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Advanced Polymers for Biomedical Applications: Mini Review

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ABSTRACT

Macromolecules known as polymers have a wide range of structural, chemical, and physical properties. They have numerous applications in bioengineering, healthcare, electronics, and other fields of science and technology. Biomedical polymers are particularly noteworthy among these polymers due to their low toxicity in vivo, ease of processing and disinfection, longer shelf life, light weight, and exceptional properties suited to the applications. This mini review provides a brief overview of the current research situation in the field of using polymers for biomedical purposes. The relevance of the research topic is noted; current trends in the development of polymers and the creation of polymeric carriers for bioactive materials delivery involved in various applications are described. The characteristics of synthetic and natural polymers are presented; their advantages and disadvantages are indicated. Therefore, we aim to discuss a recent progress in design and development of polymeric carriers for some biomedical applications including; drug delivery, enzyme immobilization, and biosensors.

Keywords: Natural Polymers; Synthetic Polymers; Drug Delivery; Enzyme Immobilization; Biosensors; Biomedical Applications

Abbreviations: SA: Sodium Alginate; CA: Calcium Alginate; SIF: Simulated Intestinal Fluid; SGF: Simulated Gastric Fluid; PAE: Poly Amino Ester; TAAI: Interest In Amino Acid Therapy; Cs-Ga-DOX: Doxorubicin-Loaded Chitosan - Glutamic Acid; GDA: Glutaraldehyde ; MMA-co-GMA: Methyl Methacrylate-Glycidyl Methacrylate Copolymer; MMA-co-HEMA: Methyl Methacrylate-2-Hydroxy Ethyl Methacrylate Copolymer; CMCT: Carbodiimide Metho-P-Toluenesulfonate; PMMA-g-CS: Chitosan Grafted With Polymethyl Methacrylate; CT: Chymotrypsin; PGMA-g-pectin: Pectin Polyglycidyl Methacrylate Copolymer; EDC: Ethylcarbo Diimide Hydrochloride; PoT: Poly-O-Toluidine; BC: Breast Cancer; 3-3-APPA: 3-(3-Aminophenyl) Propionic Acid; Fc: Ferrocene-Based Polymers; PLL: Poly-L-Lysine; ATRP: Atom Transfer Radical Polymerization; APCR: Aunp-Pnipaam Composite Ring's; LSPR: Localized Surface Plasmon Resonance; DDSs: Focused Drug Transport Systems; PGMA-g-SA: Grafted With Polyglycidyl Methacrylate Hydrogels

Introduction

Materials based on polymers are one of the most needed and demanded parts of developed and modern societies. Accompanied by the improvement of biomedical studies over the previous few decades, polymeric materials have received extraordinary appeal in biomedical subject because of its ease of synthesis with tunable houses like mechanical houses, stimuli responsive etc [1]. Both natural polymers which include cellulose, chitosan, alginate, gelatin etc. [2-5], and synthetic polymers which include polylactic acid, polyacrylates and their derivatives , polyethylene glycol etc. [6-8] had been appreciably studied for biomedical packages like drug delivery system , gene delivery vector , tissue engineering , biosensors [9-12] etc. There are various types of polymers used in biomedical applications, involving hydrogels, nanoparticles, composites, porous sponges, 3D porous scaffolds , etc. [13-17] There are a variety of advantages associated with polymeric materials; however, a few modifications can be made to current natural polymers, or an alternative technique can be used to create new biopolymers in order to improve their unique properties such as solubility, degradation rate, toxicity, immunogenicity, balance, and others [18]. We will explore various biomedical applications of natural and synthetic polymers, such as drug delivery, enzyme immobilization, and biosensors, in this mini review.

Drug Delivery Systems

In current decades, focused drug transport systems (DDSs) have emerged as attractive answers for treating a lot of diseases [19]. Utilizing DDSs can improve a large variety of pharmacological and therapeutic features of drugs. Moreover, DDSs can reduce the required dosage and enhance immunity while lowering adverse effects, making them excellent interfaces between the patient and the drug. This has drawn the attention of scientists in recent years [20]. Nevertheless, drug delivery efficiency remains far from ideal despite tremendous progress. In order to control the diffusion or penetration of drugs across the cell membrane, as well as their release, it is crucial to find effective materials that regulate these activities. As a result, the selection of the appropriate binding material for the drug molecules has a significant impact on the release kinetics of the drug molecules [21]. As pH sensitive drug delivery matrices for riboflavin, Sodium Alginate (SA) grafted with PolyGlycidyl Methacrylate hydrogels (PGMA-g-SA) was prepared (RF).

The swelling, degradation, entrapment efficiency, and in vitro release of RF of the hydrogel copolymer matrices were compared to Calcium Alginate (CA) beads. FT-IR and SEM were used to characterize the structure and surface morphology of the CA beads and prepared hydrogels, as well as the chemical stability of the encapsulated drug. The results show that the best formulation was obtained with a PGMA-g-SA proportion of (0.75 mol/1 g) and a loaded RF of 0.03 g. The in vitro release study of RF from this formulation was superior to the others, with the release lasting 3 and 4 days for the simulated intestinal fluid (SIF) and simulated gastric fluid (SGF), respectively. In general, it has been demonstrated that GMA grafted onto SA improved drug entrapment efficiency while decreasing swelling and carrier degradation. Furthermore, when compared to pure SA beads crosslinked with Ca2+ ions alone, it slowed and controlled the release of RF from the PGMA-g-SA hydrogel, providing a simple and effective method to improve drug delivery systems [22].

The previous work was a trial to evaluate the synthesised slow-release system of poly poly (-amino ester) (PAE) containing drugs as antitumor for a long time period. The network structures of poly (-amino ester) were synthesized using a simplified addition polymerization method to carry drug for use as a drug delivery matrix [23]. It has the ability to hold active organic compounds (drugs) with antitumor activity in order to control their release. The active organic compounds that were loaded into the polymer matrix are a new series of heterocyclic derivatives derived from pyrimidine and naphthyridine, namely: 7-(2-methoxy phenyl) (2-methoxy phenyl) [4,3-c] -3-methyl-5-thioxo-5,6-dihydro[1,2,4] triazolo 7-(2-methoxy phenyl)-3-oxo-5-thioxo-2,3,5, 6-tetrahydro[1,2,4] triazolo [4,3-c] pyrimidine-8-carbonitrile (D1) (D2) pyrimidine-8-carbonitrile and (E)-2-((furan-2-yl)methylene hydrazine -1-(2,7-dimethyl-1,8-naphthyridin-5-y l) (D3). SEM was used to characterize the polymer structures and surface morphology of the PAE capsules before and after encapsulation with the active drugs. The SEM studies show that the drug has good dispersion and holding properties in the network structure of the prepared polymer (Figure 1). The drug release results from the PAE capsules in vitro indicated that the capsules could provide sustained drug release in DMF for up to 15 days at 25 °C.

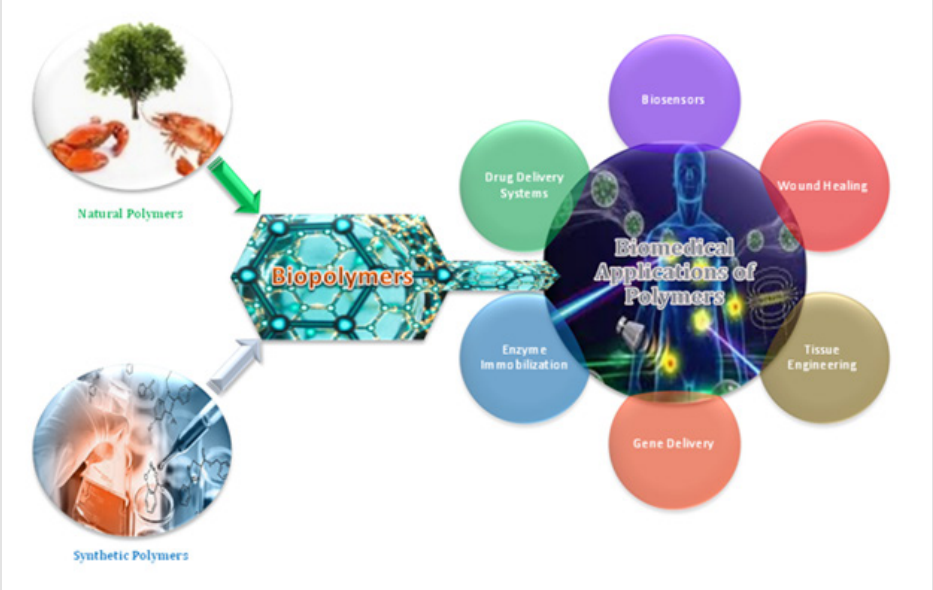

Figure 1:

The polymer containing active compounds was tested for drug delivery by exposing it to drug release in aqueous media for various time periods and examined as anti-proliferative agents against human liver (HEPG2) cancer cell line. Compound (D2) demonstrated the greatest growth inhibition activity, followed by compound (D1), while compound (D3) demonstrated the least activity against human liver (HEPG2) cancer cell line. The reveal data for the human liver cancer cell line yielded promising results [24]. Recently, there has been a

lot of interest in amino acid therapy (TAAI) for tumour treatment. In addition to our previous research in biopolymers and amino acids for medical applications, this study sought to develop a novel therapeutic regimen for cancer disease that included a combination of therapy with amino acids (TAAI) and polymer therapy. This regimen is based on ionic gelation of Doxorubicin-loaded chitosan - glutamic acid (Cs-Ga-DOX) nanoparticles. The efficiency of encapsulation was 69%. The average size was 20-37 nm, and the structure was spherical and homogeneous, with a positive zeta potential.

The formation of an amide linkage was confirmed by FTIR of Cs-Ga at 1644 cm-1. DOX in-vitro release was found to be biphasic with mutual burst release followed by sustained release for 168 hours at pH 5.5 and 25% at pH 7.4. These results indicated that Cs-Ga nanoparticles were a promising combination of glutamic amino acid and chitosan as a pH-responsive nano-carrier for anticancer drugs [25]. Because of their high potential for tuning the release and alleviating side effects, biodegradable polymeric nanoparticles are regarded as promising drug delivery systems. The immune system can detect particles larger than 200 nm. As a result, this work focused on the creation of size-controlled poly (lactic-co-glycolic acid) nanoparticles smaller than 200 nm in diameter that encapsulate a model drug. The biodegradable polymer was first solubilized in ethyl acetate before being dispersed in water using various nanoemulsification devices, including a shear mixer, sonicator, elongational-flow reactor, and micromixer.

The last two devices demonstrated the ability to generate monomodal nanoparticles of the desired size range at various continuous to disperse phase volume ratios. In a subsequent section, nanoparticles generated by the micromixer were used as nanocarriers for rifampicin, a hydrophobic antibiotic. These drug-loaded nanoparticles were created at various drug concentrations in order to investigate the effect of drug load on particle properties. To thoroughly characterize the nanoparticle diameter, size dispersity and morphology, drug encapsulation efficiency, and in vitro drug release profile, various techniques such as dynamic light scattering, transition electron microscopy, and ultraviolet spectroscopy were used [26].

Enzyme Immobilization

Enzymes are appealing catalysts because they are highly effective and specific in natural environments. The main disadvantages are their short lifetimes, the high cost of isolating them from the reaction products, and the loss of catalytic properties when exposed to non-optimal conditions. Over the last four decades, research has focused on developing methods to overcome the biocatalytic approach's shortcomings. Enzyme immobilization is one of the most effective methods, whereas immobilized enzymes have numerous applications in the medical and food industries, as well as biotechnology and biomedical engineering [27]. In this field, we have a number of outstanding research articles where enzymes were immobilized on various natural and synthetic polymers via covalent attachment and cross-linking techniques. Below we will review our most important research in this field. α-Amylase from Bacillus subtilis was immobilized on (methyl methacrylate-2-hydroxy ethyl methacrylate) copolymer matrix prepared via emulsion polymerization. Immobilized α-amylase has better stability and higher maintained activities with respect to pH, temperature and storage stability than free α-amylase [28].

In this context, α-amylase was immobilized on insoluble chitosan and its amino acid (L-glutamic acid and 4-aminobutyric acid) condensates by direct covalent bonding method with glutaraldehyde (GDA) as cross-linking agent. The fixation procedure was performed at 25 °C and pH 6.9, using 3 mg α-amylase for maximum retained activity. The properties of the immobilized α-amylase were examined and compared with those of the free α-amylase. For assays using the crosslinking method at 25 °C and pH 6.9, the retained activities of chitosan, chitosan-L-glutamic acid, and chitosan-4-aminobutyric acid crosslinked were found to be 68.59, 97.36 and 79.50, found percentage 1 % GDA. Immobilized α-amylase has better stability and retained activity than free α-amylase in terms of pH value, temperature and storage stability. In repeated application experiments, α-amylase immobilized with chitosan-GDA (1%) retained about 46.45% of its original activity after 25 applications. In contrast, the activities of α-amylases immobilized on chitosan-L-glutamic acid-GDA (1%) and chitosan-4-aminobutyric acid-GDA (1%) were within 11 times and no change after 8 applications. The above vehicles retained 79 and 71% of their activity after 25 uses, respectively [29].

In addition, cellulase [1,4-(1,3;1,4)--d-glucan 4-glucanohydrolase], was immobilized directly on chitosan, chitosan-L-glutamic acid and chitosan–4-amino butyric acid by covalent bonding and cross-linking methods. The properties of the immobilized cellulase were studied and compared with free cellulase. For the assays performed by cross-linking method at 25 oC and pH 7, the preserved activities were found to be 65.52%, 85.32% and 63.19% for chitosan, chitosan-L-glutamic acid and chitosan–4- aminobutyric acid cross-linked with 1% (GDA), respectively. Immobilized cellulase has better stability and higher maintained activities with respect to pH, temperature and storage stability than free cellulase. Immobilized cellulase had better stability and higher retained activities with respect to pH, temperature and storage stability than the free one. In contrast, the activity of immobilized cellulase on chitosan–l-glutamic acid–GDA (1%) and chitosan–4-aminobutyric acid–GDA (1%) remained unchanged after 10 and 7 times, respectively. Retained operations after 25 reuses are 70% and 50% of their original activity for above-mentioned carriers, respectively [30].

Besides that, cellulase was covalently attached and crosslinked to methyl methacrylate-glycidyl methacrylate copolymer (MMA-co-GMA) and methyl methacrylate-2-hydroxy ethyl methacrylate copolymer (MMA-co-HEMA). The properties of immobilized cellulase were studied and compared to those of free cellulase. The retained activities for immobilized cellulase on MMA-co-GMA and MMA-co-HEMA crosslinked with 0.1% of 1-cyclohexyl-3-(2-morpholino-ethyl) carbodiimide metho-p-toluenesulfonate (CMCT) were found to be 91.92% and 74.63%, respectively, for assays performed at 25 °C and pH 7. In terms of pH, temperature, and storage stability, immobilized

cellulase outperformed free cellulase. The immobilized cellulase using (MMA-co-GMA)-CMCT (0.1%) did not change after 10 and eight times of repeated use, respectively, and retained 67% and 62% of their original activities after 25 times [31]. In other interesting work, as a carrier for enzyme immobilization, chitosan grafted with polymethyl methacrylate (PMMA-g-CS) was prepared using a free radical polymerization method. In this study, α- chymotrypsin (CT) was immobilized by covalent bond on the prepared PMMA-g-CS. For encapsulating PMMA-g-CS-CT into composite beads, calcium alginate beads (CA) were developed. PMMA-g-CS particles were examined by TEM and found to have a nanoscale morphology and size according to TEM. Prior to and after the immobilization process, beads were characterized by FT-IR and SEM, respectively. The bound CT content as well as the enzyme's relative activity was also determined. The immobilized CT with pH 9 for 24 h retained a higher retention activity (97.7%). After 60 days of storage at 25 °C, the immobilized CT retained 75% of its original activity, even after 25 reuses [32].

Moreover, Pectin polyglycidyl methacrylate copolymer (PGMA-g-pectin) was prepared via emulsion polymerization technique, characterized, and used as a multisite enzyme immobilization system. In this study, Urease, an enzyme model, was sequentially immobilized on a prepared carrier by using both carboxyl and epoxy groups. Before and after immobilization, FT-IR and SEM were used to characterize the structure and surface morphology of the copolymer. The relative activity of urease was measured as well as its amount bounded. An increased activity was observed for urease bounded to PGMA-g-SA activated for 3 h with 10 mg of 1-[3-(dimethylamino) propyl]-3-ethylcarbo diimide hydrochloride (EDC). The effectiveness of urease immobilization was examined using various parameters (i.e. activation and immobilization time, pH, and concentrations of EDC and urease). The basic properties of the immobilized enzyme (optimal pH and temperature, thermal stability, storage stability, and reusability) were also determined. The results showed that the immobilized urease retained 70% of its original activity after 60 days of storage at 4 °C and maintained its excellent performance in detecting urea in 20 measurements [33].

Biosensors

A biosensor is an analytical device containing biologically identifiable material such as antibodies , enzymes, nucleic acids, or peptides [34-37], immobilized on a sensitive probe. A measurable electrical signal commensurate to the attention paid by the analyte, is generated by the ultimate after it converts the biochemical signals between the analytes and the bioreceptors. With its high sensitivity, selectivity, economy, and fast responses [38] , the system is crucial for immobilizing biological materials on the transducer surface, given its early stages of development. Besides immobilizing the biomolecule efficiently, it must be maintained with its activity, avoiding leaching processes, deterioration with time, and denaturation, preserving the electronic transfer with the transducer [39]. Thus, conductive polymers containing functional groups are a feasible alternative for modifying transducer surfaces with desirable functional groups while maintaining or increasing conductivity [40]. The development of biosensors has involved the use of a variety of polymers, including; polyaniline, poly(3,4-ethylenedioxythiophene), poly(ortho-aminophenol) , polypyrrole [41-45] . The polymerization of an aromatic structure on the surface of a transducer can produce a thin layer with functional groups that are oriented to bind biological molecules. Moreover, there is the possibility that the same layer has intrinsic conductivity [46].

In biomedical and clinical analysis, it is crucial to develop new methods for quick and ongoing urea monitoring. As a result, a conductive polymer-supported carbon nanotube was developed as an efficient electrochemical biosensing platform for the direct detection of urea in blood samples. Several conductive polymers were synthesized and tested as electrode modifiers for assay optimization; poly-o-toluidine (PoT) demonstrated the highest electrochemical signals among the tested polymers. However, when the PoT was used alone after enzyme immobilization, direct bioelectrochemical signals were not obtained. Because PoT has a lower electrocatalytic feature, the integration of a carbon nanotube into a composite with the PoT was used to enable direct electron transfer. The catalytic activity of the immobilized urease enzyme was successfully retained using the hybrid. As a result of the bioassay optimization, sensitive and specific chronoamperometric signals were obtained. A standard calibration curve for urea determination was eventually obtained. A linear range of 0.1 to 11 mM was discovered, with a detection limit of 0.03 mM. Several blood samples were successfully analyzed, and the urea level was correlated with the reference analytical method [47].

Furthermore, a new electrochemical biosensor was developed to characterize breast cancer (BC) using peptides chosen by Phage Display as biorecognition phase. To characterize patients with aggressive luminal BC, phage clones were selected against MCF-7 (ER-positive BC) proteins. Biotin-C3 and biotin-H2 peptides were chemically synthesized and validated by flow cytometry, immunofluorescence assays, and ELISA assays to be more reactive to the MCF-7 lineage. In addition, a new matrix for biomolecule coupling on the surface of graphite electrodes was created via electrochemical modification with a new material derived from 3-(3-aminophenyl) propionic acid (3-3-APPA). Electrochemical and morphological characterizations were performed, and a mechanism for electropolymerization of poly(3-3-APPA) was proposed, in which the carboxylate groups are retained in the structure of the formed polymer. The biotin-C3 and biotin-H2 peptides were then immobilized in the SPE/poly(3-3-APPA)/avidin system to detect BC tumor markers in serological samples. Finally, peptides were validated using samples from BC and Benign Breast Disease patients. Biotin-C3 peptide characterized luminal BC based on p53 status and HER2 expression, making the biosensor a superior strategy to the ELISA test. This new biosensor will pave the way for a fast and electrochemical platform for characterizing BC and its molecular subtype's [48].

As redox mediators, ferrocene-based polymers (Fc) are versatile and important in the study of glucose biosensors. As a cationic polymer,

poly-L-lysine (PLL) has good biocompatibility, biodegradability, and water solubility. In this study, PLL was modified with ferrocene carboxylate in a straightforward manner by activating the carboxyl group of Fc, which reacted with the polymer's amino groups. FTIR was used to examine the finished product. Cyclic voltammetry was used to evaluate the performance of Fc-PLL as a redox mediator with the enzyme glucose oxidase, which revealed an increase in oxidation current in the presence of glucose in PBS pH 7.4. A biosensor's performance was also assessed using amperometry, which revealed a linear range of 0–10 mM, a limit of detection of 23 M, a sensitivity of 6.55 A/cm2 mM, and high selectivity. SEM analysis revealed remarkable activity in evaluating the charged regions of Fc-PLL/GOx on the electrode surface. The Fc-PLL redox polymer has been widely accepted as a glucose biosensor, and the results demonstrated remarkable activity as an electron transfer mediator between the redox polymer and the GOx enzyme [49].

As a result of constituent interaction, self-organization facilitates the formation of specific structures. The bottom of a 500-nm hole array photoresist template that had been deposited with a hydrophobic atom transfer radical polymerization (ATRP) initiator was wetted with oxygen plasma in this study. After the photoresist template was removed, ring patterns of the ATRP initiator formed at the interface of the hydrophobic and wetting regions. The initiator's ring array was grafted with poly(N-isopropylacrylamide) (PNIPAAm) to immobilize gold nanoparticles (AuNPs) as a uniform ring array on the silicon substrate via repeated swelling/shrinking cycles. The biotin-anchored AuNP-PNIPAAm composite ring's (APCR) localized surface plasmon resonance (LSPR) peaks were used as biosensors to detect streptavidin. Biotin-streptavidin coupling resulted in asymptotical convergence from rings to discs as well as blue-shifts of the LSPR peaks. The linear correlation between blue-shift and streptavidin concentration revealed a limit of detection of 10 nM and a linear range of 10-150 nM for streptavidin detection within 30 minutes. The straightforward method of combining lithography and plasma technology creates a versatile platform for developing AuNP's scalable ring structure for highly sensitive and sensitive biosensing [50].

Conclusion

In conclusion, drug delivery, enzyme immobilization, and biosensors as biomedical applications of natural and synthetic polymers were represented. Synthetic polymers with various shapes, sizes, and functions have been extensively used in different biomedical areas due to their versatility in components, properties, and structures. Semi-synthetic biopolymers, which use blending, crosslinking, and grafting techniques to combine natural and synthetic polymers into hybrid polymers, have also piqued the interest of materials scientists. Natural polymers' biocompatibility, combined with the superior thermal and mechanical properties of synthetic polymers, resulted in semi-synthetic polymers with numerous applications in biomedicine. This study addressed issues regarding polymeric materials, their production methods, characterizations, and some of their biomedical applications. Finally, there are numerous polymers available today that have the potential to be used as biomaterials. Advances in polymer synthesis techniques have resulted in the use of polymers for all biomedical applications. Furthermore, the emergence of combination polymers holds out hope for the development of novel materials with desired properties for highly specific applications. The advancement of processing techniques is enabling the formation of particles and scaffolds with extremely complex architectures that can mimic their biological counterparts. Even though these advancements in polymer research have been crucial, it should be noted that they have also helped us to understand how biomaterials interact with the host on a cellular, tissue, organ, and systemic level thanks to advances in biological research. The recent formation of effective collaboration teams made up of chemists, biochemists, material scientists, engineering technicians, and therapists is crucial for the advancement of the field of polymeric biomaterials

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