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Review Article

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Biopolymer Nanoparticles: A Review of Prospects for Application as Carrier for Therapeutics and Diagnostics

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ABSTRACT

Biopolymer nanoparticles are molecules of interest in the direction of generation of new pre-diagnostic and treatment strategies with improved efficacy and specificity. Several methods have been developed to produce biopolymer nanoparticles. These biopolymer nanoparticles had distinct properties such as size and charge according to the production method affecting their targeting and drug encapsulation abilities. The present review highlighted the progress in the development of theronostic nanoparticles. The surface of the nanoparticles may be subjected to modification and be hidden from the immune system, so that they can stay in blood circulation for a long time to achieve their intended outcome. The safety and efficacy of most of the generated nanoparticles systems were not tested in humans in details. The synthesizable nanoparticles that are generated using biodegradable and/or biocompatible building blocks have been easy to be considered as important candidates for the usage in treatment and diagnostic evaluation plan. In-depth understanding and research must be achieved for better understanding of the mechanism of theranostic nanoparticles metabolism and their excretion out of the human body. An attempt to summarize the recent research studies in the field of therapeutics and diagnostics based on the biopolymers was achieved in this review article.

Key words: *Nanoparticles, Albumin Nanoparticles, Targeted Drug Delivery, Protein Nanoparticles, Nanomaterials*

INTRODUCTION

Recent research and brisk developments in the field of nanomaterials have been focused on the generation of new methods and options for treatment and diagnosis of some deadly diseases like cancers [1, 2]. Biopolymers hold such a promise, and their scope is continuously expanding from therapeutics to industrial applications (figure -1) [3, 4].

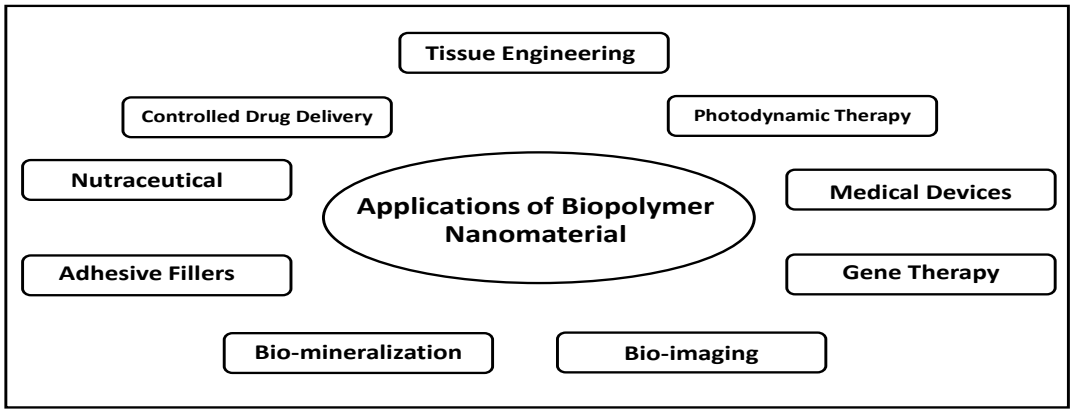

Figure 1. Various applications of biopolymer based on nanomaterials showing the expanding scopes from therapeutics to industrial applications.

Nanomaterials may be generated from inorganic or organic materials with a neutral, positive or a negative charge surface with a size ranges between one to a few hundred nanometers [5, 6]. Multifunctional nanomaterial has been designed recently for cancer imaging and therapy [7, 8]. Many functional nanomaterials have been tested as imaging agents and diagnostic sensors for drug delivery [9]. Gold nanoparticles, carbon nanotubes, magnetic nanoparticles, and silica nanoparticles were tested for gene delivery and drug delivery [10-13]. Recently, significant attention has been given to nanotechnology that was applied in cancer therapy and diagnosis. Nanoparticles can efficiently treat tumor by carrying chemotherapeutic agents to the site of tumor generation and progression [14, 15]. The theranostic protocol exhibits a synchronized plan of letting the diagnosis and treatment run at the same time using nanoparticles. Synthesis of nanoparticles can be carried out through ecofriendly approach. 'Green synthesis' in this process plant derived materials has been employed in generation of nanoparticles, it can be used as a capping agent as well as a stabilizing agent [16, 17]. The small size of the biopolymer nanoparticles, their flexible fabrication and their high surface area qualified them to be convenient drug delivery vehicles. The nanoparticles could be generated from a variety of biomaterials such as polysaccharides, proteins and phospholipids [18-20]. Materials like silk, keratin, collagen, elastin, corn zein and soy protein have been employed in nanoparticles research studies including drug delivery and biomedical fields [21-24]. Drug delivery systems have been used in medicine for protection against diseases, diagnosis and treatment. Drug delivery before the discovery of microencapsulation depended mainly upon cataplasms or oral intake of herbal ingredients which are partially effective in spite of posing unnecessary health risks to patients on which they were used [25-27]. These concerns further pushed the research in biopolymer nanomaterials to be applied in fields of health, environment and medicine.

Biopolymers used in nanoparticles research and their applications

- **Human Serum Albumin (HSA)**

Due to its circulating nature, serum albumin can be used as a drug carrier for peptide or protein based drugs [28, 29]. Binding drugs of low-molecular weight to albumin and fusion with other proteins of therapeutic and diagnostic value are the drug delivery technologies that have been recently developed for human serum protein. These technologies can be employed for conjugating bioactive proteins. Drug encapsulation can be done into albumin nanoparticles for the delivery of ligands like drugs and vitamins. In human blood, HSA has been considered as key drug-delivery as well as transporting many biomolecules in the blood stream [30]. HSA has half-life of 19 days in blood circulation. HSA is produced in the liver, about 13–14g of HAS is secreted by the liver into the circulatory system each day. Lymph circulates the extra vascular HSA into intravascular circulatory system. HSA is extensively used as a carrier molecule for imaging probes, small drugs and ligands [31-33]. HSA is biodegradable and non-toxic and is not immunogenic, these properties make HSA as an excellent candidate for usage as the excipient for vaccine and other pharmaceutical formulation. Albumin-based

drug delivery system has been used in pharmaceutical sciences for the preparation of albumin-based micro particles and nanoparticles for treating various diseases such as infectious diseases and cancer [34, 35]. HSA based nanoparticles are characterized by containing imaging agents and other reporter molecules that can be used in diagnostics [36]. Albumin nanostructures are of different shapes such as nanoparticles, microbubbles, microspheres, nano-capsules and albumin-coated liposomes. Albumin-based delivery systems can serve gene therapy applications to deliver nucleic acids to the target cells in a protected form in the bloodstream [37]. Zhang et al. (2016)a reported that albumin specifically targets tumor regions in the body because of its enhanced permeability and retention due to the receptor binding [38]. Conjugating ligands to albumin is one of the most common methods developed for protein nanoparticles due to its minimum side effects and high efficiency [39]. Albumin bound or conjugated small molecule nanoparticle increases the therapeutic efficacy of the conventional chemotherapy drugs which are in general hydrophobic, and thereby have poor solubility in blood circulation. Albumin binds to different types of hydrophobic molecules, and as a result, helps in transporting drugs in the blood stream [40-42]. Moreover, HSA being an intrinsic protein molecule in the blood averts the risk of hypersensitivity reaction that may be caused by the artificial formulation of drug compounds [43]. HSA nanoparticle complex can serve as a theranostic platform for diagnostic imaging and small ligand and drug delivery. These nanoparticles have been developed as a common nanoplatform with both imaging and therapeutic functions-theranostic nano particles. For instance, after coupling with targeting ligands and imaging moieties, iron oxide nano-particles can provide many potential applications including multimodality imaging and therapy [44]. In addition, HSA coated nanoparticles over the naked nanoparticles generally give reduced accumulation in organs related to the mononuclear phagocytic system. HSA-conjugate that is radio-labeled has also been used in internal radiotherapy of cancer [45, 46].

- **Bovine serum albumin (BSA)**

BSA is a serum albumin which has a molecular weight of about 69-kDa molecular weight protein. Because of its characteristic features illustrated in non-immunogenicity, abundance, biodegradability, biocompatibility and nontoxicity, it is commonly used in drug delivery. BSA nanoparticles have advantages in drug delivery of immunosuppressive drug tacrolimus, and there is a reduction of nephrotoxicity as compared to the drug solutions only [47]. The results of the release kinetics have shown another positive point that the release of drug from nanoparticles was followed by the sustained release of drugs [48]. More studies are required to be performed in order to solve the immunologic response developed against BSA [49, 50] which limits its application in human or *in vivo*.

- **Fibroin**

Fibroin is a protein extracted from Bombyx mori silkworm [51]. It is one of the natural polymers used for generating biomaterials. It is a very popular biopolymer due to its low cost and natural abundance. It has an isoelectric point below pH 7, and regenerated silk fibroin has molecular weight of 83 kDa, but the molecular weight may differ depending on the method of generation and the duration of the treatment with sodium carbonate. Fibroin can be extracted by the treatment with sodium carbonate, and then the removal of the external coating sericin protein. Gly-Ser-Gly-Ala-Gly-Ala amino acids are repeated in silk fibroin that leads to the stacked of anti-parallel fashion of crystalline beta-sheets [52, 53], which gives rise to robust mechanical properties and high tensile strength. In addition, silk fibroin generated nanoparticles was found effective in the delivery of hydrophilic lipophillic drugs and therapeutic proteins.

- **Keratin**

Keratin protein is a structural protein of a molecular weight of about 63 kDa. It is a left-handed alpha-helix which permits coiling with other keratin proteins to profound a polymerized complex. It contains filaments of intermediate nature that constitute soft tissues of the cytoskeleton. It is a fibrous protein present in the epidermal appendages and epidermis of the birds, mammals, reptiles, animals and human such as feathers, scales, hair and quills. The use of keratin as a biomaterial has been rapidly expanding in the last years because of its low cost, biocompatibility, safe biodegradability and abundance. Epithelial cells are the major sites where keratin protein is most commonly found [54]. Keratin helps in creating a protective layer of skin covering the sensitive and delicate internal tissues by enabling cell-cell adhesion. Owing to its negative charge, keratin protein permits the

positively charged molecules to be better adhered to the nanoparticle leading to more efficient transport. Studies have suggested immense application of keratin and keratin-based nanoparticles which act as an effective carrier for the drugs of treating cancer which have a controlled drug release and an ability for tumor targeting. The hydrogen bonds of amine groups and the disulfide bonds from cysteine residues confer keratin nanoparticles the durability of delivering high molecular weight drugs to the target sites. The pH sensitivity gives the targeting ability of keratin-based nanoparticles. The change in pH helps the keratin nanoparticles to release their drug contents in a controlled manner. The powerful water stability of keratin makes it a desirable support polymer for synthetic nanoparticle composites. In addition, silver nanoparticles coated with keratin have shown improved stability in hydrated media, whereas gold nanoparticles coated with keratin showed biocompatibility with improved antibacterial activity [55, 56]. Further studies are needed to validate the use of keratin as an ideal drug carrier for drug delivery applications.

- **Collagen**

Collagen is a type of fibrous proteins consisting mostly of the extracellular matrix and it maintains its structure. It is considered the most abundant biopolymer in the human body. Collagen mostly is present in the connective tissues of ligaments, skin and tendons. Collagen is divided according to its function and structure. Type 1 collagen is a common fibrillar collagen found in human body of a molecular weight about 100 kDa. Its triple helical structure gives it flexibility and strength. The repeated amino acid sequence Gly-X-Y, where "X" and "Y" are commonly hydroxyproline, proline or lysine or leucine. Tropocollagen is the name of the individual helix of collagen, these tropocollagen molecules bind together and form a fibrillar structure [57, 58]. In addition, collagen-based nanoparticles were also used in drug delivery of lidocaine, retinol and theophylline. Collagen has resemblance to some tumors which allows collagen nanoparticles to effectively percolate the areas and deliver anticancer drugs to tumor sites [58, 59]. Physical properties such as surface area and size can be easily designed and manipulated for collagen nanoparticles generation.

- **Gelatin**

Gelatin is obtained from the hydrolysis of collagen. It has been an attractive biodegradable material for biotechnology and pharmaceutical industry [60]. Gelatin nanoparticles have been widely used as a gene and drug carrier to targeted tissues, and has been used in the treatment of various diseases including cancer, tuberculosis, HIV infection. Due to its biocompatibility and biodegradability, gelatin has been utilized as coating material for quantum dots, coated dots with gelatin has been found to have less cytotoxicity [61]. Gelatin nanoparticles have been found to cross the blood-brain barrier, hence they can serve as a promising candidate to target brain disorders, and can serve the purpose of transportation of those drugs with are otherwise cannot penetrate the blood brain barrier [39, 62]. Gelatins have a wide range of potential applications. It is actively utilized in tissue engineering like for the construction of biological scaffolds and for bio-artificial tissues and organ production. Gelatin is generated from the insoluble Type I collagen via lyses or thermal denaturation. Gelatin has found ample application in the biomedical field because of its abundance and biocompatibility. Similar to collagen, gelatin consists of a triple helical structure of repeated proline, alanine and glycine. It is classified into type A or type B depending on the production process. Type A gelatin is positively charged, and has an IEP of about pH 9, while type B is obtained by the process under alkaline conditions, type B gelatin is negatively charged and has an IEP of pH 5, Type A gelatin is extracted through an acidic process [63]. Gelatin can also be formed into a gel [64]. Gelatin nanoparticles have been extensively used as a successful carrier for anticancer drugs and has also been used as a gene delivery vehicle. Gelatin nanoparticles have a positive point that they can deliver drugs across the blood brain barrier, this semipermeable barrier is highly studied for drug delivery systems [65]. Gelatin can also be blended with other natural polymers like alginate to enhance their therapeutic activity. Two polymers were bonded via electrostatic bond and were used for a controlled release of the drug, doxorubicin through the generation of alginate-gelatin nanocomposite [66, 67]. In future studies, gelatin could be used as a convenient mean for nanoparticle-based delivery of pharmaceutical compounds, vaccines and genes.

- **Alginate**

Alginate is natural polysaccharides, commonly used in drug delivery in the last three decades. It has been extensively studied for the generation of drug delivery platforms. It is a copolymer of α-l-guluronate (1,4) -linkedand β-d-mannuronate [68]. Alginates can be transformed to hydrogels, micro particles, nanoparticles and porous scaffolds for various applications. Alginates have carboxyl and hydroxyl functional groups. The presence of functional groups allows the easy modification to get the desired properties for transport and delivery of drugs. Important requirements of any drug delivery system includes its biocompatibility and biodegradability, and carrier molecule should protect drug molecules under harsh environmental condition of gastrointestinal tract, while remaining stable. Targeting efficiency, sustainability, and controllable release are the other important considerable parameters. Alginate based nanoparticles as drug delivery vehicles have been experimentally used for successful insulin delivery. There are reports on complex alginate nanoparticles with calcium chloride and other biopolymers like chitosan. These nanoparticles have been experimented for the effective insulin delivery. In such cases, calcium ion concentration plays an important role in the manipulation of size of the alginate nanoparticles, gelation process and drug encapsulation. Doxorubicin-loaded glycyrrhetinic acid-modified alginate nanoparticles have been experimentally used for tumor treatment, and it has been found that tumor weight and volumes were significantly reduced as compared to tumors that were treated with free doxorubicin and glycyrrhetinic acid-modified alginate nanoparticles alone. Alginate nanoparticles have also been developed to deliver hydrophobic drugs like rifampicin, isoniazid, pyrazinamide and ethambutol for the treatment of tuberculosis [69]. The matrix of formulation is assumed to be highly aqueous due to the charged nature of alginate/chitosan. A single loaded alginate nanoparticles' oral dose administration for the experimentally induced tuberculosis mice showed drug concentration in the plasma for nine, seven and eleven days in case of rifampicin, ethambutol and isoniazid/pyrazinamide; respectively [69]. In addition, they found that the free rifampicin, ethambutol and isoniazid/pyrazinamide were cleared from the circulation with 12 h. Nanoencapsulation of these drugs helped achieving a long term release of drugs that can help in reducing the dosage size and frequency to achieve the effective therapeutic outcome.

- **Chitosan**

Chitosan is a polysaccharide polymer composed of repeating 2-acetamido-2deoxy-ß-D-glucopyranoseand 2-amino-2-deoxy-ß-D-glycopyranose [70]. Chitosan is being obtained from the deacetylation of chitin. Chitosan has many characteristics similar to glycosaminoglycans which are constituting connective tissues. For this reason, recent research utilized chitosan in various applications from medicine to pharmaceutical industry. The) R applications of Chitosan include wound healing, tissue engineering, dentistry, bone regeneration and orthopedics. Chitosan is flexibile which allows polysaccharides form both linear and branched polymers, and it possesses bio-adhesive characteristics, and is structurally diverse [71-73]. Recently, many functional derivatives of chitosan were generated by chemical modifications, some of them attained solubility in some binary solvent systems and general organic solvents. Chitosan has many applications not strictly in drug delivery. The formation of a physical hydrogel can be obtained when two polyelectrolytes of opposite charge are combined. The resulted hydrogel is combined by molecular entanglements, H-bonding, hydrophobic forces or ionic forces [74]. It is worthy to mention that all of these interactions are reversible, and might be disrupted by physical condition changes like pH, temperature and ionic strength. Different gel-structures can be produced depending on the concentrations of the polyelectrolytes such as nanoparticles, beads or micro-particles. Grenha et al. (2010) also stated that polyelectrolyte complexes of carrageenan and chitosan in the form of beads and tablets were proved to efficiently deliver diltiazem hydrochloride and sodium diclofenac; respectively. Chitosan nano particles can have enough release profile; and they have reached a prominent position as a carrier-forming material. Recently, developed carrageenan and nanoparticles were found suitable to be used as controlled and sustained drug release systems [75, 76].

- **Carrageenan**

Carrageenan is a polysaccharide extracted from red seaweeds. It is composed of anhydrogalactose and galactose units connected by glycosidic linkages. Three main types of carrageenans can be obtained depending on the type of algae and the extraction method. These three types are called lambda (k), kappa (j) and iota (i), and differ in the degree of substitution of the sulfate group [77, 78] given the ionic nature of the polymer. Its gelation is strongly influenced by the presence of electrolytes. Out of these three types, only carrageenans has k- and

evidence gel-forming ability. The k-carrageenangels are firmer than those obtained with i-carrageenan, which are more elastic and soft. On the other hand the λ and κ carrageenans are sulphated polysaccharides composed of D- galactose with single, double or trible sulphate groups attached to carbohydrates [79, 80]. The *in vitro* release assay with ovalbumin showed that the chitosan/carrageenan nanoparticles gave a sustained and controlled release of the protein for a period of 3 weeks. In addition, the generated nano carriers showed low toxicity when placed with contact to fibroblast-like cells. This can be considered as a promising indicator for their safety and biocompatibility [81]. They added that these nanoparticles could be strong candidates for many biomedical applications like tissue engineering strategies and drug delivery by the absence of overt toxicity, and the controlled release profile.

Production of biopolymer based nanoparticles

The desolvation method involves a macromolecular aggregation brought by partial desolvation of the fully solvated molecules in solution, and it is frequently referred to as phase separation method or coacervation [82, 83]. Albumin nanoparticles are generally prepared by the method of desolvation [84]. In this process, ethanol is added drop by drop to an aqueous solution of albumin with the continuous stirring of the solution to get it turbid due to the desolvation of the albumin. Glutaraldehyde is gradually added for particle cross-linking. More cross linking results in small size nano particles. The solution of nanoparticles is incubated under the constant stirring to avoid settling and precipitation. This technique has been used to produce paclitexel loaded bovine serum albumin nanoparticles coated with folate [84, 85]. Emulsion droplet coalescence method involves mixing of exploits of two emulsions immersed phase droplets of each emulsion collided randomly and coalesced together, resulting in final uniform distribution of droplets. The emulsion solvent diffusion for preparing Chitosan nanoparticles when a solvent from one emulsion diffuses into another changing the behavior of the other molecules leading to the precipitation of solutes or polymers causing them to form nanoparticles. Finally, nanoparticles are isolated by centrifugation [86, 87]. Polyelectrolyte complexation is a method where oppositely charged polymers form nanoparticles upon the interaction, and generally result in large size particles. The ionic gelation produces smaller particles per higher amounts of cross-linker. This method of chitosan nanoparticles reparation has been considered simple, and thus more preferred.

DISCUSSION, CONCLUSION AND FUTURE PERSPECTIVES

There is a rapid progress in the generation of theranostic nanoparticles to be used in the treatment of diseases like cancer and tuberculosis. Biopolymer nanoparticles hold promise in applications to cancer therapy and diagnosis due to their tumor homing ability and selectivity. Biopolymers are natural macromolecules generated from animals and plants which make them available and renewable resources. The biodegradability and the tunable properties of biopolymers make them good targets for research and development in the area of theranostics, nanoparticles fabricated from biopolymer-based materials can be easily processed and are often biocompatible. The increased surface-to-volume ratio of these biopolymers offers high potential for macromolecule association. They provide a controlled release of the encapsulated drugs with a prolonged residence time at the sites of drug absorption. The surface of the nanoparticles can be easily modified to increase their blood circulation times and make them non immunizing. It is really important for the treatment of diseases like cancer where immune system is already stressed. The tumor-targeting efficiencies of the nanoparticles could be improved by functionalizing their surface with the active targeting ligand. The nanoparticles could be used as a convenient integrated platform for constructing safer and more effective drug delivery systems that have combined diagnosis, therapy and monitoring operations for the treatment of deadly diseases. Real-time non-invasive monitoring of the drug efficacy and treatment success can help physicians to take wise steps on time, and can help optimize the drug dose and drug treatment plan. Since every theranostic modality has its own strengths and limitations, there are some limitations that need be solved for the effective clinical application of theronostic nanoparticles. It is important to select an optimal combination of therapeutic and diagnostic components to achieve synergistic effects of nanoparticles. Theranostic biopolymer based on nanoparticle system development should be studied thoroughly for their safety to the human beings and environment. The structurally well-defined nanoparticles that are reproducibly synthesizable, and are derived primarily from biodegradable and/or biocompatible building blocks can be considered an excellent candidates for future research. In-depth understanding of the mechanisms by which theranostic nanoparticles are excreted from the

body, and how they interact with the immune system is another important concern that needs extensive research and enquiry.

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