

NATURAL CATIONIC POLYMERS: ORIGIN, PROPERTIES AND THERAPEUTIC APPLICATIONS

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ABSTRACT

Natural cationic polymer has remained of great interest to researchers in drug delivery as well as other fields. Their easy availability, flexible properties and biocompatibility make them favorable candidates for therapeutic use. This review is mainly focused on natural cationic polymers with emphasis on their origin, types, different properties and use in drug delivery. Some progress made in the fields of drug as well as gene delivery and tissue engineering applications have been also discussed.

Key words: Natural polymer, Cationic polymer, Applications

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INTRODUCTION

Polymers have become the main driving force of pharmaceutical as well as food and other industries [1]. As they frequently occur in nature so possess various characteristics like increased compatibility with human and other biologicals, bioactivity and biodegradation. In certain conditions where synthetic materials don't fulfil the desired requirements, natural particulate and nanomaterial materials can be used as alternatives [2]. In this review, natural cationic polymers, including cationic cyclodextrin, cellulose, gelatin, dextran and chitosan together with their use in drug delivery systems [3].

Polymers play an important role in site specific drug delivery is of immense interest with the basic to prolong the residence time and decrease dosage frequency [4, 5]. Novel as well as new routes of drug administration are identified by incorporating drug molecules into polymeric carriers such as nanogels, nanoparticles, liposomes, micelles, nano-spheres, nano-capsules, and nano-suspension [6]. Use of these

polymers have made it possible to increase the efficiency of new therapeutic agents [7]. Problems with traditional allografts and auto-grafts have been overcome by use polymers used in the field of genetic engineering and regenerative medicines. They have successfully developed newly sequenced proteins and self-assembled peptides with desired tunable properties and controlled expression of biological components. Fusion of bioactive domains and protein motifs can also be achieved [8].

Cationic polymers have significant potential and are extensively studied for various therapeutic applications [9, 10]. These polymers have the ability to form electrostatic complexes with proteins, nucleic acid and anionic biomolecules. Furthermore, their underlying bioactive properties like antimicrobial, antitumor, anti-inflammatory, and anti-oxidant and stimuli responsiveness make them more promising for enhanced therapeutic potential and use.

NATURAL CATIONIC POLYMERS

Cationic Cyclodextrin

Cyclodextrins are derivative of sugar which is produced as a result of growth of bacteria on starch. Shapes of CDs are torus. Structurally CDs are glucose. These are cyclic oligomers containing 6-8 units of glucose which are linked to each other via -1,4- glycosidic bond. Hydrocarbon and oxygen constitute the inner part of macrocyclic structure which link with the glucose units. This results in a hydrophilic exterior part surrounding the hydrophobic cavity. Commonly occurring CDs are basically composed of 6 (α , α), 7 (β , β), or 8 (γ , γ) gluco-pyranose units. But commonly beta-cyclodextrin is referred to as cyclodextrin consisting of seven glucopyranose units. Advantages of CDs include their monodispersity in saccharide structure, flexibility in chemical structure that provide ease in chemical modifications and favorable toxicology. One more property of oligosaccharide is their low immunogenicity. They provide multiple sites for binding with cell targeting moieties. Cationic derivatives of CDs have great affinity of binding with nucleotides and viral vectors have been introduced for their enhanced delivery. Apart from this, CDs have been incorporated into dendritic vectors and polycationic polymers. Because of possessing these unique properties, cationic CDs have many therapeutic applications [11, 12].

Yang et al. succeeded in synthesizing series of cationic novel star polymers having arms of oligoethylenimine (OEI) of variable lengths linked with CD core. Cationic star polymers were formed by activating OH groups of six units of glucose and grafting it with multiple arms of oligoethylenimine (OEI). 1, 1-carbonyldiimidazole (CDI) was used to activate -OH group which is followed by reacting it with large amount of OEI. This process resulted in formation of star polymer of CD-OEI. Molar ratios of OEI or CDI were maintained above 100 [13]. It ensured the absence of intra or intermolecular cross linking.

Qian et al. prepared and evaluated novel cationic β -CD polymers. They concluded that cationic β -CD with low cationic charge density and high molecular weight possesses good dissolution abilities and drug inclusion. Cationic β -CD polymers were synthesized by one-step condensation process by using epichlorohydrin choline chloride [14].

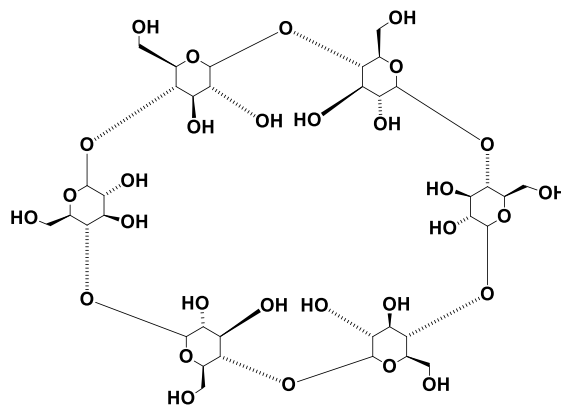


Figure 1: General structure of cationic cyclodextrin

Cellulose

Cellulose is one of the most abundant polymers found around the world. It is a linear β -1,4-D-glucan organic compound. Cationic cellulose and its derivatives are biodegradable, hydrophilic and antibacterial in nature which makes them favorable candidates for use in therapeutic application [15, 16]. Quaternized cellulose was first of all reported by Song et al. [16]. In this process, cellulose was dissolved in aqueous solution containing NaOH-urea followed by addition of 3-chloro-2-hydroxypropyl trimethyl ammonium chloride (CHPTA). Conditions were kept alkaline which acted as an etherifying agent. An in-situ epoxide was produced under these conditions followed by the formation of quaternized cellulose. The quaternized cellulose was formed due to reaction between cellulose sodium alkoxide and the epoxide or due to the addition of CHPTA. Diols were formed as a byproduct in this reaction. The resulting quaternized cellulose derivatives have proven to be an efficient carrier in gene delivery. Hydroxyethyl cellulose (HEC) and hydroxypropyl cellulose (HPC) are among the most widely used cellulose derivatives [17]. HPC as well as HPC-based

materials are FDA approved and mostly used in various food and drug formulations. Xu et al. prepared novel vectors for non-viral gene delivery. These copolymer comb shaped vectors were comprised of HPC backbones and cationic PDMAEMA side chains. These vectors were prepared by atom transfer radical polymerization (ATRP) by grafting the short PDMAEMA chains onto the long HPC backbone (HPD). In this process, bromo-iso-butyryl terminated HPC (HPC-Br) was used as macro-initiator [15].

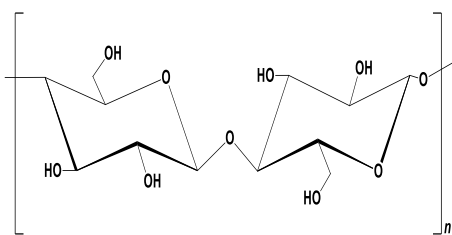


Figure 2: General structure of cellulose

Gelatin

Gelatin is derived from collagen as it is of natural origin. It is usually used for medical and pharmaceutical purposes due to its biocompatibility and biodegradability in physiological surroundings [18]. Gelatin consists of 18 non-uniformly distributed amino acids along with jointly negative and positive charges. Due to lysine and arginine residues gelatin has the inherent cationic property of gelatin mostly. The process of denaturation by which gelatin may be attained from collagen is done by basic or acidic treatment, that results in gelatin A with an isoelectric point (IEP) 4 of 6–9 and also gelatin B with an IEP of 4.7–5.4 separately. The basic procedure marks the amide groups of glutamine and asparagine and hydrolyses them into carboxyl groups, producing gelatin of a higher density of carboxyl groups, assemble it negatively charged and also dropping his IEP. In distinction, an acidic pre-treatment does not affect the amide groups. This yields in 2 charged gelatin types which are oppositely charged. Gelatin expresses cationic action on pH values under its IEP through amino group protonation.

For acidic gelatin the cationic density is more while for basic it is low. Gelatin is allocated safe excipient by The United States Food and Drug Administration, that is used nowadays as a component of numerous biomaterials [19]. By protonation of amine group Gelatin could be cationized, that happens beneath its pK or by introducing amino groups on gelatin backbone, normally realized by carbodiimide chemistry. Morimoto et al. have produced cationic gelatins through linking ethylenediamine (EDA) or spermine reaction which is EDC-mediated. In this reaction, amino groups of EDA or spermine and amide bonds among a carboxylic group of gelatin, endorses crosslinking [20]. Gelatin is normally cationically derivatized to allow interactions through biomolecules of anionic nature without capable of a pH dependence. e.g. Xu et al., for the non-viral delivery of plasmid DNA encoding insulin-like growth factor (IGF)-1, apply cationic gelatin nanoparticles in vitro to adult dog articular chondrocytes [21].

The outcomes of the research find that chondrocytes transfected by IGF-1 consuming cationic gelatin nanoparticles stayed able to uphold steady IGF-1 overexpression when subsequently grown up in cationic gelatin scaffolds in 3-dimensional (3D) culture intended for two weeks. For controlled release of 3 acidic peptide/protein drugs with different IEPs and MWs 14 Cationic gelatin with its aminated derivative are assessed [20].

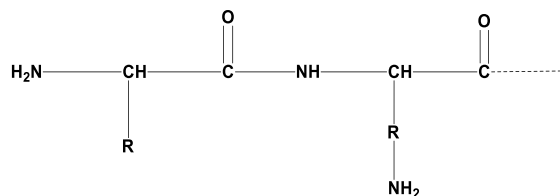


Figure 3: General structure of gelatin

Dextran

Dextran, FDA approved, branched polysaccharide and a highly water soluble polymer is widely used in pharmaceutical industry as potent drug carrier. Dextran is biodegradable and can be easily modified. Cationic dextran and its derivatives such as dextran-

spermine and diethylaminoethyl–dextran have been efficiently used for the delivery of nucleic acids. An attempt was made to prepare dextran based derivatives in which the hydroxyl groups were substituted by glycidyl-trimethyl ammonium chloride. This study was conducted by Kaminski et al and the resulting derivatives were used as alternative anticoagulant [22].

In another study, conjugates were synthesized by deductive amination of spermine and oxidized dextran. This resulted in dextran–spermine conjugates [23]. Dextran–spermine and their products have exhibited high in vitro and in vivo transfection of plasmid DNA. Employing this innovative work, Cohen et al. pooled the distinctive features of acetyl dextran (Ac-DEX) and spermine for siRNA delivery. Ac-DEX holds numerous features appropriate for the bioactive agents such as proteins delivery [24]. This novel system unites easy production steps and biocompatibility with the benefits of controlled release that is sensitive to physiologically acidic pH conditions. Acidic hydrolysis of spermine–Ac-DEX creates spermine-modified dextran, that could be additionally metabolized by enzymes in vivo [25].

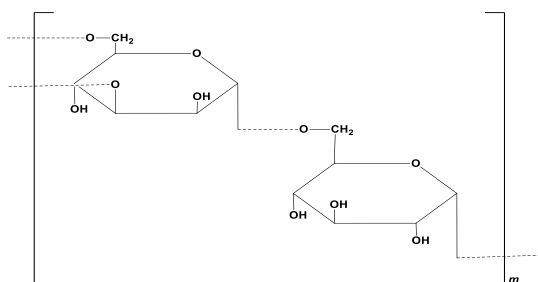


Figure 4: General structure of dextran

Chitosan

Chitosan is a naturally occurring cationic co-polymer consisted of erratically distributed D-glucosamine and N-acetyl glucosamine, wavering in sequence, composition and chain length. The non-toxicity, biodegradability, biocompatibility, antioxidant activity, antibacterial activity and muco-adhesive properties impart flexibility [26]. It is a weak poly-base with 6.5 Pk approximately, stating that the

charge density varies around pH range of 6–6.5. This gives

pH sensitivity, that is productive for numerous therapeutic applications. As the pKa is around neutral, the insoluble–soluble shift occurs at pH between 6 - 6.5, that is a useful range for biological use [27].

Chitosan cationic nature with negatively charged biomolecules qualifies the formation of poly-electrolyte complexes, the interaction with more efficient transfection and cell membranes. Decreased solubility at physiological environment and enhanced water solubility are among the major limitations of chitosan in drug delivery [28]. Modified chitosan have been introduced to counter these limitations. Modification of chitosan by using positively charged substituents has been carried out by quaternization of the amino group or by implanting polymer chains or small molecules onto the backbone of chitosan. However, these alterations do not suggest variation in the essential features of chitosan but introduce new features.

Modified chitosan offers derivatives with specific useful properties to match intended applications, e.g., improving transfection necessitates the conservation of primary amines. These types of chitosan quaternization have been studied by several research groups [29]. This approach delivers good regulation over the cationic feature without affecting its pH independency, which is intended to develop the constancy of ionic complexes. Furthermore, chitosan solubility in aqueous solution was improved rendering its solubility over a wide range of pH. The chitosan reaction with methyl iodide under alkaline pH is the most direct route for chitosan quaternizing. Among all quaternized chitosans discussed, N,N,N-trimethyl chitosan chloride (TMC) is the most extensively applied.

BIOACTIVE PROPERTIES

While designing and development of cationic polymers, bioactive properties are important parameters that need to be discussed.

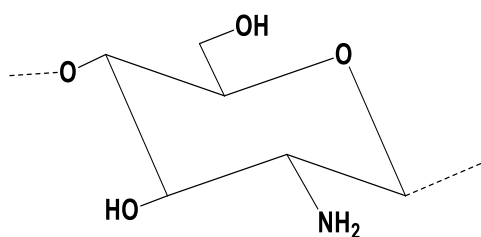


Figure 5: General structure of chitosan

Bioactive properties are also critical when the therapeutic applications of cationic polymers are concerned. Some cationic polymers are needed to be modified to exhibit required bioactive properties whereas some positively charged polymers possess inherent bioactive properties. Following important properties need to be emphasized while highlighting the bioactive properties of cationic polymers:

Stimuli-responsive

Antimicrobial

Antitumor

Antioxidant

Anti-inflammatory properties

Stimuli-responsive

Controlled intelligent systems are in demand for advanced research involving therapeutic applications. For examples nucleic acid separation, controlled drug delivery and controlled cell patterning. Responsive polymers have been proved to be very beneficial for controlled drug delivery because it allows the delivery of therapeutic agent at the required site. This system responds to the change in environment that occurred due to disease and releases the desired amount of API.

Various structural and chemical moieties are present on cationic polymers that enable them to respond to various external stimuli. For example temperature, ionic concentration, pH, electric field, light, chemicals and magnetic field. Some polymers have been developed by combining two or more stimuli responsive moieties resulting in polymers with multiple responsive properties. This section of review comprises of the development and therapeutic applications of stimuli responsive polymers.

Thermo Responsive

As the name indicates, temperature responsive polymers respond to change in temperature and are therapeutically important. Pluronic F-127 and poly (N-isopropyl acrylamide) (PNIPAM) are the examples of temperature sensitive moieties that are grafted or incorporated on cationic polymers to make them temperature responsive polymers. Though temperature responsive polymers are very advantageous, yet their immunogenicity, toxicity and circulation time upon administration are of important concern.

PEG has been proved to play its role in overcoming these difficulties by attaching it with cationic polymers. PEI-pluronicnano-capsules have been prepared by Lee et al. via an interfacial crosslinking mechanism between low molecular PEI and Pluronic F-127 using O/W interface during solvent/emulsification evaporation process. PEG was conjugated with green fluorescent protein (GFP) or vascular endothelial growth factor (VEGF) siRNA through disulfide linkage to develop nanoscale complexes with PEI-pluronicnano-capsules. Endosome compartment of transfected cell is burst out due to rapid nano-capsule volume expansion that occurs due to brief cold shock. This process enables the siRNA cargo to release into the region of cytosol and subsequently silencing target mRNA.

Iso-butyramide group exhibits thermo-responsive behavior after getting attached to hyper branched PEI side chain. Amidation reaction between iso-butyryl chloride and PEI results in the synthesis of hyper-branched polymer with iso-butyric amide end groups [30]

pH Responsive

Ionizable functional group imparts pH responsive behavior to cationic polymers. At specific pH, net charge of backbone or pendant group changes resulting in alteration in conformation of polymer or in hydrodynamic volume. This pH sensitive behavior of cationic polymer is advantageous for the biomolecular delivery in alkaline or neutral

environment. At high pH, the amine group remains unionized and polymer chain remain in collapsed state which does not allow the API to releases from dosage form. Whereas at low pH, the pendent amine group get ionized resulting in expansion of polymeric chain due to ionic repulsion. This process results in releasing the drug molecule into the surrounding medium. PDMAEMA, PEI, PAA are example of cationic polymers. These polymers possess basic functional groups (amine) that ionizes at low pH.

pH responsive behavior of PAA was investigated by Jain et al. They incorporated the ketal or acetal linkage into the backbone of polymer. When pH was low the acetal and ketal linkage degraded the polymer. These polymers exhibited increase rate of hydrolysis process when the pH was lowered from 7.4 to 5, and this pH is found in lysosomes [31].

Park et al prepared pH sensitive near-infrared optical imaging nano-probes using biodegradable polymers poly(g-glutamic acid) (g-PGA)/(PAE)[32]. They evaluated the quenching property of indocyanine green at high concentrations when combined with pH sensitive PAE particles. At low pH the particles of PAE found to be disassembled and show increase florescence intensity by releasing indocyanine green. The florescence intensity was 4.5 times higher than that was found in 7.4 buffer.

Ionic Responsive

Ions play an important role in much biological process. So the ionic responsive cationic polymers have proved to be therapeutically advantageous. Small change in ionic concentrations makes large and abrupt physical and chemical changes in ionic sensitive cationic polymers. The solvent ionic concentration has an effect on the interactions between solvent and the polymeric chain.

Sutani et al studied the PDMAEMA-co-acrylic acid copolymer. This polymer form stable complex with ionic drug metanil yellow. When this polymer was exposed to NaCl solution, the drug was released in a solution. This system provided constant drug release

profile which was found to be different from the behavior that was observed in aqueous medium [33]. In aqueous solution, the amine group of PDMAEMA chains got protonated and this resulted in change in conformation due to increased chain mobility. When NaCl was added in solution the ionic strength was increased, producing shielding effect on repulsion resulting in more coiled conformation. Peak intensity of PDMAEMA chains was decreased remarkably with increase in ionic strength [34]. There is more chain mobility in PDMAEMA units due to electrostatic repulsion caused by the partial protonation of amine moieties in aqueous environment. Increase in NaCl concentration cause enhanced ionic strength which leads to shielding of repulsion and assumption of enhanced coiled conformation. This trend is observed as the peak intensity of PDMAEMA chains was decreased with the increase in ionic strength [34].

Multi-responsive

Multi-responsive cationic polymers are sensitive against multiple stimuli. This results in effective and better targeting in complicated environment. This system is advantageous for developing novel triblock copolymer composed of PEG and PAA. These polymers have been developed into temperature sensitive hydrogels and injectable pH [35].

pH and thermo dependent polymers of PAAs were developed with vinyl group at terminal position and then end-capped by 1-adamantylamine (ADA).

ROP was used to synthesize novel pH and temperature responsive block copolymer made of PNIPAM and PLL [35]. The di-block copolymer was prepared by ROP of ϵ (benzyloxy carbonyl)-L-lysine *N*-carboxy anhydride. This process was initiated via amine-terminated PNIPAM. This process was then followed by acidic de-protection step. PNIPAM-PLL copolymers get assembled into micelle-like aggregates. Hydrophobic block was composed of PNIPAM which was responsive to high temperature and acidic pH and PLL form hydrophobic block

which was responsive to low temperature and alkaline pH [36].

Antimicrobial Properties

In many drugs, therapeutic devices, hygienic health care products the infection caused by the microbes are of great concern. The source of infection is some minor or common superficial infections e.g. candidiasis, can move to serious life compromising diseases such as invasive aspergillosis. Data show that infectious diseases are killing more people than any other single cause globally. As potential antimicrobial systems, the use of cationic polymers supports to combat, mitigate or eliminate microbial reasons for infections. The cationic polymers are gaining enlarged attention from both industrial and scientific communities therefore they are used efficiently and extensively in the antimicrobial applications.

As antimicrobial agent one of the most widely studied cationic polymers is Chitosan. It possesses the intrinsic antimicrobial activity against fungi and few Gram negative and Gram- positive bacteria and at pH 6 [37]. However, the exact antibacterial mechanism of action of chitosan is not entirely understood till now, numerous mechanisms have been proposed. Among them one occurs through alteration in the permeability of bacterial membrane, the cell lysis occurs due to the obstruction of nutrient transport or breakdown of the cytoplasmic membrane. Commonly the inhibitory mechanism of chitosan may differ depending on Mw, DD, which is type of bacterium [38].

For antibacterial studies *Staphylococcus aureus* and *Escherichia coli* remain the most regularly active bacteria and the most frequently selected parameter to estimate the activity of the antimicrobial agents is minimal inhibitory concentrations (MIC).

Chitosan antibacterial properties with N-arginine substituents was studied by Xiao et al, finding that with changing amounts of N-arginine substituents with chitosan exhibit antibacterial activity in concentration dependent manner. Samples showed

antibacterial action at a concentration W greater than 150 ppm while they were consumed in microbes and immersed as nutrients to encourage the development of microorganisms when concentration was lower than 50 ppm.

N-substituted chitosan derivative has quaternized by CHPTA to react by the primary amine groups or hydroxyl of the glucosamine units in chitosan. Minimal inhibitory concentrations exhibit greater values with larger amount of N substitution. PEGylated quaternized chitosan derivatives were reported by Li et al. as antimicrobial agents.

In another study derivatives of chitosan were synthesized. For this purpose, alkyl chains having hydrophobic nature as well as cationic charge was induced. This was done via quaternization of amino group. Hydrophilic PEG having 6-ethylene glycol and methacrylate functionality was also incorporated. These hydrogels exhibited enhanced efficacy against different bacteria e.g. *P. aeruginosa*, *E. coli*, *S. aureus* and *F. solani*. Mechanism of action was explained as that the structures these hydrogels are like anion sponge. These structures interact with anionic membrane of microbes resulting in disruption of membrane and finally their death.

Antitumor Properties

Physiological process which is involved in regulation, differentiation, apoptosis, proliferation and cell arrest can change the rate of homeostasis and also the cell function. Any dis-function in these events changes the ratio between cell death, cell differentiation and proliferation. This can lead to an increase in the number of non-regular cells which ultimately results in tumors. Recent trend in metastasis and tumorigenesis have enabled to develop novel compounds that can act on abnormal molecular and biochemical signals causing cancer. Macromolecular transport pathways across tumor vessels occur through vesicular vacuolar organelles, open gaps and fenestrations. The transportation of an anticancer drug is monitor by the physiological and also physicochemical properties of the interstitium

and also by the physicochemical characteristics of the molecule. At the tumor level and at the cellular level physiological barriers in the body must overcome to effectively transport anticancer agents to tumor cells in vivo. The opportunity of fine-tuning polymer properties has led to remarkable advancement in their role as anti-tumor agent carriers or as conjugates with antitumor drugs. Nanomaterials have revealed high targeting capability to tumor tissues and are minimally present at healthy tissue sites.

Lu et al. prepared conjugates of LPEI (M600) and b-CD to appraise their electiveness as gene carriers in glioma cancer treatment [39]. The conjugates were consisting of the antitumor drug 5-fluoro-20-deoxyuridine (FdUrd) along with b-CD and LPEI. The conjugate was functional as a new bi-functional anticancer prodrug with better therapeutic effects, while also showing good efficiency of gene transfer.

Firstly, CD-grafted PEI was synthesized by reacting CDI activated CD alone with the primary and secondary amines of PEI. Secondly, CD-g-PEIFdUrd prepared by reacting CDI-activated FdUrd with CD-g-PEI. This conjugates efficiently reserved cancer cell migration and invasion in a time and dose-dependent manner. PEGylated PLL dendrimers were synthesized and conjugated with camptothecin that is an enzyme that stabilizes and rejoins DNA breakdowns through replication [40].

Antioxidant Properties

Substances which delay/block the cellular substrates oxidation are Antioxidants. Its key character is to self-protect the body in contradiction of the impairment, produced via degenerative diseases and ROS. Three most important reactive oxygen species which are made uninterruptedly in the mitochondria by growing cells are hydroxyl radical metabolic derivatives, sunlight and hydrogen peroxide superoxide radical or made by foreign factors for example; ionizing radiation, and ultraviolet light. The reactive oxygen species (ROS) has not a clear role, on one side they stop diseases through supporting the

immune system by facilitating cell signaling and play a vital role in apoptosis. But on the other side they are the cause of large amount of pathologies such as diabetes, atherosclerosis, cancer and cardiovascular diseases. Such type of radicals is not stable and reacts directly with numerous other constituents in the body moves to tissue of cell injury.

Excess ROS can produce oxidative stress that is reserved by cellular endogenous antioxidant mechanisms in a state of a health [41].

In numerous cases such as the prevention of chain initiation, the fixing of catalysts of transition metal ion, radical scavenging, the reductive capacity and the decomposition of peroxides, the antioxidant action of polymers has been documented. The cationic chitosan that occurs naturally has shown considerable antioxidant properties. Because of the solid hydrogen giving capability of chitosan it has scavenging activity. Hydrogen in amino groups or hydroxyl of chitosan which is active atom may react with reactive oxygen species. As a result, a stable macromolecular radical is produced.

Because of free groups of amino, chitosan has large metal binding capacity. A low MW and increase concentration exhibit an encouraging impact on the antioxidant action of chitosan. On other hand, higher MW was seen to be the active feature in lowering the oxidation of lipids. Feng et al. exposed chitosan at 20 kGy, that show a high capability of reduction and stated better blockade of peroxidation of linoleic acid. It was inferred that the reason of the scavenging capacity of chitosan are amino groups and active hydroxyl. Extra factors that are too responsible for the antioxidant features of chitosan comprise of several substituting groups, Mw and DD.

Liu et al. linked different shapes of nitrogen atom comprising functional groups such as primary amines, secondary amines, imines, and quaternary ammonium groups to the antioxidant properties of chitosan [42].

In further comprehensive study of the link between the charge density of the cation and the antioxidant

action in chitosan that is quaternized, familiarized with extra influential electro negative groups, its reduction power also antioxidant activity against hydrogen peroxide and hydroxyl were evaluated in vitro. These results show that, in the quaternized chitosan the positive charges of nitrogen atoms effect the antioxidant actions. Substituted electronegative groups powers the quaternized chitosan charge density and also show too stronger hydrogen peroxide and hydroxyl scavenging actions as compared to chitosan. In other study the L-carnosine, dipeptide and its derived substances, Boc-L- 1. carnosine, was linked to PEI which drops the making of reactive oxygen species and enlarged efficiency of transfection [43].

Through the primary amine groups of PEI, Peptide moieties are connected to yield peptide – PEI hybrid polymers. The damage in cells from oxidation is reduced by the Modification of PEI–peptide conjugation, results in improve transfection efficiency and greater cell survival. In 2 primary cells, cardiac progenitor cells & cells of adipose stroma, the ROS levels as related to PEI were significantly lower by the hybrid polymers.

Anti-inflammatory Properties

Inflammation is fast response of tissue against injury or infection which is recognized by the deposition of activated cells and fluid at the site of destructed tissue. Entry or attack of any foreign agent activates the defense mechanism of host called immune system. This system uses various biological components to perform its basic function. Specific receptors are involved in the detection as well as immune response to any microbial attack. Among these receptors, Toll-like receptors (TLRs) are the most prominent. Their basic function is pattern recognition. Activity of TLR is based on nucleic acid which is released by either dying cells or dead cells. If these TLRs are incorrectly activated, it may result in various auto-immune as well as inflammatory conditions [44].

Lee et al. showed that some cationic polymers have the ability to react as scavenging agent that inhibits the abilities of an immune nucleic acid. These polymers may include PAA dendrimer, β -CD and PLL. The anti-inflammatory action of these polymers does not depend upon their structure, chemistry or sequence rather it depends upon the activation of various TLRs and also pattern recognition receptors related to cytoplasm. These receptors identify and protect various tissues from external and internal agents like damaged cells and pathogens [45].

1. THERAPEUTIC APPLICATIONS OF CATIONIC POLYMERS

Cationic Polymers as Potential Carriers for Drugs

Regular development has been done in current delivery of drug by usage of polymer carriers that is cationic used for the therapeutic action in both implanted reservoir systems and pulsatile dose delivery products. For a drug delivery system, a cationic polymer that is convenient must exceed various difficulties leading to medical application for example facing the requirement for targeted delivery, biocompatibility, and transport with in the cell though consolidating features allowing reactive actions to physiological settings. The poly-cationic drug delivery systems have been attracted considerable attention due to its exceptional features, which includes high cellular uptake efficiency and good water solubility.

Cationic gelatins are studied for the modified release of peptide or protein drugs with MW that are different. The research study by Zwiorek et al. stated that nanoparticles of gelatin are used as transporters for enhancing delivery action of immunostimulatory CpG oligonucleotides both in-vivo also in-vitro.

The CpG oligonucleotide unwanted deposition is evaded by charge on the surface of nanoparticles that is cationic, as of the surface of the carrier during the passage to the targeted cell. Such formulation comprising of immune-stimulatory oligonucleotides and antigen both might show potential against viral infections or cancer [19, 20].

The cationic polymers type that is extensively studied for the purpose of delivery of drug are PAAs. In a new study, develop an efficient protein delivery system intracellularly which are founded upon linear PAAs, which form nanocomplexes that are cationic and have the capability of auto-assembling also, through reversely charge proteins. [46].

Through Michael-type poly addition of 4-amino-1-butanol toward CBA PAAs were formulated. These PAAs now expose in the intracellular environment to fast degradation. The reason of this fast degradation is breakage of the disulfide connections due to reduction, thus liberating the therapeutic payload and reducing possible cytotoxicity of the polymer. Similar group studied was 2 model proteins, human serum albumin and b-galactosidase by an IEP of 5.3 and 4.6, correspondingly, through just mixing positively charged PAA and negatively charged protein on neutral pH. As an effect complexes were formulated that were auto-assembled polyelectrolyte along with magnitudes of Nano-size.

Tissue Engineering with Natural Cationic Polymers

Tissue engineering is a stream of extremely interdisciplinary. Tissue engineering associates the values and approaches of living sciences and engineering. They use structural as well as functional associations in normal. While in pathological tissues it brings biological substitutes proposed for upholding, reinstating, or to improve normal function of the injured tissue/organ. There is also a role reported of cationic polymer chitosan in tissue engineering, chitosan may be designed into absorbent structures which are helpful in engineering of bone tissue for osteoconduction. Chitosan scaffolds was used by Zhao et al. added with calcium phosphate cement. The Fracture and fatigue is enhanced with the help of scaffolds, this was applied in bone tissue engineering for the delivery of drug to stem cells[47].

Also, as a scaffolding substance chitosan was selected for cartilage tissue engineering, in articular

cartilage engineering because of its basic resemblance with various GAGs present in articular cartilage. The cartilage-specific ECM parts such as GAGs and type II collagen perform a vital role in controlling expression of the chondrocytic phenotype and in auxiliary chondrogenesis in vivo and in vitro [48].

For chondrocyte cells to rebuild tissue engineered cartilage and restore defects of articular cartilage in a sheep model a chitosan hydrogel has been prepared by mingling a chitosan hydrogel with sheep chondrocytes.(Hao et al., 2010. Matrix accumulation analysis and Cell survival were characterized in culture after three weeks. The reconstructions have been cultured for one day and moved to the freshly made defects of the sheep articular cartilage for enabling in vivo restoration. Defects of cartilage have been restored entirely within 6 months.

Gene Delivery In past decades, cationic polymers have been extensively studied for gene delivery. So far, considerable research has been made on gene delivery which has entered either clinical trial while some are in approval stage worldwide. Cationic polymers possess positive charge on their surface, this make the attachment of nucleic acid more easy via charge-charge interaction and thus facilitate the internalization via endocytic mechanism. Various nucleic acid used as therapeutics, can be conjugated either covalently or non-covalently to the polymeric matrix or carrier. Nucleic acid can be released from the polymeric carrier via polymer degradation, poly-anion exchange or cleavage of bond between nucleic acid and carrier. Nucleic acid is also attached via hydrogen bonding and electrostatic interaction [49]. Chitosan/siRNA nanoparticle as aerosol was successfully developed for the administration of exact siRNA into the lungs of mice. This method was non-invasive and more efficient. This approached can be efficiently used for pulmonary RNAi-based therapies [50, 51].

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BALB/c mice were successfully immunized intranasally. For this purpose chitosan–DNA nanoparticles containing “pneumococcal surface antigen A” (psaA) were used. An enhanced level of immune response was noted in mucosa, systemic and cellular immunity by intra-nasal administration of

chitosan-psaA vaccines. Decreased nasopharyngeal carriage was noted in mice which indicate that chitosan based nasal vaccination could be effectively used as non-invasive route for the efficient and easy delivery of DNA vaccines used in pneumococcal infections [52].

CONCLUSION

The main aim of this review article was to focus few natural cationic polymers that are commonly used in drug delivery. These polymers have been described shortly with little emphasis on different modifications made for enhanced and potential properties. In general, the derived or modified polymers have better characteristics as compare to the natural ones, as their properties have been tuned according to the need. The natural cationic polymer as well as their derivatives has been widely used in the field of drug delivery, genetic and nucleic acid delivery. The basic property which makes cationic natural polymers as the most favorable candidate for drug delivery is their biodegradability and non-toxicity. This short review will contribute in understanding the potential use of these polymers in various fields including drug delivery, food and cosmetics.

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