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Review Article

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Polyelectrolyte complex : A pharmaceutical review

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ABSTRACT

This review work gives a lot of information on polyelectrolyte complexes (PECs). The complex formed is generally applied in different dosage forms for the formulation of stable aggregated macromolecules. Many properties like diffusion coefficient, chain conformation, viscosity, polarizability, miscibility, etc., are drastically changed due to the introduction of a polyelectrolyte. The formation of PECs is influenced not only by chemical properties like stereochemical fitting, their molecular weight, charge densities, etc. but also by secondary experimental conditions like concentration of polyelectrolytes prior to mixing, their mixing ratio, ionic strength of the solution, mixing order, etc. The formation of PECs is described in this article and it is divided into three main classes, i.e., primary complex formation, formation process within intracomplexes and intercomplex aggregation process. There are different types of PECs obtained according to binding agents such as polymers, proteins, surfactants, drugs, etc. Other factors which affect the formation of PECs are also discussed. There are a number of pharmaceutical applications of polyelectrolytes, such as in controlled release systems, for the enzyme and cell support, for different types of tissue reconstitution, etc.

INTRODUCTION

The term polyelectrolyte denotes a class of macromolecular compounds, which when dissolved in a suitable polar solvent (generally water), spontaneously acquires or can be made to acquire a large number of elementary charges distributed along the macromolecular chain. In its uncharged state, a polyelectrolyte behaves like any other macromolecules, but the dissociation of even a small fraction of its ionic (side) groups leads to dramatic changes of its properties. The deviations from "normal" polymer behavior, arising from the electrostatic intra and intermolecular interactions after partial separation, or even complete dissociation of the ion pairs, are numerous.Many properties, like chain conformation, diffusion coefficients, solution viscosity, polarizability, miscibility, etc. Are drastically altered if ionic groups are introduced. In the solid state as well as in apolar solvents, the low molar mass counterions (LMMC) are strongly bound to the polymer ion group and the chain has no net charge. In aqueous solution, the ionic moieties are solvated and the LMMC become mobile, a process comparable to the dissolution of a simple low molar mass salt. Only a small fraction of the counterions can move away from the polymer into the bulk solution, however, due to the accumulation of charge in the polyelectrolyte domain. The remaining LMMC can move more or less freely but are restricted to the polymer domain by the electrostatic attraction of the polyelectrolyte.

Polyelectrolyte Complex

Polyelectrolyte or polysalt complexes are formed when macromolecules of opposite charge are allowed to interact. The interaction usually involves a polymeric acid or its salt with a polymeric base or its salt. Depending on a variety of factors, it may cause the system to separate into a dilute phase and a concentrated complex coacervate phase, or it may result in a more-or-less compact precipitate or gel. The complexes can also remain in solution.

Electrostatic interactions constitute the main attractive forces, but hydrogen bonding, ion dipole forces, and hydrophobic interactions frequently play a significant role in determining the ultimate structures. The formation, properties and applications of such polyelectrolyte complexes (PECs) have been described in a large number of books and reviews. The properties of PECs are known to be influenced not only by the chemical composition of the polymers (their molecular weight, stereochemical fitting, charge densities,etc.), but also by secondary experimental conditions like the concentrations of the polyelectrolytes prior to mixing, their mixing ratio, ionic strength of the solution, mixing order, etc.

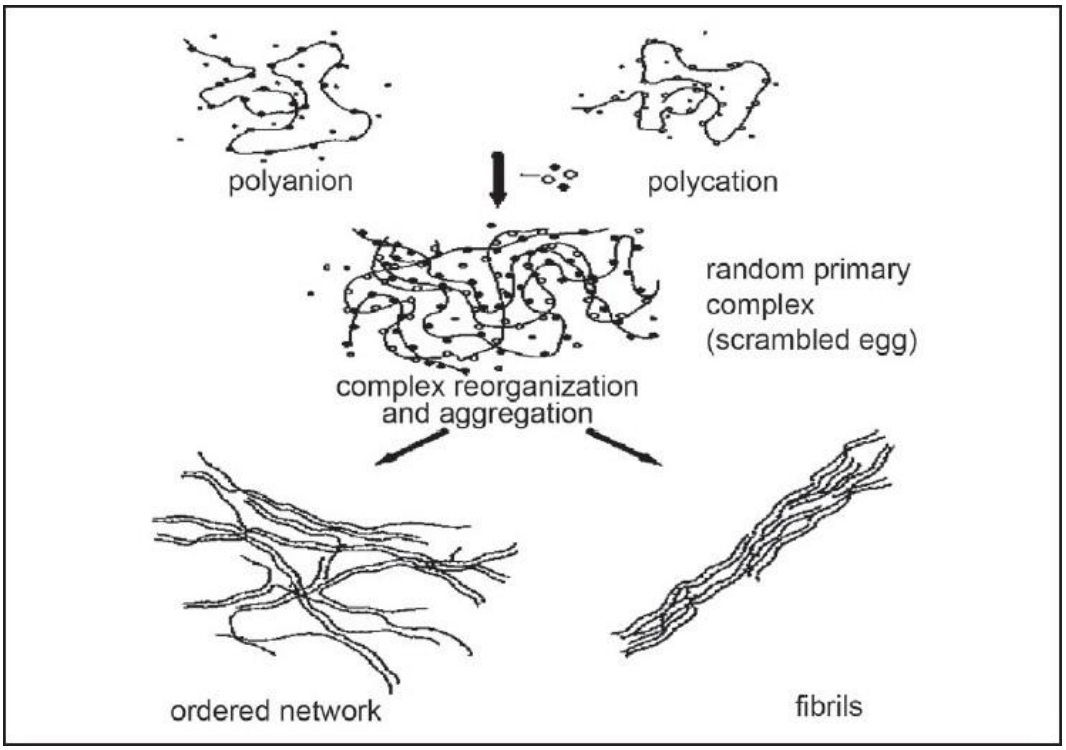

Fig.1 schematic representation of PEC formation

Polymer complexation inevitably leads to a loss of translational and conformational entropy of the polymer chain, which has to be counterbalanced if complexation is to occur. The loss in entropy (per bond formed) is largest for the first bond formed between the two polymers, but is much smaller for subsequent (neighboring) bonds. The enthalpic change (per bond) due to the interaction of the monomeric units however, is nearly constant, and it is easily understood that at a certain critical chain (or sequence) length, complexation becomes energetically favorable. The short range of these interactions (Van der Waals forces) makes a

good sterical fit between the polymers essential if complexation is to occur, leading to very high demands on the polymers' chemical structure and tacticity.

Recent Advancement in Polyelectrolyte Complex

The formation of complexes by the interaction of oppositely charged polyelectrolytes is well known. A variety of PECs can be obtained by changing the chemical structure of component polymers, such as molecular weight, flexibility, functional group structure, charge density, hydrophilicity and hydrophobicity balance, stereoregularity and compatibility, as well as reaction conditions like pH, ionic strength, concentration, mixing ratio and temperature. A great number of these compounds have been studied and characterized due to their wide variety of applications in technology, medicine and other fields. Potential field of application of PECs are as membranes for different end uses, coating on films and fibers, implants for medical use, microcapsules, beads, fibers, films, hydrogels, supports for catalysts, binding of pharmaceutical products, isolation and fractionation of proteins and isolation of nucleic acid.

Formation of polyelectrolyte complexes

The first step is realized through secondary binding sources such as Coulomb forces (very rapid). The second step involves the formation of new bonds and/ or the correction of the distortion of the polymer chain. The third step involves the aggregation of secondary complexes, mainly hydrophobic interactions.

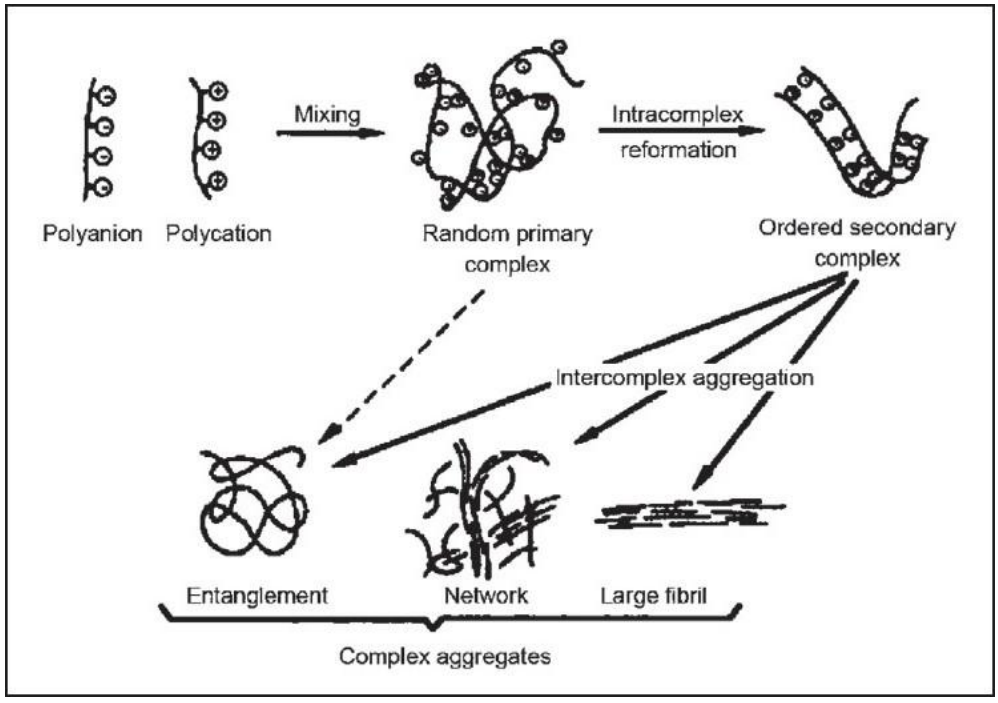

Fig.2 Aggregation of PEC

TYPES OF POLYELECTROLYTE COMPLEX

1. Polyelectrolyte complex between natural polymers

Chitosan has been used for the preparation of various polyelectrolyte complex products with natural polyanions as carboxymethyl cellulose, alginic acid, dextran sulfate, carboxymethyl

dextran, heparin, carrageenan, pectin and xanthane. Colfen et al. used for the first time analytical ultracentrifugation to study the extent of complex formation between lysozymes and a deacetylated chitosan. Hyaluronan is involved in the development of repair and disease +processes by interacting with specific binding proteins. Macromolecular interactions between negatively and positively charged proteins have been reported to enhance functional properties including foaming and aggregation phenomena or gelation. The interactions and amount of precipitation varied depending on the concentration of each protein in the mixture, the ionic strength and pH of the solution. When soya protein was mixed with sodium alginate, the two polymers interacted to form electrostatic complexes. These interactions improved the solubility and emulsifying activity.

2. Polyelectrolyte complex between a natural and a synthetic polymer

Formation of polymeric complexes of protein with synthetic polyelectrolytes is of interest to stimulate theintermolecular interactions during the formation of biological systems and evidenced by phase separation as a complex coacervate or a solid precipitate. This is observed for potassium poly (vinyl alcohol sulfate) and carboxyhemoglobin in the presence of poly (dimethyldialylammonium chloride), lysozymes and poly (acrylic acid), lysozymes and poly (methacrylic acid), RNA polymerase and poly (ethyleneimine), poly (dimethyldiallylammonium chloride) and bovine serum albumin.

The interaction between proteins and synthetic polyelectrolytes was investigated using turbidity and quasielastic light-scattering techniques. With the latter method, Park et al. have been studying the interaction between strong polycation, poly (dimethyldiallylammonium chloride), and ribonuclease, bovine serum albumin and lysozyme. The complexation of papains with potassium poly (vinyl alcohol sulfate) as a function of pH was studied using fluorescence spectroscopy. Polyelectrolyte complex formation between chitosan and polyacrylic acid has been previously reported. The composition of the complexes is a function of the initial pH of the reaction mixture. Formation of polyelectrolyte complex was investigated as a function of pH using carboxymethyl cellulose and poly (ethyleneimine). Polyelectrolyte complex between heparin and amino acetalized poly (vinyl alcohol) in aqueous media has been studied.

3. Polyelectrolyte complex between synthetic polymers

Formation of polyelectrolyte complex between synthetic polymers was performed using conductometric, potentiometric or turbidimetric titration. The characteristics of PECs between poly (sodium styrene sulfonate) and a series of synthetic polycations such as quarternized poly (4-vinyl pyridine) have been described. The preparation of three types of PECs formed between poly (vinylbenzyltrimethyl-ammonium chloride) and poly have been reported. The stoichiometry of the reactions between polycations [protonated polyethyleneimine, ionene, poly (vinylbenzyltrimethylammonium chloride)] and polyanions (sodium polyacrylate, potassium polystyrenesulfonate) has been investigated. It was found that they reacted almost stoichiometrically to give a polyelectrolyte complex.

Structure and interactions

PECs are formed by reacting two oppositely charged polyelectrolytes in an aqueous solution, as shown by infrared (IR) spectroscopy. Such a network is formed by ionic interaction as represented in fig and is characterized by a hydrophilic microenvironment with a high water content and electrical charge density. The electrostatic attraction between the cationic

amino groups of chitosan and the anionic groups of the other polyelectrolyte is the main interaction leading to the formation of the PEC. It is stronger than most secondary binding interactions, such as those, for example, allowing formation of chitosan/polyvinyl alcohol (PVA) complexes or aggregation of grafted chitosan. Moreover, additional secondary interactions such as those between crystalline domains of xylan or hydrogen and amide bonds can occur between chitosan and the additional polymer. Since chitosan has a rigid, stereoregular structure containing bulky pyranose rings, the formation of PEC can induce a conformational change of the other polyelectrolyte, if the latter has a non-rigid structure, e.g., ⟨-keratose, poly (acrylic acid), xylan or collagen. However, the influence of this change on the hydrogel or polyelectrolyte properties has not yet been studied.

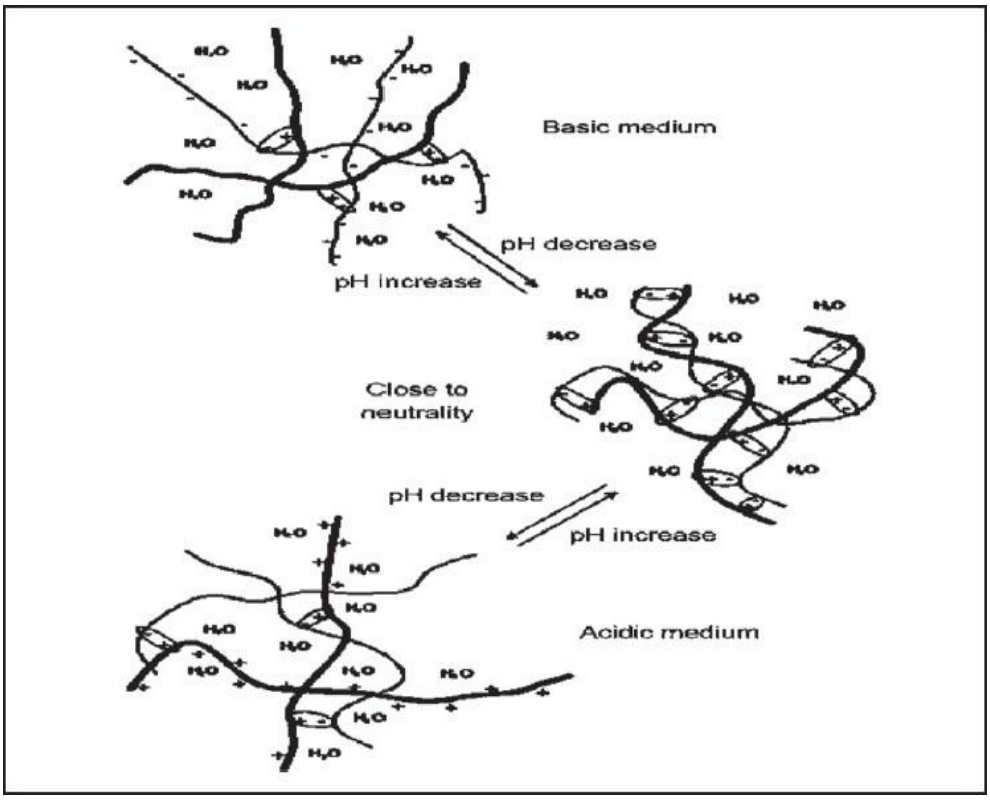

Figure 3: Structure and pH sensitive swelling of a PEC containing chitosan (– negative charge of the additional polymer; + positive charge of chitosan; oblong round indicates ionic interaction; dark continuous line for chitosan; less dark line for additional polymer)

PRINCIPLES OF FORMATION

The preparation of PEC requires, besides chitosan, only a polyanionic polymer. No auxiliary molecules such as catalysts or initiators are needed and the reaction is generally performed in aqueous solution, which represents the main advantage over covalently cross-linked networks and thus favors biocompatibility and avoids purification before administration. The most commonly used polyanions are polysaccharides bearing carboxylic groups such as alginate, pectin or xenthan. Proteins such as collagen, synthetic polymers such as polyacrylic acid (PAA) or even

DNA have also been investigated. PEC can also be formed by positively charged chitosan derivatives such as glycol-chitosan or N-dodecylated chitosan.

FACTORS INFLUENCING POLYELECTROLYTE COMPLEX FORMATION

PEC can be reinforced by additional covalent crosslinking of chitosan. This is possible with chondroitin sulfate, collagen, PAA or xylan and leads to formation of semi-interpenetrating polymer networks. However, the addition of covalent crosslinkers may decrease the biocompatibility. PEC can also be reinforced by the addition of ions inducing the formation of ionically cross-linked systems. Ca2+ can be added with alginate or pectin, Al3+ with carboxymethyl cellulose sodium salt and K+ with carrageenan. These systems are distinct from ionically crosslinked chitosan hydrogels since chitosan is not crosslinked but plays the role of the additional polymer. Nevertheless, chitosan can also be ionically crosslinked, for example, in addition to the formation of a PEC with chondroitin sulfate. Gaserod et al. concluded that in the present of Ca2+ ion, chitosan binds about 100 times more

to alginate during the formation of microcapsules. Just as cross-linking density governs the properties of crosslinked hydrogels, the properties of PEC are mainly determined by the degree of interaction between the polymers. This latter depends essentially on their global charge densities and determines their relative proportion in the PEC.

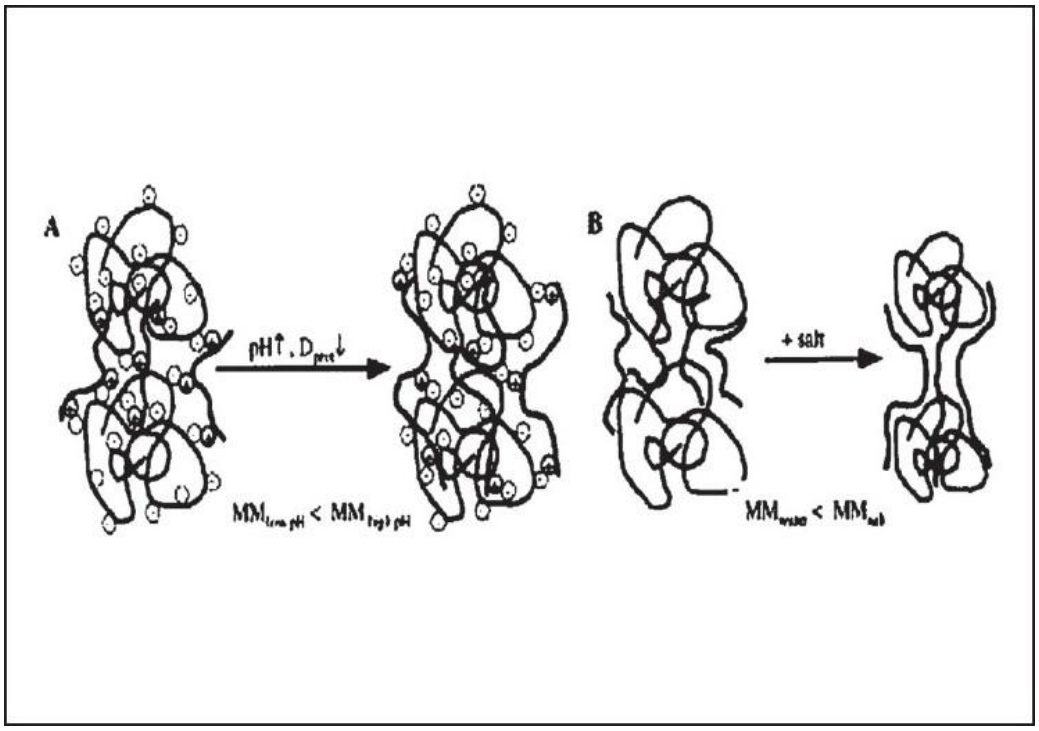

Figure 4: PECs as a function of (A) pH and (B) ionic strength

In addition, there are secondary factors related to the components that have to be considered, such as flexibility of polymers, molecular weight and degree of deacetylation of chitosan, the substitution degree of other polyelectrolyte and the nature of the solvent.

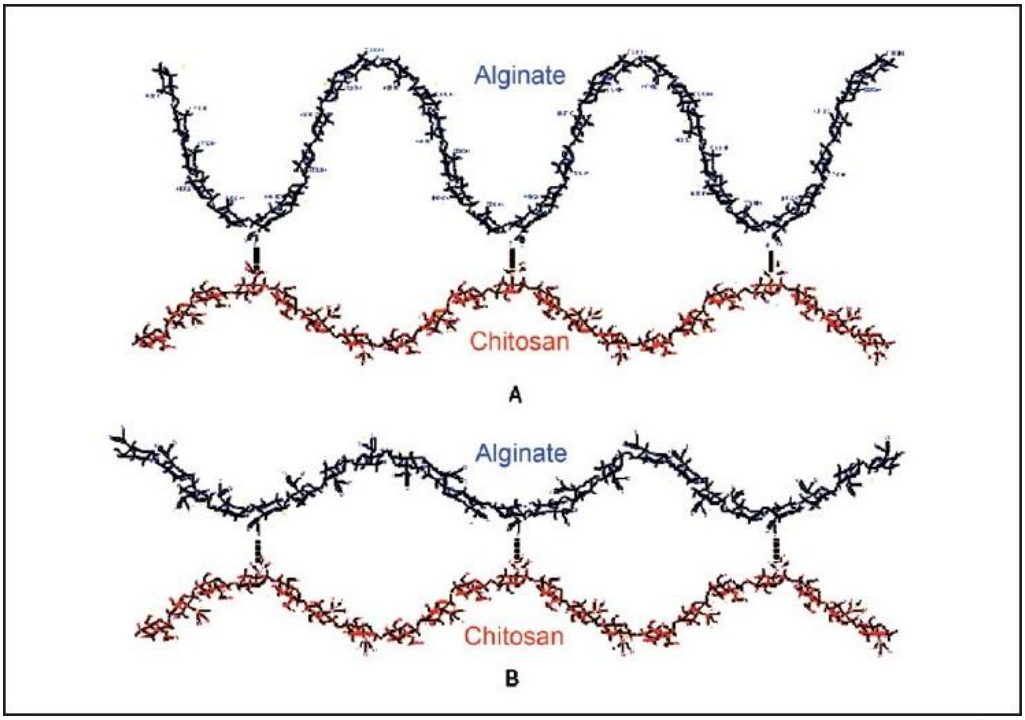

Figure 5: Schematic representation of the ionic interactions between alginate and chitosan at (a) pH 2.0 and (b) pH 6.8

Some parameters that exclusively control the properties of polyelectrolyte complex are summarized in below table

Polyelectrolyte structure	Solution properties
Molar mass	Polymer concentration
Type of charge group	Ionic strength
Charge density	pH (around the pKa)
Chain architecture	Temperature
Hydrophobicity of backbone	

Table 1: Properties of polyelectrolyte complex

Properties and applications of polyelectrolyte complexes

As PEC hydrogels are formed by ionic interactions, they exhibit pH, and to a minor extent, ion-selective swelling. In addition, they have a high water content and electrical charge density and allow the diffusion of water and/ or drug molecules. Polyelectrolytes have many applications, mostly related to modifying flow and stability properties of aqueous solutions and gels. For instance, they can be used to either stabilize colloidal suspensions, or to initiate flocculation (precipitation). They can also be used to impart a surface charge to neutral particles, enabling them to be dispersed in aqueous solution. They are thus often used as thickeners, emulsifiers, conditioners, flocculants, and even drag reducers. They are used in water treatment and for oil recovery. Many soaps, shampoos, and cosmetics incorporate polyelectrolytes. Furthermore, they are added to many foods and to concrete mixtures (superplasticizer). Some of the polyelectrolytes that appear on food labels are pectin,

carrageenan, alginates, and carboxymethyl cellulose. All but the last are of natural origin. Finally, they are used in a variety of materials, including cement. Because some of them are water-soluble, they are also investigated for biochemical and medical applications.

CONCLUSIONS

Recently, the use of natural polymers in the design of drug delivery system has received much attention due to their excellent bioavailability and biodegradability. PECs have been used in many dosage forms for the formation of stable controlled release system and also for the transplantation or tissue repairing agents. We can say that PECs will have multiple applications in future also according to its ionic interactions when combined together. Some of these applications include their use for oral drug delivery, human periodontal ligaments matrix, dermal wound healing, targeted drug release in colon, and also delivery of drugs in subcutaneous route and many more. In the pharmaceutical industries, for controlled drug delivery, PECs obtained by mixing aqueous solutions of two polymers carrying opposite charges have a very good scope in the future.

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