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Biodegradable Super Absorbent Nano Polymer: Properties and its Applications

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Abstract: *Polymers from naturally derived ones, such as polysaccharides, proteins, cellulose, and rubber, among the listed starch (polysaccharides) has found various applications due to their abundant presence in nature and their biocompatibility and elastic physicochemical properties. Polysaccharides and starch derivatives contribute a key role to the nanoparticles, Nano clay, Nano polymers, and nanocomposites preparation. Metallic nanoparticles have been prepared; aside from them, silver nanoparticles are widely used and considered a metal nanoparticle with low toxicity—naturally available and strong antimicrobial. The present study focuses on the most frequently used polysaccharides in different applications with silver or silver nanoparticles. The work also provides a detailed overview of the synthesis, physicochemical properties, toxicity, and agriculture farming.*

Keywords: *Biodegradable Nanoparticles, Silver Nanoparticles, Toxicity, Properties, Applications, and Polysaccharides.*

INTRODUCTION

Daniel and Astrum depicted and summarized the Nanoparticles' historical perspective (Harish Kumar et al. 2018) (Gitashree Darbdhara et al., 2019). Metallic Nanoparticles are uniform in size with sharp distribution in Nanoscale (David et al., 2015; Jorg Polte (2015)). These particles have been synthesized with a specific function and could be mimicked according to bind the ligand (Prerna Khanna et al., 2019). It falls at the size of 10-100nm. Metallic Nanoparticles possess unique surface Plasmon resonance and optical properties (Hardik Khandelwalin Chemi (2020)). In the gold solution in golden yellow color but 20nm gold Nanospheres in red ruby color whereas 200nm Nanospheres look like bluish color. Various research fields revealed that the silver and gold metals are noble metals in Nanoparticle preparation for different applications ((2019): Nanoscale Materials in Water Purification). Faraday documented the metallic nanoparticles in 1908, and Mie gave the quantitative clarification of the metallic Nanoparticle color (Tiwari et al., 2015).

Metallic nanoparticles are being used to decorate the cathedral in the primitive era (Shivarama Krishnan., Gurumurthy and Balasubramanian (2017)). A predictable feature of Nanoparticles is the ratio of surface area to volume, which allows them to interact and diffuse directly to treat the damaged tissues or cells at low temperatures. Raman spectroscopy with fluorescence enhances the surface and refractive index. Sensing nanoparticles have application in the field sensitive optical process (Avantes (2020)). The visible region of wavelength resonance is influenced by the localized surface Plasmon directed by metal nanoparticles' optical properties. The growth of gram-positive and gram-negative bacteria growth was inhibited by the silver and gold nanoparticles (Anes Al-Sharqi et al., 2019). Living organisms acting as a production system for Nano devise but have difficulty in synthesis due to the formation of toxic metallic nanoparticles (Manoj et al., 2016). Fungi, Bacteria, and Plants are alternatives to the production of metallic Nanoparticles.

Stabilizing agents, reducing sugars, metal ion kinetic interactions, size, stability, physical, chemical properties, morphology, etc., are the factors that influence the metallic nanoparticles' characteristics (Ajay Vasudeo Rane et al., 2018). Physical and chemical properties metal nanoparticles have many industrial applications, including mechanical strengths, high surface area, low melting point, optical properties, and magnetic properties (Chavali and Nikolova (2019)). Gold Nanorods used as storage enhanced more than 100 times than the common disk with optical properties (Nikalje, Anna. (2015)). The optical properties of gold, silver, lead, platinum nanoparticle arise from the resonant oscillation of their free electrons in the presence of light, also known as Localized surface Plasmon resonance (LSPR) (Organic Electronics, (2014)). Silver is a valuable property, and pure compare to gold. Silver has many medicinal properties, anti-bacterial and

antiseptic properties (Josh Axe, DC, DMN, CNS (2019) Vijilvania, et al., 2020). Cisplatin (platinum) has antitumor activity (Heyam Saad Ali et al., 2020). Gold nanoparticles are used to treat fever and syphilis (Baker and Perianova (2019)).

BIODEGRADABLE/BIO-BASED POLYMERS CLASSIFICATION

Depending on the synthesis, process biopolymers are classified into three categories, and these include (Wound Healing Biomaterials 2016). Polymers from biomass; Polymers from microbial synthesis and chemically and conventionally synthesized from biomass monomers.

BIODEGRADABILITY OF POLYMERS

Biodegradable plastic is defined as those that degrade from the action of under the action of microorganisms. Biodegradable polymers occupy a tremendous role in agricultural products and waste disposal problems and bioplastics resources' sustainability (Trivedi et al., 2016). Alone natural polymers have drawbacks and not that effective in the action or functioning of polymer (Khalid Mahmood et al., 2017). Hence, there is a demand for blending synthetic and natural polymers to become popular with vital applications, such as cutlery, flowerpots, and food trays (Brittter Horst et al., 2019). Bioplastics are manufactured in two forms: wet and dry (Luzi et al., 2019). In the wet process, biopolymers dispersion in a film-forming solution and is used edible film coatings but has the drawback is not eco-friendly (Ilyas et al., 2020). In case dry, melt process, thermoplastic nature of the biopolymer used in edible coatings. Biopolymers degrade through the enzymatic action of bacteria, fungi, algae, and other living organisms. The degradation products are carbon dioxide, new biomass, and water (Nair et al., 2017). Degradation comparison is difficult to establish due to different composting conditions such as humidity and temperature (Siracusa, Valentina. (2019)). Some general rules are applicable in estimating the evolution of biodegradability, and these include an increase in hydrophobic character, molecular weight, and crystalline nature of the size of spherulites decrease biodegradability, and on the contrary, the presence of polysaccharides favors degradation (Özçimen, Didem, et al., 2017; Ambrish Singh (2011)).

Principally biodegradable compounds must have suitable chemical nature and other factors, which contribute to biodegradability, namely polymer morphology, radiation and chemical treatments, and molecular weight, which tend to cleanse to degrade the environment (Naba Kumar et al., 2020). Take care and must-see while synthesizing the polymer; chains must be flexible enough to fit into the enzyme's active site (Yajaman et al., 2006). Therefore, that degradation using the enzyme, catalysis would be comfortable. Proteins are natural polymers, which differ from synthetic polymers in the composition, but proteins do not have equivalent repeating units present in the entire peptide chain (James, Leo, and Tawfik, Dina. (2002)). So due to its irregular nature, it has biodegradable. The effect of molecular weight plays a vital role in the biodegradability of a polymer by conducting the experiments with microbial enzymes, namely Exo and endoenzymes, which could not degrade the polymer instantly, while molecular weight increases (Koutny, Marek, et al., 2006). Current status and future trends: Bio-based feedstocks are not a novel concept in the chemical sector, and are industrially feasible and are avail more than a decade ago (Ndolo Obonyo et al., 2019; Kiran and Patil, Kiran. (, 2014).

The bio-based polymer industry easily spread with the fossil fuel-based chemical industry in the last 20 years. It leads to a foundation for the advancement of white biotechnology in the real world and bio-based polymers and other chemicals from renewable resources (Bikash Kumar and Pradeep Verma (2020)). In this connection, the first-generation used food resources such as corn, starch, rice, etc., to produce bio-based polymers (Deepak Kumar and Vijay Singh (2019)). Further focused on cellulose-based feedstocks ascended on waste from food, wood, paper industries, plant waste, solid waste, municipal waste, etc., were screened. The final stage of this full-pledged chemicals took more than 20 years to span to give the shape (Peter Kalmus (2017)). In the coming years, challenges that we have to face to solve include managing raw materials, the performance of bio-based materials, and their cost for production (Lidija Runko and Luttenberger (2020)). To produce economical bio-based monomers and polymers from renewable sources is another challenge ahead. New technologies' experience and survival rate, implementation, and functioning of technology and its supply and demand matter to balance (Majidian, Parastoo 2017; Lin Lina Zhou 2011). Bio-based industry effort to make bio-versions of existing monomers and polymers. The functioning of these products is actively known.

It is very easy to replace the existing product with similar bio-versions (Hamad, Kotiba. (2015)). All the polymers mentioned above often display similar properties to current fossil-based polymers. Many efforts were towards introducing new bio-based polymers with higher performance and value (Raghvendra Kumar Mishra et al., 2018). Several modifications were, made to develop various polyamides, polyesters, polyhydroxyalkanoates, etc., with a high differentiation in their final properties in automotive, electronics, and biomedical applications (Aitor Larrañaga and Erlantz Lizundia (2019)). New bio-based polymers could not fit in the current processing equipment is the main drawback (Storz, Henning. (2014);). This may be overcome by additive-based chemistry development that improves the bio-based polymers' fitment and function (Andrea Sorrentino., Giuliana Gorrasi, and Vittoria Vittoria (2007)). Bio-based polymers like PLA and PHA, additives, industrialized to improve their performance by blending with other polymers, or making new copolymers (Lee et al., 2020). Nanoparticles are being used as an additive to improve the polymer functioning for petroleum-based polymers (Dangge Gao et al., 2015).

Renewable feedstocks used for manufacturing bio-based monomers and polymers often compete with requirements for food-based products (Selorm Torgbo and Prakit Sukyai (2020)). The expansion of first-generation bio-based fuel production was not favorable and causes a threat to the viability of biochemical and biopolymer production as it is to food production (Shaoqing Cuia et al., 2019). The European Commission has declared that the survey tells about first-generation biofuels downfall market, and preference given for non-food sources of sugar for biofuel production (Eleni Stylianou et al., 2020). May trail and errors were initiated to produce the sugars as a feedstock for biofuels, biochemicals, and biopolymers (Oscar Rosales-Calderon and Valdeir Arantes (2019)).

NATURAL FIBERS AS REINFORCING FILLERS FOR COMPOSITES

Biodegradability uses natural fibers as plasters due to environmental and disposal concerns for non-biodegradable materials (Seema Agarwal (2020)). One of the Natural fibers, cellulose, comes under the main vegetable fiber used in composites (Layla Filiciotto and Gadi Rothenberg (2020)). Natural fibers are widely used in polymeric materials to improve mechanical properties (Khubab Shaker Yasir Nawab and Madeha Jabbar (2020)). These fibers can be classified as bast, leaf, or see-hair fibers (Murugesh Babu, (2018)). Depending on the natural fiber properties, the origin, quality of the plant's locations, the plant's age, and the preconditioning (Mohau Moshoeshoe 2017). Natural fibers have many drawbacks: poor wettability, incompatibility with some polymer matrices, moisture absorption and low processing temperatures due to fiber degradation, or the possibility of volatile emission that could affect the composite performance (Soo-Ling Bee et al., 2018). According to the main demerit to supplement, the natural fibers were manipulated to prepare composites (Alan Kintak Lau and Karen Hoi Yan Cheung (2017)). The natural fiber is the lack of strong plaster nature to the matrix adhesion, which reduces the composite activity overcome by the physical treatments, including cold plasma treatment and corona treatment. Chemical treatment includes maleic anhydride, organosilanes, isocynates, sodium hydroxide, permanganate, and peroxide (Yinji Wan et al., 2019).

BIOPOLYMERS FOR RESTORATIVE RELEVANCE IN NANOTECHNOLOGY

Nanotechnology was used in various engineering, electronics, mechanical, biomedical, and space engineering (Trepti Singh et al., 2017). The biomedical field applied much more in different aspects, including controlled drug/gene delivery, tissue engineering, imaging of specific sites, and DNA structure probing (Ibrahim Khan et al., 2019). Therapies using nanoparticle application are widely used to treat cancer, diabetes, allergy, infection, and inflammation (Mona Elsayed and Ayman Norredin (2019)). The fact behind nanoparticle application in therapies is that the particle exists in the same size domain as proteins, and large surface areas can allow a number of ligands (Jagpreet Singh et al., 2018). In addition, biopolymers have a rapid absorption with high diffusion and volume change (Physiologic Factors Related to Drug Absorption (2017)). According to the requirement, the particle size and surface characteristics can be tailored or controlled (Ruslan Melentieva and Fengzhou Fanga (2020. Organic and inorganic combination mixture has been used to produce nanoparticles. Polymeric nanoparticles have also been used in therapeutic applications. Biomaterials are a delivery carrier of therapeutic molecules such as drugs and genes and tissue engineering scaffolds (Yongda Sun (2016)).

Even though polymeric nanoparticles were having difficulty scaling up and low drug-loading capacity (Carina et al., 2017), compared to ceramic or metal nanoparticles, polymeric nanoparticles have wide sustainability to the local drug therapeutic agents up to weeks (Carina I.C. Crucho and Maria Teresa Barros (2017)). Both naturally derived and synthetic biomaterials have advantageous features (Mojtaba Abbasian, 2019). Synthetic polymers give well-defined and fine-tunable degradation kinetic and mechanical properties (Fa-Ming Chen and Xiaohu Liu (2016)). Proteins offer many advantages when compared to natural, synthetic. Peptides are easily digestible by metabolizable by digestive enzymes and tixic degradation products (Alejandra Acevedo-Fani 2020). It is more potent to the site-specific target drug delivery (Yaghoub Safdari et al., 2016); as cited above, polysaccharides are also digested by the specific enzyme (Sagar Aryal (2019)). Polysaccharides have advantages over synthetic polymers, for example, PEG (Thomas, Barclaya, et al., 2019).

NANOPARTICLES FOR DRUG/GENE ACCOUCHEMENT

Polymeric drug/gene-loaded nanoparticles were injected into bodies, passed through epithelial barriers, and circulate in the blood vessels before reaching the target site (Thomas Malachowski and Austin Hassel (2020)). Escape of nanoparticles from the vascular circulation occurs in either continuous or fenestrated tissues (Raquel Ferreira and Liliana Bernardino (2020)). Therefore, the drug nanoparticle particle penetration enhanced and accumulates drugs in tumor sites called enhanced permeation and retention (Ting Jiang et al., 2017). Tumor growth induces neovasculature development characterized by discontinuous endothelium with large gaps (200-700 nm), allowing nanoparticle passage (Lakshmi Pallavi Ganipineni et al., 2018). While passing into the tissue, interactions may cause toxicity will happen (fluids, cells, and tissues), which drives the possible direction of entry pathway into the target organ (Amanda Lautieri and Sophie Stein, (2019)). Nanoparticles trigger the mediators at the target organ site to activate the inflammatory or immunological responses due to maintaining the specific size (Richard Nho (2020)). Particle sizes, solubility, biodegradability, and surface properties play a vital role in the site-specific delivery or controlled drug delivery, and the internalized mechanism triggers endocytosis (Sarita Rani et al., 2017).

In encapsulated drugs, released by diffuse or degrade controlled by stimuli, namely temperature, pH, or ionic strengths (Sarita Rani et al., 2017). Effective drug delivery application of nanoparticles depends on pH sensitivity range for normal tissues (7.2-7.4) but in solid tumors (6.2-6.9) (Carmen Alvarez-Lorenzo et al., 2013). Gene therapy is also done in particular diseases to cure, namely cancer, AIDS, and cardiovascular diseases, by replacing mimicked or mutated genes into specific patients' specific cells (Iftikhar et al., 2015). While transferring the genes at the site of the mimicked gene in the cell, care must be taken to avoid the nucleases and endocytosis enzymes until they reach the target (Yi Li et al., 2016). In gene therapy, both viral and non-viral vectors have been used, and the most suitable and convenient one is non-viral vectors because of low immunogenicity (Lesca M. Holdt et al., 2018). The nanoparticles of genes and the cationic polymers could be modified with proteins (knob, transferrin, or antibodies/antigens) to allow for cell-specific targeting and enhanced gene transfer (BAlicia Rodri'guez Gasco'n 2012). Nitric oxide-releasing materials (nanoparticles) potential therapeutics in wound healing antimicrobial actions and it acts as biocompatible nanomaterial matrices (chitasone and dextrose are used as matrices) (Zeenat Mirza and Sajjad Karim (2019)).

NANOPARTICLES FOR TISSUE ENGINEERING

It is the one kind of drug delivery system with controlled release, enhancing tissue engineering's efficacy (Yasuhiko Tabata (2005). Therapeutic genes could enhance the absorption of the tissue construct, growth, and digestion with neighboring tissues (Yang et al., 2020). Biopolymer gene function as a DNA complexing agents and structural scaffolds involves cell growth and maintenance in the tissue engineering application, leading to foundation treatment in regeneration medicine (Narmatha Christya et al., 2020). GAM (gene-activated matrix) blends both the DNA complexing agents and structural scaffold strategies and serves as a local bioreactor (Hasan Uludag et al., 2019).

PROTEIN-BASED NANOPARTICLES FOR DRUG DELIVERY

Natural proteins called collagen, elastin, and fibronectin have been used extensively as biomaterials (Hasan Uludag et al., 2019). They are cheap polymers with low toxicity, no antigenicity, high nutritional value, high stability, and binding capacity of various drugs such as paclitaxel and ibuprofen with biodegradability (Showkat Ahmad Bhawani et al., 2019). Moreover, nanoparticles have the capability of emulsification, gelation, and water-binding (Ahmed O.Elzoghbya et al., 2012). Genetically engineered proteins and peptides tools have been used to mimic the polymer properties such as degradation rate, biocompatibility, and cell penetration ability to generate new protein sequences, including bioactive domains or protein motifs Elastin-like polypeptides (ELP) (Wensi Zhanga et al., 2018). Stable and precise biodegradable nanopolymers with determined or known size polymers can utilize various proteins such as silk, albumin, collagen, and elastin. Protein-based nanoparticles are easily self-assembled to form particles, fibers, sheets, etc. (Malgorzata. Et al. (2020)

SILK-BASED NANOPARTICLES

Recombinant silks particles are synthesized by the elucidation of silk genetics, structures, and biophysics. Silk fibroins are stable, spherical, negatively charged, and low toxic silk nanoparticles (150–170 nm) procured from Bombyxmori and tropical Tasar silkworm Antheraea mylitta (Chandra Mohan Srivastava et al., 2019). Silk fibrin nanoparticles have been used in cancer treatment. They show good recovery, and sustained growth factors were found within 3 weeks of treatment (cytosol of murine squamous cell carcinoma cells) (Mhd Anas Tomeh et al., 2019). Conjugated Silk fibroin and chitosan polymers were blended non-covalently to form nanoparticles (<100 nm) for local and sustained therapeutic curcumin delivery to cancer cells (Raluca Ioana Teleanu et al., 2019). The crystalline silk protein nanoparticles (40–120 nm) have been conjugated with insulin via covalent cross-linking (Fatemeh Mottaghital et al., 2015). Silk fibroin was also bio-conjugated with L-asparaginase to form crystalline nanoparticles with 50–120 nm in diameter (Shuangquan Gou et al., 2019). Nanoparticles were composed of DNA and recombinant silks, which contained cell-penetrating peptide, tumor-homing peptide, Arg-Gly-Asp (RGD) motifs cationic sequences, have been designed for gene therapy (Laura Chambre et al., 2020).

Collagen and Gelatin-Based Nanoparticles:

Collagen is an extracellular matrix widely used as biomaterials with promising biocompatibility, low antigenicity, and biodegradability (Socrates Radha Krishnan et al., 2019). It forms hydrogels without chemical cross-linking, but it needs chemical treatments due to weak mechanical strength (Parinaz Nezhad-Mokhtari et al., 2019). Controlling the particle sizes, a large surface area, high adsorption capacity, and dispersion ability in the water, collagen nanoparticles exhibited sustained releasing of various drugs (Raj Kumar et al., 2018). The acid-alkaline hydrolysis has separated gelatin from collagen, consisting of glycine, proline, and 4-hydroxyproline residues with a typical structure of-Ala-Gly-Pro-Arg-Gly-Glu-4Hyp-Gly-Pro (Showkat Ahmad Bhawani et al., 2019). Gelatin solution undergoes coil-helix shift followed by aggregation of the helices through the formation of collagen-like triple-helix, enabling the formation of nanoparticles (Maria Helminger et al., 2014). Polymer functional groups chemically modified ex; cross-links, ligands (Rajiv M.Desai et al., 2015). Insulin-loaded gelatin nanoparticles were prepared for diabetes therapy by a novel water-in-water emulsion technique with gelation by glyceraldehyde (Momoh A.Mumuni et al., 2020). Blood glucose level curves showed obvious decreases in the first 4hour in rats indicating their fast and stable hypoglycemic effect (Lin-Lin Pan et al., 2019).

ß-CASEIN-BASED NANOPARTICLES

ß-Casein is the major milk protein used as delivery carriers and self-assembled into the micellar structure by intermolecular hydrophobic interactions due to its amphiphilic nature (Tomasz Konrad Glab and Janusz Boratynski (2017)). 15–60 ß-casein molecules together form ß-casein micelles with a radius of 7–14nm (MoLiac Remco et al., 2019). Alterations in the properties like temperature, pH, ionic strength, water activity, and high hydrostatic pressure treatment arrange the size distribution according to the micelles requirement, leading to self-developing the rigid three-dimensional tertiary structure. ß-casein micelles have demerit critical to stabilizing the micelles by cross-linking (Lehninger Principles of Biochemistry (2011)). Crosslinking of lysine residues in casein by glutamine residues of transglutaminase (T Gase) increased the intra-micellar stability of casein micelles (Min Yang, Ying Shi, and Qi Liang (2016)). These are all edible or oral delivery systems used in cancer and gastric cancer (Bingren Tian et al., 2020).

ZEIN-BASED NANOPARTICLES

Zein is a protein derived from corn kernels, soluble in both water and alcohol (Shukla, Rishi, and Cheryan, Munir (2001)). Hydrophilic and hydrophobic amino acid residues are promising carriers for encapsulation and controlled release of hydrophobic compounds (Solmaz Maleki Dizaj et al., 2014). In vivo studies revealed that the particles were mostly accumulated in the liver and adequately remained in the blood for at least 24h due to tis relatively higher molecular weight and smaller particle size (34th Annual Meeting 2019).

ALBUMIN-BASED NANOPARTICLES

Albumin is a plasma protein's main protein with a molecular weight of 66.5 kDa (Shijie Li et al., 2015). Human serum albumin (HSA) is one of the smallest and the most abundant proteins present in blood plasma, indicating many metabolic compounds and therapeutic drugs, transported by HAS (Yujie Zhang., Tao Sun and Chen Jiang (2018)). Unisized albumin particles with controlled desolvation, thermal gelation, emulsion formation, and self-assembly come under the preparation of albumin-based nanoparticles (Elmira Karami et al., 2020). Albumin nanoparticles are separated by continuous dropwise addition of ethanol to an aqueous solution and continuous stirring by phase separation (Showkat Ahmad et al., 2019). Additional treatments such as cross-linking are often required to stabilize the nanoparticle morphology (Evangelos Georgilis et al., 2020). HSA-based nanoparticles are prepared by desolvation method and stabilized by cross-linking with glutaraldehyde or heat denaturation(Weber et al.,2000). Sulfhydryl groups were added by covalent linkage to the HSA-based nanoparticles to increase the reactive sites (Mohamad et al., 2017).

Nanoparticle albumin-bound (nab)-technology is a new technology for anti-cancer drug delivery system that has been developed by American Bioscience, Inc. Albumin particles with paclitaxel (nab-paclitaxel, 100–200 nm) was approved in 2006 for use in patients with metastatic breast cancer due to their superior antitumor efficacy over paclitaxel (Ahmed., Elzoghby Wael et al., 2015). Ibuprofen encapsulated BSA-dextran nanoparticles (70nm) were prepared by heat treatment method. Conjugation of dextran and BSA stabilization of nanoparticles in aqueous solution (Krishnendu Chatterjee et al., 2014). Self-assembly of albumin to form nanoparticles by adding lipophilic drugs and diminishment of primary amino groups on protein surfaces (Hasan Kouchakzadeh et al., 2015).

POLYPEPTIDE NANOPARTICLES

Proteins are mimicked into polypeptide-based nanoparticles are synthesized to produce the desirable characteristic proteins (Evangelos Georgilisa Mona et al., 2020. ELP can be produced recombinant and is composed of the repeating amino acid sequence (Val-Pro-Gly-Xaa-Gly) m. Xaa is the hydrophobic domain that facilitates self-aggregation and elastomeric functions (Nasim Annabi et al., 2013). Nanoparticles were produced by self-assembly of ELP with a sequence of VPAVG and showed a sustained release of loaded dexamethasone phosphate for about 30 days (Ahmed O.Elzoghbya Wael et al., (2012). Well-designed ELP block copolymers are often produced to control their phase separation behavior, add stimuli-responsivity, and introduce the cross-linking domain into ELP (Machado, Raul, et al., 2012). Temperature-triggered micelle assembly of ELP was achieved by the modulation of the local density of arginine (Arg) residues of diblock ELP (Sarah, Mac Ewan, and Ashutosh Chilkoti (2014)). ELP-based nanoparticles (~40 nm) were further formed from the diblock ELP decorated with the knob domain of adenovirus serotype 5 fibrous proteins for drug and gene delivery (Iraklis, Kourtis, et al., 2013). Thus, they have been widely used in drug delivery and tissue engineering fields (Xiao-Xia Xia et al., 2011). Other polypeptides are also produced recombinantly to form nanoparticles (Oyarzun-Ampuero, Felipe, et al., 2014).

Nanoparticles (100–200 nm) formed from cationic polyarginine and anionic hyaluronic acid is one of the examples (Lee, Mihyun., Zenobi-wong, Marcy and Chang, Jin (2019)). Another example is the zwitterionic diblock copolymer consisting of poly (L-glutamic acid)-b-poly (L-lysine) (PGA-b-PLys) (María Gabriela Villamizar-Sarmiento et al., 2019). This block copolymer self-assembled into schizophrenic vesicles that can reversibly be produced in moderate acidic or basic aqueous solutions. Polysaccharides are highly stable, biocompatible, and biodegradable (Aja Aravamudhan et al., 2014). Thus, polysaccharides and their derivatives are commonly used for applications in food, biomedical, and environmental fields (Tinesha Selvaraj Veeradasan et al., 2020). Their native charges classify polysaccharides that have been used for the preparation of nanoparticles; cationic (chitosan), anionic (alginate, heparin, hyaluronic acid), and nonionic (pullulan, dextran) (Ida Idayu Muhamad et al., 2019). The most commonly used polysaccharide for

nanoparticle fabrication is chitosan. Chitosan is a linear cationic heteropolymer of N-acetyl-d-glucosamine and D-glucosamine linked by beta-(1–4) glycosidic bonds. It is obtained by the partial deacetylation of naturally derived chitin (Einallah Khademian et al., 2020).

In particular, due to its mucoadhesive property, chitosan-based gene delivery systems have been successfully applied to oral and nasal route gene therapy systems, which will be discussed below (Chandra, Dinesh, et al., 2014). Alginate is a linear anionic polysaccharide composed of alternating blocks of 1,4-linked ß-D-mannuronic acid (M) and a-l-guluronic acid (G) residues (Rajalekshmy G.P.Lekshmi et al., 2019). Alginate has some advantages in its high mucoadhesiveness, aqueous solubility, and a tendency for gelation in proper condition, biocompatibility, and non-toxicity (Gheorghe Adrian et al., 2019). Insulin-loaded nanoparticles were prepared from calcium cross-linking, alginate-chitosan, or –alginate complexes with sufficient insulin loading capacity (Jayanta Kumar Patra et al., 2018). Even delivery of genes loaded in alginate-based nanoparticles has been successful (Yuefei Zhu et al., 2019). In this study, alginate-chitosan nanoparticles showed high transfection ability while maintaining biocompatibility and low toxicity (Dileep Janagam et al., 2017).

POLYSACCHARIDE NANOPARTICLES BY CROSSLINKING

Preparation of polysaccharide nanoparticles by cross-linking can be achieved by either ionic cross-linking (physical cross-linking) or covalent cross-linking (chemical cross-linking) (Patil, Sachinkumar, and Jadge, (2008)). Covalently cross-linked polysaccharide nanoparticles enable the network structure to be permanent since irreversible chemical links are formed unless biodegradable or stimuli-responsive crosslinkers are employed (Nimish Shah et al., 2013). The rigid network allows absorption of water and bioactive compounds without dissolution of the nanoparticles even when the pH drastically changes (Amir Sheikhi et al., 2020). An oil in water (o/w) emulsion polymer cross-linking method was employed to prepare tamoxifen citrate (a non-steroidal antiestrogenic drug)-loaded guar gum nanoparticles cross-linked with glutaraldehyde. (Jianyu Xu et al., 2018). This method gives nanoparticles reversibility and is considered biocompatible due to the lack of harsh preparation or toxic crosslinkers (Daniel Klinger Katharin and Land fester (2012)).

Ionically-crosslinked nanoparticles are generally pH-sensitive, a suitable feature for stimuli-sensitive controlled release (Lei Xing et al., 2019). Tripolyphosphate (TPP), a non-toxic anionic molecule, has been widely used to prepare cross-linked chitosan nanoparticles, and several drugs have been encapsulated within these nanoparticles (Ai Wu Pan Bei et al., 2019). TPP cross-linked chitosan nanoparticles have been used for protein, oligonucleotides, and plasmid DNA deliveries due to their high physical stability and encapsulation efficiencies (Loïc Bugnicourt and Catherine Ladavière (2016)). CS/TPP nanoparticles (300 nm) showed high encapsulation efficiencies both for plasmid DNA and dsDNA oligomers (20-meters), high physical stability, and high gene expression levels in HEK 293 cells (Maria Abdul Ghafoor et al., 2015). Chitosan/TPP nanoparticles were also used to improve cyclosporine A's delivery to the ocular mucosa (Dileep R.Janagam., Linfeng Wu, and Tao L.Lowe (2017)). Cyclosporine A was specifically concentrated in external ocular tissues (i.e., cornea and conjunctiva) during at least 48 h with maintaining negligible or undetectable CyA levels in inner ocular structures, blood, and plasma (Basaran, Ebru et al., 2011). Other examples of ionic cross-linking of polysaccharides are using of inorganic ions such as Fe(CN)64-, Fe(CN)63- citrate, and calcium ions as crosslinkers (Carmen Alvarez-Lorenzo et al., 2013). For example, alginate's carboxylic acids were cross-linked by calcium ions to form nanoparticles (80 nm), exhibiting a high transfection rate of plasmid DNA into non-phagocytic cells via endocytosis pathway (Julieta C.Imperiale et al., 2018).

POLYSACCHARIDE NANOPARTICLES BY POLYION-COMPLEX

Polysaccharide nanoparticles are also prepared by direct electrostatic interactions of oppositely charged polysaccharides in solution (Swierczewska et al., 2013). Chitosan is the most commonly used cationic polysaccharide for polyion-complex. In contrast, carboxymethyl cellulose (CMC), dextran sulfate, carrageenan, heparin, hyaluronic acid, alginate, and carboxymethyl pachyman are used as anionic polysaccharides (Leena Kumar and Hemant Ramachandra Badwaik (2019)). Chitosan-CMC was subsequently coated with plasmid DNA for genetic immunization. Both chitosan and a chitosan oligomer could complex CMC to form stable cationic nanoparticles for subsequent plasmid DNA coating. Corporation of polyelectrolyte complexation and ionic gelation prepared Chitosan/carrageenan/TPP nanoparticles (150–300 nm)(Fatemeh Farjadiana et al., 2019). Sufficient loading capacity of insulin in the nanoparticles showed their application as an oral insulin delivery (Gonçalves, Nádia, et al., 2012). A pH-sensitive polyion complexes (average particle size <200 nm) were formed from trimethyl chitosan and a-galactosidase A through self-assembly (Statements of Significance, (2019). These nanoparticles were able to release the enzyme at acidic pH and were efficiently internalized by human endothelial cells and mostly accumulated in lysosomal compartments. ?-Poly (glutamic acid) (PGA) was combined with chitosan to form nanoparticles for transdermal delivery of DNA.

POLYSACCHARIDE NANOPARTICLES BY SELF-ASSEMBLY

The introduction of hydrophobic segments into hydrophilic polysaccharide backbones enables the forming of self-assembled structures such as micelles, particles, and hydrogels (Tianxin Miao et al., 2018). Deoxycholic acid,

cholesterol, carboxylic acids, and hydrophobic polymers are examples of such hydrophobic segments. By manipulating the introduction condition such as polysaccharide/hydrophobic segments molar ratios and the lengths of polysaccharides and hydrophobic segments, nanoparticles are formed to minimize interfacial free energy. Grafting hydrophobic groups from hydroxyl, amino, or carboxyl groups of the main polysaccharide chains (Mosaiab et al., 2019) introduces hydrophobic segments polysaccharides. These chemically modified amphiphilic macromolecules can self-associate in an aqueous solution by intra- and inter-molecular hydrophobic interaction, forming nanoparticles (Martin Gericke, Peter Schulze, and Thomas Heinze (2020). Water-insoluble drugs are solubilized and encapsulated within the hydrophobic core and become soluble in water due to the hydrophilic shell. The drugs are then released from the nanoparticles' inner core via outer stimuli changes such as pH, temperature, and ionic strength by Luo et al., 2020). Recently, there have been a number of studies on the syntheses of polysaccharide-based self-aggregated nanoparticles for drug delivery systems (Amin Shavandi et al., 2019). Chitosan has been chemically modified by grafting hydrophobic groups from amino groups of the main chains. The amine groups' proportion depends on the acetylation degree of the polymer (Paripurnanda Loganathan et al., 2020).

Doxorubicin, paclitaxel, ibuprofen, and the amphiphilic adriamycin have been loaded in chitosan-based nanoparticles. Plasmid DNA was introduced into nanoparticles (160 nm) aggregated from deoxycholic acid-grafted chitosan, and their efficient transfection of COS-1 cells was detected (Nitta and Numata, 2013). Dextran was chemically modified by grafting bile acids, a natural product consisting of a facially amphiphilic steroid nucleus with a hydrophobic ß-side and a hydrophilic aside lauryl chains (Sachiko Kaihara Nitta and Keiji Numata (2013)). Self-assembly assisted graft copolymerization of acrylic acid from dextran under the presence of crosslinker produced pH-sensitive nanoparticles (40–140 nm) (Huanli Sun et al., 2018). Dextran could form interpolymer complexes with poly(acrylic acid) (PAA) in acid medium owing to hydrogen bond interaction of carboxyl groups and proton-acceptors in glucose units. (Peipei Zhang et al., 2015). Plasmid DNA was loaded into complex nanoparticles (100–150 nm), which had high gene transfection yield, efficient gene delivery ability in different cancer cell lines, especially in MCF-7cells (Steinman, Noam, et al., 2020). Similarly to chitosan and dextran, hyaluronic acid (HA) was chemically modified with the 5ß-cholanic acid to form self-assembled nanoparticle (200–400 nm) that combine both passive tumor targeting based on the EPR effect and a more specific or active targeting exploiting the affinity of HA towards CD44(Goodarzi et al., (2013), Yujie Zhang et al., 2018). Amphiphilic block copolymers were also synthesized to form nanoparticles via self-assembly.

Doxorubicin loaded nanoparticles based on poly (?-benzyl L-glutamate)-block-hyaluronan were produced by self-assembly. These particles could be used as a self-targeting drug delivery cargo in over-expressed CD44 glycoprotein cells of breast cancer (Platt et al., (2008), Swierczewska et al., 2015). Nonionic pullulan is also modified by hydrophobic molecules such as cholesterol and cancer drugs. The cholesterol-bearing pullulans with different molecular weights and degrees of substitution have been synthesized to form self-assembled nanoparticles (Liming Yuan et al., 2019). A recent study demonstrated paclitaxel-incorporated nanoparticles prepared from pullulan hydrophobically modified by acetic anhydride to evaluate their antitumor activity in vitro and in vivo (Abbass and Hashim (2012)). These nanoparticles showed lower antitumor activity in vitro against HCT116 human colon carcinoma cells and reduced tumor growth in vivo using HCT116 human colon carcinoma-bearing mice (Suhail Ahmad et al., 2020).

Propyl-starch nanoparticles were reported to increase the polymer's solubility in low hazardous organic solvents and high encapsulation efficiency for model drugs (Alain Dufresne (2014)). Effective controlled release of doxorubicin was shown from drug-conjugated dialdehyde starch nanoparticles. Docetaxel, an anti-cancer agent, was loaded in nanoparticles prepared from a hydrophobic propyl starch with a controlled degree of substitution via the solvent emulsification/diffusion technique (Qingjie Sun (2018)). It was confirmed that nanoparticle enhanced internalization by the cancerous cells (Caco-2 and NHDF-p cells), and their peri-nuclear localization was detected (Dandekar et al., 2012). Heparin, a negatively-charged polysaccharide used as an anticoagulant, is often applied for the preparation of self-assembled nanoparticles (Stefano Rimondo et al., 2019). A self-assembled nanoparticulate system (140–190 nm) composed of a folate-conjugated heparin-poly (ß-benzyl-L-aspartate) (HP) amphiphilic copolymer was proposed for targeted delivery of the antineoplastic drug paclitaxel (Li Li et al., 2012). The presence of folate enhanced intracellular uptake via endocytosis, and these nanoparticles exhibited great cytotoxicity in KB cells. Deoxycholic acid bearing heparin amphiphilic conjugates (120–200 nm) with different degrees of substitution were also synthesized (Mona Alibolandi and Mohammad Ramezani (2018)).

AN OPINION ARRIVED AT THROUGH A PROCESS OF REASONING

Biodegradable nanocomposites and nanoparticle preparation, manufacturing, and production still have many demerits and are accompanied by the consumer economically and not affordable. Among the discussed metallic nanoparticles, silver nanoparticles have versatile utility. Remained practiced metallic nanoparticles have narrow application and are restricted to the special constraint or for a single application but not versatile and cost-effective: platinum, gold, and other metallic nanoparticles rather than silver nanoparticles. Genetically mimicking metal tolerance and increasing application

activity and the functional feature will compete with commercial polymers and biopolymers. Henceforth green or natural polymers have more compatibility to enhance the rate of demand and produce a novel Nano metallic compound for feature use.

SELF-REVELATION

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