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USE OF BORON IN CHROMATOGRAPHY AND DRUG DELIVERY : A REVIEW

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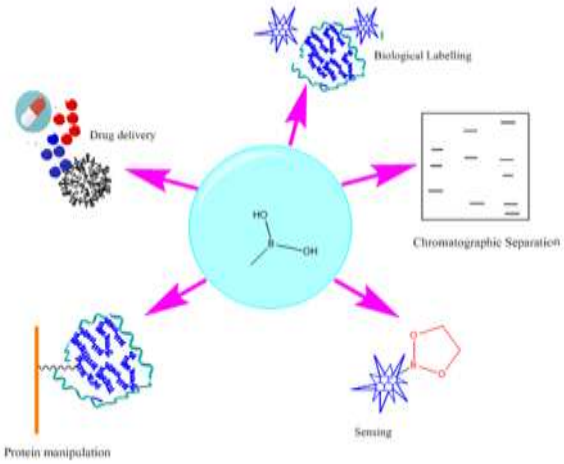
Graphical Abstract



Abstract:

The electron deficiency of boron imparts unique coordination capabilities to the element. Boron is versatile in its ability to interact with different classes of proteins due to its reversible covalent mode of interaction with nucleophilic residues. Boron based affinity materials for enriching bioactive molecules is an attractive strategy in targeted drug delivery, electrochemical detection of biologically significant molecules like saccharides, bio separation etc. Boronic acid ligand -functionalised materials such as various types of nano particles, bioactive glasses, polymeric scaffold etc were reported for inhibition against viral entry, biofilm formation, enhancing bone/soft tissue regeneration, construction of pH sensitive drug delivery nano vehicle, detection and separation of biologically significant molecules like saccharides etc.

Keywords: Boronate affinity material, boronolectin, phenylboronic acid, viral entry inhibition, intracellular delivery of therapeutics, biofilm inhibition, affinity chromatography

Introduction

Boronic acid derivatives forming reversible cyclic ester bond with diols has been extensively employed in diversified applications. The interaction of boronic acid and diol perceive remarkable scope as it leads to the formation of a class of sugar binding moieties called boronolectins. The binding of phenyl boronic acid (PBA) and the hydroxyl group of saccharides is covalent in nature and leads to the formation of five or six membered ring structure which are stable under alkaline condition. These interactions were used to develop therapeutic strategies in the treatment of viral

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infections like Hepatitis C virus (HCV), Human Immunodeficiency virus (HIV) etc., which features highly glycosylated envelope proteins. It is also used in the design of carriers for the intracellular delivery of proteins and drugs. PBA based - affinity chromatography was developed as a valuable tool for the specific capture of cis diol containing compounds and this property was utilized in the isolation of certain significant biomolecules and also as biosensors. Borate based glasses are receiving considerable interest for tissue engineering applications. This approach resulted in bioactive borosilicate and borate glasses with controllable degradation rates and bioactive potential by varying the SiO_2 to B_2O_3 ratio of the glass. Studies have shown that these have the capacity to support the proliferation of osteoblasts and find application as implants in local drug delivery in the treatment of osteomyelitis and regeneration of bones.

(I) Viral entry inhibitory agents based on boronic acid modified nanoparticles

The use of para substituted phenyl boronic acid attached on iron oxide, silica or diamond derived nanoparticles as viral entry inhibitors have been recently studied (1). The nano particle surfaces are initially modified by the 4-azidobenzoic ester functions. The azide terminated nano structures were then reacted with 4-[1-oxo-4-pentyn-1-yl) amino]phenylboronic acid by a Cu(1) catalysed Huisgen cycloaddition to result in the corresponding boronic acid modified nanoparticles (NP) called boronolectins.

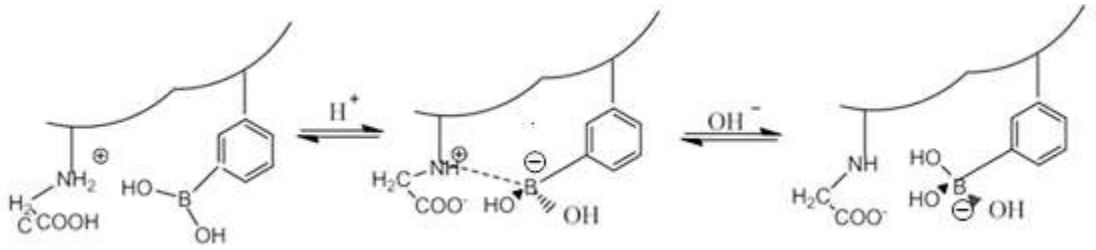

Fig.1 Boronic acids in nano materials for drug delivery

The potential of these sugar binding protein moieties as viral inhibitors was investigated against the Hepatitis C virus. These nano particles have viral entry inhibitory activity and exhibit much reduced cellular toxicity compared to alternate nano particles. The increased potential of drug conjugated nano particles is due to the presence of multiple copies of drug molecule on the surface of the particle (2-4). One of the important ligands in medicinal field is boronic acid. The ability of boronic acid to form tetravalent cyclic diesters with saccharides is the basis of its viral inhibition. The affinity of the boronic acid derived moieties to bind to saccharides make it a potential therapeutic system against Human Immunodeficiency virus HIV (5,6). There are reports which shows that significant number of PBA moieties are required to exhibit anti HIV activity. Such multivalent analogues of boronic acid can be prepared on a polymeric scaffold and it can prevent the attack of the HIV on the host cell and reduce the infection more effectively (6-9).

The contagiousness of the liver by HCV results in chronic infection which can lead to cirrhosis and hepatocellular carcinoma in the course of time. Several glycan recognizing proteins and natural products like pradimicin shows viral entry inhibitory activity to HCV due to their interaction with the glycosylated envelope of HCV. But the high cost, low stability and vulnerability to proteolitic cleavage and mitogenicity of these protein based therapeutics necessitated the need for a synthetic alternative antiviral drug against HCV.

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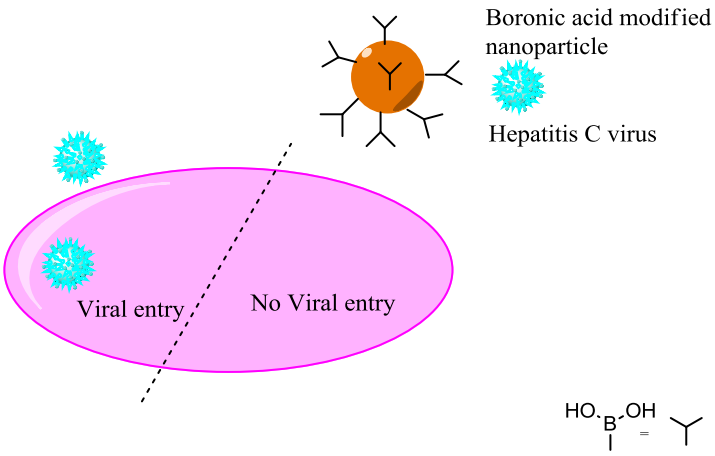

Fig.2 Boronic-acid-modified nanoparticles as HCV entry inhibitors

Nanoparticles of various types, conjugated with PBA have been developed recently which have the advantage of low cost of production and purification, stability and non-mitogenicity (10). When multiple copies of the relevant boronic acid species are introduced into the scaffold, there should be a corresponding increase in the affinity towards it from the glycosylated envelope of the virus. The NPs are specifically designed for behaving as HCV entry inhibitors. Magnetic, silica and diamond nano particles were subjected to the development of nano particle derived borono lectins which includes multiple surface conjugated boronic acid group. In addition to the enhanced ability to combine with glycoproteins all of them exhibit viral entry inhibitory activity of varying extend to HCV. Azido group was incorporated into the different types of nanoparticle surfaces by a series of chemical processes. The conversion of silica/diamond/magnetic - N_3 to boronic acid modified nanoparticles is achieved through click reaction by mixing it with 4-[(1-oxo-4-pentyn-1-yl) amino]phenylboronic acid and CuI (PPh_3)

The tuning of the nanoparticles towards the capture of saccharides requires the estimation of boronic acid function which can bind with the sugars. The diameter and surface area of the nano particles are in the ratio ND-BA< MP-BA < silica-BA. The lowest sugar binding efficiency of MP-BA in spite of its high surface area shows that affinity of the nano particles to saccharides is not a function of its surface area. The boronic acid modified nano particles bind with the saccharides depending on the number of available surface boronic acid units and its capability of forming cyclic diesters with sugars at physiological pH. Due to the high pKa value of the unsubstituted PBA, it combines with sugars effectively only at alkaline pHs (11). The substitution of the PBA with electronegative substituents on the phenyl ring (12), multimeric boronic acid units (13), dative bond formation with boron (14-16) etc will reduce the pKa value and hence extends its sugar binding ability to physiological pHs. The intermolecular interaction between the nitrogen and oxygen functions with neighbouring boronic acid groups due to multivalent occurrence of triazole functions and of residual surface hydroxyl groups decrease the pKa value of ND-BA and silica-NP-BA. But the low pKa value observed for MP-BA cannot be expected from this effect alone. The presence of the electron withdrawing NO_2 group on the phenyl ring of PBA (13) and the presence of unreacted amino group of dopamine on the surface which can act as a ligand forming dative bonds with boronic acid (17,18).

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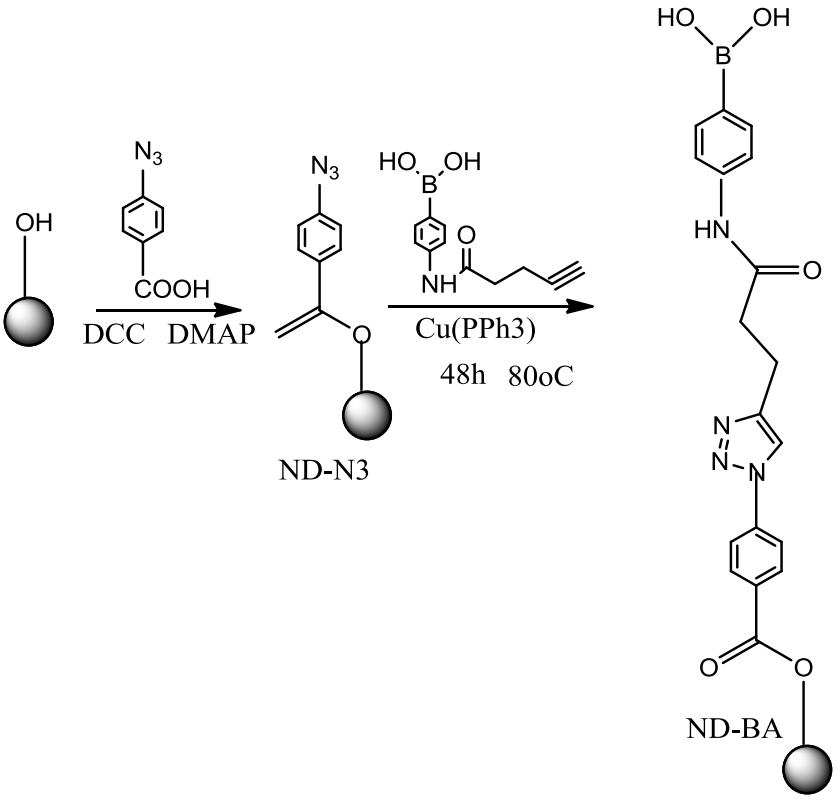

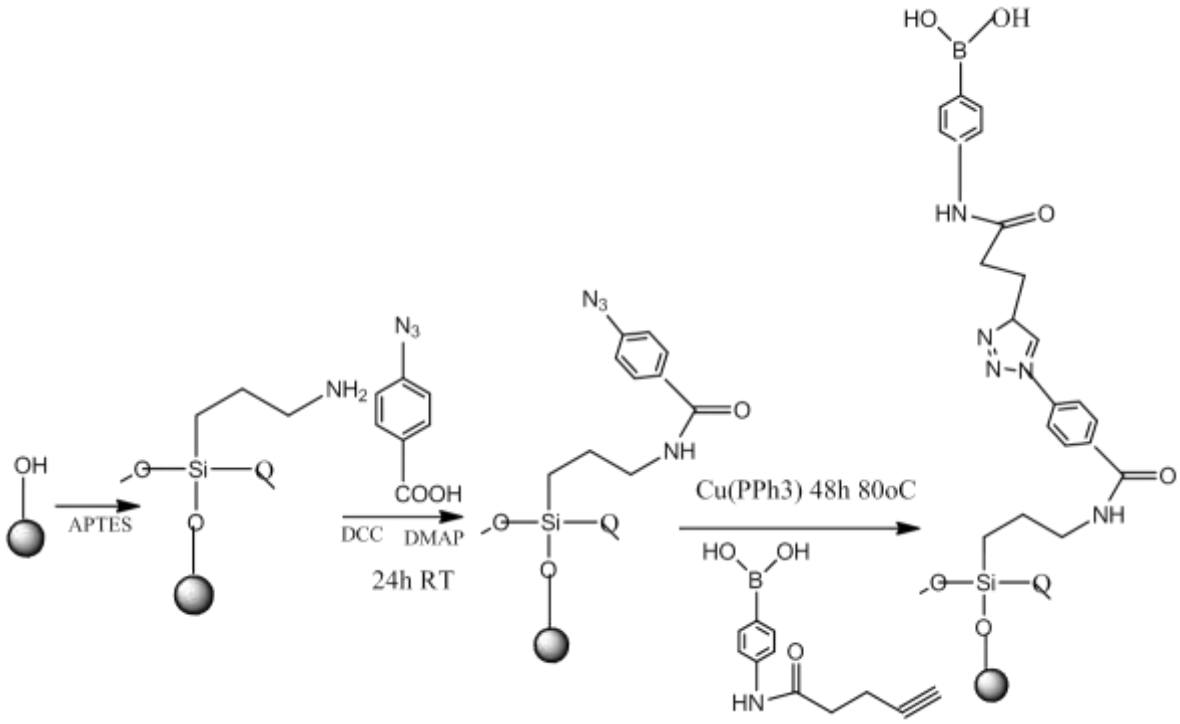

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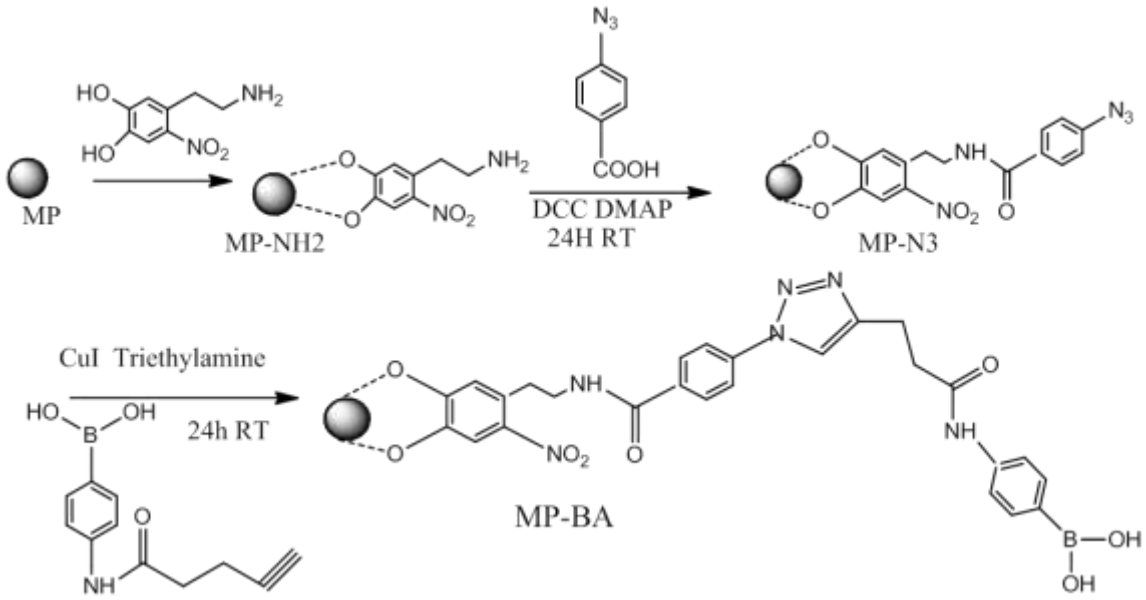

Fig.3 Schematic illustration of the fabrication of boronic-acid-modified nanoparticles

are factors which contribute to this. Cell viability studies of the NP-BAs were carried out on Huh-7 cell lines. The ND-BA and MP-BA do not exhibit any cytotoxicity even at their highest concentration, which render them highly biocompatible (18,19). The presence of nitro dopamine on the surface of the iron containing MP-BA will substantiate its cell viability and stability (20). Though silica-NP-BA shows cytotoxicity its effect depends on the physical, chemical and structural features of the specific particle formulation (21-23). An assay using modified JFHI virus to evaluate the potential of the various NP-BAs towards the inhibition of virus (24) shows that silica NP-BA has the highest viral entry inhibitory potential followed by ND-BA. Silica NP-BA is least biocompatible. The relatively lower viral entry inhibition of MP-BA is expected from the lower number of boronic acid functionality on the nano particle surface. Any of the nano particles without the boronic acid incorporation was not showing any HCV inhibition even at high concentration. Also no increase in the viral entry inhibition was observed by increasing the concentration of any of the NP-BAs. Absence of any viral entry inhibition in a similar assay with monomeric boronic acid shows that only the multivalent BA is effective in the inhibition of HCV. These synthetic NP-conjugates may be considered as functional analogue of the natural lectin cyanovirin-N and griffithsin, both of which are reported to exhibit viral entry inhibition through their ability to interact with high-mannose glycans present on HCV envelope glycoproteins.

(ii) Intracellular delivery of glycoproteins and drug molecules

Effectiveness of many macromolecular drugs is largely limited due to inadequacy of cellular delivery. Design of biotherapeutic carriers has immense significance in the delivery of enzyme based drugs into cells and thus to derive the full clinical potential of the drug without being affected by the immune system (25). The carriers which are responsive to stimuli like pH and redox are especially valuable as they can ensure the release of the therapeutic cargos in the cellular environment (26).

Boronic acids contain trivalent boron atoms bonded to one alkyl/aryl substituent and two hydroxyl groups ($R\text{-}B(OH)_2$) (27). Since the binding of boronic acid and diol of glycosylated proteins is reversible and not very effective under physiological pH (28), owing to the low Ka value of the compound, the introduction of OH or amino substituents on the phenyl ring of PBA cause the pKa of

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the PBA to decrease and the stability of PBA-diol complex increases at physiological pH. Side chain substituted amino acids can interact with substituted PBA to give polypeptide modified with PBA. If the polymer is non-degradable it will cause environmental concern.

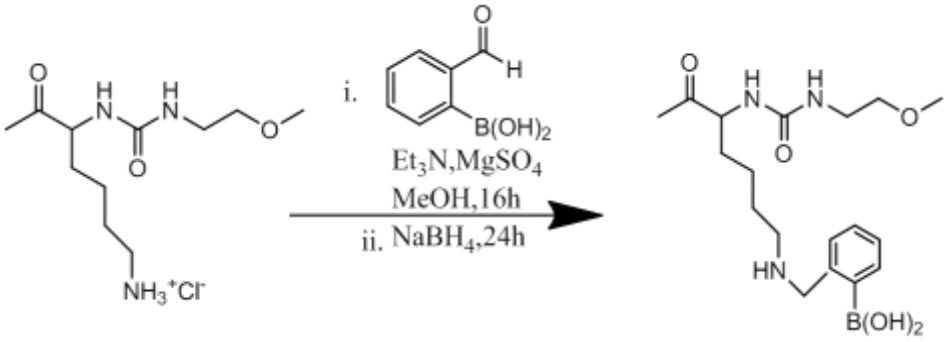

Fig. 4 pH dependent release using boronic acid

Poly(L-lysine)-b-poly(ethylene glycol) copolypeptides K_8PEG_{44} have been reported(29), where the side chain amine group of lysine residues have been modified to contain o- amine substituted phenyl boronic acid (WBA-Wulff type PBA) to produce $\mathbf{K^{WBA}{}_8PEG_{44}}$. The carbohydrate binding and pH response etc are improved by the introduction of this WBA group. These block copolymers can form nano scale complexes with glycosylated proteins at physiological pH and decompose and release the glycoprotein under acidic conditions, which exists in the endosomal or lysosomal compartments within cell. So WBA modified polypeptides can be developed as potential candidates in intracellular protein delivery. WBA functionality has been introduced to degradable polypeptide segments to improve their biodegradable characteristics during the delivery of protein therapeutics. WBA functionalized, oligo(l-lysine) segment exhibits reasonable solubility in water and hence the block copolymer $K^{WBA}{}_8PEG_{44}$. The PEG segments act as biocompatible, non-interacting, water solubilizing chains to limit aggregation of WBA–diol complexes (23). The resultant WBA containing copolymer $K^{WBA}{}_8PEG_{44}$ was water soluble over a range of pH from 3.0-9.0. It can reversibly bind glycosylated protein moieties like HRP with a total carbohydrate content of 18-20 %, α-L-iduronidase (IDUA). The interaction between the copolymer and the glycosylated protein is pH dependent and the exact ratio of the polymer and the protein in the complexes is yet to be determined (24). The complexes formed between the copolymer and HRP possessed a diameter which permits blood stream circulation and passive targeting. An assay using a chromogenic HRP substrate ABTS was conducted and showed that complexed HRP did not lose activity relative to free HRP. Complexation reaction conducted between $K^{WBA}{}_8PEG_{44}$ and a non-glycosylated protein BSA shows that participation of glycosylated sites on HRP is key during its aggregation with $K^{WBA}{}_8PEG_{44}$. The structure of WBA group greatly enhances complex stability at physiological pH and allows HRP release at acidic pH (5.0). The nano scale dimension of the complexes and the pH dependent interconversion of the complexed and non-complexed state makes the boronic acid incorporated copolymers, future material to be developed for intracellular delivery of glycosylated proteins.

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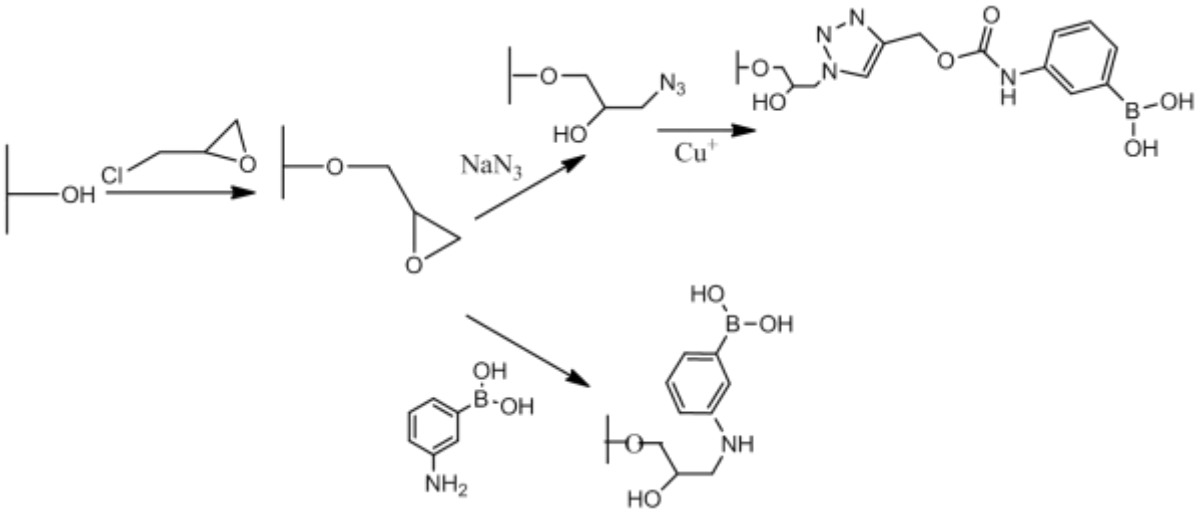

Fig.5 Carbohydrate biomarker recognition using synthetic lectin mimics

Therapeutic applications of many proteins are still hampered by various delivery related issues and so there is an urgent need to improve this aspect of these vital biologics (31). Chemical modification using boronic acid moiety have been successfully used to improve the bioavailability of protein drugs (32). Versatility of boronic acid incorporated biomaterials is due to its ability to bind to saccharides and by exploiting this phenomenon in a multivalent manner.

The efficiency of chemotherapy can be improved by ligand mediated targeting of nanocarriers to tumour cells. PBA can selectively recognise sialic acid (SA). Sialylated glycans are overexpressed in tumours. PBA attached micellar nanocarriers are used as the drug delivery platform of the anticancer drug oxaliplatin for targeting sialylated epitopes overexpressed on cancer cells (33,34). Following PBA installation the micelles showed high affinity for SA even at intra tumoral pH (6.5), enhancing their in vitro cytotoxicity against B16F10 murine melanoma cells. PBA complexed drug maintains its accumulation level in the tumour with improved retention of drug at the tumour sites resulting from the affinity of the boronic acid moiety for the SA moiety on the surface of cancer cells. These results support the application of the PBA conjugation of the micellar nano carriers on the polymeric surface for specific targeting of tumour-associated carbohydrate antigens at intra tumoral pH conditions.

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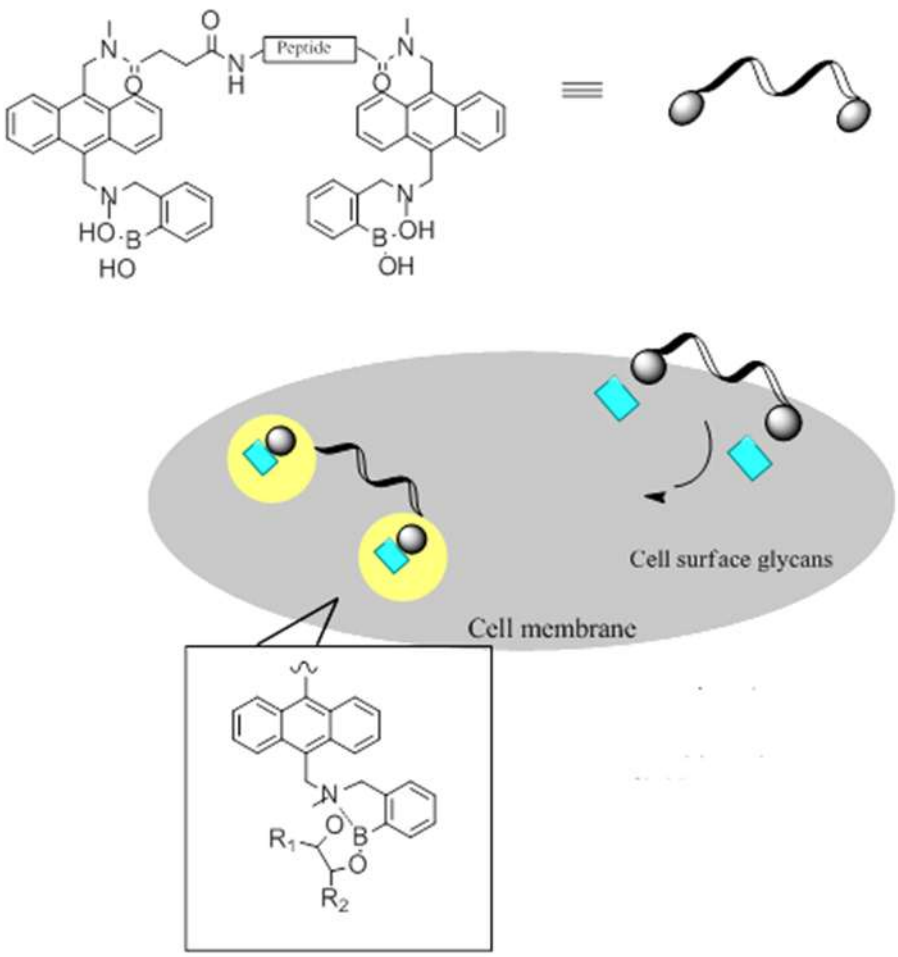

Fig. 6 Phenyl boronic acid groups for in situ recognition of cell-surface glycans and targeted imaging of cancer cells

A pH-sensitive Polymeric Nano Vehicle (PNV) is constructed by the spontaneous grafting of phenyl boronic acid modified cholesterol on to catechol-pending methoxypoly(ethylene glycol)-block-poly(L-lysine). The pH sensitivity is achieved through the spontaneous formation of covalent bonding between the boronic acid and diol group of catechol under neutral conditions and the bond is reversibly cleavable in an acidic environment. The restructuring of this entity results in a micellar nanoform which is able to encapsulate hydrobhobic drug molecule. Drugs like doxorubicin when entrapped in these nano micellar structure cause cell death similar to that of the free drug whereas the blank micelles do not show in vitro cytotoxicity. The decrease in pH occurring at the cancerous site can trigger dissociation of the nano construction due to the acid labile nature of the catechol-boronate linkage. This will accelerate the liberation of the encapsulated drug (35,36). Many anticancer drugs, such as doxorubicin (DOX) and camptothecin, cannot elicit therapeutic action unless they enter into nuclei. Slow release of the drug inside the cells will slow down the influx of the drug into the cellular nuclei. The entry of the drug into the nuclei is governed by the concentration gradient between the nucleus and cytoplasm (37,38). Moreover the drug is deactivated due to prolonged existence within the lysosome. The pH responsive PBA based PNVs, facilitates cytosolic drug release and the

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subsequent influx of free drug into the cellular nuclei and effective intracellular internalisation of nano assemblies.

(iii) Bioactive glasses in tissue regeneration

The use of bioactive glasses as bone materials owes to its biocompatibility and non- cytotoxicity which makes them fit to bond with bones. 45S5 Bioglass was developed to treat non self –healing bone defects (39,40). This property has been extended to soft tissue repair applications (41-45). Poor wound healing after chronic illness and trauma are often associated with the failure to regulate the healthy tissue repair responses like cell proliferation, vascularization, transportation of nutrients to the cells within the network. Due to the better disintegration of borate based bioactive glasses, they act as ideal scaffolds which decays upon neogenesis with the formation of a hydroxyapatite like material (46-49). The dissolution of BGs releases ions which can influence the cellular processes like cell adhesion and proliferation in the early stages of soft tissue regeneration. BGs are also reported to have high potential for angiogenesis. Surface of BGs in contact with the relevant fluids releases metallic ions and result in the formation of a hydroxy apatite layer (50). BGs also exhibit antibacterial activity and found to be useful in the treatment of bone infections. Though the bones/skeletal tissues have considerable matrix of blood vessels, the selective drug delivery in these tissues still remains crucially ineffective. Poor perfusion of the affected tissues, the detrimental action of the drug on the neighbouring tissues etc are some of the reasons which limits the drug action (51) A precise control on the BG dissolution products can aid in bone regeneration, gene upregulation in osteoblast cells, increased mineralization of extracellular matrix etc (52). Bioactive borate glasses were successfully employed as vancomycin carriers in the treatment of osteomyelitis in rabbits. The implant exhibited excellent biocompatibility, compressive strength, full osteointegration with direct opposition of the newly formed bone and stimulation of bone regeneration (53,54). An ideal system for local delivery of antibiotics should provide controlled delivery of higher concentrations of antibiotics to the infectious site and simultaneously minimize the risks of toxicity to other sites. The delivery system should be bio-resorbable to avoid the need for a second operation to remove a non-degradable carrier. The carrier system should provide a medium for supporting osseous regeneration(55). This is particularly advantageous in bone infections associated with infected prosthetic implants in which bone loss is inevitable, when well-fixed, infected metal implants are removed.

The application of BGs in soft tissue engineering has been successfully applied in angiogenesis, nerve repair and chronic wound healing (56). Angiogenesis is a vital step in tissue regeneration. The direct introduction of angiogenic factors like growth promoters, signalling molecules etc are not only expensive but also their release kinetics are somewhat intricate. On the other hand the BG dissolution products not only possess angiogenic potential (57), but also stimulates the production of appropriate growth drivers namely vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF) in fibroblast cells (58). The effect on the angiogenesis and production of growth factors by BGs is probably due to the combined action of various released ions. So the effect of individual metallic ions and specific ratio of ionic concentration etc are to be understood further. The metabolic activity and the multiplication rate in mammalian cells were also enhanced by the pH increase during the precipitation of HA surface layer followed by the dissolution of BGs in relevant solution. 45S5-Bioglass-based scaffolds was found to have both in vitro and in vivo angiogenic potential (59). Ionic extracts released from BGs were found to have profound influence on the migration and proliferation of the cells under study, VEGF and bFGF production, upregulated expression of their respective receptors together with those of nitric oxide synthase which is an

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important angiogenic marker. A boron doped 45S5 BG (45S5.2B) was investigated using an embryonic quail choroallantoic membrane model. Bioactive glasses play an active role in the clinical context of wound healing. More recently, the potential of a borate glass which is produced by replacing the SiO_2 in silicate-based bioactive glass with B_2O_3, has been explored for finding the biomedical applications. The application of borate glass fibres in providing cellular mechanical support and tissue regeneration has been reported (39). The BG implant when incorporated subcutaneously into surgical incisions was found to be disintegrating after a few weeks without any inflammation of the neighbouring tissue. The stimulation of angiogenesis is the origin of cell migration and proliferation by the BGs, particularly having fibrous morphologies which render them outstanding wound healing property.

The application of BGs in the area of nerve regeneration was studied extensively. A composite material was fabricated (60) with poly-(ε)-caprolactone (PCL) and BG blended sheets of various compositions and it is found to be a promising alternative in the context of artificial nerve graft.

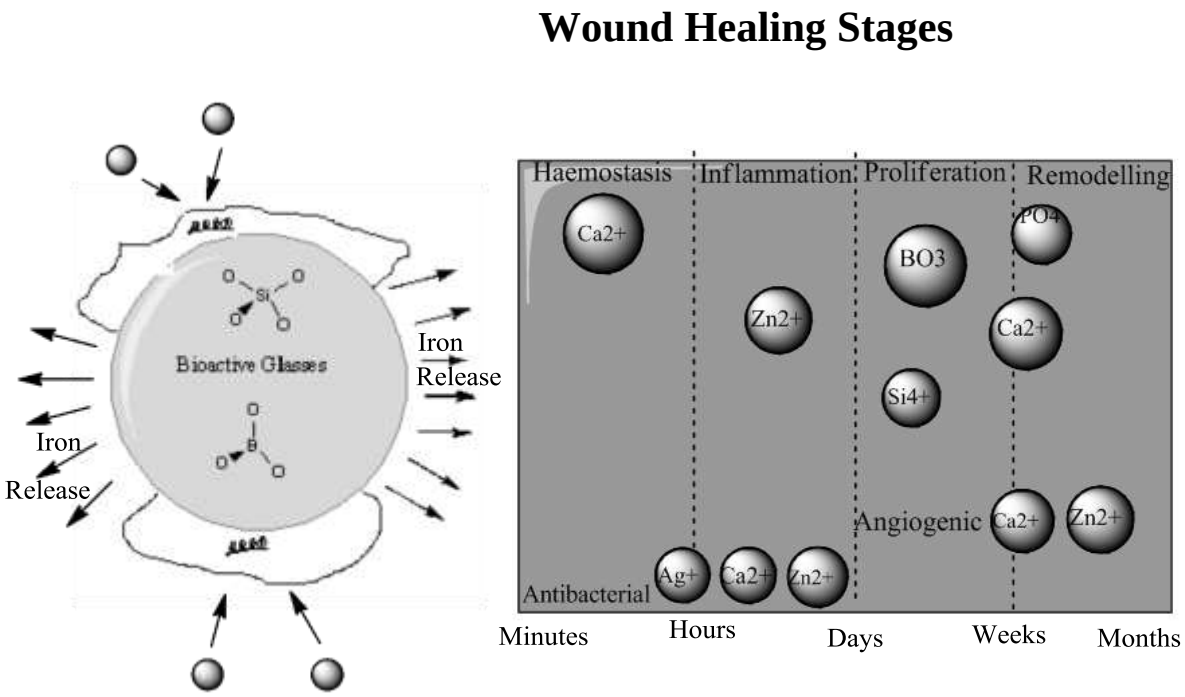

Fig.7 Bioactive glass in wound healing

Borate Glasses are reported to find application in the regeneration of peripheral neurons after traumatic damage (60). BBG has better ability of healing wounds compared to non- glass condition (58). BBGs are more biodegradable than other BGs and are converted into hydroxyapatite layer in the environment of the body fluid, which together with the cells around the wound fastens the healing process (61,62). The dissolution of BBG releases, boron and calcium ions forming calcium phosphate layer to be set up on the unreacted glass surface. Borate ions enhance the bioactivity and it influences the formation of the HA layer (63,64). BBG microfibers incorporating the borate ions stimulate angiogenesis and the released boron ions improve vessel formation. Hence BBG does not produce

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chemical residues incompatible to the cellular condition. Tuning of the BBG composite for the specific applications is done by varying its chemical formulations, physical forms etc (65). In addition of doping BBG with various elements, incorporation of growth factors and drugs have wide range of applications (66). Doping with Fe and Ce will enhance bone tissue regeneration. Doping with Ce, Cu, Ag, Zn and Ga have been shown to impart antimicrobial activity. Doping with yttrium (Y) provides structural support to the biomaterial (60). The cerium and yttrium nanoparticles act as direct antioxidants to limit the amount of reactive oxygen species required to kill the cells. It follows that this group of nanoparticles could be used to modulate oxidative stress in biological systems (67).

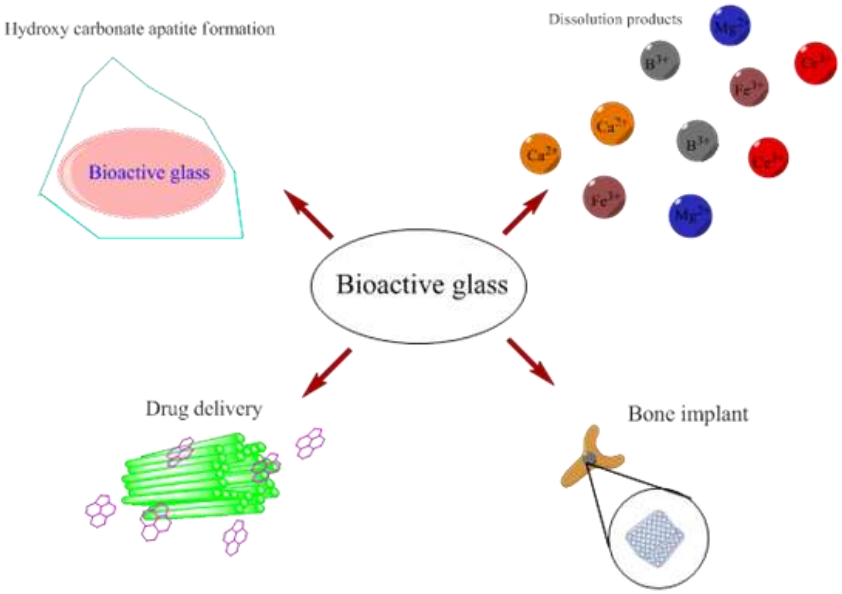

Fig.8 Dental applications of nanostructured bioactive glass and its composites

A multicomposite scaffold material have been successfully designed for peripheral neural regeneration by immersing BBG in poly ε-caprolactone (PCL). Various elements like Ag, Ce, Cu, Fe, Ga, I, Y, and Zn may be doped in to BBG which may impart an advantageous effect on cells (67-70). The release of boron or dopant from BBG is controlled by the composition of BG and the nature of the dopant added, circulation of the media during culture and saturation of the media with the ions released. BBG has different effects on the survival of neurons and support cells and the nature of the dopant is very crucial in this. Moreover the survival of the neuronal cells by doped BBG was found to be time-dependent and in many cases an opposite effect is observed in the survival of support cells. Chemical dopants have differential effects on the outgrowth of neurons from the body of the DRG explant. Neuron regrowth was enhanced in the presence of BBG and the alignment of BBG rods stimulates directional neurite regrowth (71). It thus leads to join the gap between the ends of the severed nerves. BBG could be formulated in different physical forms and it can be finely tuned by varying its chemical composition. The exact effect of different dopants on BBG in the ionic release and neuronal/support cell regrowth is of key importance in achieving the desired result in the engineering of soft tissue. Ce doping was found to improve osteoconductive ability, antimicrobial activity and regeneration capacity of bone tissue (72). The mechanism of bonding between the bioactive glasses and tissues essentially involves the formation of HA layer at the interface of the BG and the physiological fluids which will obviously be influenced by the released ions on the BG

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surface in contact with the fluid (73). The formation of the mineral layer is moderated by the extracellular matrix molecule. The composition of BG is very much decisive in the nature of the ions which are set free at the surface and the local pH increase at the interface. The HA layer provides the medium of prolonged bondage between the BG and the tissues (74). There are many propositions regarding the mechanism of bonding like the attachment of collagenous constituents of soft tissues on BG surfaces and the area is to be investigated further for the development of the BG strategy in nerve regeneration. The possibility of developing patient-specific therapies which is an incredible achievement for the mankind can be hopefully conceived due to the ionic stimulation and genetic up-regulation offered by the bioactive glass.

(iv) Bioactive borate glasses for biofilm inhibition

Bio active glasses (BGs) have been widely reported against planktonic bacterial cultures (75-79). The antibacterial property is enhanced by introducing the appropriate compounds into the BG structure to make it effective against biofilms. Biofilms are collection of different species of microorganisms organized in an extracellular polymeric substance (EPS matrix). EPS matrix allows genetic information exchange and chemical signalling between microbial cells by a mechanism called quorum sensing. This phenomenon acts as a blockage between the drug and the immune system of the host. Most of the bacterial infections are caused by biofilms having high population of pathogenic bacteria. Bone infections are especially difficult to treat by systemic antibiotic therapy, as confining therapeutic action of the drug to the affected part is rare to achieve due to the vascular insufficiency and chances of developing side effects in the patient is very high (80,81). The antibiotic can be inactivated in the bloodstream and its curative action at the surgical site of implant is obviated. Mesoporous bioactive glasses (MBGs) have been developed as alternative drug delivery system for the effective recovery of such sepsis (82,83). The formulation of MBGs can be varied to cause the bioactive ionic release and pH increase etc which have very crucial role in bone tissue engineering (84-86). The high surface area and adjustable pore size etc of the MBG enable successful encapsulation of the drug and their controlled delivery at the target site. The MBGs can make use of the increase in the local acidosis of the surgical receptor region resulting from bacterial metabolism. Hence, they can be designed as pH sensitive controlled drug delivery system with improved therapeutic effect and devoid of detrimental side-effects. Borate glasses are superior to many 'standard' controlled drug delivery platforms like calcium sulphate, PMMA etc (87, 88). Borate glass scaffolds are resorbable, and it can stimulate the regeneration of the osseous tissue, without causing any inflammatory response, inhibiting bacterial adhesion and biofilm formation (89).

BGs incorporated with antibiotics was found to be effective against biofilm infections (90,91). But many drug-BG combinations have many adverse aspects like the possible bioaccumulation due to the hydrophobicity and can affect the hormone production in mammals. The combination of BG and Phyto therapeutics can alleviate many of these drawbacks besides having desirable antibacterial effectiveness.

They can induce heath enhancing factors at the bone infection site. Neem leaf (Azadirachta indica) powder incorporated into BGs were found to have antimicrobial/antibiofilm activity and low cytotoxic effect (92). BGs incorporated with propolis, which is a natural compound produced by honey bees could be developed as excellent biofilm inhibiting materials in view of the favourable bioactive properties of propolis (93). Propolis is very effective in preventing bioaccumulation, bacterial adhesion and reducing pathogenic elements of S mutans and non-cytotoxic effects (94). The natural organic compounds in combination with BGs are to be investigated further both in vivo and in vitro to explore the successful clinical outcomes in living tissue engineering (95). A dual drug

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delivery structure has been successfully employed in which nanomicells encapsulated with hydrophobic naproxen (Nap) were adsorbed on the surface of MBG loaded with hydrophilic gentamicin sulphate (GS) (94). GS release from MBG surface quickly occurs at acidic pH whereas the release rate of Nap is minimum under low pH and increases as the medium becomes basic. Thus change in pH brings about controlled release of the dual drug delivery system. The significance of developing potential antibiofilm agents arises from the fact that many of the bone infections in humans is caused by multi-species biofilms which can both increase bacteria pathogenicity and antibiotic resistance.

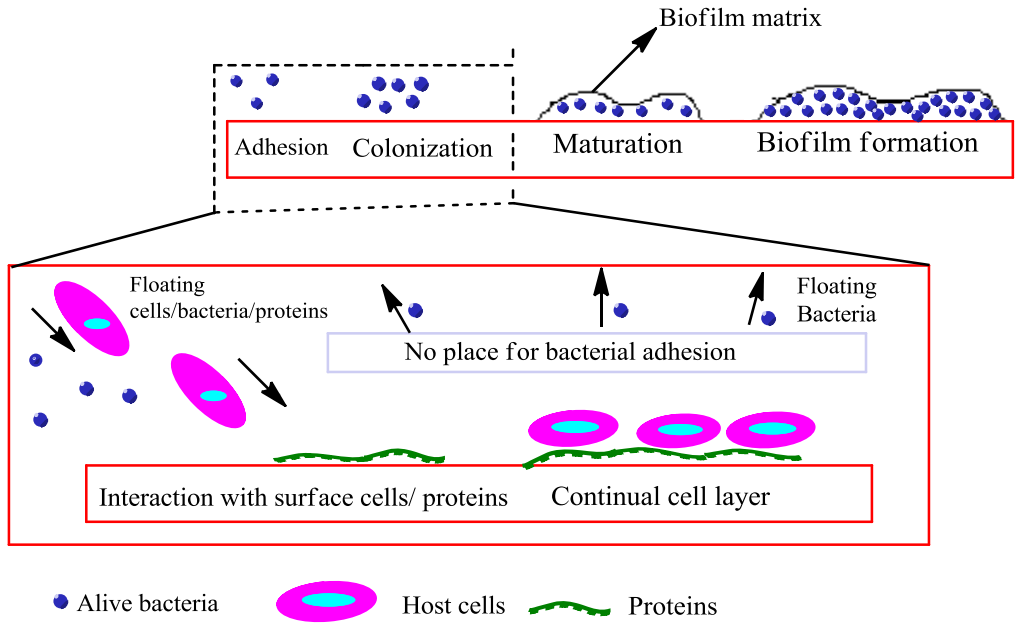

Fig. 9 Mesoporous silica nanoparticles for the treatment of complex bone diseases

(v) Boronate affinity materials in chromatography

Boronic acid units can be incorporated in polymer chains attached on solid materials and these boronate affinity materials can be used for the separation of cis –diols. The fundamental principle is the bond formation between boronate ligand and cis diols. The ester formation is enhanced when the two hydroxyl groups of diols are on adjacent carbon atoms and in nearly coplanar configuration. Separation of a wide range of compounds like nucleic acids, nucleosides, nucleotides, enzymes, carbohydrates etc having 1,2 diol group as a structural feature were reported based on the specificity of boronate group towards esterification with this group **(**96, 97**).**

A polymer brush containing boronic acid repeating units is installed on the silica surface. Boronic acid monomer is first prepared from an azide tagged fluorogenic boronic acid and an atom containing acrylate by Cu(I)-catalysed 1,3-dipolar cycloaddition reaction (98). The boronic acid monomer is then grafted to the surface of the silica gel by surface-initiated atom transfer radical polymerization (ATRP). The resultant composite material Si@poly(APBA-PA) shows ability of binding to simple saccharides at physiological pH and this is accompanied by fluorescence intensity changes. These materials could be used to develop methods for the fast separation of glycopeptides and large glycoproteins based on boronate affinity interaction. PBA can form reversible cyclic esters with diols in aqueous medium under alkaline pH which results in five and six membered rings. Hence PBA have been utilized to design functional materials for separation and detection of saccharides

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(75,98,99). Due to high affinity and flexibility offered by boronic acid to the binding of the carbohydrate diols, they can be designed as better functional materials for the separation and sensing of biological cis-diol compounds. The boronic acid function can be reused due to the immobilization of the material in to a polymer. The incorporation into the polymer also enhances the molecular recognition of the boronic acid to functional polymers and supramolecular structures. Si@poly(APBA-PA) was studied for the separation of monosaccharides. The binding of the silica bound polymer brush with the various sugars like glucose, fructose etc was analysed using fluorescence spectroscopy. The material was also showing similar behaviour to polypeptides and large glycoproteins like horseradish peroxidase (HRP).

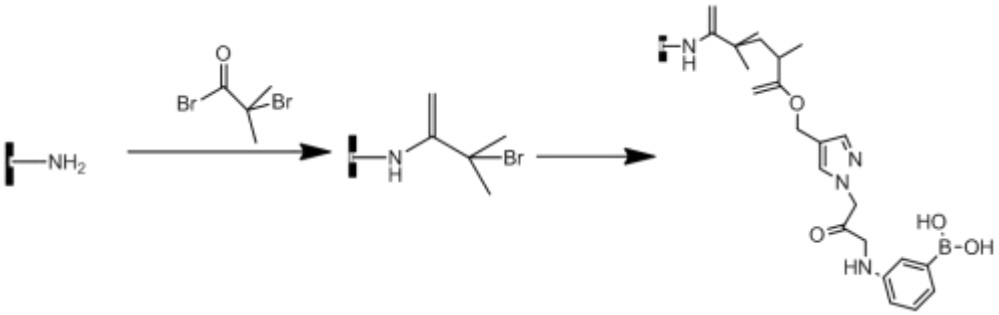

Fig. 10 Surface initiated ATRP for the synthesis of poly(APBA-PA)

The application of silica grafted polyAPBA-PA for the separation of monosaccharides was investigated using fructose as a model through equilibrium binding experiments (100). The binding of the sugar is entirely due to the interaction between the saccharide and the boronic acid moiety and this view is substantiated by the observation that such a binding is not occurring with initiator modified silica in the same experiment. Glycoprotein separation was carried out using a solid column of Si@poly(APBA-PA). The polymer brush retains the fluorogenic property of the monomer. The composite material also has high density of the boronic acid function appended on the polymer chain and hence can be used for the effective separation of simple saccharide, glycopeptides and large glycoproteins. Boronic acid based affinity materials can be developed by controlling the architecture and sequence of boronic acid moieties through ATRP.

A boronic acid based nanohybrid material composed of silica core and flexible polymer brushes, denoted as Si@poly(NIPAm-co-GMA)@APBA, was synthesised by ATRP in combination with Cu(I)-catalyzed azide-alkyne cycloaddition click reaction (101). The composite material is ideal for the capture of glycoproteins which is based on the unique cis-diol binding property of boronic acid which is essentially a covalent interaction. The structure and homogeneity of the polymer brushes on the surface could be effectively controlled by Si-ATRP and the click reaction enabled ligand immobilization.

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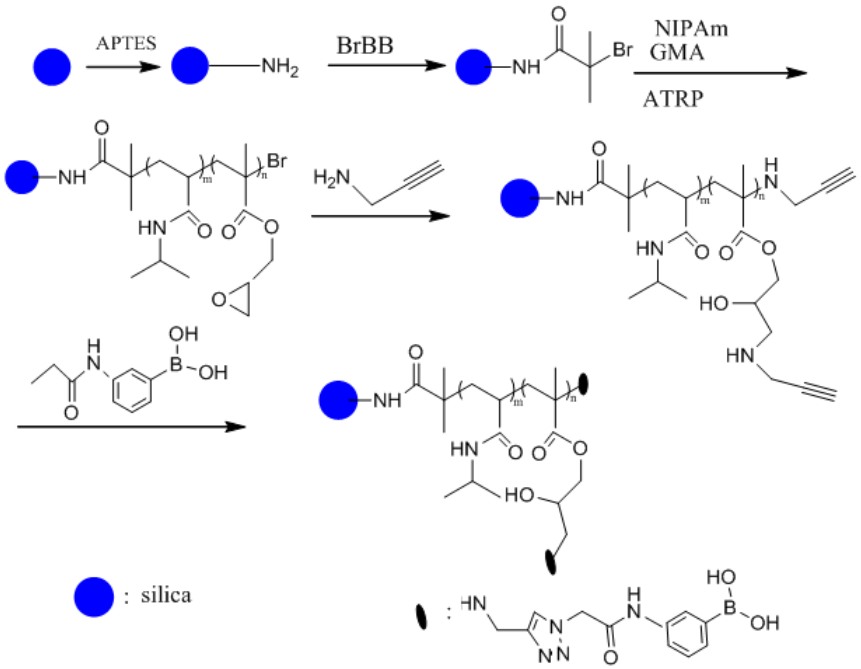

Fig.11 Synthesis of Si@poly(NIPAm-co-GMA)@APBA particles by combining Si-ATRP with CuAAC click reaction.

Poly(anilineboronic acid) (PABA) nanofibers with U-shaped and ring-shaped morphologies with excellent electrochemical redox activity have been reported (102). 3-aminophenyl boronic acid was polymerised in the presence of cetyltrimethylammonium bromide (CTAB) and NaF. The concentration of APBA and CTAB are crucial in determining the size and the morphology of the PABA nanofibre. These nanofibres find application in the electrochemical detection of glucose due to the reversible complexation of phenyl boronic acid compounds with compound containing diol moieties. The boronic acid substituted polyaniline is particularly interesting in the application of biosensors for the detection of biologically important molecules (81). This is due to the fine tuning possible in its electronic structure and optical properties.

The PABA nanofibers exhibit high sensitive detection of D-glucose in phosphate-buffered saline stock solution (PBS, pH 7.4). The concentrations of APBA and CTAB have tremendous impact on the morphology and size of the PABA nano fibres. Here CTAB acts as a structure directing molecule. The high surface area of the nanofibers increases the density of the boronic acid moieties available for complexation. The reversible covalent interaction of boronic acid with cis diols to form cyclic five or six membered cyclic esters enable saccharide sensing and can be developed into boronic acid based synthetic chemo sensors (103-105). A copolymer gel based on PBA has been developed which exhibit abrupt volume changes in response to the changes in the concentration of naturally occurring monosaccharides like glucose under physiological aqueous conditions. This can be utilized to develop self-regulated insulin delivery systems in the treatment of diabetics that can tolerate long term use and storage unlike other protein based traditional materials (106).

Conclusion: Variations in the structure of boronic acid can result in systems with improved affinity and selectivity towards saccharides, modulated pH optima etc. The PBA analogues were better streamlined towards a broad spectrum of tissue engineering and therapeutic applications. We have probed boronic acid functionalised nanoparticles as viral entry inhibitors and PBA modified copolymers as degradable carriers for intracellular protein delivery. The biomaterials to be used in

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local drug delivery of antibiotics requires a combination of functions including the ability to serve as scaffold with adequate mechanical strength, angiogenic potential, physicochemical characteristics necessary for osteoconduction, growth factor delivery, controllable degradation rates etc. This review considers the suitability of bioactive glasses as bone filling materials, dental implants, soft tissue regeneration, wound healing agents and anti biofilm agents. The ionic product of BG dissolution in physiological fluids stimulate angiogenesis, osteogenesis and neurogenesis leading to osteoblast proliferation and neuronal cell survival. The fast and stable bond formation between boronic acid and diols to form boronate esters results in the formation of reversible molecular assemblies which exerts this moiety into a manifold of applications including sensing and sequestration of biologically important molecules like saccharides.

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