Review Article

Polyelectrolyte Complexes: Based Drug Delivery Devices.

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ABSTRACT

Polyelectrolyte Complexes (PECs) are the association complexes formed due to the electrostatic interactions between oppositely charged particles. It is formed between cationic(Chitosan) polymers and oppositely charged anionic polymers. It forms amorphous aggregates, held together by reversible ionic/hydrophobic cross-links with predominantly random charge-compensation within the complex. The PECs particle sizes and surface charge can be maintained by varying the concentration of the polymers. IR spectroscopy, NMR, thermal analysis, pKa and X-ray diffraction, are used to evaluate the inter polymer complexation. Based on the structures, PECs can be categorized into different subtypes: soluble, colloidal stable and coacervate complexes. PECs can be used as membranes for coating on films and fibers, for isolation and fractionation of proteins, for isolation of nucleic acid, for binding pharmaceutical products, as supports for catalyst and for preparation of microcapsules for drug delivery. This paper gives a concise review of PECs formation and its application in the drug delivery technology. PECs can be used for the both the deliveries of immediate release (Phenytoin sodium) and as well as in controlled release (Propranolol HCL). PECs can be able to modify the release, improve the stability and character of the drug substances. Hence there is a great prospective in utilizing these PECs in biotechnology and Pharmaceutical technology.

Keywords: Complexation, drug delivery devices, macromolecules, polyelectrolyte complexes, polymers.

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INTRODUCTION

Polyelectrolyte complexes (PECs) are the association complexes formed between oppositely charged particles (e.g. polymer-polymer, polymer-drug and polymer-drug-polymer). These are formed due to electrostatic interaction between oppositely charged polyions [1]. 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 [2]. 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 [3]. 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 [2].

Polymer complexation 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 [6,7]. The short range of these interactions (Vander 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 [6].

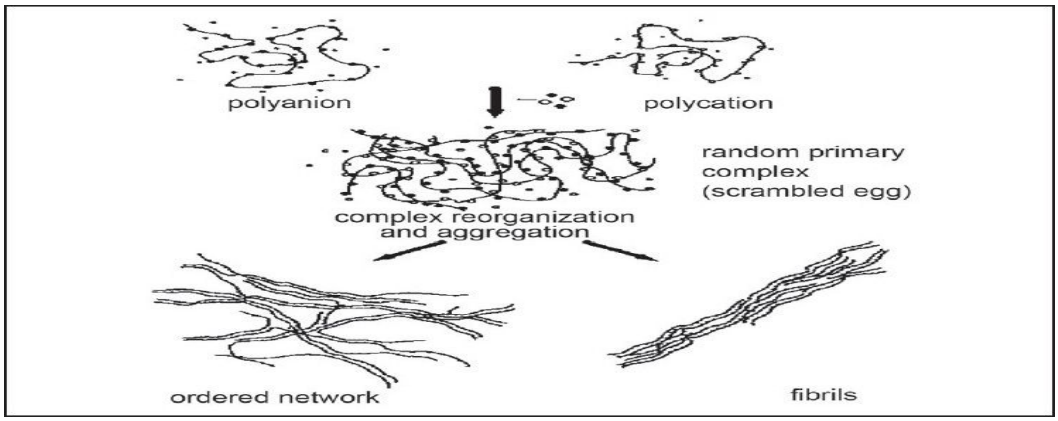

Figure 1: Schematic Representation of Formation of PECs.

The term "scrambled egg structure" is an imaginative description of the complex that is formed after mixing of the two polymers, it is shown in fig1. In such complexes, mainly random change-compensation is found, mostly this situation changes once the complex has been formed [4]. A part from the (quasi-) soluble non-stoichiometric complex (NPEC), 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) [4]. 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 responsible for the high biocompatibility of PECs and for the ion selectivity of PEC-membranes [8]. Another important feature of PECs is their high swellability in aqueous systems. Most PECs contain well over 85% mass of solvent, comparable to free polymer coils, and if their particle size is kept low, they provide excellent accessibility to bound moieties [4]. 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 [9].

FORMATION OF POLYELECTROLYTE COMPLEXES

Formation Complexion involves 3 steps: [10]

1. Primary complex formation: Secondary binding forces like Coulomb forces are responsible.

2. Formation process within intracomplexes: It involves the formation of new bonds and/or correction of the distortion of the polymer chain.

3. Intercomplex aggregation process: It involves aggregation of secondary complexes mainly by hydrophobic interactions.

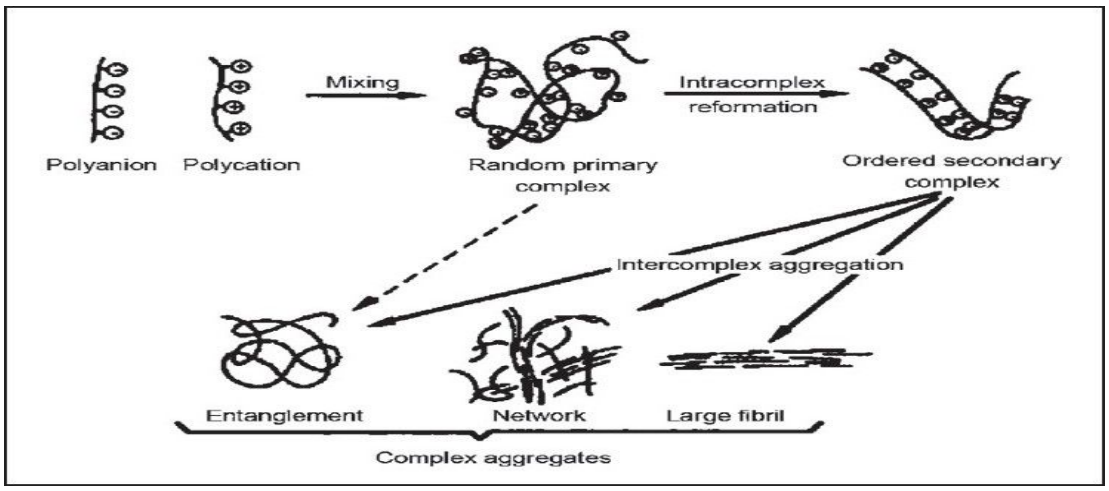

Figure 2: Formation of Polyelectrolyte Complex.

The active components will be encapsulated in the polymer matrix at molecular level.

The active substances can be incorporated in to PECs by four ways [12].

- The active substance can be entrapped from the solution during precipitation of the complex, as shown in the fig 2.
- The active substance can be absorbed from the solution and gets incorporated into the already formed complex on contact.
- The active substance may be chemically bound to at least one complex partner and precipitates during complexation.
- In the last case the active compound itself may act as polyion and form PEC as shown in figure 3.
- The active substance from these PECs will be released either by solution equilibration or by ion exchange mechanism or by charge interaction and slow decomplexation as well as breakdown and dissolution of the complex.

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.

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, hydrophilic and hydrophobic balance, stereo regularity and compatibility, as well as reaction conditions like pH, ionic strength, concentration, mixing ratio and temperature [11].

Factors affecting the formation of PECs:

Formation of PECs is influenced by many factors .The formation of PECs is influenced not only by chemical properties like stereochemical fitting, their molecular weight, charge densities, ion site etc, but also by secondary experimental conditions like concentration of polyelectrolytes prior to mixing, their mixing ratio, pH, ionic strength of the solution, mixing order, solvents and temperature etc[4,5]. Changing the ionic strength by addition of salt can modulate the electrostatic interactions in a polyelectrolyte solution [13].

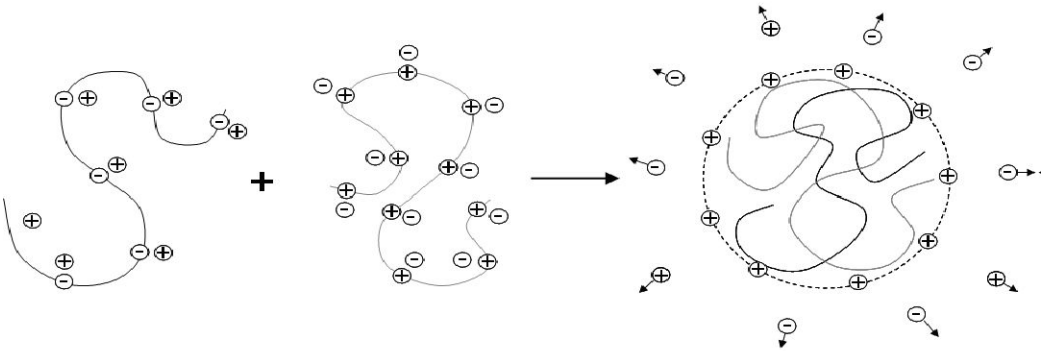

Figure 3: Representation of release of counter ions upon PECs.

Table 1: Properties of PECs based on Polymer Solution.

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

The electrostatic interactions can be weakened by the addition of inorganic salts into the solutions as shown in (**Table1**). Thus, an increase of the ionic strength of the solution depresses the complexation between polyions, because of the screening of opposite charges of the macromolecules by low molecular weight ions. By varying the pH environment during PEC formation, the degree of ionization of weak polyelectrolyte's can be controlled [14,15]. This was found to affect multilayer properties such as layer thickness, the degree of interpenetration between layers, surface wettability and number of unbound functional groups. Therefore, by choosing the right pH conditions, a platform may be found with properties that are advantageous for loading charged small molecules into the film via electrostatic interactions.

pH and conductivity study

Polyions possess certain charge when they are present in the aqueous solution. Oppositely charged polyions form an insoluble PEC in the aqueous medium. There is a possible change in the charge that may occur when the PECs interact and form complexes. These interactions and the formation of PECs can be well judged by pH and conductivity studies.

Influence of salt on PEC structure

After the changes in ionic strength; swelling or deswelling of the PECs occurs immediately, whereas coagulation is a much slower process, dependant on the concentrations of the colloidal particles [58]. Two major effects on the formation of PEC in the presence of salt were found [59]. First, the presence of a very small amount of salt during formation gave a dramatic decrease in level of aggregation, probably due to the less stiff and more coiled structure component. Other studies have shown that the valence (uni- or divalent) of the salt and even the specific ions involved (e.g., K+, Na+, or Li+) seem to be important for the interaction between the polyelectrolyte's [60,61].

Effect of polymers mixing ratio

The polymers mixing ratio influences the polyelectrolyte complex yield due to the interaction of the two polymers.

Effect of pH

Polyelectrolyte complexation is a pH sensitive process. At the pH values where the charges are not balanced, a reduction in the interaction between the polymers causes a reduction in the PEC yield.

Effect of ionic strength

Neutral salts influence the complexation process due to the screening of the charge

groups on the poly electrolytes. Increasing ionic strength results in decreased attraction between the polyions and the tendency to form polyelectrolyte complex.

Theoretical aspects of PECs

Many researchers extensively investigated the properties of the polyelectrolyte and the formation of PECs [14-17]. There have been theories proposed based on the electrostatic forces and Flory-Huggins mixing free energies of the polyelectrolytes to explain the mechanism of formation of PECs [18,19]. In general the backbones of the two polymers are not compatible and repel to each other, however, the charge fraction of the polymers determines the type of interaction going to occur between the polymers. When the charge fraction is low, the polymer backbone repulsion (Flory interaction parameter) is dominant and the solution separates in to two phases each containing mostly one of the polymers. At high charge fraction, the attractive electrostatic interactions between the polymers dominate and they precipitate to form a complex. In an intermediate range of charge fraction, the equilibrium state can be a meso phase where the two polymers only separate microscopically. Depending on the stoichiometry of the mixture (the relative concentrations, the relative chain lengths and charge densities), one observes mainly two types of complex formations, a macroscopic phase separation between the solvent and the polymers or a partial aggregation of the polymer chains [20].

Characterization of PECs

The interaction between polymers can be investigated by various methods [21]. Methods like light–scattering infrared spectroscopy (using KBr discs), NMR, thermal analysis, pKa and X-ray powder diffraction are used to evaluate the interpolymer complexation. [22-24].The different structures of a PEC can be categorized into different subtypes. Three types, soluble are colloidally stable and coacervate complexes, and the type of complex formed is governed by pH, salt, and polymer concentration, and is characterized using turbidimetric or light scattering techniques [54].

Water-soluble PECs Under certain salt conditions, combinations of polyions with significantly different molecular weights and weak ionic groups in a mixture of non-stoichiometric proportions result in water-soluble PECs (a longer host chain with several small guest chains)[55]. The complex adopts a conformation similar to that of the ladder model, with hydrophilic single-stranded segments and hydrophobic double-stranded segments [56]. The presence of a small amount of salt enables rearrangements, which in turn allow the complex to reconfirm to a structure closer to its thermodynamic equilibrium. At slightly higher salt concentrations, a shrinking of the PECs, due to the shielding of polyelectrolyte charges caused by the electrolytes, occurs. A further increase in salt concentration leads to completely complexed, precipitating species; eventually, the precipitates dissolve again and both components exist as free polyelectrolyte's in solution [55-57].

Colloidally stable PECs

PEC formation between strong polyelectrolytes results in highly aggregated or macroscopic flocculated systems [57]. In extremely dilute solutions, the aggregation can be stopped at a colloidal level (with diameters of 10–100nm), and a polydisperse system of nearly spherical particles is usually achieved.

Coacervates

A coacervate is formed when the mutual binding of opposite polyelectrolytes is of moderate strength as a result of low charge density. The coacervate is a liquid-like, mobile, and reversible structure [62]. The formation of such complexes, for example, from cationic polyacrylamide (CPAM) and sulphonated Kraft lignin, has been investigated, and it was found that the molecular weight of the CPAM was a very important factor for coacervate formation, since a shorter chain can more easily adopt a coiled structure, which will precipitate [63].

Applications of Drug Delivery Devices with PECs:

PECs have gained much attention in the past few years because of their potential applications. These can be used as membranes[25-28], for coating on films, fibers for isolation and fractionation of

proteins [29,30] for isolation of nucleic acid [31-33] for binding pharmaceutical products as supports for catalyst [34,35] and for preparation of microcapsules for drug delivery [36-37].

Kawashima *et al.* reported a novel method for the preparation of theophylline granules coated with a PEC of sodium tripolyphosphate and chitosan [37]. The prepared granules containing sodium tripolyphosphate were stirred in an HCL solution of chitosan. During the mixing, the dissolved sodium tripolyphosphate in the granules moved to the surface and reacted with the chitosan, resulting in the formation of a PEC film. The drug-release pattern of the coated granules was of zero-order kinetics and the release rate was significantly reduced compared to that of the original granules.

Shiraishi *et al.* studied the controlled drug release behaviour of indomethacin by chitosan-PEC [38]. They also optimized the formulation conditions and reported its *in-vivo/in-vitro* evaluation studies. PEC of indomethacin prepared by using complexation of sodium tripolyphosphate and chitosan. Here the effects of the molecular weights of chitosan hydrolysates on the release and absorption rates of indomethacin from gel beads were examined. The release rates of drug decreased with increasing of molecular weight.

Jimenez-Kairuz *et al.* produced and characterized swellable drug-polyelectrolyte matrices (SDPM) using carbomer and different basic drugs like atenelol, lidocaine and metoclopramide [39]. The drugs can be loaded in a high proportion on to the polymer and therefore the resulting SDPM material could be diluted with other polymers to modulate delivery properties of SDPM. Matrices of atenolol and lidocaine exhibited vigorous delivery properties with regard to change in proportion of loading drug.

Tapia *et al.* evaluated the possibility of using mixtures of PECs from both chitosan (CS)-alginate and (CS) carrageenan as prolonged release systems [40]. Different dissolution profiles for diltiazem clorhydrate were obtained by changing the polymer matrix system and the method used to include these polymers into the formulation (physical mixture or PEC). Drug dissolution profiles from the matrices have been discussed by considering the swelling behavior of the polymers used. It was reported that CS-alginate systems were considered to be better in prolonging the release, when compared to CS-carrageenan systems.

Liao *et al.* developed drug-loaded chitosan-alginate fibers by interfacial polyelectrolyte complexation technique [41]. Depending on the component properties, the release time of encapsulated components from these fibers could range from hours to weeks. Dexamethasone was completely released within 2 h, whereas charged compounds such as bovine serum albumin, PDGF-bb, and avidin showed sustained release for 3 w.

Paloma *et al.* prepared polyionic complexes of CS and poly (acrylic acid) (PAA) in a wide range of copolymer composition and with two kinds of drugs (amoxicillin trihydrate and amoxicillin sodium) [42]. Release from the different complexes was also studied. The swelling behavior of and solute transport in swellable hydrogels were investigated to check the effect of polymer/polymer and polymer/drugs interactions. The electrostatic polymer/polymer interactions took place between the cationic groups from CS and the anionic ones from PAA. The diffusion of amoxicillin trihydrate was controlled only by the swelling/eroding ratio of the polyionic complexes. The swelling degree of amoxicillin sodium hydrogels was more extensive when compared to the swelling degree of amoxicillin trihydrate formulations. From the studies it was known that the water uptake was mainly governed by the degree of ionization. Restriction of amoxicillin sodium diffusion could be achieved by polymer/ionized-drug interaction that retards the drug release.

Petzold *et al.* prepared different PECs from poly(diallyl-dimethyl-mmoniumchloride) and two different polyanions and characterized their application as flocculants [50]. The results showed that the most important advantages of PEC were the high velocity of sedimentation and a

very broad range of the optimum flocculation concentration

Win *et al.* developed PEC gel beads based on phosphorylated chitosan (PCS) for controlled release of ibuprofen in oral administration [44]. The PCS gel beads were prepared from soluble phosphorylated chitosan by using an ionotropic gelation with counter polyanion, tripolyphosphate (TPP) at pH 4. Surface morphology studies for the prepared beads were done by using SEM. The percentage release of ibuprofen from PCS gel beads was found to be increased as the pH of the dissolution medium increased. The release rate of ibuprofen at pH 7.4 was higher than the release rate at pH 1.4 due to the ionization of phosphate group and higher solubility of ibuprofen at pH 7.4 medium. The ability of the prepared copolymer to be used as drug carrier for colon-specific drug delivery system was estimated using ketoprofen as model drug.

Rolfes *et al.* reported a method of making a solid interpolymer complex for use as a controlled release matrix for oral administration [45]. It involved mixing of two oppositely charged polymers and spray-dried to evaporate the solvent and to prepare solid particles of interpolymer complex. An active agent such as drug can be preferably embedded or encapsulated in the interpolymer complex before spray drying or may be incorporated by suitable means at a later stage.

Mi *et al.* used the enzyme hydrolyzed CS to prepare CS tripolyphosphate and CS polyphosphoric acid gel beads using a polyelectrolyte complexation method for the sustained release of anticancer agent, 6-mercaptopurine[46].

Nandini and Cherng-Ju prepared drug PECs with poly (acrylamido-2-methyl-1-propansulfonate sodium-co-methyl-methacrylate [47]. They studied and reported that the release kinetics were strongly dependent on the drug solubility rather than on the type of amine in the drug. The release of drugs from the tablets of drug-poly(acrylamide-2-methyl-1-propane sulfonate sodium-co-methyl methacrylate complex were well described by the dissociation/erosion mechanism.

Albeno *et al.* obtained a patent for preparation of stable water insoluble complexes of poorly soluble compounds molecularly dispersed in water insoluble ionic polymers[48]. The compounds were micro precipitated in the ionic polymers in amorphous form. The complexes according to the present invention significantly increased the bioavailability of poorly soluble therapeutically active compounds.

Sabar MH *et al.* studied variables affecting the formulation of Ketoprofen sustained release oral tablet using Polyelectrolyte complex as a matrix former [43]. It was found that as the strength of the PEC was increased, the release rate of Ketoprofen was found to be increased.

Stefania R*et al.* worked on the preparation and characterization of a new type of microparticles based on the complexes between chitosan(CH) and two poly(carboxybetaines) (PCB), in view of their use in medical fields as potential drug carriers.they found that the drug retention capacities were larger in the case of microparticles based on CH-PCB complexes than those based on chitosan[50].

Taira Y *et al.* concluded by their findings that a low molecular weight chitosan (MW 38kDa) is an effective inhibitor for oxidative stress in various LMW chitosans (MW 10-100kDa) [51]. It was found that the low molecular weight Chitosan-Theophylline anhydrous tablet was a safe and non-toxic extended release tablet with high antioxidant activity.

Sanem AS *et al.* studied the effect of complexation conditions on xanthan – chitosan polyelectrolyte complex gels [52]. For developing hydrogels with desired mechanical and controlled release properties the characterization of the factors contributing to the cross-linking density of xanthan-chitosan network were important. The results obtained from Swelling degree (SD) and Differential Scanning Colorimetry (DSC) showed that the cross-linking density of xanthan-chitosan network was dependent on the complexation conditions. There was complete cross-linking of the hydrogel capsules at all the conditions, when the initial xanthan solution concentration was at 1.5 % (w/v). The increase in the xanthan

concentration affected the degree of swelling of the hydrogel at two different chitosan concentrations. The effect of chitosan solution pH on the degree of swelling is more pronounced at 0.7% (w/v) than at 1.0% (w/v) chitosan concentration. The conformational changes of chitosan polymer chains, which are dependent on the solution pH, were critical in determining the crosslinked network structure which affects the SDs of the gels. It was concluded that pH and concentration effects on the xanthan-chitosan network properties are depended on each other, which can be modulated by changing operationally controllable parameters, especially xanthan concentration and chitosan solution pH.

Rishabha M *et al.* worked on the preparation, characterization and evaluation of chitosan- gum arabic Coacervates as excipients in Fast dissolving/ disintegrating dosage form.[53] The study revealed that the presence and interaction of two different polymer solutions may lead to formation of a characteristic composite which can enhance the release of drug from the dosage form. They proved that formulating fast disintegrating tablets using Chitosan–gum arabic coacervates can give a dosage form that can be used for the treatment of chronic disorders at the initial stage of chronic attack.

Baloglu E *et al.* evaluated the performance of swellable polymers (chitosan and carrageenan) in the form of layered matrix tablets to provide controlled therapeutic effect of Metaprolol tartrate for twice daily administration[64]. They found that the carrageenan three layered matrix tablet formulation is an effective and promising drug delivery system for twice daily administration of Metaprolol tartrate.

Ala F. Eftaiha *et al.* formulated Metronidazole with chitosan and xanthan gum hydrophilic polymers has proven to be a well representative example of a sustained release solid dosage form preparation [65]. The formulation was found to attain prolonged *in vitro* drug release, strong bioadhesivity, when tested on a sheep duodenum, and a high *in vivo* bioavailability thus it was found to be superior in all aspects of *in vitro-in vivo* analysis.

There are a number of pharmaceutical applications of polyelectrolytes, such as in controlled release systems are listed in table 2, for the enzyme and cell support, for different types of tissue reconstitution etc.

Table 2: List of API formulated along with PECs.

API	Cationic	Anionic	Formulation	References
Metaprolol tartrate	chitosan	carrageenan	CR	64
Phenytoin sodium	chitosan	Gum arabic	FDT	54
Glipizide	chitosan	Xanthan gum	SR	69
Phenytoin sodium	chitosan	Sodium alginate	FDT	53
Ketoprofen	chitosan	Carbopol- 940	SR	50
Diltiazem HCL	chitosan	Gum ghatti	SR	68
Diltiazem HCL	chitosan	Sodium alginate Sodium CMC Carbopol 940	Hydrogel	67
Metronidazole	chitosan	Xanthan gum	SR	65
Propronolol HCL	chitosan	Xanthan gum	CR	66

CR: Controlled release, SR: Sustained release, FDT: Fast disintegrating Tablets.

CONCLUSION

A broad research is going on, in the area of polyelectrolyte complexes (PECs). Most of the PECs are formed with cationic Chitosan (natural polymer) i.e. with ionic polymers. There is a great prospective in utilizing these PECs in biotechnology and Pharmaceutical technology. PECs have multiple applications according to the ionic interactions, when the polymers are combined. It is used for sustaining and controlling the release of drug and also for fast disintegrating dosage forms. By their capacity to entrap the drug at molecular level, PECs can be able to modify the release, improve the stability and character of the drug substances, which ensures their great potential in designing novel drug delivery devices.

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