



INTERPOLYELECTROLYTE COMPLEXES AS PROSPECTIVE CARRIERS FOR CONTROLLED DRUG DELIVERY

Kaur Jasmeet*, Harikumar S.L., Kaur Amanpreet

Department of Pharmaceutics, Rayat and Bahra Institute of Pharmacy, Sahauran, Punjab, India

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*Email: jas.saini246@gmail.com

ABSTRACT

In the current scenario, polymers as carriers have revolutionized the drug delivery system. A more successful approach, to exploit the different properties of polymers in a solitary system is the complexation of polymers to form polyelectrolyte complexes. These complexes circumvent the use of chemical crosslinking agents, thereby reducing the risk of toxicity. The complex formed is generally applied in different dosage forms for the formulation of stable aggregated macromolecules. There are two structural models for polyelectrolyte complexes - ladder like structure and scrambled egg model. Number of factors affects the formation and stability of polyelectrolyte complex. Polyelectrolyte complexes have been classified on the basis of type of macromolecules and the interaction forces involved in complex formation. Polyelectrolyte complexes have aroused as an emerging system to deliver drug at target sites, controlling the release rate of drug by acting as carriers and thereby prolonging the therapeutic action. They can be used as coating films for binding pharmaceutical products and in preparation of microcapsules. Complexation between selected natural and synthetic polymers and the applicability of complexes as in nanoparticles, microparticles, buccal films, sponges and matrix type tablets is discussed. The present review emphasizes entirely on polyelectrolyte complexes, their classification, formation, characterization, utilization and future perspectives in concern to optimal drug delivery system.

KEYWORDS: Complexation, controlled delivery, polyelectrolyte, polyelectrolyte complex, polymer.

INTRODUCTION

The new techniques of drug delivery which makes the system capable of controlling the rate of drug delivery, sustaining the duration of therapeutic action and most focused on targeting of drugs to specific sites have aroused as revolution in pharmaceutical field, thereby, giving rise to novel drug delivery systems. Polymers have gained much importance in novel drug delivery especially those which respond in some desired way to change in pH, temperature, electric or magnetic field. For this reason they are frequently and extensively used as excipients in design and advancement of controlled and/or sustained release products. The physicochemical properties of the polymers tend them to be served as coating material, film forming agent, drug carrier, granulating agent, tableting excipients (as binder, disintegrant, filler) and solubilising agents¹. Most often polymers convert the active substance into non deleterious form which is administrable and also have specific effect on biodistribution and bioavailability of active substance. Polymer complexes which are formed due to association of repeating units on different chains or on separate region of the same chain bear properties like insolubility and macromolecular structure². The polymer complexes are categorized as stereocomplexes, interpolyelectrolyte complexes (or polyelectrolyte complexes, IPECs) and hydrogen bonded complexes.

The interaction between two oppositely charged polymers gives rise to polyelectrolyte complex³. This polyelectrolyte complex collectively is a biocompatible polymer system and is an association complex formed due to electrostatic interaction between oppositely charged polyanions (e.g. polymer-polymer, polymer-drug, and polymer-drug-polymer)⁴.

POLYELECTROLYTES

Many researchers have explored widely, the properties of polyelectrolytes. Nowadays it is rapidly growing field of

research. Polyelectrolytes are the charged polymers⁵ and their every repeating unit is capable of bearing electronic charge. The term polyelectrolyte can be more precisely defined under class of macromolecules, as the polymers that contain a net negative or positive charge at near neutral pH. Above all, the polyelectrolyte belongs either to the group of cationic or to the group of anionic polyelectrolytes depending whether the polyelectrolyte carries positive or negative charges. Mixed architectures with both negative and positive monomeric units belong therefore to the class of polyampholytes. A special case of polyampholytes is given by polybetaines (positive and negative charges on each repeating unit). Irrespective to the sign of charge it can be distinguished between two other types of polyelectrolytes: strong (quenched) or weak (annealed) polyelectrolytes. The number of nominal charges is irrespective to changes in pH for strong polyelectrolytes, whereas the number of nominal charges can be easily adjusted by pH for weak polyelectrolytes. Polymers made of monomers, which are strong acids or bases or which are the salts of strong acids or bases belong usually to the class of strong polyelectrolytes. Therefore the charged groups are fully deprotonated for anionic polyelectrolytes. Monomers, which are weak bases or acids themselves, form usually weak polyelectrolytes. The polyion's counter-ions are an integral part of the polyelectrolyte. The polymeric backbone bears charges, whereas compensation of all polymeric charges by counter-ions is required due to electroneutrality. Polyelectrolytes are ubiquitous in nature. Most of the proteins are polyampholytes, though a regular array of charges along the biopolymers is hardly found in nature. When the polyelectrolytes are dissolved in suitable polar solvent (generally water), they acquire spontaneously large number of elementary charges distributed over macromolecular chain due to the dissociation of the electronic group. Polyelectrolyte at surface and interface represents an example

of both two and three dimensional polyelectrolyte solution in which local polymer concentration is controlled by interactions between substrate and polyelectrolyte chains⁶.

POLYELECTROLYTES CLASSIFICATION

Polyelectrolytes can be classified into various types on the basis of their origin, composition and molecular architecture as depicted in Figure 1.

Some of the important polyelectrolytes are quoted below:

Natural polyelectrolytes: Nucleic Acids, Carrageenan, Alginates

Chemically modified polymers: Pectin, Chitin, Cellulose based, Dextran based

Synthetic polyelectrolytes: Poly (vinylbenzenetrialkylammonium, Poly (vinyl sulfonic acid), Poly(acrylic or methacrylic acid), Poly(styrene sulfonic acid), Poly(acrylamidoalkyl trialkyl ammonium)

POLYELECTROLYTE COMPLEX

Polyelectrolyte complexes are ionically bonded hydrogels⁷. Structurally these are neutral polymer – polymer complexes composed of macromolecules carrying charges of opposite sign causing the macromolecules to bind together by electrostatic interactions. Hydrogen bonding, ion dipole interactions and hydrophobic interactions also play significant role in formation of polyelectrolyte complex which avoid the use of covalent crosslinking agents hence reducing the possible toxicity and undesirable effects of chemical reagents. Depending on variety of factors, it may cause the system to separate into dilute phase and concentrated coacervate phase or compact precipitate like gel.

Polymer complexation leads to loss of conformational and translational entropy of polymer chain which has to be counterbalanced if complexation has to occur. The formation and stability of polyelectrolyte complex depend on many factors^{8, 9, 10, 11} such as:-

- Degree of ionization of each of oppositely charged polyelectrolyte.
- Density of the charges on polyelectrolytes.
- Position of ionic group on polymeric chain.
- Charge distribution over polymer chains.
- Temperature of the reaction medium.
- Ionic strength of the reaction medium
- Molecular weight of polyelectrolytes.
- Concentration of polyelectrolytes.
- Polymer chain flexibility.
- Duration of interaction.
- Nature of ionic groups.
- pH of the medium
- Mixing ratio.
- Mixing order.

FORMATION OF POLYELECTROLYTE COMPLEXES

Polyelectrolyte complex is formed when a polycation and a polyanion are mixed together in an aqueous solution. In general, an equimolar complex is formed by mixing oppositely charged strong polyelectrolytes. In the case of the complexation of polycations with weak polyacids, the composition and the structure of the polyelectrolyte complexes obtained depend on the degree of neutralization of the polyacid, polymer structure, hydrophobicity, the concentration of the complex, pH, ionic strength, and so on¹². Complex formation proceeds cooperatively, and the

stability constant increases with the degree of polymerization, i.e., the charge number on one chain. When a polyelectrolyte is added to the polymer complex, a cooperative interpolymer substitution occurs if the adding polymer can interact more strongly with the constituent of the complex. Auxiliary molecules such as catalysts or initiators are not required and reaction is generally performed in aqueous solution. The reaction can only occur at pH values in the vicinity of pKa interval of two polymers. The process of formation of polyelectrolyte complex involves three main steps¹³:-

Primary complex formation

Coulomb forces are responsible for this step.

Formation process within intracomplexes

It involves the formation of new bonds and/or correction of distorted polymer chains.

Intercomplex aggregation process

It involves the aggregation of secondary complexes mainly through hydrophobic interactions.

TYPES OF POLYELECTROLYTE COMPLEXES

On the basis of conjugating molecules

The different types of polyelectrolyte complexes¹⁴ on the basis of conjugating molecules are discussed in Table 1.

On the basis of interaction forces²⁰

On the basis of interaction forces polyelectrolyte complexes can be classified as depicted in Table 2.

A polyelectrolyte complex formed should have the following features:

- Amorphous aggregates held together by ionic / hydrophobic crosslinks.
- Highly dynamic crosslinks.
- Highly swollen and permeable gel particles.

STRUCTURAL MODELS OF POLYELECTROLYTE COMPLEXES

Two structural models for polyelectrolyte complexes are discussed in literatures which are ladder like structures and the scrambled egg model²⁴. These models have been extensively studied and it was concluded that most experimental structures 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 conformational adaptation. This structure consists of hydrophilic single stranded and hydrophobic double stranded segments.

The Scrambled egg model

In this, large numbers of chains are incorporated in particle's architecture. 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 stoichiometry.

Incorporation Of Active Substance Into The Polyelectrolyte Complex

Polyelectrolyte complex have gained much importance in past few years because of their potential applications. The active substance can be incorporated in polyelectrolyte complexes by four ways²⁵ quoted below:

In first case, active substance will be entrapped from solution during precipitation of complex; in second case, active substance will absorb from solution and get incorporated in already formed complex on contact; in third case, active substance may chemically bond to at least one complex

partner and precipitate during complexation; and in last case, active substance may act as polyion and form polyelectrolyte complex and active substance will be released either by solution equilibrium or by ion exchange mechanism or by charge interaction and slow decomplexation.

CHARACTERIZATION OF POLYELECTROLYTE COMPLEXES

Various methods have been investigated to study polymer interaction. Measurement of turbidity, ionic strength²⁶, pH, viscosity²⁷ flow properties, light scattering, infrared spectroscopy, nuclear magnetic resonance, thermal analysis and powder X-ray diffraction can be employed to evaluate polyelectrolyte complexes.

Micrometric and flow properties of polyelectrolyte complexes

The particle size analysis of polyelectrolyte complex can be done by sieve analysis using standard set of sieves of sieve numbers #20, #30, #40, #60, #80 and #100. Amount retained on sieve is determined and static angle of repose is measured as per fixed funnel and free standing cone method. Compressibility on tapping can be measured using graduated measuring cylinder.

Fourier Transform Infrared Spectroscopy

Fourier Transform Infrared (FTIR) spectroscopy can be used to characterize polymer blends, polymer complexes, dynamics, surfaces, and interfaces, as well as chromatographic effluents and degradation products. It provides information about the complexation and interactions between the various constituents in the polymer electrolyte²⁸. It is capable of qualitative identification of the structure of unknown materials as well as the quantitative measurement of the components in a complex mixture. FT-IR spectra of physical mixture and as well as polyelectrolyte complex can be determined by FT-IR spectrophotometer using KBr disc method in the range of 4000- 250 cm⁻¹.

X-Ray Diffraction

The diffraction of X rays has become a powerful tool in the study of structure of polymers. X-ray diffraction and scattering experiments involve placing the sample in the path of a monochromatized X-ray beam of low divergence. The scattered X-rays from the regularly placed atoms interfere 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 disposition of the atoms within the unit cell. The powder X-ray diffraction patterns of both physical mixture and complex can be recorded using automated Siemens D/5000. The samples are irradiated with monochromatized Cu K α radiation between two angles. The time, voltage and current are set up as per depending on case to case.

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) measures the heat required to maintain the same temperature in the sample versus an appropriate reference material in a furnace. 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 reactions affecting the sample can be determined.

Thermogravimetric analysis

Thermogravimetric analysis provides a quantitative measurement of any mass change in the polymer or material associated with a transition or thermal degradation. TGA can directly record the change in mass due to complex formation, dehydration, decomposition, or oxidation of a polymer with time and temperature. Thermogravimetric curves are characteristic for a given polymer or complex of polymers because of the unique sequence of the physicochemical reaction that occurs over specific temperature ranges and heating rates and are a function of the molecular structure. The changes in mass are a result of the rupture and/or formation of various chemical and physical bonds at elevated temperatures that lead to the evolution of volatile products or the formation of heavier reaction products.

Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy is a most effective and significant method for observing the structure and dynamics of polymer complexes both in solution and in the solid state. Undoubtedly the widest application of NMR spectroscopy is in the field of structure determination. The identification of certain atoms or groups in a molecule as well as their position relative to each other can be obtained by one-, two-, and three-dimensional NMR²⁹.

Light Scattering

Light scattering from solution of polyelectrolyte complexes allows the determination of the molecular parameters (molecular weight, dimensions, and shapes) of the scattering particles and thermodynamic quantities (virial coefficients, chemical potential, preferential adsorption coefficients, and excess free energies of mixing).

APPLICATIONS

Polyelectrolyte complex has aroused as an emerging way to deliver drug at target sites, controlling the rate of release of drug by acting as carriers and thereby prolonging the therapeutic action. Along with these main functions, these can be used as membranes³⁰, films and fibers coatings³¹, for isolation and fractionation of protein, for isolation of nucleic acids, for binding pharmaceutical products and for preparation of microcapsules.

Extensive research has been done to form various polyelectrolyte complex using different polymers. Examples are quoted in Table 3 representing investigated polyelectrolyte complexes and their contribution towards controlled drug delivery.

CONCLUSION

A wide-ranging research is going on in the area of polyelectrolytes and polyelectrolyte complexes. Polyelectrolyte complexes are capable of merging the unique properties of different polymer without losing their high stability and biocompatibility. We can say that polyelectrolyte complexes will have multiple applications in future in the field biotechnology, medicine, pharmaceutical technology and in the design of novel drug delivery system.

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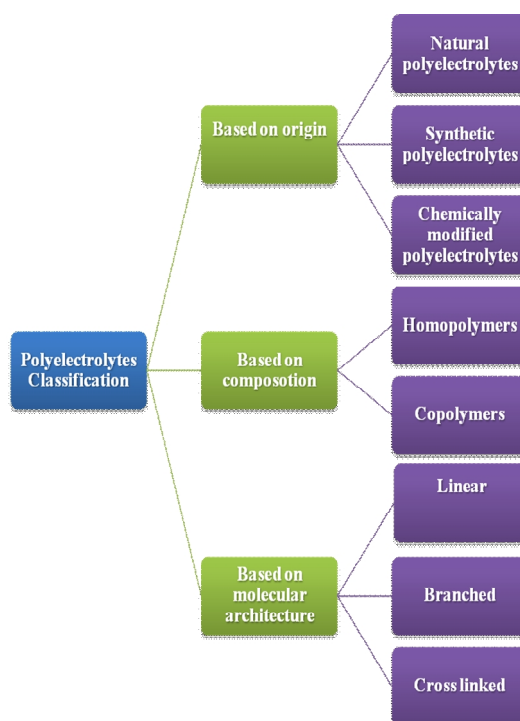


Figure 1: Classification of Polyelectrolytes.

Table 1 Types of Polyelectrolyte Complexes based on Conjugating Molecules

TYPES	DESCRIPTION	EXAMPLE
Polyelectrolyte complex between Natural polymers	Macromolecular interactions between negatively and positively charged groups of the polyelectrolytes occur which enhance functional properties as foaming and aggregation or gelation.	Chitosan- Alginate polyelectrolyte complex fibres exhibited promising results for controlling the release of charged molecules and showed higher encapsulation efficiency ¹⁵
Polyelectrolyte complex between natural and synthetic polymers	Formation of polymeric complexes between natural and synthetic polyelectrolytes occurs through intermolecular interactions and is evidenced by phase separation as a complex coacervate or a solid precipitate.	Gelatin- Sodium Carboxymethyl Cellulose polyelectrolyte complex microparticles for Controlled Delivery of Isoniazid ¹⁶ .
Polyelectrolyte complex between synthetic polymers	This type of complex shows sigmoid type adsorption behavior.	Polyelectrolyte complexes formed between poly (vinylbenzyltrimethyl -ammonium chloride) and poly (methacrylic acid) ¹⁷ .
Complex formation between surfactants and polyions	This type of complex offer similarities with biological assemblies.	The interactions of conventional cationic, i.e. dodecyl , tetradecyl, and hexadecyl trimethylammonium bromides and dimeric cationic surfactants, i.e. dimethylene bis decyl-(10-2-10), and dodecyl dimethylammonium bromides (12-2-12) with anionic polyelectrolytes, were studied by fluorescence measurements ¹⁸ .
Protein polyelectrolyte complexation	Interaction between polyelectrolytes and proteins result in formation of amorphous precipitates, complex coacervates, gels, fibres or of soluble complexes.	Interaction between bovine serum albumin and poly (diallyl dimethylammonium chloride) poly (acrylamidomethylpropyl sulfonate), poly (methacrylamidopropyltrimethylammonium chloride) and an acrylamide random copolymer ¹⁹ .

Table 2 Types of polyelectrolyte complexes based on interacting molecules

TYPE	DESCRIPTION	EXAMPLE
Water Soluble Polyelectrolyte complex	Combination of polyions with significantly different molecular weight and weak ionic groups in a mixture of non stoichiometric proportions under certain salt conditions results in water soluble polyelectrolyte complexes.	Complex formation between oppositely charged polysaccharides when brought into contact in aqueous solution ²¹ .
Colloidally stable polyelectrolyte complexes	Aggregated and flocculated system is achieved when polyelectrolyte complex is formed between strong electrolytes.	Colloidal Complexes from Poly (vinyl amine) and Carboxymethyl Cellulose Mixtures ²² .
Coacervates	The coacervate is liquid like, mobile and reversible structure which is formed when the mutual binding of opposite polyelectrolyte is of moderate strength as a result of low charge density.	Complex between cationic polyacrylamide and Kraft lignin ²³ .

Table 3 Applications of polyelectrolyte complexes

Polymers employed in Polyelectrolyte Complex	Drug employed	Applications	References
Gelatin-Sodium carboxy methyl cellulose	Isoniazid	Microparticles formed	16
Cationic Guar Gum- Xanthan Gum	Domperidone	Bioadhesive Films with enhanced Bioavailability.	32
Methyl cellulose-Carboxy vinyl polymer	Phenacitin Insulin	Controlled release Solid Dispersions Excipient in matrix	33
Chitosan- Polycarbophil	-	System for controlled release.	34
Carbopol-Chitosan	Theophylline	Controlled release tablet	35
Chitosan-Carboxymethyl tamarind kernel powder	Budenoside	Colon Delivery	36
Gum kondagogu- Chitosan	Diclofenac	Controlled Delivery	37
Chitosan-Pectin	Carvedilol	Bioadhesive Drug Delivery	38
Poly(vinyl pyrrolidone)- Poly (acrylic acid)	Ketoprofen	Transmucosal drug delivery	39