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Review on Polyelectrolyte Complex as Novel Approach for Drug Delivery System



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Shailesh L. Patwekar^{1*}, Ashwini P. Potulwar¹, Snehal R. Pedewad¹, Manoj S. Gaikwad¹, Shaz. A Khan², Arvind B Suryawanshi²

School of Pharmacy, Swami Ramanand Teerth Marathwada University Nanded Maharashtra – 431606 India.

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ABSTRACT

In the current knowledge, polymers as carrier have revolutionized the drug delivery system. A more successful approach to an achievement of the different properties of polymers in an occupied system is the complexation of polymers and to form polyelectrolyte complex. Their complexes avoid the use of chemical agents, thereby reducing the risk of toxicity. The complex formed is generally used in different dosage forms for the formulation of stable aggregated macromolecules. There are two types of PECs structure ladder like structure and scrambled egg model. There are number of factors that affect the formation and stability of PEC. Polyelectrolyte complexes are classified on the basis of type of macromolecules and interaction forces involved in complex formation. Polyelectrolyte complex has an emerging system to deliver drug to target sites, sustained and controlled release rate of the drug by acting as carriers and thereby prolonging the therapeutic action. Hence, the present review focuses entirely on polyelectrolyte complex and their a method of preparation.

INTRODUCTION

In the current area, it is necessary to develop the new technique for the drug delivery which is the novel drug delivery system. The new techniques of drug delivery which are capable to control the drug delivery, sustain the duration of therapeutic action and the target the specific site. From these above characteristics of drug delivery techniques show the revolution in pharmaceutical field.¹ Recent two decades use of polymer has given more attention as a material for biomedical application and drug delivery. The biopharmaceutical characteristics of polymer should be well-documented biocompatibility and low toxicity.²

The polymer is a proper tool for the control the rate of drug delivery and sustain the therapeutic action of the drug.³ Due to the different physicochemical properties of the polymer its served as coating material, film forming agent, drug carrier, granulating agent, tableting excipients (as binder, disintegrant, filler) & solubilising agents.⁴ Polymer system undergo the phase transition in response to external stimuli such as temperature, electric potential, PH, ionic strength because of their scientific and technological importance.⁵ The polymeric drug delivery achieve by polyelectrolyte complex dispersion which is currently available systems. These systems have some features such as water soluble, biodegradable, biocompatible, non toxic etc. which is alternative system to those system uses the organic phase as solvent. Complexes are prepared by oppositely charged polyelectrolyte which have electrostatics interaction in aqueous solution. Polyelectrolyte complexes (PECs) are an ideal tool for achieving the drug more soluble, stable, controlled and sustained release.⁶ The various methods of preparation complex are discussed. There are more use of PECs in biomedical application. It also necessary to overview the PECs in pharmaceutical field to prepare the dosage form in properly. Therefore this review focuses on the polyelectrolyte complex and their method of preparation.

POLYELECTROLYTE

Polymer compounds that contain net positive and negative charge at neutral pH called as polyelectrolyte. There are many substances consider as polyelectrolyte because they have the ionic group consisting positive or negative charge on their surfaces. For example natural polysaccharide of vegetable origin such as acacia, tragacanth, alginic acid and pectin contain the carboxylic groups, which are ionised in neutral to alkaline media. Synthetic carboxylated polymer includes Carbomer a copolymer of acrylic acid.⁷ Polyelectrolyte complex classified on

the basis of origin, composition, molecular structure, and electrochemistry. Based upon origin it is classified as

Natural Polyelectrolyte ⁸	Synthetic Polyelectrolyte ⁹	Semisynthetic polyelectrolyte ¹⁰
Chitosan	Poly(lactide) (PLA)	Chitin Cellulose Dextran based
Gelatin	Poly(glycolide) (PGA)	
Sodium alginate	Poly(lactide-co-glycolide) PLGA	
Pectin	Polyethylenimine (PEI)	
Xanthan gum	Polycaprolactone (PCL)	
Carboxymethyl cellulose	Poly(cynoacylates) (PCA)	

POLYELECTROLYTE COMPLEX

The electrostatic interaction between two or more opposite charged polyelectrolyte in solution form complex are called as polyelectrolyte complexes.^{11,12} It involves interaction between the polymer-polymer, polymer-drug, polymer-drug-polymer.¹³ And also other interactions such as Vander walls forces, hydrogen bonding and hydrophobic dipole interaction can also contribute to complexation process.¹⁴ Polyelectrolyte complex roughly divide into two types 1) First type is PECS of cationic and anionic polyelectrolyte. 2) Second type is PE-Surfs are complex of anionic polyelectrolytes and cationic surfactants vice versa.¹¹

The oppositely charged polyelectrolyte contact can take place in bulk solution or on an interface. According to this PECS prepared by mixing method and interfacial complexation method.¹⁵ The complex which is obtained from polyelectrolyte having different molar masses, mixed in non-stoichiometric ratio, where water-soluble aggregates at the molecular scale.¹² During the PECs formation complexes release the low molecular counterions that initially bound to the ionic group of polyelectrolyte, which is entropy-driven process. These counterions release at higher level of entropy process.^{16,17} PECs formation is the spontaneous process after mixing the both polycations and polyanions solution without any cross-linking agent. PECs formation takes place in less than 5ms shown by stop flow measurement. The formation and stability of PECs could be governed by some kinetic and thermodynamic factors such as the pH, ionic strength, molecular weight, charge density, temperature, mixing ratio of polyelectrolytes.¹⁵

ADVANTAGES OF PECs FORMATION

1. Less energy required.¹⁸
2. Fast process.¹⁷
3. Does not require a heavy use of solvents.¹⁹
4. Does not produce any toxic product.¹⁹
5. Produce high yield and drug content.¹⁸
6. PECs minimizing possible damage to drug during formation.⁹
7. It is inexpensive, biodegradable and biocompatible.²⁰
8. To prepare PECS, there is no need to use sophisticated instruments.¹⁹

OBJECTIVE OF PECs

1. PECs loaded dosage form enhances the sustained and controlled drug release such as nanoparticles, hydrogel, nano/microcapsule, nanosuspension, nanoemulsion.^{21,22}
2. Its potential application as both nanocarrier, surface-modifying reagent and membrane separation.^{12,15,23}
3. Used to control the stability, adhesion properties, and rheology of colloids.²⁴
4. Enhance dissolution rate and solubility increased by the formation of nanoplex.²⁵
5. To obtain the uniform particle size nanoparticles.

TYPES OF AQUEOUS PECs^{26,27,28}

Different types of aqueous PECS have been prepared in solution such as-

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

TYPES OF PECs ON THE BASIS OF INTERACTION^{29,30}

- 1) Polyelectrolyte complex between natural polyelectrolyte
- 2) Polyelectrolyte complex between synthetic polyelectrolyte
- 3) Polyelectrolyte complex between natural and synthetic polyelectrolyte
- 4) Protein – polyelectrolyte complexation

METHODS OF PREPARATION OF PECs

PECs formation have important properties is the interpolymer ionic condensation due to their extreme long-ranged interaction, accordingly phase separation occurs and the solution separate out in two immiscible liquid phases, on the basis of this theory PECs formation is nothing but aggregation of macromolecules which deserving phase separation phenomena such as precipitation, gelation, coacervation, crystallization or liquid crystallisation and self-assembly of biopolymer.²²

Methods of preparation of polyelectrolyte complexes is

- 1) Polyelectrolyte Titration
- 2) Jet Mixing
- 3) Emulsification Solvent diffusion method
- 4) Ionic gelation method
- 5) Nanoprecipitation method
- 6) Self-assembly method
- 7) Salting- out method
- 8) Interfacial polycondensation method
- 9) Hot-melt Extrusion method

1) Polyelectrolyte Titration –This method of titration involves slowly addition of one polyelectrolyte (less than 1 ml/min) to another oppositely charged polyelectrolyte solution with continuous stirring. During the titration process, titrant dilute the oppositely charged polyelectrolyte because of polyelectrolyte consumed by complexation process which is the drawback of this method. Formation of complex depends on the Titrant Addition Rate(TAR).^{31,32} Ecaterina et al, in these studies formation of some polyelectrolyte colloidal dispersions (PCDs), and there high colloidal stability, in aqueous salt free solution, was profoundly researched in the

paper as a function of polyanion structure and rate of titrant added. Preparation of PCDs are also related to the average charge density polyanion and the structure of the non-ionic monomer at constant TAR. The polyanions of lowest charge density resulting in the highest turbidity's and lowest colloidal stabilities. The higher the TAR was, the higher the storage colloidal stability.³³

2) Jet mixing- It is recently used techniques for the preparation of polyelectrolyte complex. Complex formation depends upon two parameters, mixing time and length of time required to complexation. Caroline et al, in these studies PECs was investigated using two complexation techniques such as polyelectrolyte titration and jet mixing. Comparing these techniques, it is observed that jet mixing produced smaller complexes and mixing time allowing to control the size of PEC because of vigorous mixing in the jet mixer may disrupt longer aggregates. The formation of PECs in jet mixer, the diffusion process was important for the initial formation of pre-complexes, whereas the function of the continuous mixing was to harm these pre-complexes from forming larger aggregates. The smaller PEL, smaller complexes were formed due to the rapid diffusion while for larger PEL, larger complexes were formed especially with very shortest mixing times. Higher starting concentrations of PEL resulted in larger complexes, due to their more collision frequency. It also demonstrated that increasing pH value of the PEC solutions after preparation continuously increased the particle size of the complexes, whereas decreasing the pH value did not affect PEC size. The adsorption phenomenon of PECs formed from weak polyelectrolyte was studied the result indicates that increasing the pH increased the amount of PECs adsorbed to the model surfaces, however, the quantity of PECs adsorbed to the model surface was less compared with other systems.³²

3) Hot melt extrusion method – Christoph et al in these studies PECs composed of poorly soluble acid drugs Naproxen and basic polymer polymethacrylate by hot melt extrusion makeable a tailor-made release pattern by the addition of inorganic salts. In PECs, solid state behaviour was studied by XRPD and DSC measurements knowing an amorphous one phase system. Additional analysis with 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. Drug release could be immediately activated by addition of pH neutral alkali-halogen electrolytes. The amount of electrolyte to be considered in the ionic strength of dissolution medium played role in

controlling drug delivery. This knowledge was applied to create tailor-made dissolution profiles typical for immediate and modified release.¹³

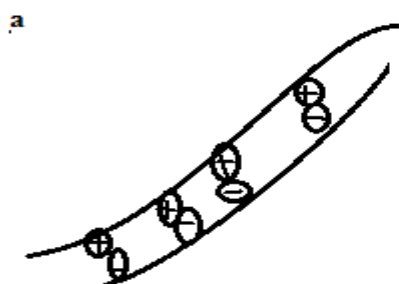
4) Self-Assembly Methods – This process involving electrostatics interactions can be used to form multilayered. Alternating exposure of charged surface to oppositely charged polyelectrolyte solution. Each adsorption step leads to charge inversion on surface which leads to strong electrostatics force. Such self-assembled polyelectrolyte multilayers (PEMs) have utilised for incorporation of various charged compound and nano-objects. Polymer used are Poly(allylamine hydrochloride) PAH, poly(dimethyldiallyllamide ammonium chloride) PDDA, chitosan, sodium alginate poly (styrene sulfonate) PSS etc. Wean Sin et al. In these studies, the dissolution rate and solubility of poorly soluble drug enhanced by developing them into stable amorphous nanoparticle complex (nanoplex). For this purpose, drug-polyelectrolyte complexation process developed which is a highly sustainable self-assembly. Ciprofloxacin and dextran sulphate as the drug and dextran sulfate as a polyelectrolyte models. The nanoplex are prepared by mixing two components in aqueous solutions one of them containing drug and another one is oppositely charged polyelectrolyte. To obtain stable nanocomplex suspension is transformed into dry powder form by freeze drying. The dissolution rate and solubility of the nanoplex are examined and compared to raw drug crystals. Spherical amorphous nanocomplex having fairly uniform sizes in the range of 200-400nm, 80% drug loading, >80% complexation efficiency and yield. The complexation efficiency is influenced by, the ratio of drug concentration to the salt concentration. The nanoplex powders show approximately twice higher dissolution rate and solubility than raw drug crystals, remain stable after one month storage. From this, it predicts that amorphous nanocomplex represent a promising bioavailability-enhanced formulation of poorly soluble drugs give their superior characteristics and ease of preparation.^{25,34}

STRUCTURE OF PECs

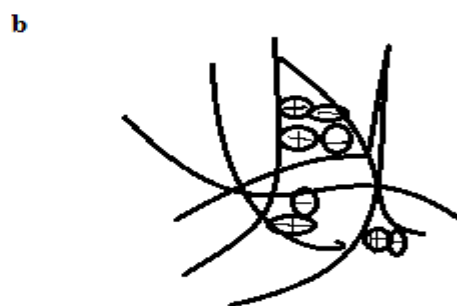
PECs structure is divided into two on the basis of characteristics such as Molecular weight, Stoichiometry, and Polyion groups. Structure as given below.^{15,20}

Sr.no.	Ladder like structure	Scrambled –egg model
1.	Prepared at very low concentration of PECs.	Prepared at higher concentration of PECs.
2.	Contain limited number polyelectrolyte chain.	Contain a large number of polyelectrolyte chain.
3.	Structure obtained by the combination of low or high molecular weight polyion with weak ionic group	Combination of comparable molar mass of polyion with strong ionic group.
4.	Molecular aggregation under certain stoichiometric conditions.	Highly aggregated complex formation.
5.	Insufficient ion pairing occurs.	Sufficient ion pairing occurs.
6.	Form initially soluble PECs after addition of HMW polyion which is insoluble.	Form Insoluble PECs.
7.	Provide Micro sized product.	Provide Micro and Nano sized product.

SCHEMATIC STRUCTURE OF PECs



Ladder likes structure



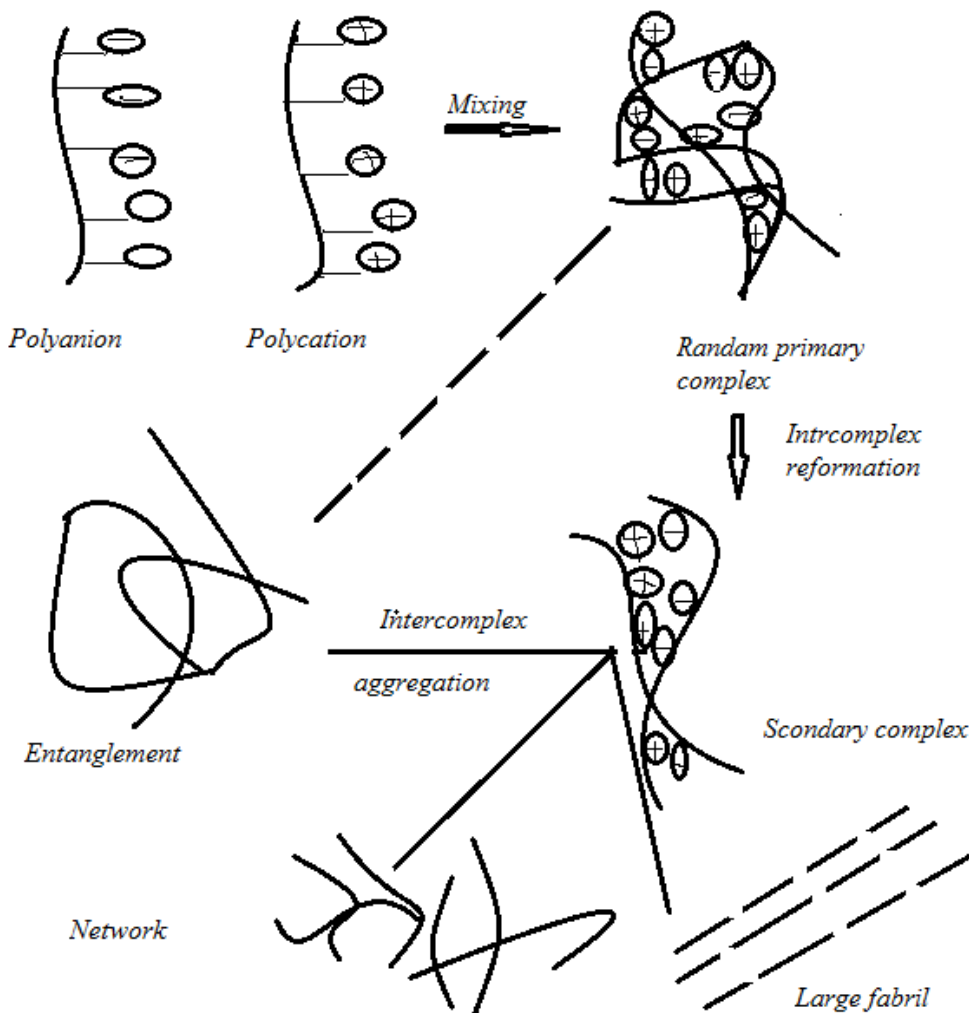
Scrambled egg structure

Schematic Structure PECs

FORMATION OF PECS^{35,36}

1. Primary complex formation- Primary complex formation occurs immediately mixing oppositely charged polyelectrolyte solutions, this reaction proceeds rapidly. It starts through secondary binding source such as Coulomb forces.
2. Formation process within intra complexes- Formation of new bonds and proceeds within the order of an hour.
3. Intercomplex aggregation process- Involve the hydrophobic interactions due to the aggregation of secondary complex.

Representation of Formation of Polyelectrolyte Complex



Representation of Formation of Polyelectrolyte Complex

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FACTORS AFFECTING PECs PREPARATION

- 1) Charge Density – The minimum charge density required for the formation of multilayers. The thickest multilayers are obtained for charge density within the threshold and the nominal 100% charge density level. If the degree of charges increases, the solubility of polyelectrolyte increase. Which influence the ability for adsorption.^{14 38}
- 2) Salt Concentration – The increasing concentration of salt reduces the stability of polyelectrolyte complex and decrease number of density. The counterion interacts with functional groups of polyelectrolyte it results in weak the complexation between polycation and polyanion. The threshold salt concentration stable-unstable depend upon which type of salt used and charge density of the polyelectrolyte.^{14 38}
- 3) pH - PECs formation is the pH sensitive process. Complexation yield vary with changing the pH. Because of changing charge and charge density.³⁷
- 4) Ionic Strength – Neutral salt effect the complexation process due to the screening of charge groups on the polyelectrolyte. Increasing ionic strength resulted in decreased attraction between the polyions, less tendency to form polyelectrolyte complex. Increasing ionic strength effect on the charges, polyelectrolyte chains are screened and the polyelectrolyte becomes more flexible and coiled.³⁷
- 5) Molecular Weight – Low molecular weight polymer occurs sufficiently to form stable complexes. Low molecular weight of the polyelectrolyte form small size of PECs. Large molecular weight of the polyelectrolyte form large size of PECs.³²
- 6) Mixing Ratio- Low molecular weight polyelectrolyte required shorter time to mix subsequently form small size PECs. At certain level PECs size decreased with decreasing mixing time after which it started 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.^{32,38}

CHARACTERISATION OF PECs^{19,39}

- 1) Complexation Efficiency – It was calculated by measuring the optical density of the supernatant layer after first centrifugation of the complex formation.
- 2) Percentage Yield – Percentage yield was calculated from weight of dried nanoparticles.
$$\% \text{ yield} = [\text{Practical mass of nanoparticles} / \text{Theoretical mass of polymer + drug}] * 100$$

- 3) Drug Loading – Drug loading was evaluated using calorimetric method.
- 4) Particle size analysis – Particle size of the formulation was determined by using Optical microscopy method.
- 5) Zeta Potential – Zeta potential was measured by dynamic light scattering, measurement was done at fixed scattering angle of 90.
- 6) Differential Scanning Calorimetry (DSC)- The thermal behaviour of sample was studied by Thermograms obtained by DSC.
- 7) X-ray Diffraction – X-ray powder diffractometry to obtain diffraction pattern by using powder to predict the change of drug crystallinity.
- 8) Scanning Electron Microscopy (SEM)- To find the particle size and surface morphology of sample by using SEM technique.
- 9) Dissolution Study – Dissolution study was done by dialysis bag method to determine the drug release.
- 10) 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.
- 11) Stability Study – The sample is placing it in environmental stability chamber.

APPLICATION OF POLYELECTROLYTE COMPLEXES ^{20,40}

- PECs applied in gene delivery, microencapsulation of various cell and tissue types.
- PECs functionalisation as therapeutic, targeting, or imaging agent.
- Oral delivery of protein by using interpolymer polyelectrolyte complexation.
- Use of interpolymer complexes for modifying the membrane.
- Used in delivery of protein and peptide drug.
- Enhancement of solubility and dissolution rate.

CONCLUSION

The future of polymeric drug and gene delivery lies in developing multi-component drug delivery. An extensive research is going on in the area of polyelectrolyte and polyelectrolyte complexes. There is more potential in utilizing these PECs in Biotechnology, Pharmaceutical

technology, Ecology and Medicine. Therefore, the polyelectrolyte complexes have great capability in the design of novel drug delivery systems.

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