Nanocarriers for Ocular Drug Delivery - the importance of drug loading

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ABSTRACT SUMMARY

A nanocarrier based on large unilamellar vesicle (LUV) with an average size of 100 nm has been developed for sustained delivery of latanoprost in the anterior eye segment. Animal studies have shown that a single sub-conjuctival injection of this formulation results in stable control of intra-ocular pressure (IOP) for over 90 days. The key to such a long duration of action is the extent of drug loading that is possible without disruption of vesicle structure. Additional studies to explain the mechanism of drug-vesicle interactions, that shed light on the high drug loading, will be presented.

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness in the world. The modifiable risk factor for glaucoma, IOP, is controlled by topical drugs which suffers from poor bioavailability and frequent administration. There is a definite need for sustained delivery of drugs for this condition. The successful development of such a sustained-delivery system to date has been largely hampered by insufficient drug loading in the carrier, which is ideally sub-micron sized.

EXPERIMENTAL METHODS

The drug-incorporated nanocarriers (LUVs) were prepared by the film rehydration technique. The carriers were characterized for size using dynamic light scattering; molar masses as well as number of lipid molecules/vesicle were obtained using static light-scattering. Isothermal calorimetry (ITC) was utilized to study the drug-lipid interactions. An animal study was carried out in white New Zealand rabbits to evaluate the effects of both topical drops and the nanocarrier on IOP.

RESULTS AND DISCUSSION

The results show that stable IOP control is achievable for up to 90 days with a single sub-conjuctival injection of the latanoprost-loaded LUV. The average size of the LUVs was 100 nm and was unaltered with drug incorporation or release. See Fig 1. Approximately 10% of drug by weight was incorporated into the LUV and released over 60 days. The ITC data clearly showed two sites of interaction, one with the polar head group and a second one with the lipid backbone.

Transmission electron microscopy (cryo-TEM) shows the particles to be nearly spherical as well, with without added drug. See Fig 2. Addition of up to 10% of drug by weight does not disrupt the spherical shape, neither does it cause aggregation. This is substantially higher drug loading than usually reported.

Fig 1: Size distribution of drug-incorporated vesicles before (red) and after (green) release of drug from vesicles; Malvern zetasizer data

Fig 2: Cryo-TEM pictures of latanoprost-loaded liposomes
Based on a drug to lipid ratio of 0.1, the release curves obtained in vitro are shown in Fig 3.

![Graph showing release curves](image)

**Fig 3:** Daily release rate for latanoprost-loaded liposomes compared to eye drops (5% bioavailability)

When injected sub-conjunctivally into rabbit eyes, the intra-ocular pressure is lowered over 90 days in rabbit eyes. Compared to eye drops, the injected nanocarriers show enhanced IOP control. In addition no side-effects, such as eye reddening or inflammation, is noted over the 90-day period.

![Images of injection and bleb formation](image)

**Fig 4:** injection of drug-loaded nanocarrier in rabbit eyes: A: sub-conjunctival injection; B-bleb formed immediately after injection; C- 30 days post-injection; D-30 days of eye drops in rabbit eye

The drug-vesicle interactions were studied using isothermal calorimetry. Special methods were employed to assess the interaction energies. Model fitting allowed the identification of specific interactions, which will be discussed in the presentation.

**CONCLUSIONS**

For drugs of moderate potency, a significant percentage of the carrier must be loaded with drug. For our selected liposomal formulation, we were able to incorporate up to 10% by mass of the liposome, without disrupting the spherical structure of the vesicle or rendering it unstable. This level of drug loading leads to efficacious control of the intra-ocular pressure for up to 90 days with a single sub-conjunctival injection in rabbits.

**REFERENCES**