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A BRIEF REVIEW OF POLYELECTROLYTE COMPLEX: AN UPDATE

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Abstract

This review work gives a lot of information on polyelectrolyte complexes (PECs). These complexes used in different dosage forms for the formulation of stable aggregated macromolecules. In the current scenario, polymers as carrier have revolutionized the drug delivery system. These PECs avoid the use of different chemical agents, thus reduce the risk of toxicity. By introducing polyelectrolyte many properties like viscosity, polarizability, diffusion coefficient, chain conformation, miscibility etc., are significantly changed due to the introduction of a polyelectrolyte. The PECs influenced not only by chemical properties like molecular weight, stereochemistry, charge density, etc. Polyelectrolyte complex prolong the therapeutic action by delivering drug target sties, sustained and controlled release rate of the drug by acting as carrier. Thus, the present review focuses on polyelectrolyte complex and their method of preparation.

Keywords: *Polyelectrolyte complexes, viscosity, polarizability, diffusion coefficient, chain conformation and miscibility*

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INTRODUCTION:

In the current area, it is necessary to develop novel drug delivery system by developing the new technique for the drug delivery. This new technique of drug delivery is capable to control the drug delivery, sustain and controlled the duration of therapeutic action and then target the specific sites. The polymer is a proper tool for control the rate of drug delivery and sustains the therapeutic action of the drug. The polymeric drug delivery achieve by forming polyelectrolyte complex dispersions which is used currently. These shows some features such as biodegradable, water soluble, biocompatible, non toxic etc. which is used as alternative in place of system which uses organic phase as solvent[1].

Polyelectrolyte complexes are prepared by oppositely charged polyelectrolytes which have electrostatics interaction in aqueous solution. PECs are an ideal tool for achieving the drug as stable, more soluble, sustained and controlled release. Polyelectrolytes are the polymeric compounds that contain net positive and negative charge at neutral pH. So there are many substances considered as polyelectrolytes because they have the ionic group as positive and negative charge on their surfaces. Example such as natural polysaccharide of vegetable origin such as tragacanth, acacia, pectin and alginic acid contains carboxylic groups, which are ionized in neutral to alkaline media. Synthetic carboxylated polymer includes carbomer a copolymer of acrylic acid[2].

Polyelectrolyte denotes a class of macromolecules compounds, which when dissolved in a suitable polar solvent generally water, and can acquire large number of elementary charges distributed along the macromolecules chain. The polyelectrolyte on its uncharged state behaves like any other macromolecules, but on dissociation of polyelectrolytes even a small fraction of its ionic (side) groups leads to dramatic changes of its properties. Polyelectrolyte unlike neutral polymers is long chained molecules bearing charges on their backbone which dissociate into polyions and the associated counterions in solutions. Polyelectrolytes are also known as poly salts because it exhibit similar behavior to both the polymers (high molecular weight compounds) as well as the electrolyte (slats). They are highly conductive same as salt solutions and highly viscous similar to the polymer solutions.

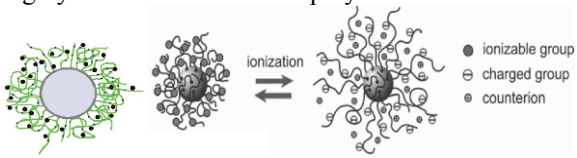

Fig.1 Spherical polyelectrolyte brush[3]

They are classified as cationic and anionic polyelectrolytes depending on whether they carry positive and negative charges. Examples of the cationic polyelectrolytes are Poly - L - lysine, Polyallylamine hydrochloride while the sodium sulfonated polystyrene, Polyacrylic acid negatively charged polyelectrolytes. The figure following the text shows the structure of these polyelectrolytes[3].

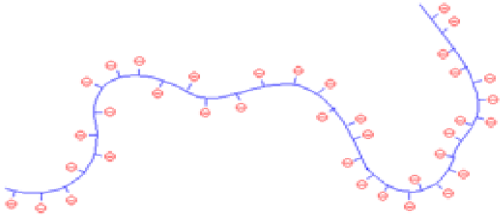

Fig. 2 Stretched polyelectrolyte chains[3]

POLYELECTROLYTE COMPLEX

Polyelectrolytes or polysalt complexes are formed by the interaction of macromolecules of opposite charges. The interaction usually involves a polymeric acid or its salt with a polymeric base or its salts. The various factors affecting these 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[4]. These complexes remain in solution. The structure is determined by hydrogen bonding, ion dipole forces, and hydrophobic interactions and the main attractive forces are electrostatic interaction

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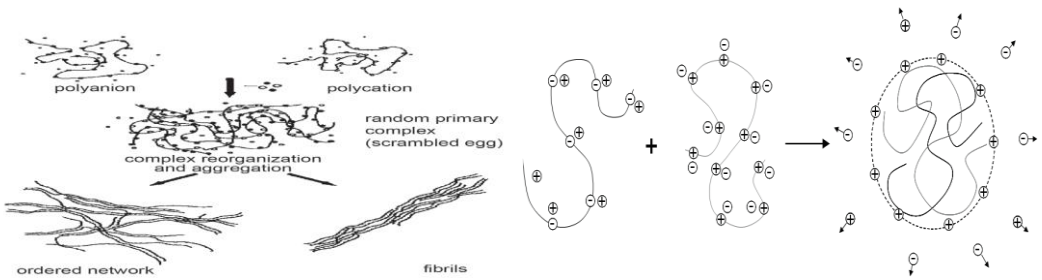

Fig 3: A. Schematic representation of PEC formation, B. Schematic diagram of the release of counterions upon polyelectrolyte complex formation[5]

Features of polyelectrolytes complexes:

- Amorphous aggregates, held together by reversible ionic/ hydrophobic cross-links with random charge reparation within the complex;
- Highly swollen and permeable gel particles in aqueous solution forming stable suspensions due to their surface charge;
- Highly dynamic cross-links, especially when a low molar mass salt and an organic solvent are present in the solution[1].

TYPES OF POLYELECTROLYTE COMPLEX ON THE BASIS OF INTERACTION

a. Polyelectrolyte complexes between natural polymer

Chitosan has been widely used for preparation of various polyelectrolyte complex products with natural polyanions as carboxymethyl cellulose, heparin, pectin, carboxymethyl dextran, carrageenan, xanthane, aliginic acid and dextrin sulfate. Colfen et al. used the first time analytical ultracentrifugation to study the extent of complex formation between lysozymes and a deacetylated chitosan. Hyaluronan involved in the development of repair and disease processes by interacting with specific binding proteins. The interaction between macromolecules of negative and positively charged proteins enhances functional properties including foaming and aggregation phenomena or gelation. It is depend upon the concentration of each protein in the mixture, pH and the ionic strength of the solution[6].

b. Polyelectrolyte complexes between natural and synthetic polymer

Formation of polymeric complexes of protein with synthetic polyelectrolytes is of concern to stimulate the intermolecular interaction for the formation of biological systems and evidenced by phase separation as a complex coacervate or a solid precipitate. It is observed in potassium poly (vinyl alcohol sulfate) and carboxyhemoglobin in the presence of poly (dimethyldialylammonium chloride), lysozymes and poly (methacrylic acid), lysozymes and poly (acrylic acid), poly (dimethyldiallylammonium chloride), RNA polymerase and poly (ethyleneimine) and bovine serum albumin[7]. Using turbidity and quasielastic light-scattering techniques the interaction between proteins and synthetic polyelectrolytes was investigated. By using the fluorescence spectroscopy the complexation of papains with potassium poly (vinyl alcohol sulfate) was studied[7].

c. Polyelectrolyte complex between synthetic polymer

Interaction between poly and a series of synthetic polycation such as quaternized poly (4-vinyl pyridine) and polyelectrolyte complex formulation between synthetic polymers was done by using potentionmetric, conductimetric and turbidimertric titration. PECs preparation of three types of was formed between poly (vinyl benzyl tri methyl ammonium chloride) and poly (methacrylic acid) has been reported. The stoichiometry of the reactions between polycations poly (vinylbenzyltrimethylammonium chloride)] [protonated polyethyleneimine, ionene, and polyanions (sodium polyacrylate, potassium polystyrenesulfonate) have been investigated. It was found that they reacted almost stoichiometrically to give a polyelectrolyte complex. This showed sigmoid-type adsorption behavior similar to the adsorption behavior of a hydrophilic material[8].

d. Complex formation between polyions and surfactants

They show intriguing similarities with biological assemblies so polymer–surfactant complexes are been very interesting. For ionic surfactants above the critical micelle concentration, the complexation is a consequence of the coulombic interaction of the polyion and the charged micelle. The soluble complexes of sodium dodecyl sulfate (SDS)/triton X-100/poly (dimethyldiallylammonium chloride) was studied 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. These complexes show polyelectrolyte behavior when redissolved in polar organic solvents[9].

e. Protein–polyelectrolyte complexation

Proteins interact strongly with both synthetic and natural polyelectrolytes. These interactions may result in complex coacervate, gels, amorphous precipitates, fibers or the formation of soluble complexes. The polyelectrolyte complexation of proteins includes:

- Immobilization or stabilization of enzymes.
- Modification of protein–substrate affinity and
- Protein separation; protein recovery.
- Electrostatic interactions between proteins and nucleic acids[10].

f. **Semisynthetic polyelectrolyte-** Chitin, Cellulose and Dextran based[11]

g. **Polyelectrolyte complex between polymers and oppositely charged drugs**
Ionic drugs form complexes with the polyelectrolytes, 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[12].

Table1. Name of some natural, synthetic and Semisynthetic polyelectrolyte [3]

Natural Polyelectrolyte	Synthetic Polyelectrolyte	Semisynthetic polyelectrolyte
Chitosan Gelatin Sodium alginate Pectin Xanthan gum Carboxymethyl cellulose	Poly(lactide) (PLA) Poly(glycolide) (PGA) Poly(lactide-co-glycolide)(PLGA) Polyethylenimine (PEI) Polycaprolactone (PCL) Poly(cynoacylates) (PCA)	Chitin Cellulose Dextran based

1. TYPES OF AQUEOUS PECS

Table2. Different types of aqueous PECs have been prepared in solution such as[6]

S.No.	Types	Characteristics
1.	Soluble PEC	Small PEC aggregate soluble in microscopically homogenous system
2.	Turbid colloidal	System with suspended PEC particles in transition range to phase separation. Shows light scattering or Tyndall effect.
3.	Two phase system	Supernatant liquid and precipitated PEC which are readily separated as solid after washing and drying.

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.

Table 3: Properties of polyelectrolyte complex[11]

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	

3.STRUCTURAL MODELS OF POLYELECTROLYTE COMPLEXES

Two structural models for polyelectrolyte complexes are discussed in literature which are ladder like structure and scrambled egg model. These models have been extensively studied and is concluded that most experimental structure lie between the two models though probably closer to the scrambled egg than the ladder type model.

The ladder like structure

The complex formation takes place on molecular level via conformation adaptation. This structure consists of hydrophilic single stranded and hydrophobic double stranded segments. These are prepared at very low concentration of PECs. It contains limited number of polyelectrolyte chains. The structure is formed by the combination of low or high molecular weight polyions with weak ionic group. They form an insufficient ion pairs. It forms microsized products[12].

The scrambled egg model

Large numbers of chains are incorporated in particle's architecture prepared by higher concentration of PECs. Contains a large number of polyelectrolyte chains. This model refers to the complexes that are product of combination of polyions with strong ionic groups and comparable molar masses yielding insoluble and highly aggregated complexes under strict 1:1 stochiometry. Formation of higher aggregated complex. So they form a insoluble PECs. They form micro and nano sized products[13].

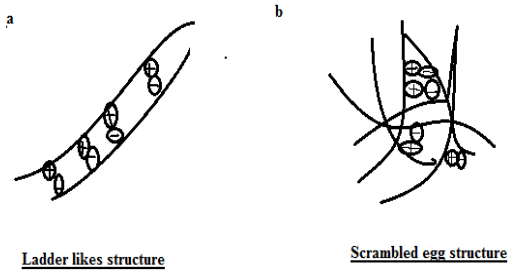

Fig. 4: Schematic Structure PECs[12]

1. ADVANTAGES OF PECS FORMATION

- Less energy required for polyelectrolyte.
- Does not require a heavy use of solvents.
- Fast process.
- Non toxic.
- Yield of product is high and drug content.
- Inexpensive, biodegradable and biocompatible process.
- During PECs formation there is no damage to any drug.
- No need of sophisticated instruments to prepare PECs[13].

2. FORMATION OF PECs

1. **Primary complex formation-** it can occur during mixing oppositely charged polyelectrolyte solutions, this reaction proceeds rapidly. It starts through secondary binding source such as Coulomb forces[14].
2. **Formation process within intra complexes-** formation of new bonds and proceeds within the order of an hour.
3. **Intercomplex aggregation process-** involves the hydrophobic interaction due to the aggregation of secondary complex[15].

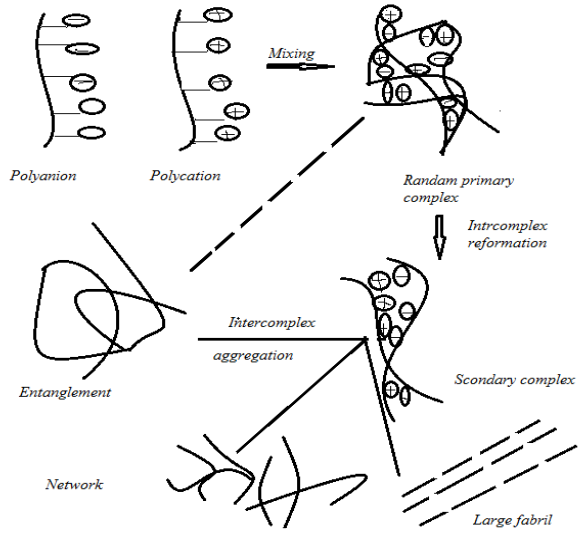

Fig 5: Representation of Formation of Polyelectrolyte Complex[15]

3. FACTORS AFFECTING POLYELECTROLYTE

PEC can be long-lasting by additional covalent cross linking of chitosan. This is possible with collagen, chondroitin sulfate, PAA or xylan and leads to formation of semi-interpenetrating polymer networks. But, 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. Al3+ with carboxymethyl cellulose sodium salt and K+ with carrageenan Ca2+ can be added with alginate or pectin. These systems are distinct from ionically cross-linked chitosan hydrogels since chitosan is not crosslinked but plays the role of the additional polymer. If Ca2+ ion, is present then chitosan binds about 100 times more to alginate during the formation of microcapsules. PEC is mainly determined by the degree of interaction between the polymers as cross-linking density governs the properties of cross-linked hydrogels[16].

The changes in chemical environment and proportion is 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, order of mixing and ionic strength is also important. 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. There are secondary factors related to the components that have to be considered, such as molecular weight, flexibility of polymers, and degree of deacetylation of chitosan, the substitution degree of other polyelectrolyte and the nature of the solvent [10].

a. Density of the charges on polyelectrolyte- The charge densities and determines their relative proportion in the PEC. In fact, 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

b. Degree of ionization of oppositely charges polyelectrolyte.

c. Polymeric chains and position of ionic group.

d. Reaction medium temperature[13]

e. Slat concentration- as the salt concentration increases the stability of polyelectrolyte decreases and decreased the number of density.

f. The ionic strength of reaction medium- neutral salts effect the complex formation due to screening of charge groups on the polyelectrolyte. Increasing ionic strength result in decreased attraction between the polyions which shows fewer tendencies to form polyelectrolyte complex. Increasing ionic strength effect on the charges, polyelectrolyte chains are screened and the polyelectrolyte becomes more flexible and coiled.

g. Different properties of polyelectrolyte such as molecular weight and concentration.

h. Duration of interaction.
i. Flexibility of polymer.
j. pH of the medium- it is affected by changing pH due to change in charge and charge density.
k. Nature of ionic group.
l. Mixing order and mixing ratio- low molecular weight polyelectrolyte required less time for mixing. As the mixing time decreased the level of PECs size decreased but after sometimes it starts increasing again. High molecular weight polyelectrolyte need more time to mix to form large size PECs. By increasing mixing ratio the colloidal stability suddenly decreases
m. Molecular Weight – Low molecular weight polymer occurs sufficiently to form stable complexes and form small size of PECs. Large molecular weight of the polyelectrolyte form large size of PECs[17].

1.METHOD OF PREPARATION OF POLYELECTROLYTE COMPLEXES

a. Jet mixing- it is currently used for the preparation of polyelectrolyte complex. It depends upon two parameters the length of time required and mixing time. It is observed that jet mixing produced smaller complexes and mixing time is allow to controlling the size of PECs. In this processes the diffusion process was important for the initial formation of pre-complexes, whereas in continuous mixing there is harm for pre-complexes for forming large aggregates. In case of formation of smaller polyelectrolyte, smaller complexes were formed due to the rapid diffusion while for larger polyelectrolyte complexes were formed especially with very shortest mixing time. Due to more collision frequency it results in the formation of larger complexes. As the pH increases in PEC solution it increased the particle size after formation of complexes, but in decreasing the pH it did not affect the PEC size[11].

b. Polyelectrolyte titration- in this method continuous stirring is required and slowly adding one polyelectrolyte (less than 1 ml/min) to another oppositely charged polyelectrolyte solution. During this process, titrant dilutes the oppositely charged polyelectrolyte because of polyelectrolyte consumed by complexation process which is the drawback of this method. It is depends upon the average charge density polyanions and the structure of the nonionic monomer at constant TAR[9].

c. Hot-melt Extrusion method- In PECs, solid state behaviour was studied by XRPD and DSC measurements knowing an amorphous one phase system. In addition molecular spectroscopy methods (FTIR and Raman) exposed ionic interactions in the melt. Ionic form of naproxen produced in the melt forming a polyelectrolyte complex. Dissolution experiments showed complex stability in aqueous media of low strengths. The amount of electrolyte to be considered in the ionic strength of dissolution medium played role in controlling drug delivery. Drug release could be immediately activated by addition of pH neutral alkali-halogen electrolytes. This method is used to create tailor-made dissolution profile typical for immediate and modified release drug.

d. Self assembly method- This process used to form multilayered formulations and involving electrostatics interactions. It includes alternating exposure of charged surface to oppositely charged polyelectrolyte solution. Each adsorption step leads to charge inversion on surface which leads to strong electrostatics force. Such self-assembled polyelectrolyte multilayers (PEMs) have utilised for incorporation of various charged compound and nano-objects. Polymer used are Poly(Allylamine hydrochloride) PAH, chitosan, sodium alginate poly (styrene sulfonate) PSS poly(dimethyldiallyllamide ammonium chloride) PDDA,etc.

e. Ionic gelation method
f. Emulsification solvent diffusion method
g. Nanoprecipitation method
h. Salting out method
i. Interfacial polycondensation method[17]

2. RECENT ADVANCEMENT IN POLYELECTROLYTE COMPLEX

PECs formed by interaction of oppositely charged polyelectrolytes are well known. By changing the chemical structure of component polymers we can form the variety of PECs such as flexibility, molecular weight, functional group structure, hydrophilicity, charge density and hydrophobicity balance, compatibility and stereo regularity as well as reaction conditions like pH, concentration, mixing ration, ionic strength and temperature. Due to wide variety of applications such as in technology, medicine and other fields these components can be studied and characterized. Significantly PECs are used as membranes for different end uses, implants for medical use, coating on films and fibers, beads, films, fibers, microcapsules, hydrogels, binding of pharmaceutical products, supports for catalyst, and isolation of nucleic acid and fractionation of proteins[18].

3. FORMATION OF POLYELECTROLYTE COMPLEXES

Formation of PECs is divided into three main classes

- Primary complex formation.
- Intercomplex aggregation process.
- Formation process within intracomplexes[19].

4. CHARACTERIZATION OF POLYELECTROLYTE COMPLEXES

Various methods have been investigated to study polymer interaction. Flow property, pH, viscosity, Measurement of turbidity, ionic strength, light scattering, nuclear magnetic resonance, infrared spectroscopy, thermal analysis and powder X-ray diffraction can be employed to evaluate polyelectrolyte complexes.

1. **Percentage yield-** it is calculated from weight of dried nanoparticles.
   % yield = [Practical mass of nanoparticles/ Theoretical mass of polymer +drug]*100
2. **Drug Loading –** Drug loading was evaluated using calorimetric method[20].
3. **Particle size analysis –** Particle size of the formulation was determined by using Optical microscopy method.
4. **Zeta Potential –** Zeta potential was measured by dynamic light scattering, measurement was done at fixed scattering angle of 90.
5. **Micromeritics and flow properties of polyelectrolyte complexes-** The particle size analysis of polyelectrolyte complexes can be done by sieve analysis using standard set of sieves of sieve number #20, #30, #40, #60, #80 and #100[21].
6. **Complexation Efficiency –** It was calculated by measuring the optical density of then supernatant layer after first centrifugation of the complex formation.
7. **Fourier Transform Infrared Spectroscopy-** It is used to characterize dynamics, surface and interfaces, polymer blends, polymer complexes, as well as chromatographic effluents and degradation products. It provides information about the complexation and interaction between the various constituents in the polymer electrolyte. It is capable of qualitative identification of the structure of unknown materials as well as the quantitative measurement of the component in a complex mixture. FT-IR spectrophotometer is done by using KBr disc method in the range of 4000-250 cm-[22].
8. **Diffraction Scanning Calorimetry-** A number of important physical changes in a polymer may be measured by DSC. These include the glass transition temperature, the crystallization temperature, the melt temperature and the degradation or decomposition temperature. Chemical changes due to polymerization reactions, degradation reactions, complexation and other reaction affecting the sample can be determined[23].
9. **X- Ray Diffraction-** The diffraction of X- rays has become a powerful tool in the study of structure of polymers. It is done by X-rays diffraction and scattering experiment which involve the placing of the sample in the path of a monochromatized X-ray beam of low divergence. The scattered X-ray from the regularly placed atoms interferes with each other, giving strong diffraction signals in particular directions. The directions of the diffracted beams are related to the slope and dimensions of the unit cell of the crystalline lattice, and the diffraction intensity depends on the deposition of the atoms within the unit cell. The powder X-ray diffraction patterns of both physical mixture and complexes can be recorded using automated Siemens D/5000. The samples are irradiated with monochromatized Cu Kα radiation between two angles. The time, voltage and current are set up as per depending on case to case[24].
10. **Scanning Electron Microscopy (SEM)-** To find the particle size and surface morphology of sample by using SEM technique.
11. **Dissolution Study –** Dissolution study was done by dialysis bag method to determine the drug release.
12. **Saturation Solubility Study –** The solubility of drug that of formulation are determined using the orbital flask method. The concentration of drug is determined from absorbance, through Spectrophotometric analysis.
13. **Stability Study –** The sample is placing it in environmental stability chamber[25].

CONCLUSIONS:

The polyelectrolyte complex are for increasing the penetration rate, Recently, the use of natural polymers in the design of drug delivery system has received much attention due their excellent bioavailability. The drug having limited penetration rate than we made the polyelectrolyte complex (PECs) to increase the drug penetration rate and increasing the bioavailability by using different grades of polymer. Due to excellent bioavailability and biodegradability, the natural polymers used in the design of drug delivery system have received much attention recently. PECs have been used in many dosage forms for the formation of stable controlled release system. When combined together PECs will

have multiple applications in future according to its ionic interactions. Some of these applications include human periodontal ligaments matrix, their use for oral drug delivery, dermal wound healing, targeted drug release in colon, and also delivery of drugs in subcutaneous route and many more. A wide research is going on in the area of polyelectrolyte and polyelectrolyte Complexes. There is more prospective in utilizing these PECs in Pharmaceutical technology, Biotechnology, Ecology and Medicine. The polyelectrolyte complexes have great capability in the designing of novel drug delivery systems.

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