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Chitosan Based Materials and its Applications

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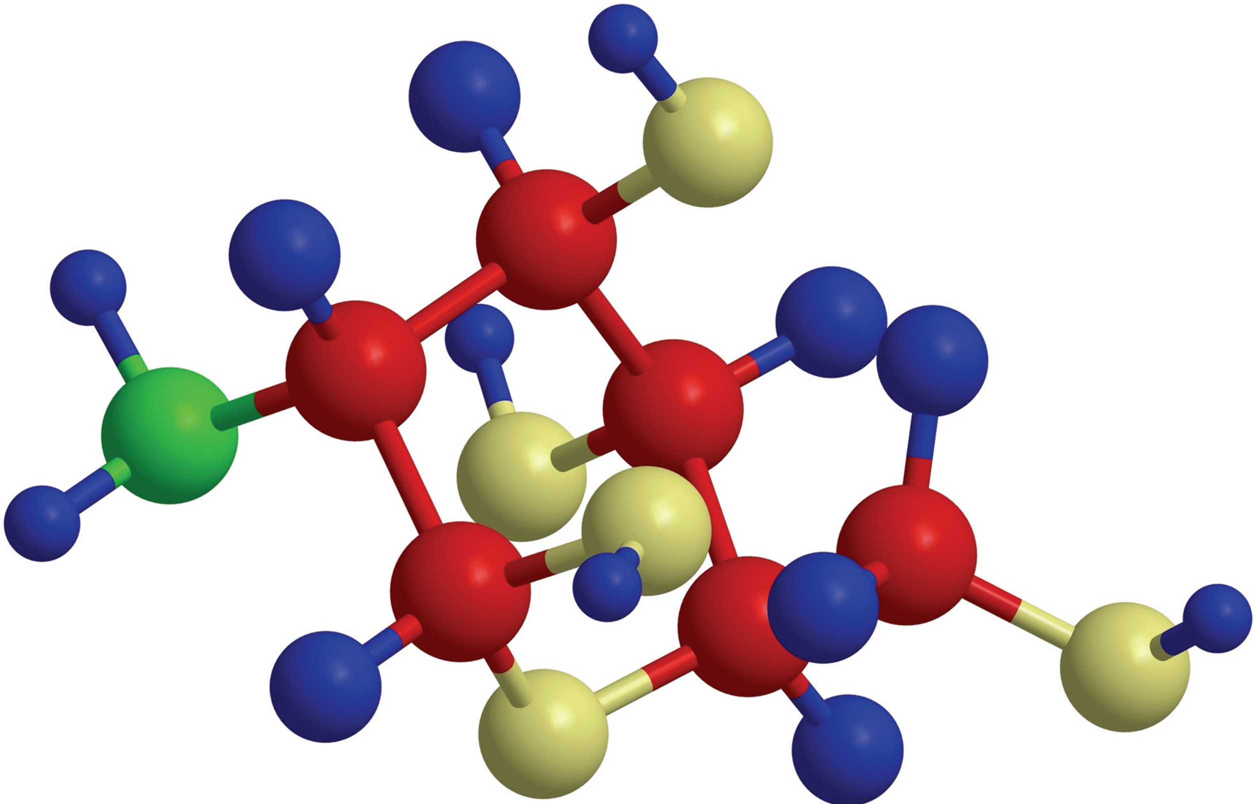

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Frontiers in Biomaterials

(Volume 3)

(Chitosan Based Materials and its Applications)

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CONTENTS

FOREWORD

Petroleum is an important source of energy and materials in our world and many products we use every day are derived from it. However, environmental and economic considerations lead to consider new sources to allow less dependency on fossil fuels. Natural polymers may be one of these alternatives, and among them, polysaccharides form a large class containing a number of industrially-important ones. Chitin, despite constituting the second most abundant natural polymer has not achieved the same commercial importance as for, cellulose, starch or alginate. Academic as well as industrial scientists have developed strong energy to find new and potential applications for this material and most preferentially for chitosan, being its major derivative. The latter presents very specific properties particularly due to its capacity to be polycationic in acidic medium but also a great interest considering the multiple forms in which it can be processed. As a consequence, possible applications cover a wide domain, and this book in a comprehensive manner summarizes many of the most recent technical and research accomplishments in chitosan covering its acquisition processes, characterization, chemical modifications and specific applications such as dyes and metals removal, drug delivery, coatings (especially for food applications), and permeation processes.

The contents of this book highlight the most important challenges and information needed to understand chitosan science. Chitosan is derived from chitin and many processes were designed for deacetylation reaction leading to acquire this derivative. For a few years, microwave-assisted as well as ultrasound processes have been developed and found to be of great interest as it is developed in this book. The characterization of obtained chitosans is of major importance and still remains a challenge for users. The used techniques are discussed in this book and this will strongly help the chitosan users. But chitosan as well as other polysaccharides, do not exhibit all the required properties necessary for specific applications. As a consequence, it is necessary to carry out modifications and the presence of amino groups in chitosan structure allows selective reactions which are described in this book. It is possible to prepare cationic, anionic, amphiphilic or crosslinked materials demonstrating the versatility of this polysaccharide. All of these actions allow the chitosan to be used in applications, covering wide domains as biomedical or pharmaceutics, cosmetics, food, agriculture, water treatment and permeation.

This book is a very useful addition to literature on chitin and chitosan, particularly for those working on the development of new products for specific applications. The authors have to be thanked for their successful contribution to chitosan development demonstrating its strong interest and unlimited potential of applications and it will stimulate researchers in order to continue their efforts so that chitosan finds the place within the polysaccharide world.

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PREFACE

Chitosan is an alternative, low cost and available biomaterial, which can be obtained from natural and renewable resources. Chitosan can be obtained from chitin deacetylation and, its properties are dependent on the used method and the experimental conditions. Chitosan has several interesting properties from industrial and technological viewpoints, such as, biocompatibility, bioavailability, adhesivity, film forming properties and is polycationic in acid mean. Chitosan can be processed in the form of films, membranes, hollow fibers, nanofibers, nanoparticles and scaffolds. On the basis in these interesting properties, chitosan has an unlimited potential of application, for example, in agriculture, medicine, odontology, pharmacy, engineering and other fields. Studies involving chitosan increased significantly in the last 15 years. Consequently, many frontiers were overcome and new research fields were opened. Based on the above mentioned facts, the traditional and new trends about chitosan based materials were organized in a book: "Chitosan Based Materials and its Applications". It is expected that these information will assist future research in the chitosan field.

This book consists of 10 contributions or chapters. The chapters were developed by eminent researchers from Brazil, Portugal, the United Kingdom and Poland, which worked on chitosan and chitosan based materials. Chapter 1 shows general considerations about chitosan and its based materials, while chapter 2 is focused on the obtention processes and characteristics. In chapters 3 to 5, chitosan based materials like nanofibers, nanoparticles, nanocapsules and chemically modified chitosans are addressed. The characterization techniques for chitosan and its based materials are presented in chapter 6. Chapters 7 to 10 are focused on the applications such as, water treatment, drug delivery, edible films and pervaporation membranes. Based on this interesting material, we believe that this book continue to inspire the development and implementation of technologies involving chitosan based materials in the academic and industrial fields.

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CHAPTER 1

General Considerations about Chitosan

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Abstract: Chitosan is a polysaccharide composed of repeated units of N-acetyl-2-amino-2-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose, which are linked by β-(1→4)-glycosidic bonds. This biopolymer was discovered in 1859, and the industrial scale production started from 1971. During the last 20 years, a considerable interest for chitosan based materials has been observed. Chitosan is mainly obtained from crustacean shells, but other sources are also possible. In general, the shells are submitted to sequential steps of demineralization, deproteinization and deodorization to obtain chitin. Chitosan is then obtained by alkaline deacetylation of the chitin. The quality of chitosan is evaluated taking into account the characteristics such as, molecular weight, deacetylation degree and crystallinity. These characteristics are responsible for properties like biocompatibility, bioadhesivity, solubility and polycationic character. The properties of chitosan make this biopolymer an excellent and attractive material for several chemical and physical modifications, aimed at diverse applications. This chapter presents some general considerations about the biopolymer chitosan, including, definitions, history, main sources, obtention processes, characteristics, properties, chitosan-based materials and their unlimited potential applications.

Keywords: Applications, Biopolymers, Characteristics, Chitin, Chitosan, Production processes, Properties.

INTRODUCTION

Chitosan is a polycationic biopolymer composed of 2-acetamido-2-deoxy-β-D-glucopyranose and 2-amino-2-deoxy-β-D-glucopyranose residues [1] (Fig. **1**). It is known that the NH_2 and OH groups in its structure are mainly responsible for its properties and unlimited potential applications [2]. Chitosan was discovered

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by Rouget [3] in 1859, when studying deacetylated forms of chitin. Production in industrial scale was first registered in 1971 in Japan. The "1st International Conference of Chitin and Chitosan" occurred in 1977 (Boston, USA). From this conference, the scientific and industrial communities demonstrated an exponential interest in chitin and chitosan [4]. From 2010 to 2015, more than 15,000 articles and about 20 books on chitosan were published worldwide.

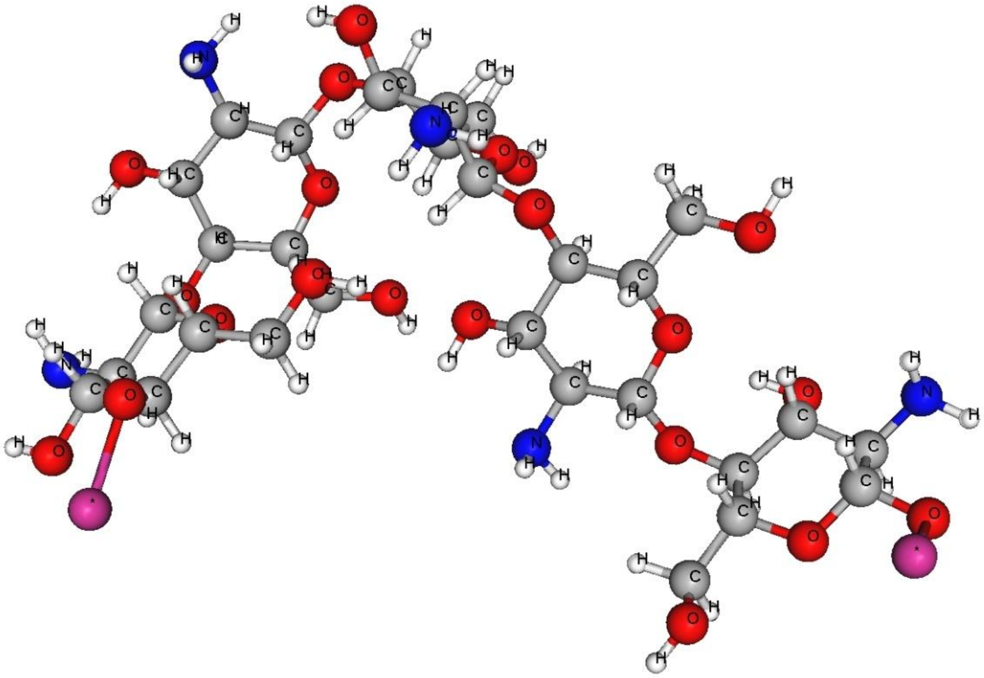

Fig. (1). Three-dimensional chemical structure of the chitosan biopolymer (from the authors).

Crustaceans, insects, mollusks and fungi are the main sources of chitosan [5]. Industrially, chitosan is obtained from shrimp and crab shells, which are wastes from the seafood industries [6]. First, the crustacean wastes are submitted to demineralization, deproteinization, deodorization and drying steps, in order to obtain chitin [5 - 8]. Afterwards, the chitin is deacetylated, purified and dried to obtain chitosan [9, 10]. This process is economically feasible since the raw material has zero cost and can include the recovery of astaxanthin [6]. Nowadays, chitosan is commercially produced in Japan, India, China, Italy, Canada, Chile, Poland, Norway, USA and Brazil [5, 7].

The price of powdered chitosan depends on the range of application, characteristics and purity [5]. For example, the price of chitosan for agricultural use is about US$ 20/kg; for water treatment is about US$ 30/kg; for food applications is US$ 150/kg; for general use in laboratory is US$ 500/kg. The price of high purity 99% chitosan (1 kg) varies from US$ 1000 to 1300.

The main characteristics that define the chitosan biopolymer are its molecular weight and deacetylation degree [11]. Other features such as, crystallinity, surface area, particle size, moisture and ash contents are important [12]. These characteristics are fundamental to ensure the chitosan properties, including, solubility, polycationic character, antimicrobial, biocompatibility and bioadhesivity [7]. Furthermore, the abovementioned characteristics are responsible for determining what chitosan based material could be prepared (films, nanofibers, nanoparticles, nanocapsules, scaffolds, hydrogels) and what the possible application of the biopolymer will be (water treatment, food industry, cosmetics, agriculture, biomedicine) [11 - 13].

Taking into account the importance of chitosan for the academic, scientific and industrial communities, this chapter intends to present some general considerations about this biopolymer. The definitions, main sources, obtention processes, characteristics, properties, chitosan based materials and their unlimited potential of application are presented in general lines. Specific discussions about chitosan based materials, their characteristics, properties and applications are presented in the other chapters of this book.

MAIN SOURCES

Crustaceans

Shrimp and crab wastes are the main sources of the industrial production of chitosan [5, 14]. Chitosan is obtained from α-chitin, which is a component of the exoskeleton of these crustaceans. The exoskeletons are wastes from the seafood industries. It is estimated that the total global annual generation of seafood wastes is around 5.1×10^6 metric tons [15]. The chitin content in the dried exoskeletons varies from 5% to 42%, depending on the crustacean species [5]. Nouri and coworkers [16] used Persian Gulf shrimp wastes to produce chitosan and, obtained a good product with a deacetylation degree of 89% and molecular weight of 806 Da. Yen and coworkers [17] prepared chitosan from crab shells, obtaining a biopolymer with a deacetylation degree higher than 80% and molecular weight of about 500 kDa. In brief, chitosan obtained from shrimp and crab wastes is very attractive, since these sources are available, renewable and have zero cost. Furthermore, it is an alternative form of appropriate management of solid wastes in the seafood industries.

CHAPTER 2

Obtention Processes and Main Characteristics

Anderson Fiamingo, Jorge Augusto de Moura Delezuk, Regiane Cristina Corrêa and **Sergio Paulo Campana-Filho**[*]

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Abstract: The occurrence of chitin and chitosan is discussed with emphasis on the main biomasses used as industrial raw material to produce the former polymer. Some potential sources which nowadays are not important for sustaining large scale production are highlighted as well. The main procedures used to extract alpha-chitin from crustaceans shells and beta-chitin from squid pens are presented and its advantages and drawbacks are discussed. The production of chitosan *via N*-deacetylation of chitin is addressed with emphasis on thermochemical processes based on the alkaline treatment of chitin. Some unconventional processes are focused as well, mainly the ultrasound-assisted deacetylation, which allows the efficient conversion of beta-chitin into extensively deacetylated chitosan of high molar weight. The main characteristics of chitin and chitosan, namely; the average degree of acetylation ($\overline{DA}$), the pattern of acetylation (PA), the average degree of polymerization ($\overline{DP}$) and dispersity (Đ) are addressed and its influence on some polymer properties are also discussed.

Keywords: Alpha-chitin, Beta-chitin, Crustaceans shells, Chitosan, Freeze - pump out - thaw deacetylation, FPT process, Squid pens, Sponges, Thermochemical deacetylation, Ultrasound-assisted deacetylation, USAD process.

INTRODUCTION

The literature on chitin and chitosan in the latter three decades is abundant and mainly focused on applications of these polymers and their derivatives as well. Indeed, some biological activities displayed by such polymers, especially by chitosan and its derivatives, such as biocompatibility, biodegradability, low toxicity, mucoadhessiveness and antimicrobial activity, have attracted the interest

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of academics and industrials as well, mainly for applications in Biomedicine, Pharmacy, Dentistry and other health-related fields. Thus, several chitosan-based materials, such as nano and microparticles, gels, sponges, films and membranes, have been developed for applications in drug delivery and wound healing, and to compose scaffolds for tissue regeneration, among others. However, despite the success of several studies which showed the potential of such chitosan-based materials in many of the above-mentioned applications, and although the huge number of scientific documents and patents, there are few registered products and yet less commercially available products based on chitin, chitosan and derivatives. Indeed, chitosan has been considered as a very promising biopolymer for a very long time but several initial promises have not been achieved, mainly due to poor properties reproducibility, severely precluding the development of commercial products. Currently, it is well known that the structure and microstructure of chitosan, mainly the content of 2-acetamido-2-deoxy-D-glucopyranose (GlcNAc), expressed as the average degree of acetylation ($\overline{DA}$) and 2-amino-2-deoxy-D-glucopyranose (GlcN) units and its distribution along the chains, as well as its average molecular weight, strongly affect its physical chemical properties, functionalities and biological activities. Therefore, elucidating the structure-function relationship at a molecular level is a main breakthrough toward the precise control of chitosan characteristics and properties, allowing the production of tailored chitosan according to the desired application. As chitin extracted from biomass is the main raw material for producing chitosan, it is also important to address the natural sources and the processes used to extract chitin, as they affect the characteristics of chitosan. Additionally, the reaction conditions used to promote the chemical conversion of chitin into chitosan *via N*-deacetylation of GlcNAc units strongly affect the characteristics of chitosan and such a theme will also be discussed in the following sections.

Chitin Structure and Occurrence

Native chitin is idealized as a linear homopolymer composed by 2-acetamido-2-deoxy-D-glucopyranose (GlcNAc) units (Fig. **1a**) and linked by β(1 → 4) glycosidic bonds but some 2-amino-2-deoxy-D-glucopyranose (GlcN) units (Fig. **1b**) can occur depending on the biomass and on the procedures used to extract chitin from it. Indeed, as chitin generally occurs strongly associated to proteins and carbonates, such as in the exoskeletons of crustaceans, its extraction from the biomass calls for chemical treatments that can provoke side reactions, such as partial *N*-deacetylation of GlcNAc units, oxidation and depolymerization, depending on the severity of the treatments.

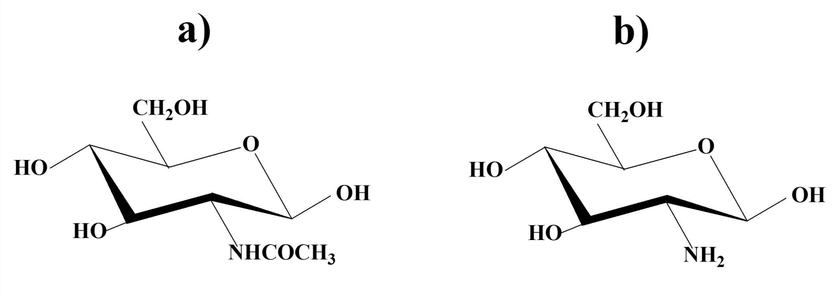

Fig. (1). Structures of (**a**) 2-acetamido-2-deoxy-D-glucopyranose (GlcNAc) and (**b**) 2-amino-2-deoy-D-glucopyranose (GlcN).

Chitin is a semi-crystalline polymer and depending on the organism in which it occurs and to the function it plays, the chitin chains adopt different arrangements in the solid state, resulting in three different allomorphs, namely alpha-chitin, beta-chitin and gamma-chitin [1]. Alpha-chitin, the more stable and widely spread allomorph, occurs where rigidity and mechanical resistance are required, such as in the shells of crustaceans, and it adopts a dense packing due to numerous inter, intra-chains and interlamellar hydrogen bonds, strongly favored by the anti-parallel orientation of the polymeric chains in the ordered domains. In beta-chitin, which occurs where flexibility and toughness are important, such as in squid pens, the polymer chains are disposed in parallel orientation, disfavoring the establishment of hydrogen bonds involving chains pertaining to different lamellae and resulting in a less dense packing as compared to alpha-chitin. The allomorph gamma-chitin, much rarer as compared to alpha- and beta-chitin, is less studied and some authors claim that it has characteristics from both, alpha- and beta-chitin [2]. The characterization of the chitin allomorphs is usually carried out by using infrared and solid state NMR spectroscopy and X-rays diffraction [3].

Chitin is present in the exoskeletons of insects [4, 5], spiders [6] and crustaceans, including shrimps, crabs, crayfish, lobsters and krill [1, 7], in squid pens [3], in bony fish [8], in the cell wall of some fungi [9], such as Ascomycetes, Zygomycetes, Basidiomycetes and Deuteromycetes, and in algae such as diatoms [10]. Additionally, the occurrence of chitin in marine [11] and freshwater sponges [12] has been reported. Depending on the source, chitin occurs combined with proteins, carbonates, silicates, lipids and pigments in different proportions, the chitin content ranging in a relatively ample interval (10% - 40%) as a consequence (Table **1**) [1, 7, 13 - 15].

According to some authors [13, 14, 16, 17], chitin is the second most naturally abundant polysaccharide after cellulose and although it is not fully accepted, it is recognized that the replenishment rate of chitin is higher (≈2x) as compared to

CHAPTER 3

Chitosan Nanofibers

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Abstract: Chitosan is a natural polymer produced from the chitin deacetylation. Chitosan has good biocompatibility, biodegradability, antimicrobial activity, wound healing property and antitumor effect. In recent years, chitosan nanofibers have become interesting, due to amazing characteristics such as, large surface area to volume ratio and high porosity with very small pore size. It can be readily produced using different methods. These nanofibers can be promising for many applications including filtration, removal of metals, drug-delivery, wound dressing, cell culture, tissue engineering, cosmetic, gas sensing and catalysis. The chapter will address diverse types of nanofibers produced from chitosan, their derivatives, and blends with several polymers.

Keywords: Analytical characterization, Biomedical applications, Chitosan, Nanofiber, Polymer, Water treatment.

INTRODUCTION

In the field of nanotechnology, polymer nanofibers have become a great interest for various applications such as, filters, skin masks, semi-permeable membranes, clothing and medical materials [1]. Electrospinning is one of the conventional, simple, versatile and efficient methods used to prepare nanofibers [2]. The generated nanofibers have unique characteristics like large surface area to volume ratio, high porosity, good pore interconnectivity and the possibility to incorporate active components on a nanoscale [1].

Recently, nanofibers have been used in drug delivery systems, tissue engineering scaffolds, vascular grafts, filter formation, sensing applications and biological wound dressings [3, 4]. A large number of research groups are dedicated to produce new and improved nanofibers, synthesizing and modifying biocompatible

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materials, in particular using biological materials such as, chitosan. The natural polysaccharide chitosan has attracted much attention due to its natural origin, biocompatibility, biodegradability, functionalizability, antibacterial activity, non toxic and excellent processability [5, 6].

Chitosan is a linear copolymer of β-(1-4) linked 2-acetamido-2-deoxy-β-D-glucopyranose and 2-amino-2-deoxy-β-D-d-glucopyranose (Fig. **1**). It is obtained by deacetylation (alkaline conditions or enzymatic hydrolysis) of chitin, a polysaccharide widely distributed in nature (*e.g.* crustaceans, insects and certain fungi) [7 - 9]. The deacetylation degree (DD) of chitosan (indication of the number of amino groups along the chains) is calculated as the ratio of D-glucosamine to the sum of D-glucosamine and N-acetyl D-glucosamine. Chitosan DD greatly varies between 60 and 100% while its molecular weight typically ranges from 300 to 1000 kDa, depending on the source and preparation [9].

Chitosan is also widely applied for the removal of heavy metal ions from aqueous solutions, due the presence of amino and hydroxyl groups in its structure. Therefore, it is used for the treatment of wastewaters, purifying them by recovering heavy metals [9]. Chitosan offer advantages, being processed into gels, membranes, beads, microparticles, nanoparticles, scaffolds, sponges and nanofibers [8, 10, 11]. In this way, chitosan and its derivatives can be used in various industrial fields [12].

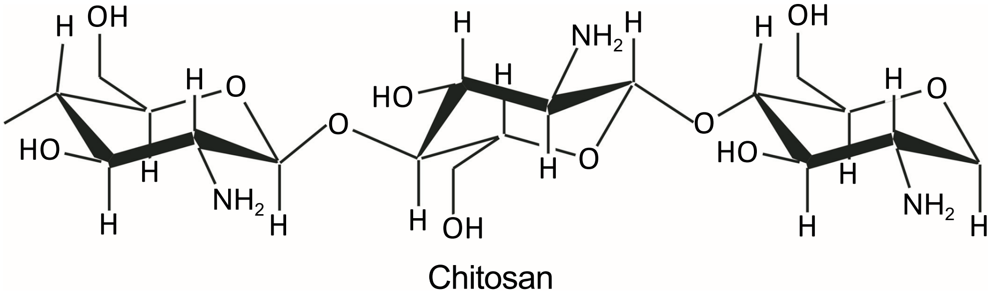

Fig. (1). Chitosan structure [8].

CHITOSAN NANOFIBER PRODUCTION

There are several ways to produce chitosan nanofiber such as, Eletrospinning [13], Forcespinning® [14], Solution Blowing [15], Coaxial Electrospinning [16], Centrifugal Electrospinning [17], Ultrasonic Atomization and Freeze Casting [18]. In this chapter, the different methods of preparation of chitosan nanofibers are reported and their applications in several fields are detailed.

Electrospinning

Electrospinning is a simple and versatile method which produces fibers ranging from the submicron level to several nanometers in diameter in a high voltage electrostatic field [13, 19]. This method is a relatively old approach to fiber production, but is currently one of the most advanced techniques in manufacturing high performance nanofibers [13]. These have been introduced into various technological fields due of their distinct characteristics, such as high surface area to mass ratio (typically 40-100 m^2/g), high porosity, and special chemical and physical properties, which result from their unique structure [13, 20].

The formation of nanofibers through electrospinning is based on the uniaxial stretching of a viscoelastic solution. A typical electrospinning setup consists of three basic components: a capillary tube with a needle, a high voltage supply, and a collector, as shown in Fig. (**2**) [21].

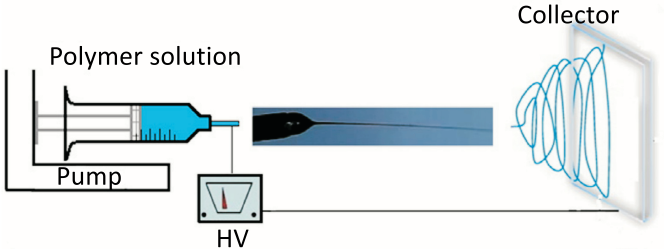

Fig. (2). Schematic diagram of the typical electrospinning setup [21].

In an electrospinning technique, an electric field is applied between the tip of a syringe and a collector plate. Polymer solution is put into a syringe and mounted on a pump, which produces a constant flow rate. When the electric field reaches a certain critical value (which the repulsive electrostatic forces overcome the surface tension), the charged fluid jet is ejected from the tip of the conical protrusion commonly known to as Taylor cone. The jet is continuously lengthened and whipped, resulting in solid nanofibers deposited on the collector with simultaneous rapid evaporation of the solvent [21 - 24].

Important parameters in electrospinning process are solution parameters and process parameters. Solution parameters are determined by solvent and polymer characteristics, including polymer type and concentration, molecular weight, viscosity, conductivity, surface tension and dielectric constant. Process parameters include voltage, nozzle tip-to-collector distance, flow rate of polymer solution, nozzle design and placement, collector composition, geometry, and rotation speed. Ambient parameters include temperature, humidity, and air velocity [21, 25 - 27].

CHAPTER 4

Chitosan Nanoparticles and Nanocapsules

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Abstract: Technological advances achieved by biocompatible systems in several areas have attracted increasing interest in the development of nanometric systems based on biopolymers. In this context, this chapter describes the use of chitosan biopolymer as a carrier and base matrix for the development of nanoparticles and nanocapsules. Chitosan is an abundant natural biopolymer in nature, which is renewable, biocompatible, has hemostatic and mucoadhesive characteristics, and is an interesting polymer material in the development of nanometric systems. Most of the preparation methods are based on green routes without the presence of organic solvents and toxic agents. Chitosan based nanoparticulated systems can be easily reproduced through simple and easy routes, and applied in various fields such as: food and nutrition industry, agricultural, pharmaceutical, medical, renewable materials, controlled delivery, nanoencapsulation, environmental remediation, adsorption, among others.

Keywords: Characterization, Incorporation methods, Nanoparticles, Nanocapsules.

INTRODUCTION

Chitosan is a polysaccharide widely found in nature. It is obtained by deacetylation of chitin, which is derived from crustacean exoskeletons and is naturally found in fungi and yeasts [1, 2]. Chitosan has a chemical structure similar to cellulose, presenting amine and acetamide functional groups which can modify the polymer properties [3], and also contains many amine and hydroxyl groups that can effectively bind to negatively charged substances by electrostatic interactions or hydrogen bonding [4].

This biopolymer attracts attention by presenting biological properties and uses in several areas such as biomedical [5, 6], food industry [7], agriculture [8], among others [9, 10]. Chitosan therapeutic properties such as biocompatibility [11], bio-

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availability [12], microorganisms growth inhibition [13, 14], pain relief, hemostasis promotion and cell growth assistance are also reported [12, 15], making this biopolymer attractive in medical and pharmaceutical areas [16].

As vector system, chitosan has been attracting attention in recent years in the development of carrier materials, due to its biological and physicochemical properties, leading to the recognition of chitosan as a drug delivery medium and a promising material specifically for the delivery of macromolecules [1, 17, 18]. Chitosan and its derivatives have been widely used for the development of nanoparticles which could increase the drug oral bioavailability, present good mucoadhesive character, enhance the bioavailability and dissolution rates of hydrophobic drugs and enhance the stability of labile drugs, drug bioavailability and controlled drug release owing to the fact that particles in the nanosize ranges are efficient in crossing permeability barriers.

In this sense, chitosan-based delivery systems ranging from microparticles to nanoparticles (NP) and composite films are widely described in the literature [19 - 21]. However, there are some disadvantages of this polysaccharide as drug delivery system, such as poor solubility at physiological pH that ends up impacting the administration [14, 22, 23], causing presystemic metabolism when drugs are orally administered [14], and the ability of chitosan alone to encapsulate water-insoluble drugs is poor, because the loading efficiency is usually rather low [24]. Various chitosan derivatives have been made and presented success, especially when they are in the NPs form [14, 22, 23], in order to transcend these disadvantages.

The examples of nanoparticulated systems obtained by chitosan and its derivatives are presented in Table **1**. This description presents preparation methods, main characteristics of the final materials and their applications. Preparation, characterization methods and applications of chitosan and its derivatives NPs are described later.

Polymeric NPs are commonly described as solid colloidal particles, ranging in size from 10 nm to 1 μm. NPs are used in several areas as system for incorporation and storage of active compounds, and are designed from macromolecular and/or molecular assemblies, in which the active principles such as drugs are dissolved, entrapped, encapsulated, or even adsorbed or attached to the external interface. Nanoparticles can be categorized into two main groups based on their morphology: nanospheres, in general, are solid systems, presenting a homogeneous, matrix structure in which the actives are uniformly dispersed; and nanocapsules, showing a typical core-shell structure present a polymeric membrane an inner core [42, 43].

Table 1. Nanoparticulated systems of chitosan and its derivatives: characteristics and applications.

Biopolymer	Obtaining Method	Functionalizer Agent	System	Characteristics	Application	Ref.
CS and poly(ethylene glycol)-grafted (PEGylated) CS	Ionic gelation	TPP	Anti-β-catenin siRNA-loaded CS NP and anti-β-catenin siRNA-loaded PEGylated CS NP	100-150 nm Encapsulated up to 3 nmol of si-RNA, 48 h after transfection, NPs as effective as Lipofectamine 2000	Cancer treatment	[25]
CS	Ionic gelation	TPP	Extracts of *Gymnema sylvestre* leaves and *Cinnamomum zeylanicum* bark-loaded CS NP	58-120 nm Cytotoxic activity against the SiHa cells	Cancer treatment	[26]
CS	Ionic gelation	Sulphobutylether-β-cyclodextrin	Nag-loaded sulfobutylether-β-CD/CS NP	165-215 nm Higher ophthalmic bioavailability and prolonged residence time of Nag	Drug delivery	[27]
CS	Ionic gelation	Sulphobutylether-β-cyclodextrin	CS, HA and sulphobutyl-ether-β-CD and with or without curcumin	169-338 nm Encapsulation efficiency for lipophilic molecules and stability in water	Cancer treatment	[28]
CS	Emulsion (o/w) and ionic gelation	Essential oils	CS and TPP with essential oil extracted of dried leaves of summer savory (*S. hortensis L.*)	135 - 237 nm; −7.54 to -21.12 mV; Size and zeta potential are dependent of pH of CS and TPP concentration	Antimicrobial, cytotoxicity	[29]
CS	Emulsion (o/w) and ionic gelation	Ascorbyl palmitate (AsP)	CS and TPP	250-930 nm Dependent with the increasing of AsP concentration	Antioxidant	[30]
CS	Emulsion (o/w) and polyelectrolyte complexation	Curcumin	CS and AG	Size and zeta potential are dependent: pH of CS solution and mixing ratio of CS:AG	Antioxidant	[31]

CHAPTER 5

Chemically Modified Chitosan Derivatives

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Abstract: Some chemical modifications aiming to introduce a new functionality, to improve and/or develop a given property of chitosan are addressed. Given the great number of possible reactions, focus is put only on some representative chitosan derivatives, exploring examples of those exhibiting anionic, cationic, amphiphilic and hydrophilic character, as well as on crosslinked derivatives. The main synthetic routes used to produce such chitosan derivatives are discussed as well as their structural and physicochemical characterization and some examples of applications in different fields. The effects of the characteristics of the parent chitosan, the *locus* of chemical modification, the nature and the content of substituent's on the properties of the chitosan derivatives are discussed. Some applications of chitosan derivatives are discussed as well.

Keywords: Amphiphilic derivatives, Anionic derivatives, Chitosan, Chemical modifications, Cationic derivatives, Genipin-crosslinked *N,O*-carboxymehtyl chitosan, *N,O*-carboxymehtylchitosan, *N*-(2-hydroxyl)propyl-3-trimethylchitosan, *N,N,N*-trimethylchitosan, *N,O*-methoxypoly(ethyleneglycol)-*g*-chitosan.

INTRODUCTION

Chitosan exhibits several interesting physical and chemical properties along with biological activities but some drawbacks, such as the effect of pH on its polycationic character, solubility and mucoadhessiveness, limit its applications in drug delivery systems. Additionally, when chitosan is used to develop bandages, biomaterials for implants and scaffolds for biomedical applications, one must be aware that adequate mechanical properties will not develop unless cross-linking is

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carried out frequently by using cross-linker agents, or if stable polymer networks are formed *via* physical interactions, including hydrogen bonds, hydrophobic and electrostatic interactions. Thus, to overcome some of the inherent limitations of chitosan, several chemical modifications have been proposed to improve a given physical chemical property and/or to enhance specific functionalities and biological activities. Owing to the presence and nucleophilicity of hydroxyl and amino groups, these are the preferential sites for carrying out chemical modifications on chitosan. Although chemical modifications can be carried out at the acetamido groups pertaining to GlcNAc units of chitosan, they are rarely performed owing to low reactivity as compared to hydroxyl and amino groups and due to the effect on chitosan biodegradability as, for instance, lysozyme is active to hydrolyze chitosan only at the chain regions containing at least some diads GlcNAc / GlcNAc. Additionally, unless if preserving the degree of polymerization of chitosan is not important or if the production of chitooligosaccharides is aimed, strongly acid reaction media should be avoided as chitosan is susceptible to depolymerization *via* acid hydrolysis. The preparation, properties and applications of some chitosan derivatives, focusing on the examples of anionic, cationic, hydrophilic, amphiphilic and crosslinked chitosan derivatives, are addressed in the following.

CARBOXYMETHYLCHITOSAN

Carboxymethylchitosan (CMCh), an anionic derivative of chitosan which can be prepared *via* reaction at amino and hydroxyl groups of chitosan, is soluble in an ample range of pH, including neutral and alkaline media, as compared to the parent chitosan which is soluble only in moderately acidic media [1 - 3]. Depending on the reaction conditions, mainly reaction temperature, and on the acylating reagent, namely monochloroacetic acid or glyoxylic acid, the carboxymethylation of chitosan results in *O*-, *N*-, *N,O*- or *N,N*-carboxymethylchitosan [4, 5]. When monochloroacetic acid reacts with chitosan at room temperature in concentrated aqueous NaOH/isopronanol, *O*-carboxymethylation predominates as the strong alkaline medium that promotes the polymer swelling and enhances the nucleophilicity of hydroxyl groups [6 - 8]. However, it is worth mentioning that if chitosan carboxymethylation is carried out at elevated temperatures, *N,O*-carboxymethylchitosan (*N,O*-CMCh) will be produced [9]. When glyoxylic acid is employed as the alkylating agent, a soluble aldimine is firstly produced, which is then reduced by reaction with sodium cyanoborohydride, resulting in *N*-carboxymethylchitosan (*N*-CMCh). According to Muzzarelli *et al*. [10], the production of soluble *N*-CMCh is associated with an equimolar ratio of glyoxylic acid and chitosan amino groups, since the excess of glyoxylic acid leads to insoluble products, while to produce *N,N*-dicarboxymethylchitosan (*N,N*-CMCh), chitosan may react with glyoxylic acid in the presence of water, glacial acetic acid and sodium borohydride [11 - 13]. Additionally, the carboxymethylation of chitosan can be carried out under microwave irradiation to increase the reaction rate and to avoid the use of organic solvents [14].

The structural modifications introduced by carrying out carboxymethylation can be observed by comparing the FTIR and ^{1}H NMR spectra of chitosan and CMCh. The FTIR spectrum of CMCh displays intense bands at 1600 cm^{-1} and 1411 cm^{-1} which are attributed to the symmetric and asymmetric axial deformations of -COO$^-$ group, respectively, confirming the introduction of carboxymethyl groups on chitosan chains [15, 16]. The ^{1}H NMR spectrum of *N,O*-CMCh shows the occurrence of *N*-carboxymethylation as the signals at 3.1 - 3.4 ppm are assigned to mono and disubstitution at amino groups [17], while *O*-substitution is evidenced by the presence of signals at 4.5 - 4.0 ppm due to the hydrogens of carboxymethyl substituents inserted at 6-O and 3-O of the glycopyranose ring [15, 18]. The main characteristics of CMCh are its average degree of substitution ($\overline{DS}$), average molecular weight and dispersity (Đ). The precise determination of $\overline{DS}$ is usually carried out by using ^{1}H NMR [18] and ^{13}C NMR [19] spectroscopy [18, 19] while weight average molecular weight ($\overline{Mw}$) and dispersity of CMCh can be determined by size exclusion chromatography coupled to multi-angle static light scattering detector (SEC-MALS).

Compared to chitosan, the solubility of CMCh in aqueous solution is remarkably improved due to the introduction of carboxymethyl groups along the polymer chains, however the water-solubility of CMCh calls for $\overline{DS} > 0.4$ [20]. In addition, CMCh presents better moisture retention, membrane forming, flocculating, chelating and sorption properties as compared to chitosan [21]. However, carboxymethylchitosan is thermally unstable and adopt a less ordered arrangement as compared to chitosan as demonstrated by thermogravimetric and X-ray diffraction analyses, respectively [6, 16].

Carboxymethylchitosan can affect cell functioning, antioxidant and antiapoptotic activities, while its antimicrobial activity is affected by $\overline{DS}$, the distribution of carboxymethyl groups and polymer average molecular weight. Thus, *N,O*-CMCh exhibits less effective antibacterial activity as compared to chitosan, which is attributed to the decrease in the content of amino groups as a consequence of *N*-carboxymethylation [22].

Due to its improved water-solubility [6, 23], gel-forming capacity [24, 25], biocompatibility [26], biodegradability, low immunogenicity [27], antimicrobial [28 - 31] and antioxidant activities [32, 33], carboxymethylchitosan presents a

CHAPTER 6

Characterization Techniques for Chitosan and its Based Materials

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Abstract: All synthesized material needs to be characterized before application. For each type of application there are a number of possible techniques that may be used in order to identify specific material properties and their behaviors during a particular test. Currently a series of chitosan based materials have been synthesized and applied in various fields of science due the versatilities of the materials and its applications. Drug delivery systems, cellular interactions, *in vivo* studies, nanoparticles encapsulated vesicular systems, wastewater treatment and recovery of precious metals, are some of the applications of chitosan and its based materials found in the scientific literature. Thus, this chapter presents a series of techniques used in the characterization of materials, searching to relate the techniques used with the scientific applications. Analyses that aim at to determine the mechanical and chemical properties of the new material are presented, as well as the ways of monitoring and evaluation of interactions between cells and materials synthesized in cell interactions and *in vivo* systems.

Keywords: Cellular interactions, *In vivo* characterization, Material characterization.

INTRODUCTION

The chitosan based materials possess applications in different technological area. In order to characterize and evaluate the performance of the new material, a series of analyses is necessary. The chitosan composites have influence in various biochemical and physiological processes involved in wound healing, because the chitosan provides antimicrobial activity, cell stimulation, and filmogenicity. In the

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treatment of healing lesions or ulcers, in vascular problems and systemic diseases, the association of the chitin and chitosan with a foam-like dressing can effectively induce nearly physiological repair. Many forms of chitosan nanoparticles have been produced and are suitable as drug vehicles. Results confirm the potential of this drug delivery platform and the subsequent need of a full preclinical evaluation in order to satisfy the specific regulatory demands of this mode of administration [1]. Chitosan is also a protagonist in the delivery of DNA for gene therapy, due to its unique characteristics that include polyelectrolyte complex formation with favorable complex stability values during delivery [2].

Chitosan composites result in a new class of biomaterials that possess mechanical, physicochemical, and functional properties, which have potential for use in different applications [3]. However, before the application of the chitosan material, it is necessary to identify the chemical and physical characteristics of this material using many different analytical techniques.

In some cases, it is necessary to identify the thermal characteristics of the new material, and the DSC and TGA analyses need to be evaluated. The porosity and the superficial area are fundamental information when a mass transference study is performed and, in this case, the BET analysis is imperative. When chemical modification is carried out in the chitosan polymer chains, like a crosslinked or a grafting, the modification in the functional groups can be identified using FTIR and RMN spectroscopic analyses. The removal of ions from the solvent using chitosan material as adsorbent to wastewater treatment and precious metals recovery are extensively studied in the literature.

Thus, many other characterization techniques can be utilized in the elaboration and in the application of these materials in drug delivery systems, cellular interactions, *in vivo* studies, nanoparticles encapsulated vesicular systems, wastewater treatment and precious metals recovery. In this chapter, some of the most important chitosan-based structures are concisely described with their characteristics and applications.

MATERIAL CHARACTERIZATION

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) is a technique that enables accurate determination of the temperature at which structural changes occur in the sample. This can lead to develop new products with enhanced textural attributes. Thermal changes can occur as either the first or second order transitions. First order transitions can be associated with endothermic or exothermic changes, such as crystallization and melting. On the other hand, a glass transition is a second order transition, and it involves a stepped change in the heat capacity. DSC analysis has been used especially for the development of new polymers, with the idea of identifying their technological applicability, thus, overcoming their limitations [4].

Martínez-Camacho, [5] studied the thermal characteristics of the pure chitosan films and the chitosan composite in order to evaluate the antifungal activity of the same. Chitosan composite was obtained by the addition of 20% sorbitol (w/w with respect to the amount of chitosan) as a plasticizing agent, and was compared with pure chitosan film. In these assays, it was observed a single value of Tg, so it can be assumed that sorbitol and chitosan were miscible.

Another applicability of chitosan base materials is their use in the treatment of liquid effluents containing recalcitrant molecules, as colorants. With the aim to evaluate possible dye-films interactions, Dotto *et al*. [6] studied the characteristics of the chitosan film after and before the adsorptions of two food dyes from aqueous solutions. In DSC curves, it was observed an endothermic peak at 75.3 °C with enthalpy of 89.1 J g^{-1}. This peak was attributed to evaporation of residual water. For the chitosan films adsorbed with acid red 18 and adsorbed with FD&C blue no. 2, the peak was shifted to 70.3 °C (enthalpy of 62.6 J g^{-1}) and 73.7 °C (enthalpy of 64.7 J g^{-1}), respectively. These alterations suggested that the interactions between films and water were weakened after adsorption. This can be occurred due to the migration of large dye molecules into the biopolymer chains.

Thermal Gravimetric Analysis TGA

Thermal gravimetric analysis (TGA) is a thermal analysis in which changes in physical and chemical properties of the materials are measured in function of the temperature, like mass loss. It is an especially useful technique for the characterization of polymeric materials, including thermoplastics, elastomers, composites, plastic films, and coatings [7, 8].

In the biosorption of azo dyes from aqueous solution using glutaraldehyde-crosslinked chitosan, the thermal decomposition of the microparticles was analyzed by Chen *et al*. [9]. The decomposition temperatures of the microparticles prepared from three different methods were of 273.5, 224.3 and 260.9 °C. These results indicated that the microparticles formed from sodium tripolyphosphate solution were more easily decomposed than those formed from the sodium hydroxide solution. These characteristics were attributed to the decomposition of tripolyphosphate into phosphoric acid.

One of the main characteristics of an adsorbent is its surface area. In order to increase the surface area of chitosan, Li *et al*. [10] studied the preparation and

CHAPTER 7

Application of Chitosan Based Materials for Dyes/Metals Removal

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Abstract: Application of chitosan based materials in wastewater treatment has received considerable attention in last years. The most frequently applied technique for this purpose is the adsorption operation, which typically use activated carbon as adsorbent in the industrial wastewater treatment systems, because it has a large specific surface area. However, there has been an increasing interest in utilizing adsorbents from renewable sources for dyes/metals, removal from wastewater. Chitosan based materials has been widely used to remove heavy metals and dyes due to its high content of amino (-NH_2) and hydroxyl (-OH) functional groups, which have high activity as adsorption sites. This chapter presents some applications of chitosan based materials for dyes/metals, removal from aqueous medium, providing information obtained using batch and continuous adsorption systems. The effects of parameters in the adsorption capacity, such as chitosan characteristics, process variables, chemistry interaction adsorbent/adsorbate, equilibrium, kinetics and thermodynamics are presented and discussed. The chapter also presents the equilibrium and kinetic models most commonly used and the thermodynamic studies reported for adsorption onto different chitosan based materials. Several examples are discussed to demonstrate the versatility of the material and its application as an adsorbent. Desorption performance and the structural parameters of the polymer in relation to regeneration as well as the development of new adsorbents are presented.

Keywords: Adsorption, Chitosan, Dyes, Materials, Metals.

INTRODUCTION

The increasing demand for new materials for the removal of substances, like synthetic dyes and metal ions, from industrial liquid waste has led many

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researchers to evaluate the possibility to use renewable based materials to uptake these elements [1, 2]. Currently, several adsorbents have been used to remove different types of dyes and metal ions from wastewater especially activated carbon, clays and biopolymers [3].

Polysaccharides, as a class of natural macromolecules, have the tendency to be extremely bioactive and are generally derived from agricultural feedstock, as cellulose, starch, pectin, or crustacean shell wastes, as chitin and chitosan [4]. In terms of availability, chitin is the second most important natural polymer in the world [5], it is also obtained from fungi and bacteria [6]. Chitosan is obtained on an industrial scale by the alkaline deacetylation of chitin [7]. Both chitin and chitosan are linear copolymers of D-GlcN and D-GlcNAc distributed randomly and which are linked fully in the β-1,4-configuration, generating in an organizing rigid and unbranched structure. The abundance of hydroxyl groups (1 primary hydroxyl at C-6 and 1 secondary hydroxyl at C-3) and highly reactive amino group (at C-2) or its N-acetyl counterpart (wholly in chitin) with concomitant tendency for intra and intermolecular hydrogen bonds results in the formation of linear aggregates with extensive crystallinity. The main sources exploited are marine crustaceans, mainly shrimp and crabs. In particular, the development of chitosan-based materials as useful adsorbent polymeric matrices is expanding in area of adsorption science [8]. Chitin and chitosan are biopolymers with immense structural possibilities for chemical and mechanical modifications to generate novel properties, functions and applications. Chitosan is a good adsorbent to remove various kinds of anionic and cationic dyes as well as heavy metal ions [9, 10].

Chemical modifications that lead to the formation of chitosan derivatives, grafting chitosan and chitosan composites have gained much attention, and have been extensively studied and widely reported in the literatures. Application of chitinous products in wastewater treatment has received considerable attention in recent years [11 - 14]. This chapter provides information relevant on the application of chitosan materials for removing dyes and heavy metal ions from aqueous medium. Adsorption capacity and the experimental conditions have been presented, including the parameters that might be involved during adsorption operation. The uptake performance, the process variables, the chitosan characteristics, the chemistry of the dye and the solution conditions used in batch and continuous systems are evaluated. Studies on the biosorption capacity, equilibrium and kinetic models, and the thermodynamic studies reported for biosorption onto chitosan and chitosan based materials systems are presented.

INFLUENCE OF PROCESS VARIABLES

Adsorption is the phenomenon in which the spontaneous adhesion of molecules present in a fluid (adsorbate) to a solid surface (adsorbent) is observed. The degree of adsorption depends on the thermodynamic conditions, adsorbent surface and interaction between adsorbent and adsorbate. This occur due to the existence of unbalanced forces on the solid surface, leading to the attraction of the molecules present in the fluid in contact with the solid adsorbent for a certain time [15].

The adsorption phenomena are classified as the responsible forces in two types: chemical adsorption and physical adsorption. The chemical adsorption or chemisorption, is so called because in this process occurs an effective exchange of electrons between the solid and the adsorbed molecule, resulting in the following characteristics: forming a monolayer on the solid surface, irreversibility and release of a considerable amount of energy (in the order of a chemical reaction). Physical adsorption is a reversible phenomenon, generally observed when occurs the deposition of more than one layer of adsorbate onto adsorbent surface. The forces acting on physical adsorption are identical to the cohesive forces that operate in liquid state, solid and gas. The released energies are relatively low and rapidly reach the equilibrium [15, 16].

Regarding the removal of metallic ions and synthetic dyes from aqueous medium, the adsorption appears as an alternative method, due to its ease of operation and efficiency over conventional methods, which are expensive or technically complicated. Moreover, it is a versatile method that has wide application range and an interesting relation cost / benefit, especially when using adsorbents from industrial waste. Usually, the adsorption processes in batch or continuous systems are studied in relation to their equilibrium conditions, kinetic, thermodynamic and mechanisms involved [1 - 3, 17, 18].

For a better understanding of a process that uses adsorption operation must be designed studies in order to elucidate the relevant factors in the system, such as adsorption capacity parameters and physicochemical parameters. In this context, authors have developed works for the adsorption of metal ions and synthetic dyes using models isotherms and kinetics and thermodynamic models [19 - 21], seeking more detailed explanations of the adsorptive processes and how they can be applied. The distribution of adsorbate between solid phase and liquid is reached by varying the initial concentration of the adsorbate, C_o, keeping the solution volume, V, and adsorbent mass, m constant. The residual concentration of the adsorbate solution is used to calculate the adsorption capacity of the mass balance using eq. (**1**).

CHAPTER 8

Application of Chitosan Based Materials for Drug Delivery

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Abstract: One of the main challenges in drug delivery field is the development of formulations or devices designed to allow the transport of a suitable amount of the active pharmaceutical substance to the site of action in the body, and improve its efficacy by controlling the rate, time and place of release. The distribution of the drug to tissues different than the target place is unnecessary, wasteful, and a potential cause of toxicity. Chitosan, a versatile hydrophilic polysaccharide derived from chitin, is a non-toxic, biocompatible and biodegradable polymer which has attracted significant scientific interest, for its fundamental role in the progress of drug delivery technology. This natural biopolymer has inspired the development of safe and effective drug carrier systems due to its unique physicochemical and biological characteristics. The cationic character, exclusive of the chitosan, is attributed to the primary amino groups in the main backbone, which make its surface positively charged under acidic conditions; an important requirement that has been responsible for the enhancement of the load capability, tailoring the release profile of the drug and increasing the solubility. This chapter focuses on the use of chitosan-based therapeutic systems, including particles, hydrogel, film and scaffolds, through various anatomical routes by which the drug may be introduced in human body, such as oral, nasal, ocular, transdermal and local administration.

Keywords: Biomedical applications, Chitosan, Drug carrier, Hydrogel, Membrane, Nanoparticles, Route of administration.

INTRODUCTION

Chitin, a naturally abundant polysaccharide, is well known to be the main component of the exoskeleton of crustaceans and insects, which, by deacetylation,

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can lead to chitosan, although this reaction rarely is 100% complete, normally a partial N-deacetylation of chitin occurs [1, 2]. Therefore, chitosan is a linear copolymer consisting of glucosamine (β(1-4)-linked 2-amino-2-deoxy-D-glucose) and N-acetyl-glucosamine (2-acetamido-2-deoxy-D-glucose)), showing a rigid crystalline structure through inter- and intramolecular hydrogen bonding [3 - 5].

The history of chitosan dates back to the 19th century, when Charles Rouget boiled chitin in a concentrated alkali solution and found a new product soluble in the organic acid in 1859 [3, 6]. Later research confirmed that the product obtained was deacetylated chitin and therefore named it chitosan [7]. Chitin shows poor solubility in aqueous solution and organic solvents, limiting its use for practical applications whereas, chitosan is more suitable for bioapplications [4, 8].

Despite the fact that chitosan is not extensively present in the environment, it can be easily obtained by chemical or enzymatic hydrolysis of a natural polymer: the chitin. From a functional point of view, chitosan is quite a unique material; its intrinsic properties are so singular and valuable that it has inspired a wide variety of academic and industrial research for pharmaceutical and medical applications, especially in the field of controlled drug delivery [9 - 12]. The interest in this polymer originates in its positive facets such as biocompatibility, biodegradability, low toxicity, mucoadhesion, stimuli response and versatile biological activities as antimicrobial activity and low immunogenicity [3, 13 - 16].

The presence of reactive amino (NH_2) group in the chitosan structure makes this polymer the only polysaccharide that possesses high density of positive charges, thus the multiple free amino groups can be protonated in dilute acid solutions with pH below 6.0 creating NH_3^+ groups, which readily bind to negatively charged molecules or materials [4, 17].

Some remarkable properties of chitosan as biomaterial, previously mentioned, are based on its cationic character. The mucoadhesive properties, for example, can be explained by the electrostatic interaction developed by the presence of negatively charged sialic acid residues in the mucin [5, 18, 19]. The mechanism responsible for permeation enhancing effect is also linked to the positive charges, which seem to interact with the negative part of the cell membrane resulting in a structural reorganization and an opening of the tight junction proteins [10, 20, 21]. The analgesic effect can also be related to the polycationic nature of chitosan, once the amino groups of the D-glucosamine residues can protonate in the presence of proton ions that are released in the inflammatory reaction [22, 23]. Finally, the haemostatic activity where the positive charges of polymer have strong affinity to bond with red blood cells, activates the platelets and forms a gel-like coagulum which promotes hemostasis and seals bleeding of vessel [5, 24, 25].

Modification of chitosan can be made to improve its sensitivities to the environmental changes. Various innovative chitosan derivatives have been obtained by chemical modification, such as acylation, tosylation, alkylation or silylation, using the reactive activities of hydroxyl and amino groups [26 - 29]. In particular, the primary amino group has nucleophilic property and could generate reactive sites for many others functional compounds. The association of bioactive molecules to the chitosan provide versatile materials with specific functionality, allowing an easy modification of its biological and physical properties [2, 30 - 32].

The oral administration of chitosan has shown to result on its partial hydrolysis by lysozymes in human serum [33] and digestive enzymes in the gastrointestinal tract that generate monomers, chitooligomers and glucosamines. Among polysaccharides, chitosan is the unique in terms of susceptibility to enzymatic depolymerization, cationicity, supply of cell-activating oligomers, and supply of *N*-acetylglucosamine for rebuilding of other biopolymers [34]. The degradation by lysozymes is very relevant as they exist in various human body fluids and tissues with concentrations from 4 to 13 mg/L in serum and from 450 to 1230 mg/L in tears [35].

Chitosan degradation is dependent on the deacetylation degree (DD), wherein a higher deacetylation leads to slower degradation [36]. Chitosan matrices with various degrees of N-acetylation were subjected to *in vitro* lysozymic degradation. Chitosan matrices with DD of 93.5%, 81.7%, and 71.7% experienced very slow degradation process, while those with DD of 62.4%, 56.1%, and 52.6% underwent significant degradation [35]. This has been used to control the degradation rate of chitosan formulations for specific uses. For instance, the biocompatibility and degradation rate of chitosan based nerve guidance channel were tuned by the acetylation degree [37]. Chitosan degradation can also be varied by carboxymethylation, bimodal molecular weight distribution of chitosan [38] or thiolation [39]. Particular attention should be paid to cross-linkers as they affect the degradation profile. Particularly, noncrosslinked chitosan films were digested by both pancreatic and colonic enzymes, while glutaraldehyde crosslinked ones were resistant to both enzyme systems and tripolyphosphate crosslinked ones were resistant only to pancreatic digestion [40].

Regarding the *in vivo* degradation, no abnormal symptom was observed with several animals when chitosan was orally administered at a dosage of 0.7-0.8 g/kg body weight/day for up to 239 days or intravenously at a dosage of 4.5 mg/kg body weight/day for 7-11 days. Also, chitosan was about 39-79% digested in rabbits and almost completely by hens and broilers [41].

CHAPTER 9

Application of Chitosan Based Materials as Edible Films and Coatings

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Abstract: Chitosan is the only pseudo-natural cationic polymer and, owing to its biocompatibility, biodegradability, non-toxicity, and antimicrobial activity, combined with its cationic character, is considered as the greatest potential polymer for obtaining food packaging, especially in the form of edible films and coatings. The successful manufacture of edible films and coatings for food applications is based on specific functional properties that the biopolymer should meet for each type of food, due to the different properties of the various components (nanoparticles, lipids, plasticizers, proteins, *etc.*). The addition of these compounds can be beneficial in the films production, with superior functional properties and thus extend their applications. In this chapter, we highlight the application of chitosan-based materials as edible films and coatings for food protection. The manufacture, and mechanical properties and the water vapor permeability (WVP) of the films and coatings are also discussed.

Keywords: Mechanical properties, Packaging materials, Polysaccharide, Water vapor permeability.

INTRODUCTION

Owing to concerns about limited natural resources and environmental impacts caused by the use of synthetic polymers and rigid packaging, there is a renewed interest in developing biopolymers based materials used as food packaging [1]. The edible films and coatings are formed from the natural polymers of animal or vegetable origin, and when released into the environment, they are converted into simple mineralized compounds. These in turn, are redistributed through the carbon, nitrogen and sulfur cycles, causing no harm to the biosystem. Films are

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defined as stand-alone thin layers that are applied to the material surface. Films can form pouches, wraps, capsules, bags, or casings through further fabrication processes. Coatings are a particular form of films directly applied to the surface of materials. The removal of coating layers may be possible; however, coatings are typically not intended for disposal separately from the coated materials. Therefore, coatings are regarded as a part of the final product [2 - 4].

Besides the possibility of returning to the biological cycle after use, biopolymer based films can be developed in order to obtain properties that meet the demanding applications, such as mass transfer barrier (water vapor and gas), transport of food additives (pigments, aromas, flavors) and controlled release of active ingredients (antioxidants and mycotic agents) [5]. Moreover, they should prevent physical damage to the material during the stages of handling, transport and storage. Thus, they must have the capability of deformation and mechanical strength [6]. Bio-based films offer advantages such as edibility, non-toxicity, biocompatibility, non-polluting and low cost [7]. Two major promising applications of such films are the replacement of short-life plastic in food packaging and use as edible food coatings [8].

In the past decades, several natural polymers have received increased attention for their applications in food, biomedical, and chemical industries [9, 10]. The main biopolymers used to obtain films are carbohydrates (polysaccharides, pectins and starches) [11 - 13], proteins [14], lipids [15] or combinations thereof [16, 1]. In particular, chitosan, a polysaccharide, is the only pseudonatural cationic polymer and, owing to its biocompatibility, biodegradability, non-toxicity, and antimicrobial activity, combined with its cationic character, is considered as the greatest potential biopolymer for obtaining food packaging, especially in the form of edible films and coatings [17]. In this chapter, we highlight the application of chitosan based materials as edible films and coatings for food protection. The manufacture, mechanical properties and water vapor permeability (WVP) of the films and coatings are also discussed.

MANUFACTURE METHODS OF EDIBLE FILMS AND COATINGS

The formulation of edible films and coatings requires using at least one component (macromolecule) capable of forming a structural matrix with a sufficient cohesiveness. Only high molecular weight polymers, owing to their sufficient cohesive strength and capacity for coalescence, can produce such film or coating structure [18]. In addition, in general, one needs a solvent and a plasticizer [19]. The formation of these materials usually involves associations or inter and intramolecular crosslinking of polymer chains. Plasticizers increase the space between the chains, causing a reduction of intermolecular forces along the matrix [20, 21], decreasing the glass transition temperature and increasing flexibility [22]. In structural terms, a semi rigid three-dimensional network that traps the solvent is formed [23].

The formation of edible films and coatings may involve one of the following mechanisms [24]:

- Simple coacervation: achieved by the precipitation of a hydrocolloid that is dispersed in aqueous solution. This precipitation can be obtained by precipitation from a solvent, by adding a non-electrolyte solute and in which the hydrocolloid is not soluble, by the addition of an electrolyte which induces the precipitation of the components or intersection, or by altering the solution pH;
- Complex coacervation: achieved by obtaining the precipitation by mixing two solutions of hydrocolloids with opposite electrical charges, which interact to form the complex polymer;
- Thermal gelation or coagulation: achieved by heating the macromolecule, leading to a denaturation and gel formation or precipitation. The gel can also be obtained by cooling the hydrocolloid solution.

The films are obtained from a solution or dispersion of film forming agent, followed by the formation of a thin layer using techniques such as casting, extrusion, thermoforming, blow molding, among others [18, 22]. The casting technique is widely used in laboratory studies; it does not require special equipment and large quantities of raw materials. This technique involves spreading the film forming solution (macromolecules, solvent, and plasticizer) in a container, which is then subjected to drying for solvent evaporation [19]. Extrusion has the advantage of low cost, in addition to having a system of versatile and continuous production, suitable for industrial scale [25].

Coatings are formed directly on the food product using either liquid film forming solutions (or dispersions) or molten compounds (*e.g.* lipids). They can be applied by different methods: with a paint brush or by spraying, dipping-dripping, fluidizing, *etc.* [26].

CHITOSAN FILMS

Chitosan, a high molecular weight polysaccharide consisting of (1,4)-linked 2-amino-deoxy-β-d-glucan, is a deacetylated derivative of chitin, which is the second most abundant polysaccharide found in nature after cellulose [27, 28]. The cationic nature of chitosan is owed to the free amino groups left by partial remotion of chitin acetyl groups. Chitosan is a linear polyelectrolyte at acidic pH with good film forming capacity [29]. Chitosan has been compared with other biomolecule based films used as packaging materials and the reported results

CHAPTER 10

Application of Chitosan Membranes for Permeation and Pervaporation

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Abstract: This chapter provides a comprehensive overview on the application of chitosan membranes in pervaporation and permeation processes. Pervaporation is a widely used membrane process for volatile liquid mixture separation. The separation of solvents is of extreme importance in a variety of industries ranging from chemical to food and pharmaceutical. The main thrust of research efforts has been concentrated on the polymeric membranes: investigation of new polymeric materials, modeling of component transport through dense polymers and description of their application. Chitosan membranes, owing to their hydrophilicity, biocompatibility, and ease of modification have been extensively applied for numerous pervaporation processes. The general overview of the preparation and application of different kinds of chitosan membranes *e.g.* crosslinked, blended, hybrid, grafted and chitosan membranes on porous support, in the separation of various solvents is presented. The progress of research, challenges and opportunities, as well as the prospect of pervaporation technique are also discussed.

Keywords: Blended chitosan membranes, Chitosan membranes on porous support, Crosslinked chitosan membranes, Grafted chitosan membranes, Hybrid chitosan membranes, Pervaporation.

INTRODUCTION

Pervaporation is recognized as a separation process that has elements in common with reverse osmosis and membrane gas separation. The concept of pervaporation separation dates from the early twentieth century. In 1917, the phenomenon of pervaporation was first discovered by Kober, who introduced the term in a paper reporting selective permeation of water through cellulose nitrate membranes from albumin and toluene aqueous solutions [1 - 9].

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Pervaporation is a widely used membrane separation process for the separation of liquid mixtures. During pervaporation, the separated mixture is in direct contact with one side of membrane, whereas the permeate vapor is removed from the opposite side in a vapor state under a vacuum. The permeate vapor can be condensed and collected or released as desired. The driving force for the mass transport of permeants is a gradient of chemical potential, which is established by an existing difference in the partial pressures of permeants across the membrane. The difference in partial pressures can be created either by reducing the total pressure by using a vacuum pump system or by sweeping an inert gas on the permeate side of the membrane [1 - 9].

Pervaporation transport is usually described by the generally accepted solution-diffusion (dual sorption) mechanism of mass transport through the nonporous membranes. According to this mechanism, the transport process can essentially be visualized to occur by the following three steps: (a) selective sorption of the components on the membrane surface; (b) diffusion of the components through the membrane; and (c) desorption on the permeate side. The sorption of the permeate component can be controlled by the affinity for the membrane material. The diffusion can be described as the permeation rate of the component through the membrane. Desorption is a very rapid step when permeate pressures are low. However as the permeate pressures approach the partial vapor pressure of the permeating species, the permeate flux becomes dependent on the rate of vaporization [1 - 9].

Pervaporation has substantial advantages in the separation of azeotropes, *i.e.* close boiling mixtures, and thermally sensitive compounds, and removing species present at low concentrations. Only a fraction of a mixture is vaporized during pervaporation, and lower temperatures than those required in distillation are usually used. Pervaporation can be mainly applied in the three fields classified as follows: (a) dehydration of aqueous organic mixtures; (b) removal of low concentrated organic compounds from organic aqueous mixtures and (c) separation of liquid organic mixtures [1 - 9].

The dehydration of organic solvents is the most important application of pervaporation. The first commercial application was the dehydration of ethanol, using a hybrid system with a distillation column. The ability to selectively separate ethanol and other alcohols from water by pervaporation has attracted significant attention over the years as alternatives to conventional separation processes. Considering that, it is the most widespread distillation, characterized as high energy and high capital cost, currently, in chemical engineering, membrane based pervaporation (PV) is widely used as one of the most effective methods for the separation of azeotropic mixtures, isomeric mixtures and temperature sensitive solutions. In the pervaporation process, water vapor diffuses faster than alcohol, and consequently leaves the alcohol to be dehydrated (purified) to the desired level of purity. In contrast, distillation enables the purification only up to the level of azeotrope (98.6% of ethyl alcohol) and needs heating [10 - 13].

For the dehydration of organic solvents, hydrophilic membranes are generally used because of the favorable solubility and diffusivity for selective permeation of water. Many researchers are making continuous efforts to develop new polymeric membranes. Recently, several reports have been published on using different types of hydrophilic polymers including poly(vinyl alcohol) (PVA) [14, 16], sodium alginate [11, 17, 19] and chitosan [19, 20]. Furthermore, hydrophilic polymers modified by grafting [21, 22], blending [18, 23, 24] and filler incorporated membranes [25 - 27] have been recently more promising in pervaporation dehydration of aqueous organic mixtures than plain membranes.

The second field, of enormous importance, is the water purification. Wastewater generated from various chemical products including commonly used refrigerants, plastics, adhesives, paints, petroleum products, and pharmaceutics, as well chemical plants is a serious environmental problem [28 - 32]. The wastewater mainly contains volatile organic compounds (VOCs), which are particularly halogenated hydrocarbons known for their negative effects on the environment and human health, with the most common ones being the depletion of stratospheric ozone, formation of the ground level smog, origination of the annoying odors and induction of the chronic toxicity [33 - 36]. Traditional VOCs control technologies such as conventional distillation process [37, 38], adsorption [39, 40] and biological treatment [41, 42] do not always provide a complete and economically reasonable solution, because the concentration of VOCs in the wastewater is usually very low. The pervaporation process is appropriate for the removal of VOC traces from the wastewater [34 - 36]. Membranes with high organic permeability and low water permeability are required in these processes. A typical organic permselective material for pervaporative membranes is poly(dimethylsiloxane) (PDMS) also known as silicone rubber [43, 44] or zeolite membranes [45, 46].

The third field of application of pervaporative separation is in the separation of the aromatic/aliphatic mixtures, such as benzene/cyclohexane [47 - 50], toluene/n-heptane [51 - 54] or toluene/octane [55 - 57]. This kind of separation is one of the most important and difficult process in the chemical and petrochemical industries, including the production of cyclohexane [47, 50], removal of benzene from gasoline [58, 59], and naphtha reforming [60, 61]. Many of these mixtures are difficult to separate because they contain close boiling point components that generally have similar physical and chemical properties, and/or the existence of

SUBJECT INDEX

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He is a professor in Chemical Engineering Department at the Federal University of Santa Maria (UFSM). He is a permanent member of the Chemical Engineering post-graduation program and also of the Chemistry post-graduation program. He attained his B.Sc., M.Sc. and PhD in Food Engineering from the Federal University of Rio Grande (FURG). His research is focused on the following areas: transport phenomena, unit operations, wastewater treatment, physicochemical treatments for wastewater and separation processes. In these research areas, he has published more than 80 articles and is reviewer of more than 90 international journals. He is also an editor of the Environmental Science and Pollution Research Journal-Springer and, is an editorial board member of Journal of Environmental Chemical Engineering-Elsevier.

Sergio Paulo Campana-Filho

In 1981, Prof. Sergio Paulo CAMPANA-FILHO joined the staff of the University of São Paulo as an assistant professor and is a member since then. He received his Ph. D. in Physical Chemistry from the University of Sao Paulo in 1990 and since then he has been working with natural polymers, as bacterial polysaccharides, cellulose, chitin and chitosan, proposing new derivatives of such polymers, investigating their physical chemistry properties and developing their applications in different fields as, for instances, biomaterials for Regenerative Medicine and nanocarriers for the controlled release of drugs.

Luiz Antonio de Almeida

Prof. Luiz A. A. Pinto is a graduate in Chemical Engineering by Federal University of Rio Grande (1977), has his Master's Degree (1992) and PhD (1996) in Chemical Engineering from the Federal University of São Carlos. He is a full professor at the Federal University of Rio Grande (FURG), Brazil. His expertise lies in the areas of Chemical Engineering and Food Engineering, with emphasis in Industrial Production of Foods and in Processes of Separation and Mixing, acting mainly in the following themes: food drying, adsorption, transport phenomena, unit operations, fish waste, effluents treatment and statistical modeling..