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Application of polymer in biomedical implication

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Abstract

Polymers are serving the mankind in various ways since long. Over the previous number of years, these polymers have found great demand in various domains. These materials are intensively studied over the years for a various range of applications Polymeric materials have found notable applications within the sphere of biomedical. This might ensue to their useful properties, such as: easy processing, lightweight and suppleness, high strength to weight, availability and recyclability. Polymeric materials also are able to alter their chemical or physical properties upon exposure to external stimuli. Thanks to these properties, they're widely applied for biomedical applications like drug delivery, tissue engineering scaffolds, wound dressings, and antibacterial coatings.

Keywords: Polymer; Hydrophobicity; Antioxidant; Biomedical applications; Tissue/Born regeneration

1. Introduction

Due to the in vivo degradation characteristics of many polymers, they are used as commodity materials in our daily life and they have had a historical application in the biomedical community [1]. In biomedical, electronics, super capacitors, sensors, batteries and structural composites, different types of polymeric materials have been used [2-5].The class of biomaterials which are degradable and natural polymers, more often used for cosmetic and biomedical applications as nano-carriers or tissue engineering scaffolds [6, 7]. Inflammation is a fundamental natural defense process during the body's response to pathogens and in the triggering of tissue repair. But when inflammation is uncontrolled, it is associated with chronic diseases and in the formation and progression of cancer. The characteristics of inflammation microenvironment is the increased permeability of the blood vessels, up regulation of specific cell surface receptors, reduced pH, high oxidative stress, and overexpression of inflammatory and matrix-remodeling enzymes, have been exploited in the development of inflammation-responsive polymeric systems for more effective treatment of these diseases. Via passive targeting, these macromolecular systems can be selectively accumulated in the inflammatory area [8, 9].Poly (glycolic acid) (PGA), poly (lactic acid) (PLA), poly (α-hydroxyacid)s and polydioxanone (PDS) are the most common synthetic biodegradable polymers in medical applications. In controlled/triggered/targeted drug delivery vehicles, tissue engineering scaffolds, cell culture supports, bio separation apparatus, sensors, and actuators/artificial muscles some smart polymers have been used for biomedical applications .Therefore, they complement typical nano-particulate systems which are employed in medicine, e.g. polymers, metallic nanoparticles (like gold), iron oxide nanoparticles (like magnetite) and quantum dots (like CdS) [10-12].

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2. Polymer in Biomedical

Over hundreds of millions of years, all living systems including humans represent the most sophisticated "technologies" in nature and their building blocks are made up of polymeric, macromolecular, and supramolecular assemblies, to a large extent [13]. Some smart polymers are used in the development of new therapies for the treatment of several diseases or sophisticated medical devices that react to the environment of the surrounding tissues (pH, temperature, enzymes, or analytes concentration) or external stimuli (light or magnetic radiation) in the biomedical field. Due to its chemical similarity to human hard tissue (bone and teeth) Calcium phosphate has excellent biocompatibility. Biscnoff and Walden in 1893 introduced a widely used synthetic polymers named poly (lactic acid) (PLA). Natural polymers, such as polysaccharides or proteins and synthetic polymers, such as: poly(glycolic acid) (PGA), poly(hydroxyl butyrate) (PHB) and poly (ε-caprolactone) (PCL) [16]. Polypropylene (PP), polyurethane (PU) and polyethylene (PE) have equally found useful importance in biomedical applications. Some other polymers that are soluble in water {poly (vinyl alcohol) (PVA), poly (ethylene glycol) (PEG), poly (vinyl acetate), poly (acrylic acid) (PAA) and guar gum}, have also been used for biomedical applications for their biocompatibility, controllable degradation rate and their degradation into non-toxic components activities [14-16].

2.1. Polymer

Polymer term stems from the Greek roots poly (many) and meros (part), means "many parts" and designates a molecule made up by the repetition of some simpler unit called a mer. Polymers made by thousands to millions of atoms in a molecule called macromolecules. The preparation of polymer occurred by joining a large number of small molecules which is named as monomers [17]. Polymer systems are widely used because of their unique attributes such as ease of production, light weight, and often ductile nature. However, compared to metals and ceramics polymers have lower modulus and strength [18, 19].Generally, three main types of polymer structure composite morphologies may be observed, Micro composites, Intercalated nano-composites and Exfoliated nano-composites. In micro composites materials, polymer molecules are not able to invade into the galleries between layers. Intercalated structures are formed when several polymer chains are inserted between interlayers. The idealized exfoliated structures consist of individual, nm-thick layers suspended in a polymer matrix, and are a result of extensive penetration of the polymer and delamination of the layer structure [20, 21].

2.2. Desired Properties for Biomedical Application

In biomedical applications, level of safety of materials is important because they have direct interaction with the human body. It must be non-toxic, biodegradable, and biocompatible and meet the required specification for which it will be used. Super hydrophobicity, adhesion and self-healing are also very essential. Research works are on-going to develop materials that will meet all the requirements mentioned above [14]. Sorption and transport properties of water and Water vapor are of noticeable importance in polymeric materials in many industrial sectors. Several applications such as packaging materials for consumer products (e.g. food, pharmaceutical sand microelectronics) through to damp-proofing materials, and reverse osmosis membranes and corrosion barrier films. In the polymer packaging industry, the water vapors barrier property provided by polymer films is a key factor in determining performance [22-24].

2.2.1. Super hydrophobicity:

In biomedical applications, super hydro phobic property is very important. Because of this property they reduce the chances of blood coagulation as a result of unfavorable platelet adhesion. Several biomaterials with this property have been produced [14, 25, 26].

2.2.2. *Adhesion:*

This is another important property. It is displayed by plants and animals and also essential for organisms to survive. This is helpful for organisms to attach themselves either temporally or permanently to their host or vice versa. According to Bassas-Galiaet at, adhesion abilities are very important and used by bacteria, animals and plants. He also said that polymeric materials with this property have been developed and used in biomedical applications [14, 25].

2.2.3. Self-healing:

Self-healing is known as such a way that whenever there is an injury, it repairs or replaces the damaged tissues. It is human body's engineered mechanism. If any injury or damage is beyond self-healing, in form of an implant, there is a need for the introduction of alternative 'material'. Different kinds of polymers and their composites have been used largely due their ability to handle the disadvantages associated with the polymer matrix. For example, they have the ability

- To repair the damaged portion of materials many times
- To naturally heal the material
- To improve the materials with defects of any size
- To decreased maintenance cost

It must exhibit equal or better performance, Should be economical than the materials already in use, in comparison with the traditional materials. [14, 27, 28]

2.2.4. Anti-oxidant and anti-inflammatory activities [29-31].

2.2.5. Regulation of immune responses [29, 32-34]

2.3. Application of Polymer

Now a day the use of polymers as restoration for other materials such as metals, wood, and ceramics has increased significantly. This is thanks to the benefits that polymers offer over conventional materials, including simple processing, productivity, and value reduction [35,36].In recent year's polymer/layered silicate (PLS) nano-composites have attracted great interest, both in industry and in academia, because they often exhibit remarkable improvement in materials properties in comparison with virgin polymer or conventional micro and macro composites. These improvements can include high moduli; increased strength and warmth resistance decreased gas permeability and flammability, and increased biodegradability of biodegradable polymers. On the opposite hand, there has been considerable interest in theory and simulations addressing the preparation and properties of those materials, and that they also are considered to be unique model systems to review the structure and dynamics of polymers in confined environments [37- 49].

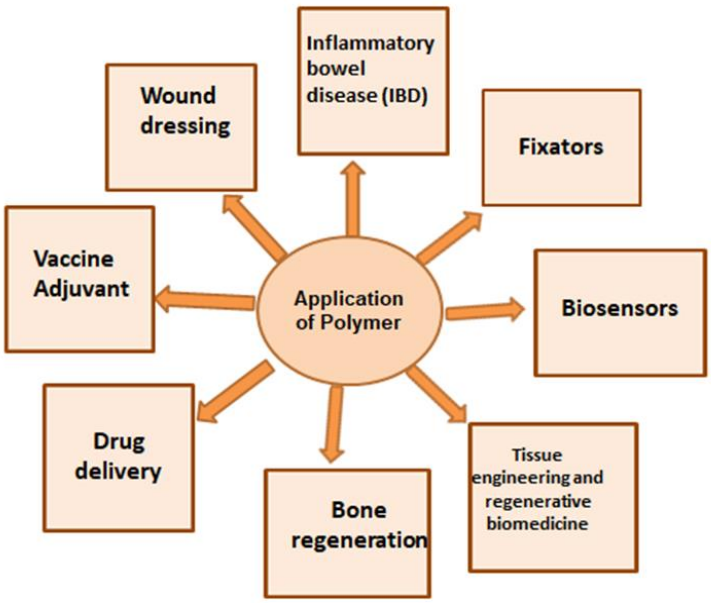

Figure 1 Applications of Polymer [7, 14, 37-49]

3. Role of Polymer in Biomedical

On account of rapid development of novel biomedical technologies, including tissue engineering, regenerative medicine, gene therapy and controlled drug delivery, new materials are being developed to satisfy specific requirements of those fields [50].

3.1. Tissue engineering and regenerative biomedicine

Tissue engineering is an interdisciplinary field within which engineering principles are applied for the event of biologic functional substitutes in body that restores, maintains, or improves tissue functions [51-53]. It involves the utilization of living cells, manipulated through their extra cellular environment or genetically, to develop biological substitutes for implantation into the body and/or to foster remodeling of tissues in some active manner. For instance, a multifunctional

material for bone tissue regeneration should induce formation of recent bone tissue without an addition of organic bone growth factors (e.g. BMP-2), degrade progressively at a rate matching the regeneration of new bone, and induce new blood vessels formation and exhibit antibacterial and anti-inflammatory activity. Silicon may be involved in bone formation and mineralization, whereas orthosilicate acid (Si (OH) 4) at physiological concentration of 10 μmol was shown to stimulate formation of type I collagen in human osteoblastic cells (HOC) and to stimulate cell differentiation [50, 54, 55]. The purpose of tissue engineering is to repair, replace, maintain, or enhance the function of a specific tissue or organ. There are some basic requirements that are widely accepted for designing polymer scaffolds. Firstly, a scaffold should possess a high porosity, with an appropriate pore size distribution. Secondly, a high extent is required. Biodegradability is one more requirement, with the degradation rate matching the speed of neo-tissue formation. Fourth, the scaffold must possess the specified structural integrity to forestall the pores of the scaffold from collapsing during neo-tissue formation, with the acceptable mechanical properties. Finally, the scaffold should be non-toxic to cells and be biocompatible, positively interacting with the cells to market cell adhesion, proliferation, migration, and differentiated cell function. For instance, collagen could be a major natural ECM (Extracellular matrix) component, and possesses a fibrous structure with fiber bundles varying in diameter from 50 to 500nm. In morphology, electrospun nanofiber mat is incredibly like human native ECM, and hence may be a promising scaffolding material for cell culture and tissue engineering applications. Shalumon et al. (2009) reported an electrospun water-soluble carboxymethyl chitin (CMC)/PVA blend for tissue engineering applications. The concentration of CMC (7%) with PVA (8%) was optimized, blended in several ratios (0–100%) and electrospun to induce nanofibers. Fibers were made water insoluble by cross-linking with glutaraldehyde vapors followed by thermal treatment. The prepared nanofibers were found to be bioactive and biocompatible. Cytotoxicity and cell attachment studies of the nanofibrous scaffold were evaluated using human mesenchymal stem cells (hMSCs) by the MTT assay. Cell attachment studies revealed that cells were able to attach and spread within the nanofibrous scaffolds. These results indicated that the nanofibrous CMC/PVA scaffold supports cell adhesion/attachment and proliferation and hence this scaffold may be a useful candidate for tissue engineering applications.

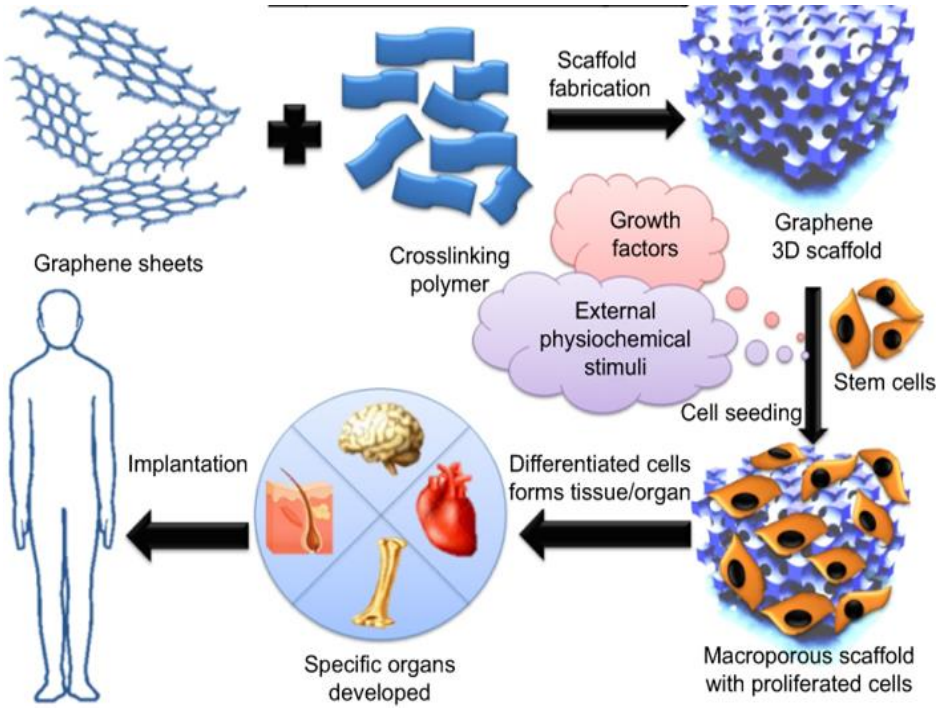

Figure 2 3D scaffold in tissue engineering [69]

Chitin and chitosan may be used as bone substitute for bone repair and reconstruction given that its mechanical property may be improved with addition of biomaterials like hydroxyapatite (HAp), bioactive glass ceramic (BGC), etc. BGC are a gaggle of osteoconductive silicate based materials used for bone repair. BGC are reported to influence osteoblast and bone marrow stromal cell proliferation and differentiation. It's been reported that bioactive glass could directly influence cells at the genetic level. The power of silica to induce apatite formation has already been examined. Hench proposed that a mix of high pH and repolymerization of SiO2 from surface Si–OH groups is sufficient to accumulate CaO and P2O5 from the body fluids, thereby aiding the nucleation and growth of apatite layer [56-63]. A variety of polysaccharides, like alginate ,chitin, chitosan, hyaluronic acid, cellulose, chondroitin sulfate, starch and their

derivatives, are developed as biomaterials for tissue engineering applications as reviewed above and previously elsewhere. Application of polysaccharides as scaffolds in tissue engineering must fulfill the necessities like biocompatibility and nontoxicity, biodegradability with controllable degradation rate, appropriate Porosity, and structural integrity [64-66]. The architecture of blending polymer-based nano fibers with biocompatible, natural materials produces scaffolds with high mechanical strength that also are bio-mimetic,with bio-functional characteristics which will resemble those of natural bone [67,68].

3.2. Bone regeneration

Bone could be a large hard animal tissue that supports and protects various internal organs and provides structural integrity to the body. Defects in large bone are considered one among the main issues caused by infection and trauma. Despite many efforts, like those using bone grafts and implants, there are still limitations and downsides in bone tissue engineering that require to be overcome. Over the past few decades, bone tissue engineering (BTE) has been proposed as a promising alternative to classical therapies. One among the foremost significant aspects of bone tissue engineering could be a suitable scaffold design that may modulate bone healing and mimic the role of the ECM in bone tissue. Thus, suitable scaffolds should contain materials that are biodegradable and biocompatible, which possess appropriate porosity, pore size, mechanical properties, and osteo-conductivity.Zhang et al created a biomimetic nanocompositenanofiber of hydroxyapatite/chitosan (HAp/CTS) prepared by combining an in place coprecipitation synthesis approach with an electrospinning process.Guided bone regeneration (GBR) could be a technique which is widely used as a surgical approach within the augmentation of alveolar bone deformities that are frequently observed in edentulous patients. Recently, Wu et al. improved the steadiness and properties of surface butyrylated chitosan nanofiber (BCSNF) membranes that greatly enhance their potential in GBR. Jalvandi et al incorporated a levofloxacin-conjugated chitosan into PVA nanofibers. The findings showed that the controlled release of levofloxacin (LVF) can be achieved by covalently binding LVF to low relative molecular mass chitosan (CS) via a cleavable amide bond then blending the conjugated CS with PVA nanofibers before electrospinning. They fabricated PVA/LVF and PVA-CS/LVF nanofibers as controls. Levofloxacin release profiles showed that the burst release decreased from 90% within the control PVA/LVF electrospun mats to 27% within the PVA/conjugated CS-LVF mats after 8 h in phosphate buffer at 37 °C. The results indicated that conjugation of the drug to the polymer backbone is a good way of minimizing burst release behavior and achieving sustained release of the drug LVF [67, 70-74]. It is important to contemplate that through the current time, tissue engineering, as an excellent method for the repair/ regeneration of damaged tissue, has been considered as an approach with the potential to transcend the restrictions of both autologous and allogenic tissue repair. The current a part of the review summarizes the varied properties of the biological polymers which were utilized in the skin tissue engineering. Collagen, Fibrin, Fibronectin, Gelatine, Chitosan, Elastin, Alginate, Keratin, mucopolysaccharide (hyaluronan), Polyethylene glycol (PEG), Poly-b-hydroxybutyrate (PHB), Polycaprolactone[75-77].

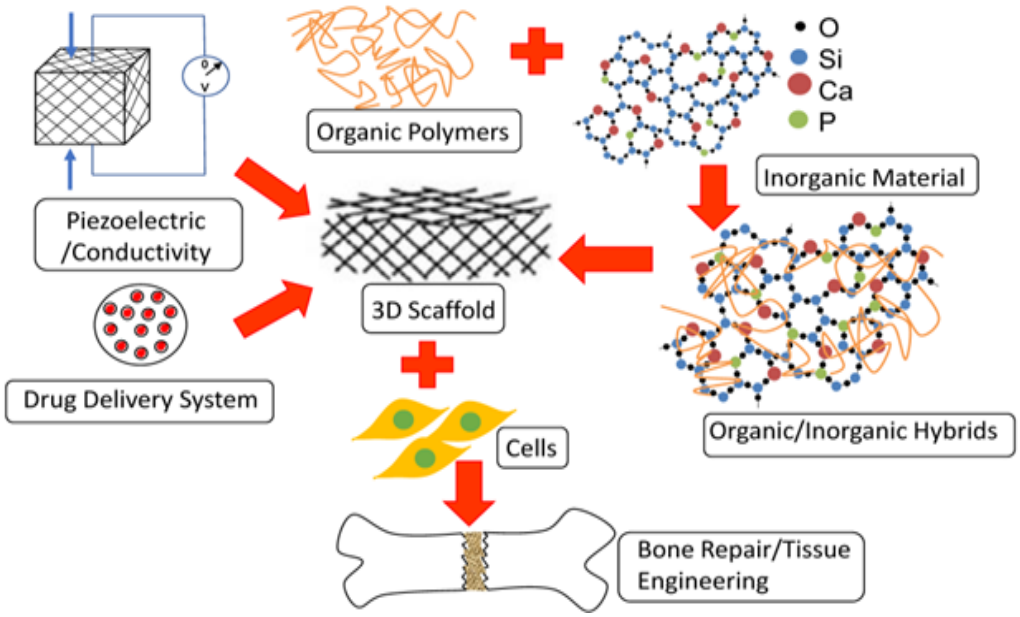

Figure 3 Bone regeneration by polymer based materials [78]

3.3. Drug delivery

Advances in biotechnology have led to a growing number of peptide-, protein-, and antibody-based drugs. Polymers can enable delivery of those drugs [79].Numerous polysaccharide-based drug delivery systems are developed for specific targeting delivery or controlling release, for cover of medication from premature degradation, for improving intracellular penetration and transporation, for enhancing stability and bioavailability of medication, or for the delivery of biomolecules like genes, antigens ,and small interfering RNA[65,80-83].Oral drug delivery is one in every of those applications, during which the polysaccharide excipients are accustomed increase the solubility and bioavailability of the active drugs, to attain a particular release profile from the ultimate formulation, and to reinforce the steadiness of the ultimate drug products[84,85].Water-soluble carboxymethyl chitin (CMC) was used for drug delivery applications. Dev, Binulal, et al. (2010) prepared poly (lactic acid) (PLA)/CS nanoparticles by emulsion method for anti HIV drug delivery applications. The hydrophilic antiretroviral drug lamivudine was loaded into PLA/CS nanoparticles. The encapsulation efficiency and in vitro drug release behavior of drug loaded PLA/CS nanoparticles were studied using absorption spectrophotometry. Additionally, the cytotoxicity of PLA/CS nanoparticles using MTT assay was also studied. The in vitro drug release studies showed that the drug release rate from PLA/CS nanoparticles decreased when the pH of the medium changed from alkaline too acidic to neutral. The drug release rate was lower within the acidic pH in comparison to alkaline ph. This might thanks to the repulsion between H+ ions and cationic groups present within the polymeric nanoparticles. These results indicated that the PLA/CS nanoparticles are a promising carrier system for controlled delivery of anti HIV and cancer drugs. Similarly, mannose receptors, which are studied for his or her functional applications, targeted cancer diagnosis [63, 86-88].Similarly, NFC (nanofibrillated cellulose) film networks are studied to entrap drugs and used for long lasting drug release, as an example the entrapped poorly water soluble drugs within the NFC film network scan sustainably release over weeks (e.g. indomethacin,1–2 weeks) or perhaps months (e.g. beclamethasone dipropionate and itraconazole,3monthes). Exploring the employment of chitin or chitosan as bio-molecular delivery vector is of accelerating interest in drug delivery for therapeutic application, like genes, antigens, small interfering RNA carrier (siRNA), and cells and Proteins[65,89-92].Collagen based biomaterials provide a perfect and unique matrix for drug delivery because of its biocompatibility. The micro and nanofabrication of collagen based biomaterials result in different physicochemical characteristics viz. porosity, density, and hydration dynamics. These physicochemical properties influence drug release pattern because the drug liberation is controlled by swelling of the matrix and diffusion process, and might be tailored by combining the materials' chemistry of other synthetic polymers. Kanungo et al. developed a collagen–PCL based biomaterial for insulin delivery. The formulations are optimized with varying molar ratios of collagen and PCL. There are some drawbacks of animal derived collagens, like presence of unwanted substances with pathogenic substances, thermal instability, and problems during their modifications. Therefore, synthetic collagen is employed in such cases because it also explains the stabilization effect and triple coil organization of varied organic compound residues [5,93-100].Synthetic polymers have various advantages like stimuli responsiveness, flexibility and functionality in architecture [101,102],mechanical power and biocompatibility [103].One of the foremost important classes of stimuli-responsive polymers used for controlled drug delivery is cross-linked polymer networks, e.g., hydrogels and microgels. Supported the structures and properties of hydrogels, most of them are used for transdermal drug delivery or injectable drug delivery systems. For transdermal drug delivery, micro-needles improve drug permeability into skin by providing a transparent entry pathway; this improves the delivery efficiency of vaccines and pharmaceutical agents (such as small molecules, protein, DNA). Recently, the Gu group also developed micro needle array based patches with responsive properties for smart insulin and controlled antibody delivery. a completely unique glucose-responsive insulin delivery device was reported supported micro needle array patches integrated with hypoxia-sensitive mucopolysaccharide (HS-HA) vesicles containing insulin and glucose oxidase (GOx)[12,104-106].Liposomes probably are the foremost widely used and best characterized lipid-based drug carriers. In most cases, a typical liposome consists of one bilayer lipid membrane (unilamellar liposomes) or several bilayers lipid membranes (multilamellar liposomes). The outer surface of liposomes is commonly modified by polymers mainly poly (ethylene glycol), PEG). In most cases liposomes suitable for drug delivery have a size range of 50–500 nm, while larger size liposomes also are been employed [107].

3.4. Vaccine Adjuvant

Adjuvants, like polymers that are immunologically inert but capable of inducing an immunologic response when given with an antigen, have several advantages. Generally, they act as depot carriers through slow release of the antigen, thereby modulating the following immune responses. Polymers mixed with an antigen can follow different signaling pathways. For example, the polymer–antigen are often phagocytized and processed through proteasomes, activation of inflammasome pathway via secretion of IL-1b cytokine, ligand for toll-like receptor(s) or directly interact with B cells. Alternatively, processed antigens are often presented by antigen-presenting cells via major histocompatibility complex (MHC) molecules to naive T cells, which successively can become activated and release various cytokines resulting in enhanced T and lymphocyte interactions. The activated B cells successively can undergo differentiation into antibody-secreting plasma cells and also the antibodies thus produced can activate the downstream events of the effector phase

of an immune response involving various chemokines, cytokines, proteases and effector cell populations like neutrophils, macrophages, osteoclasts, mast cells and eosinophils.

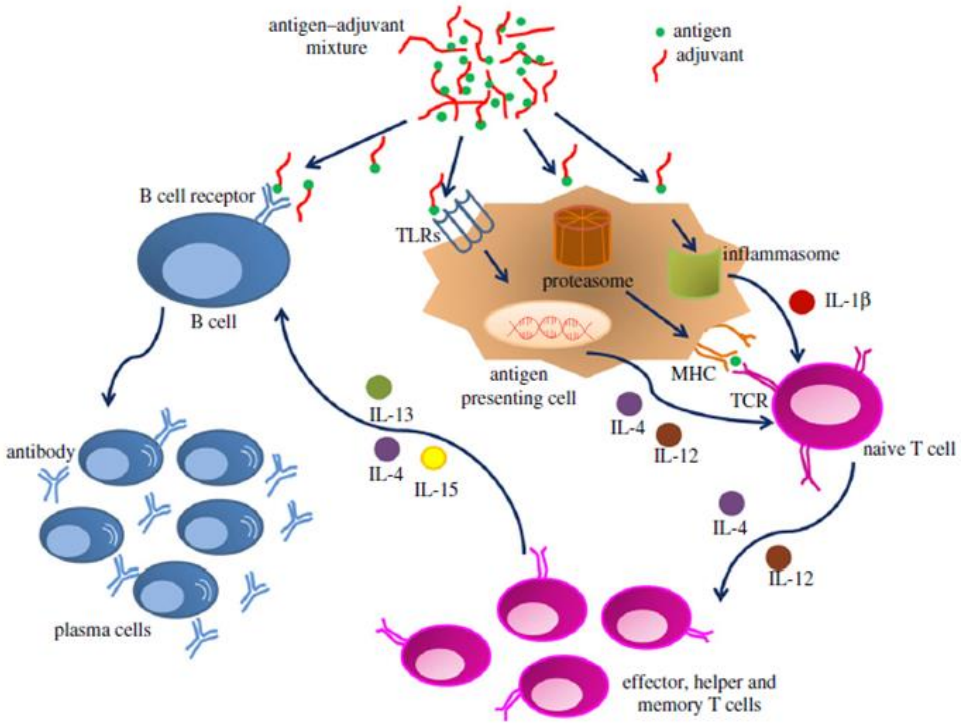

Figure 4 Possible mode of action of polymeric adjuvants [108]

Glycoproteins are accustomed prepare anticancer vaccine by combining it with different polymers. Gold nanoparticles (AuNPs) are appropriate to develop tumor vaccines because of carrier properties. They're inert, non-hazardous and rapidly endocytose by antigen containing cells (APCs). AuNP based vaccine is created through direct gold reduction, when gold is reacted with NaBH4 within the presence of thiol terminated glycopeptides polymers. However, this process involves limitation therefore glycopeptides is assembled to PEGylated AuNPs. Cai et al. reported the formation of anticancer vaccine that focus on MUC1.MUC1 and T-cell epitope P30 when combined with PEGylated AuNPs, providing capability to stimulate antibodies in vivo 3c. Nanoparticles synthesized in line with this method, plays a crucial role within the development of anticancer vaccines. Anticancer vaccine prevents the expansion of cancerous cells. Many vaccines are synthesized from samples taken from the patient, and are specific thereto patient [97,109].

3.5. Wound dressing

A wound dressing should preserve a moist environment within the wound area properly, absorb exudates from the wound surface and act as a barrier against the microorganisms together with a tailor made gaseous exchange. an ideal wound dressing should even be non-toxic, non-allergenic with high cytocompatibility with antimicrobial properties to accelerate the wound healing process. Chitosan is well-known for its wound healing behavior, and thus could be a good material for the fabrication of those antimicrobial dressings. It absolutely was found that chitosan activates macrophages and accelerates the wound healing process. Besides, chitosan develops connective tissue construction and also collagen synthesis by fibroblasts by inducing the migration of polymorphonuclear neutrophils (PMNs) at the first stage of the wound healing process. Furthermore, an affirmative result from chitosan on the re-epithelialization and regeneration of the granular layer of the skin has been reported[3,110-112].A number of studies have reported the utilization of chitosan scaffolds and membranes to treat patients with deep burns, wounds etc. Recently, Madhumathi et al. (2010) developed novel chitin/nanosilver composite scaffolds for wound healing applications. These - chitin/nanosilver composite scaffolds were found to possess excellent antibacterial activity against *S. aureus* and *E. coli*, combined with good blood coagulation ability. These *in vitro* results suggested that chitin/nanosilver composite scaffolds may be used for wound healing applications [63,113].Similarly; Sudheesh Kumar et al. (2010) developed and characterized chitin/nanosilver composite scaffolds for wound healing applications using chitin hydrogel containing silver nanoparticles. The antibacterial, blood clotting, swelling and cytotoxicity of the prepared composite scaffolds were studied. These chitin/nanosilver composite scaffolds were found to be antibactericidal against E. coli and S. aureus

and showed good clotting ability still. Additionally-chitin/nanosilver composite scaffolds were evaluated for his or her cell adhesion properties using epithelial cells (Vero cells)[58,114,115].For example, hyaluronan, a serious extracellular component with unique hygroscopic, rheological, and viscoelastic properties, has been extensively developed for tissue repair purposes thanks to its physicochemical properties and specific interactions with cells and extracellular matrix. All natural composite wound dressing films prepared by dispersion and encapsulation of essential oils in sodium alginate matrices are reported to point out remarkable antimicrobial and antifungal properties and will find applications disposable wound dressings. Silver nanoparticles containing polyvinyl pyrrolidone and alginate hydrogels were synthesized using nonparticulate radiation and showed the power of preventing fluid accumulation in exudating wound [68,116-119].

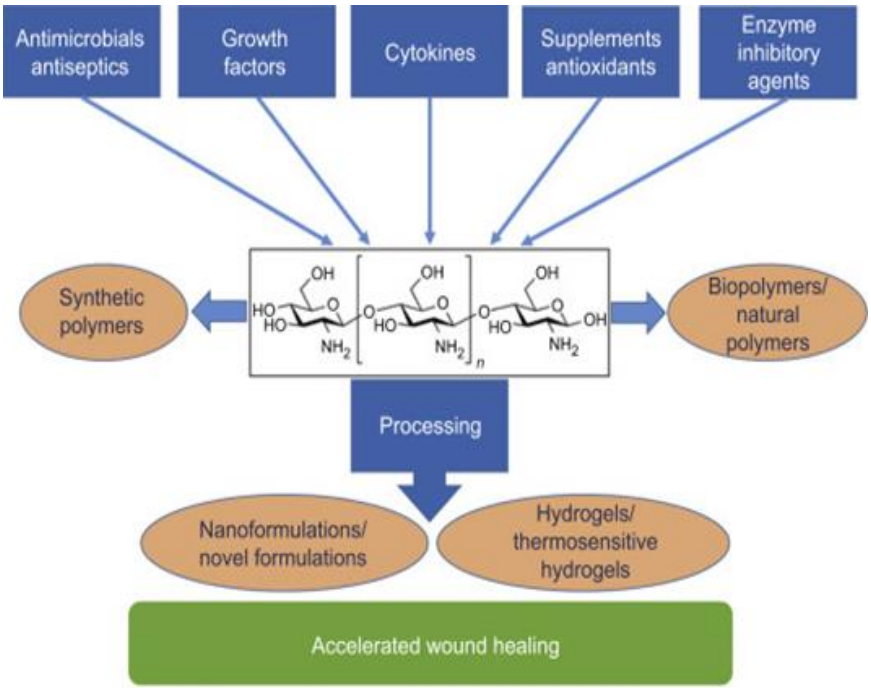

Figure 5 Acceleration of wound dressing by polymer [120]

3.6. Fixators

The polymers may serve multiple functions so as to actively affect how and where a therapeutic payload is delivered. Duvall et al. [121] generated a di-block copolymer via RAFT for conjugation to a proapoptotic peptide, a possible anti-cancer agent. The RAFT agent employed contained a pyridyl disulfide for subsequent attachment via a terminal cysteine on the peptide. An example of direct grafting from a protein was provided by De et al., wherein the authors covalently linked a maleimide-bearing RAFT agent to a free thiol side chain of a cysteine residue within the model protein (BSA)[122, 123]. RAFT agents with orthogonally reactive moieties will be accustomed generate homo or copolymers with a reactive handle for subsequent conjugation to small molecule drugs, peptides or larger bio-macromolecules. Alternatively, the RAFT agents will be conjugated to the therapeutic agent for subsequent direct polymer grafting from reactions. An example of the previous, Tao et al. generated an amine-reactive RAFT polymer via polymerization of poly (N-(2-hydroxypropyl) methacrylamide) (poly (HPMA)) with a thiazolidine-2-thione functionalized RAFT agent. The polymer was conjugated via amide bond formation via incubation with themodel protein (lysozyme). Due to their ubiquity in proteins, amines are an apparent choice for bioconjugation of polymers so amine-reactive handles (e.g. succinimidyl esters, pentafluorophenyl esters, thiazolidine-2-thione) are often included on RAFT agents [124-126].

3.7. Inflammatory bowel disease (IBD)

Inflammatory situation of the colon and tiny intestine is named inflammatory bowel disease (IBD). This disease not only affects the massive and tiny intestine but can even disturb the esophagus, mouth, anus, stomach, colon and rectum [127, 128]. Drugs that are needed within the strong tissues and inflammation sites may danger systemic absorption thanks to poor effects.

Table 1 Some natural polymers used for colon targeting [134]

Polymers	**Examples**
Diasaccharides	Lactose Maltose
Oligosaccharides	Cellobiose Cyclodextrins Lactulose Raffinose Stachyose
Polysaccharides	Polysaccharides Alginates Pectins Chitosan Chondroitin sulphate Dextran Inulin Xantham gum Guar gum Starch Tragacanth Locust bean gum Cellulose Arabinogalactan Amylase

Drug release systems depend upon physiological parameters, which aren't related to the inflammation sites. Therefore, nanoparticle drug delivery systems are developed which reduce these drawbacks. This method targets the powerful cellular protected systems found within the inflamed region also as permits the selective accumulation of the targeted region and enhances healing effect. Moulari et al. modified lectin with polystyrene fluorescent nanaoparticles (PS-NPs) and employed in IBD treatment to focus on the inflamed epithelium. Such modification increased sticking capacity of NP to to inflamed tissues and increased the aptitude of NP loaded drug. The bioadhesion was also observed, supported a sugar and lectin sticking method. Hence, this epithelial active targeting method is suitable for delivering differing types of medicine and more usefully for anti-inflammatory treatment of IBD consequently provides an alternate for ineffective drugs that can't be employed in IBD treatment thanks to their limitations [97,129-133].

3.8. Biosensors

Numerous investigations, research studies, and innovations are referring to the physical, chemical, mechanical, and biocompatibility properties of stimulus-sensitive hydrogels have contributed to our understanding of their novel potentials for biological signal sensing in medical and biomedical activities. Using biosensors to watch physiochemical changes within the body provides opportunities for early diagnosis, treatment, and management of disease. Despite some limitations concerning accuracy, significant progress has been made in producing advanced biomaterials that facilitate a replacement generation of biosensor design and construction, minimizing imprecision and slow responses to physiological conditions, for enhanced therapeutic effect. As well, the successful integration of small bio-receptors with sensing components, a significant step towards miniaturization, has made the bio-sensing process more developed and attractive [135,136].

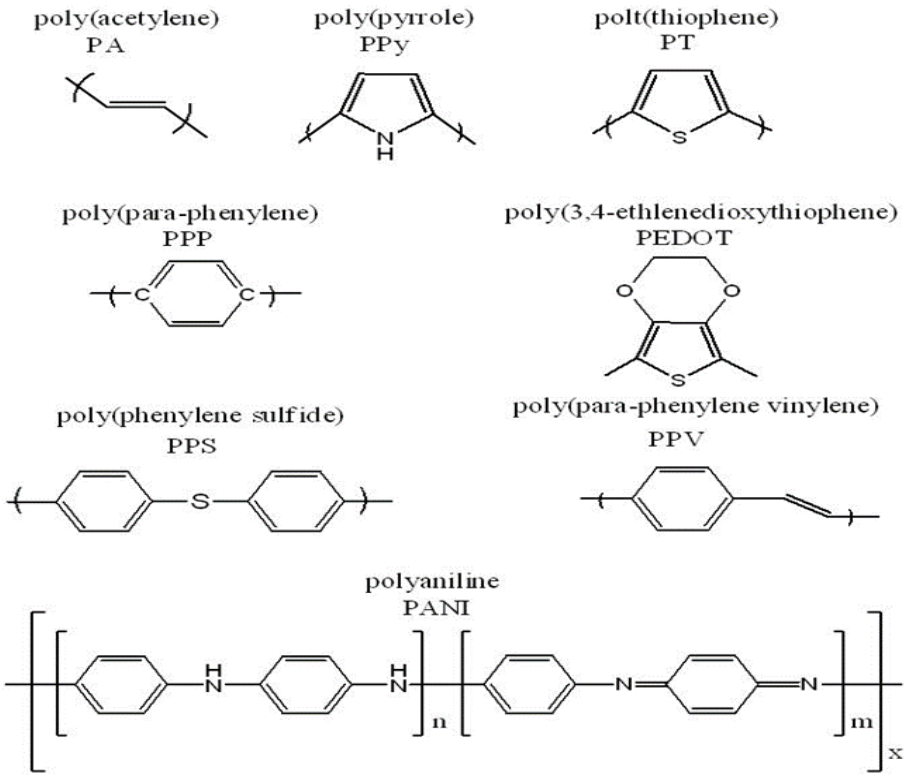

Figure 6 Structures of some conducting polymers commonly used in biosensors [137].

4. Conclusion

This review summarizes the biomedical applications of styles of polymer and polymer based nanomaterial' s in tissue engineering, wound dressing, drug delivery, cancer diagnosis and lots of other fields due to their unique properties. In recent years, tissue engineering has evolved as a unique interdisciplinary field to repair or replace injured/damaged parts and thus, restore their function. We seriously hope that the tissue engineering approaches with novel polymer materials for example will provide methods for developing a stronger understanding of body parts and associated pathologies. Due to its additional properties, like low cost, high biocompatibility, ability to solubilize in solution, easy availability in varied commercial forms, and skill to make thin films, immobilization matrix for fabrication of wide selection of biosensors and lots of other biomaterials.

Recommendation

From these studies, it'll be possible to search out innovative cosmetic and biomedical applications, further on identify new bio markers and therapies for fungal and other pathological conditions.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors would like to mention that there is no conflict of interest regarding this manuscript.

References

[1] Williams CK, Hillmyer MA. Polymers from renewable resources: a perspective for a special issue of polymer reviews. *Polymer reviews*. 2008; 48(1): 1-10.

[2] Miculescu M, Thakur VK, Miculescu F, Voicu SI. Graphene-based polymer nanocomposite membranes: a review. *Polymers for Advanced Technologies*. 2016; 27(7): 844-859.

[3] Thakur VK, Ding G, Ma J, Lee PS, Lu X. Hybrid materials and polymer electrolytes for electrochromic device applications.*Advanced materials*. 2012; 24(30): 4071-4096.

[4] Thakur VK, Kessler MR. Self-healing polymer nanocomposite materials: A review. *Polymer*. 2015; 69: 369-383.

[5] Thakur VK, Kessler MR. Synthesis and characterization of AN-g-SOY for sustainable polymer composites.*ACS Sustainable Chemistry & Engineering.* 2014; 2(10): 2454-2460.

[6] Damodaran VB, Bhatnagar D, Murthy NS. Biomedical Polymers: Processing. *In Biomedical Polymers*. 2016; 55-71).

[7] Morganti P, Febo P, Cardillo M, Donnarumma G, Baroni A. Chitin nanofibril and nanolignin: *Natural polymers of biomedical interest. J. Clin. Cosmet.Dermatol.* 2017; 1(1).

[8] D'Arcy R, Tirelli N. Fishing for fire: strategies for biological targeting and criteria for material design in anti-inflammatory therapies.Polym. *Adv. Technol*. 2014; 25: 478–498.

[9] Aguilar MR, San Román J. Introduction to smart polymers and their applications.In Smart polymers and their applications. 2017; 1-11.

[10] Lasprilla AJ, Martinez GA, Lunelli BH, Jardini AL, MacielFilho R. Poly-lactic acid synthesis for application in biomedical devices—A review.*Biotechnology advances*. 2012; 30(1): 321-328.

[11] Middleton JC, Tipton AJ. Synthetic biodegradable polymers as orthopedic devices.*Biomaterials.* 2000; 21(23): 2335-2346.

[12] Wei M, Gao Y, Li X, Serpe MJ. Stimuli-responsive polymers and their applications.*Polymer Chemistry*. 2017; 8(1): 127-143.

[13] Klein J. Polymers in living systems: from biological lubrication to tissue engineering and biomedical devices. *Polymers for Advanced Technologies*. 2012; 23(4): 729-735.

[14] Ibrahim I, Sadiku E, Jamiru T, Hamam A, Kupolati WK. Applications of polymers in the biomedical field.*Curr Trends Biomed EngBiosci*. 2017; 4: 9-11.

[15] Epple M, Ganesan K, Heumann R, Klesing J, Kovtun A, Neumann S, Sokolova V. Application of calcium phosphate nanoparticles in biomedicine.*Journal of Materials Chemistry*. 2010; 20(1): 18-23.

[16] Zare Y, Shabani I. Polymer/metal nanocomposites for biomedical applications. *Mater SciEng C Mater BiolAppl* 2016; 60: 195-203.

[17] Chanda M. Introduction to polymer science and chemistry: a problem-solving approach. CRC Press. 2006.

[18] Akita H, Hattori T. Studies on molecular composite. I. Processing of molecular composites using a precursor polymer for poly (p-phenylenebenzobisthiazole). *Journal ofPolymer Science Part B: Polymer Physics*. 1999; 37(3): 189-197.

[19] Jordan J, Jacob KI, Tannenbaum R, Sharaf MA, Jasiuk I. Experimental trends in polymer nanocomposites—a review.*Materials science and engineering*: A. 2005; 393(1-2): 1-11.

[20] Alexandre M, Dubois P. Polymer-layered silicate nanocomposites: preparation, properties and uses of a new class of materials. *Mater. Sci. Engng*. 2000; 28: 1–63.

[21] Liu J, Boo WJ, Clearfield A, Sue HJ. Intercalation and exfoliation: a review on morphology of polymer nanocomposites reinforced by inorganic layer structures. *Materials and Manufacturing Processes*. 2006; 21(2): 143-151.

[22] Ray SS, Okamoto M. Polymer/layered silicate nanocomposites: a review from preparation to processing. *Progress in polymer science*. 2003; 28(11): 1539-1641.

[23] DR Paul, LM Robeson. Polymer nanotechnology :nanocomposites, *Polymer*. 2008; 49(15): 3187–3204.

[24] Tan B, Thomas NL. A review of the water barrier properties of polymer/clay and polymer/graphenenanocomposites.*Journal ofMembrane Science*. 2016; 514: 595-612.

[25] Bassas-Galia M, Follonier S, Pusnik M, Zinn M. 2-Natural polymers: A source of inspiration, Bioresorbable Polymers for Biomedical Applications. *Perale G Hilborn J Eds*. 2016; 31-64.

[26] Mao C, Liang C, Luo W, Bao J, Shen J, et al. Preparation of lotusleaf-like polystyrene micro-and nanostructure films and its blood compatibility. *Journal ofMaterials Chemistry*. 2019; 19(47): 9025-9029.

[27] Thakur VK, Kessler MR. Self-healing polymer nanocomposite materials: A review. *Polymer*. 2015; 69: 369-383.

[28] Deka H, Karak N, Kalita RD, Buragohain AK. Bio-based thermostable, biodegradable and biocompatible hyperbranched polyurethane/Ag nanocomposites with antimicrobial activity. *Polymer Degradation and Stability.* 2010; 95: 1509-1517.

[29] Deniaud-Bouët E, Hardouin K, Potin P, Kloareg B, Hervé C. A review about brown algal cell walls and fucose-containing sulfated polysaccharides: Cell wall context, biomedical properties and key research challenges. *Carbohydrate polymers*. 2017; 175: 395-408.

[30] Dore CM, Alves MG, Will LS, Costa TG, Sabry DA, de Souza Rego LA et al. A sulfated polysaccharide, fucans, isolated from brown algae Sargassumvulgare with anticoagulant, antithrombotic, antioxidant and anti-inflammatory effects.*Carbohydrate Polymers*. 2013; 91(1): 467-475.

[31] Pomin VH. Sulfated glycans in inflammation.*European Journal of Medicinal Chemistry*. 2015; 92: 353-369.

[32] Cho M, Lee DJ, Kim JK, You S. Molecular characterization and immunomodulatory activity of sulfated fucans from Agarumcribosum.*Carbohydrate Polymers*. 2014; 113: 507-514.

[33] Choi EM, Kim AJ, Kim YO, Hwang JK. Immunomodulating activity of arabinogalactan and fucoidan *in vitro.Journal of Medicinal Food.* 2015; 8(4): 446-453.

[34] Ferreira SS, Passos CP, Madureira P, Vilanova M, Coimbra MA. Structure–function relationships of immunostimulatory polysaccharides: A review. *Carbohydrate polymers*. 2015; 132: 378-396.

[35] Saheb DN, Jog JP. Natural fiber polymer composites: a review. Advances in Polymer Technology: *Journal of the Polymer Processing Institute.* 1999; 18(4): 351-363.

[36] Matabola KP, De Vries AR, Moolman FS, Luyt AS. Single polymer composites: a review. *Journal of Materials Science*. 2009; 44(23): 6213-6222.

[37] Okada A, Kawasumi M, Usuki A, Kojima Y, Kurauchi T, Kamigaito O. Synthesis and properties of nylon-6/clay hybrids. In: Schaefer DW, Mark JE, editors. Polymer based molecular composites. *MRS Symposium Proceedings, Pittsburgh*. 1990; 171: 45–50.

[38] Biswas M, Sinha Ray S. Recent progress in synthesis and evaluation of polymer–montmorillonitenanocomposites.*AdvPolymSci.* 2001; 155: 167–221.

[39] Ray SS, Okamoto M. Polymer/layered silicate nanocomposites: a review from preparation to processing. *Progress in polymer science*. 2003; 28(11): 1539-1641.

[40] Giannelis EP. Polymer-layered silicate nanocomposites: synthesis, properties and applications. *ApplOrganometChem*. 1998; 12: 675–80.

[41] Xu R, Manias E, Snyder AJ, Runt J. New biomedical poly(urethane uera)-layered silicate nanocomposites. *Macromolecules.* 2001; 34: 337–9.

[42] Kojima Y, Usuki A, Kawasumi M, Fukushima Y, Okada A, Kurauchi T, Kamigaito O. Mechanical properties of nylon 6–clay hybrid. *J Mater Res*. 1993; 8: 1179–84.

[43] Gilman JW, Kashiwagi T, Lichtenhan JD. Flammability studies of polymer-layered silicate nanocomposites. *SAMPE. J.* 1997; 33: 40–5.

[44] Gilman JW, Jackson CL, Morgan AB, Harris Jr R, Manias E,Giannelis EP, Wuthenow M, Hilton D, Phillips SH. Flammability properties of polymer-layered silicate nanocomposites. Propylene and polystyrene nanocomposites. *Chem Mater.* 2000; 12: 1866–73.

[45] Sinha Ray S, Yamada K, Okamoto M, Ueda K. New polylactide/layered silicate nanocomposite: a novel biodegradable material. *Nano Lett*. 2002; 2: 1093–6.

[46] Dabrowski F, Bourbigot S, Delbel R, Bras ML. Kinetic molding of the thermal degradation of polyamide-6 nanocomposite. EurPolym J. 2000; 36: 273–84.

[47] Ginsburg VV, Balazs AC. Calculating phase diagrams for nanocomposites: the effect of adding end-functionalized chains to polymer/clay mixture. *Adv Mater*. 2000; 12: 1805–9.

[48] Hackett E, Manias E, Giannelis EP. Molecular dynamics simulations of organically modified layered silicates.*J ChemPhys.* 1998; 108: 7410–5.

[49] Manias E, Kuppa V. Relaxation of polymers in 2-nm slitpores: confinement induced segmental dynamics and suppression of the glass transition*. Colloids Surf. A*. 2001; 187–188: 509–21.

[50] Dziadek M, Stodolak-Zych E, Cholewa-Kowalska K. Biodegradable ceramic-polymer composites for biomedical applications: A review. *Materials Science and Engineering: C*. 2017; 71: 1175-1191.

[51] Langer R, Vacanti J. engenharia do Tecido. Ciência. 1993; 260: 920-6.

[52] Dvir T, Timko BP, Kohane DS, Langer R. Nanotechnological strategies for engineering complex tissues. *Nat. Nanotechnol.* 2010; 6: 13–22.

[53] Bhattarai D, Aguilar L, Park C, Kim C. A review on properties of natural and synthetic based electrospun fibrous materials for bone tissue engineering.*Membranes*. 2018; 8(3): 62.

[54] Carlisle EM. Silicon: a requirement in bone formation independent of vitamin D 1. Calcified tissue international. 1981; 33(1): 27-34.

[55] Reffitt DM, Ogston N, Jugdaohsingh R, Cheung HFJ, Evans BAJ, Thompson RPH, Hampson GN. Orthosilicic acid stimulates collagen type 1 synthesis and osteoblastic differentiation in human osteoblast-like cells *in vitro*. *Bone.* 2003; 32(2): 127-135.

[56] Farquhar MG, Hay ED. Cell biology of extracellular matrix. 1991.

[57] Jayakumar R, Prabaharan M, Nair SV, Tamura H. Novel chitin and chitosan nanofibers in biomedical applications.*Biotechnology advances*. 2010; 28(1): 142-150.

[58] Shalumon KT, Binulal NS, Selvamurugan N, Nair SV, Menon D, Furuike T, Jayakumar R. Electrospinning of carboxymethyl chitin/poly (vinyl alcohol) nanofibrous scaffolds for tissue engineering applications. *Carbohydrate Polymers*. 2009; 77(4): 863-869.

[59] Hench LL. Bioceramics: from concept to clinic. *Journal of the american ceramic society*. 1991; 74(7): 1487-1510.

[60] Bosetti M, Cannas M. The effect of bioactive glasses on bone marrow stromal cells differentiation. *Biomaterials*. 2005; 26(18): 3873-3879.

[61] Foppiano S, Marshall SJ, Marshall GW, Saiz E, Tomsia AP. Bioactive glass coatings affect the behavior of osteoblast-like cells. *Actabiomaterialia*. 2007; 3(5): 765-771.

[62] Hench LL. Genetic design of bioactive glass.*Journal of the European Ceramic Society*. 2009; 29(7): 1257-1265.

[63] Jayakumar R, Menon D, Manzoor K, Nair SV, Tamura H. Biomedical applications of chitin and chitosan based nanomaterials—A short review. *Carbohydrate polymers*. 2010; 82(2): 227-232.

[64] Oliveira JT, Reis RL. Polysaccharide-based materials for cartilage tissue engineering applications.*Journal of tissue engineering and regenerative medicine*. 2011; 5(6): 421-436.

[65] Liu J, Willför S, Xu C. A review of bioactive plant polysaccharides: Biological activities, functionalization, and biomedical applications. *Bioactive Carbohydrates and Dietary Fibre*. 2015; 5(1): 31-61.

[66] Khan F, Ahmad SR. Polysaccharides and their derivatives for versatile tissue engineering application.*Macromolecular Bioscience*. 2013; 13(4): 395-421.

[67] Kalantari K, Afifi AM, Jahangirian H, Webster TJ. Biomedical applications of chitosan electrospunnanofibers as a green polymer–Review.*Carbohydrate polymers*. 2019; 207: 588-600.

[68] Wang H, Li Y, Zuo Y, Li J, Ma S, Cheng L. Biocompatibility and osteogenesis of biomimetic nano-hydroxyapatite/polyamide composite scaffolds for bone tissue engineering. *Biomaterials.* 2007; 28(22): 3338-3348.

[69] Bai RG, Muthoosamy K, Manickam S, Hilal-Alnaqbi A. Graphene-based 3D scaffolds in tissue engineering: fabrication, applications, and future scope in liver tissue engineering. *International journal of nanomedicine*. 2019; 14: 5753.

[70] Soundarya SP, Menon AH, Chandran SV, Selvamurugan N. Bone tissue engineering: Scaffold preparation using chitosan and other biomaterials with different design and fabrication techniques. *International journal of biological macromolecules*. 2018.

[71] Nourmohammadi J, Ghaee A, Liavali SH. Preparation and characterization of bioactive composite scaffolds from polycaprolactonenanofibers-chitosan-oxidized starch for bone regeneration.*Carbohydrate Polymers*. 2016; 138: 172–179.

[72] Zhang Y, Venugopal JR, El-Turki A, Ramakrishna S, Su B, Lim CT. Electrospun biomimetic nanocompositenanofibers of hydroxyapatite/chitosan for bone tissue engineering. *Biomaterials.* 2008; 29(32): 4314-4322.

[73] Ghadri N, Anderson KM, Adatrow P, Stein SH, Su H, Garcia-Godoy F, Bumgardner JD. Evaluation of bone regeneration of simvastatin loaded chitosan nanofiber membranes in rodent calvarial defects. *Journal of Biomaterials and Nanobiotechnology*. 2018; 9(02): 210.

[74] Wu C, Su H, Karydis A, Anderson KM, Ghadri N, Tang S, Bumgardner JD. Mechanically stable surface-hydrophobilized chitosan nanofibrous barrier membranes for guided bone regeneration.*Biomedical Materials*. 2017; 13(1): 1-10.

[75] Jalvandi J, White M, Gao Y, Truong YB, Padhye R, Kyratzis IL. Polyvinyl alcohol composite nanofibres containing conjugated levofloxacin-chitosan for controlled drug release. *Materials Science and Engineering C*. 2017; 73: 440-446.

[76] Khan Y, Yaszemski MJ, Mikos AG, Laurencin CT. Tissue engineering of bone: material and matrix considerations. *Jbjs*. 2008; 90: 36-42.

[77] Rahmani Del Bakhshayesh A, Annabi N, Khalilov R, Akbarzadeh A, Samiei M, Alizadeh E, Montaseri A. Recent advances on biomedical applications of scaffolds in wound healing and dermal tissue engineering. *Artificial cells, nanomedicine, and biotechnology*. 2018; 46(4): 691-705.

[78] Aslankoohi N, Mondal D, Rizkalla AS, Mequanint K. Bone Repair and Regenerative Biomaterials: Towards Recapitulating the Microenvironment. *Polymers*. 2019; 11(9): 1437.

[79] Siegwart DJ, Oh JK, Matyjaszewski K. ATRP in the design of functional materials for biomedical applications.*Progress in polymer science*. 2012; 37(1): 18-37.

[80] Csaba N, Köping-Höggård M, Alonso MJ. Ionicallycrosslinked chitosan/tripolyphosphate nanoparticles for oligonucleotide and plasmid DNA delivery.*International journal of pharmaceutics*. 2009; 382(1-2): 205-214.

[81] Mao W, Li H, Li Y, Zhang H, Qi X, Sun H, Chen Y, Guo S. Chemical characteristic and anticoagulantactivityof the sulfatedpolysaccharideisolatedfrom Monostromalatissimum (Chlorophyta). *International JournalofBiological Macromolecules*. 2009; 44(1): 70–74.

[82] Mizrahy S, Peer D. Polysaccharides as building blocks for nanotherapeutics.*Chemical Society Reviews*. 2012; 41(7), 2623-2640.

[83] Valo H, Kovalainen M, Laaksonen P, Hakkinen M, Auriola S, Peltonen L, Linder M, Jarvinen K, Hirvonen J, Laaksonen T. Immobilizationofprotein-coateddrug nanoparticles innanofibrillarcellulosematrices–enhanced stability andrelease*. Journal of ControlledRelease*. 2011; 156(3): 390–397.

[84] Reddy K, Krishna Mohan G, Satla S, Gaikwad S. Natural Polysaccharides: Versatile Excipients for controlled drug delivery systems. *Asian Journal of Pharmaceutical Sciences*. 2011; 6(6).

[85] Martinichen-Herrero JC, Carbonero ER, Sassaki GL, Gorin PAJ, Iacomini M. Anticoagulant and antithrombotic activities of a chemically sulfated galactoglucomannan obtained from the lichen Cladoniaibitipocae. *International journal of biological macromolecules.* 2005; 35(1-2): 97-102.

[86] Jayakumar R, Prabaharan M, Nair SV, Tokura S, Tamura H, Selvamurugan N. Novel carboxymethyl derivatives of chitin and chitosan materials and their biomedical applications.*Progress in Materials Science*. 2010; 55(7): 675-709.

[87] Dev A, Binulal NS, Anitha A, Nair SV, Furuike T, Tamura H, Jayakumar R. Preparation of poly (lactic acid)/chitosan nanoparticles for anti-HIV drug delivery applications. *Carbohydrate polymers*. 2010; 80(3): 833-838.

[88] Higuchi Y, Oka M, Kawakami S, Hashida M. Mannosylated semiconductor quantum dots for the labeling of macrophages.*Journal of Controlled Release*. 2008; 125(2): 131-136.

[89] Marchessault RH, Ravenelle F, Zhu XX. (Eds.). Polysaccharides for drug delivery and pharmaceutical applications.*American Chemical Society*. 2006.

[90] Francis MF, Piredda M, Winnik FM. Hydroxypropylcellulose in oral drug delivery. In Polysaccharides for Drug Delivery and Pharmaceutical Applications, Marchessault RH, Ravenella F, Zhu XX, Editors, *ACS Symposium Series*. January 2006; 934.

[91] Jain AK, Söderlind E, Viridén A, Schug B, Abrahamsson B, Knopke C, Richardson S. The influence of hydroxypropyl methylcellulose (HPMC) molecular weight, concentration and effect of food on *in vivo* erosion behavior of HPMC matrix tablets.*Journal of controlled release*. 2017; 187: 50-58.

[92] Li J, Mei X. Applications of cellulose and cellulose derivatives in immediate release solid dosage.In Polysaccharides for drug delivery and pharmaceutical applications, ACS Symposium series. *American chemical society*, Washington, DC. January 2006; 934: 19-56.

[93] Kolakovic R, Peltonen L, Laukkanen A, Hirvonen J, Laaksonen T. Nanofibrillar cellulose films for controlled drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*. 2012; 82(2): 308-315.

[94] Chen MC, Huang SF, Lai KY, Ling MH. Fully embeddable chitosan microneedles as a sustained release depot for intradermal vaccination.*Biomaterials.* 2013; 34(12): 3077-3086.

[95] Mao S, Sun W, Kissel T. Chitosan-based formulations for delivery of DNA and siRNA.*Advanced drug delivery reviews*. 2010; 62(1): 12-27.

[96] Shelke NB, James R, Laurencin CT, Kumbar SG. Polysaccharide biomaterials for drug delivery and regenerative engineering.*Polymers for Advanced Technologies*. 2014; 25(5): 448-460.

[97] Sundgren A, BarchiJr JJ. Varied presentation of the Thomsen–Friedenreich disaccharide tumor-associated carbohydrate antigen on gold nanoparticles.*Carbohydrate research*. 2008; 343(10-11): 1594-1604.

[98] Tabasum S, Noreen A, Kanwal A, Zuber M, Anjum MN, Zia KM. Glycoproteins functionalized natural and synthetic polymers for prospective biomedical applications: A review. *International journal of biological macromolecules*. 2017; 98: 748-776.

[99] Friess W. Collagen–biomaterial for drug delivery.*European Journal of Pharmaceutics and Biopharmaceutics*. 1998; 45(2): 113-136.

[100] Ferreira AM, Gentile P, Chiono V, Ciardelli G. Collagen for bone tissue regeneration.*Actabiomaterialia*. 2012; 8(9): 3191-3200.

[101] You JO, Auguste DT. Conductive, physiologically responsive hydrogels.*Langmuir*. 2010; 26(7): 4607-4612.

[102] Barth D, Kyrieleis O, Frank S, Renner C, Moroder L. The Role of Cystine Knots in Collagen Folding and Stability, Part II. Conformational Properties of (Pro-Hyp-Gly) n Model Trimers with N-and C-Terminal Collagen Type III Cystine Knots.*Chemistry–A European Journal*. 2003; 9(15): 3703-3714.

[103] Boudko SP, Engel J. Structure formation in the C terminus of type III collagen guides disulfide cross-linking. *Journal of molecular biology*. 2004; 335(5): 1289-1297.

[104] Rathfon JM, Tew GN. Synthesis of thermoresponsive poly (N-isopropylmethacrylamide) and poly (acrylic acid) block copolymers via post-functionalization of poly (N-methacryloxysuccinimide). *Polymer*. 2008; 49(7): 1761-1769.

[105] McCormick CL, Sumerlin BS, Lokitz BS, Stempka JE. RAFT-synthesized diblock and triblock copolymers: thermally-induced supramolecular assembly in aqueous media. *Soft Matter*. 2008; 4(9): 1760-1773.

[106] Shunmugam R, Tew GN. Efficient route to well-characterized homo, block, and statistical polymers containing terpyridine in the side chain.Journal of Polymer Science Part A: *Polymer Chemistry*. 2005; 43(23): 5831-5843.

[107] Tavakoli J, Tang Y. Hydrogel based sensors for biomedical applications: an updated review. *Polymers*. 2017; 9(8): 364.

[108] Shakya AK, Nandakumar KS. Applications of polymeric adjuvants in studying autoimmune responses and vaccination against infectious diseases.*Journal of the Royal Society Interface*. 2013; 10(79): 1-16.

[109] Zhang Q, Colazo J, Berg D, Mugo SM, Serpe MJ. Multiresponsivenanogels for targeted anticancer drug delivery.*Molecular pharmaceutics*. 2017; 14(8): 2624-2628.

[110] BernadeteRiemma Pierre M, Cristina Rossetti F. Microneedle-based drug delivery systems for transdermal route.*Current drug targets*. 2014; 15(3): 281-291.

[111] Hong X, Wu Z, Chen L, Wu F, Wei L, Yuan W. Hydrogel microneedle arrays for transdermal drug delivery. *Nano-Micro Letters*. 2014; 6(3): 191-199.

[112] Gomes SR, Rodrigues G, Martins GG, Roberto MA, Mafra M, Henriques CMR, Silva JC. *In vitro* and *in vivo* evaluation of electrospunnanofibers of PCL, chitosan and gelatin: A comparative study. *Materials Science and Engineering: C*. 2015; 46: 348-358.

[113] Madhumathi K, Kumar PS, Abhilash S, Sreeja V, Tamura H, Manzoor K, Jayakumar R. Development of novel chitin/nanosilver composite scaffolds for wound dressing applications. *Journal of Materials Science: Materials in Medicine.* 2010; 21(2): 807-813.

[114] Sarhan WA, Azzazy HM, El-Sherbiny IM. Honey/chitosan nanofiber wound dressing enriched with Allium sativum and Cleome droserifolia: enhanced antimicrobial and wound healing activity. *ACS applied materials & interfaces*. 2016; 8(10): 6379-6390.

[115] Jayakumar R, Prabaharan M, Kumar PS, Nair SV, Tamura H. Biomaterials based on chitin and chitosan in wound dressing applications. *Biotechnology advances*. 2011; 29(3): 322-337.

[116] Sudheesh Kumar PT, Abilash S, Manzoor K, Nair SV, Tamura H, Jayakumar R. Preparation and characterization of novel -chitin/nano silver composite scaffolds for wound dressing applications.*Carbohydrate Polymers*. 2010; 80: 761–767.

[117] Anilkumar TV, Muhamed J, Jose A, Jyothi A, Mohanan PV, Krishnan LK. Advantages of hyaluronic acid as a component of fibrin sheet for care of acute wound. *Biologicals*. 2011; 39(2): 81-88.

[118] Chen WJ, Abatangelo G. Functions of hyaluronan in wound repair. *Wound repair and regeneration*. 1999; 7(2): 79-89.

[119] Liakos I, Rizzello L, Scurr DJ, Pompa PP, Bayer IS, Athanassiou A. All-natural composite wound dressing films of essential oils encapsulated in sodium alginate with antimicrobial properties. *International journal of pharmaceutics*. 2014; 463(2): 137-145.

[120] Ghadi R, Jain A, Khan W, Domb AJ. Microparticulate polymers and hydrogels for wound healing. *In Wound Healing Biomaterials*. 2016; 203-225.

[121] Singh R, Singh D. Radiation synthesis of PVP/alginate hydrogel containing nanosilver as wound dressing. Journal of Materials Science: *Materials in Medicine*. 2012; 23(11): 2649-2658.

[122] Duvall CL, Convertine AJ, Benoit DS, Hoffman AS, Stayton PS. Intracellular delivery of a proapoptotic peptide via conjugation to a RAFT synthesized endosomolytic polymer. *Molecular pharmaceutics*. 2010; 7(2): 468-476.

[123] Fairbanks BD, Gunatillake PA, Meagher L. Biomedical applications of polymers derived by reversible addition–fragmentation chain-transfer (RAFT).*Advanced drug delivery reviews*. 2010; 91: 141-152.

[124] De P, Li M, Gondi SR, Sumerlin BS. Temperature-regulated activity of responsive polymer– protein conjugates prepared by grafting-from via RAFT polymerization.*Journal of the American Chemical Society*. 2008; 130(34): 11288-11289.

[125] Tao L, Liu J, Davis TP. Branched polymer– protein conjugates made from mid-chain-functional P (HPMA). *Biomacromolecules.* 2009; 10(10): 2847-2851.

[126] Tao L, Liu J, Xu J, Davis TP. Synthesis and bioactivity of poly (HPMA)–lysozyme conjugates: the use of novel thiazolidine-2-thione coupling chemistry. *Organic &biomolecular chemistry*. 2009; 7(17): 3481-3485.

[127] Andrianifahanana M, Moniaux N, Batra SK. Regulation of mucin expression: mechanistic aspects and implications for cancer and inflammatory diseases. *BiochimicaetBiophysicaActa (BBA)-Reviews on Cancer*. 2006; 1765(2): 189-222.

[128] Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. *The Lancet*. 2007; 369(9573): 1627-1640.

[129] Lamprecht A. Nanomedicines in gastroenterology and hepatology.*Nature Reviews Gastroenterology &Hepatology.* 2015; 12(4): 195.

[130] Meissner Y, Lamprecht A. Alternative drug delivery approaches for the therapy of inflammatory bowel disease. *Journal of pharmaceutical sciences*. 2008; 97(8): 2878-2891.

[131] Nakase H, Okazaki K, Tabata Y, Uose S, Ohana M, Uchida K, Ikada Y. An oral drug delivery system targeting immune-regulating cells ameliorates mucosal injury in trinitrobenzene sulfonic acid-induced colitis. *Journal of Pharmacology and Experimental Therapeutics*. 2001; 297(3): 1122-1128.

[132] Laroui H, Dalmasso G, Nguyen HTT, Yan Y, Sitaraman SV, Merlin D. Drug-loaded nanoparticles targeted to the colon with polysaccharide hydrogel reduce colitis in a mouse model. *Gastroenterology*. 2010; 138(3): 843-853.

[133] Moulari B, Béduneau A, Pellequer Y, Lamprecht A. Lectin-decorated nanoparticles enhance binding to the inflamed tissue in experimental colitis. *Journal of controlled release*. 2014; 188: 9-17.

[134] Sharma PK. Novel prospective in colon specific drug delivery system.*Polim. Med*. 2014; 44(2): 109-118.

[135] Park TH, Shuler ML. Integration of cell culture and microfabrication technology.*Biotechnology progress*. 2003; 19(2): 243-253.

[136] Kuzmov A, Minko T. Nanotechnology approaches for inhalation treatment of lung diseases. *Journal of controlled release*. 2015; 219: 500-518.

[137] Wang X, Uchiyama S. Polymers for biosensors construction.*State of the Art in Biosensors—General Aspects*. 2013; 3: 67-84.