RADIOPAQUE MATERIALS FROM NATURAL POLYMERS:

Special emphasis on chitosan and natural rubber

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Certificate

This is to certify that the research work presented in the thesis entitled **"Radiopaque materials from Natural Polymers: Special emphasis on Chitosan and Natural Rubber"** is an authentic record of research work carried out by Ms. Nisha V.S under my supervision in the Department of Polymer Science and Rubber Technology, Cochin University of Science and Technology, in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Polymer Science and Rubber Technology, Cochin University of Science and Technology. No part of the work reported in this thesis has been presented by her for any other degree from any other institution.

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PREFACE

Polymers are used in every sphere of life now a days. Superior properties such as high strength / weight ratio, low energy requirement for processing, good insulation and excellent water resistance are responsible for replacement of conventional products by these materials. Polymers are used from domestic to industrial, insulation to conduction and water resistance to water absorption applications. Today polymers are being used in agriculture, medical, sports, ablative, automobile, aerospace applications etc.

Degradable polymers are currently being evaluated as medical implants in a wide range of applications, such as orthopaedic bone fixation devices, drug delivery systems, cardiovascular implants and scaffolds for the regeneration / engineering of tissues. Such polymers when used as implants are non-traceable without invasive procedures. A radiopaque polymer would offer the unique advantage of being traceable via routine X-ray imaging. The study of radiopaque polymers has been based on empirical approaches that have led to more systematic investigation in the past few years.

The main aim of the present work is to impart radiopacity in various natural polymers like chitosan, natural rubber and derivatives of chitosan and to characterize it. Also this thesis collated the radiopaque properties of these radiopaque polymers and various technological applications in the medical field.

Contents of the thesis:

The thesis is divided in to six chapters.

Chapter 1: A comprehensive introduction and literature survey of radiopaque materials, chitosan and natural rubber are presented in chapter 1. It also includes a review of the most relevant reports pertaining to the field of work. The scope and objectives of the present investigation is summarized.

Chapter 2: Details of the materials and experimental methods used for the present study are given in chapter 2.

Chapter 3: It is divided in to two parts. Part I gives details on the preparation of chitosan microspheres from different emulsion systems and their characterization. Chitosan microspheres were prepared using different emulsion systems and depending on the morphology of the resulting microspheres, the most desirable one was selected. The microspheres prepared from the optimized system showed better radiopacity by the incorporation of barium sulphate. The radiopaque chitosan microspheres were characterized using IR, X-ray, SEM, XRD etc. Part II of this chapter deals with the preparation of radiopaque microspheres from water soluble derivatives of chitosan and their characterization. Chitosan derivatives like chitosan formate, chitosan acetate and carboxymethyl chitosan were prepared and used as matrices for the preparation of radiopaque microspheres. In order to get good spherical morphology, carboxymethyl chitosan/PVA blend microspheres were prepared. The radiopacity of all systems were studied.

Chapter 4: The iodination of natural rubber to make it radiopaque is presented in the first part of chapter 4. Iodinated NR was compounded at high temperature and its properties like radiopacity, tensile strength, tear strength etc. were studied. In order to retain radiopacity after the curing processes, the room temperature vulcanization of NR was adopted. The radiopaque NR was characterized using UV, X-ray and TGA. The antibacterial properties of iodinated NR was studied by using zone inhibition method. The optical density of INR was also studied using

densitometer. Part II of this chapter comprises the studies on the radiopaque properties of radiopacifier filled NR. Natural Rubber was compounded with barium sulphate and commercial zinc oxide to make it radiopaque. Natural Rubber compounded with 150 phr barium sulphate gave better radiopacity than zinc oxide system. The compounds were characterized using X-ray, TGA, Densitometer etc.The physical properties of this system were also elaborated in this part.

Chapter 5: A detailed study of preparation of a radiopacifier (zinc oxide) in chitosan medium is described in this chapter. This chapter is divided into two parts. The preparation and characterization of zinc oxide prepared from different zinc salts was included in part I. The zinc oxide was prepared from different salts of zinc such as zinc chloride, zinc nitrate and zinc acetate. The zinc oxide formed was studied using SEM and XRD. The effects of respective morphology variation on radiopacity and mechanical properties of the matrix polymer have been evaluated. NR was compounded with zinc oxide precipitated from zinc chloride, zinc nitrate and zinc acetate and the radiopaque properties were evaluated using X-ray and densitometer analysis. Among these systems NR compounded with zinc oxide precipitated from zinc acetate showed excellent radiopacity.

Chapter 6: The comprehensive summary and conclusions of the study are presented in chapter 6.

At the end of each chapter a list of pertinent references is given. A list of abbreviations used in this thesis is also cited.

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

For the last few decades, polymeric materials have emerged as unique class of materials due to their versatility and appeal with outstanding mechanical properties, tailorability, functional properties, environmental stability, ease of processing into customer-desired products and host of other desirable properties. Polymer science and technology in the new millennium are facing new challenges and opportunities. Exhilarating developments are expected in almost all existing areas. The developments in the area of biomedical field are quite amazing. Material science and the new field of nano technology have opened up several possibilities for the engineering of better and smaller devices not only for technological applications, but also for use in humans. Biomedical applications of polymers ranging from diagnostic appliances, prosthetics and stents to engineered biopolymers, is increasing rapidly world over. Polymers when used as implants are non-traceable without invasive procedures. A radiopaque polymer would offer the unique advantage of being traceable via routine X-ray imaging. Radiopaque materials open up a new outlook to various technological applications like biomedical, radiation shielding, toy manufacturing, plastic explosives etc.

1.1 BIOMATERIALS

A biomaterial can be defined as a material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body[1]. The term biomaterial include all materials used for medical applications that are interfaced with living systems or other systems developed for extra corporeal use. The natural tissues in our body can get damaged due to diseases, trauma or aging. Allografts appears to be the ideal and logical materials for replacement. Shortage of organs for implantation and the need for chronic immunosuppression, however, make them less reliable. Therefore, a variety of other materials have been tried as biomaterials. These include metals, glasses, polymers, ceramics, carbon and composites of various combinations of these[2]. They are used singly and in combination to form most of the implantable devices available today. Metals and alloys have high impact and tensile strength. Stainless steel, gold, titanium and cobalt alloys are the commonly used materials in this group. Ceramics and composites have good biocompatibility and corrosion resistance. Since polymers can be tailor-made to match the mechanical and physical characteristics of many parts of the body, they find maximum applications as biomaterials. Some of the most commmonly used biomaterials and their applications are shown in table 1.1.

Table 1.1: Some of the most commonly used biomaterials and their applications

Field	Applications	Material used
Implants	Cardiovascular	Poly(ethylene terephthalate), Poly(tetrafluoroethylene)
	Facial implants	Collagen, Silicones, Poly(glycolic acid)
	Breast implants	Silicones, Polyurethanes
Dentistry	Dental waxes	Polyethylene, Poly(oxyethylene glycol)
	Dental cements	$Zn_3(PO)_4$, ZnO, Eugenol, Silicates
	Restoratives	Alloys, Resins, Silicates
Devices	Sutures	Polypropylene, Teflon, Dacron
	Pacemaker	Epoxy resins, Dacron, Silicones
	Catheters/tubings	Poly(vinyl chloride), Teflon
	Artificial heart	Polyurethanes, Silicone rubber
Orthopaedic applications	Artificial joints	Ultra high molecular weight poly ethylene (UHMWPE)
	Bone cements	Acrylic resins
	Tendons, ligaments	Polyethylene, Silicones
Ophthalmology	Intraocular lenses	Poly (methyl methacrylate) (PMMA)
	Contact lenses	Poly (hydroxyl ethyl methcrylate) (PHEMA)
	Retinal surgery	Silicone rubber

1.2 POLYMERS AS BIOMATERIALS

The polymers can be of natural origin, (commonly termed biopolymers) and/or synthetic origin, the latter being the most extensively used. They are used in medical equipments as packing materials and as a wide variety of disposable devices. The main reason for the extensive applicability of polymers is the availability of synthetic polymers in a wide variety of chemical compositions and physical properties, their ease of fabrication into complex shapes and structures, their easily tailored surface properties and favorable cost performance ratio[3]. Thus compared to other materials, polymers are advantageous in several ways. They are,

Easy to fabricate: They can easily be fabricated into many forms of final usage, such as fluids, fabrics, films and solids.

Compatible to tissues: Many polymers bear a close resemblance to natural tissues such as collagen, which render them suitable for medical applications.

Available with wide choice: They are available with different properties, transparent ones being suitable for ocular implants, opaque for orthopaedic implants and as adhesive for replacing sutures.

Non-corrosive: Unlike many metals, polymers are non corrosive.

Low in density: The density of most of the polymers are closer to the density of the natural tissues.

Thus polymers constitute, by far, the broadest and most diverse class of biomaterials, making the medical market the fourth largest area of polymer application[4]. The first medical application of polymers made use of commercially available ones, adapted as necessary. Although the science and technology of polymers for biomedical application is at an early stage of development, recent

progress has been dramatic. Polymers penetrate virtually every aspect of medicine, though the science of polymeric biomaterial is much more recent than that of other high molecular weight polymers. Only a few polymers have been specially designed for medical uses, e.g., hydrogels for soft contact lenses, poly (glycolic acid) for absorbable sutures, special ion exchange resins, semipermeable membranes and silicone rubber.

Hundreds of synthetic polymers are available. However, only ten or twenty of them are mainly used in medical device fabrications from disposable to long term implants. This is because, the success of a biomaterial in the body depends on factors such as material properties, design and biocompatibility and hence these aspects should be rigorously satisfied. Some of the polymers commonly used as biomaterials and their applications are shown in table 1.2.

Table 1.2 Commonly used polymers and their medical applications

Polymer	Applications
Polyethylene	Catheter tubes, films for sterile conditioning sacs, syringe pistons, needle covers
Polypropylene	Yarns for surgical sutures, films for sterile conditioning sacs, cast bodies for syringes, rigid nozzles, sterilizable vessels
Poly (vinyl chloride)	Blood bags, medical tubings, dialysis tubings
Polyurethane	Adhesives, emulsions, dental materials, suture materials, blood pumps
Poly(Methyl methacrylate)	Bone cement, intraocular lenses, hard contact lenses
Polycarbonate	Sterilisable feeding bottles, syringes, plasma vials, arterial tubules
Silicones	Dental prostheses, artificial ventricles
Polyamide (Nylon 6,6)	Packaging, hypodermic syringes, inhalator
Chitosan	Coating material, blood anti-coagulant, drug delivery, tissue engineering
Poly (vinyl alcohol) (PVA)	Drug delivery, particulate emboli
Poly (hydroxyl ethyl methacrylate)	Contact lenses, particulate emboli

Search for new biomaterials has expanded rapidly over the last few years[5]. It is important to realize that successful application of a biomaterial is possible only if stringent requirements are met. Some of these are,

Biocompatibility: The material should not induce any undesirable or harmful effect such as blood clotting, allergic reaction, tissue death, inflammation, foreign body reaction etc.

Physical properties: Strength, elasticity, permeability etc. must fit within the application and should be maintained through out the service life of the material.

Manufacture: It should be possible to fabricate, purify and sterilize the part without major hiccups.

Among these properties, the most important requirement of a biomaterial is its biocompatibility. Biocompatibility can be defined as the ability of a material to perform with an appropriate host response in a specific situation[6]. Usually, compatibility of a new material is evaluated as far as possible, through a battery of in vitro tests and a follow-up of in vivo or ex vivo evaluation, using animal models.

Research on new polymeric biomaterials has expanded rapidly over the last couple of decades. It would be very helpful to have a technique for non-invasive evaluation of polymeric implants. This would put the researcher into a position from which it is relatively easy to make observations as a function of time without sacrificing the animal model. X-ray and ultrasound radiographic imaging techniques are the most commonly used non destructive techniques to evaluate materials. The search for a non destructive method of polymer evaluation has ended up to a new area of research, comprising of radiopaque polymers.

1.3 RADIOPAQUE POLYMERS

X-ray and ultra sound depends on variations in density between a specimen and its surroundings[7]. Based on casting shadows, radiographic imaging techniques incorporate the principle of radiopacity, which is the physical property of absorbing X-rays or reflecting ultra sound waves. Light materials are moderately radiopaque while heavy materials strongly absorb X-rays and produce good contrast[8]. The ultra sound imaging approach however suffers from the fact that it has only moderate sensitivity. X-ray imaging being fast, reliable, convenient and non-destructive, is commonly used in clinical practice. A relatively new and perhaps more promising approach for non-invasive evaluation of the performance of a biomaterial is to impart radiopacity to such materials so that they can be monitored for their function and performance in a non-invasive manner.

Radiopacity is now considered as a desirable property of implants used in surgery as it follows the post operative assessment of the fate of the implant using X-radiography[9]. Radiopacity is widely acknowledged as a property of all intra oral materials including denture base materials, denture liners etc. Elastomeric impression materials, endodentic sealers, posts and restorative materials, direct filling restorative materials and resin cement luting agents are all radiopaque[10].

However, until recently, these techniques were not sufficiently sensitive to direct polymers so that the physical changes that occur in polymer implants could be observed. Polymers cannot be detected by imaging techniques because they mainly contain the elements such as carbon, hydrogen, oxygen, nitrogen and in some cases elements like silicon (e.g. silicon rubber). Consequently, polymers exhibit relatively low electron density, which render them radiolucent. Sharp images can be obtained only from materials of high electron density[11,12]. Research into radiopaque polymers explore methods of increasing average electron density

and specific gravity of polymers by incorporating heavy elements into these systems. One of the common practice is to introduce radiopacity via radiopaque fillers. Additives[13-18] such as barium sulphate, zirconium oxide, bismuth halides are incorporated to achieve the necessary X-ray contrast when they are produced by molding, casting, extrusion etc. The incompatibility of inorganics such as barium, bismuth or silver with the polymer matrix often affect the physical and mechanical properties of the implant adversely. Moreover, the possibility of the inorganic ions leaching into the body fluid over long periods of time also causes a threat both from the stand point of the stability of the implant and the toxicity of the metal ions[19].

1.3.1 RADIOPACIFIERS

Radiopacifiers are the substances added to a polymer matrix to impart radiopacity. The following are the commonly used radiopacifiers:

1. Metal inserts such as fine wire, gold gauze or lead foil have been introduced into dental methacrylic resin.

2. Barium sulphate: It is the most widely used compound for dental resins and bone cements. It is very stable, less expensive and can be made in to different colours.

3. Bismuth compounds: It is more expensive than barium sulphate. It has higher density and may produce a brighter and sharper X-ray image than barium sulphate.

4. Tungsten: It is compatible with most polymers. It is more than twice as dense as bismuth and provides a high level of radiopacity. Loading levels of up to 95 % by weight are possible. Host compounds containing tungsten are dark grey in color, which limits coloring option.

One of the most important versatile radiopacifier is triphenyl bismuth. It forms miscible and often optically transparent blends of high opacity with a wide range of polymeric materials including polystyrene, polyvinyl chloride, polyalkenes, polyacrylates and epoxy resins. Low molecular weight iodine compounds in transparent plastic materials and toys provide improved X-ray contrast. Incorporation of elements of high atomic mass to increase the average electron density and specific gravity of polymers is done in many ways.

Based on the preparation, radiopaque polymers are classified into three groups. They are radiopaque polymer blends, radiopaque polymer salt complexes and polymerization products of radiopaque monomers.

1.3.2 RADIOPAQUE POLYMER BLENDS

Radiopaque polymer blends are produced by incorporating the radiopacifying agents as a physical mixture with the polymer. The introduced agent can be a heavy metal, inorganic salt of a heavy element or an organic compound containing a heavy atom substituent. Barium sulphate is an additive commercially used for denture resins and bone cements to make them radiopaque. It does not affect the hardness, solubility or absorption of the resin and tissue implants of the material[20]. But barium sulphate reduces the tensile strength and minimizes the modulus of elasticity. It was observed that polymers containing zirconium dioxide show a high degree of radiopacity than those containing barium sulphate[21]. Metal inserts such as fine wire, gold gauze or lead foil may also be introduced into resins to make them radiopaque. Small quantities of inorganic salts have been added for obtaining radiopacity. Many simple high boiling aromatic and aliphatic halides have been added to the polymerization solution to make them radiopaque[22]. The main drawback of these systems is that the radiopaque additives are not

chemically incorporated into the resin. Many of the metal salts leach into the body fluids over a long time, which makes their radiopacity a temporary phenomenon[23].

1.3.3 RADIOPAQUE POLYMER-SALT COMPLEXES

Radiopaque polymer-salt complex systems are produced by the incorporation of a radiopaque heavy metal into an appropriate polymer ligand via chelation. The resulting systems are homogeneous and posses both polymeric and ionic character X-ray imaging demonstrated that the radiopacity of these systems are high. Cabasso[24] *et al* investigated polymers and monomers that can solubilize heavy metal salts such as barium bromide, bismuth halides, uranyl nitrate and lanthanides. Polymer salt complexes of bismuth tribromide and uranyl nitrate with acrylated polyphosphonates[25] have been synthesized, where the phosphoryl group is believed to provide a strong coordinating site to the metal ion. Similar complexes with polymers containing carbonyl function have also been synthesized[26].

1.3.4 POLYMERIZATION PRODUCTS OF RADIOPAQUE MONOMERS

Polymerization products of radiopaque monomers are produced by the introduction of the radiopacifying element either electrovalently or covalently into the monomer unit prior to polymerization. Barium and zinc acrylates have been reported as radiopacifier and it can be copolymerized with methyl methacrylate (MMA)[27]. However, the ionic nature of these resins leads to significant absorption of water and the slow hydrolysis of poly (zinc acrylates) leading to the loss of the opacifying atoms. The best method to produce radiopaque polymers is to synthesize reactive monomers having covalently bound heavy atoms and use these monomers as building blocks for new polymeric biomaterials that can exhibit intrinsic radiopacity. Such materials can offer vital advantages since no compromise can be made between the introduction of radiopacity on the one hand

and the preservation of physico-mechanical properties on the other. The disadvantage of radiopaque system formed from covalently bound heavy element is its relatively high cost.

1.4 A REVIEW OF COMMONLY USED RADIOPAQUE SYSTEMS

1. Cyanoacrylic derivatives: Isobutyl 2-cyanoacrylate (IBCA) and N-butyl 2-cyanoacrylate

Isobutyl 2-cyanoacrylate (IBCA) rapidly found acceptance for embolic vascular occlusion, especially for the treatment of arteriovenous malformations (avm's). The main advantage offered by this derivative is its low viscosity and rapid polymerization when in contact with vascular endothelium or ionic solutions such as blood. The injected fluid gets rapidly polymerized by forming a hard intravascular cast trapping blood element.

Besides an uncompleted biocompatibility evaluation for intravascular use, IBCA also exhibits some undesirable characteristics such as an exothermic reaction during polymerization, difficulty to control polymerization time, lack of visibility, possible premature polymerization inside the catheter and rendering control of implantation difficult or hazardous. To avoid premature polymerization, the use of 5 % glucose solution to flush all ionic materials from the system are mandatory, as also modifying polymerization time. A chemically similar monomer (NBCA) was proposed as a fast polymerizing agent for the endovascular treatment of 'avm'. This derivative showed a shorter polymerization time than IBCA by the addition of iophendylate oil or acetic acid.

In-vitro studies showed that the polymerization time was delayed by increasing the proportion of contrast medium ratio, which provided an optimal embolization material with good flow properties. Another acrylic derivative, the ethyl-

cyanoacrylate was patented as an embolic material, but no major advantages were found[28].

A vascular graft catheter comprises highly radiopaque polyolefin compound, where the radiopaque material in the said compound is substantially uniformly dispersed and held within a polymer matrix. During the method, the first step is to heat low density polyethylene to it's melting temperature. The amount of polyolefin is equal to 10 % by weight of the compound. Then an amount of radiopaque metal powder equal to 90 % by weight of the compound is added. The metal powder is preferably tantalum, tungsten, gold or platinum. Thereafter, an amount (at least 0.2 % by weight of the compound) of dispersing agent is added to polyolefin to form a mixture. The dispersing agent is preferably zinc stearate, aluminium stearate or calcium stearate. At last the mixture is mixed and cooled below its melting temperature to form the compound. Once the compound is formed, it can be cut into pellets and then is extruded into a tubular form for making tubular tip.

2. Methyl methacrylate Derivatives

Methyl methacrylate derivatives with an average of twenty two ethylene units were synthesized and chelated with barium bromide. However, permanent radiopacity was not achieved with these derivatives and this limit the potential for their clinical application. Cation-chelating monomers were developed to achieve complete solubilization of heavy salts.

Blends of poly(methyl methacrylate) and heavy metal salts were developed by dissolving bismuth tribromide or sometimes bismuth chloride in MMA up to 40 % by weight. The high solubility of the salt resulted from the interaction between carbonyl group and bismuth because the electron donating monomer would readily interact with radiopacifying heavy metal.

Clear solutions of $BiBr_3$ could also be obtained with other monomer containing a carbonyl functional group. For eg. MMA /$BiBr_3$ mixture was polymerized to form solid resins. The presence of about 40 wt% of the salt decreased the molecular weight of PMMA from 1,20,000 to about 80,000 g/ml and slightly increased the glass transition temperature from 108° C to 123° C. PMMA-$BiBr_3$ resins develop opaqueness on contact with water. The influence of $BiBr_3$ content in PMMA on biocompatibility was tested and no sign to mutagenicity was revealed.

PMMA containing organo bismuth radiopacifying additive has also been reported. The X-ray contrast agent used was triphenylbismuth (PH_3Bi) and it was soluble in PMMA up to 70 %. A minimum of 23 % halogenated derivative was necessary to obtain the same radiopacity as the aluminum standard. Bismuth compound acts as a plasticizer and the glass transition temperature of PMMA was reduced. PH_3Bi is very resistant to moisture and water. Therefore it avoids leaching out in an aqueous environment. It is very stable to heat and air. PH_3Bi also shows lower toxicity as PMMA alone. Radiopaque derivatives could also be prepared using triphenyl bismuth and polystyrene.

Transparent, hard materials were obtained by copolymerizing MMA and styryldiphenylbismuth at 65°C with benzoyl peroxide as initiator. The synthesized products had a glass transition temperature of 100-110° C, close to that of PMMA because the heavy metal was a part of the backbone of the product. Thus, the thermal and mechanical properties of the polymers, in comparison to materials containing heavy metal components as additives only, were improved. Permanent chemical incorporation into the polymer structure prevented the leaching out of the heavy metal X-ray contrast agent in any kind of solvent. Identical copolymerization could be obtained with other monomers such as styrene or other vinyl monomers[29].

Another approach to opacify PMMA has been patented and was achieved by incorporating bromine into the PMMA resin. The synthesis of 2,3-dibromopropyl methacrylate was carried out by refluxing methacrylic acid and 2,3 dibromoproponol in toluene. The product obtained was a colorless liquid with a boiling point 82 – 86° C. It is possible to polymerize the 2, 3-dibromopropyl methacrylate to obtain a homopolymer that possess a high bromine content (55.9 wt%) and hence highly satisfactory radiopacity, but is also highly brittle. To improve the mechanical properties of the brominated polymer, copolymerization of poly (2, 3-dibromopropyl methacrylate) with MMA at 70° C using azo-isobutyronitrile as initiator was employed. The synthesized copolymers had a cross linked structure and their equilibrium water absorption decreased with increasing content of poly (2,3-dibromopropyl methacrylate). The flexural strength decreased continuously while the elastic modulus increased proportionally to the content of the brominated polymer. The loss of tensile strength and impact strength was minimized until 60 % of the bromination.

Synthesis and polymerization of iodine containing methacrylate have been reported. Variable radical polymerization behavior was exhibited when comparing similar methacrylic monomers. For example 2,3,6-triiodophenyl methacrylate showed a poor tendency to homopolymerization and gave only oligomeric product, while 2,3,5-triiodobenzoyloxy alkyl methacrylate yielded polymers with number average molecular weight about 58,000 - 1, 47,000 under similar conditions. The 2,4,6-triiodophenyl methacrylate reduce the MMA polymerization and thus decreased the number average molecular weight of the formed polymers.

1.5 APPLICATION AREAS OF RADIOPAQUE POLYMERS

Manufacturing industries of plastics, biomedical polymers, defense materials etc. explore the properties of radiopaque polymers extensively are indicated below.

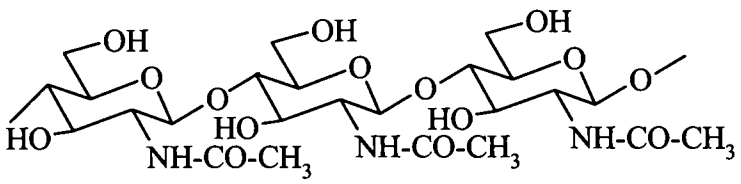
- In biomedical field it is used for the preparation of implants, catheters, medical adhesives and in dentistry for prosthetic applications such as denture or restorative resins
- It is also used for the detection of changes within the body organs such as the kidneys, blood vessels, heart or gastrointestinal system
- Radiopaque compounds are also used to produce shielding components to enclose radiation generating sources
- It is used in toy manufacturing to enable radiographic detection of toys swallowed by children
- Radiopaque polymers are used in plastic explosives, which cannot be detected by conventional X-ray techniques. Incorporation of heavy metal salts into these systems can facilitate their detection for security

1.6 NATURAL POLYMERS USED FOR THE PRESENT STUDY

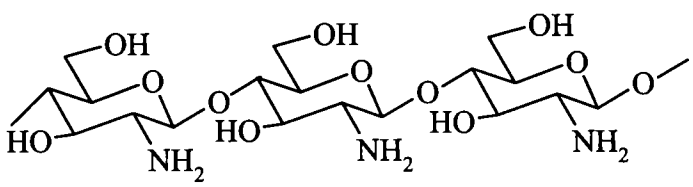
In this thesis an attempt has been made to prepare radiopaque, biocompatible polymers and to explore their radiopaque properties. To this end, we use chitosan and natural rubber as matrix polymers. The chemistry and the applications of these two are reviewed in the following sections.

1.7 CHITIN AND CHITOSAN

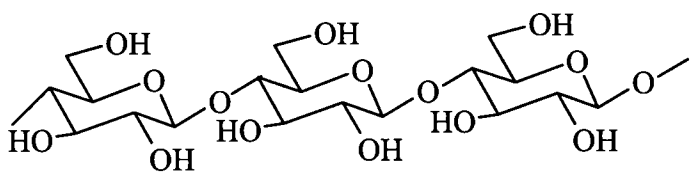
Nature has chosen two different but related polysaccharides to provide structure and integrity to plants and animals like crustaceans and insects. Plants have cellulose in their cell walls while insects and crustaceans have chitin in their shells. Cellulose molecules are large chains of glucose units while chitin molecules are large chains of N-acetyl glucosamine units. Cellulose and chitin are two of the most abundant biopolymers on earth. Chitin is a highly insoluble material resembling cellulose in its solubility and low chemical reactivity. It may be regarded as cellulose with hydroxyl at position C-2 replaced by acetamido groups. The principle derivative of chitin is chitosan[30]. It is formed through N-deacetylation of the chitin molecule. The structures of chitin, chitosan and cellulose are shown in figure1.1.



Chitin



Chitosan



Cellulose

Figure 1.1: Structure of Chitin, Chitosan and Cellulose

Thus chitin is a nitrogenous polysaccharide which is white, hard and inelastic. It is found in the outer skeleton of insects, crab, shrimp and lobsters and in the internal structure of other vertebrates[31]. Chitin has a crystalline structure and it constitutes a network of organized fibers. Chitosan also occurs naturally in some fungi but its occurrence is much less widespread than that of chitin[32].

1.7.2 PROCESSING OF CHITIN AND CHITOSAN

Chitin is widely distributed both in the animal and plant kingdom. In animals, the most readily associated sources are in the shells of crustaceans and mollusks, the backbone of squids and the cuticle of insects. Japan is the major manufacturer of chitin with an annual production of about 500 tones. Serious environmental problems caused by prawn shell waste can be avoided by using it as a raw material for the production of chitin and its derivatives. In addition to control environmental pollution, it is a valuable recourse for more employment and additional income.

In crustaceans chitin is found as a constituent of a complex network with proteins into which calcium carbonate deposits to form the rigid shell. The interaction between chitin and protein is very intimate with covalent bonding, and in essence is a polysaccharide protein complex[33]. The processing of crustacean shells mainly involves removal of proteins and dissolution of calcium carbonate which is present in crab shells in high concentrations. The resulting chitin is deacetylated in 40 % sodium hydroxide at 120 °C for 1-3 h (figure 1.2).

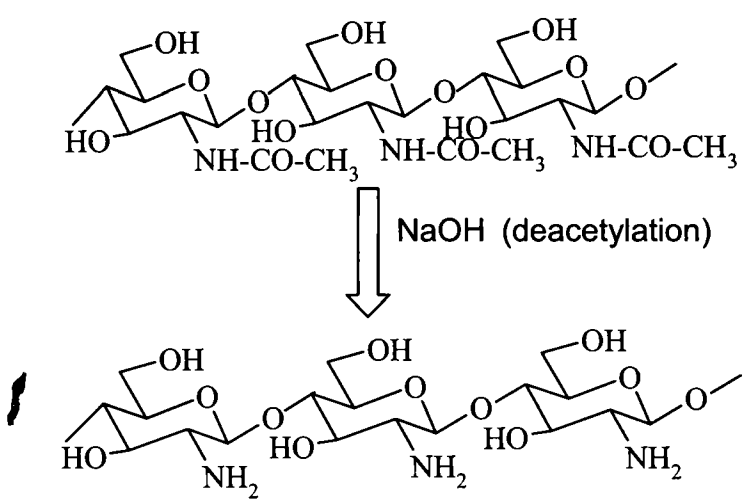


Figure 1.2: Deacetylation of chitin

Deproteinisation is done with dilute alkali and demineralization with dilute acids. Variations in the reagent used and their concentration, as well as the time and temperature of treatment determine the quality and performance of the product[34].

1.7.3 PHYSICOCHEMICAL CHARACTERISTICS OF CHITOSAN

Most of the naturally occurring polysaccharides such as cellulose, dextran, pectin, agar etc. are neutral or acidic in nature, while chitin and chitosan are highly basic polysaccharides. Their unique properties include polyoxysalt formation, ability to form films, chelate metal ions and optical structural characteristics[35].

1.7.3.1 Degree of N-acetylation

Chitosan is characterized by either the degree of acetylation (DA), which corresponds to the N-acetylamine groups or the degree of deacetylation DDA (DDA=100-DA), D-glucosamine groups. The degree of acetylation has an influence on all the physicochemical properties (molecular weight, viscosity, solubility etc.). Many techniques have been tried to determine the degree of acetylation more precisely which include IR spectroscopy, pyrolysis gas chromatography, gel permeation chromatography and UV spectrophotometry[36-45]. The most appropriate technique for rapid characterization seems to be IR spectroscopy.

1.7.3.2 Molecular weight

The knowledge of average molecular weight of chitin and chitosan is very important for industrial uses and for critical applications fields. Although the primary structure of chitosan comprises a backbone of (1-4)-β-D-glucosamine residues randomly acetylated to various extents, the name chitosan is in fact a collective term for deacetylated chitin differing in terms of crystallinity, optical characteristics, degree of deacetylation, impurity content and average molecular

weight. Chitosan molecular weight distribution has been obtained using HPLC[46]. Viscosity measurements are widely used. More recently gel permeation chromatography (GPC) or gel filtration chromatography (GFC) has been applied to study the molecular weight.

1.7.3.3 Solubility

Chitin is highly hydrophobic in nature and is insoluble in common organic solvents as well. It is soluble in hexafluoroisoproponol, hexaflouroacetone, chloroalcohol in conjugation with aqueous solution of mineral acids and dimethyl acetamide containing 5 % lithium chloride[47]. Chitosan, the deacetylated product of chitin, is soluble in dilute acids like acetic acid, formic acids etc. Hydrolysis of chitin with concentrated acids produces relatively pure amino sugars, D-glucosamine. The nitrogen content in chitin varies from 5 to 8 % depending on the extent of deacetylation.

In fact, chitosan is soluble in dilute acids on account of protonation of free amino groups. As in all polyelectrolytes, the dissociation constant of chitosan is not constant but depends on the degree of dissociation at which it is determined. The solubility of chitosan depends on its degree of dissociation.

1.7.3.4 Crystallinity

On the basis of the crystalline structures, chitin is classified into three forms: α,β and γ- chitins (hydrated, anhydrous crystal, and non-crystal). These forms can be examined easily by measuring the X-ray powder diffraction pattern of a chitosan sample[48]. The modified forms of chitosan are less crystalline than pure deacetylated chitosan.

1.7.4 DERIVATIVES OF CHITOSAN

1.7.4.1 Chemical modification of Chitin and Chitosan

Chitosan can carry a large number of amine groups on its chain and thus can form multiple complexes. At higher pH levels (over 4) it can form complexes with colorants and heavy metals. The presence of the pair of free electrons of the amine groups is assumed to be the origin of the dative bonds, an idea confirmed by the observation of a much weaker fixation in chitin. Several chemical modifications can be done on chitin and chitosan. These are acylation, aldimination, carboxymethylation, sulphation, complexation with metal cations and some miscellaneous reactions.

1.7.4.2 N-acetylation

N-acetylation of chitosan leads to fully N- acetylated chitin. Complete N-acetylation may be achieved in 3 minutes at room temperature using a highly swollen chitosan in organic aprotic solvents. Chitosan boiled with large excess of hexanoyl or dodecanoyl chlorides in dry pyridine or chloroform gave fully acetylated derivatives[49]. An aspirin carrier is prepared by the reaction of chitosan with 2-acetoxy benzoic anhydride.

1.7.4.3 Carboxylate derivatives

The insertion of carboxylic functions in chitosan has been widely studied. O-carboxymethylation is achieved with monochloroacetic acid and sodium hydroxide. Carboxymethylation is supposed to proceed preferentially at C-6 as implied from the results of backbone hydrolysis[50]. Crosslinked carboxymethyl chitin or chitosan show high capability of separating bovine serum fibrinogen and albumin. Muzarelli[51] et al demonstrated that N-carboxymethylation could be obtained first, reacting the amino group on chitosan with glyoxylic acid which