Phenylboronic Acid Modified Mucoadhesive Hydrogel Materials for Ophthalmic Drug delivery Applications

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Statement of Purpose: Mucosal membranes are the moist surfaces of various body cavities including respiratory, gastrointestinal, reproductive tracts and the nostrils, the eyes and the mouth. Mucoadhesion is the attractive interaction at interface between biomaterial and a mucosal membrane. Using mucoadhesive biomaterials in drug delivery can increase drug residence time, improve drug bioavailability, reduce administration frequency and enhance special site targeting.[1]

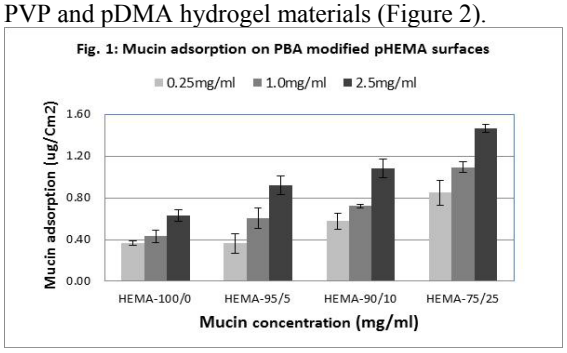
Recent studies suggest that boronate-containing materials exhibit mucoadhesive property to facilittate drug delivery and cell adhesion due to intermolecular interaction of boron atom with n-acetyl groups and diol groups of biomolecules, such as sugar, nucleotide, glycoprotein etc. [2,3] Mucosa tissues are coated with mucins which are high molecular weight glycoproteins and they play important role on mucoadhsion. Phenylboronic acid (PBA) is such a synthetic ligand which can form a complex with mucins by binding oligosaccharide side chains at neutral and weakly basic environment (at pH 7-9) where ocular mucosa (pH7.8) is. In this work, PBA is employed to modify bulk and surface of hydrogel ophthalmic materials including poly(2-hydroxyethylmethacrylate) (pHEMA), polyvinylpyrrolidone (PVP) and poly(*N*,*N*-Dimethyl allylamine) (pDMA) etc. to enhance mucoadhesion facilitating drug delivery to the eye.

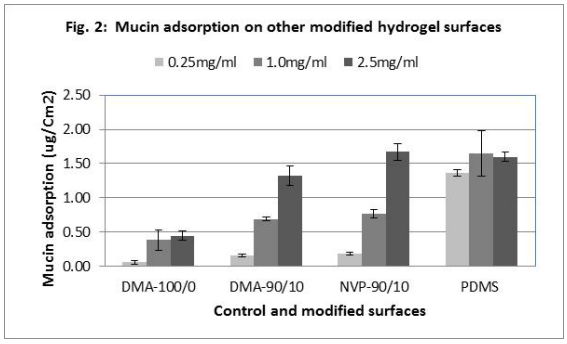
Methods: To prepare polymerizable PBA, acryloyl chloride reacted with 3-aminophenylboronic acid in basic aqueous solution to introduce vinyl group to PBA and form N-acryloyl-m-aminophenylboronic acid (NAAPBA) (Scheme 1). Due to existence of vinyl group, NAAPBA further copolymerized with other hydrogel monomers including HEMA, DMA, NIPAAm and NVP to introduce mucoadhesion to these ophthalmic biomaterials using UV initiated free radical polymerization method. Copolymerizing NAAPBA with methacrylic acid or acrylic acid can also further enhance bioaffinity due to negative charge adhesion effect. A method using PBA to modify hydrogel nanoparticles was also proposed.

Scheme 1: synthesis of N-acryloyl-m-aminophenylboronic acid

H-NMR was used to confirm formation of NAAPBA. Mucin was labeled with I^{125} using the iodine monochloride method. Mucin adsorptions on control and modified surfaces were quantified by gamma radiation intensity. Water content and water contact angle of materials were also examined.

Results: NAAPBA was successfully synthesized and the yield of NAAPBA was about 50%. NMR spectrum confirmed its structure (chemical shifts at 5.7, 6.3, 6.45, 7.2-8.0 and 10.0). Furthermore, the purified NAAPBA was used for UV initiated free radical homo-polymerization. Viscous liquid formed without adding crosslinker and gel material formed with adding crosslinker EGDMA. The homo-polymerization of NAAPBA provided an evidence of existence of vinyl group attached to the PBA molecules. Due to the less hydrophilic nature of PBA, water contents and water contact angles of modified materials slightly decreased (data are not shown here). As seen in Figure 1, after 10-25% of NAAPBA incorporation into PHEMA by copolymerization, mucin adsorption increased significantly. The same trend was observed from modified PVP and pDMA hydrogel materials (Figure 2).





Conclusions: NAAPBA was synthesized and it was further successfully incorporated into pHEMA, PVP and pDMA hydrogel respectively to form transparent modified materials. Increased Mucin adsorption on modified surfaces suggested mucoadhesion effect of these materials. Ophthalmic drug delivery using these mucoadhesive materials will be examined and mucoadhesive particle synthesis will be performed 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