Innovative Drug Delivery System using Graft Copolymers: Recent Advances and Challenges

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Abstract

Natural polymers have received more attention because of their advantages over synthetic polymers such as abundant availability, low cost, biodegradability and non-toxicity. However, natural polymers suffer some limitations such as drop-in viscosity upon storage, uncontrolled hydration, solubility, inability to perform under high temperature and pressure (thermal stability), etc. In recent years, the chemical modification of natural polymers, polysaccharides in particular, by graft polymerization or by introduction of some functional groups, represents one of the most accessible and attractive method to obtain the polymeric materials with desired properties. Selection of proper polymer system is a critical step involved in the formulation of dosage form. Type of polymer/s incorporated in pharmaceutical formulation majorly decides the stability of formulation and drug itself, mechanism, and rate of drug release. Pharmaceutical and biological therapeutics are suffered from disadvantages such as short half-lives, poor bioavailability, and physical and chemical instability. Delivery of drugs to target site at a specific concentration for a specific time can be successfully achieved by the use of suitable polymer/s. Thus, it is not necessary that available polymer till the date should have all ideal properties with respect to above. Polymer-based drug delivery systems may significantly improve cancer therapy.

Keywords: Copolymers, Drug delivery system, polysaccharides.

I. Introduction

With the increasing demand of new and advance materials for biomedical applications, overpowering research has been done in developing advanced functional materials with remarkable properties in drug delivery system, using polysaccharides.

A brief overview of different physical and chemical crosslinking approaches has been reviewed and discussed in details in this study to design polysaccharides derived biomaterials. The present approach is considered towards recent advances and its challenges. Owing to their inherent biocompatible and biodegradable properties, polysaccharides-based biomaterials are being extensively explored for performing a difficult task under complex biological atmosphere.

It is fact that the new therapies are diverse from the traditional small molecules and current large molecules which are frequently intended at aims on the cell surface or delivered without a specific molecular targeting strategy. Accordingly, we need advanced drug delivery systems for targeted and controlled release of our novel molecules in tissues and cells so as to optimise their potential benefits for patients.

Various scientists are committed to breaking down the barriers between our most promising new drug candidates and their targets in tissues and cells. They are developing a broad range of nanoparticles that aim to deliver our new modalities to previously un-drugged targets and precisely control their release in formulations that are easy to use and convenient for patients. They are also investigating innovative ways of getting oral formulations of biologic drugs across the intestinal wall something which has eluded generations of drug designers. Polysaccharides comprise of repeated mono or disaccharide units connected via enzyme-susceptible glyosidic bonds, which support their applications as controlled release drug carriers.

The polysaccharide-based advanced drug delivery system owing to their biocompatibility, ability to encapsulate the drug molecules in their interspaces, and ability to achieve a controlled release of the cargo drug molecules result in improved drug pharmacokinetics.

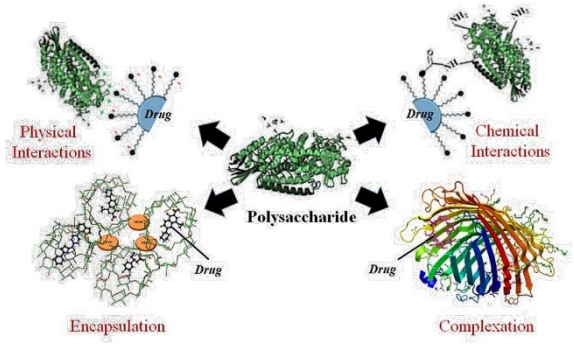

Figure 1: Graphical presentation of the polysaccharide-based advanced drug delivery system.
(Source: www.sciencedirect.com)

Graft copolymerization is one of the most advance and promising techniques uses to modify the properties of naturally available polymers with a minimum loss in their native characteristics. Accordingly, efforts made to overview towards recent advances and further challenges in this book.

A. drug delivery systems:

Drug delivery systems (DDS) are used to transport therapeutic drugs in the body as needed to safely achieve the desired therapeutic effect. Such systems are usually designed to

i) Improve aqueous solubility and chemical stability of active agents,

ii) Increase pharmacological activity

iii) Reduce side effects. Modern drug delivery systems have undergone continuous progress since the 1950s, when the first sustained release formulation Dexedrine was introduced[1]. The goal of any drug delivery system is to provide and maintain therapeutic concentrations of drug at the target biological site.

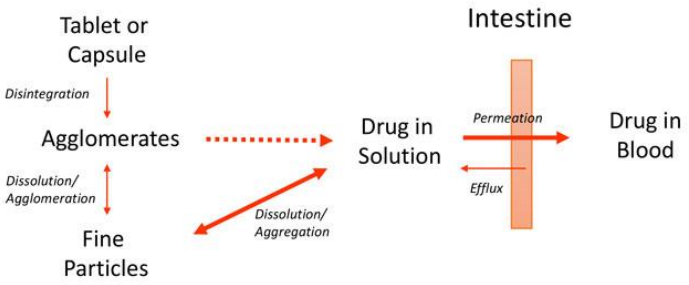

Figure 2: A simplified depiction of the oral absorption process

Among present drug delivery systems, nanoparticles as carriers have shown great potential in recent years, e.g. liposome drug delivery systems can improve bioavailability, increase efficacy and reduce toxicity. Several successful liposome-based drugs have been approved by the U. S. Food and Drug Administration (FDA).

B. New strategies for drug delivery: (Stimuli-responsive strategy)

Currently, stimuli-responsive delivery has been the most attractive strategy in the field of drug delivery. This strategy has been actively explored in order to achieve the tumor-specific delivery and controlled release of their cargoes, where endogenous or exogenous triggers can be employed. The endogenous triggers including pH-sensitive, ROS (reactive oxygen species) sensitive, redox-sensitive, enzyme-sensitive and temperature-sensitive delivery strategies towards some disease sites like tumors. Exogenous triggers include light-triggered and temperature-triggered strategies induced by exogenous methods. Magnetic-triggered, and X-ray triggered delivery strategies have also been used in the design of stimuli-responsive systems. Ultrasound can also serve as a trigger for remote control of drug release deeply within the body. The use of focused ultrasound has the advantage of delivering spatially localized heat, thus improving site-specific controlled release by destabilizing the structure of such delivery systems.

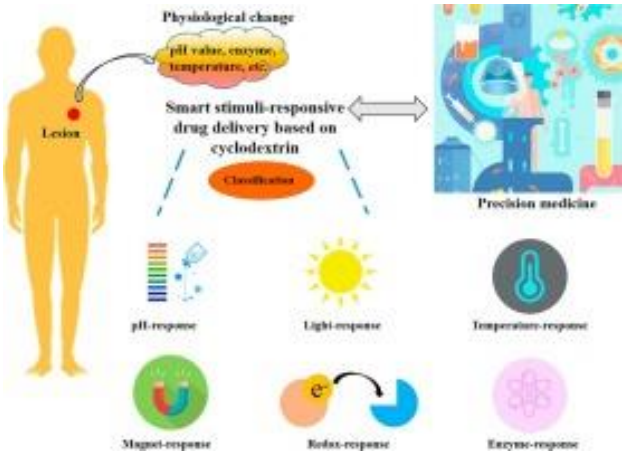

Figure 3: Smart stimuli responsive drug delivery based cyclodestrin. [2]

II. Physicochemical Properties

Their remarkable physicochemical and physiological properties such as biocompatibility, biodegradability and low immunogenicity to further validate the drug delivery applications. [1] Usually, such natural polysaccharides are easily available from the plant, animals and microbes. Such polysaccharides possess various physicochemical properties such as being neutral or having positive or negative charge, being able to have linear or branched molecular structure, and their molecular weight can vary from a few hundred to several thousand Daltons. Due to these properties, the polysaccharides have considerable impact on the bio-distribution of carrier drug molecules in-vivo [1].

Numerous polysaccharides could even adhere to the layer of mucus, which covers epithelial surfaces throughout the body. Thus, the polysaccharide-based carrier systems have extended *in vivo* residence time in gastrointestinal (GI) tract, thereby increasing drug

bioavailability. Cationic polysaccharides such as chitosan and its derivatives have the capacity to open the tight interconnections among epithelial cells, thereby increased hydrophilic drug permeability through mucus membranes.

III. Physicochemical Advances:

The polysaccharides possess an inherent ability to recognize specific receptors, which over-express on the surface of morbid tissues. As such, hyaluronic acid specifically binds to the over-expressed CD44 receptor of several tumor cells. In addition, pullulan reportedly possesses a high specificity towards asialoglycoprotein receptors that express at the surface hepatocytes. The unique binding of these polysaccharides with certain receptors permits a rational designing of novel carriers, which selectively deliver the cargo drugs by means of receptor-mediated endocytosis.

A. Drug delivery system using grafted polysaccharides and the applications:

Besides, the natural polysaccharides offer advanced applications as multi-drug delivery systems. In this review, we present a comprehensive survey of the advanced applications of Polysaccharides in drug delivery and other biomedical applications and the various factors that determine the efficacy of these applications.

- **Polysaccharide drug conjugates**

Numerous natural and synthetic water-soluble polymers reportedly exhibit conjugation with therapeutic molecule through chemical conjugation. Pharmacokinetic investigations of drug-conjugating polysaccharides have documented the implications of natural and sustainable polymers as robust drug delivery systems. In addition to the synthetic, water-soluble polymers, the natural polymers such as dextran, chitosan, hyaluronic acid, and cellulose seem to have a tremendous drug carrier potential.

- **Polysaccharide drug-loaded through self-assembling**

Hydrophilic polysaccharide backbones construct the self-assembling frameworks, such as niosomes and liposomes, when they are introduced to hydrophilic polymers. The self-assembly of hydrophobic polysaccharide formulates from the polymer backbones treated with hydrophobic sections of hydrophilic polysaccharides containing hydroxy, amino or carboxy groups that eventually form amphiphilic macromolecules. This solubilizes the hydrophobic drugs molecules in the self-assembling.

- **Polysaccharide based controlled release and targeted formulations:**

Unlike the synthetic hydrophilic polymers, polysaccharide possess a variety of hydrophilic the synthetic functional groups on its structure like OH, COOH, and NH2 group which are responsible for water absorption and further swelling of polysaccharide. These groups grant a variety of functional capability to the polysaccharide-based systems such as bio-adhesion and control release property. Controlled release property of polysaccharide-based drug delivery systems has been explored extensively for achieving a comprehensive study.

- **Polysaccharides as emulsion stabilizers:**

The amphiphilic nature of chemically modified polysaccharides causes their adsorption at the interface of oil and aqueous solvents that results in the stabilization of the emulsion. This property of polysaccharides proved highly beneficial for the delivery of lipophilic or non-polar therapeutics at their target site. As such, the native cellulose does not offer emulsion stabilization due to its non-solubility in water.

IV. Recent development in polysaccharides-based drugs:

Recently, the potential of polysaccharides-based formulations has also been explored in the direction of developing novel drug delivery systems with the capability of releasing multiple drugs simultaneously or sequentially to achieve enhancement in dedicated therapy.
Here, the drugs can be released in response to a variety of stimuli such as enzymes, temperature, pH etc. based on the composition of the developed system, booming research interest has also been shown in fabricating polysaccharides based biomaterials for achieving cell encapsulation and developing tissue engineering scaffolds. In this study here, polysaccharides have appeared as an immensely used building block owing to low cost, ease of processing, possibilities of functionalization, suitable interaction with nearby tissue, outstanding biocompatibility and biodegradability. The recent developments in the area of polysaccharides based biomaterials for drug delivery and tissue regeneration mainly over the last five years.

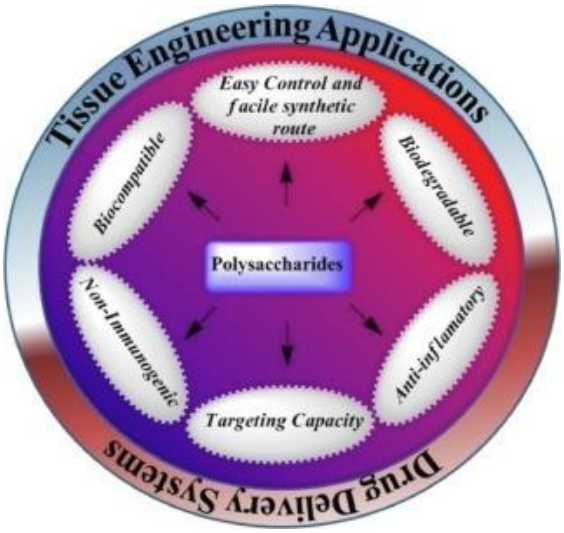

Figure 4: Schematic representation of the properties of polysaccharides used for drug delivery and imaging applications. Source: [3]

Table 1. Details of polysaccharides-based drug delivery systems through physical drug entrapment. Source: [3]

Sl No	Carrier	Material	Therapeutic molecule	Target
1.	Nanovesicles	dextran, poly(l-lactide) (pla)	hemoglobin	General
2.	Nanoparticles	Acetylated dextran	Insulin	Diabetes
3.	Nanoparticles	Dextran, PLGA	Ifosfamide	Bone cancer
4.	Nanoparticles	Dextran	5-Fluorouracil	Colorectal cancer
5.	Nanoparticles	Chitosan	Rampipril	Transdermal
6.	Microparticles	Chitosan, Poly(lactic acid)	Montmorillonit, Curcumin	Transdermal
7.	Nanoparticles	Chitosan, Poly(N-vinylcaprolactam) (PNVCL)	Doxorubicin	Breast cancer
8.	Microbeads	Sodium alginate, Starch	Ciprofloxacin	General
9.	Nanoparticles	Alginate	Miltefosine	Candidiasis and Cryptococcosis
10.	Hydrogels	Alginate, Chitosan	Risedronate	Osteoporosis
11.	Nanoparticles	Alginate	Theophylline	General
12.	Nanoparticles	Pullulan, Human serum albumin (HSA)	Mitoxantrone	General
13.	Nanoparticles	Pullulan, Cholesterol	Mitoxantrone	Cancer
14.	Hydrogels	Cellulose, Pullulan	GDF-5 and TGF-β1 (growth factors)	Vertebral disk
15.	Microdevices	Chitosan	Ketorolac	Gastrointestinal tract
16.	Nanocomposites	Cellulose, Titania	Diclofenac sodium, Penicillamine-D, Phosphomycin	Dermal
17.	Nanocrystals	Cellulose	Hesperidin	General

Sl No	Carrier	Material	Therapeutic molecule	Target
18.	Nanocrystals	Cellulose, Titania	Triclosan	General
19.	Nanogels	Heparin	Doxorubicin	General
20.	Nanosponge	Heparin	bFGF, VEGF, BMP-2, and HGF (growth factors)	General
21.	Hydrogels	Heparin, Collagen	Pleiotrophin	Vascular

V. Polysaccharides based biomaterials for tissue engineering

Tissue engineering involves damaged tissue regeneration or repairing of the malfunctioning tissue by providing suitable 3D microenvironment for the cell attachment, differentiation and proliferation. To achieve the required 3D microenvironment several advanced material-based 3D scaffolds are being developed which can mimic the naturally occurring extracellular matrix (ECM) and provide a support for desired cell growth. [4]

In this regard, numerous synthetic and natural polymers have been used individually or in combination for fabricating tissue engineering scaffolds. [5] Here, natural polymers like polysaccharides provide extra advantage of being biocompatible and mimicking ECM. [6] Hence, polysaccharides-based biomaterials have emerged as a capable platform for tissue engineering applications.

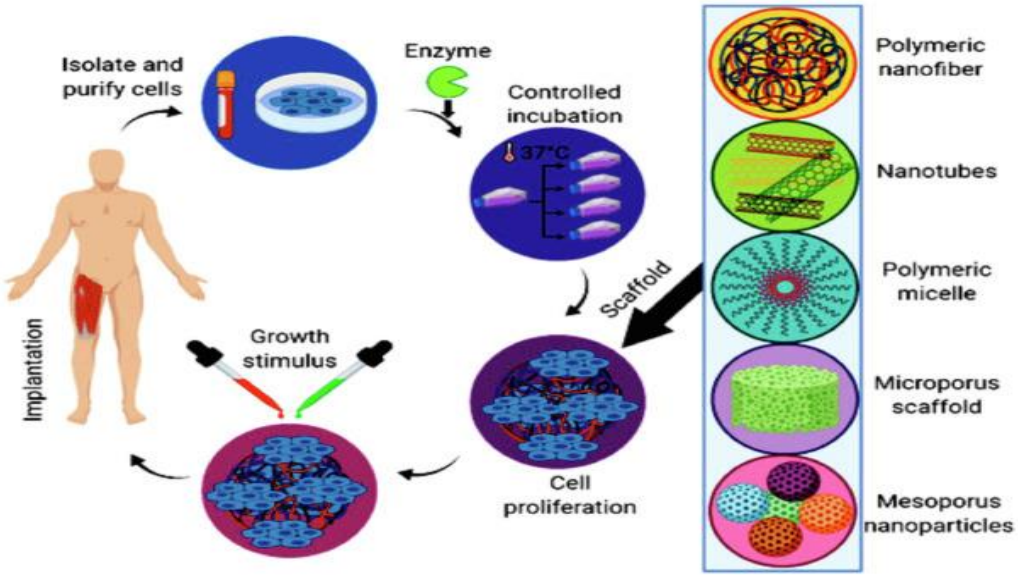

Figure 5: Schematic representation of the different processes involved in the field of tissue engineering to develop a scaffold ready for implantation. [3]

Chitosan is categorized as natural polycationic polysaccharides and it can show electrostatic interactions that can be used for the production of biomaterials. It can be an interesting choice of material in a physiological environment, where most biomolecules are anionic. [7] This, in combination with properties such as its biodegradability, biocompatibility, increased cell adhesion and antimicrobial properties marks the success of chitosan as a potent material in the field of tissue engineering. [8] Yu et al. designed chitosan (CS) based hydrogels containing graphene oxide (GO) and hydroxyapatite (HA) NPs. [9]. The hydrogels were prepared by simultaneous crosslinking of CS and reduction of GO. Hydrogels displayed high mechanical properties and porosity owing to their dense and oriented microstructures. These biocompatible, ternary hydrogels could be used for bone engineering application. Chitosan has been further used in combination with other polysaccharides for designing scaffolds for tissue regeneration. Rao et al. reported the use of chitosan and xanthan gum with iron oxide magnetic NPs to develop magnetically responsive hydrogels as scaffolds for tissue regeneration. [10] Cellulose is one of the most abundant naturally occurring polymers and hence, immense efforts have been given to develop cellulose based scaffolds for tissue regeneration. [11] Presence of hydroxyl groups in the cellulose molecule restricts the use of cellulose in the

preparation of hydrogels with varying structures and properties, thus hampering the use of cellulose as a platform for tissue engineering applications. Cellulose is non-biodegradable in human body. Therefore, the regenerated new tissue cannot replace the cellulose from the place of regeneration which is a possible drawback associated with cellulose based scaffolds. On the other hand, continuous structural support provided by non-degradable cellulose based scaffolds constantly encourages researchers to develop new derivatives of cellulose.

Alginate based hydrogels has immense applications in the field of regenerative medicine and tissue engineering. Interaction of alginate with bivalent cations results in the development of cross-linked polymer chains to form a 3D structure supporting tissue regeneration. Studies have revealed the importance of alginate stimulating the proliferation and differentiation of osteoblasts at *in vitro* level. [12] Further, injectable alginate/peptide-based hydrogels for bone tissue regeneration have been studied by many research groups in an attempt to meet the high demand of tissue engineering scaffolds.

It is to mention here that the degradation of alginate based hydrogels is very slow and cells do not have the necessary enzymes to cleave alginates. Also, the lack of protein adsorption onto alginates presents another challenge. These factors motivate researchers to constantly look for chemical modification of alginate backbone which could improve the cell adhesion. Apart from biocompatibility, low production cost of alginate makes it a material of choice for many researchers in various biomedical and tissue engineering applications. The summary of different polysaccharides with their scaffold types and targeting tissues is tabulated in Table 2.

Table 2. Details of polysaccharides-based biomaterials and scaffold types used for various tissue engineering applications.

SI. No.	**Applications**	**Components**	**Scaffolds**
1.	Skin tissue engineering	Sodium alginate, Fibrinogen	Sponge
2.	Bone tissue engineering	Alginate, Gelatin PVA	Nanofibers
3.	Tissue engineering (General)	Alginate, Silk fibroin	Hydrogels
4.	Cartilage tissue engineering	Carboxymethyl chitosan, Sodium alginate	Hydrogels
5.	Skin tissue engineering	Alginate, Collagen, Chitooligosaccharides	Sponge
6.	Cartilage tissue engineering	Alginate, Collagen	3D scaffolds
7.	Cartilage tissue engineering	Chitosan	Porous scaffolds
8.	Cartilage tissue engineering	Chitosan,Poly(glutamic acid), Albumin, Elastin, Poly-L-lysine	3D Scaffolds
9.	Bone tissue engineering	Chitosan	Hydrogels
10.	Tissue engineering (General)	Chitosan, Cysteine, RGD peptide	3D porous scaffolds
11.	Bone tissue engineering	Cellulose, Hydroxyapatite	Porous scaffolds
12.	Tissue engineering (General)	Cellulose	Hydrogels

VI. **Challenges in future:**

We highlighted structure, physicochemical properties and functionalization of various polysaccharides such as alginate, chitosan, cellulose, and hydrogel. We also summarized various physical and chemical crosslinking methods to fabricate functional

polysaccharides based biomaterials. The occurrence of diverse functional groups in polysaccharides gives the possibility of facing new challenges with other chemical groups which could very be helpful for further research.

It is mentioned here that biocompatibility and biodegradability are the important parameters for using a material for biomedical applications. As polysaccharides inherently possess these properties, they often act as a suitable polymer matrix for designing new materials.

The successful and widespread use of polysaccharides-based biomaterials requires performing interdisciplinary research taking into consideration various cutting edge tools provided by different disciplines including chemistry, material science, biotechnology etc. For achieving efficient drug delivery to diseased site without affecting the healthy cells, the developed biomaterials should be decorated with targeting ligands such as folic acid. The presence of targeting ligand provides cytotoxic specificity and prevents the adverse effects on normal cells. Additionally, the biomaterials should be designed in such a way so as to reduce the leakage of drug in blood, prevent drug resistance and achieve longer blood circulation. Furthermore, the delivery system should be able to present high encapsulation efficiency along with the possibility of sequential or simultaneous multiple drug release to achieve the synergistic effect. Development of novel delivery vehicles with incorporated contrast agent will be useful for simultaneous imaging and drug release. Further, polysaccharides also show immense potential for tissue regeneration owing to low cost, ease of processing, biocompatibility and biodegradability. Development of polysaccharides-based biomaterials loaded with drugs, growth factors, proteins and peptides open a new pathway for tissue regeneration.

The polysaccharide-based drug-delivery vehicles traversed a long journey for the controlled release of pharmaceuticals at the target site with minimized ensuing side effects caused by the customary delivery vectors. The biodegradability and trivial immunogenicity of the polysaccharide-based drug delivery vehicles makes them the material of the future. The controlled release profile offers improved drug pharmacokinetics thereby leading to ameliorated local action, and effectivity.

Thus, the overall endeavored was bridging the areas of inorganic chemistry and medicine. advantages over the conventional polymers by being non-toxic, biodegradable and available at cost effective. Biochemical changes of polysaccharides through graft copolymerization improves the properties of polysaccharides. Graft copolymerization is one of the most advance and promising techniques uses to modify the properties of naturally available polymers with a minimum loss in their native characteristics Hence, recent developments by using graft polysaccharide derived biomaterials especially for drug delivery and tissue engineering applications have been discussed at length.

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