Synthesis of Hydrogel with Neem Gum/ 3-APBA/PVA using PBA-diol ester bond

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CANDIDATE'S DECLARATION

I, Prerna Dhamija (24/MSCCHE/48) and Ananya Singh (24/MSCCHE/52), students of M.Sc. (Chemistry), hereby declare that the project dissertation titled "**Synthesis of Hydrogel with Neem Gum/3-APBA/PVA Using PBA-Diol Ester Bond**" submitted by us to the Department of Applied Chemistry, Delhi Technological University, Delhi, in partial fulfillment of the requirement for the award of the degree of Master of Science, is original and has not been copied from any source without proper citation. This work has not previously formed the basis for the award of any Degree, Diploma, Associateship, Fellowship or other similar title or recognition. The experimental details, methodology, interpretation of results, figures, tables, and references have been compiled and written in accordance with the prescribed project report format. All sources used in the preparation of this dissertation have been acknowledged through in-text citation and reference listing.

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CERTIFICATE

I/We hereby certify that the Project Dissertation titled "Synthesis of Hydrogel with Neem Gum/3-APBA/PVA Using PBA-Diol Ester Bond" submitted by Prerna Dhamija (24/MSCCHE/48) and Ananya Singh (24/MSCCHE/52) , Department of Applied Chemistry, Delhi Technological University, Delhi , in partial fulfillment of the requirement for the award of the Master of Science, is a record of the project work carried out by the student under my supervision. To the best of our knowledge, this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

Place: Delhi

Date: June, 2026

PROF. ROLI PURWAR

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ABSTRACT

Hydrogels are three-dimensional networks of hydrophilic polymers which can absorb large quantities of water and can retain the absorbed water without disintegrating. The present dissertation reports the synthesis of a neem gum/3-aminophenylboronic acid/polyvinyl alcohol (NG/3-APBA/PVA) hydrogel through PBA-diol ester bond formation. Neem gum was selected as a renewable natural polysaccharide, PVA was used as a hydroxyl-rich synthetic polymer, and 3-APBA was introduced as a boronic acid-containing linker. Neem gum was first oxidized using hydrogen peroxide to produce oxidized neem gum (O-NG), followed by EDC/NHS-mediated grafting of 3-APBA through amide bond formation. The grafted polymer was then mixed with PVA under alkaline conditions to promote PBA-diol ester interactions, and freeze-thaw cycling was used to obtain stable hydrogel networks. The synthesized materials were characterized by FTIR spectroscopy, swelling analysis, rheology, syringeability testing, and self-healing evaluation. FTIR confirmed oxidation of neem gum, amide bond formation after 3-APBA grafting, and retention of boronic acid functionality in Hydrogel A and Hydrogel B. Hydrogel A showed higher swelling of approximately 93%, whereas Hydrogel B showed lower swelling of approximately 75%, indicating a denser network under higher alkaline conditions. Rheological results confirmed elastic solid-like behavior, shear-thinning viscosity, and successful hydrogel network formation. Both hydrogels were syringeable through a 16G needle, with Hydrogel A and Hydrogel B showing syringeability values of 81% and 79.9%, respectively. Partial self-healing after 24 hours further supported the dynamic nature of the PBA-diol ester network. Overall, the study demonstrates that neem gum can be chemically modified and combined with PVA to form a functional dynamic hydrogel system.

Keywords: Neem gum, PVA, 3-APBA, hydrogel, PBA-diol ester bond, FTIR, swelling, rheology, self-healing.

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1. INTRODUCTION AND OBJECTIVES OF WORK

1.1 Background of Study

The rapidly changing landscape of materials science has focused increasingly toward the creation of functional polymeric systems capable of interacting with the surroundings. In the larger field, hydrogels have a unique place within it as the polymer network has a high water uptake. The specificity of this structure enables hydrogels to act as soft "wet" solids whilst still being able to swell, be sensitive to stimuli and allow the passage of solutes[1]. Due to their watery characteristics, hydrogels are particularly useful for those applications which demand compatibility with biological or aqueous systems.

Generally, hydrogels are defined as more or less rigid three-dimensional polymer networks which have hydrophilic functional groups, hydroxyl, carboxyl, amide, or ionic, in their structure. These groups are so good at interacting with water that the network can absorb water without dissolving, if there are enough crosslinks [1]. These crosslinks could be permanently covalent linkages, reversible covalent linkages, reversible physical association, the formation of crystalline domains, hydrogen bond, ionic coordination, or supramolecular interactions[2]. A certain type and density of crosslinking determine the final material's mechanical characteristics, swelling capacity, degradability and capacity for self-healing.

The present work presented an attempt of the synthesis of a hydrogel of neem gum, 3-aminophenylboronic acid (3-APBA) and polyvinyl alcohol (PVA). Two significant chemical events are used as the basis for the network design. Neem gum is firstly oxidized and then amide bond formation with 3-APBA. Secondly, the hydroxyl group of PVA will interact with boronic acid groups attached via 3-APBA to create PBA-diol ester bonds. As boronic ester linkages are temperature and pH-reversible, they can render hydrogel network dynamic[3]. This dynamic behavior is closely tied into the swelling control as well as partial self-healing and shear thinning behaviour.

The study becomes important since neem gum is a renewable plant derived polysaccharide from Azadirachta indica and PVA is widely used hydrophilic synthetic polymer which shows good biocompatibility and processability. A mixture of PVA and a natural gum can lead to a hybrid material containing both biofunctional/hydrophilic properties from the natural gum and film-formation support/rich in diol groups for borating esterization from PVA. When 3-APBA is employed, a chemical bond is formed between these two polymeric components which is conducive to the formation of a responsive polymeric network.

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1.2 Hydrogels and Their Importance

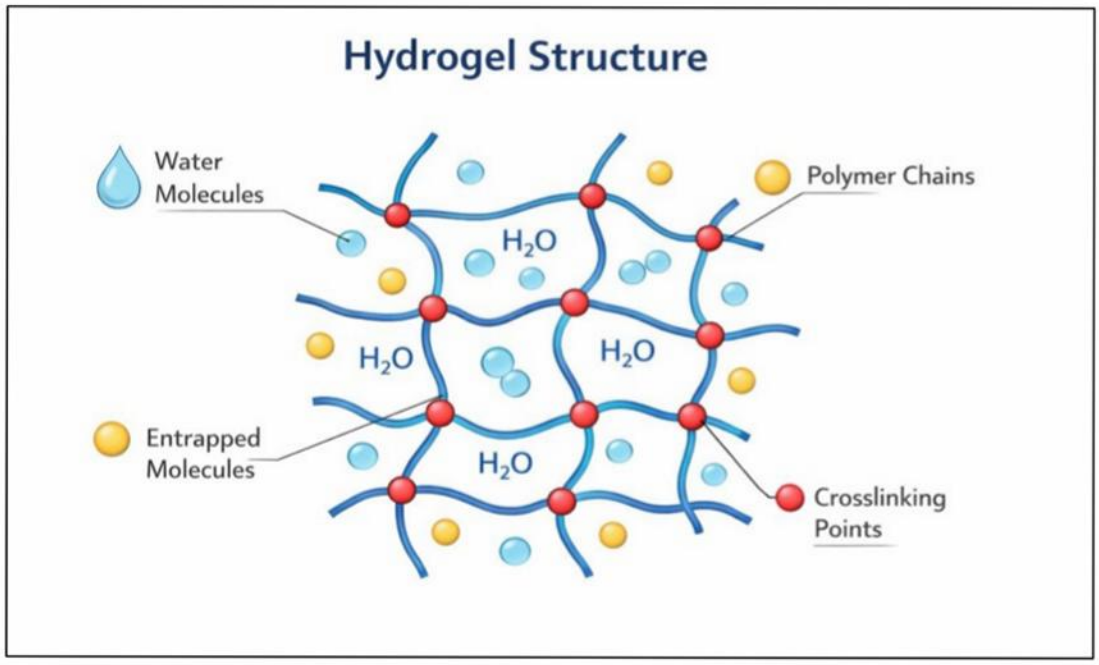


Figure1. Hydrogel 3-D network structure

Hydrogels are significant due to their property which can be modified by altering polymer composition, chemistry of cross linking, solvent environment and manner of preparation. Based on these ideas, a lightly crosslinked hydrogel could be able to absorb a great deal of water, but possibly might exhibit low mechanical stability, while a highly crosslinked hydrogel could exhibit improved mechanical stability, yet possibly low water absorption capacity. It is a balance between water uptake and the strength of the network which is the key in the design of hydrogels [1]. In the biomedical/pharmaceutical field, a helpful hydrogel needs to be strong enough to preserve any shape, porous enough to allow diffusion and soft enough to interact safely with tissue.

Hydrogels have several uses like drug-delivery matrices, tissue engineering, scaffolds, wound dressing, biosensors, diagnostic devices, agriculture, purification of water and biomaterials for injection . Hydrogel dressings can help to create a moist environment and absorb exudate in wound care. Therapeutic molecules can be loaded in the internal water phase and the porous network, respectively, to release them in a controlled way in drug delivery. In the field of environmental applications, hydrogels can swell or bind water or contaminants based on their chemical makeup. Researchers are still actively studying hydrogels due to their wide range of applications.

Dynamic hydrogels are one of the interesting newer systems based on hydrogels. Dynamic hydrogels are hydrogels with reversible interactions, which are able to dissociate and re-establish under certain conditions. Such systems may exhibit self-healing, injectable properties or adaptive stiffness or stimulus-responsive swelling properties. Various research has been done on dynamic covalent bonds, such as the boronic ester bond, imine bond, disulfide bond as well as the Diels-Alder bond to crosslink advanced hydrogels, as these can interconvert between being open and closed, or reacted and unreacted.

This thesis describes the PBA-diol ester bond which falls under this category of reversible covalent interactions.

The present study does not consider the hydrogel merely as a material that absorbs water, but sees it as bio-functional network. Boronic acid functionalities introduced by 3-APBA may cross link with hydroxyl groups in PVA and this may be sensitive to alkaline conditions. This is because the quantity of the boronic ester formed during the preparation – a parameter like the concentration of NaOH used in the preparation – can influence the extent of boronic ester formation and thus the swelling and the rheological properties. Hydrogel A and Hydrogel B with their properties are an experimental basis for observing this composition – property relationship.

1.3 Neem Gum : An Organic Polysaccharide

Neem gum is a natural gum exudate extracted from the bark of Azadirachta indica – the neem tree. Neem is a hardy evergreen plant, native to tropical and subtropical regions and known for its medicinal and agricultural value. The gum fraction is a complex heteropolysaccharide with numerous hydrophilic functional group which can involve in many water absorption, hydrogen bonding and chemical modification. However, the above properties make neem gum an ideal polymer for developing natural polymer based hydrogel systems[4].

There is an important interest in natural gums for hydrogels due to their renewable nature, biodegradability, attractiveness in terms of both low cost and structural richness in hydroxyl and other polar groups. But in some cases, natural gums will need to be modified chemically (or mixed with synthetic polymers) to achieve the desired functional properties and mechanical strength. The only difference in the present work is that neem gum is first oxidized with hydrogen peroxide. This oxidation step will generate carboxyl groups in the polymer structure providing sites for the subsequent grafting with 3-APBA by amide bond.

The use of neem gum in a 3-APBA/PVA network is significant as it opens the scope of neem use for getting beyond traditional pharmaceutical excipients. Hence, use of neem gum in a hydrogel matrix also aids in the development of bio-based polymer systems based on natural origin and engineered responsiveness. Here, the introduction of the neem gum is not done for a filler purpose, it is actually used as the main polysaccharide base chain which is modified and added to the crosslinked fabric.

1.4 Polyvinyl Alcohol-Based Hydrogels

Synthetic polymer that dissolve in water and has a high hydroxyl group density is called polyvinyl alcohol(PVA). The hydroxyl groups of PVA are very hydrophilic, allowing PVA to possess strong hydrogen bonding capacity and form physical crystallites and bind boronic acid containing molecules. PVA is frequently utilized to create hydrogel, its advantage is it is biocompatible, have relative low toxicity and functional mechanical property, and can be made into relatively stable hydrogel through physical or chemical crosslinking.

There are several approaches to the preparation of PVA hydrogels: firstly, some of them are chemically crosslinked, secondly, they are irradiated and thirdly, they are made by repeated freeze-thaw cycles and blending techniques with natural polymers. The freeze-thaw process is particularly advantageous, as it can be used to produce physically crosslinked PVA networks without resorting to a toxic chemical cross linker. At the freeze temperatures the polymer chains are compressed together by the production of ice crystals and encourages microcrystalline domains. During thawing process the network decompresses, but keeps the points of physical joining. Such repetition can facilitate improvement of the gelation and mechanical stability.

In this current research PVA has two significant different roles. First, it offers a hydrophilic synthetic polymer phase to contribute to the support of a hydrogel network. Secondly, it is bound with much hydroxyl groups, which act as diol-rich binding sites of phenylboronic groups. In the presence of alkaline condition, the 3-APBA-grafted neem gum when mixed with PVA, may participate in forming PBA-diol ester linkages between PVA hydroxyl groups. Hence, PVA can serve as a structural polymer and as a chemical partner for dynamic cross-links formation.

1.5 Phenylboronic Acid and PBA-Diol Ester Bond Chemistry

The phenylboronic acid derivatives are known to reversibly bind cis-diols. With appropriate diols, the boronic acid group can form cyclic boronate ester structures with these, which is highly pH-dependent and depends strongly on the structure of the boronic acid as well as that of the diol. In alkaline conditions, the groups that can be recognised as boronic acids are more likely to be in the tetrahedral form in the form of a boronate and would therefore be more prone to reacting with the diol groups by forming esters.

The usefulness is provided particularly by 3-Aminophenylboronic acid due to the presence of both amino and boronic acid group in it. The amino group can be coupled with activated carboxyl groups of oxidized neem gum by amide bond formation using EDC/NHS. The amino group is not involved in the following reaction and is free to undergo further reaction with PVA hydroxyl groups. Thus, 3-APBA can be grafted as a linker molecule and used as a functional crosslinker. It links the natural polymer backbone to the dynamic boronic ester chemistry necessary for accomplishing hydrogel formation.

PBA-diol ester bond have useful applications in the formation of reversible networks in a hydrogel system. The stress-induced dissociation of crosslinks and its reformation after the strain are the basis for such networks to possess injectability, self-healing and shear-thinning qualities. In this work, such reversible interactions are confirmed in the experiment through the observation of the rheological behaviour, syringeability and partial self healing.

1.6 Research Gap and Novelty

The use of PVA as a precursor for polymerizing into a functional hydrogel, as well as the use of natural gums as a novel precursor material for polymer hydrogels, has been investigated and demonstrated;

however, the group of neem gum, 3-APBA, and PVA have not received a lot of attention for use in a chemically functional material that could be turned into a hydrogel. Currently used boronic acid (BA) based hydrogels include classical polysaccharides like dextran, hyaluronic acid, cellulose derivatives or polymeric matrices (synthetic). The neem gum which is a chemically modified backbone for the synthesis of PBA functionalized hydrogels has received less attention.

Importance of present research is the design of a novel hydrogel network of oxidized neem gum as a polymeric network and chemically grafted it with 3-APBA and thereafter PVA is added to it via PBA-diol ester formation. Here, the concept is unified as one material system of a natural gum, a biocompatible synthetic polymer and a dynamic covalent crosslinking motif. Two different volumes of NaOH are also used to prepare two different hydrogel formulations and the effect of alkaline conditions on swelling, rheology, syringeability and self-healing behaviour are discussed in the study.

The project is thus expected to make a contribution to hydrogel research, as it is showing an easy and effective method to create a responsive hydrogel network from neem gum. The work also lays the groundwork for future optimization of drug delivery systems, wound dressings, systems of injectable hydrogels, and biofunctional soft materials.

1.7 Objectives of Work

This project's primary objective is to synthesize and characterise a neem gum/3-APBA/PVA hydrogel by the PBA-diol ester bond formation. The specific learning goals are:

- To oxidize neem gum with hydrogen peroxide and to introduce the reaction sites, carboxyl groups into the natural polysaccharide backbone.
- For the functionalization of oxidized neem gum with 3-aminophenylboronic acid by amide bond formation by using EDC/NHS mediated chemistry.
- Preparation of the PVA solution and exploiting the hydroxyl-rich polymer structure as the diol component in the formation of PBA-diol ester bonds.
- For synthesizing Hydrogel A and Hydrogel B by changing the volume of NaOH and conducting repeated freeze-thaw cycle.
- The synthesized hydrogels are characterized by FTIR spectroscopy, swelling studies, rheological analysis, syringeability testing and self-healing evaluation.
- To perform comparative analyses of Hydrogel A, and Hydrogel B to compare their structure properties, and elucidate structure property relationship by chemical bonding, swelling, viscoelasticity, functionality to injectability and self-healing ability.

1.8 Scope and Significance of the Study

The purpose of the present thesis is to produce NG/3-APBA/PVA-scalable laboratory scale related to PVA hydrogels and investigate their physicochemical properties. This work is aimed towards the chemical modification of neem gum and the generation of PVA and PBA diol ester linkage, as well as

comparison between two types of hydrogel formulations developed under two different alkaline processes. Biological testing, drug loading, degradation kinetics and in vivo evaluation are not covered in the study. The identification methods used, however, do provide good initial insights concerning the structure and functional character of the hydrogels.

The study is significant because it incorporates neem gum as one of the renewable natural polysaccharide in a dynamic covalent hydrogel system. Neem gum has been investigated, but not as broadly, as other polysaccharides such as alignate, chitosan, hyaluronic acid, dextran or cellulose, for functionalization in PBA. Neem gum has also been studied but less widely than other polysaccharides, particularly cellulose and chitosan, alginate, dextran or hyaluronic acid, for PBA. In this work, therefore, the authors have shown the possibility of the oxidation and chemical grafting of neem gum with 3-APBA and the incorporation of it with PVA via boronic ester chemistry, and this work gives the benefit of contributing further. This wide-ranging enables wider choice of the material platform for bio-responsible hydrogels.

The study has also some importance in the structure-property aspect. By comparing the Hydrogel A and Hydrogel B, it can be seen that a slight difference in vol. of NaOH causes a difference in swelling, stiffness, viscosity, syringeability and self healing behaviors. It is important for such observations as the performance of hydrogel is not solely dependent on the kind of polymer but also on the conditions of its preparation. To be able to optimize the material for any particular use, one needs to be familiar with this relationship.

The synthesized hydrogels can act as a basis for further research regarding the area of targeted drug delivery, injectable biomaterials and soft matrices that react to stimuli. The network includes every bond having a natural component as well as a PVA and boronic ester bond, giving it a hydrophilicity, polymer compatible interaction, and dynamic interaction. Although it would be desirable to carry out additional biological and mechanical testing before any biomedical application, the preliminary breakdown and characterization work reported herein is important.

2. LITERATURE REVIEW

This literature review is based on the structure, crosslinking and the behaviour of networks about hydrogels based on dynamic bonds. The chapter thus summarizes the salient features of hydrogel systems, neem gum, PVA, boronic acid chemistry, swelling, rheology, injectability and self-healing properties relating to the discussed NG/3-APBA/PVA hydrogel system.

2.1 Hydrogel Systems and Dynamic Networks

3-D dimensional hydrophilic polymer networks known as hydrogels can absorb human tissues or biological fluids in substantial quantities and yet retaining the integrity of the structural network. This is directly relevant to the present work as blended synthetic material of NG/3-APBA/PVA should possess the ability to hold its shape when it is hydrated and it must be capable of significant swell, demonstrable to a certain point. The interaction between the polymer network and the solvent determines the hydrogels performance, as well as by the composition of the polymer and the amount of cross-linking, Ahmed added. These are important factors to consider when discussing and explaining differing swelling numbers of Hydrogel A vs. Hydrogel B.

Self-healing hydrogels consists of dynamically formed covalent cross-links and how such dynamic cross-links can function as transient and temporary junctions in the polymer network. This discussion is significant to the present thesis because the PBA-diol ester bond that is created between 3-APBA and PVA is reversible covalent. This bond–reversal capability allows for a chemical basis to be proposed for shear-thinning and partial self-healing characteristics in NG/3-APBA/PVA hydrogels.

Previous research concentrated on dynamic, biomaterials with pockets of the borox imine type, which are constructed from polysaccharide building blocks. It has several similarities to the thesis as the gum that they discuss is polysaccharide, and 3-APBA has boronic acid groups that can undergo B-O based dynamic interactions. The finding of Aeradou et al. reinforces the hypothesis of the use of boronic acid-polysaccharide systems for the design of adaptive and responsive hydrogel networks.

Song et al.[5] presented the increasing interest towards multifunctional hydrogels with mechanical toughening, shape memory, self-healing and biocompatibility. While it is a basic, rudimentary hydrogel system for the moment, the concept that one polymer network can perform multiple roles applies here. The desired properties are the swelling characteristic, elastic property, syringeability and partial self healing property for NG/3-APBA/PVA hydrogels.

The reversible covalent and non-covalent interactions such as borate ester, imine, disulfide, hydrogen bonding, ionic interaction and host-guest complexation[6] .They have worked on it because they put PBA-diol ester bonds in the broader context of the different dynamic crosslinking strategies of

hydrogels. In this thesis, the neem gum hydrogel system follows a particular path of covalent bonding, however there are other dynamic hydrogel pathways that can be compared.

The current thesis is this idea. The NG/3-APBA/PVA hydrogel is prepared by permanent crosslinking of the NG with 3-APBA through amide bonds, whereas, linkage between PVA and 3-APBA is achieved via PBA-diol bonds which are reversible and dynamic[7]. The mixture of dynamic and permanent interactions is a good explanation for the stability and responsiveness.

2.2 Natural Polymer-Based Hydrogels

Natural polymers, synthetic polymers or a mix of natural and synthetic polymers can be used to create hydrogels. Biocompatibility, biodegradability and functional group diversity are desirable properties for natural polymer hydrogels. But, many natural polymers need the modification or blending to have better mechanical strength and stability. In the present work this hybrid approach has been undertaken and chemically modified neem gum along with PVA has been used.

Recent research pointed out the usefulness of polysaccharides in building structured and functional hydrogels from polysaccharides, and their hydroxyl-rich functional groups facilitate hydrogen bonding and boronic ester formation. Neem gum is in this class as it has hydrophilic groups that help to take up water and also offer sites for chemical changes. This thesis reports the oxidation and grafting process which transforms neem gum into a more functional hydrogel precursor from a natural gum.

Shobana et al. isolated and characterized polysaccharides found in gum from two plants, Moringa oleifera and Azadirachta indica, demonstrating the complex nature of the polysaccharides of Moringa gum[4]. They have directly used the neem gum as a polymeric compound for hydrogel production. The advantage of this complex structure of neem gum is that heteropolysaccharides, usually, have more than one functional group that likes to interact with water and for reagents as well as polymer chains[8]

The medicinal and biological significance of neem and its wide-ranging applications in making nanomaterials have been reviewed[9]. Biological activity is not assessed in the present thesis although the usage of neem trees is a long history, the utilization of neem gum in biomaterial-oriented hydrogel systems bear a positive rationale. In the future, the utilization of neem gum in wound dressing or drug delivery matrix would be beneficial.

Previous researchers have investigated the neem gum in covalent and supramolecular interactions for hydrogel dressing[10] . In particular, their work shows that neem gum can serve its purpose in network formation and it can be used in functional soft materials. How different the present study is, is that it does two things: (1) It introduces boronic acid chemistry to a neem gum-based hydrogel platform, using PVA and 3-APBA to create PBA-diol ester bonds and (2) It proves that boronic acid chemistry for water-based hydrogels is feasible[11]

2.3 Neem Gum and Related Plant Gum Hydrogels

Azadirachta indica is a fast-growing, hardy evergreen plant and is suitable for tropical and subtropical areas[12] .The level of ecological availability, which includes materials extracted from neem, makes the research of sustainable polymers using neem materials and products possible. The natural origin and availability of neem gum makes it a good alternative for a renewable polysaccharide in the synthesis of hydrogels, especially when the polysaccharide sources are renewable[13].

Shobana et al. reported that the neem gum is an exudate extracted from neem bark and has a complex heteropolysaccharide (HPS) composition with an appearance of clear brown gum. Therefore, it justifies the selection of neem gum as the natural polymeric precursor used in this study. Neem gum consists of repeating carbohydrate units and functional groups which are polar that can be oxidized and chemically grafted for the production of hydrogels[14].

Traditional medicine uses all of the neem tree's components, such as its leaves, bark, fruits, gum and oil[15]. This general uses, gives an insight into the biological and cultural backgrounds of the utilization of neem gum. The present thesis does not consider neem gum as a traditional medicine but rather as a bio-derived polymeric material which can be modified by oxidative and grafting reactions.

Apart from the traditional applications ,neem gum and its derivatives were also considered as polymeric materials[13] .They conclude that the neem gum is possible to be modified into a function matrix, based on their analysis. One such modification strategy is the oxidation and 3-APBA grafting process that is followed within this thesis.

Recent studies show that hydrogels based on neem gum can be created by combining covalent and supramolecular interactions. It is noteworthy that more than one type of interaction is combined in this study. Organic functionalization (amide-bond formation during grafting of 3-APBA) and physical structuring (esterification with PBA and freeze-thaw) both are expected to help create the final network of the hydrogel formation.

2.4 PVA Hydrogels and Freeze-Thaw Crosslinking

PVA is a molecule which is useful for three reasons: its solubility in water, its hydroxyl rich structure and its biocompatibility which make it a useful molecule for hydrogel formation and as a network former[16]. The work is used as a basis for the choice of synthetic polymer in this thesis, namely PVA. The importance is that the hydroxyl groups of PVA play a crucial role as they do upon reaction with the boronic acid groups of 3-APBA to create PBA-diol ester linkages[17].

The advancement in PVA-based hydrogels in recent years were discussed and the preparation techniques and applications were highlighted. PVA can be chemically or physically crosslinked, as well as blended with natural polymers, and modified to achieve desired mechanical swelling

characteristics[18]. In addition to being a structural polymer, the present NG/3-APBA/PVA hydrogel is a also reactive diol-containing polymer utilized for a boronic ester formation[19].

One of the most commonly used methods of physically crosslinking the PVA is via freeze-thaw treatment, as toxic cross-linking agents are not necessary in the process and forms crystallite-based junction zones[20]. In the current paper, chemical mixing prior to freeze-thaw cycling is utilized for not only supporting gel formation but network stability too.

Previous review have concentrated on the fabrication techniques and biological applications of PVA hydrogels, highlighting the role of crosslinking mechanism in determining the final product properties. Their talk provides insight into the properties of the NaOH content why the NG/3-APBA/PVA hydrogel can exhibit different behaviors. Excessive alkalinity would promote the formation of boronate esters, but may result in the loss of swelling capacity and/or changes in mechanical flexibility if the crosslink is too strong or if the number of crosslinks is too high[21].

Polyvinyl alcohol (PVA) based hydrogels were created with a water- retention addition, revealing that the water content of the hydrogel could be regulated by modifying it's network properties. This is in keeping with the overall idea of mixing PVA with natural or semi-natural materials. Therewith in this Thesis neem gum is used as natural polymeric partner and 3-APBA as a functional linker.

2.5 Boronic Acid and PBA-Functionalized Hydrogels

Guan & Zhang critically discussed boronic acid containing hydrogels and explained how they were synthesized, their characteristics and applications[22]. Their work is one of the key theoretical supports for the present thesis as they consider about glucose sensitivity, the reversibility and the self-healing potential of boronic acid groups in the formulation of hydrogels. In the current study, the 3-APBA moiety is incorporated into the structure of neem gum.

Aspiring to this idea, research on phenylboronic acid based hydrogel systems was done and the effective chelating ability of the phenylboronic group towards diol containing molecules was discussed[23]. This is the chemical link that is known as a PBA-diol ester bond and is the basis used in this thesis. It is found that PVA has numerous hydroxyl groups which can show its diol rich polymeric nature and interact with (3-APBA-grafted) neem gum.

Terriac et al. reviewed boronic ester hydrogels for biomedicine and highlighted the role of biomedicine in material chemistry in regulating the behavior of boronic ester networks[11]. Their study demonstrates that the concept of boronic ester crosslinks can be considered a novel method to create hydrogels that are responsive, injectable and self-healing. The NG/3-APBA/PVA hydrogel here fabricated is an example of this chemistry that is based on neem gum.

Morariu et al. provided a general overview of glucose-sensitive phenylboronic acid-based gels and its application to the creation of glucose-responsive polymer networks[24]. The PBA-diol chemistry is also

the crosslinking chemistry that is the core of this dissertation, although it is not the central experiment in this dissertation. The current hydrogel could thus be used as a foundation for future release and sensing research.

Shi et al. also fabricated injectable hydrogels with a dual functionality of dynamic and injectable hydrogel ,using PVA and hyaluronic acid (HA) grafted with PBA[25]. It particularly is relevant due to its natural polysaccharide, modified with PBA, that is crosslinked with PVA by the formation of boronic ester bonds. The present thesis adopts a similar rationale of design and use the replacer of hyaluronic acid with neem gum as an alternate polysaccharide in PBA-PVA hydrogel system.

2.6 Swelling, Rheology, Syringeability, and Self-Healing

When a dry swellable hydrogel is exposed to water, it absorbs the liquid and expands in volume, initiating the swelling process[26]. Their research helps in comparing the two Hydrogels, A and B, over time , which was the purpose of this thesis. A difference in swelling between Hydrogel A (approximately 93%) and Hydrogel B (75%) clearly shows that network density has a significant influence on swell.

Viscosity is a direct indicator of a material's resistance to deformation under stress. It also assesses how effectively hydrogel formulation respond to changes in shear stress during injection[27]. The NG/3-APBA/PVA hydrogel exhibits shear thinness, which is highly desirable, namely, its viscosity drops at high shear rates. This behavior can be applied to the creation of injectable hydrogels, and helps with the process of extrusion through a needle.

Syringeability is the ability of a hydrogel to be extruded through a needle[28]. In the present work, both the Hydrogel A and Hydrogel B were extruded through the 16G needle which showed that extrudability of the formulations is feasible under the applied pressure.

Boronic ester-connected self-healing hydrogels have been reported by Yesilyurt et. al. ,who demonstrated that the reversible boronic ester interactions play role in self-healing and biomedical functions[29]. Their results back this interpretation of this thesis's findings of partial self-healing. After 24 hours the cut hydrogel surfaces partially reconnected, indicating that reversible PBA-diol interactions were related to the recovery of the interface.

Previous research described the principles behind self healing in reversible covalent hydrogels in terms of the mobility of the chains along the hydrogel and the facility of the bonds to reform after damage. This provides some understanding of why the NG/3-APBA/PVA hydrogel demonstrated only partial healing. Even though boronic ester bonds are dynamic, these bonds represent a high proportion of the processing volume, the chain is not diffused, it can be hydrated, and the network is stiff.

2.7 Summary of Literature Gap

Lu et al. demonstrated that polysaccharide-boronic acid hydrogels are a significant category of dynamic biomaterials but most of the studies reported are related to the use of along-used polysaccharide in such system instead of neem gum. This means that it is a particular deficit of how the use of neem gum as a PBA-functionalized natural polymer backbone is constructed[30].

Although the feasibility of PBA-polysaccharide/PVA dynamic hydrogel has been demonstrated in few cases, using neem gum as a polysaccharide instead of the conventional polysaccharide is less explored[31]. The present work thus helps in the above direction by utilizing a system based on neem gum with the same boronic ester design concept.

PVA-polymeric hydrogel continues to be important but polymeric material alone may not be able to gives all the characteristics required for the advanced materials[32] .The synergistic effect of blending PVA with chemically modified neem gum and 3-APBA offers a pathway to explore the ability to combine hydrophilicity, natural polymer content, dynamic crosslinks and application potential

Boronic acid hydrogels are widely employed in controlled distribution and sensing, but the material must be optimized for various polymer combinations[33]. This need is addressed in the present thesis by comparing the swelling, rheology, syringeability and self-healing behavior of Hydrogel A and B in relation to the network formation with the addition of NaOH.

3. MATERIALS & METHODS

3.1 Introduction

Targeted in this chapter are the experimental materials and methodology employed in the synthesis of NG/3-APBA/PVA hydrogels.The materials and methodology used in the NG/3-APBA/PVA hydrogels synthesis are described in the chapter. The process is divided into three basic steps: oxidation of Neem gum, grafting of 3-APBA by amide bond formation and formation of the hydrogel network by the PBA-diol ester bonding with PVA. Then repeated freeze-thaw cycle was employed to foster a gel with enhanced network stability.

Two types of hydrogel A and B were formulated. The only difference between these formulations was the amount of NaOH added when mixing. 2 ml NaOH was used for preparing Hydrogel A while the Hydrogel B was prepared with the use of 3ml NaOH. This variation was introduced to investigate the effect of alkaline conditions on the formation of PBA-diol ester bond, swelling behaviour and mechanical response.

3.2 Materials

The chemicals and reagents used during the experimental work are presented in Table 1. Every reagent was used exactly as supplied, requiring no additional purification. The entire synthesis process was performed using deionized water to prevent the possibility of unwanted ionic contamination when preparing solutions or forming hydrogels.

Table 1. Materials and reagent specifications used for hydrogel synthesis

Material/Reagent	Specification/Source	Role in synthesis
Neem gum	Procured from Indian Jadibooti Pvt. Ltd., Tamil Nadu, India	Natural polysaccharide backbone
Hydrogen peroxide	30% w/v, Rankem	Oxidizing agent for neem gum
3-Aminophenylboronic acid	98%, BLD Pharm	Boronic acid grafting linker
EDC.HCl	SRL	Carbodiimide coupling agent
NHS	Laboratory reagent	Activation agent for amide bond formation
Polyvinyl alcohol (PVA-hot)	Mw 60,000-125,000, hydrolysis 87-89 mol%, CDH	Diol-containing synthetic polymer
Sodium hydroxide	Laboratory reagent	Alkaline medium for PBA-diol ester formation
Deionized water	Laboratory supply	Solvent for all solutions

3.3 Oxidation of Neem Gum

Hydrogen peroxide was used as an oxidizing agent in the first step of the neem gum synthesis process. A desired amount of neem gum (0.5 g) was dissolved at room temperature in 10 millilitre of deionised water. The solution was hydrated and stirred at 400 rpm for 1 hour to get uniform dispersion of neem gum chains in the aqueous medium.

Once it was completely dissolved and hydrated, hydrogen peroxide (4ml) was added to the neem gum mixture. The blend of reaction mixture was agitated for 30 minutes at the temperature of 65°C. This oxidation step was aimed towards getting carboxyl groups into neem gum structure. The oxidized neem gum sample was labelled O-NG.

3.4 Grafting of 3-Aminophenylboronic Acid on Oxidized Neem Gum

The second step was amide bond grafting of the oxidized neem gum with 3-APBA. The EDC/NHS coupling chemistry was used for the activation of the carboxyl groups produced. Here 0.5g of EDC and 3g of NHS were incorporated in the oxidized neem gum solution, and the mixture was agitated at room temperature for half an hour.

Following activation 0.5g of 3-APBA was introduced into the solution. 3-APBA was stirred with activated carboxyl groups of O-NG to form amide bonds; the whole process was carried out for 24 hr at a temperature of 10°C. This grafted solution was labelled Solution 1.

3.5 Preparation of PVA Solution

The PVA mixture was prepared as separate solution. 1g of PVA was dissolved in 20 mL of a deionized water solvent. Stirring the mixture for 20-30 minutes at 85°C and 400 rpm produced a homogenous solution . The necessity of heating step was due to the fact that PVA is commonly hard to fully dissolve in the solution caused by strong intermolecular hydrogen bonding and crystallinity.

A solution of PVA was prepared to which we called Solution 2. The hydroxyl groups on PVA can serve as diol rich groups for further interaction with boronic acid groups of 3-APBA-grafted neem gum. PVA was hence not just a supporting polymer, but also a chemical participant in the formation of PBA-diol ester bond.

3.6 Formation of PBA-Diol Ester Bond and Hydrogel Network

Solutions 1 and 2 were mixed under alkaline conditions to perform hydrogel formation. In a test tube 5 ml of Solution 1 and 5 ml of Solution 2 along with 2 ml of NaOH was mixed for Hydrogel A. For Hydrogel B , 5 mL of solution 1 were combined with 5 mL of solution 2 and this was mixed in with 3 mL of NaOH. The mixture was homogenized well to ensure the good interaction between 3-APBA-grafted neem gum and PVA.

The alkaline environment was formed with the help of NaOH, which is necessary for the formation of boronic acid-diol esters. In these circumstances, the boronic acid group is more effective to interact with hydroxyl groups of PVA. It was hoped that the various NaOH volumes would affect the network density. Hydrogel B was not expected to present as favorable crosslinking conditions for PBA-diol compared to Hydrogel A as it was made with higher quantities of NaOH.

Table 2. Experimental composition of Hydrogel A and Hydrogel B

Sample	Solution 1	Solution 2	NaOH volume	Processing condition
Hydrogel A	5 ml O-NG-g-APBA solution	5 ml PVA solution	2 ml	Freeze-thaw cycles repeated 3 times
Hydrogel B	5 ml O-NG-g-APBA solution	5 ml PVA solution	3 ml	Freeze-thaw cycles repeated 3 times

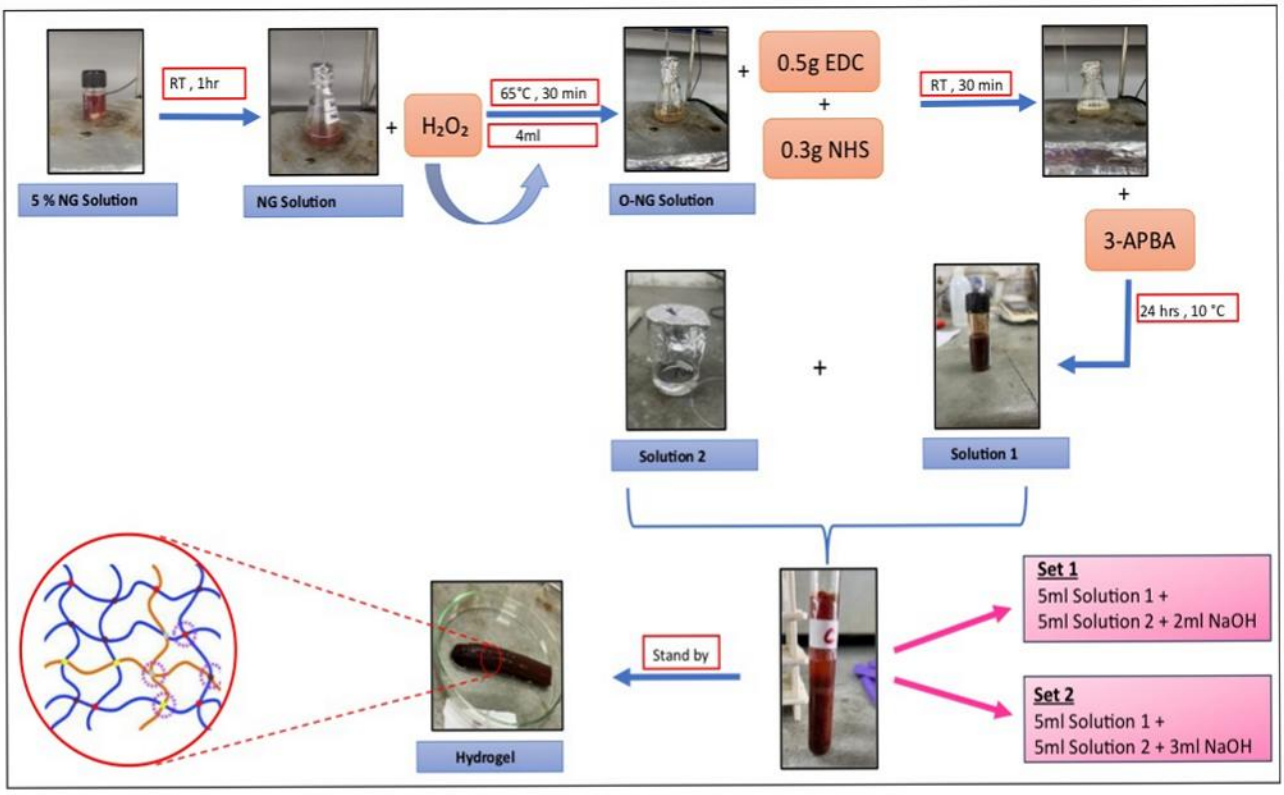


Figure 2. Research methodology for synthesis of hydrogel from neem gum

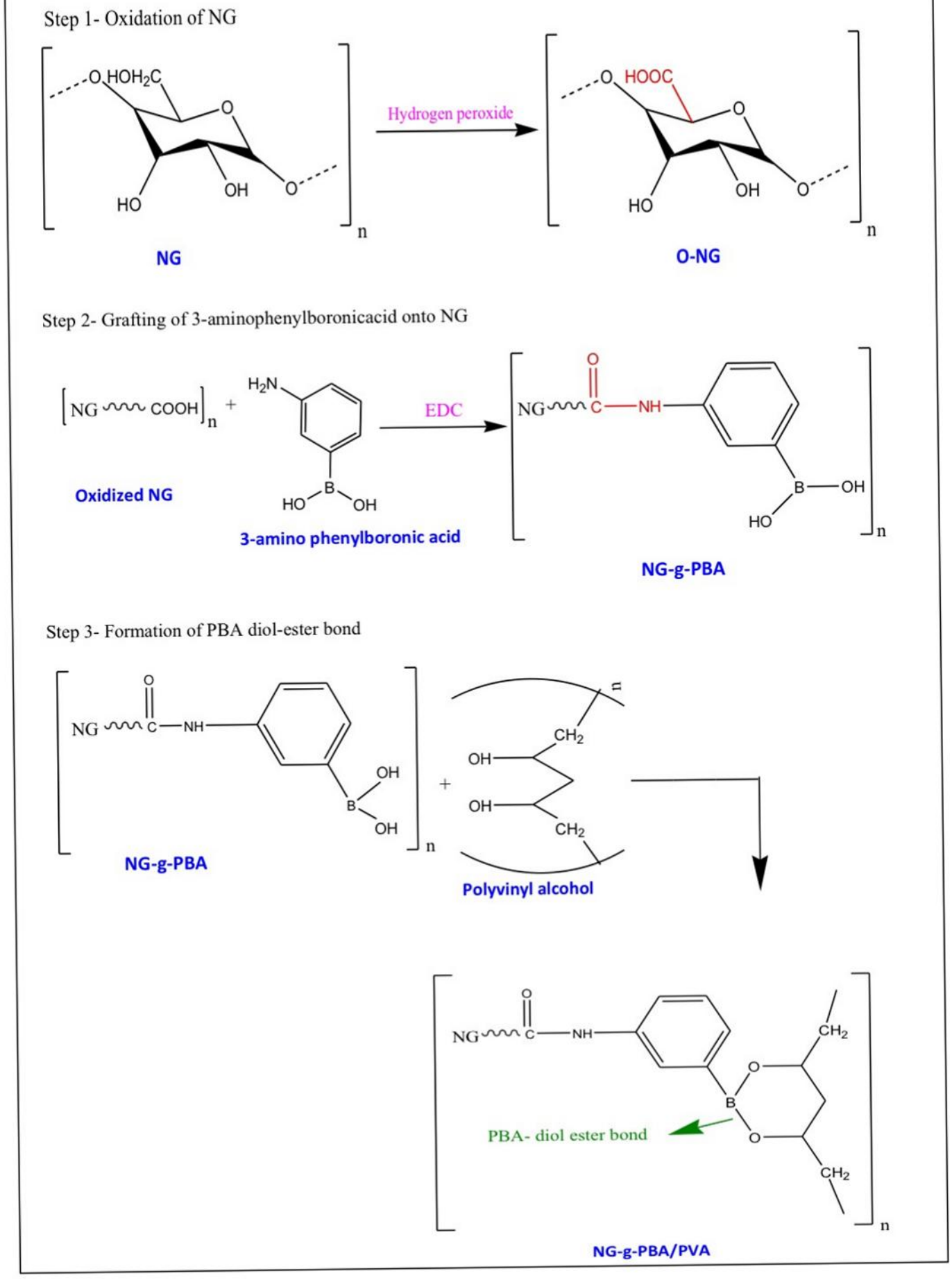


Figure 3. Reaction scheme showing oxidation of NG, amide bond formation, and PBA-diol ester bond

3.7 Freeze-Thaw Technique

The total time the test tubes with the mixture of hydrogels were kept in the refrigerator after mixing was 22 hours, followed by 6 hours at room temperature. This was repeated three times of freezing and thawing. It is a physical gelation technique that often uses the freeze-thaw method to induce the crystallite growth and formation of physical junction zones in the PVA-based systems without need of additional toxic crosslinkers.

In freezing, the ice phase removes polymer molecules from the unfrozen phase thus enhancing the chances of chain association and the establishment of physical junctions. The network relaxes during the thawing of the material, but the crosslinked domains remain. In the existing system, the hydrogel network became stable as a result of the combination of the freeze-thaw cycling and the PBA-diol ester formation.

3.8 Characterization Methods

The prepared hydrogels and intermediate products were investigated to measure their FTIR spectroscopy, swelling studies, rheological measurements, syringeability and self-healing characteristics. These methods have been chosen due to their complimentary information with respect to chemical bonding, water absorption, viscoelastic properties, flow through a needle, and network recovery from damage.

FTIR spectroscopy was used to verify the oxidation of neem gum and boronic acid functionality along with grafting of 3-APBA in hydrogels. The study performed on Hydrogel A and Hydrogel B revealed a comparison of their water uptake properties by swelling studies and their storage modulus, loss modulus, frequency and viscosity properties by rheology. To evaluate the application-oriented performance, the following tests were conducted: syringeability test and self-healing test.

Table 3. Characterization methods and their purpose

Characterization method	Sample(s)	Purpose
FTIR spectroscopy	O-NG, O-NG-g-APBA, Hydrogel A, Hydrogel B	Functional group and bond confirmation
Swelling study	Hydrogel A, Hydrogel B	Water uptake and network density
Amplitude sweep	Hydrogel A, Hydrogel B	Linear viscoelastic region and strain stability
Frequency sweep	Hydrogel A, Hydrogel B	Elastic/viscous response with frequency

Viscosity measurement	Hydrogel A, Hydrogel B	Shear-thinning behavior
Syringeability test	Hydrogel A, Hydrogel B	Extrusion through 16G needle
Self-healing test	Hydrogel A, Hydrogel B	Interfacial recovery after cutting

3.9 Experimental Considerations and Mechanistic Basis

The type of experimental design will rely on a set of reactions that are SECURE. Oxidation prior to 3-APBA grafting was done since unmodified neem gum itself does not have enough carboxyl groups for coupling. Hydrogen peroxide was chosen as oxidant since it can be used to oxidize molecules in relatively mild conditions in water. Samples were oxidized for a specific period of time and at a specific temperature to encourage carboxyl group formation without over degrading the polysaccharide backbone.

To enhance the formation of the amide bond was incorporated the EDC/NHS coupling step, between O-NG's carboxylic group and 3-APBA's amino group. EDC is used to activate carboxyl groups and NHS to increase the stability of the activated intermediate. When 3-APBA is added, nucleophilic attack can occur by the amino group leading to an amide linkage. This reaction is critical as it importantly and covalently attaches boronic acid functionality to the backbone of neem gum.

Alkaline mixing step was essential for the development of the hydrogel network. Boronic acid groups are stronger interacting with molec with diol at alkaline conditions. There are repeated hydroxyl groups present in PVA that offer various binding sites for the 3-APBA modified neem gum. This comparison between 2 ml and 3 ml NaOH was thus performed to assess whether additional alkalinity would also impact on the nature and/or extent of interaction between the PBA and the diol, as well as the final properties of the hydrogel.

Homogeneity of the solution, the formation of the gel and the manipulation of the sample were vital for all the stages. If neem gum or PVA does not get dissolved completely in water, it can give non-uniform gels. If the solutions are not well mixed adequate concentration gradients could develop. Thus, the speed of stirring, the temperature, the reaction time and the number of freeze-thaws for both formulations were kept constant. This was important in order to ensure that the volume of NaOH was the only variable between Hydrogel A and Hydrogel B.

4. RESULTS AND DISCUSSION

4.1 Introduction

The results obtained when characterizing O-NG, O-NG-g-APBA, Hydrogel A, and Hydrogel B are presented and discussed in this Chapter. This is discussed in relation to the synthesis pathway outlined in Chapter 3. The chemical changes are confirmed by FTIR spectroscopy, water uptake is compared by swelling studies, viscoelastic properties evaluated by rheology and practical performance is realized by syringeability and self-healing tests.

Hydrogel samples both exhibited similar chemistries, but different physical reaction. This is not unusual since Hydrogel A and Hydrogel B is made with the same polymer and different amounts of NaOH. It is expected that the alkaline gradient-induced difference in the formation and formation efficiency of PBA-diol ester bonds has effects on the network density, swelling ability, stiffness, shear response, and self-healing abilities of the precursor systems.

4.2 FTIR Analysis of Pure NG, O-NG, O-NG-g-APBA, Hydrogel A, and Hydrogel B

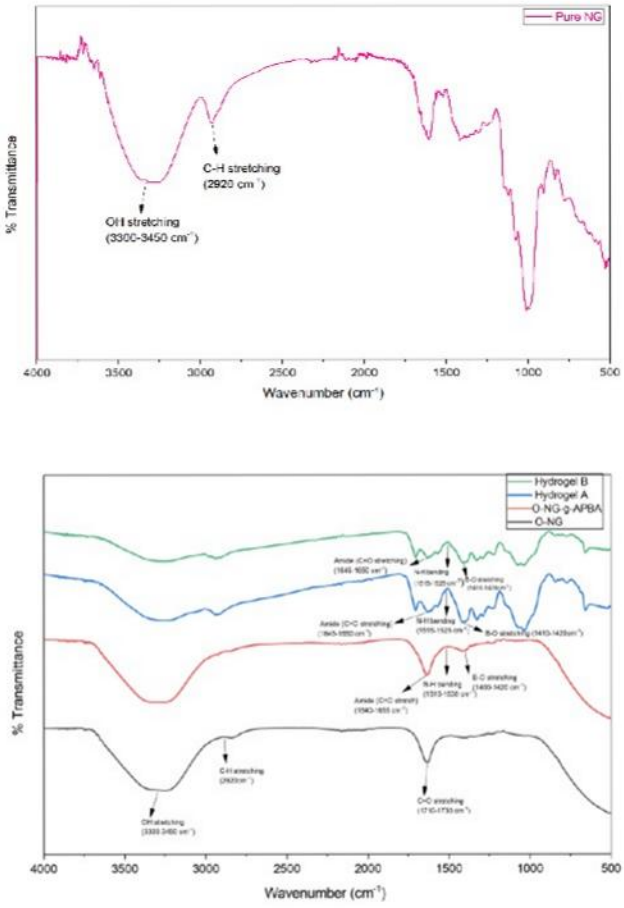


Figure 4. FTIR spectra of Pure NG, O-NG, O-NG-g-APBA, Hydrogel A, and Hydrogel B

FTIR spectroscopy was conducted for the wavenumber range of 500 to 4000 cm^{-1} to confirm whether a chemical change had taken place in each step in the process of synthesis of the hydrogel. The spectra of oxidized neem gum (O-NG), 3-APBA grafted oxidized neem gum (O-NG-g-APBA), Hydrogel A and Hydrogel B were compared. The FTIR results support oxidation, formation of amide bond, retention of boronic acid and the formation of a hydrogel network.

O-H stretching band are visible in pure neem gum at about 3300-3450 cm^{-1}, and the C-H stretching at 2920 cm^{-1}[34] .In the O-NG spectrum, there was a broad O-H stretching band between 3300-3450 cm^{-1}, which was assigned to the polysaccharide chain. This general band is typical of hydroxyl-rich polysaccharides and hence indicates a lot of hydrogen bonding. The C-H stretching band was present around 2920 cm^{-1}, suggesting that the oxidized polysaccharide still contained the organic polysaccharide backbone. Most importantly is to indicate the formation of carboxyl groups by hydrogen peroxide mediated oxidation by a carbonyl absorption band in the region of 1710-1730 cm^{-1}. The presence of such a carbonyl band was considered as the main criterion for successful neem gum oxidation.

The O-NG-g-APBA spectrum exhibited characteristic changes after grafting with 3-APBA. A new band that is attributed to the Amide I vibration and is mainly connected to the C=O stretching of the new amide bond emerged in the 1640- 1655 cm^{-1} range. The second band localized in the 1510-1530 cm^{-1} region was identified as the Amide II vibration which is related to the bending vibration of N-H. These bands establishes that the activated amino group of 3-APBA got coupled with the oxidized carboxyl groups of neem gum through EDC/NHS method.

The presence of boronic acid related functionality was additionally verified by the presence of a band ascribed to the B-O stretching vibration in the 1400- 1420 cm^{-1} range, after 3 – APBA grafting. The appearance of this band is significant because the boronic acid group is needed for interactions with PVA in later phases of the PBA-diol ester. Simultaneously a change in the 1710-1730 cm^{-1} carbonyl band intensity was seen showing some loss of carboxyl groups during amide bond formation.

Table 4. FTIR peak assignments of O-NG, O-NG-g-APBA, Hydrogel A, and Hydrogel B

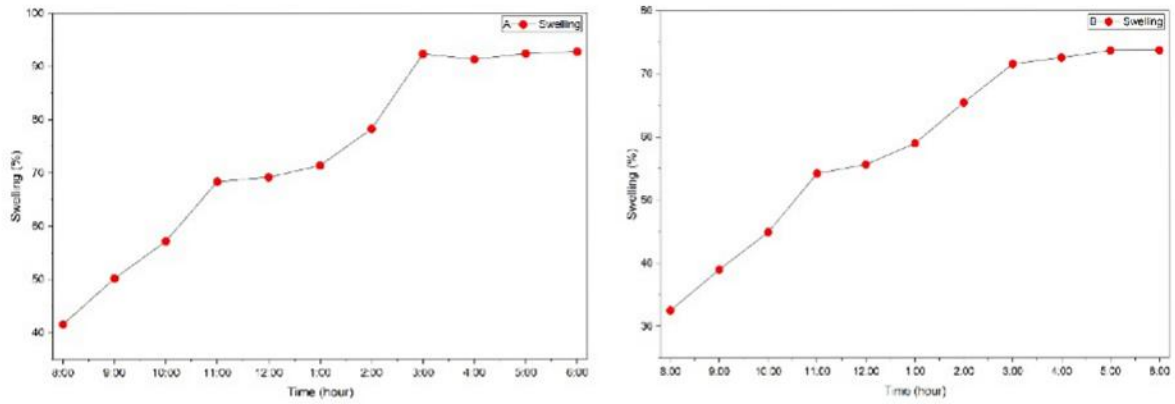
Wavenumber region (cm^{-1})	**Assigned vibration**	**Interpretation**
3300-3450	O-H stretching	Hydroxyl groups in neem gum/PVA and hydrogen bonding
~2920	C-H stretching	Aliphatic organic backbone retained after oxidation
1710-1730	C=O stretching	Carboxyl group formation in oxidized neem gum

1640-1655	Amide I (C=O stretching)	Amide bond formation between O-NG and 3-APBA
1510-1530	Amide II (N-H bending)	Confirmation of grafted 3-APBA linkage
1400-1420	B-O stretching	Retention of boronic acid functionality

The spectra of Hydrogel A and Hydrogel B were quite similar in most part to that of the O-NG-g-APBA. The Amide I band, Amide II band, and B-O stretching band were both seen for both hydrogel spectra. The indices can be seen as being spectrally consistent, showing that the amide bonds and boronic acid functionalities used for grafting were spectrally stable during the preparation of the hydrogels and the freeze-thaw cycling. The ability of boronic acid group to retain its functionality allows the formation of PBA-diol ester interactions with PVA hydroxyl groups.

FTIR does not directly measure the number or density of crosslinks, but rather helps to confirm the presence of functional groups. Thus, FTIR profile of Hydrogel A and Hydrogel B can be similar even though there may be changes in the physical network of the hydrogel. The effect of volume of NaOH was found greater in swelling behavior and rheology properties. This is why it is extremely important to confirm successful chemical synthesis with FTIR and differences in network density with swelling and rheology.

4.3 Swelling Studies



(A) (B)

Figure 5. Swelling study of hydrogel A and hydrogel B

The swelling properties of the NG/3-APBA/PVA hydrogels were determined by recording the swelling percentage for various periods of time. Absorptive-cum-retentive capability of the polymeric network is embodied by its swelling capacity, and it is one of the significant properties of a hydrogel[35]. The

swelling process starts when water molecules enter into the dry or partially hydrated network of the hydrogel, interacting with the hydrophilic groups.

Hydrogel A and Hydrogel B both showed swelling over the period of time. The first few minutes the water absorption was very high; ample hydrophilic sites and free volume spaces existed in the polymer network. The swelling rate was seen to decrease over time and eventually the rate of swelling became approximately zero, which is referred to as the equilibrium state. This plateau point represented the configuration where the driving force to absorb water, which is osmotic pressure, had balanced out with the water pull-back force of crosslinked hydrogel network[36].

The increase in sample volume for Hydrogel A was about 93% whereas the increase in the sample volume for Hydrogel B was about 75%. This difference is important since the same amount of neem gum, 3-APBA, and PVA was used for preparation of the two hydrogels but different quantities of NaOH. The comparatively looser network, higher free volume, and higher chain mobility of Hydrogel A prepared from 2 ml NaOH solution suggest that it exhibited a higher porosity. A higher porosity for Hydrogel A prepared by 2 ml NaOH solution was suggested, as the network was loose, the free volume was high, and the chain mobility was high. This made it possible to enter and to stay more water molecules within the structure.

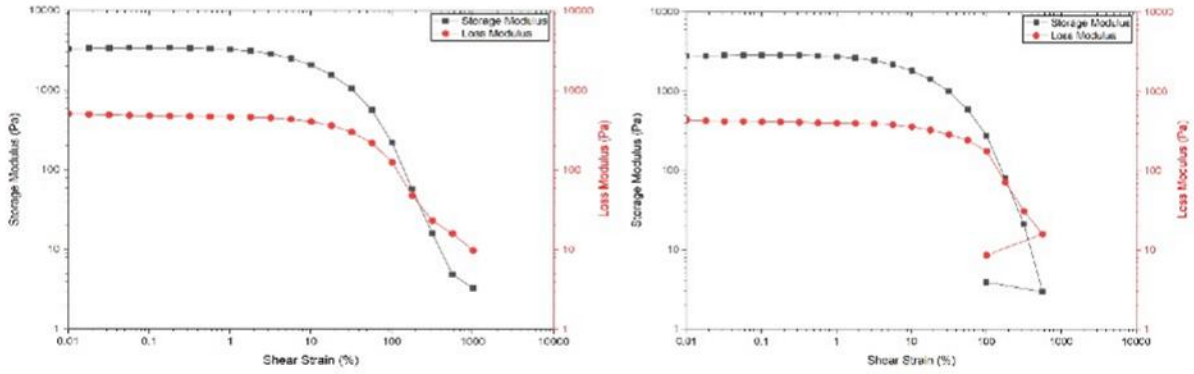
Lower swelling was exhibited in the Hydrogel B which was prepared using 3 ml of NaOH. Boronic acid groups are more favourable for the formation of a boronic acid ester with the hydroxyl groups of PVA under more basic conditions[37]. This enhances interactions resulting in compacting the network and decreasing chain mobility and water uptake[38][39]. Thus, the lower swelling of Hydrogel B is considered a measure of the higher or greater degree of crosslinking of the PBA-diol ester with respect to Hydrogel A.

Table 5. Comparative swelling behavior of Hydrogel A and Hydrogel B

Sample	**NaOH volume**	**Maximum swelling**	**Network interpretation**
Hydrogel A	2 ml	~93%	Looser network, higher free volume, greater water uptake
Hydrogel B	3 ml	~75%	Denser network, stronger PBA-diol interaction, reduced water uptake

4.4 Rheological Analysis

4.4.1 Amplitude Sweep



(A) (B)

Figure 6. Amplitude sweep of hydrogel A and hydrogel B

Amplitude sweep analysis was used to assess the hydrogel viscoelastic characteristics at a constant angular frequency, 10 rad/s, and increasing amplitude of oscillatory strain. This test is valuable to identify the region of linear viscoelasticity (LVR) with no rupture in the internal network structure and where the storage modulus (G prime) is approximately constant. The LVR presents the data on the range of the strains for which hydrogel can be used as a stable elastic material[40].

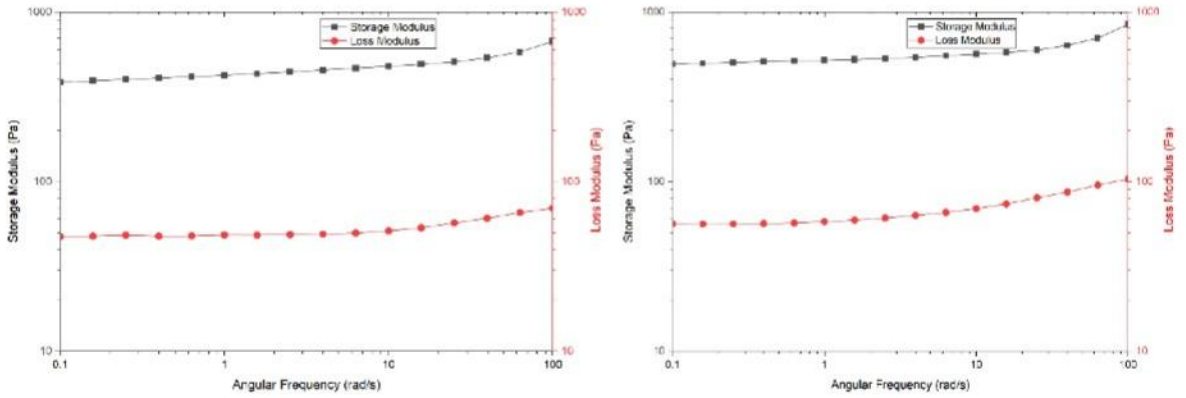
At low strain, the value of storage modulus was greater than that of loss modulus for both Hydrogel A and Hydrogel B. This means that under small deformations they are elastic solid-like networks. Storage Modulus is the amount of elastic energy stored when the material is stretched, whereas loss modulus is the amount of energy that flows through the material[40]. The significant contribution of storage modulus implies the successful development of a 3-D storage gel network.

It was discovered that when strain increased, the storage modulus dropped, as storage modulation represents the internal network which is disrupted when the strain increases. At higher strain values, the location where the storage modulus crossed over the loss modulus was an indicator of the change from solid-like to liquid-like behavior[40]. This transition represents failure of the hydrogels' structure due to shear. It is a common feature of physically and dynamically crosslinked hydrogels in which the network junctions may be broken apart by appropriate mechanical force[41].

The comparative analysis with the two samples was performed in such a way that the linear viscoelastic region was found to be wider in the case of Hydrogel A, and that it possessed a better structural stability under strain. The hydrogel B exhibited relatively premature deviation from the linear regime, which is indicative that the material might be more densely crosslinked and less flexible to deformation. This is because a more dense hydrogel is not necessarily more mechanically sound. Overcrosslinking or more

intense crosslinking can lead to increased stiffness, but the capacity of the network in terms of spreading strain will decrease.

4.4.2 Frequency Sweep



(A) (B)

Figure 7. Frequency sweep of hydrogel A and hydrogel B

To observe the hydrogel's viscoelastic reaction, frequency sweep measurements run over a range of angular frequency. Here, the strain is maintained in the material's linear viscoelastic area and frequency is changed. Typical properties of stable hydrogel network have storage modulus greater than loss modulus across the frequency range under investigation.

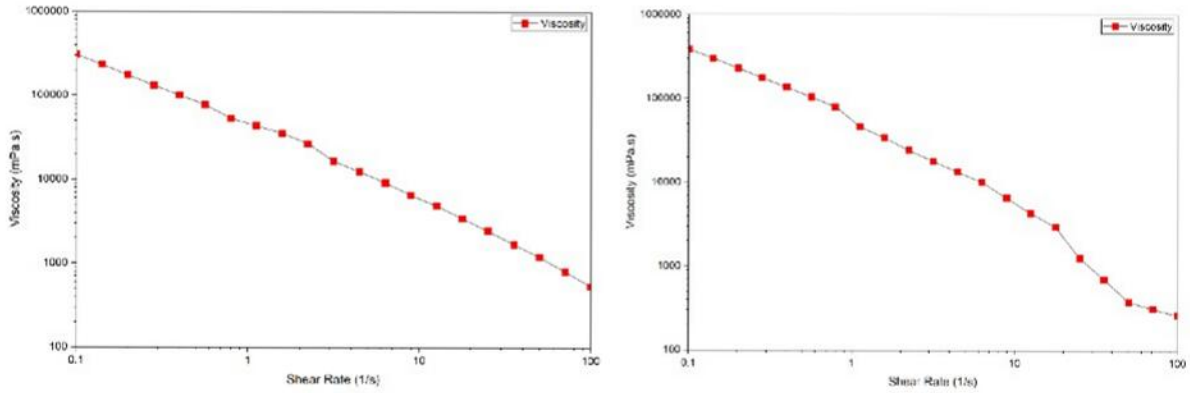
The frequency sweep data indicated that both Hydrogel A and Hydrogel B recorded higher storage modulus value than their loss modulus value. This is an indication that these two samples were elastic gel-like objects and not viscous liquids. The relatively constant modulus response suggests there is a reasonably developed 3-D network. This matches well with the visual observation of gelation and the FTIR analysis for evidence of chemical network formation.

The storage modulus values of hydrogel B were slightly higher in the frequency sweep, implying that it made a stiffer network. This aligns with the results of the swelling uptake obtained for Hydrogel B which gave more information of a denser structure. The resistance to large deformation of Hydrogel B, however, was lower, when compared with the amplitude sweep results. So, it is important to note that the response of Hydrogel B can vary from that of a more stiff material under small oscillatory, but less under larger applied deformation.

The combination of results represents an important structure-property relationship. The volume of NaOH can be increased to favour PBA-diol ester crosslinking and to also increase the stiffness of the networks at small strains but may also decrease network flexibility. The swelling ratio and strain tolerance of the systems were lower in hydrogel A, which was prepared using less NaOH, when compared to the other hydrogels.The swelling ratio and strain tolerance were higher for hydrogel A,

which was made with less NaOH, than for the other hydrogels. When adding a greater amount of NaOH to the mixture, hydrogel B is compacter, stiffer and less flexible.

4.4.3 Viscosity Behavior



(A) (B)

Figure 8. Viscosity curves of neem gum hydrogel A and hydrogel B

The flow behaviour of Hydrogel A and Hydrogel B were evaluated by viscosity measurement which was conducted as a function of shear rate; both of the hydrogels exhibited shear-thinning characteristic (when the shear rate increased, the viscosity decreased). Polymeric and dynamically crosslinked hydrogel systems are examples of biocompatible systems in which shear-thinning occurs due to alignment, reorganization or partial degradation of the internal structure under shear[42].

The shear thinning property of the hydrogel is key to practical applications because the material becomes flowable under stress but returns to a more solid-like once the stress is released. This property is very desirable for injectable hydrogel systems, since it enables pushing the material through a needle in the syringe with minimum shear resistance[43] . The shear at the exit from the needle may have time to let the network reconform slightly.

Hydrogel B exhibited greater viscosity in low shear rate suggesting that it has higher interactions or dense internal network. This phenomenon is in harmony with swelling and stiffness measurements which were performed on three large blocks of Hydrogel B, showing a lower swelling and a higher small-strain stiffness. The viscosity of Hydrogel B however, had a steeper drop at shear rate >2.0 s-1 suggesting that the network structure is more shear sensitive. The lower viscosity and the more gradual decrease of Viscosity in Hydrogel A indicated that the network in this sample was more flexible but less densely crosslinked.

The swelling measurements then agree with the results of viscosity tests. The swelling data thus corroborates the results of the viscosity tests. Hydrogel A can be seen to have a less compact and more flexible network, whereas for Hydrogel B the network is more compact but seems to be more shear-sensitive. The flow properties of both systems are beneficial but their differences indicate that optimization of NaOH concentration is required to meet the different applications. For use in absorbent

material a highly swellable formulation may be desirable, and for desired dimensional stability a stiffer formulation may be needed.

Table 6. Summary of rheological behavior of Hydrogel A and Hydrogel B

Test	Hydrogel A	Hydrogel B	Interpretation
Amplitude sweep	Broader LVR and better strain stability	Earlier deviation from LVR	A is more deformation-tolerant
Frequency sweep	Elastic solid-like behavior	Slightly higher stiffness	B is stiffer under small deformation
Viscosity	Lower viscosity, gradual shear-thinning	Higher low-shear viscosity, sharper decline	B has denser but more shear-sensitive network

4.5 Syringeability Test

(A) (B)

Figure 9. Syringeability test of Hydrogel A and Hydrogel B using 16G needle

To assess syringeability of the synthesized hydrogels, a syringeability test was conducted to determine if the hydrogels can be extruded through a 16G needle with pressure applied continuously. 2 ml of each hydrogel was placed into a syringe with a 16G needle, and extruded under constant pressure for 5 seconds. The aim of this test was to test the ability of the hydrogel flowing through the needle without any clogging and without any break in the flow.

The syringeability percentage (SP%) was determined according to the procedure established by Kumar & Purwar[44] with minor modifications.: $SP\% = \frac{W_2 - W_3}{W_2 - W_1} \times 100$

here W_1 the weight of an empty syringe with a needle, W_2 represents the weight of a syringe with a needle and loaded gel, and W_3 represents the weight of a syringe with a needle following extrusion. The syringeability value of Hydrogel A and Hydrogel B were about 81% and 79.9%, respectively. The values exhibited that take good extrusion forward both of hydrogels through the needle.

Both samples were successfully syringeable which is equally consistent with their shear-thinning. The amount of shear stress is high in the needless during the extrusion process in which the hydrogel is passed into the needle. In this condition the viscosity is reduced allowing flow to occur. Once it is extruded into the petri dish, the material may regain some gel-like properties. This behaviour is important for potential future applications in 3-APBA/PVA soft materials, where obtaining shape memory is desired through shape change after the polymer is treated with light.

The slightly larger syringeability for Hydrogel A is possibly due to the fact that the network density is lower for this material, there is more swelling, and there is less viscosity. The extrudability of Hydrogel B is established, however, it might be slightly better because of the closer network and the stronger interaction of Hydrogel B. The difference in both is quite close so both are essentially injectable under the condition tested.

4.6 Self-Healing Behavior

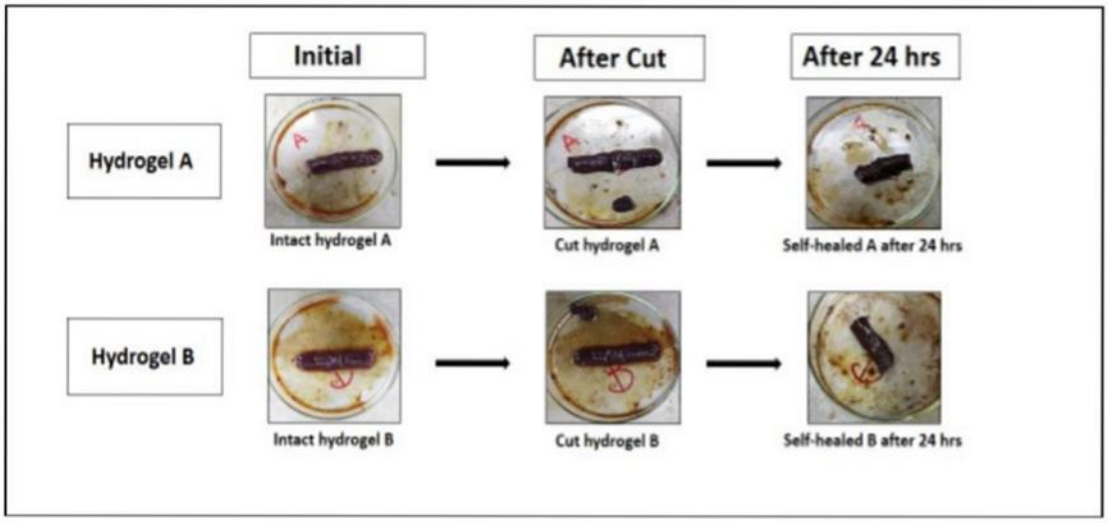


Figure 10. Self-healing behavior of NG/3-APBA/PVA hydrogels

Self healing behavior was qualitatively assessed by dividing each sample of hydrogel into two segments, and reuniting the two halves. Samples were then allowed to sit at room temperature for 24 hours. The goal was to see if the hydrogel surfaces will re-join because of the reversible interaction between the polymer network.

Partial self-healing occurred in both Hydrogel A and Hydrogel B after some time had passed.After 24 hours, we could see that both Hydrogel A and Hydrogel B had a partial healing effect. The dis-joining cut surfaces showed varying extent of interfacial recovery but no mechanical recovery was observed.

This means that irreversible interactions were found, but not enough to completely restore the original strength of the material under given conditions of testing. The partial healing behavior is in line with the idea of dynamic PBA-diol ester linkages between PVA units and 3-APBA[45].

Hydrogel A demonstrated relatively higher self healing property as compared to Hydrogel B. This may be due to the fact that Hydrogel A was made with a less densely crosslinked network; therefore the polymer chains at the cut interface could more easily move and re-associate. The flow of chains in Hydrogel B with a higher density of chain association may be lower, reducing the likelihood of broken interfaces re-forming. The swelling and amplitude sweep results are also interpreted in the same way, and are indicative of Hydrogel A's increased water uptake and improved deformation stability.

The fact the self-healing was partial implies that further optimization is necessary. The modifications can be made by tuning the 3-APBA grafting density, concentration of PVA, amount of NaOH, healing condition by water, healing temperature or healing time. There must be an appropriate balance in the number of dynamic bonds for healing and chain mobility for reformation at the interface. Self-healing hydrogels should have an optimal balance, which is one of the more difficult challenges in designing them.

4.7 Comparative Structure-Property Discussion

Finally, it can be concluded that both Hydrogel A and Hydrogel B were successfully synthesized and exhibited different structure-property behavior of the synthesized hydrogels. The essential functional groups that are involved in the reaction of amide bond and in boronic acid were identified by FTIR analysis and found present in both the hydrogels. Network density and flexibility were observed, however, through swelling, rheology, viscosity, syringeability and self healing became apparent.

The swelling, strain tolerance, partial self healing properties and the syringe ability of the Hydrogel A and B were compared, with Hydrogel A exhibiting higher swelling, wider strain tolerance, slightly superior syringe ability and improved partial self healing. The above properties indicate that the network in Hydrogel A is relatively loose, flexible. The relatively low amount of NaOH could have been enough to form PBA-diol ester, leading to a stable hydrogel, but maintaining chain mobility and free volume. This balance seems to be beneficial in water uptake and subsequent recovery from the deformation.

Under small deformation, the swelling of hydrogel B was lower, and the stiffness was higher. The above features indicate better interaction between PBA and diol in higher amount of NaOH. The denser network, however, showed lower water uptake and it could have decreased flexibility under higher strain. Thus Hydrogel A is a more swellable and adaptable formulation and Hydrogel B is a more compact and stiff formulation.

These outputs show the results that a higher level of cross-linking is not positive. For hydrogel design it will be dependent on the desired application. If too much crosslinking occurs it may inhibit water uptake and chain mobility of the absorbent or self --healing system. For mechanically stable systems,

low crosslinking could be the cause of a weak gel. Thus it is necessary to optimize the NaOH concentration, PVA content and 3-APBA grafting density in NG/3-APBA/PVA system.

Table 7. Overall comparison of NG/3-APBA/PVA hydrogel samples

Property	**Hydrogel A**	**Hydrogel B**	**Preferred sample**
Swelling	Higher (~93%)	Lower (~75%)	A for absorbency
Small-strain stiffness	Moderate	Higher	B for stiffness
Strain stability	Better	Lower	A for deformation tolerance
Viscosity	Lower	Higher	Depends on application
Syringeability	81%	79.9%	Both acceptable; A slightly better
Self-healing	Partial, comparatively better	Partial, less effective	A for recovery

4.8 Mechanistic Interpretation of Hydrogel Network Formation

The overall results are consistent with a mechanistic model in which the network of the hydrogels is stabilized by several interactions. The backbone of neem gum is the first level of structure, which consists of a hydrophilic polysaccharide backbone. The second level is the amide structure created by –CO(NH)– linkages between the oxidized neem gum and 3-APBA. This linkage is significant as it permanently makes the natural polymer boronic acid-derivatised. The dynamic PBA-diol ester interaction between boronic acid groups and PVA hydroxyl groups is the third level. The fourth level is physical structuring due to freeze-thaw cycling of mixture containing PVA.

The multi-interaction network can well explain why the hydrogels exhibited both stability and dynamics. Chemical functionalization with permanent amide bonds ensures complete maintenance of 3-APBA functionality, while reversible boronic ester bonds provide some rearrangement under water uptake, shear and cutting. The freeze-thaw cycle also adds another layer of association of the PVA chains within the network. Thus, the final material does not constitute a single physisorhetical crosslinked polymer, but rather a hybrid of physical – dynamic covalent hydrogel.

Mechanistically, there is also a difference between Hydrogel A and Hydrogel B. Hydrogel A is probably enough PBA-diol interactions for it to form a gel but not so many as to seriously reduce chain movement and free volume. This leads to more swelling, more strain tolerance and more partial self-healing. This suggests that more boronate ester formation occurs in the presence of the more alkaline Hydrogel B that leads to a more compact network. This enhances stiffness and diminishes swelling, as well as interfacing and recovery.

The results, therefore, showed a need for careful control of the crosslinking density. Higher crosslinking could enhance the shape stability, but might lead to less swelling and self-healing in the dynamic hydrogels. Reducing the crosslinking can lead to increased water uptake and mobility but to decreased mechanical strength. These properties are of the hydrogel to be formulated vary from one application to the other. With the same regard to the present system, Hydrogel A is more balanced and Hydrogel B can be employed in a situation that less swelling and higher stiffness are desired.

4.9 Potential Applications and Limitations

The NG/3-APBA/PVA hydrogels produced in this research presents some properties that could be helpful in other applications. They uptake water when being immersed, which indicates their possibilities as absorbent soft materials. They show shear-thinning behavior and they are syringeable, can be explored further as syringable, injectable, hydrogel matrices. They demonstrated a partial self healing effect, suggesting that reversible boronic ester bonds do play a role in recovery of networks under repeated deformations that are likely to occur for soft materials.

The biomedical application of such a hydrogel system could involve using a hydrogel-aided wound dressing matrix, for localized drug delivery, for soft materials that would be in contact with the tissues, or for injectable carrying materials. The addition of neem gum can prove beneficial as neem materials have always been significant in the biological world and PVA is a recognized biocompatible polymeric platform. But the present research does not validate the biomedical suitability. All the properties that make devices safe for biomedical use must be assessed prior to any claim—cytotoxicity, sterility, antimicrobial activity, degradation, hemocompatibility and behaviour in vivo.

The hydrogel can be used in the fields of environment or agriculture as a material that retains water in its structure or as a controlled release medium. Swelling capacity of Hydrogel A is high may be useful to absorb water, and the dense network of Hydrogel B may be useful to give slower diffusion. Prior to such uses, however, there needs to be a systematic testing of environmental stability, biodegradation, soil compatibility and release behavior of such products.

The main drawback of the present work is that the analysis is done based upon the preliminary synthesis and selected characterization techniques. FTIR is used to ascertain functional groups but not to measure grafting density. Information from swelling results is important but should be complemented by calculations of gel fraction and equilibrium water content. Rheology shows viscoelasticity, but some

compressive strength and cyclic recovery test is also required. In a similar fashion, the self-healing was qualitatively tested and should be measured mechanically in the future.

4.10 Conclusion and Future Scope

Synthesis of the NG/3-APBA/PVA hydrogels was successfully demonstrated in the present study by forming PBA-diol ester bond. Hydrogen peroxide was used to oxidize neem gum to produce carboxyl containing O-NG. The EDC/NHS mediated amide bond formation reaction was used for the grafting of 3-APBA onto O-NG. Dynamic PBA-diol ester linkages have been introduced into the grafted polymer under alkaline conditions to prepare the PVA/PBA gel and freeze-thaw cycles are adopted to reinforce the hydrogel formation.

The successful chemical transformation at every stage has been confirmed by FTIR analysis. The presence of carbonyl, amide and B-O bands was indicative of oxidation, amide bond formation and maintaining of an intact boronic acid. The results of the swelling studies found that the lower the amount of NaOH used, the larger the swelling, which was verified in Hydrogel A, compared to Hydrogel B. Rheological study showed the elastic solid-like behavior in both hydrogels, and viscosity measurements showed the shear-thinning behavior. Both hydrogels had the desirable property of being syringeable with a 16G needle, and had some degree of self healing after 24 hours.

Whereas Hydrogel A has a more favorable swelling-deformation-tolerant-syringeability–self-healing balance, Hydrogel B lacks tolerance for the former two properties but delivers superior self-healing and syringeability. Hydrogel B had a relatively high stiffness and low swelling that can be beneficial at the need of a more dense network. These findings show the importance of the volume of NaOH and subsequently boronic ester cross-linking environment to hydrogel properties.

The following further studies are recommended: quantitative determination of grafting efficiency, quantitative gel fraction analysis, compressive strength, long-term stability, pH-sensitive swelling property, drug loading and release property, cytocompatibility, antimicrobial property and microscopic morphology. Further experiments such as SEM, NMR, TGA and DSC as well as mechanical compression testing would give more insights into the hydrogel structure. Further optimized NG/3-APBA/PVA hydrogels can be used for biomedical dressings, injectable hydrogel matrices, controlled release systems and other functional application of soft material.

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