Development of Novel Formulation Excipients for Oral Hygienic Products

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ABSTRACT SUMMARY

The focus of this project is to develop novel formulation excipients for oral hygienic products, which could retain active ingredients on tooth surface. To achieve this goal, pyrophosphate (PPI) was conjugated to the chain termini of Pluronic P123. The modified P123 (PPI-P123) forms tooth-binding micelles (TBM), which could easily incorporated antimicrobials (e.g. triclosan). Competition of salivary proteins with TBM for binding sites on hydroxyapatite (HA) was found to be limited. In in vitro cariogenic biofilm study, the TBM treatment showed significantly better efficacy than the controls. No toxicity was found to be associated with PPI-P123. Collectively, these data suggest that PPI-P123 represents a new class of functional excipients, which could greatly improve current oral hygienic products.

INTRODUCTION

Mature dental plaque is a complex multispecies biofilm that grows on the tooth surface and is embedded in a protective matrix of host and bacterial polymers [1]. It initiates dental caries and periodontal inflammation by converting dietary carbohydrates into demineralizing acids or stimulating uncontrolled inflammation and bone resorption in surrounding tissues [2]. Antimicrobial therapy is still one of the most effective management strategies against dental plaque related diseases [3]. One major concern with antimicrobial therapy is, however, the inability to maintain the minimum inhibitory concentration (MIC) of the drug on tooth surface microenvironment. To address this issue, our group has successfully developed a tooth-binding micelle delivery system (TBM), which could quickly bind to the tooth surface upon exposure and gradually release encapsulated active compounds over time. At the center of this technology is the tooth-binding Pluronic, which was synthesized by conjugating a tooth-binding moiety to the chain termini of Pluronic copolymers [4, 5]. This approach not only increases the water solubility of hydrophobic compounds, but also enhanced their retention on the tooth surface. During the initial development of this functional excipient, alendronate (anti-osteoporosis drug, ALN) was used as the prototype tooth-binding moiety. The clinical translation potential of such excipient, however, is limited due to the concern over ALN-associated side effects (e.g. ONJ or osteonecrosis of the jaw). To address this safety concern, we replaced ALN with pyrophosphate (PPI), which has similar tooth-binding capability as ALN, but degrades into phosphate in vivo. Using PPI-conjugated Pluronic P123 (PPI-P123), we prepared triclosan-containing TBMs and characterized their binding kinetics and drug release profiles in the presence of saliva. The anti-plaque efficacy of TBMs was evaluated using an in vitro biofilm model. Acute and chronic toxicology studies were preformed to validate the safety profile of PPI-P123.

EXPERIMENTAL METHODS

The conjugation of PPI to the chain termini of P-123 is straightforward as shown in Fig 1. It was used to form triclosan-loaded TBM by direct dissolution as previously described [4]. The in vitro binding of TBM to tooth surface and the potential impact of human saliva to the binding process was evaluated using hydroxyapatite (HA) powder or discs as model tooth surfaces. The release of triclosan from TBMs was evaluated using a dialysis method. The binding stability of TBMs on HA surface was evaluated by measuring TBM detachment from HA surface in the presence human saliva or salivary enzymes over time. HA discs were treated with TBM and then incubated with S. mutans UA159 bacteria culture for 48 h to
evaluate its potential in biofilm prevention. It was also used to treat 48 h old preformed biofilm to verify its treatment efficacy. To understand its safety profile, PPi-P123 was given to SD rats through oral gavage as a single dose at 1000 mg/kg or daily doses at 5 mg/kg for 6 months to evaluate its acute and chronic toxicology, respectively.

RESULTS AND DISCUSSION

Neither acute nor chronic toxicity was found to be associated with PPi-P123. In the HA binding kinetic study, we found that the PPi-P123-based TBM has a very fast binding kinetics, with majority (~50% of total binding) of the binding occurred within 1 min. The TBM also demonstrated sustained, close to linear triclosan release (~1%/day), where the presence of human saliva had no impact on the releasing profile. The salivary proteins do compete with TBM for binding sites on HA disk. But the binding capacity can still be maintained at >60% (Fig 2A). The binding of the TBM to HA surface was found to be stable with only ~5% of TBM released after 24 h incubation with salivary enzymes or human saliva.

The PPi-P123-based triclosan-containing TBM was found with much stronger biofilm inhibition on HA surface than the non-binding micelle (NBM). Such efficacy was not altered in the presence of human saliva (Fig 2B-D).

CONCLUSION

Novel formulation excipient pyrophosphate-Pluronic P-123 (PPi-P123) has been successfully developed and found with excellent safety profile. Upon formulation with hydrophobic compounds (e.g. triclosan), the resulting micelle (TBM) demonstrated excellent binding potential to model tooth surface even in the presence of human saliva. When tested against cariogenic S. mutans biofilm, the TBM showed outstanding inhibition efficacy. Future application of such novel functional excipient in oral hygienic products (e.g. toothpaste, mouthrinse, etc) will greatly improve their clinical performance.

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