Spotlight on Polyelectrolyte Complexes and Their Medical Application in Drug Delivery

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Abstract:

Polyelectrolyte complexes (PECs) are class of macromolecule compound formed by electrostatic interaction of oppositely charged polymers. The main objective of this review is to show the formation mechanism of PECs and their characterization, factors affecting their formation, their pharmaceutical application in drug delivery system with some of the dosage form that utilize PEC technique in their formulation, also this review talks about the most common polymers used in the preparation of PECs.

Key words: chitosan, polyelectrolyte complex, PEC application, drug delivery system, sodium alginate.

تسليط الضوء على مركبات المعقدات المتعددة الشحنات وتطبيقاتها الطبية في توصيل الادوية.

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الخلاصة:

تعتبر المعقدات المتعددة الشحنات نوع من انواع مركبات الجزيئات الكبيرة والتي تتكون نتيجة الحث الكهربائي بين البوليمرات او الجزيئات ذات الشحنات المتعاكسة. تهدف هذه المراجعة الى استعراض ميكانيكية تكوين هذه المعقدات وتشخيصها، بالإضافة الى العوامل المؤثرة في تكوينها وتطبيقاتها الصيدلانية في انظمة التوصيل الدوائي مع امثلة لبعض لأشكال الدوائية التي تستخدم هذه التقنية في صناعتها او تحضيرها. كما تتحدث هذه المراجعة عن أكثر المواد البوليمرية المستخدمة في تحضير هذه المعقدات.

الكلمات المفتاحية: الكيتوسان, معقد متعدد الشحنات، تطبيقات المعقدات، نظام توصيل دوائي، الجينات الصوديوم.

1. Introduction

The combination of solutions of polymers (in an ionizing solvent such as water) with opposing charges causes spontaneous association by establishing electrostatic connections ,which result in the formation of polyelectrolyte complex (PEC) [(1)]. PEC considered as macromolecule structure with repeating unit [(2)]. A polyelectrolyte complex is often formed when a polyanion reacts (such as xanthan gum) with polycations (such as chitosan) [(3)], as shown in figure (1).

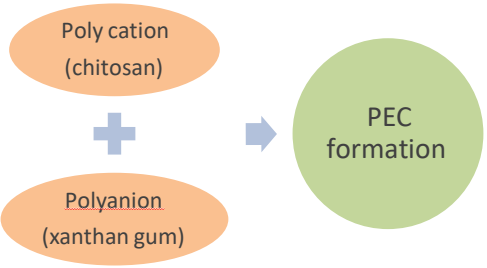

Figure (1): Polyelectrolyte complex (PEC) formation.

PEC is created in three steps: the creation of primary complexes, secondary complexes, and intercomplex aggregation[4]. Due to its inherent biocompatibility, biodegradability, and capacity to enhance the bioavailability of the active constituent, PEC have attracted interest recently in the field of drug administration. Polyelectrolyte complexes (PECs) are hydrogels that exhibit a high degree of similarity to biological tissue, hence ensuring their safety when used in vivo [5, 6]. Maximum electrostatic contacts in PEC would result in a tighter structure and improved network stability, both of which would result in less swelling and slow drug release. Reduced swelling and increased crosslinking density also minimize burst release, lowering the potential of dosage dumping that may be dangerous to patients[7].

2. Method of preparation PEC and characterization

The general preparation method for the fabrication of PECs follows the below steps [8]:

A- Preparation of polyelectrolyte solution: The two oppositely charged polyelectrolytes are dispersed in asuitable solvent (usually deionized water) at various concentrations and in defined ratios, so as to obtained the solutions of both polyelectrolytes with required molar concentrations. A polysalt (like sodium chloride) can be added to obtain required ionic strength. Finally, pH is adjusted to a desired value. All prepared solutions are filtered through membrane filter before use.

B- PEC formation: The PECs are generally prepared at room temperature using either polycation or polyanion as the starting solution. The complex formation process, in general, can be conducted using either the slow addition of polyanionic solution dropwise at a predetermined flow rate to polycationic solution of same ionic strength or the rapid one-shot addition of one polyelectrolyte solution to oppositely charged polyelectrolyte solution of similar ionic strength under a constant speed stirring .

C- Particle refinement: Particle refinement is done by centrifugation process and is necessary in order to avoid physisorption of free polymers onto the surface of already formed PECs. The final product is either re-suspended in a minimum volume of deionized water for immediate characterization or is lyophilized for better stability

It was suggested that the driving force of complex formation is mainly the gain in entropy due to the liberation of the low molecular counter ions. However, other interactions such as hydrogen bonding or hydrophobic ones may play an additional part [9] . According to the figure 2, the steps involved in the production of PECs may be split into three categories [8].

1- Primary complex: Due to the binding pressures, the primary complex can form right away after combining the

two oppositely charged PE solutions. This procedure moves quickly.

2- Intracomplexes: After mixing, this intermediate complex typically takes 1-2 hours to develop. New electrostatic bonds may develop during this process, and/or the polymeric chains may change.

3- Intercomplex/aggregation: Aggregation of intermediate complexes occurs during this phase, mostly as a result of hydrophobic interactions.

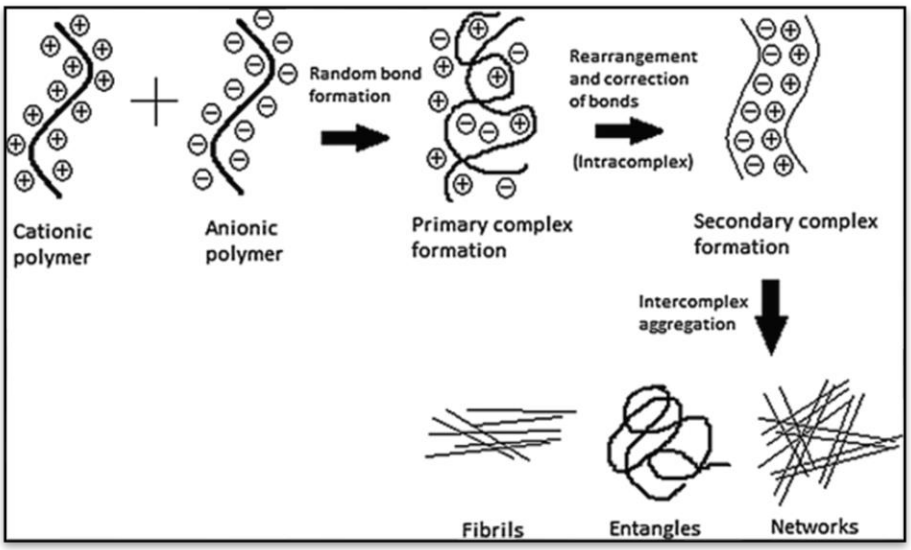

Figure (2) :Polyelectrolyte complex formation scheme[10].

PEC formation leads to quite different structures, depending on the characteristics of the components used and the external conditions of the reaction, two models are noticed:

a- The ladder-like structure, where complex formation takes place on a molecular level via conformational adaptation (zip mechanism).

b- the scrambled egg model, where a high number of chains are incorporated into a particle.

The characterization of PEC is mostly composed of physicochemical, morphological, and solid state analyses of the PEC particles in dispersion[11]. Turbidity measurement, ionic strength, pH, weight ratio of polymer in the media, viscosity, electron and X-ray absorption microscopy, Fourier transform infrared spectroscopy, scanning electron microscopy, powder X-ray diffraction, atomic force microscopy, differential scanning calorimetry, were employed to evaluate the complex formation [8] .

3. Factors affecting PEC formation

Polyelectrolyte complex (PEC) formation is influenced by a number of variables involving factors such as charge density or degree of ionisation, mixing order, polyelectrolyte polymers concentration, molecular weight of polymers, and the position of ionic groups along polyionic chains. Additionally crucial are the medium's pH and temperature [12]. Formation of PECs and their stability mainly depend on the pH of the PEs used. Phase changes of PECs can happen owing to the changes of the concentration of PEs and the pH of the solution , so suitable pH environment is required for significant degree of

polymerization[13]. For example developed hydrogels of polysaccharides for potential application as pH-sensitive, extended-release vaginal delivery systems using sodium alginate and chitin nano-whiskers in various molar ratios with metronidazole as the model drug, The manufactured particles' hydrodynamic diameter varied according to their pH; as a result, when the pH dropped from 9.3 to 2.4, the particles' hydrodynamic diameter reduced by about a factor of two [14]. Another example is the formation of PEC gel of chitosan and carrageenan at awide range of pH (2-8), the result showed best complexation pH was pH 5 with complexation yield 85% due to charge densities of the polymers were stoichiometrically balanced allowing for greater complexation[15]. While the effect of molar mass on PEC system was shown in the preparation of PEC platform for controlled drug delivery of ibuprofen formulated using different mass ratio of chitosan and xanthan polymers (1:1,1:2,1:3), where the result showed the mass ration 1:2 (chitosan :xanthan) the drug delivery system exhibited controlled release of the drug through zero-order kinetics, demonstrating a high level of drug yield and efficiency in entrapping the drug [16]. The charge density of PEC component has an effect on the formation and structure of the PEC network. precipitation rather than coacervation will occur if the charge density is too high while a stable solution (single phase) will result for very low charge densities[17]. For example coacervation of chitosan and hyaluronic acidwith different charge density ratio (by altering the concentration of one of the component), coacervation of the two polymers was observed when the ratio[-]/[+] was 0.46 but when increase to 0.7 (by increasing hyloroinic acid (negative charged polymer) concentration) precipitation was occurred, which may be due to the ‘‘mismatch’’ (inequivalence) in charge spacing of the chains would also work in favor of coacervation rather than precipitation. Charge mismatch will not allow tight contact between hyaluronic acid and chitosan. Therefore, loops which might form instead of these ‘‘contact ion-pairs’’ could maintain a certain level of hydration for non-stoichiometric coacervation. At a higher charge ratio, an increasing amount of hyaluronic acid closes the gap in charge mismatch, and leads to precipitation[18]. Also, the concentration of polyelectrolyte has an effect on the cross linking density of the PEC network for example combination of xanthan gum and chitosan in various concentration the result show best complexation degree at high concentration of both polymers compared to low concentration[19]. While complexation of hylouronic acid with diethyleaminoethyle dextran in high polymer concentration result in larger particle size of PEC than low polymer concetration during preparation of nanocarriers for encapsulating therapeutic agent [20].The effect of molecular weight on the viscoelasticity of polymers has been reported including the density and type of entanglements . For the PECs, the chain rigidity and chain length of the two reacting polyelectrolytes greatly affected the reaction strength and conformation[21]. For example preparation of PEC nanoparticles of chitosan (with different molecular weight) and enoxaparine , the result showed that the particle size of PEC nanoparticles was dependent on the molecular weight of the chitosan , as the molecular weight of chitosan decreased from 400kDa to 10 kDa due to the fact that increase molecular weight means high number of macromolecular coils at the outer part lead to formation of compact and strong complexation[22].

4. Polyelectrolyte complexes application

PECs have received a lot of attention in the pharmaceutical and biomedical fields over the past few decades biomaterials utilized in tissue engineering and cartilage regeneration,

in addition to drug delivery systems designed for oral, parenteral, and localised use [23]. Numerous biomedical systems, including dental adhesives, pulp regeneration, controlled-release devices, and medication administration, utilized polyelectrolytes [24].

4.1 Oral application

The oral drug pathway delivers medication via the gastrointestinal tract and emphasis's the expectation of systemic effects. It entails the proper dose form being swallowed, followed by the medicinal substance being absorbed via the intestinal wall once it has successfully crossed various chemical (e.g., pH, enzyme) and penetration-related (e.g., mucus layer, absorption membrane) limitations [25]. It has been suggested that using biocompatible and biodegradable PEC, which offers a stable environment for the pharmaceuticals enclosed, is a potential method for oral delivery of bioactive compounds, such as insulin. Because of enzymatic breakdown and physical hurdles in the gastrointestinal tract, developing an effective oral delivery method for insulin is still difficult. A new pH-sensitive PEC for insulin delivery that can be taken by mouth was prepared through electrostatic self-assembly of two oppositely charged nanoparticles (chitosan- and alginate-coated nanoparticles) which can overcome the enzymatic degradation of insulin [26].

4.2 Nasal delivery

Mucosal sites have been interested in the nasal route as non-invasive systemic delivery of drugs having limited oral bioavailability, such as protein and peptide drugs. In comparison to other methods, the nasal route is more accessible and provides a fast and easy way for self-medication, which increases patient compliance. The rapid removal of non-mucoadhesive dose forms from the absorption site via the mucociliary clearance process, is a significant issue with nasal medication delivery [27]. A novel nasal dosage form for systemic ondasteron hydrochloride delivery through the nose is in situ gelling nasal inserts with mucoadhesion properties by PEC techniques using chitosan (as polycation) and gellan gum (as polyanion), in which drug incorporated in three-dimensional network. When PEC lyophilized, the resulting complex had improved viscosity and produced a solid structure in the shape of a bullet [28]. Another example is the formulation of insulin as PEC nanoemulsion, by incorporating insulin (as negative part) with chitosan (as positive part) resulting in faster mucosal permeation of insulin compared to the free peptide[29].

4.3 Buccal drug delivery

Buccal mucosa is regarded as one of the most advantageous drug delivery methods for delivering medications locally or everywhere the body. It is discovered to be an appealing alternate route for orally delivered medications because of the vast surface area (about 50 cm^2), profuse vascularization, low enzymatic activity, and high permeability. Despite the benefits, challenges to buccal drug administration still exist, such as the continual flow of saliva into the mouth cavity or the possibility of inadvertently ingesting the medication. Polyelectrolyte complexes (PECs) have gained attention as a potentially effective platform for buccal medication delivery to overcome the limitation of buccal delivery [30]. PEC techniques used for the formulation of antifungal drug clotrimazole as PEC film with mucoadhesive properties for buccal administration. The produced films were recognized as complex pH-responsive devices with strong antifungal capabilities and a respectable safety record. Chitosan was added, which increased the drug's antifungal properties [31].

4.4 Skin drug delivery

The delivery of medications through the skin has proven to be both an intrinsic and difficult scientific topic [32]. A popular alternate route

for medication delivery is through the skin, which improved patient comfort and prevents the negative effects of parenteral and oral administration [33]. One of the most significant benefits of topical medication administration versus systemic drug delivery is lower toxicity since non-target organ exposure is minimal or nonexistent [32, 33]. The ideal material for a wound dressing which applied topically should be antimicrobial, promote cell adhesion and proliferation, have the optimum porosity for gaseous exchange, function as a dermal replacement at the wound site, and offer a moist environment [34]. Numerous concerns persist regarding wound dressings, including suboptimal biocompatibility of polymers, overuse of cross-linking agents, and adverse effects associated with antimicrobials. The nature-based polyelectrolyte complex membrane can assist to address the drawback of traditional membranes' incapacity to degrade biologically and foster environmental sustainability [35].for example preparation of chitosan-xanthan membranes (1:1 mass ratio) as topical wound dressing were successfully integrated with the anti-inflammatory drug indomethacin with a higher than 95% incorporation efficiency, the drug released in six hours from membranes synthesized with an initial indomethacin concentration of 20 mg per gram of biopolymer was very similar to the specified therapeutic dosage [36]. Also skin can deliver drug transdermally inside the body utilizing PEC techniques for example formulation of transdermal chitosan – alginate PEC film for controlled release of asthmatic drug ketotifene fumarate as alternative to the available dosage form [37].

5. Dosage form containing PEC

The PEC systems have been created in a variety of formats, such as hydrogels, fibers, films, nanoparticles, beads, or capsules, for different purpose [38].

5.1 Films

Films intended for medication administration must ensure a medication distribution that is controlled in order to meet the therapeutic goals. The PEC films that have been created are thin with a highly dense cross-sectional morphology and a uniformly smooth surface morphology [39]. FTIR-ATR and DSC verified the development of the PEC, additionally, 40% of the dried polymer weight can be loaded without influencing the formation of the PEC. Transdermal delivery methods for peptides, proteins, and other medications have shown a variety of applications for bioadhesive films composed of biocompatible polymers, such alginate-chitosan complexes. Transdermal films of ketotifine fumarate, which formed through complexation of chitosan and sodium alginate was flexible, and high in bioadhesiveness, used for the treatment of asthma and allergy [37]. Another example for a buccal mucoadhesiv film where chitosan-gum Arabic and chitosan-polygalcturonic acid polyelectrolyte films loaded with nystatin were produced. The films produced showed sustained release kinetics that were explained by the Korsmeyer-Peppas model. This means that the drug is released in a manner that is similar to administering a loading dose that releases the drug gradually over time, which may be advantageous in oral application. The initial drug release was quick [2].

5.2 Hydrogel containing PEC

Hydrogels are crosslinked polymeric networks with a high water content that can be designed to carry out a variety of desired mechanical, morphological, biocompatible, and biodegradable/non-biodegradable characteristics, depending on the conditions chosen for gel fabrication and the chemical structures and compositions of the building blocks used in their synthesis[40].

Hydrogels are opening up new possibilities for several medicinal applications[41]. Their

poor mechanical strength and uncontrolled swelling have hampered their usefulness in biotechnology and biomedicine [42]. Because the electrostatic interactions inside PEC gels are significantly stronger than those within most secondary binding interactions, PEC gels, which are created by the electrostatic attractions between two oppositely charged polyelectrolytes mixed in aqueous solution, are known to exhibit unique physical and chemical properties. Polysaccharide-based hydrogels offer good biocompatibility and a customizable swelling profile due to variations in physicochemical. As oppositely charged polymers, carboxymethyl celloidose and chitosan combine to generate a hydrogel network that exhibits positive biological response in the form of cell adhesion, migration, proliferation, and differentiation [43]. For example the delivery of vitamin C, a new PEC hydrogel was effectively created by self-assembling salecan and chitosan in various ratios, The results of an in vivo release experiment showed that the PEC hydrogel's maximal release amount reached 90.0% in blood after 10 hours [44].

5.3 Beads containing PEC

For patient treatments, Numerous unit systems, including beads, spheroids, pellets, and microparticles, have been developed and are often used. These multiple unit systems may limit exposure to greater drug concentrations, minimize the chance of localized mucosal tissue injury, and avoid the whims of stomach emptying since they can mix with gastric fluids and disseminate throughout a vast gastrointestinal tract and to lessen the incidences of these adverse events [45] . For example; A wide range of unit systems, including pellets, spheroids, beads, and microparticles, have been developed and are frequently implemented. By combining with gastric secretions and distributing throughout the entire gastrointestinal tract, these various unit systems effectively circumvent the fluctuations of gastric emptying, safeguard against the exposure of elevated drug concentrations, and diminish the probability of localized mucosal tissue injury. The release of diclofenac sodium in vitro from different PEC beads made with chitosan in a pH 6.8 phosphate buffer demonstrated a consistent medication release profile over six hours. It is evident from the worked results that these kinds of chitosan: gums such as gellan, gum ghatti, and gum using Karaya PEC beads as possible multiple-unit methods using polymeric carriers for prolonged delivery of irritants to the stomach, such as sodium diclofenac [46] .

5.4 Fibers containing PEC

Materials made of fiber and thread are used frequently. The pharmaceutical sector has just recently begun to use fiber materials, despite the fact that they are widely used in medical technologies. For example, special fibers are utilized to perform esophageal biopsies while consuming cytosponges or as self-degrading surgical sutures [47] . A novel methodology has been developed to continuously produce PEC fibers by employing a watery based wet-spinning process and a core-shell spinneret. The core-shell structure of the resulting fibers consists of a low-density core and an 800-micrometer-diameter polyelectrolyte complex shell made of chitosan, polystyrene sulfonate, and polyethylene oxide. Additionally, the rate and extent of enlargement were significantly reduced in aqueous environments, thereby enhancing the stability of the scaffold in the cell culture medium. The successful cultivation of human HeLa cells on PEO-doped PEC scaffolds for a duration of four days serves as evidence for the biocompatibility and suitability of CHI/PSS-PEO fibers in the field of tissue engineering [48].

6. Most common polymers used to prepare PEC

Polyelectrolytes are an intriguing family of macromolecules that are a particular form of polymer with dissociated ionic groups. Due to their combined characteristics of a macromolecular chain and a high charge, these molecules display intriguing behaviors [49].

6.1 chitosan

The general name "chitosan," which refers to a chitin in its deacetylate state is a kind of presumably pure poly-(beta-1-4) N-acetyl-D-glucosamine compounds (figure 3). Chitosan (Cs) is produced by a variety of living things, including fungus, insect cuticles, and the skeletons of crustaceans including crab, shrimp, and lobster. It has garnered a lot of interest because of its biocompatibility, low toxicity, and ability to break down with human enzymes [50]. Other biological features include wound healing ability, antibacterial activity, and hemostatic activity. It can be processed into fibers, gels, microspheres-microcapsules, and micro/nanoparticles and is a great film forming [51]. Cs is available in a broad variety of molecular weights, typically fall within the range of 10 to 1000 kDa, and deacetylation degree range from 70% to 95%, which are thought to be crucial for its quality and physicochemical behavior [23]. a pH-responsive PEC hydrogel for transdermal drug administration of diclofenac sodium(which has low oral bioavailability),was prepared using new polyelectrolyte through combination of carboxymethyl agarose (CMA) and chitosan (Cs) in ratio 2:1 and it show better pharmacokinetics than the commercial product [52].

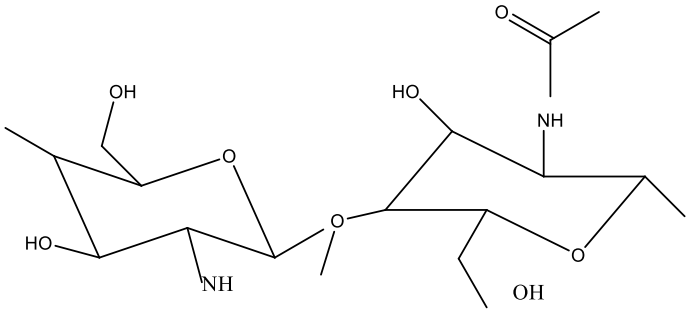

Figure (3): chitosan structure

6.2 Alginate

Alginate (Alg) is a negatively charged polysaccharide [53], The polymer alginate is composed of (1-4)-linked dmannuronate (M) and l-glucuronate (G) residues. Sea weeds serve as the primary source of this polysaccharide [54] (as shown in figure 4). Because of its anionic nature, Alg has the ability to form complexes with polymers that possess a positive charge, like chitosan. Alginate can be dissolve in both neutral and basic water solutions[55]. In both neutral and alkaline solutions, sodium alginate is soluble (pKa = 3.38–3.65). It shown that a variety of variables influence solubility, such as the solvent's pH, ionic strength, and the existence of gelling ions [53]. The polysaccharide degrades by gradually eluting calcium ions that have been cross-linked, and then the polymer dissolves in an aqueous environment. Instances of its application include stabilisation, viscosity control, and gelling in the biotechnology, pharmaceutical, textile, and food industries. It is biocompatible and non-toxic [53]. Numerous available products containing sodium alginate, such as suppositories for haemorrhoids and anti-reflux pharmaceuticals (tablets, suspensions), and wound dressings [23]. It has been

demonstrated that the fibrillary structure of chitosan/alginate PECs provides accurate control over the release of diclofenac; therefore, these substances are viable vehicles for controlled sodium release of diclofenac [56].

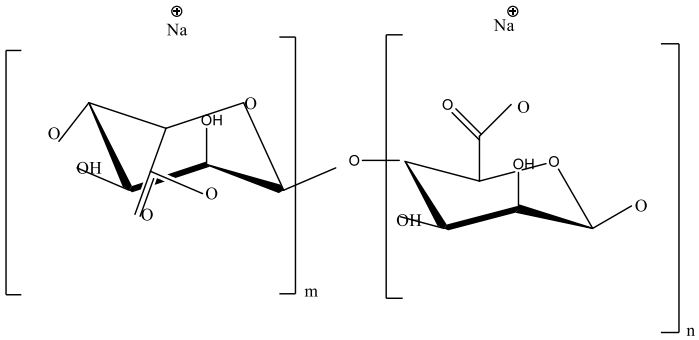

Figure (4): Alginate structure.

6.3 Xanthan gum

Xanthan gum is an extracellular polysaccharide with a high molecular weight[57].The bacterium Xanthomonas campestris produces xanthan gum, a naturally occurring heteropolysaccharide that is very hydrophilic. Five repeating sugar units make up the polymer's main structure: consisting of two mannose units, two -D-glucose units in the basic chain, and one glucuronic acid unit in the side chain. It is believed that xanthan gum could be a viable alternative to chitosan when combined to produce PECs drug carriers [58]. The non-ionic structure of xanthan gum makes it soluble in cold water, and solutions show a strong pseudo plastic flow. Over a broad pH and temperature range, its viscosity exhibits outstanding stability [57]. Pharmaceutical technology frequently utilizes it as a stabilizing agent, viscosity enhancer, and prolonged-release agent in order to expand the applicability of other compounds [30]. Xanthan gum provides the added advantages of compatibility, inertness, and the potential to provide time-independent release kinetics in addition to slowing drug release [57]. For example; the polyelectrolyte complexation process was used to create terbinafine-loaded chitosan\ xanthan gum nanoparticles, which were then included into carbopol gel. The drug's percentage retention reached up to 80.5%, which was much higher than that of the drug's commercial version. When comparing the developed formulation to the control and commercial formulations, in vivo experiments demonstrated that the developed formulation eradicated the fungal burden promptly and completely [59] .

Conclusion

PECs have been employed in a variety of dosage forms for the creation of stable controlled release systems as well as for drugs that promote tissue regeneration or transplantation. According to their coupled ionic interactions, PECs will likely have a variety of applications in the future. These uses range from targeted medication release in the colon to orally administering drug, human periodontal ligament matrices, dermal wound healing, and subcutaneous medication administration, and many more. PECs produced by combining aqueous solutions of two polymers having opposing charges have a very strong future in the pharmaceutical sectors for regulated drug delivery.

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