Mucoadhesive Nanoparticles for Topical Ocular Drug Delivery

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Introduction

Eye drop solutions undergo rapid clearance from the corneal surface due mainly to tear turnover, which is responsible for the clearance of about 95% of administered drugs. Drugs must, therefore, be administered frequently (i.e. twice daily) in order to achieve therapeutic efficacy. Frequent administration, however, increases the potential for side effects and the cost of therapy, while reducing patient compliance.

Formulations using NPs as drug carriers have been proposed to overcome these limitations [1-2]. Dextran-based amphiphilic block copolymer, poly(D,L-lactide)-b-Dextran (PLA-Dex), can self-assemble into core-shell nanoparticle (NP) structures. PLA-Dex NP sizes can be precisely tuned between 20 to 60 nm in diameter by simply adjusting the molecular weight of the two polymer chains [3]. Dextran coated NPs showed excellent colloidal stability in physiological media [3], and their abundant functional hydroxyl groups can be modified to target the ocular surface (mucoadhesion), and thus prolong corneal retention of the drugs encapsulated in the NPs by circumventing the precorneal clearance mechanisms.

In this study, PLA-Dex NPs were surface functionalized with phenylboronic acid (PBA) molecules which can specifically target the sialic acid residues on the ocular mucosa. Cyclosporine A, which is prescribed for dry eye disease, was used as a model drug for *in vitro* evaluation.

Materials and Methods

PLA (Mw ~ 20 kDa) and Dextran (Mw ~ 10 kDa) were conjugated using previously reported method [3]. Cyclosporine A (CycA), 3-Aminophenylboronic acid monohydrate (PBA) and Type III mucin from porcine stomach (sialic acid 0.5 - 1.5%) were used in this study. Simulated tear fluid (STF) was prepared for the *in vitro* release experiment [4].

PLA-Dex NP surface modification was performed in three step: first, PLA-Dex NPs were formed through nanoprecipitation method, second, the Dextran surface was oxidized using $NaIO_4$ to yield reactive aldehyde groups, and third, the aldehyde groups were conjugated with the amine groups of PBA in the presence of $NaCNBH_3$.

The PBA conjugation efficiency on the PLA-Dex NP surfaces were evaluated along with the resulting particle sizes. The NPs' ability to encapsulate and release Cyclosporine A was analyzed. Using an *in vitro* method, NPs' adhesiveness toward mucin particles were also studied.

Results and Discussion

PBA conjugation efficiency on the surface of the NPs was dependent on the amount of PBA molecules added in the conjugation reaction. PBA surface modification decreased the NP size compared to unmodified NPs (Figure 1). The size and the spherical morphology was further verified using Transmission Electron Microscope (TEM). The size decrease may be due to a decrease in hydrophilicity of the Dextran as a result of PBA modification. The packing number of the PLA-Dex may also have been altered due to the increase in the apparent volume ratio between the hydrophilic and hydrophobic chains of PLA-Dex polymers.

Formulation	PBA:Dex[a)] (mol%)	Diameter (nm)
PLA-Dex	0	47.9 ± 0.5
PLA-Dex_10PBA	2.85 ± 0.03	27.5 ± 0.9
PLA-Dex_40PBA	12.2 ± 0.2	26.7 ± 0.1
PLA-Dex_160PBA	22.9 ± 0.3	25.2 ± 1.0
PLA-Dex_320PBA	34.6 ± 0.2	28.1 ± 0.3

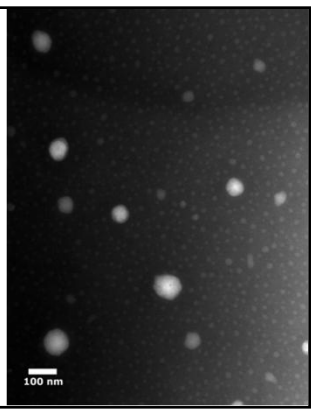

Figure 1. [a)]Mol% of PBA:Dextran monomers. TEM image of PLA-Dex_320PBA NPs (Right).

Maximum loading of 13.7wt% CycA was achieved with PBA modified PLA-Dex NPs, which allows therapeutically relevant dosage easily achievable by adjusting the NP/drug concentration in the formulation. In *in vitro* release studies, both PBA modified and unmodified NPs showed a total release for up to 5 days (Figure 2, left). Thus, these NPs may potentially reduce the administration frequency (i.e. from twice daily to about once every 5 days). *In vitro* periodic acid/Schiff base staining method was used to predict the mucin-NP interaction [5]. PBA modified NPs showed improved mucin-NP interaction compared to unmodified NPs. However, excess PBA (PLA-Dex_PBA) showed decrease in mucoadhesion possibly due to the compromise in colloidal stability. The extent of mucin-NP interaction is significantly higher than similar NPs (chitosan based NPs and thiolated NPs) reported in the literatures [5]. The current results show promising potential of PLA-Dex_PBA NPs to improve the ocular bioavailability of drugs for front-of-the-eye delivery.

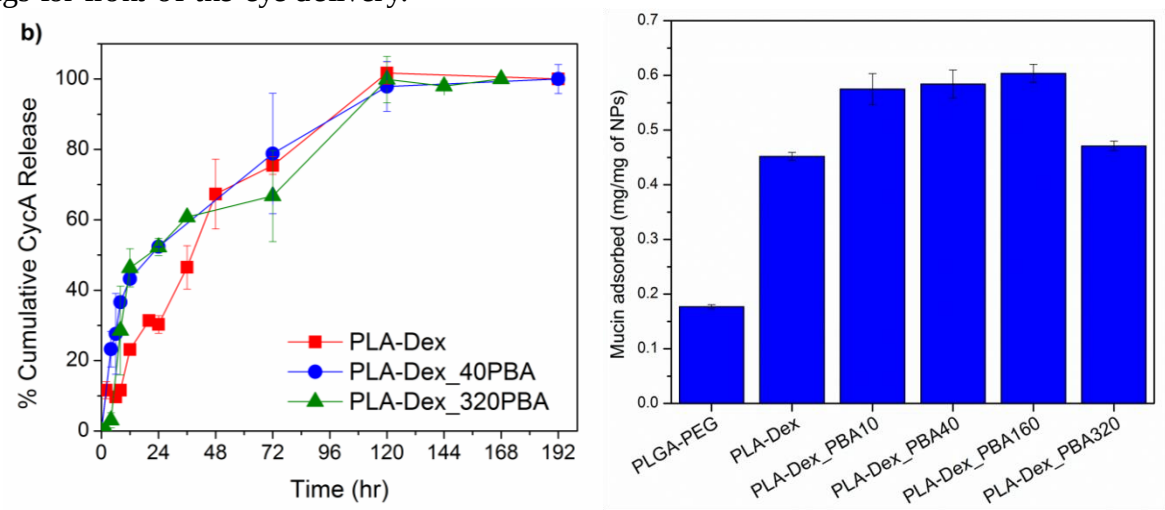

Figure 2. In vitro CycA release from PLA-Dex_PBA NPs (left). In vitro mucoadhesion analysis of PLA-Dex_PBA NPs (right).

References

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