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POLYELECTROLYTE COMPLEX FOR PHARMACEUTICAL AID

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Abstract

Comprehensive research on polyelectrolytes at a basic and useful level is increasing since the compensation of sustainability are being established in university and industrial research setting. Throughout current decades, polyelectrolytes become individual of the mainly attractive subject of scientific research due to their large prospective in the area of higher technologies. Polyelectrolytes are a category of polymer to contain infinite ionizable purposeful groups.

Polyelectrolyte complexes (PECs) characterize a particular category of polymeric compound consisting of oppositely charge polyions to be able to contain each cationic or anionic charges. Appropriate to their charge they be hydrophilic, and in general water soluble, and be able to exist use in a range of application, resembling as drug release, coating, shampoos, or as flocculating agents in water management. These complexes evade the employ of chemical cross linking agent thus to dropping the possibility of toxicity.

The present object provide a complete review on PECs and their advantages in the arrangement of PECs, objective of PECs, Types and structure of PECs, formation and factors affecting of PECs and their wide range of applications in various fields. This analysis effort gives a group of information lying on PECs. The complex produced is usually applied in different dosage forms for the formulation of established aggregate macromolecules. Several property similar to distribution coefficient, chain conformation, thickness, polarizability, miscibility, etc., are considerably altered owing near the beginning of a polyelectrolyte.

Keyword: Polyelectrolyte complex, Polyions, Composition, factors affecting PECs and Applications

1.INTRODUCTION

Polyelectrolytes (PECs) explain their great significance in superior technologies and molecular biology and they are mainly attractive subject of scientific research in recent decades. A PECs is defined as any macromolecular material that has repeat unit and separate into a extremely charged polymeric molecule upon being placed in any ionizing solvent (e.g., H_2O) form also a positively or negatively charged polymeric chain [1]. Polyelectrolytes are charged macromolecules that contain opposite charges. Expected to particular charges they are hydrophilic, and usually water soluble, and can be use in a variation of approach, corresponding as drug delivery, covering, shampoos, or as flocculating representative in sea management [2]. The mixing of oppositely charged polyelectrolytes lead to the formation of a complex whose composition, in general, is responsive to such reaction condition as the composition of the reaction mixture, the order of mixing, and the polyion concentration at which the reaction is approved elsewhere.[3].

A succession of particular surface properties, excellent emulsifying properties or diverse scales of PEC can be obtain base on the different reaction degree of materials. The encapsulation characters of PECs directly

encourage research and development of controlled release system. PECs have be useful in the meadow of agriculture, biotechnology, food flavoring, biomedicine, cosmetics and textile [4] . The PECs are energetic resources due to their reversible electrostatic bonds and charged groups which make them highly responsive to their nearby environment (especially to pH, ionic strength and PE concentration).This vibrant structure can lead to controlled swelling and degradation, and may, therefore, be used for applications such as drug delivery and antifouling surfaces in varying physiological environments [5].

Encapsulation of substances, drug delivery systems, and waste-water treatment, among others are the broad range of application of polyelectrolyte complex they present. The PECs prepared from natural ionic polysaccharides are normally non-toxic and biocompatible, properties that are very important for their use in medicine and pharmacy. In reliance of their ultimate utilize, PECs can be produce as powders, membranes, sponges, fibers, gels, spheres or in solutions [6].

In aqueous solution of polyelectrolyte complexes (PEC) the oppositely charged polyions (polycation, PC and polyanion, PA) are dissolved it is well known. the subsequent three different type be able to be distinguished:

a] The so-called soluble complexes, which accommodate small PEC aggregate and consequently they form macroscopically homogeneous system.

b] Turbid colloidal system by means of balanced complex particle in the transition range to phase separation.

c] Phase separation by precipation of PEC-polysalt [7].

PECs are of significance due to their superficial preparation and responsiveness to environmental stimuli. Furthermore, by means of water like a solvent, PECs are attractive for biomedical applications. Examples contain controlled drug delivery system, enzyme and DNA carriers, surface modification of medical implants, membranes for cell culture and growth, biosensors, and nanostructured resources [8].

The aqueous solutions of oppositely charged polyelectrolyte chains are the numerous investigation focused in recent years. The strong electrostatic desirability among the oppositely charged polymers lead to associative phase separation, thus form macroscopic polymer-rich phases known as polyelectrolyte complexes (PECs) [9]. Exclusive of the aid of result initiators, catalysts or crosslinkers the strong electrostatic attractions happen in the development of PECs. The removal of these additives renders most PECs are non-hazardous and easy to make and this lowers the cost in research and development of drug formulations. Moreover, some polymers cannot be efficiently used for drug delivery except they form a complex. For example, the use of a polyacrylic acid matrix frequently consequences in immediate drug release and this belongings is recognized to its understanding to ionic environments and high water solubility [10]

2.POLYELECTROLYTES

Polymer compounds are opposite charge at neutral pH known as polyelectrolyte. There are more substances known as polyelectrolyte that contain oppositely surfaces charges. For example vegetables that contain natural polysaccharide such carboxylic groups rich in acacia, tragacanth, alginic acid and pectin , which are ionised in neutral to alkaline media. Synthetic carboxylate polymer includes Carbomer a copolymer of acrylic acid. The commencement, structure , molecular structure, and electrochemistry that basis the polyelectrolyte complex are classified. Based upon origin it is classified as [11]

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

3.POLYELECTROLYTE COMPLEX

The word polymer comes since the Greek language *poly*, significance several, furthermore *meros*, significance

component. An electrolyte is a material to facilitate be able to separate interested in liberated ions (from the Greek *lytos*, implication "that may be dissolved"). Polyelectrolytes are consequently polymers among at least one repeat unit that can separate. while such polyelectrolytes are dissolve in water, they grow a firm electrical charge, also be furthermore accompany by counterions. The polyelectrolyte dissolution help the release of counterions during water. Positively charged polymers are frequently referred to as polycations and negatively charged polymers as polyanions. The charge of weak polyelectrolytes differ with solution pH ,while the charge of well-built polyelectrolytes have stable charge densities.

In a complexation method directly connected to self-assembly process, the polyanions and polycations can act in reaction in aqueous resolution and form polysalts .The gain in entropy cause by the free of low-molecular-weight counterions is the general conception of the most important dynamic force of complex development. Other interactions, such as hydrogen bonding and hydrophobic interactions, can also contribute to the complexation process but are not, as such, driving force for the complexation [2]

Figure 1. Schematics of the release of counterions upon polyelectrolyte complex formation.

4.ADVANTAGES OF PECs FORMATION

1. In the formation of polyelectroyte complex there is a less energy required [11]
2. There is a fast process for the formation of polyelectrolyte complex than synthetic polyelectrolyte[11]
3. polyelectrolyte complex are formed without the use of heavy solvents. [11]
4. Does not produce any toxic product [11]
5. PECs produce high yield and drug content [11]
6. PECs minimizing possible damage to drug during formation [11]
7. PECs are inexpensive, biodegradable and biocompatible [11]
8. There is uncessary to use sophisticated instruments for the preparation of PECs [11]
9. PECs improve the limited efficiency and stability [12]

5.FOLLOWING ARE THE OBJECTIVE FOR CONSIDERATION OF POLYELECTROLYTE COMPLEX FORMATION

1. PECs indicative dosage form improve the prolonged and immediate drug deliver such as microparticles, hydrogel, nano/microcapsule, microsuspension, microemulsion [11,13,]
2. Its possible desire as both nanocarrier, surface-modifying reagent and membrane
Separation [11,14]
3. Used to limit the stability, adhesion properties, and rheology of colloids [11]
4. Increase dissolution rate and solubility improve by the formation of nanoplex [11]
5. To obtain the uniform particle size nanoparticles [11]

6.TYPES OF AQUEOUS PECs [11,15,16]

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

Sr. No.	Types	Observation
1.	Soluble PEC	Small PEC aggregates soluble in microscopically homogeneous systems and larger PECs are not soluble in homogenous system.
2.	Turbid colloidal	System with dispersed PECs particles in range extent to Appearance dissociation. Shows light scattering or Tyndall effect.
3.	Two phase system	Of supernatant liquid and precipitated PEC which are casualy divide as solid after remove and not wet.

7.TYPES OF PECs ON THE BASIS OF INTERACTION [17]

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

7.1. Polyelectrolyte complex between natural polyelectrolyte

Sr.no.	Natural polyelectrolyte
1	Chitosan-Alginate
2	Chitosan-Carrageenan
3	Chitosan-Pectin
4	Chitosan-Xanthan gum
5	Chitosan –Hyaluronic acid
6	Chitosan -Gelatin

a] Chitosan-alginate polyelectrolyte complex

In unreliable extent the alginate is a ordinary, linear, unbranched, environmental polysaccharide and it contain of 1,4-linked β-D-mannuronic acid as well as α-L-guluronic acid monomers. Alginates be take out from brown seaweeds and marine algae such as *Laminaria hyperborea*, *Ascophyllum nodosum* and *Macrocystis pyrifera* [18].

Through the positively charged amino group of chitosan interact electrostatically through the negatively charge carboxylic acid class ahead of manuronic and guluronic acid unit in alginate to structure a polyelectrolyte complex.[19]

Alginate is one of the most studied anionic polyelectrolytes in complexation with chitosan the polyelectrolyte complex is formed between this two polymer due to their biodegradable and biocompatible nature . This polyelectrolyte complex is reluctantly stronger at lower pH values somewhere chitosan dissolves [18].

For controlling the liberate of charged molecules chitosan-alginate polyelectrolyte complex fibers exhibit the hopeful results and these molecules exhibit high encapsulation efficiency [18].

b] Chitosan-carrageenan polyelectrolyte complex

Carrageenan is the common name obtained from a firm type of red seaweeds and it belongs to the family of high molecular weight sulphated polysaccharide . There are three fundamental types of carrageenan, namely kappa (κ), iota (ι) and lambda (λ) carrageenan. It was shown that the nature or category of carrageenan significantly control the distinctiveness of the polyelectrolyte complex to facilitate is produced with chitosan. The mechanical strength of polyelectrolyte complex gels produced among chitosan and dissimilar carrageenans be in the arrangement of λ- > ι- > κ-carrageenan. [19]

The temperature sensitive gels obtained from ι- and κ-carrageenan because of the helix–coil conformational transitions in their molecules [18].

c] Chitosan-pectin polyelectrolyte complex

The cellulose, hemicelluloses as well as pectin be the plant cell wall obtain from polysaccharide. Pectin is a linear polysaccharide collected of α-1,4-linked D-galacturonic acid units, though, this linear composition is alternating by way of very divided regions in the polymer chain . The constitution of the pectin molecule differ from origin to origin, e.g. pectin from citrus fruit

contains fewer neutral sugars and have a smaller molecular size than pectin from apples.[19]

A homogenous mixture is obtain when acidic chitosan and pectin mixtures are mixed devoid of any ionic interactions among the two polymers. The negatively charge carboxylic acid class of pectin as well as the positively charged amino class of chitosan the electrostatic interaction can happen at a value of pH 5.5 . Moreover, the mixture a polyelectrolyte complex could be obtain by balancing the pH. [18].

d] Chitosan-xanthan gum polyelectrolyte complex

Xanthan gum be an exopolysaccharide concealed as of *Xanthomonas campestris*. It contain of a cellulosic backbone, namely β-(1,4)-d-glucopyranose glucan, with a trisaccharide side chain, namely (3,1)-α-d-mannopyranose-(2,1)-β-d-glucuronic acid-(4,1)-β-d-mannopyranose, taking place each second glucose deposit.[19]

Outcome obtain from a modulated differential scanning calorimetry examination and the swelling degree of microcapsules arranged from chitosan-xanthan gum polyelectrolyte complexes show that the cross-linking density was mutually dependent on xanthan concentration, chitosan concentration and chitosan solution pH [18].

e] Chitosan-hyaluronic acid polyelectrolyte complex

Hyaluronic acid or hyaluronan or hyaluronate is the single nonsulfated glycosaminoglycan establish in the extracellular matrix throughout connective, epithelial and neural tissues.[18]. It is formed by bacterial fermentation of streptococcus category or by means of extraction processes as of rooster comb, umbilical cords, synovial fluid otherwise vitreous humour for commercial purposes. β (1,3)-*N*-acetyl-d-glucosamine and α (1,4)-d-glucuronic acid repeating units linked by β (1→3) bonds . [19]

It was revealed to facilitate the polyelectrolyte complex among chitosan and hyaluronic acid protect hyaluronic acid beside enzymatic hydrolysis, but simply at pH values diverse from the optimal pH of the enzyme. The results from this study exposed that the chitosan-hyaluronic acid polyelectrolyte complex unfortunately had fewer cell proliferation and wound healing property compare to chitosan only. [19]

f] Chitosan-gelatine polyelectrolyte complex

A pH value of 4.7 represent the isoelectric position of gelatin. Above a pH value of 6.2 chitosan begins. The only one or multi-stranded polypeptides consisting of gelatin and gelatine is a diverse combination of protein fraction. It is obtain by incomplete hydrolysis of animal collagen resulting as of skin, white connective tissues and bones. Here be two type of gelatine: type A and type B. Type A gelatine is resulting from pig skin through way of acid hydrolysis and type B gelatine is obtain by alkaline hydrolysis of cattle conceal and bones [18,19].

It was revealed so as to the polyelectrolyte complex among chitosan and gelatine can only happen at a pH value more than 4.7 and lower than 6.2. More than this importance the remaining charge on gelatine type B is negativeto precipitate out of elucidation.[18,19].

7.2. Polyelectrolyte complex between synthetic polymers [19,20]

Sr.no.	Synthetic Polyelectrolyte
1	Poly(lactide) (PLA)
2	Poly(glycolide) (PGA)
3	Poly(lactide-co-glycolide)(PLGA)
4	Polyethylenimin e (PEI)
5	Polycaprolactone (PCL)
6	Poly(cynoacylate s) (PCA)
7	Poly (vinyl benzene tri alkyl ammonium
8	Poly (vinyl sulfonic acid)
9	Poly (acrylic or methaacrylic acid)
10	Poly (styrene sulfonic acid)
11	Poly (acryl amido alkyl trialkyl ammonium)

7.3. Polyelectrolyte complex between a natural and a synthetic polymer [17,20,21]

Sr.no.	Natural and synthetic polyelectrolyte
1	Potassium poly(vinyl alcohol sulfate)
2	Carboxyhemoglobin
3	Poly (acrylic acid)
4	Poly (dimethyldialylammonium chloride)
5	Lysozymes
6	Poly (methacrylic acid)
7	RNA polymerase
8	Poly (ethyleneimine)
9	Bovine serum albumin
10	ribonuclease
11	Carboxymethyl cellulose
12	Heparin
13	Amino acetalized poly(vinyl alcohol)

7.4. Protein–polyelectrolyte complexation [17]

Sr.no.	Protein polyelectrolyte
1	poly (l-glutamic acid)
2	poly (ethylene imine)
3	poly (l-lysine).

8. STRUCTURE OF PECs [11]

On the basis of characteristics such as Molecular weight, Stoichiometry, and Polyion class PECs structure is divided Structure as given below.

Sr.no.	Ladder like structure	Scrambled –egg model
1.	PECs are prepared at very low concentration	PECs are prepared at higher concentration.
2.	They contain limited number polyelectrolyte chain.	They contain a huge number of polyelectrolyte chain.
3.	Insufficient ion pairing take place.	Sufficient ion pairing take place.
4.	Give micro sized product.	Give micro and Nano sized product.
5.	Molecular aggregation underneath secure stoichiometric stipulation.	Highly aggregated complex formation will occur.

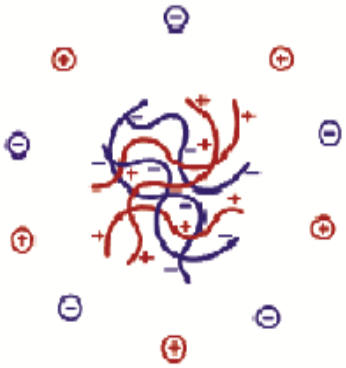
6.	Structure obtained by the combination of decrease or increase molecular weight polyion with weak ionic group.	Combination of comparable molar mass of polyion with strong ionic group.
7.	Form initially soluble PECs after addition of HMW polyion which is insoluble.	Insoluble PECs will formed.

Fig.2

[A] [B]

9.SCHEMATIC STRUCTURE OF PECs

Ladder like structure



Scrambled egg structure

10.Formation of PECs

There are mainly 3 steps the process is appear in fig. 3. Coulomb forces and primary complex formation are the first step responsible for the PECs formation. Second step:-the process within intracomplexes are the second step involve for the PECs formation. It involves development of new bonds and/or the expansion of the misinterpretation of the chain of polymer. They mainly involves the secondary complexes by aggregation through hydrophobic interactions there is a third intercomplex cluster process.[23]

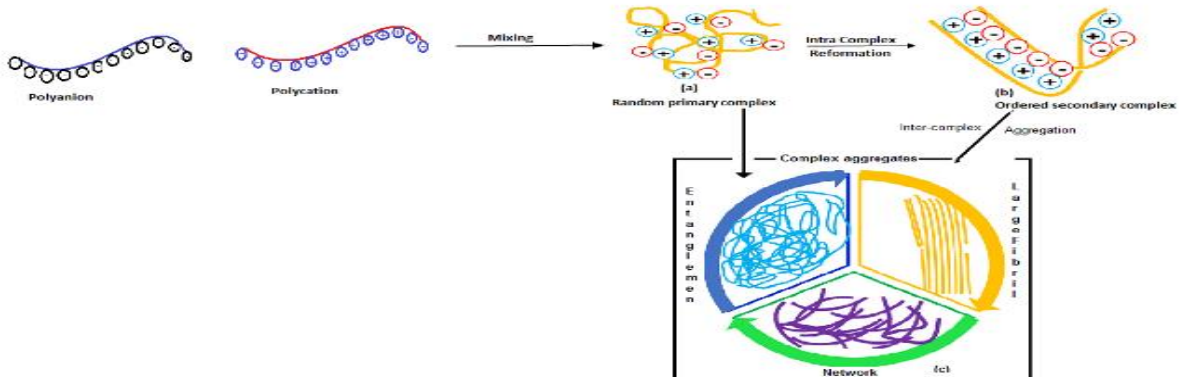


Fig.3 Diagrammatic representation of the emergence and agglomeration of PECs

(a) formation of primary complex (b) Formation process inside behind complexes (c) Inter complex agglomeration process

11.FACTORS AFFECTING THE FORMATION OF PECS

The PECs formation are known to effect the number of parameters. These are anion site, charge substances,

PEC concentration, pH, ionic capability, solvents and temperature. There are many elements achieving the emergence of PECs with different polymeric admix that are evaluated by several workers . Effecient desirability due to charge variations is caused by precipitation and by short range desirability among monomers. Impressive in the situation of the polyanionic stoichiometry are studies of layer emergence from actively unequal pairs of polyions. giving polyions with a lessen charge density along the chain, i.e. comprising of opposite co-monomers, it was perceive that a least charge density is required for polyelectrolyte adsorption. altering the ionic durability by incorporation of salt[able regulate the electrostatic co-operation in a PECs solution. The electrostatic interactions can be weakened by incorporation of inorganic salts into the solutions. Thus, an expand of the ionic durability of the solution destroyed the complexation between polyions, because of the concealing of contrasting charges of the nucleic acid by low molecular weight ions. By differing the pH environment throughout PEC formation, the level about ionization of delicate polyelectrolytes can be composed. This was found to affect many more layer premises such as coating thickness, the level of explanation among layers, surface wettability and number of unbound functional groups. Therefore, by selecting the proper pH conditions, a programme may be establish with premises that are superior for filling charged small molecules into the film via electrostatic interactions.[23]

12.THE LIST OF FACTORS THAT AFFECTING THE FORMATION OF POLYELECTROLYTE COMPLEX ARE AS FOLLOWS :-

1) Charge-to-charge stoichiometry
2) Charge density
3) Molecular weight
4) Polyelectrolyte concentration
5) Ionic strength
6) Mode of mixing polyelectrolyte solutions
7) pH
8) Order of addition
9) Mixing Ratio
10) salt concentration

12.1. Charge-to-charge stoichiometry

whereas investigate polyelectrolyte complexation, what needs to be studied is the net ratio of positive to negative charges of the oppositely charged polyelectrolytes concerned in fabricate PECs. This part is referred as charge ratio and denote as Z, with the subscripts (+/_or_/+). The PECs is formed by charge to charge stoichiometry and is denoted as Φ. S-PECs (Φ=1) are adequately hydrophobic suitable to the common showing of the charges also precipitate as of the aqueous solution. but the N-PECs (Φ=1) are prepared, by the polycation or polyanion due to their excess overcharging effects are either practical.[24].

12.2. Charge density

The authority of charge density was address in early work of Dautzenberg and colleagues by means of a system of cationic and anionic copolymers of acrylamide. They show that for equal charge density of the PEL components, the "symplex" particles accept a compact structure, while in systems with strongly conflicting charge density of the PEL mechanism a loose "changeable" structure prevail. This judgment was in line with soon after work of Dautzenberg and Jaeger on cationic copolymers of DADMAC and N-methylvinyl acetamide (NMVA) and anionic PSS. [25]
Though, apparently in contrast to the latter findings are recent studies of Claesson and coworkers based on a cationic copolymer of methacryloxyethyl trimethylammonium (METAC) with unreliable portion of the nonionic poly(ethylene oxide) ether methacrylate (PEO45MEMA) and anionic PSS. They show that with falling charge density it was potential to get soluble PEC particles with falling hydrodynamic radii to around 20 nm and increase stability, even for 1:1 stoichiometry. This detection was explain by steric stabilization via the hydrophilic PEO-ornament shell, which prohibited secondary aggregation.[26]

12.3. Molecular weight

The polyelectrolyte multilayer (PEM) feature are increase by the alternate evidence of polyanions and polycations taking place a charge solid substrate . In this study, we examine the enlargement process of hyaluronic acid/poly(L-lysine) (HA/PLL) and poly(L-glutamic acid)/poly(allylamine) (PGA/PAH) films, two films whose expansion is primarily exponential, while the expansion development enter the linear system. We center, in specific, on the impact of the molecular load (*M*w) of the polyelectrolytes. Intended for both system, we discover to the film width enlarge per polyanion/polycation deposition step in the linear growth system is rather free of the molecular weights of the polyelectrolytes. We moreover discover to facilitate after the (HA/PLL)*n* films be create with small molecular mass PLL, these chains be able to disperse into the complete film throughout each buildup sequence, still used for extremely broad films, while the PLL diffusion of high molecular weight chains is controlled to the higher fraction of the film.

The increase of "exponentially" increasing PEM films by the control of the polyelectrolyte molecular weights in this study we consider. As previously report, the thickness of all the films first increases exponentially with the number of evidence steps previous to entering a linear growth system.Kujawa et al. previously investigate the control of the polyelectrolyte molecular weights on the exponential growth phase for the hyaluronic acid/chitosan structure. These authors found that polyelectrolytes of elevated molecular weights led to thicker films subsequent to a given number of statement steps. Though, according to them, this is not due to the exponential increase rate, which is self-determining of the polyelectrolyte molecular weights, but slightly to an previous start of the vertical exponential growth phase when elevated polyelectrolyte molecular weights are use. [17]

12.4. Polyelectrolyte concentration

Schatz et al. (2004a) report the enlarge in size of CHT/DS biopolyelectrolyte complex particles among increase DS concentration, but simply at elevated combination ratios $n+/n^-$ Muller et al.

(2011) recommended that, base happening the form of aggregation of most important PEC to less important PEC particle owing to small variety dispersive connections, increase polyelectrolyte concentration results in compact electrostatic repulsion among like-charged most important PEC particles and hence, in their high dispersive desirability. Also, an enhance in polyelectrolyte concentration strength also result in a huge number of primary PEC particles per volume. Together could direct to better secondary PEC particle. Beyond firm polyelectrolyte concentration standards can also show the way to precipitation [24].

12.5. Ionic strength

The study of the ionic potency reliance of the binding constant acceptable the purpose of the total number of released counter-ions throughout the formation of the PEC, which be able to be evaluate to the sum figure of counter-ions primarily condensed on the individual polyelectrolyte associates by the involvement. Fascinatingly, this portion of free counter-ions, which was robustly reliant on the PLL molar mass, was approximately self-determining of the PAMAMPS charge thickness. These conclusion are helpful to expect the binding constant according to the molar mass and charge density of the polyelectrolyte associates.

The consequence of the PLL molar mass on the necessary position continuous and stoichiometry of PLL-PAMAMPS complexes be thoroughly investigate by FACCE for dissimilar ionic strengths. Increase the molar group of the PLL series has two moderately spontaneous effect: (i) the obligatory site constants improved due to an increase of the number of electrostatic anchor point; and

(ii) the stoichiometry of interaction decreased [28]

12.6. Mode of mixing polyelectrolyte solutions

Combination of polycation and polyanion solutions to make PECs is probable to be dependent on the mixing type, mixing protocol, and the tool use. Ankerfors et al. (2010) report the control of mixing procedure on the complexation of poly(allylamine) (PAH) and PAC by compare jet mixing with the regularly use colloid titration. They acquire high molecular weight polyelectrolytes PEC size first decrease with decrease mixing time awaiting a smallest and then increase over again while for small PECs for together small molecular weight polyelectrolytes on small mixing period. This performance was recognized to the diffusion-controlled formation of pre-complexes happening adequately rapidly so that established complexes be produced.

Though, for better polyelectrolytes non-balance pre-complexes level to aggregation be produced.
Compare the two mixing events, jet mixing give minor PECs, allow mixing time to organize PEC size, where colloid titration give better PECs. Sæther et al. (2008) observe with increasing mixing rate by means of an Ultra-Turrax process and reduce in particle size of chitosan-alginate PECs.[24]

12.7. pH

The molar proportion of polycation (pAH) to polyanion (pAA), within the structure are the mainly direct inconsistent for controlling coacervate configuration is the charge stoichiometry. Together of the polymers use inside this study are weak polyelectrolytes; the pKa for pAA is around pH 4.5, although the pKa for pAH is approximately pH 8.5 . Therefore, we prepared the assumption that at pH 6.5, which is two pH units off from the pKa of all polymer, together polyelectrolytes must subsist together completely and similarly charged. Furthermore, the data report now be obtain in adding up pAA to a solution contain a mixture of pAH and the preferred amount of salt. Though, we do not monitor important difference in our information as a consequence of reverse the order of polyelectrolyte adding
For the symmetric case at pH 6.5 where both polymers are of equal length and equal charge, we
observe a maximum in coacervate formation close to 50/50 mol% pAA/pAH.This composition corresponds to the condition of charge neutrality in the system, where the number of charges from the polycation (pAH) equals the number of charges from the polyanion (pAA).[29]

12.8. Order of addition

A extremely responsive experimental changeable was investigate by some researchers, the array of polyelectrolytes adding up, whereas polyelectrolyte solutions are mixed gradually with one an additional (Mende et al. 2004) [7] . Schatz et al. (2004a) [30] compare the regular deliberate dropwise mixing through speedy one-shot addition for the preparation of CHT-DS PECs. Fast one-shot mixing process give PECs with small diameter and advanced stability compare to the PECs ready by a slow dropwise mixing procedure. Although addition the titrant solution dropwise to the preparatory solution,the order of mixing was necessary and the polymer in evade has to be supplementary to the one in overload in order to avoid the collective formation. (Schatz et al. 2004a) [30].

12.9. Mixing Ratio

Mixing ratio is the parameter that is by extreme the mainly used and various in experimental studies on PEC particles, in which the mainly regular recognizable is turbidity. Mixing ratio is also used to influence PEC particle size.
In a more established report by Dautzenberg , the molecular weight and size of PDADMAC/PSS particle be studied in reliance of the mixing ratio. A small reduce in molecular weight and a strong reduce in the size from around 400 nm (X ¼ 0.1) to 200 nm (X ¼ 1.0) was establish with increase mixing ratio in the saltless system, which was qualitatively interpret as an increase in structural thickness when X approaches 1:1 stoichiometry because mutual charge-compensated chains capacity be added closely coiled [25].

12.10. salt concentration

Salt plays an significant fraction in the development of extremely aggregate PECs. Frequently, salts decrease the interaction among the PEs and allow the relocation procedure. The presence of salt throughout PEC formation lead to strong reduction of aggregation due to a less firm and more-coiled constitution. A more raise in salt awareness (i.e., ionic strength) cause secondary aggregation most important to macroscopic flocculation [1].

13.APPLICATIONS OF POLYELECTROLYTE COMPLEX IN VARIOUS FIELDS

Fig4. Applications of polyelectrolyte complex in various fields

A] Application of Polyelectrolyte Complex In Drug Delivery System:-

a) Applications of PECs in drug delivery

1) Application Of Polyelectrolyte Complex In Pharmacy

Table 1. Applications of PECs as drug delivery carriers.

Polycation	Polyanion	Drug/method	Formulation	Target disease	Reference
Chitosan	Dextran sulfate	Curcumin	PEC nanoparticles	Cancer	[24,31]
TMC	Alginate	Curcumin	PEC	Cancer	[24,32]
Chitosan	Poly(L-malic acid-co-D,L-lactic acid)	Doxorubicin	PEC nanoparticles	Cancer	[24,33]
Chitosan	Dextran sulfate	Tenofovir	PEC nanoparticles	HIV/AIDS	[24]
Chitosan	Dextran sulfate, heparin	Adenosine 50-monophosphate Monohydrate	PEC nanoparticles	HIV/AIDS	[24,34]
Chitosan	Carrageenan	NS	PEC	Gastric ulcer	[24,35]

Chitosan	Neem gum, Hupu gum	Vancomycin	PEC nanoparticles	Staphylococci infections	[24,36]
Eudragit RL 30D	Carboxymethyl kappa carrageenan	Miconazole	Bioadhesive matrix tablets	Fungal infections	[24]
Chitosan	Pectin	Chitosan/pectin Prepared by precipitation method.	PEC membrane	Anti-diarrheics, detoxicants and as protectors of the gastrointestinal tract	[24,6]
Chitosan	Hyaluronan (HYA)	Tenofovir	PEC nanoparticles	HIV/AID	[24,37]

b) Colon-Specific Drug Delivery System :-

Table 2. Applications of PECs in colon specific drug delivery system

Polycation	Polyanion	Drug	Formulation	Method	References
Chitosan	Pectin	Vancomycin	Tablets	1)Preparation of chitosan/pectin complex and solid complex weight measurement 2) Tablet preparation	[38]
Dimethyl aminoethyl methacrylate	Acrylic acid	Ketoprofen	Hydrogel	1) Preparation of AAc/DMAEMA gels 2) Preparation of Ketoprofen-loaded gel 3)Crosslinking technique.	[39]
Chitosan (CS),	Eudragit RL100(EL)	Ibuprofen (IBF).	Tablets	Nonstoichiometric method wet granulation	[40]
Chitosan	Pectin	Theophylline	Enteric coated tablets	Wet granulation method	[41]
Chitosan	Carboxymethyl starch	Acetaminophen	Tablet	Purification method	[42]
Gelatin	Pectin	Metronidazole	Gel	Coacervation	[43]

c)Polyelectrolyte Complex In controlled Drug Release :-

Table 3.Applications of PECs in controlled drug release

Polycation	Polyanion	Drug	Formulation	References
polyvinyl pyrrolidone	Carbopol	Diclofenac sodium	Tablets	[44]

N-trimethyl chitosan (TMC)	N-carboxymethyl chitosan (CMCh)	Dexamethasone (DMS)	Microcapsules	[45]
Chitosan	Carbopol	Theophylline	Matrix table	[46]
Chitosan	Gum kondagogu (GKG)	Diclofenac sodium	Pellet	[47]
Gelatin	Sodium Carboxymethyl Cellulose	Isoniazid	Microparticles	[48]
Chitosan	Carbopol	Pentoxifylline	Tablet	[49]
Poly(l-lysine) (PLL)	Two cellulose sulfates (CS)	Rifampicin (RIF) and bisphosphonate risedronate (RIS)	Films	[50]

B] Application of PECs are as per formulation

a) In Tablet :-

Table 4. Applications of PECs in Tablet dosage form

Sr. No.	Polycation	Polyanion	Drug	Formulation	Application	References
1.	Chitosan[ά-(1,4)2-amino-2-deoxy-β-D-glucon]	Alginate, carboxymethylcellulose sodium, carbopol and pectin	Diltiazem HCl,	Matrix tablets	1)Diltiazem HCL works by relaxing the muscles of your heart and blood vessels. 2)It is used to treat hypertension, angina and certain heart rhythm disorders.	**[51]**
2.	Chitosan	Okragum mucilage	Diclofenac sodium	PEC Matrix tablet	Diclofenac sodium is a nonsteroidal anti-inflammatory drug. It relieve pain,swelling and joint stiffness caused by arthritis.	[52]
3.	Chitosan	Pectin	Bupropion hydrochloride	Sustained release matrix tablets.	Bupropion hydrochloride is an Antidepressant medication used to treat major depressive disorder and seasonal affectivedisorder.	[53]
4.	Chitosan	Carbopol	Pentoxifylline	Mucoadhesive matrix tablets	Pentoxifylline used to treat peripheral arterial disease.	[49]
5.	Chitosan	Sodium alginate (SA), Guar gum (GG), and Xanthan gum (XG)	Isosorbide mononitrate	PECs-based matrix tablets	Isosorbide mononitrate used in the treatment of cardiovascular disorders and prophylaxis of angina Pectoris	[54]

6.	Eudragit E	Sodium alginate	Diltiazem hydrochloride	Matrix tablet	Diltiazem hydrochloride used in the treatment of angina and hypertension	[55]
7.	Chitosan	Pectin	Theophylline	Enteric coated tablets	Colon targeted drug delivery. Theophylline used to treat lung diseases such as asthma and COPD.	[41]

b) In Nanoparticles :-

Table 5. Applications of PECs in nanoparticles

Polycation	Polyanion	Formulation	Active agent/drug	Method	Application	References
Chitosan	Pectin	Nanoparticles	Nisin	1. The Effect of m (PE): m (CHI) Ratio on the Stability of PE-CHI Complex Colloid 2. The Effect of pH on the Stability of PE-CHI Complex Colloid 3. Preparation of Nisin Nanocapsules with PE-CHI Complex 4. Nisin Loading Capacity and Encapsulation Efficiency	Antibacterial activity	[56]
Chitosan	Pectin	Nanoparticles	Sodium tripolyphosphate	Ionic gelation method	Chronic wound healing	[57]
Chitosan (CS) is a polycationic polymer at acidic pH conditions, while TMC has cationic property at acid, neu-tral and alkaline	Sodium alginate	Silver nanoparticles	Gentamycin [Drug].	PECs is formed via electrostaticinteractions and intermolecular/intramolecular secondary forces	Anti-tumor properties.	[58]

pH conditions,						
Chitosan	Dextran sulfate	Nanoparticle	Lutein	Polyelectrolyte complexation technique	1.In the eye, lutein blocks blue light and is thought to function as an antioxidant. 2.The efficacy of lutein as an antioxidant stems from the fact that it can quench and scavenge light-induced intracellular reactive oxygen species (ROS)	[59]
N-[(2-hydroxy-3-trimethylammonium)-propyl]chitosan (HTCC)	Chondroitin sulfate (ChS)	Nanoparticles	Glycidyl trimethylammonium chloride (GTMAC)	A facile polyelectrolyte complexation method	Osteoarthritis	[60]
chitosan (CH)	Dextran sulfate (DS)	Nanoparticles	Amphotericin B (AmB)	Polyelectrolyte complexation technique	Treat systemic fungal infections	[61]
Chitosan	Chondroitin sulfate	Nanoparticles	Metoclopramide	Ionic gelation method	Potential novel delivery system for the transport of hydrophilic compounds such as proteins.	[62]

c)In Microparticles :-

Table 6. Applications of PECs in microparticles

Polycation	Polyanion	Drug	Method	Applications	References
Chitosan.	Moringa gum	Sofosbuvir	Polyelectrolyte complexation	Treatment of hepatitis C,	[63]
Chitosan	Pectin	Aceclofenac	Preparation of aceclofenac-loaded chitosan-pectin complex	Symptomatic treatment of pain and inflammation. It is also used in the treatment of arthritis, osteoarthritis and rheumatoid arthritis	[64]
Cationic guar gum	Xanthan gum (XG)	Diclofenac sodium (DS)	1. Turbidity measurements 2.Viscosity measurements 3. pH measurements	Long-term symptomatic treatment of an kylosing spondylitis, osteoarthritis and rheumatoid arthritis	[65]
Chitosan	Ca-alginate	5-aminosalicylic acid (mesalamine)	Ionotropic gelation	Used to treat ulcerative colitis, Drug delivery to colon and treatment of colitis	[66]
chitosan	Ca-alginate	Naproxen	Ionotropic gelation	Used to treat osteoarthritis, rheumatoid arthritis, and colitis	[67]

d) In Pellets :-

Table 7. Applications of PECs in Pellets

Polycation	Polyanion	Drug	Method	Site Of Action	References
Chitosan	Sodium alginate	Acetaminophen	Extrusion–spheronization method	It is typically used for mild to moderate pain relief.	[68]
Chitosan	Carbopol-71G	Miconazole nitrate	Fluid Bed Process (FBP) method	Vaginal candidiasis.	[69]
Gelatin	κ-carrageenan	Zaltoprofen	Extrusion-spheronization technique	Rheumatoid arthritis, osteoarthritis, and other chronic inflammatory pain conditions	[70]

e) In Beads :-

Table 8. Applications of PECs in Beads

Polycation	Polyanion	Drug/main component/formulation	Method	Application	References
Chitosan	Carrageenan	Sodium diclofenac [drug]	Crosslinking method	Diclofenac is used to relieve pain, swelling (inflammation), and joint stiffness caused by arthritis.	[71]
Poly(methylene-co-guanidine) (PMCG)	Cellulose sulphate (CS)	Cyclohexanone monoxygenase [is an enzyme]	Encapsulation techniques	Cylohexanone monoxygenase is use as biocatalyst in the food, fine chemicals, agrochemicals, and pharmaceuticals industries.	[72]
Chitosan	Carrageenan	Multilayered beads[formulated product].	Layer-by layer technique	Their potential application in encapsulation.	[73]
Chitosan	Chondroitin sulfate	Chitosan-chondroitin sulfate PEC Ag microbead.[formulated product]	Emulsification to produce microbeads	Articular cartilage has a limited healing capacity that complicates the treatment of joint injuries and osteoarthritis.	[74]
Polyallylamine (PAH)	Poly(styrene sulfonate) (PSS)	Payload [as a model small molecule]	Phase inversion	Vehicles for controlled release,and for protection of cells and enzymes.	[75]
Low molecular weight chitosan (LMCH)	Gellan gum (GG)	Rifabutin[drug]	Ionotropic gelation technique	Helicobacter pylori infection.	[76]
Water-soluble chitosan (WSC)	Sodium Alginate	Bovine serum albumin. [main component]	Dropping method	Wound dressing application	[77]
Chitosan	Sodium Alginate	Ciprofloxacin [drug]	Simple ionic cross-linking	Treatment of urinary tract infections	[78]

Chitosan	Carrageenan	Sodium benzoate (NaB) and rhodamine B[main component]	1)Preparation of PECs beads. 2) Loading the Drug or Dye and Performing Release Studies. 3) Drying and Rehydration.	In order to produce PEC beads more suitable for applications after invasive surgeries.	[79]
Chitosan	Poly(acrylic acid-co-maleic acid)	Genipin [main component].	Crosslinking technique	1) Genipin used in the treatment of gastric infections supported by Helicobacter pylori. 2)Genipin involve in stem cell transplantation, and development of contraction free biomaterials suitable for cartilage engineering	[80]

f) In Microcapsules :-

Table 9. Applications of PECs in microcapsules

Polycation	Polyanion	Active agent	Intended application	References
Chitosan	Alginate	Nitrofurantoin	Controlled drug release in an oral sustained delivery system	[66,81]
Chitosan	Alginate	Guaifenesin	Controlled drug release	[66,82]
Chitosan	Alginate	Albumin	Delayed release system for the delivery of orally administrated protein	[66]
Chitosan	Alginate	Hemoglobin Immunoglobulin G (IgG)	Study of capsule stability and permeability	[66]

g) In Microspheres :-

Table 10. Applications of PECs in microspheres

Polycation	Polyanion	Active agent	Intended applications	References
Chitosan	Alginate	Sudan orange G	Oral controlled release system for short-life oil-soluble drugs	[66,83]
Chitosan	Alginate	Hemoglobin	Controlled release of proteins administrated orally	[66,84]
Chitosan	Alginate	Isoniazid	Microencapsulation by adsorption to overcome the limitation caused by hydrophilic characteristics	[66,85]

2) Application Of Polyelectrolyte Complex In Biotechnology

Table 11. Applications of PECs in Biotechnology

Polycation	Polyanion	Formulation	Action/enzyme	Method/active agent	References
Chitosan	Xanthan gum	Polyelectrolyte complex gel	Showed pH-sensitive swelling	Swelling method.	[86]
Tanfloc	Sodium alginate (AG)	AG/TN hydrogel	Bactericidal and antioxidant activity	Polyelectrolyte complex preparation.	[87]
Chitosan	Carrageenan	The pH responsive chitosan-carrageenan polyelectrolyte complex	Increased oral bioavailability of peptide and protein drugs	Salt induced impeding of polyplex formation method	[88]

Polyacrylamides (c-PAM)	Poly(γ-glutamic acid) (γ-PGA)	Protease-polyelectrolyte complexation	Hyperactivation of enzymes	1) Cell culture, expression and purification. 2) Proteolytic activity assays. a] Proteolytic Activity: Suc-AAPF-pNA assay. b] Proteolytic Activity: Skim-milk assay. c] Solubility assay to measure proteolytic degradation of protein-mixtures from a cotton surface. d] Evaluation of proteolytic performance and boosting. 3) Molecular Modeling.	**[89]**
Chitosan	Sodium alginate	Compact polyelectrolyte complexes (CoPECS) as natural and functional biomaterials	Intrinsic anti-inflammatory activity	b-cyclodextrin[active agent]	**[90]**
Chitosan	Pectin	Complex Colloid Particles.	Pectin methyl esterase (PME).[is an enzyme]	Turbidity titration and colorimetric method was used to determine the stability of complex colloid particles.	**[91]**

a) Applications of PECs in vaccine delivery :-

Table 11. Applications of PECs in vaccine delivery

Polycation	Polyanion	Model antigen	Application	Reference
Thiolated trimethyl chitosan (TMC-SH)	Thiolated hyaluronic acid (HASH)	Ovalbumin (OVA)	Potential nasal and intradermal vaccine delivery system	[24]

b) Applications of PECs in gene delivery :-

Table 12. Selected examples of PECs in gene delivery applications

Polycation	Polyanion	Formulation	Therapeutic outcomes	Reference
Chitosan	pDNA	Nanocomplex	Nanocomplexes exhibited high pDNA transfection efficiencies in HEK293 cells in vitro	[24,92]

Chitosan	pDNA	Nanocomplexes	ELISA assay revealed an efficient expression of PDGF-BB and FGF-2 with specific antibodies in mice sera	[24,93]
Polyethylenimine	pDNA	Nanoparticles	Nanoparticles exhibited high transfection efficiency with the gene encoding human urokinase plasminogen activator (Hu-uPA)	[24]
Chitosan	DNA	Chitoplexes	High binding affinity of chitosan to DNA was obtained at pH 5.4 At high charge ratio, the spherical nanocomplexes were formed, without free DNA	[24,94]
PEI-PEG-PCP	siRNA	Polyplexes	Polyplexes exhibited high VEGF inhibition efficiency in human prostate carcinoma (PC-3) cells	[24,95]
PEI	siRNA	Polyplexes	High uptake of siRNA by HeLa cells at higher concentration of copolymer used to modify the surface of polyplexes	[24,96]
PEI-DA	siRNA	Polyplexes	The polyplexes showed high stability against heparin exchange reaction and improved gene silencing efficacy	[24,97]
PFNBr	siRNA	Nanocomplexes	Nanocomplexes showed enhanced cellular uptake in PANC-1 cells	[24,98]

c) Applications of PECs in protein and peptide delivery :-

Table 13. Applications of PECs in protein and peptide delivery

Polycation	**Polyanion**	**Therapeutic protein/peptide**	**Formulation**	**References**
Chitosan	Dextran sulfate and alginate	Insulin	PEC nanoparticles	[24,99]
Chitosan, polyethylenimine, poly-L-lysine	Dextran sulfate	VEGF	PEC nanoparticles	[24,100]
APEG	PMMA	BSA	PEC nanoparticles	[24]

Chitosan, polyethylenimine, poly-L-lysine	Dextran sulfate	Repifermin_	PEC nanoparticles	[24,101]
Chitosan	Alginate	bFGF	Scaffolds	[24,102]
Chitosan	Hyaluronate	Insulin or vancomycin	Nasal insert	[24,103]
Chitosan	Alginate	Ovalbumin	Nanocomplex	[24]
Chitosan	Poly(_-glutamic acid)	SDF-1	Multilayer films	[24]
Chitosan	NaCS and PPS	Lactoferrin	PEC capsules	[24,104]

VEGF, vascular endothelial growth factor; PMMA, poly(methacrylic acid); APEG, bis-(2-aminopropyl)poly(ethylene glycol); bFGF, basic fibroblast growth factor; SDF-1: stromal-derived factor 1; BSA, bovine serum albumin; NaCS, sodium cellulose sulfate, PPS, sodium polyphosphate.

3) Application of polyelectrolyte complex in tissue engineering

Table 14. Applications of PECs in Tissue engineering

Polycation	Polyanion	Formulation	Application	References
Poly(vinylamine-co-vinylformamide)	Carboxymethyl cellulose (CMC)	PEC films	Chemical Engineering	[105]
[Poly(vinyl methyl pyridinium) chloride	[Sodium poly(styrene sulfonate)	"Complex coacervates"	Industrial and Engineering chemistry application.	[106]
Chitosan	Poly(L-glutamic acid)	Multilayered films	Cartilage tissue engineering.	[107]
Chitosan	Sodium alginate	Polyelectrolyte-complex fiber	Tissue engineering	[108]
Chitosan	Gelatin	Scaffold,	Tissue enginering	[109]
Chitosan	Alginate and/or heparin	Fiber Formation by Interfacial Polyelectrolyte Complexation	Biomedical Engineering	[110]

4) Application Of Polyelectrolyte Complex In marine

Table 15. Applications of PECs in Marine

Polycation	Polyanion	Method	Formulation	References
Low Molecular Weight Chitosan	Insulin	USP HPLC methods	PEC nanoparticles	[111]
Chitosan	Pectin,	Self-assembly Method.	Tablets	[112]
Chitosan	Alginate	Extrusion; one-stage: alginate into chitosan w/or w/o calcium; two-stage: alginate into calcium followed by chitosan coating	Nanoparticles; microparticles; hydrogel beads; gels; tabets; films/membranes	[113]
Chitosan	Gelatin	Viscometric and turbidimetric methods	Hydrogels	[114]
Chitosan	Gelatin	Stoichiometric method	Bio-polyelectrolyte complex (PEC)	**[115]**

5) Diagnostic and imaging applications of PECs

Table 16. Applications of PECs in Diagnostic and imaging

Polycation	Polyanion	Chemical element	Method	References
Chitosan	Dextran sulfate	Gadolinium (Gd).	Complex coacervation	[24]

6) Biomedical application of Polyelectrolyte complex

Table 17. Applications of PECs in Biomedical

Polycation	Polyanion	Method	Formulation	References
Weak polyelectrolytes: chitosan and poly(allylamine hydrochloride)	Poly(acrylic acid) (PAA) and poly(2-acrylamido-2-methylpropanesulfonic acid – co – acrylic acid) (PAMPSAA)	a)As colloidal dispersion b)Turbidimetry,DLS and AFM have been used as complementary mathods to described	PECs nanoparticles	[8]

		the characteristic of the PEC dispersion		
Polyallylamine-poly(acrylic acid) (PAH-PAA)	Poly(styrene sulfonate) (PSS)	Layer-by-layer (LbL) deposition method	Protein-polyelectrolyte complexes (PPCs)	[116]
Polyacrylamides (c-PAM)	Poly(γ-glutamic acid) (γ-PGA)	1) Cell culture, expression and purification. 2) Proteolytic activity assays. a] Proteolytic Activity: Suc-AAPF-pNA assay. b] Proteolytic Activity: Skim-milk assay. c] Solubility assay to measure proteolytic degradation of protein-mixtures from a cotton surface. d] Evaluation of proteolytic performance and boosting. 3) Molecular Modeling	Protease-polyelectrolyte complexation	[89]

7) Clinical Application Of Polyelectrolyte complex

Table 18. Applications of PECs in clinical studies

Polycation	Polyanion	Formulation	Action	Reference
TypeB gelatin	Pectin	Pectin-type B gelatin PECs	Anticancer Therapy	[117]

8) Other application of polyelectrolyte complex

Table 19. Applications of PECs in other formulation

Polycation	Polyanion	Drug/method	Formulation	References
Chitosan	Sodium alginate	Ranitidine	Gel formulation	[118]
Poly(diallyldimethylammonium)-dominated	Poly(styrenesulfonate)-dominated	Layer-by-layer deposition technique	Polyelectrolyte complex films	[119]
Chitosan	Alginate	Chlorhexidine digluconate	Inserts	[120]

Chitosan	Alginate	Dexamethasone BSA Growth factor Avidin	Fibers	[121]

14.CONCLUSION

A extensive variety of research is available on the PECs.Newly, the use of natural polymers in the design of drug delivery system has established much awareness owing to their tremendous bioavailability and biodegradability. A lot of particular complexes are novel, eco-friendly, biocompatible and be able to be use for range of application into the pharmaceutical and biomedical field. These complexes merge the property of two different polymers without behind their distinctiveness.

PECs have been used in a lot of dosage form for the arrangement of constant controlled release system and too for the transplantation or tissue repairing agent. The development of PECs is inclined not simply through element property similar to stereochemical appropriate, their molecular weight, charge density, etc. other than besides through secondary experimental situation like concentration of polyelectrolytes earlier toward mixing, their mixing ratio, ionic potency of the solution, mixing order, etc. The formation of PECs is describe in this article and it is separated into three main module, i.e., primary complex arrangement, configuration procedure inside intracomplexes and intercomplex aggregation process. The pharmaceutical industry must believe PECs as successful pharmaceutical excipients as replacement for ordinary polymers and they might consequently reside in a essential consign in the marketplace.

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