of a weight and drug content equivalent to that of a disc, were loaded to steady state conditions with pilocarpine and their release characteristics compared. The release profile of the disc was assumed to be that required for optimum therapeutic activity. It was of course understood that by using the same weight and drug content for discs and entities there would be less chance of obtaining the same profile. However, the results were used to pinpoint those parts in the profile of the discs most affected by the increase in surface area. Recommendations on how to modify these parts were then proposed. The effect of different loadings of pilocarpine (obtained by soaking in solutions of a different concentration) was also studied. 2 preliminary studies were also carried out:

1) to test the compatibility of poly-HEMA material and pilocarpine hydrochloride since no literature to test their compatibility could be found, and

2) to investigate the uptake characteristics of pilocarpine by poly-HEMA in order to determine the time required by discs and entities to reach steady state with different loadings of pilocarpine. Hillman (1974) had stated that a prolonged soak to a state of equilibrium produced a more standardised form of lens material.

Methodology

Experiment 1:

Compatibility of Poly-HEMA Material and Pilocarpine hydrochloride

6 discs of approximately the same thickness (0.503±0.002mm) and UV-visible light transmission but with the same weight and diameter, were examined for gross irreversible damage after (i) immersion for a week at room temperature in a 10% w/v pilocarpine solution and (ii) extensive twice daily washing with normal saline for 2 weeks. Changes in diameter, thickness, colour, UV-visible light transmission and deposit formation were used as a way to examine for permanent damage:

Experiment 2:

Uptake characteristics of Poly-HEMA Material in Suspension Form

Discs and entities were each soaked in freshly prepared solutions of concentration 1,2, and 4% w/v for a period of time ranging from 3 to 48 hours, maintained at a temperature of 20°C in a water bath. They were then transferred to 5ml aliquots of distilled water and left for another 24 hours. Filtration was carried out prior to transfer in the case of particles, scrapings and f.c. scrapings. It was assumed that the amount of drug released in each 5ml fracton would be propotional to the amount of drug absorbed in a particular period of time. Steady state conditions were assumed to have been reached when drug release in 24 hours was practically constant. Analysis of drug release into each 5ml fraction was carried out by a colorimetric method.

Experiment 3:

Release characteristics of Poly-HEMA Material in Suspension Form

Charged discs and entities were placed separately in 5ml aliquots of distilled water, maintained at 20°C. They were then successively

transferred, at intervals of time ranging from 0.5 to 31.5 hours, to fresh aliquots of distilled water. Analysis of drug release into each 5ml fraction was carried out by the same above-mentioned colorimetric method.

For each experiment, the procedure was carried out twice and the results averaged.

Results

Experiment 1:

Compatibility of Poly-HEMA Material and Pilocarpine Hydrochloride

No deposits and no changes in the colour and diameter of the discs were found. Very small changes in the thickness and spectrophotometric readings were detected.

Experiment 2:

Uptake characteristics of Poly-HEMA Material in Suspension Form

Size did not appear to have affected the total amount of drug absorbed. However, increasing the concentration of the soaking solution from 1% to 4% w/v was found to have increased (i) the total quantity of drug taken up (the increase was found to be 1.19 and 1.43 per cent when soaked in 2% and 4% w/v solutions respectively, as compared to soaking in a 1% w/v solution) and (ii) the time of soaking required to reach steady state conditions by both discs and entities. The rate of uptake was observed to follow the order of f.c. scrapings > scrapings > particles > discs.

Experiment 3:

Release characteristics of Poly-HEMA Material in Suspension Form

It was found that:

1) the release profiles of both the discs and the entities followed an exponential decay pattern, that is, an initial burst release in the first half hour of soaking, which was followed by a rapid drop in pilocarpine release an hour later, after which the release rate

continued to decline - Figure 1 illustrates the typical release profiles of the discs and the entities;

2) increasing the drug content produced (i) an increase in the initial burst followed by a longer sustained release of pilocarpine to higher levels and (ii) an increase in the total amount of pilocarpine released, and

3) reducing the discs into smaller entities caused (i) an increase in the initial burst which was followed by a heavier drop in pilocarpine release an hour later (the particles produced increases of 14.92, 15.02 and 15.08 per cent in the burst release when presoaked in 1, 2 and 4% w/v solutions respectively, while the f.c. scrapings produced increases of 21.72, 25.85 and 25.66 per cent; as regards the drop, the particls caused decreases of 42.55, 32 and 36.69 per cent when presoaked in 1, 2 and 4% w/v solutions respectively, while the f.c. scrapings showed decreases of 50.48, 53.35 and 50.71 per cent), (ii) a more prolonged release of the drug and (iii) an increase in the cumulative amount of pilocarpine eluted; the order of increase was observed to be: f.c. scrapings > scrapings > particles > discs (Table 1).

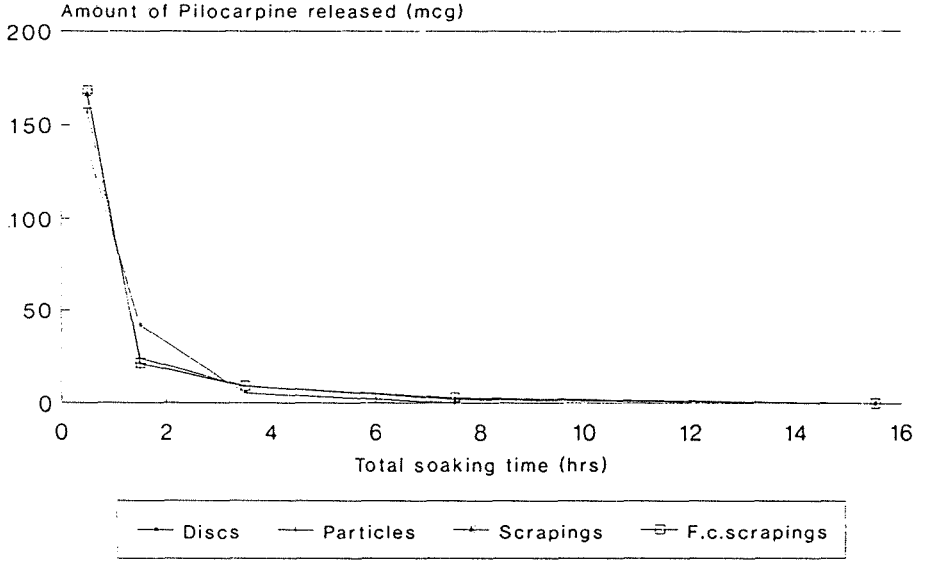
Table 1: Total elution time and Cumulative amount of pilocarpine released for discs and entities as a function of the concentration of the presoaking solution (%w/v)

	1% w/v		2% w/v		4% w/v	
	TET* (hrs)	CAR+ (mcg)	TET (hrs)	CAR (mcg)	TET (hrs)	CAR (mcg)
Discs	7.5	184	15.5	248.3	31.5	313.05
Particles	15.5	193.45	31.5	257.55	63.5	324.55
Scrapings	15.5	199.4	31.5	261.7	63.5	327.05
F.C. Scrapings	15.5	200.4	31.5	263	63.5	327.4

* TET = Total elution time

+ CAR = Cumulative amount of pilocarpine released

Fig. 1: Comparison of Pilocarpine Release from Discs & Entities presoaked to steady state in a 1% w/v solution



Discussion

As expected, the results indicate that on the same weight and drug content basis, an aqueous suspension would not be a suitable alternative to a lens. It is anticipated that the increase in the burst release could enhance the severity of the local side effects of the drug, such as blurred vision and browache; on the other hand, the heavier drop in pilocarpine release an hour later could result in the earlier elution of therapeutically ineffective levels of the drug. In addition, the results also imply that entities smaller than the ones studied, which would presumably be more suitable for placement in the eye, would further amplify the burst and hence the drop in pilocarpine release.

In the light of the above findings, it was reasoned that the burst release effect should be reduced. It is suggested that there are 2 main ways how this effect could be decreased:

1) retaining the same weight and lowering the drug content or using a reduced weight and the same concentrated soaking solution: it is in turn thougt that since an increase in drug content has been observed to increase the sustained release of pilocarpine to higher levels, further reducing the weight of the lens material but at the same time using a higher drug content, could also result in (i) an improvement in the sustained release effect, and (ii) a release profile even nearer to that of a lens, and

2) adding crosslinking agents such as allyl methacrylate and ethylene dimethacrylate to poly-HEMA: such agents have been used to slow drug release from lens material.

The most unexpected result was that the entities provided a more prolonged release of pilocarpine than discs. The increase in the cumulative amount of pilocarpine eluted by the entities when compared to that of discs, might suggest that an amount of drug in the discs, most likely from the deep parts of their interior, was not being released. It also indicates that the diffusional path in a disc can be relatively so large that that amount of drug would probably take too long to reach its surface and be eluted. Hence, reducing a disc to smaller entities decreased this diffusional path and improved its capacity to provide additional drug for a longer period of time. However, there appears to be a limit to how much the size of the entities can be reduced and the sustained release effect prolonged. This was manifested by the particles and the scrapings

and f.c. scrapings having the same elution time (notwithstanding their difference in surface area), whether presoaking had been done in a 1,2 or 4% w.v solution.

References

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