Polyelectrolyte Complex for Drug Delivery in Biomedical Applications: A Review

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Abstract. There are so many significant developments made in drug delivery system (DDS) in which Polymer DDS has reached great developments. The main motive of this paper is to focus on DDS developing by Polyelectrolytes. Polymers have achieved much importance in DDS. Polyelectrolytes shows an exceptional category of polymer compounds containing of opposite charged polyions which are mainly cationic or anionic charges; they are hydrophilic in nature because of presence of opposite charge, can be used in various of applications in DDS. Polyelectrolytes (PE) exhibits various types of reactive groups that permits easy, adaptable modification with functional agents such as targeting molecules. Further, the oppositely charged nature exist in polyelectrolytes been used to transport macromolecules such as DNA and nanoparticles. Significance of smart polyelectrolyte is growing day by day from last several year. In the last several years, polyelectrolytes representing promising means for targeted based drug delivery and gene treatment. In the present paper, polyelectrolyte, polyelectrolyte complexes, deposition method for multilayer system, features, characterization of polyelectrolytes, and applications are reviewed.

Keywords: Chitosan, DNA, Drug Delivery, Polyelectrolyte, Macromolecular characterization

1. Introduction

Rapid Researchers have focused on designing smart drug carriers to enhance medical treatment using “on demand” targeting approaches. Using such an approach, a smart drug vehicle carries therapeutic agents to be released at targeted sites with minimal damage to healthy cells [1]. Polymeric material is extremely attractive to specific conditions. According to pH, temperature, magnetic and electric fields have become extremely attractive in DDS. In DDS, factors such as toxicity, biocompatibility, degradability, and sustainability of releases are considered and therefore the design of systems is usually so much more complicated. Polyelectrolyte have emerged as potential materials for creating these carriers due to their tunable size and biocompatibility. Polyelectrolytes hold great features, such
as fine-tuning of thickness, stiffness, stability, morphology, and topography; they may exhibit special biological properties, such as muco adhesion. Weak PE is permissible for a varied range and they are useful in the formation of “smart” materials for chemical separations [2]. For the selection of polymer material, it is important to select the material, which can control the encapsulation efficiency, rate of deliver of drug, and time required to release the drug. colloidal transporters (micro, nanoparticles, micelles), implantable networks, and polymeric medicine these are the three main classes observed in the polymeric DDS[3]. Polyelectrolytes and functionalized polymers presently play an essential part in the development of DDS by providing precise transport of remedial agent.

Over the last 20 years, statistics as a discipline has expanded tremendously. Statistics has a role whenever there is a demand for quantification. Statisticians are a key collaborator in the creation of new pharmaceuticals because of their capacity to conceive in terms of variability, to extract signals from noise, to control sources of bias and variation, and to optimise under given conditions. For conventional, sustained release, and controlled release DDSs, changes in plasma drug concentrations over time [4].

2. Drug delivery system (DDS)
Drug delivery is a means of administering medicine in such a way that the medication concentration in some sections of the body is higher than in others. Drug delivery aims to concentrate drug in the tissues of interest while lowering its relative concentration in the remainder of the body. This increases the efficacy of the while lowering the adverse effects. The delivery of drugs to receptors, organs, or any other specified portion of the body to which the drugs to be delivered is known as drug targeting exclusively[5]. The therapeutic index of a drug is a measure of how effective it is at treating a specific condition as determined by its pharmacological response Access and specific introduction are essential for safety of the drug and its potential receptor. The various parameter used in the DDS is explained below.

2.1 Controlled release
Maintaining the concentration within the therapeutic window can improve drug efficacy (effective dose). By managing drug diffusion, the rate of dissolution, or carrier degradation, polymer carriers loaded with medicines provide controlled temporal and spatial release of a drug[6].

2.2 Targeted delivery
Localization at the organ, tissue, cellular, or organelle level can improve drug efficacy while reducing toxicity. Coating or conjugating the carrier with affinity reagents allows for targeting nucleic acids, peptides, antibodies, and other molecules that bind to specific targets. Proteins, nucleic acids, and polysaccharides are all examples of cell receptors[7].

2.3 Solubility enhancement
Low drug solubility and stability can significantly limit the efficacy of a potential treatment candidate. To increase the in vivo solubility of lipophilic and hydrophobic drugs, drug delivery systems can be created. Hydrophobic medicines can be delivered either via encapsulating in a drug delivery carrier or by injection[8].

3. Polyelectrolyte
Most of the highly charged molecules Polyelectrolyte when placed in ionized solvent, a macromolecular material that has repeating units and dissociates into highly charged polymeric molecule. Polyelectrolytes is a polymer of electrolyte with several repeating chain units or bear repeating units of electrolyte group [9].The study of the polyelectrolyte has considerable potential in the field of controlled and targeted delivery. Polyelectrolytes extensively used in controlled DDS to stabilise drugs and alter the drug release features. The opposite charge present on the repeating units of the polyelectrolyte is nullified by oppositely charged ions which can be able to form electro
neutrality[10]. Polyelectrolytes has particular advantages over the non-polar polymers for example 1) In aqueous solution, the method of coating can be accompanied and it helps to reserve the bioactivity of fragile proteins. 2) By use of the polyelectrolyte, it allows the control of the release behaviour by choosing suitable polymers. polyelectrolytes are capable materials for the development of the controlled DDS[11].

3.1 Polyelectrolyte Complex (PECs)
One of the significant features of polyelectrolyte is that capability of the formation of the complex, when mixed with other the opposite charged poly electrolyte. (PECs) and polyelectrolyte multilayers contributes similar physical, chemical type of properties in form of their internal, physical structure also morphology[12]. PECs have the capacity of the formation of the complexes with multiple various oppositely charged particles. Interactions between polycations and polyanions (Due to electrostatic force of attraction) over the mixing of aqueous solutions of the opposite charged PEs, it tends to produce dense phase which is different from the solvent[13]. Considering factors such as origin, composition and molecular construction, polyelectrolytes are classified. Some of main PEs are: 1) natural PE (Nucleic acid, pectin, Carrageenan, Alginate(refined from brown seaweed)). 2) Chemically adapted PE (Pectin, Chitin), 3) artificial polymer (Polyvinyl ,poly benzene trialkyl ammonium, Poly vinyl sulfonic acid, Poly acrylic or methacrylic acid), Poly styrene (sulfonic acid, Poly acryl amido alkyl trialkyl ammonium)[14].

4. Characterization of PECs
Depending on macromolecular and electrochemical properties, polyelectrolyte properties differentiated in two direction.

4.1 Macromolecular characterization
4.1.1. Chromatographic method. Field-flow fractionation, electrophoresis and size exclusion are some macromolecular properties of PECs. Main beliefs of selective polyelectrolyte coacervation might be functional to chromatography, if the polyelectrolyte were restrained on a chromatographic support part[15].

4.1.2. Osmatic Pressure measurement. Molecular mass of PEs can identify using osmatic pressure measurements (OPM). Because of their dissociation nature, osmotic pressure of the Polyelectrolytes differs frequently. Osmotic pressure can be find by a pressure difference between the sample section and a section with pure solvent or an electrolyte solution (OPM)[16]. At low salt concentration polyelectrolyte solution displays its exclusive feature as its osmotic pressure considerably go beyond the osmotic pressure of discharged polymers at the equal polymer concentrations[17].

4.1.3. Light scattering method. To illustrate Polyelectrolytes in solution form, light scattering systems are commonly used. This technique can deliver complete data on particle size of PE, shape of PE and mass of the scattering elements, particle solvent contact and polydispersity[18]. Polyelectrolyte solution properties have been studied mainly by viscosity in aqueous solution. This is because light scattering in aqueous solution is difficult to measure and shows some anomalies, through light scattering is a major method for studying solution property[19].

4.1.4. Ultracentrifugation. Ultracentrifugation is a organized technique used to find molar weight of PEs in series of 100- 10^8 gm/mol[20]. In ultracentrifugation technique, the centrifugal force present at high velocity performed on the PE solution, which comes to sedimentation of the macromolecule. sedimentation velocity can be connected to molar mass of the polyelectrolyte[21].
4.2 Electrochemical characterization

4.2.1. Potentiometric method. This method is utilized to guess the ion activities of H+ion via selective and reference electrodes[22], pKa, degree of ionization, pH are the basic capacities to characterize PEs[23].So the pKa value of polyelectrolyte has been determined experimentally by potentiometric titration system and computed with molecular dynamics and constant pH method.

4.2.2. NMR spectroscopy. To calculate the chemical arrangement of the macromolecule, NMR spectroscopy is used. NMR spectroscopy technique gives us additional data about molecular dynamics present in the bulk state[24]. NMR (Proton nuclear magnetic resonance)spectroscopy technique is used for study of the changes in the chain structure and dynamics during the temperature-induced phase separation in polymer solutions[25].The resolution which is given by the NMR method permits the signal of polycation and polyanion to be monitored distinctly for straight observation of the (LBL) growth[26].

5. Deposition methods

Polyelectrolyte multilayers were deposited by two techniques 1) Dip coating. 2) Spincoating. In dip coated PEM, an interfusion of polyelectrolyte layer was observed while flat and clearly separated layer were deposited by spin coating[27]. The exchanged dip coating is one of the easy method suitable for use. To increase the speed of the deposition of drug, spray deposition and spin coating has considered as a noble option. Spin coated films are narrow, extra apparent and of advanced elasticity produced through alter dipping [28]. Layer by layer (LBL) assemblies have just undertaken wide study for drug delivery application. The benefit observed by (LBL)technique is that rate of the growth of the film has measured by nanometre scale [29]. Capsule sort of LBL method has specific attention due to their potential for targeted distribution in body. Film sort of assembly cannot usually transportable over body but film kind of assembly technique can be dominant approach for the covering of biomedical devices requires constant delivery of drug [30]. Film formed in a regular method can deposited on a various substrate in a robotized way using different techniques like alternated dip coating, spin coating or spray deposition. Films prepared up by using polyelectrolyte substances is easy deposition technique, which intensely makes differences with the difficulty of the fundamental mechanism. For the duration of the film deposition, various properties can be found by shifting the operational parameters with certain grouping of interacting species [31]

5.1 Layer-By-Layer (LBL) assembly

Gero Decher and Hong first experimentally found LBL assembly method. Coating collides and consequent shell development are some applications of LBL which was invented after several years[32]. Highly efficient DDS is every time made through hybridisation of many constituent and assembly technique and every technique holds its own unique part in DDS. The (LBL) adsorption method offers vast opportunity in the suitable material selection similarly flexibility of the structural architecture for material, which is fully matched fabrication of the drug delivery substance demanding difficult drug design [33]. In (LBL) self-assembly technique it frequently give rise to a linear growth, for film thickness. Collective number of polyelectrolyte deposition layer, it is detected that film thickness raises exponentially and these occurrence be observed for the weakly charged polyelectrolyte multilayer [29]. LBL assemblies in recent times go through extensive research for drug delivery application. Capsule sort of LBL has been of specific concern due to their potential for directed delivery in body. Film sort of assembly cannot transportable throughout the body but this one is the dominant method for the covering of biomedical apparatus which requires essential persistent delivery of drug[34], [35]. The build-up of LbL multilayers focused by the electrostatic interaction among the opposite charged particles. Multiple function of LBL methods can be presented by the occurrence of different materials in the multilayers like PE, metallic oxides, Nano objects and catalytic enzymes[35]. Benefit of polyelectrolyte capsules (PCs) as distribution transporters is that the capsules prepared by polymeric substance keep the medicine from degeneration on the way to the cell and
defend the body from the damaging side reaction of the drug. For micro or nano capsules to be functional as remedial delivery of transportation. There is three main parts: (i) the encapsulation (ii) the targeting of the capsules in bio system, and (iii) the exact delivery of the drug from the capsules[7]. The properties of the LbL assembly can be moderated by regulating, nearly processing factors such as covering of material, ion strength, temperature, PH, washing and drying conditions.

5.2 Procedure of layer-by-layer method

LBL assembly system contains the repeated serial dipping of a charged substrate into solutions of oppositely-charged PE, and the adsorption of the opposite charged PE give rise to the development of a multilayer nanolayers on the substrate[36]. Throughout this process, opposite charges that are present on the surface leaving additional charges upon adsorption [37]. The charge on the surface exists on the outermost layer reformed between the anionic and the cationic state. Polyelectrolyte present in the solution form the electrostatic bond with functional group of containing charge. It later offers a driving force for successive build-up of multilayers in assembly (Fig1)[38]. This result can be observed more or less irreversibly adsorbed polyelectrolyte multilayer of which thickness and interpretation can be manipulated with different type of adsorbing species, type of deposition technique and processing condition such as polyelectrolyte charge, ionic strength, salt concentration and adsorption time[39]. The development of LBL assembly multifilm are accomplished by multiple molecular interactions, which includes electrostatic force of attraction, covalent bond, hydrogen bond, van der Waals forces, hydrophobic interactions, charge-transfer interactions, host–guest interactions. Between these interactions, electrostatic force of attraction among the opposite charged components is the most frequently useful driving force used for the construction of nano structured PE multilayers. Attachment designs include electrostatic interaction, Diels alder reaction, Huisgen 1, 3 dipolar cyclo addition and maleimide Michael reaction. The use of non-covalent interactions is another way for loading drug molecules onto coated NPs. For example, electrostatic interactions between cationic-terminated self-assembly methods and anionic oligo nucleotides can be used to load DNA or RNA molecules on the particles.

![Figure 1. A LBL film of (A) polyelectrolytes and (B) polyelectrolyte/protein[32].](image)

5.3 Chitosan based self-assembly method in DDS

Chitosan is the exceptional natural cationic polysaccharide, and it is observed that a natural polycationic linear polysaccharide obtained from the process of partial deacetylation of the naturally occurring polysaccharide, chitin. Chitosan is glucosamine (amino sugar) and N-acetyl glucosamine(amide derivative of monosaccharide glucose) units allied together by β (1 → 4) glycosidic links shown in Fig.2.
Figure 2. (A) N-acetyl glucosamine(amide derivative) unit; (D) Glucosamine unit(amino sugar)[40]

Chitosan exhibits several properties such as biocompatibility, biodegradability, non-toxic material; Chitosan also shows important biological properties such as wound healing capability, antimicrobial, and hemostatic actions[5]. One of the important property of chitosan is its chemical arrangement are the hydrogen bonds (intramolecular) of CS which offer excellent resistance to heat generated due to the interaction of macromolecules[41]. Ionotropic gelation, spray drying, (water-in-oil) emulsion cross-linking, formation of reverse micelle, emulsion-droplet coalescence, nanoprecipitation, and by a self-assembly mechanism such type of various method has been used to produce chitosan nanoparticle[40]. Self-assembly method is particularly useful in the preparation of injectable thermogels. Since it exhibits hydrophobic carrier system and it has exceptional cationic property, chitosan particles can interact with anionic polymers to form the PECs. Chitosan found by N-deacetylation of chitin. 2-acetomedo 2-Deoxy-β-D glucose is obtained through a β (1→4) Linkage [42]. Alkaline hydrolysis with NAOH complete for N-deacetylation of chitin at around 120°C temperature. 40-80% deacetylated chitosan be formed in the alkali treatment. Hence, chitosan is a hetro-polymer, which exhibit (1→4) 2-amino 2-Deoxy-β-D-glucose collected with (1→4) 2-acetamido-2-Deoxy- β-D glucose elements of the unique chitin in polymeric chain (Fig3).

Figure 3. (Deacetylation of chitin into chitosan)[43]
Degree of deacetylation (DOD) is key parameter. Due to DOD, solubility of polymer and solution properties observed. The DOD is the ratio of 2-amino-2-deoxy-β-D-glucose units to 2-acetamido-2-deoxy-β-D-glucopyranose[44]. In this process, (chitin transformed into chitosan) the molecular weight observed to be lowered because of deacetylation (Fig 4). In acidic solvent, the charge distribution changed because of the amino group formation.

![Figure 4. Development of PECs between chitosan and anionic polysaccharides [45].](image)

6. Features of polyelectrolyte complex
Amorphous aggregates (natural or denatured proteins without forming a specific higher directive construction), held together by reversible ionic cross links with random charge reparation within the complex. Due to their surface charge, highly swollen and permeable gel particles present in aqueous solution forms stable suspensions. The ability to build up multi-layer coatings (LBL) means alternating positively and negatively charged polyelectrolytes. Polyelectrolyte family has familiar with the various important perception of PE physic like charge regulation, concomitant comparison between hydrophobicity and electrostatic contact, main forces in arrears liquid phase separation, dynamics of polyelectrolyte and transport kinetics across section[46].

7. Application of polyelectrolyte in drug delivery system
PECs have achieved great attention in several years because of their individual wide application. The improved biocompatibility of PE coated nano particles has managed to build potential biomedical application, including DDS, gene analysis, and cancer treatment[47]. Formation of coating on films and fibres, for separation and fractionation of proteins, for segregation of nucleic acid, for necessary pharmaceutical yields, as supports for catalyst and for research of microcapsules for drug delivery, These can be used as membranes[48]. PECs have important application, it contains microencapsulation of drugs, enzymes, cells and microorganism, control of proteins by the complex development and polycation complexes with poly nucleotides or oligo nucleotides as vectors in gene treatment[49]. As insoluble PECs indicate its exceptional efficiency hydrophilic soil binders, after the Chernobyl accident to subdue the developed radioactive aerosol in contaminated dusty zone[50]. The major of flocculants are their integral solid liquid separating efficiency. These varieties makes polyelectrolyte a unique class of polymers which catch extensive application[51]. The category of PE has its significant effect on the usage of particles and the contact of the particle with tissues and cells [45]. There are generally two approaches involved for drug delivery: targeted and non-targeted. In targeted delivery a lig and, usually an antibody or peptide is to be stick to the NP and target a receptor on a specific cell. Non- targeted delivery is the delivery without targeting exact cell, where the drug will be released to both healthy and diseased cell[43]. The nano constructed shells are appropriate as coating of living cells or artificial tissue, the necessities for this application are polyelectrolytes that are not poisonous to the tissue of the coated cell as well as transplantation site[52].
8. Conclusion
The existing research work in pharmaceutical nanotechnology, PECs Nano particles enhanced further developments of such system. The PENCs yet is capable considering the range of benefits they offer. Synthetic and natural PECs are rapidly emerging field of drug delivery. The biomimetic and bio motivated system have great potential to resolve any difficulty in DDS. Combining outlook from the biological field will offer a fresh regular standard for the design of polymeric DDS. The study for DDS method and the different approaches of the action signifies one of the frontline study regions. The DDS combines one or more old-style DDS with the support of engineering technologies, the system tries to produce the capability to precisely target the area where drug has delivered in the body also considered therate of release in the body at which it should need to release. If DDS depend on a biodegradable implant to carry drug medically or deep within the body, biodegradable and bio-absorbable polymers deliver a safe framework for transporting medicine without harm to the body. Polymer type DDS has well-defined as making that carries remedial matter into the body, this system recovers its efficiency viaregulating the rate of release in body, time of release, and place of release of drug in the body. DDS has reached remarkable evolution in the several years. However, remains a hard job to control drug approach into the body. The drug delivery area is developing at an exponential rate in work of research and evolution of new techniques.

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