Chapter 3
Natural Polymers vs Synthetic Polymer

Abstract Polymers play an important role as excipients in any dosage form. They influence drug release and should be stable, economic compatible, non-toxic, etc. They are broadly classified as natural polymers and synthetic polymers. Synthetic and natural based biodegradable polymers have received much more attention in the last decades due their potential applications in the fields related to environmental protection and the maintenance of physical health. Biodegradable materials are used in agriculture, medicine packaging, and other areas. In recent years there has been an increase in interest in biodegradable polymers. Two classes of biodegradable polymers can be distinguished: synthetic or natural polymers. Synthetic polymers are widely used in biomedical implants and devices because they can be fabricated into various shapes. Natural polymers are basically polysaccharides so they are biocompatible and without any side effects. In this chapter we have discussed various natural polymers, their advantages over synthetic polymers and role of natural polymers in designing novel drug delivery systems.

Keywords Synthetic polymer • Natural polymer • Polysaccharide • Drug delivery • Toxicity

3.1 Bioengineered Materials: Nano-Engines of Drug Delivery Systems

Engineered materials have been employed for rising smart drug delivery systems. Design and multi-functionalities synthesize efficient smart drug delivery systems are vitally necessary for medicine and healthcare development. In the material science field offers biodegradable, environment-responsive, biocompatible, and highly effective novel polymeric system for targeted delivery. Nanotechnology offers bottom-up and top-down nanofabrication with size controlled and multi-functionality of particulate for targeted delivery. Novel materials invention and advanced technology have been synergistically accomplished in drug delivery so far. The important objectives of medical pharmacology to offer the right medicine, right dosage, and right route at the right time to the right patient, so additional research required to optimize the therapeutic efficacy of the drug. This is the most important principles

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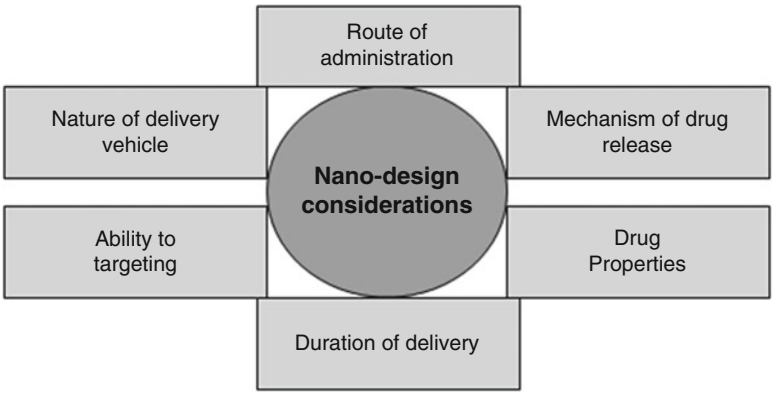

Fig. 3.1 Considerations of various factors for simultaneous reflection to design a polymeric nanoparticle for the smart drug delivery system

behind the smart drug delivery. A smart, controlled delivery system requires synergistic consideration of a number of factors summarized in Fig. 3.1. It is not easy to get all consideration factors in a smart controlled delivery system owing to other influencing factors. Also high efficiency, quality, reliability, and reproducibility are the most considerable issue while designing such a smart system.

3.2 Polymeric Nanoparticles

The polymeric nanoparticles are fabricated from biocompatible and biodegradable polymers in size between 10–1000 nm where the drug is entrapped, dissolved, encapsulated or attached to a nanoparticle matrix. Depending upon the methodology of fabrication nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is restricted to a cavity enclosed by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. The field of polymer nanoparticles (PNPs) is rapidly growing and playing an significant role in a wide spectrum of disciplines ranging from electronics, sensors, medicine, photonics, biotechnology, conducting materials, pollution control and environmental technology. PNPs are promising vehicles for drug delivery by simple manipulation to fabricate carriers with the aim of delivering the drugs to particular target, such an merit advances the drug safety. Polymer based nanoparticles efficiently carry drugs, proteins, and DNA to target cells and organs. Their nanometer size encourages effective permeation via cell membranes and stability in the blood stream. Polymers are very suitable materials for the manufacture of countless and varied molecular designs that can be integrated into exclusive nanoparticle constructs with many potential medical applications. PNPs can be expediently fabricated either from preformed polymers or by direct polymerization of monomers using classical polymerization or polyreactions. Methods like salting-out, dialysis solvent evaporation, and supercritical fluid technology, encompassing the rapid expansion of a supercritical

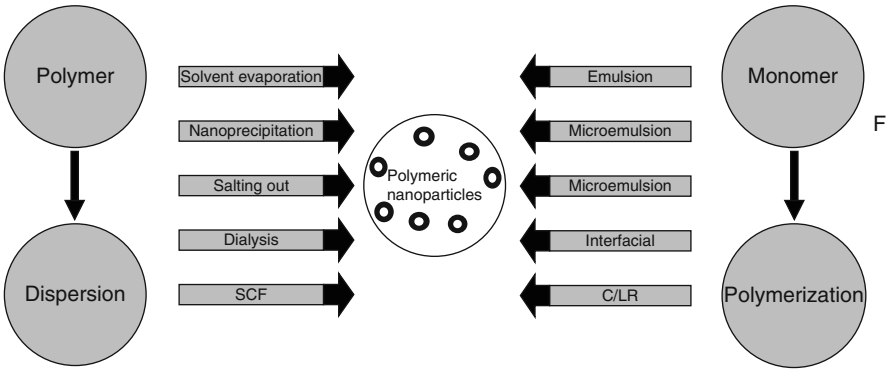

Fig. 3.2 Plan illustration of different techniques for the preparation of polymeric nanoparticles

solution or rapid expansion of a supercritical solution into liquid solvent, can be employed for the fabrication of polymeric nanoparticles from preformed polymers. Alternatively, polymeric nanoparticles can be directly fabricated by the polymerization of monomers using different polymerization techniques e.g. micro-emulsion, surfactant-free emulsion, mini-emulsion, and interfacial polymerization. A representation of various fabrication techniques for polymeric nanoparticles is mentioned in Fig. 3.2. The selection of fabrication method is made on the basis of a number of factors such as the type of polymeric system, area of application, size requirement and others.

3.3 Contemporary Methodologies for Fabrication of Polymeric Nanoparticles

In recent times, the polymeric nanoparticles have appeared as a most potential and viable technology platform for recognizing the targeted, environment-responsive and, multi-functional with navigated controlled drug delivery system. Polysaccharides in smart drug delivery is a fast rising new technological discipline in which different therapeutic applications of nanoproducts are predictable to overcome the patient complaints in healthcare. Smart delivery will offer new keys for therapeutic interventions. There is immense interest from the commencement in smart medicine of advanced and well-characterized bionanotechnological products that will be particularly effective in fighting diseases like cardiovascular diseases, aging, diabetes, cancer, some chronic metabolic syndrome and different degenerative diseases and disorders. For an instance, the innovative smart polymers with nanoparticulate drug-delivery systems can clearly advances in therapeutics by directing the drugs to target cells and reducing the adverse-effect/side-effect on well being. Presently, a number of smart polymer with multi-functioned nanoparticle system strategies in clinical trials, and it demonstrate promising result. Definitely the morbidity and mortality rate of disease affected patients could improve their lifestyle by the initial course of smart therapeutic intervention. This smart

intervention can be achieved by developing high sensitivity and reliable smart drug delivery. The quick development in the above course has been made with the initiation and development of more advanced alternative nanofabrication techniques to offer structures in various nano-scales level of controlled manners. Drug loaded polymeric nanosystems can offer controlled release of both hydrophilic and hydrophobic drugs over a long period of time while reducing undesirable side effects in the body. This encompass the fabrication of various novel biocompatible polymers with well-defined nanometers to a few micro-meters structures using several modern techniques e.g. microfluidic systems, microelectromechanical systems, microneedle based system, advanced high pressure homogenization, electrodropping system, interfacial emulsion polymerization and combined systems. Figure 3.3 explained the small number of modern techniques for polymeric nanoparticles fabrication with various concepts. The physiochemical features of polymeric nanoparticles have to be optimized based on the specific application. A variety of methodologies can be utilized to offer different nano-particulate systems with various polymers. The multifunctional polymeric nanoparticles developments e.g. coreshell nanoparticles, environment-responsive micelles, colloids, nano hydrogel, nano-spheres and coreshell nano-spheres with layer-by-layer assembly for single/dual or multi drug release have been achieved so far. So as to get the preferred features, the mechanism of formulation method plays a vital role. Therefore, it is tremendously beneficial to have synthesis mechanism at hand to approach multi-functional polymeric nanoparticles with exact physiochemical properties for a specific application.

3.4 Activation-Modulated Drug Delivery: Environmental Activation/Stimuli Responsive Smart Delivery System

The smart drug delivery with activation-modulated system has been accomplished by external or environmental stimuli. These environmental responsive smart delivery systems attained a lot more with double and multiple-responsive delivery system. Different activation/stimuli responsive drug delivery vehicles have been prepared and evaluated, in different particle sizes, ranges from nanometers to a few micro-meters sized carriers for various routes of administration. The transdermal electro-activated or electro-modulated drug delivery has been recognized as a competent model. In this assembly of activation-modulated controlled drug delivery system, the release of active agents from the systems is activated by some physical, chemical, electrical, environmental condition or biochemical processes and/or facilitated by an energy supplied externally. The release profile has been regulated by the input energy. Based on the activation/stimulation process applied or energy type used, this activation-modulated controlled drug delivery system can be classified into the different as mentioned in Fig. 3.4. These stimuli-responsive materials display variation in the physicochemical feature while the environmental condition

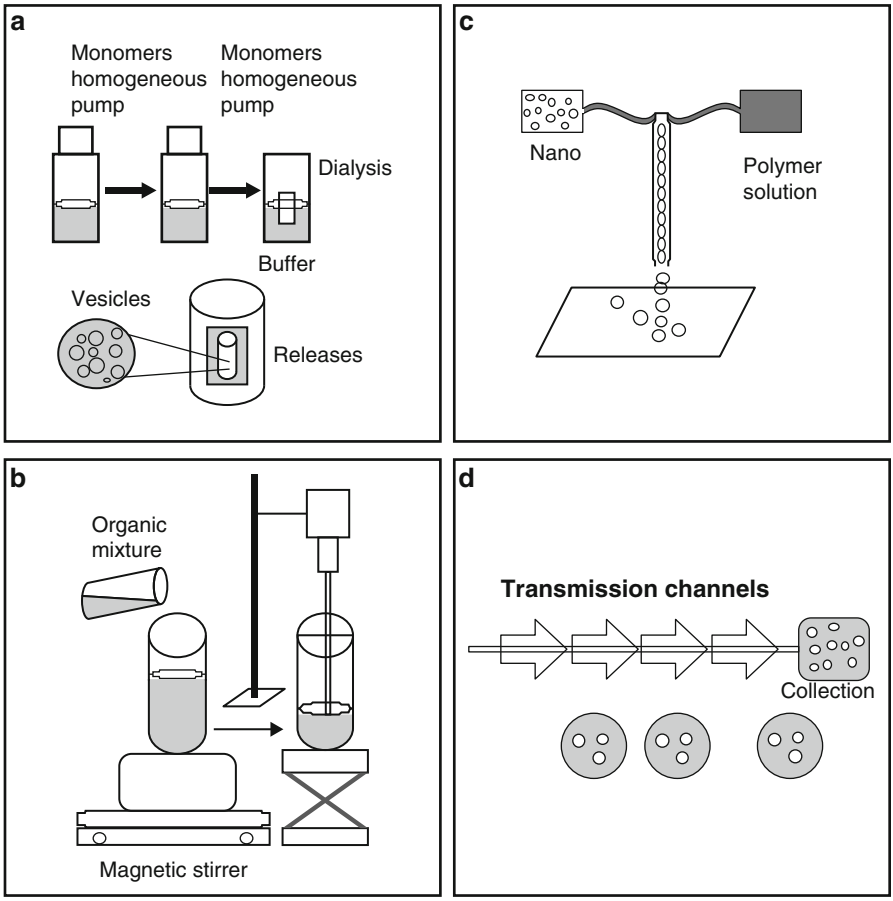

Fig. 3.3 Schematic representation of the advanced techniques of preparation of polymeric nanoparticles. (**a**) Core shell particulate system: in situ semi batch emulsion method. Size of the core controlled via surfactant. Surfactant was removed via dialysis pH-responsive polymer core-shell. (**b**) Sonication based system: mostly probe sonicator is used. Various optimization conditions require ON/OFF cycle to reduce temperature. Ice bath to maintain the temperature. (**c**) Electrodropping system: dual delivery using biocompatible care, homogeneous core shell, layer-by layer assembly possible, difference of release profile possible. (**d**) Well controlled synthesis of particles, tunable nanoparticles possible, reproducible synthesis, distinct nanoparticles for specific target

changes. These variations in features can be entirely utilized in smart delivery system, which definitely alike to the biological response behavior. Various sorts of body organs, different tissues and various types of cellular compartments might have vast dissimilarity in every stimulus with great response. Any definite behavioral changes in the system results in phase transition, these transitions will be key factors for the stimuli-responsive drug delivery system and some selected instances of applications are explained in the Fig. 3.4.

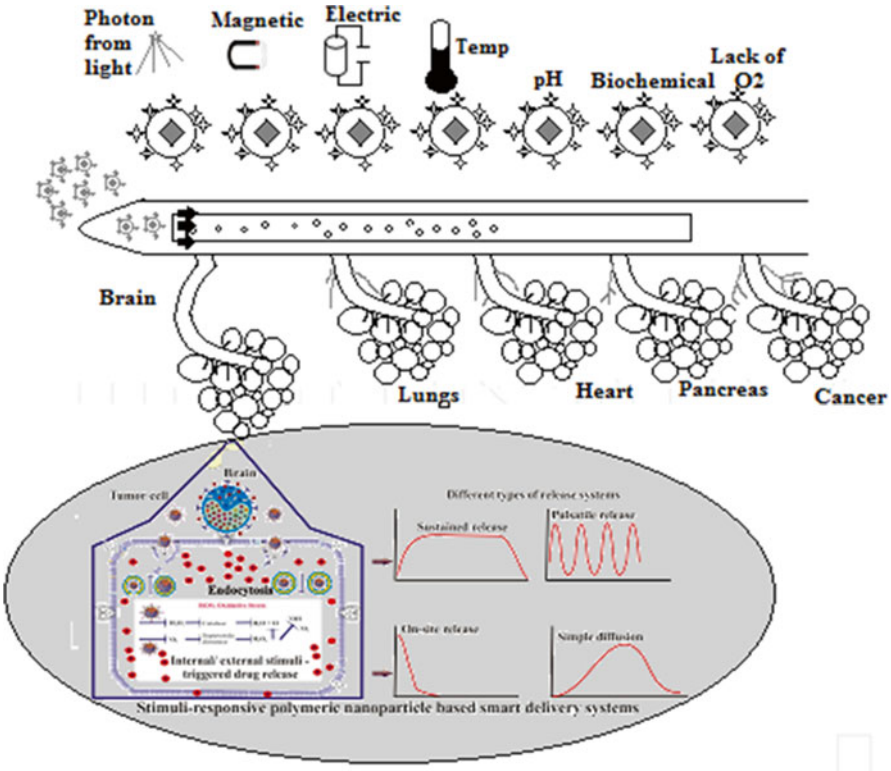

Fig. 3.4 Plan illustration representing the activation-modulated drug delivery systems, which the polymeric nanoparticles activated by different stimuli e.g. physical, chemical, biochemical, environment, and/or a combination of two or more

3.5 Time to Move on Innovative Methods of Administration

Polymers are macromolecules having repeating structural units which are typically connected by covalent chemical bonds. Synthetic and natural polymers are having various applications specifically in the pharmaceutical sector because of their economical, readily available and non-toxic nature. Additionally natural polymers are capable of chemical modifications, potentially biodegradable and with few exceptions, also biocompatible. Various applications of natural and synthetic polymers are mentioned in Fig. 3.5. Most of the pharmaceutical industries primarily manufacture/dispense drugs orally (as solid pills and liquids) or as injectables.

Owing to the recent innovations in pharmaceutical sciences most of the manufacturers are focusing on different strategies for the production of formulations that control the rate and period of drug delivery (i.e., time-release medications) and target specific areas of the body for treatment have become increasingly common and complex. Inclination of current researchers towards development of novel and potential

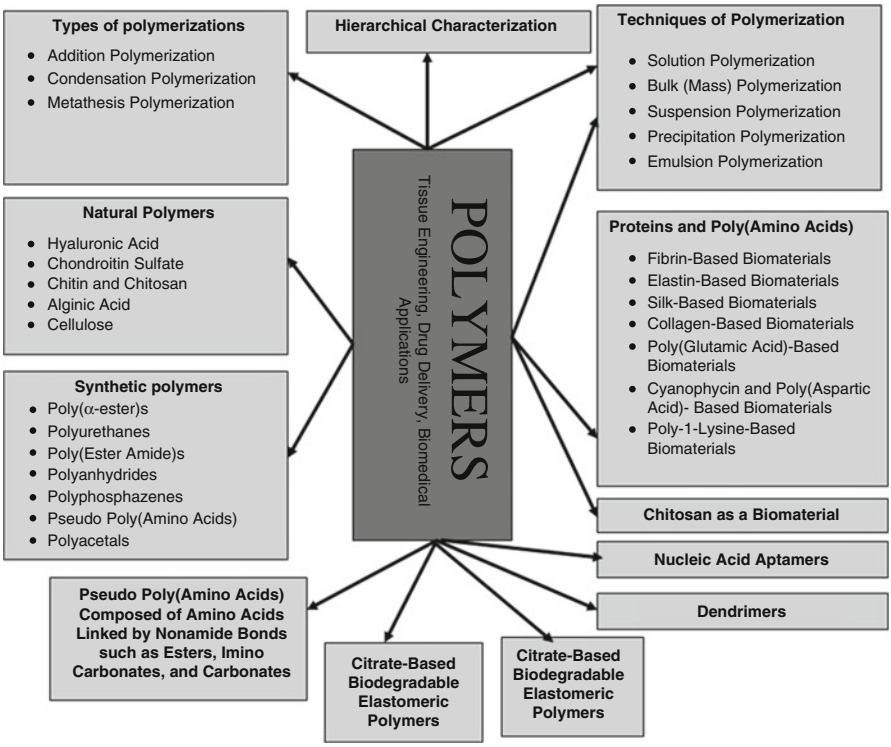

Fig. 3.5 Polymers and their diverse applications in tissue engineering, drug delivery and biomedical science

treatments and discoveries of bioactive molecules lead to exploration of mechanisms and their assisted strategic methods of administration. The most complicated work for current researchers is to design methods of drug delivery that exhibit specific problems such as limited therapeutic effects of certain drugs or their partial degradation that occurs before they reach a desired target in the body. Accountability of factors which directly or indirectly influences the pathway(s) of drug assists in designing the specified or targeted drug delivery system. Such systems not only deliver drug at targeted site but also encourage time dependent release of medications which may provide the relief from symptoms and protection from adverse events solely when necessary. Focus can also be stretched towards development of injectables drugs which could be manufactured less expensively and administered more conveniently if they could simply be dosed orally. Nevertheless such an approach cannot be achieved unless more advanced and scientific methods will be developed to safely direct medications through specific areas of the body, such as the GIT, where pH variation can destroy drug activity, or through an area where healthy bone and tissue might be adversely affected. Objective of all complicated drug delivery systems is to organize medications which can integrate to specifically targeted parts of the body through a medium. Such medium can control the therapy's administration by means

of either a physiological or chemical trigger. This objective can be achieved by designing more advance micro- and nanotechnology in form of polymeric microspheres, polymer micelles, and hydrogel-type materials. Such micro or nano scientific based delivery system can be designed in such a way where it can promote drug specificity, lower systemic drug toxicity, improves treatment absorption rates, and provide protection for pharmaceuticals against biochemical degradation.

3.6 History of Drug Delivery from the Ancient to Date

Treatments obtained from plants and other natural sources were earlier delivered either orally or topically. Various traditional system medicines (e.g. ayurvedic) and their respective formulations were highly recommended in form of oral and topically active preparations. It was later discovered that potential of these preparations is based on the integumentary and gastrointestinal (GI) system integrity. Various natural extracts were supplemented to treat the disease e.g. cinchona tree powdered bark containing quinine administered orally by native Brazilians to treat malaria [1]. Currently inspite of the development of resistant strains, quinine is still one of the core treatments for malaria [2]. Traditional ayurvedic medicines in the form of guttikas, churnas, leha, avleha, bhasmas, arishtas, asavas, and tailas form the foundation of drug delivery system. According to an interview that a pharmacist historian gave the LA Times [1], pills date as far back as 1500 BC. Earliest evidence to pills was found on papyruses in ancient Egypt, and contained bread dough, honey or grease. Pill name was introduced by Roman scholar Pliny (23–79 AD), he called them "pilula," later named as Pill. During medieval period people coated pills with slippery plant substances and gilded them in gold and silver to facilitate their swallowing more easily. The first concrete evidence of active table (sugar-coating and gelatin-coating) was explored in the 1800s and during the same time the compressed tablet also was invented in the 1800s by a Brit named William Brockedon. Later on it was realize that these formulations require more advance, more efficient and effective methods of drug delivery systems. Moreover significant role of drug delivery systems in herbal medicines was explored. For the first in 1656, Sir Christopher Wren reported the use of a syringe [3–5]. The earliest drug delivery systems, first introduced in the 1970s, were based on polymers formed from lactic acid. Later on in 1853, Scottish physician Alexander Wood and French surgeon Charles Pravaz independently publicized two extraordinary functional syringe designs [3–5]. This achievement explored the potential of different types of injectables to directly inject medications with either controlled or spontaneous rate. At last after the development of different designs of injectables, in 1960s, disposable syringes were introduced [6]. This outstanding achievement eliminated the need of boiling or sterilizing glass syringes, which resulted in improved hygiene and convenience. Thus purpose of most of the earlier delivery systems to deliver the therapeutic agent so that it will easily accumulated in target cells in optimal concentrations for a prolonged period. Nevertheless potential drug delivery via topical and systemic routes requires their transport through several

physiological barriers [7, 8]. Till today enteral (entering the body via the GI tract) or parenteral (entering the body by any route other than the GI tract) [7, 8] are the two most primary drug delivery routes used to deliver medications. Most of the manufactures designed different formula or delivery system for same medicines to control their release at the desired site. In spite of the delivery route drug features such as hydrophilic or hydrophobic nature plays an important role in determining the ultimate fate during its transport across lipidic membranes. These membranes are most permeable to lipophilic molecules nevertheless in order for a drug to dissolve in body fluids and be transported, it must also be somewhat hydrophilic [9]. Some additional factors such as low molecular weight and non-polarity improve drug transport across membranes. Strategies were developed to design more advance drug delivery system. In 1997, Glucose-sensitive hydrogel that could be used to deliver insulin to diabetic patients using an internal pH trigger was synthesized by chemical engineers at Purdue University in West Lafayette, IN, under the direction of Nicholas A. Peppas [10]. Development of different types of drug delivery system leads to the germination of new sector where drug release rate can be controlled in a more systematic and effective fashion, exclude side effects and encourages safe delivery of medication. This field is known as controlled drug delivery field began the founders who introduced this exciting and important field, and the prominent researchers who came after them [11]. This section is following the subsequent development phases of the field from its origins in the 1960s to the 1970s and 1980s, when various macroscopic "controlled" drug delivery devices and implants were developed for delivery as mucosal inserts, as implants, as ingestible capsules, as topical patches, and were approved for clinical use. Moreover these historical events section traces various phases of development in the 1960s to the 1980s and 1990s when microscopic degradable polymer depot DD systems (DDS) were commercialized [11]. Lastly the section objectives were set to explore the currently very active and exciting nanoscopic era of targeted nano-carriers, in a sense bringing to life Ehrlich's imagined concept of the "Magic Bullet". In the 1970s nanoscopic period began with systems projected which were first used in the clinic in the 1980s, and which came of age in the 1990s. These are currently emerging as exciting and clinically successful products in the 2000s. Most of these successful products are based on PEGylation and active targeting to specific cells by ligands conjugated to the DDS, or passive targeting to solid tumors via the EPR effect [11]. Key events and pioneers are highlighted in Table 3.1.

While this is of course one of the major reasons for the emergence of this field in the 1960s and 1970s, to me the surge of the field in the last 35 years is a classic example of an early form of "convergence to biomedical science", the idea promoted recently by Sharp and Langer [12]. ALZA Corporation was founded in 1967 by Alejandro Zaffaroni and immediately attracted a distinguished group of scientists from the chemical and pharmaceutical fields. A result of the introduction of mathematical models and molecular design principles in pharmaceutical formulations was the development of a new field setting the foundations, mechanisms and defining the principles of controlled release profiles. The founding of ALZA Corporation of 1967 had a significant effect on the development of the field of "controlled release".

Table 3.1 Historical events occur in drug delivery

Year	Event	Researcher	References
1960s and 1970s	Emergence of drug delivery field "convergence to biomedical science"	Sharp and Langer	[12]
1967	ALZA Corporation: Include the scientists from the chemical and pharmaceutical fields to introduce mathematical models and molecular design principles in pharmaceutical formulations This was done for the development of a new field setting the foundations, mechanisms and defining the principles of controlled release profiles	Alejandro Zaffaroni	[12]
1967	ALZA Corporation had a significant effect on the development of the field of "controlled release"	Alejandro Zaffaroni	[12]
1961	The first pharmaceutical scientist to apply physical chemical principles to the design of controlled release devices	Takeru Higuchi (professor at the University of Wisconsin and then the University of Kansas)	[13]
1960–1985	His classic equation (metamorphosed several times by 1963 to be applied also to porous systems with high or low drug solubility [4]) became the standard of design of drug delivery systems and continues to be widely used in the design of many ethical and generic products, especially of the oral/transmucosal delivery	Takeru Higuchi (professor at the University of Wisconsin and then the University of Kansas)	
1964	Developed systems of medical relevance for the prolonged drug therapy of patients	Folkman and Long	[14]
1981	Offered the first systematic, mechanism-based classification of controlled release systems	Langer and Peppas	[15]
1980	Design of drug delivery systems was a publication: provided simple but accurate solutions and design equations for drug delivery from matrices	Ping Lee	[16]
1990	Developed the first successful biodegradable systems for treatment of brain tumors	Langer and Brem, working with researchers at MIT and Johns Hopkins	[17]
1976	Speiser was the father of pharmaceutical nanotechnology, having written about nanoparticles in drug delivery as early as 1976 [16]	Speiser	[18]

(continued)

Table 3.1 (continued)

Year	Event	Researcher	References
1986	Worked on the enhanced permeability and retention (EPR) effect that explained the mechanisms of macromolecular transport and accumulation to tumors	Hiroshi Maeda	[19]
1960–1970	Resulted in historical development of nanoparticles	Contribution of Paul Ehrlich and then by Ursula Scheffel and colleagues and the extensive work by the group of Professor Peter Speiser at the ETH Zürich in the late 1960s and early 1970s	[20]

3.6.1 Historical Role of Polymers as Plastics

The plastics industry is recognized having its beginning in 1868 with the synthesis of cellulose nitrate. It all started with the shortage of ivory from which billiard balls were made. The manufacturer of these balls, seeking another production method, sponsored a competition. Johny Wesley Hyatt (in the U.S.) mixed pyroxin made from cotton (a natural polymer) and nitric acid with camphor. The result was cellulose nitrate which is called celluloid. It is on record; however that Alexander Parkes, seeking a better insulating material for the electricity industry, had in fact discovered that camphor was an efficient plasticizer for cellulose nitrate in 1862. Hyatt, whose independent discovery of celluloid came later, was the first to take out patents for this discovery. Cellulose nitrate is derived from cellulose a natural polymer. The first truly man made plastic came from 41 years later (in 1909) when Dr. Leo Hendrick Baekeland developed phenol-formaldehyde plastics (phenolics), the source of such diverse materials as electric iron and cookware handles, grinding wheels and electrical plugs. Other polymers-cellulose acetate (toothbrushes, combs, eyeglass frames etc.), urea-formaldehyde (buttons, electrical accessories), poly(vinyl chloride) (flooring, upholstery etc.) and nylon (toothbrush bristles, surgical sutures) followed in the 1920s. It is obvious that the pace of development which was painfully slow up to the 1920s picked up considerable momentum in the 1930s and the 1940s. The first generation of manmade polymers was the result of empirical activities; the main focus was on chemical composition with virtually no attention paid to structure. However during the half of the twentieth century, extensive organic and physical developments led to the first understanding of the structural concept of polymers-long chains or a network of covalently bonded molecules. In this regard the classic work of German chemist Hermann Staudinger on polyoxymethylene and rubber and of the American chemists W.T. Carothers on nylon stand out clearly. Staudinger, first proposed the theory that the polymers are composed of giant molecules and he coined the word macromolecule to describe them. Carothers discovered nylon, and his fundamental research (through which actually nylon was

discovered) contributed considerably to the elucidation of the nature of polymers. His classification of polymers as condensation or addition polymers persists today. The years following World War II (1950s) witnessed great strides in the growth of established plastics and the development of new ones. The Nobel Prize winning development of stereo specific catalysis by professors Karl Ziegler of Germany and Giulio Natta of Italy led to the ability of polymer chemists to order the molecular structure of polymers. As a consequence, a measure of control over polymer properties now exists, polymers can be tailor made for specific purposes. In recent years as a result of better understanding of polymer structure property relationship, introduction of new polymerization techniques and availability of new and low cost monomers, the concept of a true tailor made polymer has become reality. In the years ahead, polymers will continue to grow. The growth from all the indications will be not only from the development of new polymers, but also from the chemical and physical modification of existing ones.

3.7 Shift from Nature to Synthetic (Including the Merits and Demerits of Synthetic Polymers)

Polymers have become a crucial part of life, especially biodegradable polymers are of special interest since they do not accumulate in or nor harm the environment and thus can be considered as green [21].

To date, due to versatility of polymeric materials, specifically biodegradable ones, they are rapidly replacing other biomaterial classes, such as metals, alloys, and ceramics for use in biomedical applications. In 2003 the sales of polymeric biomaterials exceeded $7 billion, accounting almost 88 % of the total biomaterial for that year. The global market for biodegradable polymers increased from 409 million pounds in 2006 to 3 % an estimated 541 million pounds by the end of 2007. It should reach an estimated 1203 million pounds by 2012, a compound annual growth rate of 17 [21].

Biodegradable polymers can be either natural or synthetic. In general synthetic polymers great advantages over natural polymers since they can be tailored in such a way to yield wide array of possibilities with different types of products. Some of the natural polymers have important functional groups that are suitable for applications such as tissue engineering and less prone to produce toxic effects. Nevertheless presence of such functional groups and contaminants present in the material of natural origin may produce undesirable immunological effects [21]. On the other hand synthetic polymers are available with wide range of chemical linkages that can greatly affect the degradation and other derived properties. To obtain the intermediate property two or more polymers can be blended and or chemically linked (copolymerized). This latter approach has basically attracted lot of attention because of the possibility of generating polymers with desired properties without limitation such as phase separation [21].

Polymers are either naturally occurring or purely synthetic. All the conversion process occurring in our bodies are due to the presence of enzymes. Life itself may cease if there is a deficiency of these enzymes [22]. Enzymes, nucleic acid and proteins are polymers of biologic origin. These structures are normally very complex were not understood until very recently. Starch, cellulose and natural rubber are on the other hand example of plant based natural polymers and have relatively simple structure then those of enzymes or proteins. There are large numbers of synthetic polymers consisting of various families: fibers elastomers, plastics, adhesives. Each family itself has subgroups [22].

From last 10 to 15 years much attention has been given to the development of synthetic polymers for drug delivery devices, especially polymers those are fabricated from synthetic polymers that degrade under in vivo conditions. Various databases, literature, and scientific reports in the field polymers science have demonstrated that natural polymers to this field received far less publicity that the synthetic polymers as they play major role in drug delivery science. Three broad classes of natural polymers (proteins, polysaccharides and polyesters) derived from hydroxyacids showed the variable candidates for drug delivery applications [23]. However Kopecek and Ulbrich correctly reported the certain advantages offered by synthetic polymers over natural polymers. He has also suggested that the techniques or methodologies employed to fabricate synthetic polymers simply cannot create the well-designed molecular structures with unique properties featured by many natural polymers [23]. This is the most important reason for considering the latter. Protocol employed in the development of synthetic or natural polymers as drug carrier play a major role in deciding its ultimate applications in drug delivery. Degradation by external factors such as biodegradability by enzymatic hydrolysis or by other means is considered as the dominant feature of natural polymers. This type of degradation eventually causes a molecular weight variation which ultimately affects the molecular weight dependent biological activity of the natural polymer. Process of degradation is more advantageous when the degradation products are the part of normal metabolic process of the body. Potential of natural polymers to show bioactivity offers interesting possibilities that are being explored to some degree, but warrant further study [23]. In such cases, the carrier becomes an active participant in the therapeutic process. Nevertheless antigenicity, a form of bioactivity exhibit by natural polymers like proteins can be very dangerous, though not considered as a major problem to date. Current research cited various references for applications of collagen based drug delivery devices. Consequently it's suitable to review nature for such applications. It is relevant to point out that collagen represent complex family of numerous proteins [23]. Collagens are considered as the most important protein for connective tissue and form a major part of the organic matrix of bones. Although 11 type of collagens with varying features have been discovered and according to researchers many more will be identified in future [23].

Biodegradable synthetic polymer offers a number of advantages for application in tissue engineering and regenerative medicine [24]. The biomaterials can be easily synthesized with reproducible quality and purity and fabricated in to various shapes with desired bulk and surface properties [24]. Specific advantages include the abil-

ity to tailor the mechanical properties and degradation kinetics of these materials to suit various applications. Poly-hydroxy acids such as poly(glycolic acid), poly(L-lactic acid), and their copolymer poly(lactide-co-glycolide) are the most widely used biodegradable synthetic polymers for tissue engineering applications. The polymers have gained popularity due to their processing, consistency, adequate mechanical properties and Biodegradability and they are already FDA approved for human use in variety of applications including as sutures and in drug delivery system [24]. The ester bond in these polymers degrades non enzymatic hydrolysis and their non toxic degradation products are eliminated from the body in form of carbon dioxide and water. The degradation rate of these polymers can be controlled by alteration of their crystalline, initial molecular weight and the copolymer ratio of the lactide and glycolide and the degradation times that can be achieved ranges from several weeks to several months. Since these polymers are thermoplastics, they can be configured in three dimensional structures with a desired microarchitecture, shape and dimension, however synthetic polymer generally lacks intrinsic biological activity and their degradation products may cause adverse effects or alter local microenvironment in vivo. In addition the surface hydrophobicity of synthetic polymer may mediate protein denaturation in the vicinity of the implant and induce fibrous encapsulation [24]. A number of groups have begun to explore the synthesis of biomaterials that unite the advantages of smart synthetic polymers with the biological activities of proteins at the same chemical level. The concept of smart polymers was initially derived from the development of materials that show large conformational changes in response to micro environmental stimuli such as temperature, ionic strength, pH, or light. The responses of the polymer may include precipitation or gelation, reversible adsorption on a surface, collapse of a hydrogel or surface graft, and alteration between hydrophobic and hydrophobic state [24]. In many cases change in the state of the polymer is reversible. Biological application of this technology currently under development span diverse areas including bioseparation, drug delivery, reusable enzymatic catalysts, molecular switches, biosensors, regulated protein folding, microfluides and gene therapy. Smart synthetic polymers may offer promise for revolutionary improvements in tissue engineering scaffolds. Beyond the physical properties of these polymers, a major goal is to impart smart biomaterials with the specific properties of signaling proteins such as growth factors. Natural *polymers* are oxygen-permeable and available in large quantities from renewable sources, while synthetic polymers are produced from non renewable petroleum resources.

Biodegradable synthetic polymer exhibit number of advantages such as easy to process, bioactive molecules can be easily incorporated and mimic natural ECM structure and function. However it also exhibits numerous disadvantages less biocompatible than natural polymer and easily degrades to form bio products. Naturally derived materials are biocompatible, bioactive material can be easily incorporated, mimic natural ECM structure and composition, however its difficult to control biodegradable rate and having poor mechanical stability. Additionally they are temperature sensitive and transfer of pathogen is possible.

In contrast with natural polymers synthetic polymer enjoy the tremendous advantage of versatility. Through creative polymer chemistry, the synthetic polymer can be custom designed to meet specific needs. The toxicology of breakdown products and tissue biocompatibility of the polymers are the major issue in deciding the success of the devices. When intended as a long term delivery systems the cyto-toxicity of degraded products may be less of a problem because of the slow degradation rate and hence the low dose. Any acute inflammatory response to the implant may also have the chance of being resolved as the polymer disappears. However other potential side effects such as carcinogenicity and teratogenicity are difficult to address and evaluate. Nevertheless with the tremendous potential advantages, research in this area is still rewarded with a high benefit to risk ratio.

3.7.1 Natural Polymers and Synthetic Polymers for Scaffolds

Recent report suggested the potential applications of polymers as biomaterials for the fabrication of medical device and tissue-engineering scaffolds [25, 26]. The most preferable features for suggesting the materials as biomaterials are molecular weight, material chemistry, shape and structure, solubility, lubricity, hydrophilicity/hydrophobicity, water absorption degradation, erosion mechanism and surface energy. Owing to their distinctive properties such as high porosity with very small pore size, biodegradation, high surface-to-volume ratio, and mechanical property, polymeric scaffolds are considered for its potential biomedical applications. Their unique characteristics represent distinct advantages of biocompatibility, versatility of chemistry, and the biological properties which are significant in the application of tissue engineering and organ substitution. According to reports various researchers have worked to culture skin and cartilage [27], bone and cartilage [28], liver [29], heart valves and arteries [30], bladder [31], pancreas [32], nerves [33], corneas [34], and various other soft tissues [35]. Depending on the intended use, scaffold materials can be synthetic or biologic, degradable or nondegradable. Based on the properties of polymers such as composition, structure, and arrangement of their constituent macromolecules it can be classified into various types in terms of their structural, chemical, and biological characteristics, for example, ceramics, glasses, polymers, and so forth. In broad terms it can be classified in to naturally occurring polymers, synthetic biodegradable, and synthetic nonbiodegradable polymers used as biomaterials. According to earlier report natural polymers can be considered as the first biodegradable biomaterials used clinically [36]. Since they exhibit bioactive properties and have better interactions with the cells which allow them to enhance the cells' performance in biological system. Natural polymers can be broadly classified as polysaccharides (cellulose, amylose, dextran, chitin, and glycosaminoglycans), proteins (silk, collagen, gelatin, fibrinogen, elastin, keratin, actin, and myosin), or polynucleotides (DNA, RNA) [37]. The most dominating feature of synthetic polymer over natural polymers is that synthetic biomaterial direction provided by biomaterials may assist restoration of structure and function of damaged

or diseased tissues, thus highly considered in biomedical field. In addition their properties (e.g., porosity, degradation time, and mechanical characteristics) can be tailored for specific applications which may further encourage its utilization in biomedical field. In contrast with natural polymer, synthetic polymers are having broad class with defined purity and properties. Additionally they often cheaper than biologic scaffolds; it can be produced in large uniform quantities and have a long shelf time. It has been observed that various commercially available synthetic polymers show physicochemical and mechanical properties comparable to those of biological tissues. As discussed above synthetic polymers correspond to the largest group of biodegradable polymers, and they can be produced under controlled conditions and exhibit, in general, predictable and reproducible mechanical and physical properties such as tensile strength, elastic modulus, and degradation rate [38]. The most commonly used synthetic polymers in tissue engineering [39] are PLA, PGA, and PLGA copolymers. Among various polymers, PHA (belongs to a class of microbial polyesters) is being increasingly considered for applications in tissue engineering [40]. In soft tissue engineering bioactive ceramics (such as HAP, TCP), and certain compositions of silicate and bioactive glasses (such as phosphate glasses) and glass-ceramics (such as apatite-wollastonite) react with physiological fluids and through cellular activity form tenacious bonds to hard [41]. Nevertheless the issues related with their biocompatibility and biodegradability is often inadequate. This may limit their potential use in the clinical side. Researchers are still working on overcoming these issues by developing suitable blend of synthetic and natural polymers or by exploring composite materials that improve the scaffold properties and thereby allowing controlled degradation [42] and improving the biocompatibility in tissue engineering applications [43]. For achieving mechanical and biological performance in hard tissue the suitable blend of degradable polymers and inorganic bioactive particles can be developed. This and many other alike approaches promote their utilization in biomedical field [44].

3.7.2 Natural vs Synthetic Polymer (as Biomaterial)

Natural polymers can be found in living creatures and plants; for example, silk, protein, cotton, linen, wool and DNA. Synthetic polymers, as their name indicates, are synthesized in the lab through a series of chemical reactions. Examples of such polymers are polyvinylchloride, polypropylene, chewing gum, rubber and nylon. There are various biomedical applications of synthetic and natural polymers (Table 3.2). Synthetic and natural polymers have diverse applications in drug delivery. Natural polymers faced many problems like instability, irreproducibility, changes in aesthetics on storage, uncontrollable formulation characteristic etc. therefore novel designs were required to develop in form of synthetic polymer by some chemical processes like polymerization. Development of new structural imprints could require solutions for some of the problems that are usually associated with natural polymers. Most of natural polymers are covered by gums such as

Table 3.2 Biomedical applications of synthetic and natural polymers

Polymer	Biomedical applications
Poly (2-hydroxyethyl methacrylate)	Contact lens
Poly(dimethyl siloxane)	Breast implants, contact lenses, knuckle replacements
Poly(ethylene)	Orthopedic joint implants
Poly(ethylene glycol)	Pharmaceutical fillers, wound dressings
Poly(ethylene terepthalate)	Vascular grafts, sutures
Poly(e-caprolactone)	Drug delivery devices, sutures
Poly(lactic-co-glycolic acid)	Resorbable meshes, sutures
Poly(methyl-methacrylate)	Bone cements, diagnostic contact lenses
Poly(tetrafluoroethylene)	Vascular grafts, sutures
Poly(isoprene)	Gloves
Poly(propylene)	Sutures
Alginate	Wound dressing
Chitosan	Wound dressing
Collagen	Orthopedic repair material, Nerve repair matrices, Tissue engineering matrices
Elastin	Skin repair matrices
Fibrin	Hemostatic products, tissue sealants
Glycosaminoglycan	Orthopedic repair matrices
Hyaluronic acid	Orthopedic repair matrices

acacia, tragacanth, guargum, xanthan, etc. these polysaccharides are having molecular weight which sometime hinders its biological property. Natural polymers those are derived from the animal origin carry antigenicity and therefore interfere with function of model drug by inducing some immune reactions. Microbial based polysaccharides often carries the antigenic property which again interferes with in vivo biological reactions induced by model drug, though they are still use for various pharmaceutical applications. On the other hand synthetic polymers are either synthesized from natural polymers or completely synthesized from synthetic monomers. Synthetic derivatives like cellulose, acryl, vinyl polymers relatively address these issues. In modern day formulations well engineered polymers are gradually replacing the natural polymers. Natural polymers are less toxic, biodegradable and don't contain any synthetic chemical as synthetic polymers and derivatives contains. Though the Synthetic polymers are more stable then the natural polymers therefore synthetic polymers can be readily sterilized. Most of the natural polymers tend to change color due to the process called as auto oxidation. This will lead to the leaching of colorful substance in product which can interfere with the physic-chemical properties of parent product. Therefore plasticizer supplementation is highly recommended while fabricating natural polymer based formulation. Natural polymers have the problem of short shelf life when compared with synthetic polymer. Some of toxicities under *in vivo* and *in vitro* conditions were also highlighted in some of the reports. There are various structural variable used to control

Table 3.3 Structural variable used to control biodegradable polymer properties [45]

Variables	Effects	Examples
Inco-operation of both natural or non natural monomers	May reduce/eliminate immunologic response often found in natural derived polymers	Nonimmunologic PGA and PLA (vs collagen)
Inco-operation of labile groups in polymer chain	Control kinetics of biodegradation	Hydrolysable ester bond in PGA
Inco-operation of functional groups in side chains	Control chemical and physical properties of polymers	Hydrophilic, hydrophobic and amphiphilic polyphosphazenes
Inco-operation of chiral centers in polymeric chains	Control chemical and mechanical properties of polymers	Semi-crystalline I PLA, amorphous di PLA
Possibility of utilizing multiple monomers	Control properties of polymers	Glycolic and lactic acids in PLGA
Use of natural compounds as monomers	Biocompatible breakdown of products	Lactic acid in PLA
Use of different polymer Architectures	Control chemical and mechanical properties of polymers	Branched polymers lower viscosity

bio-degradable polymer properties (Table 3.3). Toxicity assessment of both synthetic and natural polymers can be achieved by considering the biocompatibility and biodegradability parameters which can be further assessed by *in vivo* and *in vitro* cyto-toxicity (e.g. lactate *dehydrogenase* assay).

3.7.3 Natural vs Synthetic Polymer in Tissue Engineering

Natural based polymer can be derived from the sources within the body or outside the body. One of the most common natural biomaterial found in the human body is the protein collagen. Many different type of collagen exist in different tissues and several of these particularly type I and II have been explored as biomaterials. Another protein base biomaterial fibrin, results from the combination of blood clotting factors fibrinogen and thrombin. Both fibrin and collagen have been frequently used in tissue engineering attempts to repair cartilage damage and other orthopedic applications.

In addition to proteins, naturally based polymers may be derived from sugars (carbohydrates). Hyaluronic acid is an example of carbohydrate molecule occurring in human tissue that is often employed as a biomaterial. However the source of other carbohydrate derived materials may be non human. Chitosan, a sugar based substance found in arthropod exoskeletons, agarose which is formed by algae and alginate derived from seaweed, are all currently being investigated as biomaterials for a variety of applications. For example, combination of chitosan and alginate has been examined for wound dressings.

There are advantages and disadvantages of both natural and synthetic polymer and particularly materials may lend themselves to certain applications over others. In many cases natural polymers have composition similar to tissues they are replacing. Therefore they may be more fully integrated in to the surrounding tissue over the time or more easily remolded in response to changes in tissue needs. However concerns about the feasibility of findings large amount of some these materials for clinical applications, their relatively low mechanical properties and the assurance of pathogen removal. In addition regions of these molecules may be recognized as foreign by the body immune system leading to a type of material rejection. Further potential problem arise when the biomaterial is based on not a single naturally occurring polymer, but decellularized tissue. Here unwanted calcification leading to device failure is a particular concern.

In contrast synthetic polymer can be easily mass produced and sterilized so supply issues are not a problem at all. Additionally their physical, chemical, mechanical and degradative properties can be tailored for specific applications. However unless specifically treated, most synthetic materials do not interact with tissue in an active manner and therefore cannot direct or aid in healing around the implant site. Also few synthetic polymers have been approved by regulatory agencies for use in humans in specific applications.

3.7.4 Natural vs Synthetic Polymer Hydrogels

Hydrogel can be prepared from natural or synthetic polymer using various methods. Hydrogels made from natural sources can be derived from polymers such as collagen, hyaluronic acid, fibrin, alginate, agarose, and chitosan. Many natural polymer such as collagen HA and fibrin have been used in tissue engineering applications because they are either components or have macromolecular properties similar to the natural extracellular matrix. Collagens are composed of three polypeptide strands twisted together to form a triple helix and are the main protein of mammalian ECM. Likewise hyaluronic acid an anionic glycosaminoglycan polysaccharide, is also found in nearly all adult animal tissues. Alternatively alginate, agarose and chitosan are hydrophilic, linear polysaccharides derived from marine algae sources (alginate and agarose) or crustaceans (chitosan). Another natural derived gel Matrigel™, is derived from soluble basement membrane extract of mouse tumors. Various natural polymers have specific utilities and properties based on their origin and composition. Advantages of natural polymer based gels include inherent biodegradability and biologically recognizable moieties that support cellular activities. Disadvantages of some of these hydrogels include mechanical weakness and the possibility of evoking immune/inflammatory responses. Synthetic hydrogels are appealing for tissue engineering due to amount of control scientists have over structure, such as cross-linking density and tailored properties such as bio-degradation, mechanical strength, and chemical and biological response to stimuli. Synthetic polymers such as poly(ethylene glycol) (PEG) and other PEG based polymers or

poly(vinyl alcohol) (PVA) can be reproducibly produced with specific molecular weights, block structures, degradable linkages and cross linking density and mechanical and degradation properties of the material. Hydrogels made from synthetic polymers like PVA, PEG or their derivatives do not possess the inherent bioactive properties that gels made from natural polymers do. However, they do have well defined structures and are versatile templates for subsequent modifications that yield taliorable degradability and functionality.

3.8 Natural Polymers (Reasons for Reverting to Nature)

Polymers derived from natural resources have been widely researched as biomaterials for a variety of biomedical applications including drug delivery and regenerative medicine. These molecules have biochemical similarity with human ECM components and hence are readily accepted by the body. Additionally these polymers inherit several advantages including natural abundance, relative ease of isolation and room for chemical modification to meet the technological needs. In addition these polymers undergo enzymatic and hydrolytic degradation in the biological environment with body friendly degradation bye products. Natural polymers include the list of polysaccharides and animal derived proteins. Polysaccharides are an important class of biomaterials with significant research interest for a variety of drug delivery and tissue engineering applications due to their assured biocompatibility and bioactivity. Polysaccharides are often isolated and purified from renewable sources including plants, animals, and microorganisms. Essentially these polymers have structural similarities, chemical versatilities and biological performance similar to ECM components, which often mitigate issues associated with biomaterials toxicity and host immune responses. The building block of carbohydrate monosaccharide's are joined together by o-glycosidic linkages to form polysaccharide chains. Polysaccharides offer a diverse set of physicochemical properties based on monosaccharide's that constitutes the chain, its composition and source. The popular list of polysaccharides used for a variety of biomedical applications includes cellulose, chitin/chitosan, starch, alginates, HAs, pullulan, guar gum, xanthan gum, and GAGs. In spite of many merits as biomaterials, these polysaccharides suffer from various drawbacks including variation in the material properties based on the source, microbial contamination, uncontrolled water uptake, poor mechanical strength and unpredictable degradation pattern. These inconsistencies have limited their usage and biomedical applications related technology development. Numerous synthetic polymers with well defined mechanical and degradation properties have been developed to meet the technological needs in the biomedical applications. However these polymers from the biological standpoint lack much desired bioactivity and biocompatibility and may cause toxicity and immune response. Polysaccharide structure offers freely available hydroxyl and amine functionalities that make it possible to alter its physicochemical properties by chemically modifying polysaccharide structure. For instance grafting synthetic monomers on the

polysaccharide chains offer an easy way to control polymer solubility undesired solvents, water uptake and degradation. These semi synthetic polymers offer best feature of the both natural and synthetic polymers. Various cross linking techniques to restrict the polysaccharide chain movement to control their water uptake, degradation and mechanical properties have also been developed. Polysaccharides based porous scaffolds, fiber matrices, hydrogels, and micro and nanoparticles have been developed for variety of tissue regeneration and drug delivery applications. In the recent years glycochemistry has gained research momentum for understanding carbohydrate biological functions and development of carbohydrate based drugs and vaccines. Engineered carbohydrate based polymeric structures may serve as an alternative material platform for a variety of regenerative medicine and drug delivery applications. A new nonpetroleum based biomaterial platform to meet the versatile needs in biological science and biomedical engineering could be achieved by collaborative efforts between academia, government and industry partnership. The collaborative efforts should include bringing scientist working in different disciplines of chemistry, biology, polymers, materials sciences and engineering to work toward these activities. The collaborative efforts could lead to the development of a methodology for synthesis natural polymer based semi synthetic polymers and provide a greater depth of understanding of carbohydrate biological functions, polymer structure, material properties degradation and mechanical properties. Further the development of modeling tools to predict the structure, property and biological activity of carbohydrates for biomedical applications is a step in this direction. The goal of new initiatives should focus on the development of natural polymer based orthopedic fixation devices, biomedical implants, drug delivery vehicles, carbohydrate based drugs, hydrogels, surfactants, coagulants, and absorbents for a variety of biomedical applications. The research activities in this area could generate commercially available technologies and product from the renewable resources and contribute immensely toward economic development.

3.8.1 Need of Natural Polymers

- **Biodegradable**
  Naturally occurring polymers produced by all living organisms. They show no adverse effects on the environment or human being.
- **Biocompatible and Non-Toxic**
  Chemically, nearly all of these plant materials are carbohydrates in nature and composed of repeating monosaccharide units. Hence they are non-toxic.
- **Economic**
  They are cheaper and their production cost is less than synthetic material.
- **Safe and Devoid of Side Effects**
  They are from a natural source and hence, safe and without side effects.
- **Easy Availability**
  In many countries, they are produced due to their application in many industries.

3.8.2 Disadvantages of Herbal Polymers

- **Microbial Contamination**
  During production, they are exposed to external environment and hence, there are chances of microbial contamination.
- **Batch to Batch Variation**
  Synthetic manufacturing is controlled procedure with fixed quantities of ingredients while production of natural polymers is dependent on environment and various physical factors.
- **The Uncontrolled Rate of Hydration**
  Due to differences in the collection of natural materials at different times, as well as differences in region, species, and climate conditions the percentage of chemical constituents present in a given material may vary [46].
- **Slow Process**
  As the production rate is depends upon the environment and many other factors, it can't be changed, thus natural polymers have a slow rate of production.
- **Heavy Metal Contamination**
  There are chances of Heavy metal contamination often associated with herbal excipients [47].

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