Review Article

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.[1] 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.[2] 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.[3-6] 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.[3,4,7]

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.[1]

The formation, properties and applications of such polyelectrolyte complexes (PECs) [Figure 1] have been described in a large number

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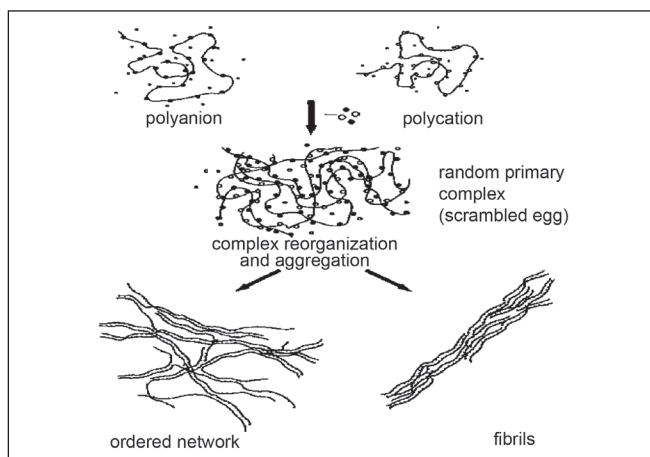Dr. Sanjay Dakhara; E-mail: sany_dankhara@yahoo.co.in

Figure 1: Schematic representation of PEC formation

of books and reviews.[8,9] 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.[9,10]

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.[11,12] 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. The complexes formed show a very high degree of ordering and crystal like properties, and have quite compact structures. These constraints probably are the main reasons for the small number of such stereocomplexes known until now.[11]

The term "scrambled egg structure" [Figure 1] is a very imaginative description of the actual morphology of the complex that is formed right after mixing of the two polyelectrolytes. In such complexes, mainly random change-compensation is found, and in most cases, this situation hardly changes once the complex has been formed.[9]

Apart from the (quasi-) soluble non-stoichiometric complexes (NPEC) mentioned below, most complexation reactions lead to the formation of gel particles. The size and composition of such particles depends mainly on the concentration, molecular weights and mixing ratio of the polyelectrolytes. While at high concentrations of the polyelectrolytes, complex formation leads to macroscopic flocculation, the growing of particles can be stopped at a colloidal level in sufficiently diluted systems ($C < 0.1$ g/ml).[9] In most cases, the particles have some surface charge as a result of an excess of either one of the polyelectrolytes. Especially, if the ratio of the polyelectrolytes is (exactly) equal to 1, the sign of the surface charge of all particles will be the same, thus stabilizing the colloidal solution. The (negative) surface charge is also believed to be responsible for the high biocompatibility of PECs and for the ion selectivity of PEC-membranes.[13]

Another important feature of PECs is their high swellability in aqueous systems. Most PECs contain well over 85% mass of solvent,[9] comparable to free polymer coils, and if their particle size is kept low, they provide excellent accessibility to bound moieties. If low molar mass salts are present, the shielding of part of the polymer-bound ions may lower the effective cross-link density of the PEC, thus allowing further swelling. Directly linked to this high swellability is the extremely good permeability for water, gasses and low molar mass electrolytes and organic molecules.[14]

A rough description of the PECs formed should include the following features:

- amorphous aggregates, held together by reversible ionic/hydrophobic cross-links with predominantly random charge-compensation within the complex;
- highly dynamic cross-links, especially when a low molar mass salt and an organic solvent are present in the solution;
- highly swollen and permeable gel particles (in aqueous solution) forming stable suspensions due to their surface charge.

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.[15]

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

Formation of PECs[15] is divided into three main classes [Figure 2].
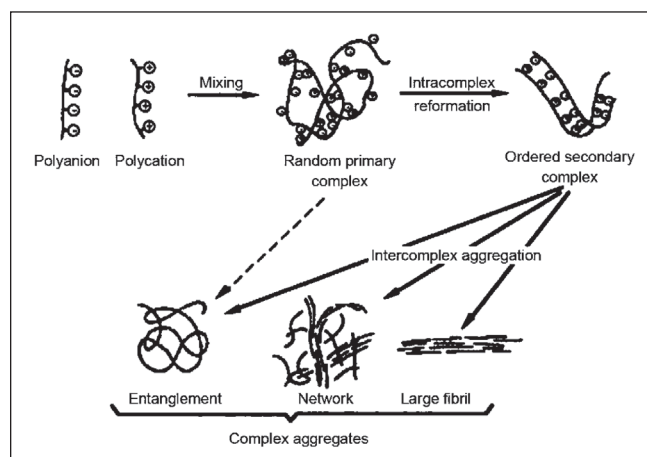- Primary complex formation

Figure 2: Aggregation of PEC

- Formation process within intracomplexes
- Intercomplex aggregation process

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.

Types of polyelectrolyte complex

The types of polyelectolyte complex[15] are discussed below.

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.

Polyelectrolyte complex between a natural and a synthetic polymer

Formation of polymeric complexes of protein with synthetic polyelectrolytes is of interest to stimulate the intermolecular 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.

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 (methacrylic acid) 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. The complex showed the sigmoid-type adsorption behavior similar to the adsorption behavior of a hydrophilic material.

Complex formation between polyions and surfactants

Polymer–surfactant complexes have proved to be very interesting because they offer intriguing similarities with biological assemblies. For ionic surfactants above the critical micelle concentration, the complexation is a consequence of the coulombic interaction of the polyion and the charged micelle.

Dubin *et al.* have studied the soluble complexes of sodium dodecyl sulfate (SDS)/triton X-100/poly (dimethyldiallylammonium chloride) by turbidimetry, viscosimetry, dynamic light scattering and ultrafiltration. Polyelectrolyte–surfactant complexes made of poly (stryenesulfonate) and different alkyltrimethylammonium derivatives have been synthesized by common precipitation in water. Redissolved in polar organic solvents, these complexes show polyelectrolyte behavior.

Protein–polyelectrolyte complexation

Proteins interact strongly with both synthetic and natural polyelectrolytes. These interactions may result in amorphous precipitates, complex coacervate, gels, fibers or the formation of soluble complexes. The practical approach of the polyelectrolyte complexation of proteins includes:
- protein separation; protein recovery,
- immobilization or stabilization of enzymes,
- modification of protein–substrate affinity and
- electrostatic interactions between proteins and nucleic acids.

The efficiency of protein precipitation depends on several variables such as (a) the number and distribution of charged sites on the protein surface, (b) the nature of the polyelectrolyte, (c) the pH of solution, (d) ionic strength and (e) polymer dosage.

The conformational changes of polypeptides associated with the formation of PECs were studied for the systems of poly (L-glutamic acid), poly (ethylene imine) and poly (L-lysine).

Polyelectrolyte complex between polymers and oppositely charged drugs

Ionic drugs form complexes with the polyelectrolytes,[16] and the

bound drug is released in exchange of ions present in the dissolution medium. Factors such as pH, viscosity of the polymer solution, ionic nature of disperse drug and ionic strength of the dissolution medium affect drug–polymer interactions. Bhise *et al*. reported that naproxen anion can interact with protonated amine group of chitosan to form naproxen–chitosan complex.

Polyelectrolyte complexes containing chitosan

PECs formed by mixing polysaccharides of opposite charge have recently attracted considerable attention because of their potential for use in drug delivery systems as well as in various biotechnological applications. Among them, chitosan is currently receiving a great deal of attention for medical and pharmaceutical applications.[17,18] Chitosan is a copolymer of β-[1→4]-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose. This linear, polycationic biopolymer is generally obtained by alkaline deacetylation of chitin, which is the main component of the exoskeleton of crustaceans such as shrimps. The main parameters influencing the characteristics of chitosan are its molecular weight and its degree of deacetylation.

Formation of chitosan hydrogels by polyelectrolyte complexation is an interesting alternative to covalently cross-linked hydrogels. PECs are generally biocompatible networks exhibiting interesting swelling characteristics.

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 Figure 3 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.[18]
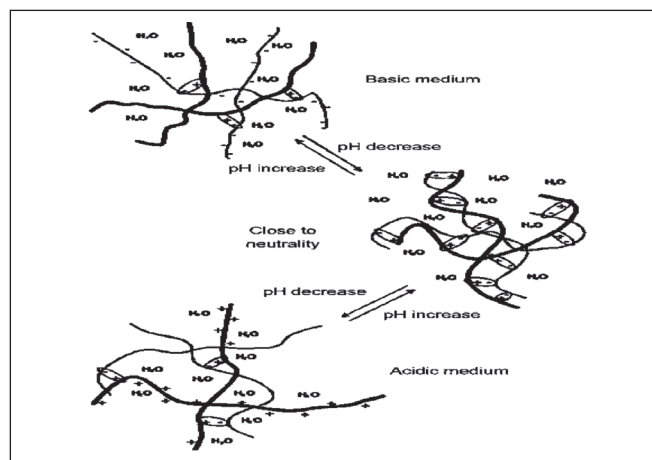

Figure 3: Structure and pH sensitive swelling of a PEC containing chitosan (– negative charge of the additional polymer; + positive charge of chitosan; oblong round indicates ionic interaction; dark continuous line for chitosan; less dark line for additional polymer)

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.

Principles of formation

The preparation of PEC requires, besides chitosan, only a polyanionic polymer.[18] 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. Polyanions that form PEC with chitosan are listed in Table 1. PEC can also be formed by positively charged chitosan derivatives such as glycol-chitosan or *N*-dodecylated chitosan.

In order to form PEC, both polymers have to be ionized and bear opposite charges. This means that the reaction can only occur at pH values in the vicinity of the pKa interval of the two polymers (the macro pKa of chitosan is about 6.5). During complexation,

Table 1: Polyelectrolytes forming PECs with chitosan[18]

Chemical class	Polyelectrolyte	Acidic group	Complex type
Polysaccharide	Acacia	—COO⁻	Precipitate
	Alginate	—COO⁻	Hydrogel, microparticle with Ca^{2+}
	Carrageenan	—OSO₃⁻	Precipitate, hydrogel with NaCl
	Chondroitin sulfate	—COO⁻ —OSO₃⁻	Hydrogel
	Carboxymethyl cellulose	—COO⁻	Precipitate, hydrogel with Al^{3+}
	Chitin derivatives bearing negative charges	—OSO₃⁻ —COO⁻ —OPO₃⁻	Hydrogel, film
	Dextran sulfate	—OSO₃⁻	Precipitate, hydrogel with NaCl
	Gellan gum	—COO⁻	Spherical droplets
	Heparin	—OSO₃⁻	Precipitate
	Hyaluronic acid	—COO⁻	Precipitate
	Pectin	—COO⁻	Hydrogel, film, microparticle with Ca^{2+}
	Xanthane gum	—COO⁻	Hydrogel
	Xylan	—COO⁻	Hydrogel, film, microparticles with additional crosslinkings
Protein	Collagen	—COO⁻	Precipitate, film
	α-Keratose	—COO⁻	Precipitate
Synthetic polymer	PAA	—COO⁻	Precipitate
	Polyphosphoric acid	—OPO₃⁻	Microparticles
	Polyphosphate	—OPO₃⁻	Microparticles
	Poly (L-lactide)	—OPO₃⁻	Porous matrices

polyelectrolytes can either coacervate, or form a more or less compact hydrogel. However, if ionic interactions are too strong, precipitation can occur, which is quite common as shown in Table 1 and hinders the formation of hydrogels. Precipitation can be avoided if electrolyte attraction is weakened by the addition of salts such as NaCl. Their presence reduces the attraction between the oppositely charged polyelectrolytes by contributing to the counter ion environment. Hence, no phase separation occurs, and a viscous and macroscopically homogeneous blend is obtained, which may gel as the temperature is lowered.

For PEC containing a synthetic polymer such as PAA, the polymerization of monomers in an aqueous solution of chitosan offers an additional means to avoid precipitation. However, the addition of auxiliary molecules may modify the biocompatibility. Furthermore, since chitosan serves as a template during polymerization, it leads to a more crystalline PEC structure, the degree of swelling of which is very different from that of PEC prepared by mixing the preformed polymers.

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. Ca^{2+} can be added with alginate or pectin, Al^{3+} with carboxymethyl cellulose sodium salt and K^+ with carrageenan. These systems are distinct from ionically cross-linked 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 Ca^{2+} ion, chitosan binds about 100 times more to alginate during the formation of microcapsules. Just as cross-linking density governs the properties of cross-linked 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. Indeed, the lower the charge density of the polymer, the higher is the polymer proportion in the PEC, since more polymeric chains are required to react with the other polymer [Figure 4].[18]

As this proportion and the chemical environment are the main factors influencing swelling, it is possible to modulate the properties of PEC by controlling the complexation reaction. The most important factor that has to be controlled is the pH of the solution, but temperature, ionic strength and order of mixing are also important.

As can be seen in Figure 5, at pH 2.0, the ionic interaction between chitosan and alginate is greatly reduced, and there is a folding of alginate with increased micropore size, which allows the greater part of the dissolution media to enter with counter ions. However, at pH 6.8, the chitosan is still protonated and forms a much stronger network with alginate with a small micropore size that restricts the entry of larger counter ions.[19]

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.

Some parameters that exclusively control the properties of polyelectrolyte complex are summarized in Table 2.

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.[20,21]

Various examples of PECs and their applications are given in Table 3.

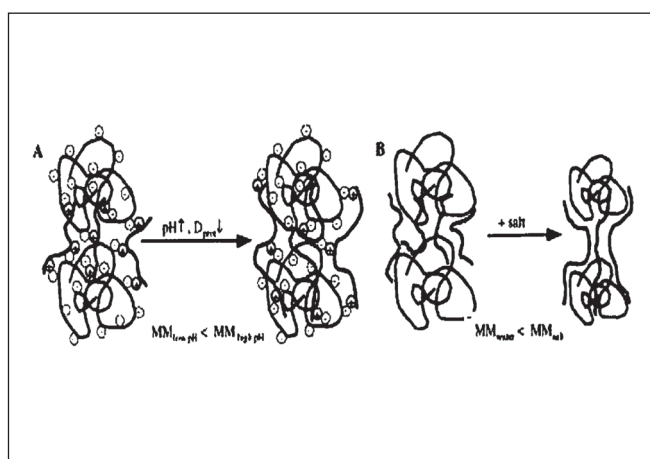| Table 2: Properties of polyelectrolyte complex[20]	
Polyelectrolyte structure	**Solution properties**
Molar mass	Polymer concentration
Type of charge group	Ionic strength
Charge density	pH (around the pKa)
Chain architecture	Temperature
Hydrophobicity of backbone	

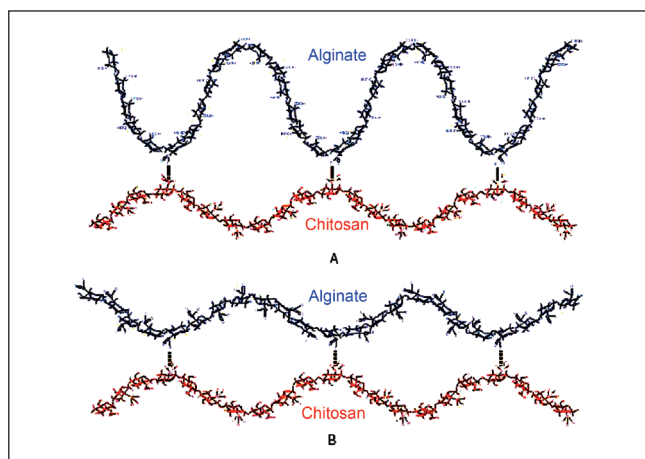**Figure 4:** PECs as a function of (A) pH and (B) ionic strength

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

Table 3: Examples of PECs containing chitosan and their applications[20]

Polyelectrolyte	Controlled release system	Enzyme and cell support	Tissue reconstruction: Bone scaffold and bandage	Various applications
Alginate	Gel microparticles for the controlled release of nicardipine HCl	Gel microparticle for cell culture or microencapsulation of biochemicals	Sponge impregnated with sulfadiazine and dehydroepiandrosterone (DHEA)	Hydrogel for the coating of seeds and food Membrane for the separation of methyl *tert*-butyl ether and methanol mixtures
Chondroitin sulfate	Hydrogels for controlled release of paracetamol or prednisolone Gel beads for the subcutaneous drug delivery of prednisolone	Hydrogel for the engineering of cartridge like tissue	Carrier gel for the transplant of autologous chondrocytes Matrix for reconstruction of skin from co-cultured human keratinocytes and fibroblasts on a dermal substrate	n.r.
Carboxymethyl cellulose	Membranes of controlled release of drugs or agricultural pesticides	Hydrogel for yeast cell immobilization in ethanol production	n.r.	n.r.
Carboxymethylated chitin	n.r.	Matrix for the culture of human periodontal ligament fibroblasts	n.r.	n.r.
Phosphated chitin	n.r.	Matrix for the culture of rat osteoblasts	n.r.	n.r.
Sulfated chitin	n.r.	Matrix for the culture of human periodontal ligaments fibroblasts	n.r.	n.r.
Dextran sulfate	Hydrogel for oral drug delivery	n.r.	Hydrogel for dermal wound healing Membrane for controlling the proliferation of vascular endothelial and smooth muscle cells	Teat dipping gel solution for lactating animals Membranes used in hemodialysis
Gellan gum	Capsule for incorporation of anionic drugs	n.r.	n.r.	n.r.
Heparin	n.r.	n.r.	Membrane for dermal wound healing	Teat dipping gel solution for lactating animals Membranes used in hemodialysis
Hyaluronic acid	n.r.	n.r.	Films or sponge for wound healing	Recovery of hyaluronic acid after its biotechnological production
Pectin	Gel particles for targeted drug release I colon	n.r.	n.r.	n.r.
Xanthane	Cream for the controlled release of vitamins, amino acids, nucleic acid or polypeptides Hydrogel for zero-order release of theophylline or isosorbite dinitrate Neomycin hydrogel for the treatment of infections in ophthalmology or gastroenterology Subcutaneous implants for the controlled delivery of drugs	Scaffold for immobilization of enzymes such as xylanase, lipase, protease and hemicellulase	Bandage formed by impregnation of woven cotton	n.r.
Collagen	Membrane for controlled drug delivery of propranolol	Skin analogue for *in vitro* toxicological tests	Wound covering for patients suffering extensive burns	n.r.
Poly (acrylic acid)	Films for the transmucosal drug delivery of triamcinolone acetonide	n.r.	Hydrogel for wound dressing	Complexes for the clarification of beverages
Polyphosphoric acid	Gel beads for the sustained release of 6-mercaptopurine in gastrointestinal tract	n.r.	n.r.	n.r.
Polyphosphate	Gel beads for controlled release of 6-mercaptopurine	n.r.	n.r.	n.r.

n.r., No available reference

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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