Mucoadhesive Surface Modification of PHEMA hydrogel for Ophthalmic Drug Delivery Application

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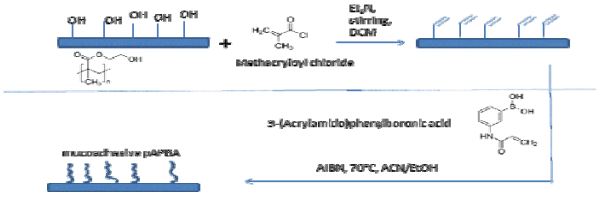
Statement of Purpose:
Using mucoadhesive biomaterials as drug delivery carrier can improve drug residence time, drug bioavailability and enhance special site specific targeting.[1] Recent studies found that Phenylboronic acid (PBA) has mucoadhesive properties which can facilitate drug delivery and cell adhesion due to interaction of the boron atom with N-acetyl groups and diol groups of mucins or polysaccharides to form a complex at neutral and weakly basic environments (at pH 7-9) such as that of the ocular mucosa (pH7.8). [2,3] Owing to its non-toxicity, non-antigenic property and good ophthalmic compatibility, poly(2-hydroxyethylmethacrylate) (pHEMA) has been widely investigated and used in ophthalmic applications in forms of contact lenses and drug delivery inserts.
In this study, 3-(Acrylamido)phenylboronic acid (APBA) was employed to modify surface of pHEMA hydrogel to enhance mucoadhesion facilitating drug delivery to the eye by promote drug bioavailability and site specific targeting. Also, polyAPBA on the surface can form a hydrophobic barrier layer to decrease diffusion of the water soluble drug, thus sustaining the drug release. For potential contact lens application, the polyAPBA modified mucoadhesive surfaces may further interact with polysaccharide wetting agents, creating a reloadable system to increase contact lens comfort.

Methods: Mucoadhesive modification was performed by surface grafting polyAPBA on pHEMA gel through a 2-step reaction (Scheme1).



Scheme 1: Synthesis of polyAPBA modified mucoadhesive surface

Firstly, to make surface polymerizable, the hydroxyl group on pHEMA surface was reacted with methacryloyl chloride in a weak organic base containing dichloromethane to attach the vinyl group on pHEMA surface. Due to existence of the vinyl group, APBA was further grafted to surface using thermal free radical polymerization methods. Thus a mucoadhesive layer formed on the hydrogel surface. ATR-FTIR and NMR were used to confirm polyAPBA grafting on the polyHEMA surface. Mucin labeled with I^{125} was used to quantify mucoadhesive interaction. Wetting agent (hyaluronic acid and hydroxypropyl guar (HPG)) interaction with surface was examined. Ophthalmic model drug dexamethasone and atropine release from the modified material were also investigated.

Results: PolyAPBA was successfully grafted to the hydrogel surface and the surface grafting was confirmed by ATR-FTIR and NMR. As show in Fig.1, the absorbance at 1550 nm which corresponds to the N-H bond in polyAPBA increased with increase of amount of polyAPBA grafting on the surfaces. Existence of polyAPBA formed in solution phase proved by NMR also provided an evidence of APBA polymerization. Due to the less hydrophilic nature of APBA, water contents and water contact angles of modified materials slightly decreased. As seen in Figure 2, after polyAPBA grafting onto pHEMA, mucin adsorption increased significantly, suggesting improved mucoadhesion. Slower and sustained release of these ophthalmic model drugs from these modified materials was also observed.

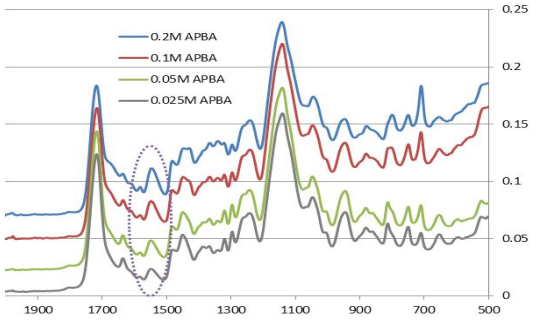


Fig.1: ATR-FTR spectra of polyAPBA modified materials

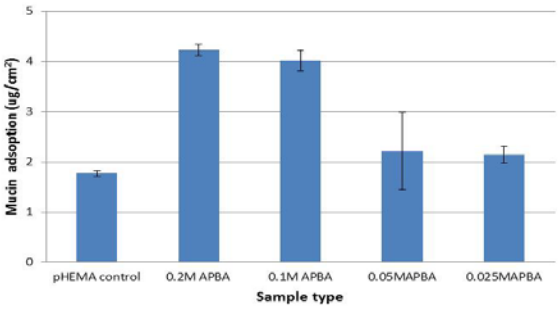


Fig.2: Mucin adsoption on polyAPBA modified polyHEMA surfaces

Conclusions: PolyAPBA was successfully grafted onto pHEMA hydrogel materials to form mucoadhesively modified hydrogel surfaces. Mucin interaction and wetting agent interaction with these materials suggest the potential applications on improving drug delivery and contact lens comfort. Same approach will be performed to prepare pHEMA mucoadhesive particle synthesis in next period.

References: 1. Khutoryanskiy V.V, Macromol. Biosci. 2011, 11, 748–764; 2. Zakir M. O. Hacettepe J. Biol. & Chem., 2008, 36 (2), 83-98; 3. Kuzimenkova M. V., Biosci. 2006, 6, 170–178