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WATER-SOLUBLE SYNTHETIC POLYMERS IN MEDICAL APPLICATIONS

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In this review, physiologically active polymers and impact of polyelectrolytes on the immunological parameters have been explored. Results obtained with addition of synthetic biopolymers show a higher protection against viral and bacterial infections which indicates a great potential for production of biotechnological vaccines. In this article the structure of polyelectrolytes is compared with natural polymers.
Keywords: *biopolymers, polymeric adjuvants, polymers in vaccine formulations*

INTRODUCTION

The basic research criteria for developing new vaccine techniques are as follows; the antigenic property of the synthetic molecule and the ability of the immune system to identify these molecules. The basis of new generation vaccines is to synthetically produce antigen of a pathogenic microorganism and use this molecule in the vaccine [1-3]. Classical Pasteur vaccines have for centuries protected mankind from various contagious diseases such as hepatitis, plague, smallpox and rabies for a century. In these classical vaccines pathogens are weakened or killed chemically and then introduced to the patient resulting with production of antibodies, defence mechanism against pathogens' antigens[4].

However, these classical vaccines are characterized by some disadvantages along its effective protection such as minute presence of viable pathogen within the vaccine solution which can cause unexpected infections through vaccination. Also nucleic acids of viruses can cause genetic alterations in the host body and traditional vaccines can cause local reactions where they are introduced. They have low solubility and stability, high production and are value, they are sensitive to light and heat so cold chain reactions must be followed strictly from the stage of production to their application[5, 6].

Vaccines are biological solutions manufactured to induce the immune system for protecting the organism against pathogens. The first ingredient of these is attenuated pathogens or antigens isolated from these pathogens. Once the vaccines are injected the immune system of the organism produce humoral response (antibody) and cellular response (cytotoxic or T cells) in order to eliminate antigens and cells contaminated with antigens. Immune response produced after an accurate vaccination should protect the organism from future infections with a long term memory mechanism. Classical vaccines are prepared by combining an attenuated virus or bacteria incubated within a continuous cell culture and an adjuvant (aluminium hydroxide or fat adjuvants known as saponins). Vaccines prepared in the presence of such adjuvants have a few disadvantages such as high viscosity, local reactions in the region of injection, high toxicity, allergenic properties and low stability which limits the practical usage of these vaccines [5, 7-10].

The use of the current technology makes it not only possible to isolate proteins or polysaccharides that cause immunity, but also chemically synthesize polypeptide antigens with the help of solid phase method and thus tie these molecules to non-toxic immunostimulant polymer adjuvant and synthesize bioconjugates and immunogenic

biopolymer that show long term protection. However, this type of vaccines is required as well. Biopolymer conjugates synthesised during the preparation of suggested polymer adjuvants showed high antigen specific antibody production *in vivo*, stimulation of cell immunity and high protection against viruses and bacteria. Polymer molecules found in immunogenic bioconjugate can also have the following functions; 1) carrier molecule 2) formulation 3) antigen targeting molecule 4) increase antigen stability [11-14].

Polymeric Adjuvants

In the last 30-50 years the investigation and practice of biologically active synthetic polymers (i.e. polymeric drugs) has developed rapidly. *In vivo* pharmacological tests of antibacterial, antiviral, antihelminik and antifungal polymers have been investigated in a broad scale and have been practiced in clinical medicine (synthetic organs, drug carriers and drug protector etc.). However, the greatest progress with polymers is shown is in adjuvant applications [3, 12, 15-27].

Polymers in Vaccine Formulations

Adjuvant property of polymers is expressed when the physical mixture of these polymers with antigens is injected to the subject or when the polymer solution and antigens are injected one after another. In these systems polymer and the antigen molecules are not bounded to each other with a chemical bond. The second method consists of binding polymer and antigen molecules via bioconjugation and then injecting these molecules into the organism. The results of latest researches made to understand the role of polymers in vaccine formulation can be summarized thusly. Biodegradable and non-biodegradable polymers can bind to organic compounds containing heptane (e.g. trinitrophenol, steroid, hormones), microbe and viral antigens that have model and practical value (bovine serum albumin, bovine gamma globulin, ovalbumin, M protein of influenza virus, (hemagglutinin + neuraminidase), F1 -protein of plague virus, cancer antigen α-fetoprotein, H- and O-antigens of *Salmonella typhimurium*, β-OLH (ovine luteinizing hormone), polypeptide epitope of α-VP1 protein from *Clostridium perfingers*, antigenic region of *Brucella Abortus,* antigenic lipopolysaccharide (LPS) of *Coxiellaburnetii*, V1 capsid protein of foot-and-mouth disease virus, NY-ESO-1 antigens of melanoma, etc.) was formed into bioconjugates by using different binding methods and different structure forming techniques, injected into mice and their ability to produce antigen specific antibodies was investigated *in vivo*. Latelyphysiological activities of polyelectrolytes whether for vaccines or for preparing drug solutions, became necessary to investigate such chemical reactions [3, 12, 15-25, 27, 28].

POLYELECTROLYTES

Electrolytes are molecules that can dissociate to positive and negative ions in aqueous environment. For example, table salt; NaCl is an electrolyte and it dissociates to positive sodium ion (cation) and negative chloride ion (anion). **Polyelectrolytes** are electrolytes showing polymeric properties. Polyacrylic acid is a good example for polyelectrolytes; when placed into water Hydrogen belonging to acid dissociates and combines with water molecule resulting with H_3O^+ ion (Figure 1). The polymer is charged negatively due to remaining negative carboxyl group [29-31].

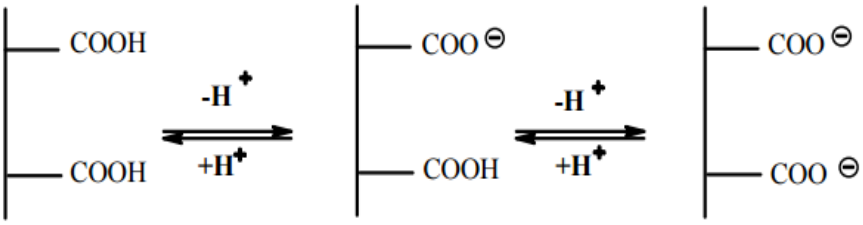

Figure 1. Dissociation of polyacrylic acid in the aqueous solution [32].

Uncharged molecules tend to take a coil shape. Because this coil shape is irregular it is commonly known as random coil. Nevertheless, when the polymer chain has a negatively charged group which repel each other the polymer cannot take a coil shape which makes the solution more viscous. When the polymer has an open structure it takes up more space compared to coil structure which allows the molecule to resist flow when the solvent molecules surround the polymermaking the solution dense and viscous. To prevent this from happening salt can be added to the solution. This allows the negatively charged chains of the polymer to interact with the positive ions obtained from the salt allowing the polymer to take a coil shape [29, 33, 34].

Polymers are divided into natural polymers and biopolymers (synthetic polymers). Biopolymers and natural polymers have different properties compared to each other;

- Synthetic polymers are composed out of chains with varying molecular weight PDn≠1, whereas natural polymers are composed out of regular chain lengths PDn=1.
- Biopolymers are not found in nature; they are synthesised usually via activation of a radical. Natural polymers are found in nature; they are usually synthesised via condensation polymerization reactions.
- Biopolymers do not have a uniform molecular structure; the organisationof the chain can vary. Natural polymers have a uniform structure; the organisation of chain does not vary.
- When the location of a molecule is changed on a biopolymer the property or the polymer does not change. In natural polymers the structure of th molecule is always the same, the organisation on the chain does not change.
- Biopolymers do not have a stable conformation; they have a coil structure in solution. Biomacromolecules have a rigid structure.

Biopolymers can be classified according to their solubility and physiological activities. Aside these classification factors, biopolymers can be divided into polyanions, polycations or ampholyte sub-groups. Conformation of biopolymers is affected from various parameters such as pH, salt concentration, temperature [35, 36].

- Interactions between biopolymers;
- Ionic interactions
- Interactions with Hydrogen bonds
- Van der Waals interactions
- Hydrophobicinteractions
- Covalent bond interactions.

Biopolymers are divided into 2 groups according to their effect mechanism;

1. Physiologically active biopolymers

Some polymers are composed out of physiologically active monomers while some monomers do not show this activity but they become active when they are polymerized.

A—A—A—A—A—A—A—A—A

(+) (+) (+) (+) (+) (+) (+) (+) (+)

As (+) increases the quantity of force applied increases and cooperative interactions take place accordingly.

Important factor in interactions;

Structure of monomer, molecular weight of the polymer and molecular weight distribution [3, 31, 37].

2. Physiologically non-active biopolymers

This type of polymers requires a physiologically active compound (PAC) such as penicillin in order to show activity (Figure 2).

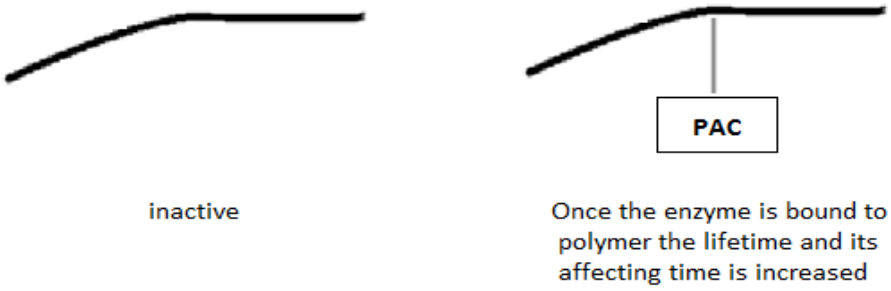

Figure 2. Physiologically inactive polymer that require a PAC.

When a small organic molecule is introduced into a biological system only 10-30% remains in the body and the rest is thrown out of the system. But when an effective molecule such as penicillin is bounded to a polymer, the circulation duration of the molecule and its effect on cell surface increases. Along this improvement the absorption of the molecule rises above 10-30%. Insulin injection for instance, the effective molecule of insulin had to be injected to the patient every 2 hours before it was bounded to polyethyleneglycole, one the molecule was tied to the polymer the duration between injection could be increased to 20 hours [31, 33, 38].

A. **Physiologically active polymers;** are water soluble. Because they are water soluble their physiologically properties such as ionic charge, pH, etc. can be investigated [39, 40].

These polymers are divided into 5 groups according to their structure.

a. **Neutral Polymers:** Physiological activity is expressed according to their physicochemical property. They have no net (-) or (+) charges in their structure. Their chemical structure can vary. These polymers weakly interact with structure elements of the organism. They usually carry a hydroxyl (-OH) group in their structure and they are water soluble. The most popular neutral polymers are polyvinylalcohol (PVA) and polyvinylpyrrolidone (PVD)[3][39, 41].

b. **Polycations:** Biopolymers containing (+) charges in their structure. Their physiologically activity is primarily dependent on the concentration and the distribution of the (+) charge followed by the type of monomers.

- Some examples of polycations are; Polyvinylamine and Poly-4-vinylpyrodine (PVP).

Application areas for polycations;

- They are popular in medicine; antiheparin is used in medicine and biology. Heparin is used to halt the blood flow, to coagulate the blood.If heparin is applied in excess quantity during a surgery which is difficult to control addition of polycations forms a complex with heparin resulting with removal of side effects and flushing out of excess heparin. Surplus coagulate can cause cardiac arrest.
- Polycations are used in the development of vaccines [3, 31, 39].

c. **Polyanions:** Polyanionic polymers contain (-) charged side chains and their activity is directly affected by the density and distribution of these groups followed by the structure of the monomers. When the polymer is introduced to the organism it will not interact with cell walls. Polyanions can compete with compounds in the organism and go under substation reactions (polyanions combine with polycations). Positively charged molecule forming a complex with DNA molecule compete with polyanions for binding. Application areas of polyanions are vast and are similar to glycoproteins or DNA.The physiologic activity of polyanions is dependent on the density of the negative charges. Because of their anticancerogenic properties these polymers are investigated to be used in cancer treatments.

d.

They have anticoagulant properties. They affect the isoelectric points of proteins. The affect he viscosity of blood and change the intracellular potassium concentration [3, 31, 38, 40, 42, 43].

Polyanions effect on the immune response;

To clarify the effects of thermal transition of polymer–protein conjugate chains on the immunogenicity of protein antigens, the immunologicalactivity of modified BSA was examined in comparison with that of the free protein. The dynamics of antibody formation, (OD405) induced by BSA (as control) and Poly (Nisopropylacrylamide-co-acrylicacid)-BSA conjugates are presented in Figure 3[11].

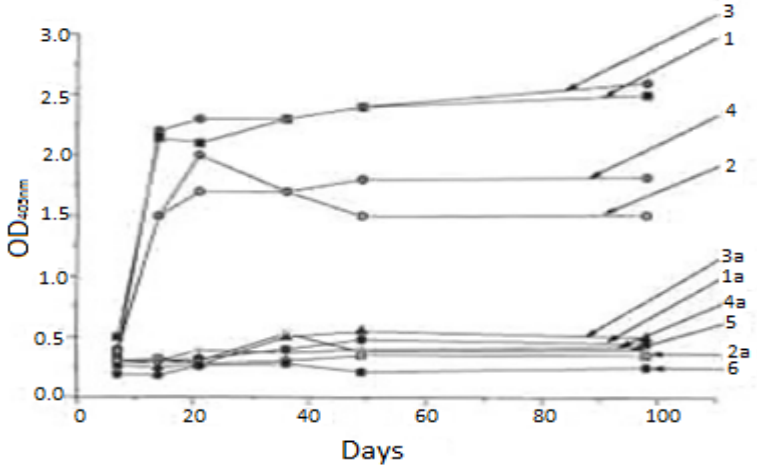

Figure 3. The dynamics of formation of protein-specificantibodies (OD405) in the blood sera of mice immunized with polymer-protein conjugate at dilute solutions. [0.1 (1a), 0.05 (2a), 0.03 (3a); 0.01 (4a) g/dl] and thermally precipitated concentration [2.286 (1); 1.346 (2); 0.673 (3); 0.448 (4) g/dl] preparing at different C protein/C polymer: 0.28 (1,1a); 0.59 (2,2a); 1.14 (3,3a); 1.70 (4,4a) pureprotein (5), serum of mice without immunization (6); protein dose: 100µg; phosphate buffer (pH7.2)[11].

e. **Synthetic Analogies of Nucleic Acids:** Polymers used as nucleic acid analogies have to have a neutral structure (it should not contain sugar or phosphate groups) which protect purine or pyrimidine bases properties[3].

f. **Biopolymers Containing Different Functional Groups:** These contain a broad type of functional groups (carboxyl, amino, etc.) and have various structures. They have ampholyte properties and react with cooperative interactions.Because the polymer has both (+) and (-) groups, the ratio of these groups can be altered by changing the pH of the environment [3].

B. Physiologically Non-Active Biopolymers;

These biopolymers do not have specific activities. They are used as blood substitute. Because of their antitoxic properties they are used against toxins. With polymers used as substitute for blood it is important to supply the equivalent volume and osmotic pressure with blood. The synthetic blood should be flushed out of body after a while otherwise these polymers can stick to kidneys [3, 10, 33].

First System: Neutral Chain

This structure does not interact with DNA. However, the resemblance of its activity to DNA is important. According to tests done with animals, electroneutral polymers introduced into a biological system, it is excluded within 10 hours. When introduced into bloodstream, it was observed that the polymer goes into the liver, spleen, thymus and brain stem. The polymer was not observed in the lung and kidneys. Going from these locations the distribution pattern of the

polymer was developed. They are not toxic in high dosage and they do not affect the immune system and macrophages. It was observed that these polymer halts the replication of leykoz virus which whitens the blood and they are spread within the spleen[3, 11, 33, 35, 39].

Second System: Anionic Chain

The second system has a polyanionic structure and shows polyanionic properties. They are not selective and do not interact with DNA [33].

Third System: Cationic Chain

These systems have different properties compared to others. Polymeric structures containing cation chains can form interpolymer complexes with polynucleotides [33].

2. PHYSIOLOGICALLY NON-ACTIVE BIOPOLYMERS

Physiologically non-active biopolymers are activated with the addition of small molecules called physiologically active compound (PAC), polymer and PAC is conjugated (Figure 4).

Figure 4. Conjugation of physiologically non-active biopolymers with physiologically active compound

Conjugating the physiologically active compound to polymer has a few advantages.

1- Polymer does not have physiologically activity on its own. It works as a carrier, as a vehicle (Figure 5). Considering the polymer is carrying a drug, the polymer should be biodegradable for it to be removed from the blood stream.

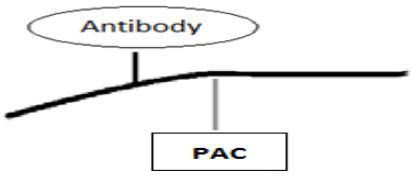

Figure 5. Binding of PAC and antibody to the polymer

2- A second molecule such as an antibody gives the polymer a targeting property. Antibody attached to polymer directs the polymer hence the drug to the appropriate antigen.

3- It provides protection against parameters such aspH,enzymes, etc. that can disrupt the structure of the drug. To protect the drug from other parameters it is covered with a polymacromolecule sheet. This capsule should be soluble in pH=7 when taken orally with water.The capsule should protect the drug until it reaches to stomach. The capsule dissolves once it reaches the acidic environment of the stomach and the effective molecule of the drug is released. By binding the effective molecule to a polymer a long term protection is achieved.

4- The duration and the strength of interaction between drug effective molecule and the receptorincreases when the effective molecule is bounded to a polymer.

5- Increases solubility in water. Water insoluble drug effective molecule becomes water soluble when bounded to a polymer. Chu and colleagues have shown water insoluble fulloren becomes water soluble when bounded to a protein which allowed for it to be injected into bloodstream.

6- By binding different drugs with same effective molecule to a polymer it is possible to make the drug affect different locations [3, 10, 33, 44, 45].

BINDING DRUG TO A POLYMER

- The drug should not lose its properties after it is bounded to polymer.
- It should be flexible.
- Free movement of the drug should be allowed.

EFFECT MECHANISM OF THE CONJUGATION

1stSCENARIO: In this scenario the polymer and the physiologically active compound work together throughout the whole process (Figure 6).

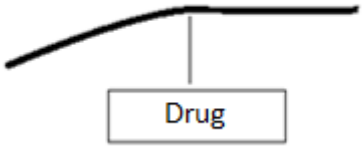

Figure 6. Cooperative work of polymer and physiologically active compound [11].

2ndSCENARIO:In this scenario the polymer and the drug work separately(Figure7).

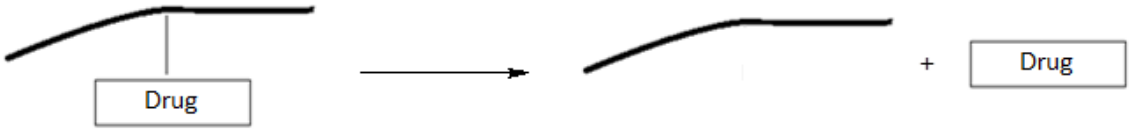

Figure7. Separate working mechanism of the polymer and PAC[11].

According to the bond character between the drug and the polymer 1st or the 2nd scenario occurs. If the bond between is biodegradable the 1st scenario takes place if the bond is not biodegradable the 2nd scenario takes place.

The separation of the drug from the polymer can occur in various places such as the blood stream, stomach, etc. and they can have various physiological activities. The polymer works as a carrier, the effective molecule travels into the cell and separation occurs here. Increasing the effective period of PAC is known as **prolongation**. Conjugate (polymer + PAC) separation occur in the bloodstream.

Another mechanism allowing the separation of PAC from the polymer is lysosomes. Conjugate entering the cell is digested with lysosomes; this is especially useful for conjugates carrying anti-tumour drugs. Again, the polymer works as a carrier. Binding the same drug to various polymer carriers changes the effecting mechanism and residence time. These factors are also affected from the molecular weight of the polymer and the effective molecule, the type of the bond formed between. For example, as the molecular weight increases the concentration depletion for the drug increases because it becomes harder for the drug to be transported [11, 13, 15, 20, 45].

The effective molecule binding to polymer

1. Can be stimulated within the bloodstream outside the cell wall;

2. Can attach to the cell wall

3. Can be stimulated within the cell after entering through the membrane.

PAC's THAT WORK INSIDE THE CELL

A. Anticoagulant Property: It is used to prevent clotting within the bloodstream.

B. Antibiotics: They affect the bacteria that are outside of the cell. The drug binds to

the polymer and the antibiotic neutralizes the bacteria.

The separation time must be chosen according to the purpose; the polymer should not depart from the PAC until it is needed. In order for the effective molecule work outside the cell the polymer should have a big molecular weight making it harder for it to enter the cell. Polymer that is too big to enter the cell barrier should have a strong bond with the effective molecule in order to be able to carry the molecule throughout the blood stream but should be weak enough to be digested by the enzymes in the environment when it reaches its destination[11, 20, 46].

1. PAC's THAT WORK ON THE CELL SURFACE

These interact with the cell surface receptors and activates there. Their penetration into the cell is unwanted; these types of conjugates are meant to work on the membrane of the cell. All of these have determined that the structure of the spacer should be developed accurately. It is desired that the spacer should work as affinity chromatography as in antigen-antibody relationship. Once the conjugate binds to cell wall receptors the PAC and the polymer should separate, pain killers work with this mechanism [11, 20, 46].

2. PAC's THAT WORK INSIDE THE CELL

90% of the biopolymers operate with this mechanism. The conjugate binds to the cell membrane and then it is taken into the cell with mechanisms such as endocytose, because the molecule is too big it is difficult to take it inside the cell via diffusion. Once the conjugate is taken inside the cell they are digested with lysosome enzymes releasing the drug inside the cell [11, 20, 46].

BIOPOLYMERS ACCORDING TO THEIR EFFECTING LOCATIONS

1. Biopolymers that act in the blood stream.

Properties of biopolymers that act in the blood stream are affected from biomacromolecules (proteins, etc.) within the blood stream and the interactions with these molecules. The most crucial factor here is to make sure that the biopolymer does not react with proteins. If such reactions take place insoluble aggregates can take place which can cause coagulation within the vein resulting with fatalities. However, if these aggregates are taken inside the cell and digested with the help of enzymes the patient can survive[11].

1. Biopolymers that act on the cell surface.

These biopolymers interact with cell membrane and react with proteins on the cell surface. The membrane structure changes when these reactions take place. Na^+ and K^+ concentrations on the sides of the membrane hence the osmotic pressure changes accordingly. Biochemical synthesis is affected and does not take place. Because the binding with the receptors in the system changes the immune systems' structure is compromised[11].

2. Biopolymers that act within the cell

Biopolymer works by reacting with organelles within the cell such as mitochondria, nucleus, etc[11].

RESULT

It is considered that, because polymeric adjuvants (polyelectrolytes) show more effective immune response and protection property as compared to classic adjuvants that finding a non-expensive technological method that is suitable to purpose will benefit the health system by producing technological vaccines that have high activity in low dosages.

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ПРИМЕНЕНИЕ ВОДОРАСТВОРИМЫХ ПОЛИМЕРОВ В МЕДИЦИНЕ

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В обзоре исследованы физиологически активные полимеры, а также влияние полиэлектролитов на иммунологические показатели. Результаты, полученные с добавкой синтетических полимеров в вакцины, продемонстрировали более высокую степень защиты от вирусных и бактериальных инфекций, что свидетельствует о большом потенциале для производства биотехнологических вакцин. В статье проводится сравнение структуры полиэлектролитов с натуральными полимерами.
Ключевые слова: *биополимеры, полимерные адъюванты, фармацевтические полимеры.*

SUDA HƏLL OLAN POLİMERLƏRİN TİBBDƏ TƏDBİQİ

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İcmalda fizioloji aktiv polimerlər, eləcə də polielektrolitlərin immunoloji göstəricilərə təsiri tədqiq olunub. Sintetik polimerlərin vaksinlərə əlavələri onların virus və bakterial infeksiyalara qarşı daha güclü müdafiəsini sübut edir, bu da biotexnoloji vaksinlərin istehsalının pespektivliyini göstərir.
Açar sözlər: *biopolimerlər, polimer adyuvantlar, farmasevtik polimerlər.*

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