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POLYMERS IN MEDICINE FROM DRUG DELIVERY TO BIOMATERIALS

Muhammad Ghous[*1], Syed Moman Ali Rizvi[2], Muhammad Salman Khalid[3], Waqas Mahmood[4], Basit Ali[5], Humera Bashir[6], Muhammad Ibraheem[7]

[*1] *Department of Biochemistry Minhaj University Lahore, Pakistan*
[2]*Department of Chemistry, University of Agriculture Faisalabad, Pakistan*
[3]*Department of Biomedical Engineering and Sciences, School of Mechanical and Manufacturing Engineering, National University of Sciences and Technology, Pakistan*
[4]*Department of Pharmaceutical Chemistry, the Islamia University of Bahawalpur, Pakistan*
[5]*Department of Chemistry, Abdul Wali Khan University, Mardan, Pakistan*
[6]*Atta-Ur-Rahman School of Applied Biosciences (ASAB), National University of Sciences and Technology (NUST), Islamabad, Pakistan*
[7]*Department of Pharmacy, the University of Lahore, Pakistan*

[*1] drmghous5@gmail.com, [2]syedmomanalirizvi5656@gmail.com, [3]mkhalid.bms22smme@student.nust.edu.pk, [4]drwaqasmta@gmail.com, [5]basitaliktk213@gmail.com, [6]humerabashir994@gmail.com, [7]ibraheem11647@gmail.com

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Corresponding Author: *

Abstract

Polymers have revolutionized the field of medicine, offering innovative solutions in drug delivery and biomaterials. Their versatility, tunable properties, and biocompatibility make them ideal candidates for various biomedical applications. In drug delivery, polymeric systems such as nanoparticles, micelles, hydrogels, and dendrimers enable controlled, targeted, and stimuli-responsive drug release, improving therapeutic efficiency and reducing side effects. Biodegradable and synthetic polymers like PLGA, PEG, and chitosan have been extensively explored for enhanced drug stability and bioavailability. Beyond drug delivery, polymers play a crucial role in biomaterials, including tissue engineering, wound healing, and medical implants. Natural polymers like collagen and alginate, alongside synthetic materials such as PEEK and PMMA, offer structural support and functional enhancements for biomedical applications. The advent of smart polymers, including pH-responsive and temperature-sensitive materials, has further advanced regenerative medicine, biodegradable implants, and biosensors. Despite their advantages, challenges such as mechanical stability, long-term biocompatibility, and regulatory approval remain. Recent advancements, including 3D printing of polymeric medical devices and bioactive polymer development, continue to push the boundaries of medical technology. This review explores the critical role of polymers in medicine, highlighting their applications in drug delivery and biomaterials, addressing current challenges, and discussing prospects in personalized medicine and smart healthcare solutions.

INTRODUCTION

Polymers, the most versatile class of materials, have changed our day-to-day lives over the past several decades. However, the distinction between temporary and permanent biomedical applications of polymers was made only 30 years ago [1]. Subsequently, the amalgamation of polymer science with pharmaceutical sciences led to a quantum leap in terms of 'novelty' (flexibility in physical state, shape, size and surface) in design and development of novel drug-delivery systems (DDSs). Polymeric delivery systems are mainly intended to achieve either a temporal or spatial control of drug delivery [2]. The introduction of the first synthetic polymer-based (polyglycolic acid) DDS led to a heightened interest in the design and synthesis of novel biodegradable polymers that obviated the need to remove the DDS, unlike the nondegradable polymeric systems. Recognizing that intimate contact between a delivery system and an epithelial cell layer will improve the residence time as well as the efficacy of the DDS resulted in the design of bioadhesive polymers [3].

Tremendous progress has been made as a result of the exploration of diffusion-controlled and solvent-activated formulations in drug delivery. Hydrogels and other polymer-based carriers have been developed to provide safe passage for pharmaceuticals through inhospitable physiological regions. Polymers of controlled molecular architecture can be engineered to give a well-defined response to external conditions as a result of a solid understanding of the underlying mechanisms and the nature of behavioral transitions. Polymers incorporated with therapeutics can be bioactive to provide their own therapeutic benefit or can be biodegradable to improve release kinetics and prevent carrier accumulation. Pharmaceutical agents have been conjugated to polymers to modify transport or circulation half-life characteristics as well as to allow for passive and active targeting. And finally, the latest drug delivery research using polymeric materials has produced precognitive systems and polymer-carriers that facilitate the cytoplasmic delivery of novel therapeutics[4].Certain polymers have been designed to swell or shrink in response to an external stimulus [5].Changes in porosity can result from leaching of ionic cross-linking molecules, which in turn alters the diffusion pathways for sensing molecules. Alginate is a commonly employed polymer that is isolated from seaweed and is relatively biocompatible. Tuning the spatial and temporal release of encapsulated materials is rather challenging, but has been successfully applied for a variety of applications using alginates. A recent example includes the sustained delivery of vascular endothelial growth factor (VEGF) and subsequent analogues from alginate to a localized region within the body. Using an injectable alginate design, the controlled release of VEGF was utilized to promote lymphatic vessel development through improved vascularization [6]. In general, these hybrid designs have the potential to create future generations of materials for the paralleled delivery of therapeutics, regional specific sensing, and secondary responses for noninvasive detection. Hydrolysis-sensitive polymeric materials have also been designed, synthesized, and implemented in vivo for drug delivery purposes. Hydrolysis prone materials by definition can be degraded by water, a trigger that is ubiquitous in the human body. This degradative process most commonly occurs through the nucleophilic addition of water into an electrophilic functional group on a polymer. Commonly employed electrophilic functional groups on polymers include esters and anhydrides, each of which have been employed in multiple types of responsive materials [7]. The Gliadel wafer is one example product on the market that demonstrates the power of hydrolysis-sensitive materials for drug deliver[8]. Consisting of the chemotherapeutic Carmustine impregnated within a polyanhydride material, the Gliadel wafer can be implanted into brain tumors for the controlled release of a chemotherapeutic to malignant gliomas. Of note, the Gliadel wafer improves the 6 month survival rate of patients diagnosed with glioblastoma multiforme[9]. Enzyme-responsive polymers have also been developed for drug delivery. The concentrations of specific enzymes including matrix metalloproteins, hyaluronidases, phospholipases, and prostate specific antigen can deviate from normal values in association with specific disease pathologies[10].

Accordingly, many enzyme-responsive polymer systems have been developed, with applications ranging from tumor imaging, to doxorubicin delivery, and minimizing inflammation in the colon, among others [11]. Despite the extensive use of polymers in medicine, challenges remain in optimizing their biocompatibility, biodegradability, and functionality for advanced medical applications. Current research focuses on improving polymer-based drug delivery systems to achieve precise targeting, controlled release, and reduced side effects, yet limitations in polymer stability, immune response, and large-scale production persist. Similarly, while polymeric biomaterials are widely used in tissue engineering, wound healing, and medical implants, there is still a need for enhanced mechanical properties, better integration with biological tissues, and reduced risk of rejection or infection. Smart and stimuli-responsive polymers hold promise, but their clinical translation requires further investigation into long-term safety and efficiency. The objective of this review is to provide a comprehensive analysis of the role of polymers in modern medicine, with a focus on their applications in drug delivery and biomaterials. This review aims to highlight recent advancements, address existing challenges, and explore future directions for polymer-based medical innovations. By summarizing key developments and identifying gaps in current research, this review seeks to contribute to the ongoing efforts in optimizing polymer technologies for improved therapeutic outcomes and biomedical applications.

Types of polymers used in medicine:

Natural polymer:

the natural polymers always show low/non toxicity, low immunogenicity and thereafter good biocompatibility, they have been the preferred polymers in drug delivery systems. Among the natural polymers, alginate has become one of the most common materials used to form microcapsules [12]. Recently, scientists have turned their attention on tuning starch and chitosan for use in nanodrug delivery. One of the ways to avoid the potential hazards of nanodrug delivery may be by using natural polymers. This is because, apart from occurring widely in nature, natural polymers are generally bio-compatible, biodegradable, non-immunogenic and safe.Natural polymers are of considerable importance because they are generally bio-compatible, bio-degradable, non-toxic and non-immunogenic. They occur widely in nature and are classified into 2 groups; polysaccharides and proteins [13]. Starch, chitosan, alginate, and dextran are examples of commonly used polysaccharides while gelatin and albumin are examples of commonly used proteins. These polymers are applied as colloidal particles of size 10nm-1µm termed nano-particles. In this system, the drug to be delivered could be dispersed within the polymeric matrix or adsorbed on the surface of the carrier in which case they are called nano-spheres or it could be encapsulated within a core surrounded by polymeric membrane and are known as nano-capsules. The method by which they are fabricated into nano-particles for drug delivery depends on their physicochemical properties and the drug to be loaded[14] .passively targeted due to their inherent properties or via the enhanced permeation and retention by surface modification with polyethylene oxide rendering them long- circulating[15]. Natural polymers have also been used as carriers of particulate drug carriers, acting as coating agents and surface modifiers[16].

Chitosan

Combination was also used by Menon et al. [17]. for therapeutic drug delivery. Nano-complexes of chitosan and polyoxometalates (POM) were tested as anti-cancer preparation. Since POM's though toxic have shown promise in being used as anti- viral and anti-tumour agent, the role of chitosan was to minimise the toxicity associated with POM, by modifying its surface properties. Monodispersed particles with size 200nm were produced using ionotropic gelation technique and the use of probe sonication was shown to control particle size and distribution compared to ultrasonication. Invitro studies showed that the nano-complex was able to sustain drug release with enhanced anti-tumour activity at much lesser doses than the POM alone.Similarly as with starch nano particles, Luo et al. [18].used chitosan oligosaccharides (COS) to coat lipid based carriers in order to enhance ocular drug delivery. This material is obtained from the decomposition of chitosan, but it is more soluble in water than chitin and chitosan. Drug introduced

into the eye have minimal residence times as they are quickly washed away and have to be re-administered regularly. But in this study, COS enhanced permeation and adhesion of the cornea. There was a 7.7 fold and 2.8-fold retention of the model drug, flubiprofen by the COS coated nano lipid carriers compared to the phosphate buffer solution and uncoated nanolipid carriers which were attributed to the mucoadhesive properties of COS. The use of COS was also found to be non-irritating to the eye, a property which is of utmost importance in the choice of a suitable eye formulation.This polymer is obtained from the partial N-deacetylation of chitin found in the shells of crustacean. It is composed of glucosamine and N-acetyl glucosamine linked by β 1-4 glucosidic bonds and is one of the most widely studied natural polymers for nano-drug delivery. The deacetylation of chitin is both concentration and temperature dependent with optimal yields achieved at temperatures between 600 C800 C using 50%w/w alkali[19].

Gelatin

Gelatin is obtained from the breakdown and hydrolysis of collagen, obtained from the connective tissues, bones and skins of animals. It is a known matrixing agent drug delivery. Bajpai and Shoubey [20]. describes a process for the controlled release of sulphamethoxazole using 2 different gelatin nano-particles {Type A (porcine skin) and type B gelatin(bovine skin)} and cross linked with gluteraldehyde; Nano-particles of varying gelatin concentrations were prepared by solvent evaporation techniques and drug release kinetics evaluated using appropriate kinetic models. Findings from this system suggest that this system could be of use in targeted drug delivery such as colon drug delivery where PH is an important consideration. Drug release was found to increase following increased swelling of the nanoparticles. In addition, swelling was further enhanced by an increase in PH with greater drug release occuring at PH 7.5 than at PH 1.8.

Synthetic polymer

Silicone

Silicones consist of an –Si–O– backbone with different chain lengths and crosslinks, which determine mechanical properties from liquid oil via a gel structure to rubber elastomer. The side chains may be modified, but in the most common poly(dimethylsiloxane) (PDMS) they are methyl groups. Silicones are hydrophobic and biostable elastomers without need of plasticizers. The biological response differs for various applications: There is high tolerance in ophthalmologic applications [21]. fibrous capsule formation at breast implants and synovitis as late complication in intraarticular implants [22]. An association with hematologic cancers and connective tissue diseases is assumed especially for silicon oil residues.

Methacrylates

Methyl methacrylates polymerize to very rigid polymers (PMMA) by radical polymerization and therefore find application in dentistry and in orthopedics. They are used for application with polymerization in situ. This polymerization process is exothermic and can cause tissue damage, so that low amounts should be applied and saline irrigation for cooling may be necessary. While the polymer is biologically inert, there can be reactions against the monomer and rest-monomers in the polymer[23] . Due to the optical properties (Plexiglasss) and inertness in the eye, they are also used as intraocular lenses. The hydrophilic side chains in the hydroxyethyl methacrylate monomer lead to the polymerization to a hydrogel (pHEMA). This has good protein repellant anti-fouling properties and is used for various applications like hemocompatible coatings [24] or as lubricant coating on contact lenses[25].

Polyesters

Biostable and biodegradable polyesters are used in biomedicine. Biostable polyesters containing aromatic groups are polycarbonates (PC), poly(ethylene terephthalate) (PET, dacron). They are used in form of membranes, filaments and meshes. Polyesters of small aliphatic glycolic acid or lactic acid present the most common degradable polymers poly(glycolic acid) (PGA), poly(L-lactic acid) (PLLA) and poly(D-lactic acid) (PDLA). Polydioxanone (PDS) is a further degradable polyester composed of multiple repeating ether-ester units. Non-enzymatic hydrolysis of is the main mode of degradation of these polymers, and the degradation products

catalyze the further degradation. The degradation rates partly depend on the monomer structure, but it is also highly influenced by molecular weight, crystallinity, fiber structure and substituting groups [26].

Bio-degradable and non-bio gradable polymer

The application of drug delivery systems is considered to be useful to overcome the problems mentioned above. In particular, for resin-based restorative materials, the use of a polymer-based carrier containing the active agents is effective. In the past, a variety of polymers, such as cellulose12), gelatin13), polysaccharide14), polyethylene glycol15), or poly (2- hydroxyethyl methacrylate) (polyHEMA)16-19), have been reported as carriers for drug delivery. These polymers form biocompatible hydrogels with excellent water absorbability to facilitate the uptake of therapeutic agents. However, most of them are targeted for regenerative therapy and degrade to release the agent in human bodies. Accordingly, they are not applicable for dental materials used for permanent restoration. In need of non-biodegradable carrier which is stable even after the active agents leach out (Fig. 1), we newly developed non-biodegradable particles for the delivery of water-soluble agents20,21). These particles are made using methacrylate polymers and are compatible with any type of resin used for restorative treatments. In the present paper, the effectiveness of this novel polymer particle as a carrier of growth factors and antimicrobials is summarized. The possible application of the polymer particles for various restorative materials is also addressed.

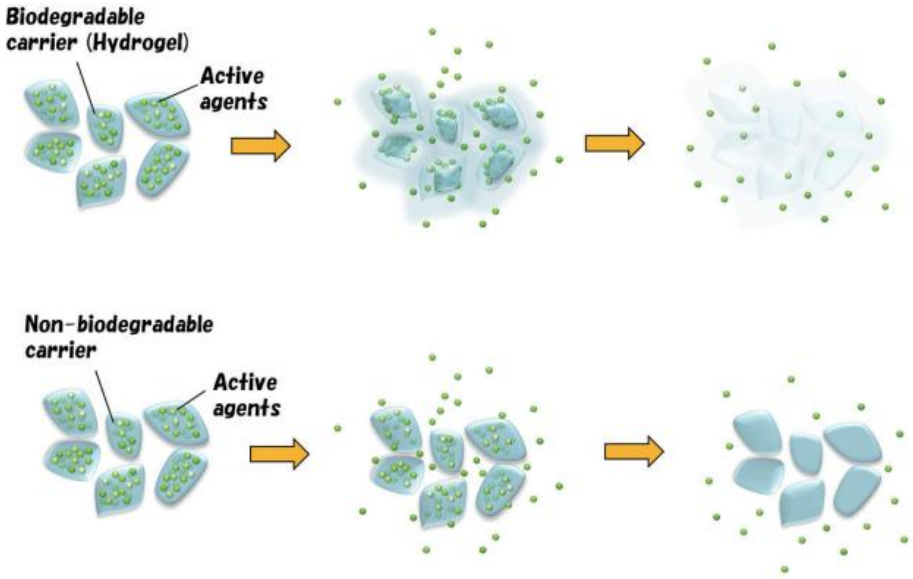

Figure 1: Schematic diagram of biodegradable and non-biodegradable polymer particles for drug delivery.[27]

Advances in Polymeric nanocarriers

Polymeric NPs are particles obtained from natural, semi-synthetic or synthetic polymers. Polymeric nanosystems are produced by a polymerization reaction of many monomer units, and under certain conditions, they can be organized and self-assemble with ananometric size (10–100 nm) [28]. Due to the high diversity of their properties, NPs attract great attention as multifunctional nanocarriers in DDSs [29]. Depending on the preparation method, drugs can be entrapped, encapsulated or bound to polymeric NPs in the form of a nanosphere, a nanocapsule or a drug conjugate (Figure 1) . Nanospheres are colloidal particles that entrap the drug inside their matrix by physical dispersion or by adsorption on the particle surface, while nanocapsules are systems consisting of a core cavity with an encapsulated drug and polymeric shell surrounding it. Polymeric capsules can be designed by the conjugation of targeting ligands that increase

selectivity for cancer cells and improve intracellular drug delivery, as well as reducing different side effects and drug toxicity. Targeting ligands of polymeric capsules are commonly monoclonal antibodies (mAbs) or antibody fragments, aptamers, peptides and small molecules, such as folic acid, which are conjugated to the shell-forming block. These ligands are specifically bound to antigens or receptors that are overexpressed on the cancer cell and they enable cellular selectivity and intracellular delivery of polymeric micelles. Different designed polymeric capsules suitable for targeting the release of drugs are shown in Figure 1. The efficacy of polymeric carriers modified with targeting ligands depends on the ligand properties, such as their density and binding affinities to receptors, which can enhance receptor internalization and the biodistribution of drugs. Drug-conjugates have a drug that is chemically bonded to the polymer through a linker/spacer. The bond drug-linker/spacer is a common breakage point when the drug is released at the target site (Figure 1).

Natural polymers are biopolymers, including different classes of polysaccharides and proteins, which, due to their biocompatibility and biodegradability, are particularly suitable for medical applications, as in cell-based transplantation, tissue engineering and gene therapy (Figure 2). Natural polymers can be combined with synthetic molecules through the chemical modification of their functional groups and so-called semi-synthetic polymers can mimic human tissue components. In formulations of controlled DDSs, synthetic polymers attract more attention than biopolymers due to the considerable potential for designing their structure and modifying their physicochemical properties (Figure 2). Synthetic polymeric micelles exhibit a high capacity to incorporate a broad range of bioactive molecules, such as antisense oligonucleotides plasmid DNA proteins, small interfering ribonucleic acids (siRNAs), messenger RNAs (mRNAs), and photosensitizers, by tailoring the core-forming segments of the block copolymers. Several poly-ion complex (PIC) micelles that incorporate negatively charged biomolecules by electrostatic interaction with positively charged block copolymers have been designed. In addition, they can be stabilized by the covalent crosslinking of their core through disulfide bonds[30]. which can be cleaved under specific intracellular conditions, enabling the complexes to escape from endosomal compartments after

endocytosis and to deliver the biomolecules to subcellular destinations without drug degradation. By introducing hydrophobic molecules such as cholesterol to the core PIC micelles become more stable, with a longer half-life in the bloodstream, allowing for the delivery of intact biomolecules to therapeutic targets. PIC micelles obtained from block copolymers with a core-forming polycation such as polyaspartamides, support enhanced delivery of biomacromolecules to the cytosol of cells, and the gene transfection in vitro and in vivo.

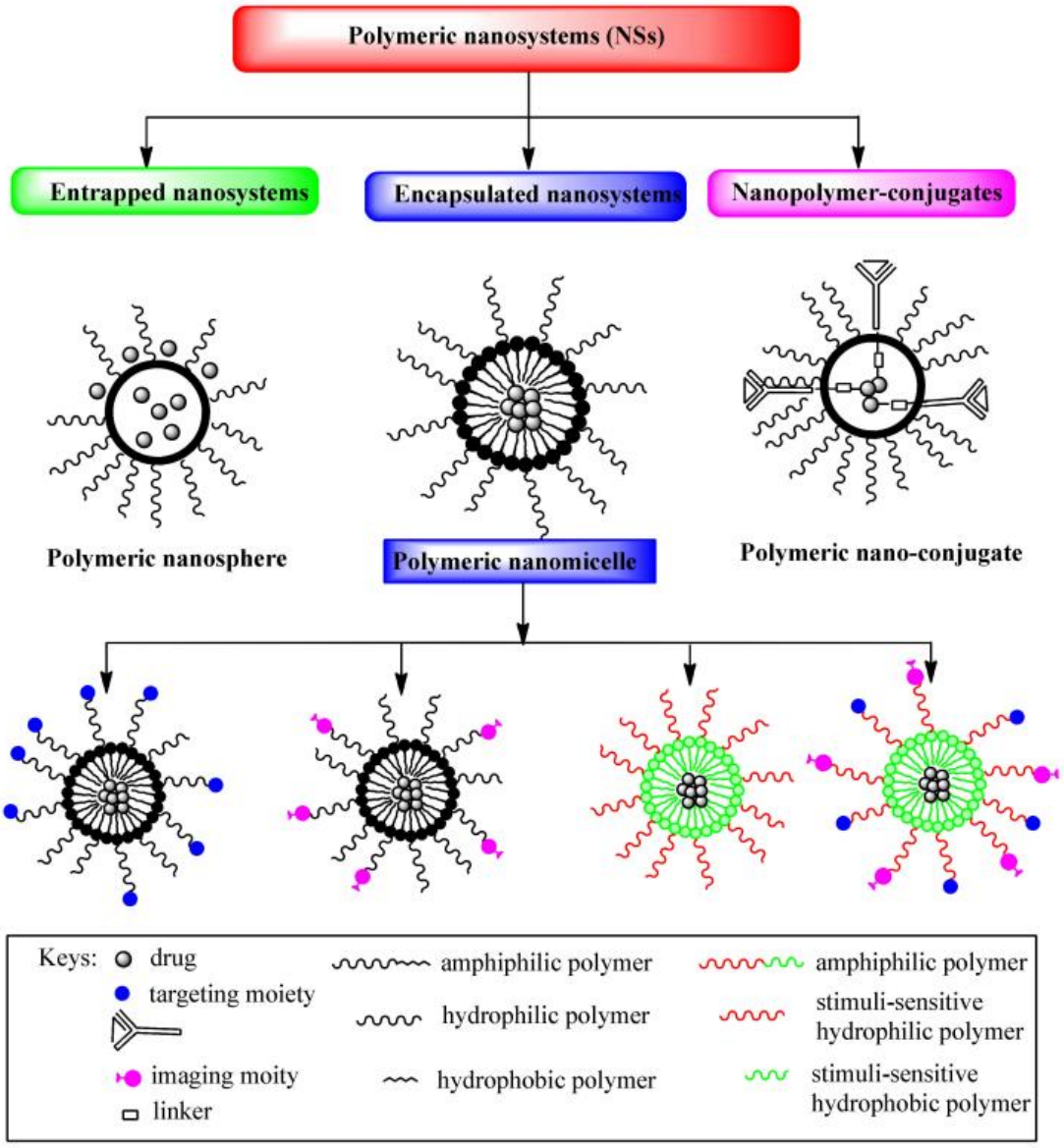

Figure 2: Schematic illustration of multifunctional drug delivery systems.

In recent years, the great potential of synthetic polymers as drug carriers has been highlighted, particularly because of the possibility to develop DDSs with a target sustained/controlled release of drugs. The encapsulation of cancer drugs in polymeric micelles with modifications for cancer targeting and triggered release results inmore efficient drug delivery (Figure 3). In addition to biocompatibility and biodegradability, synthetic polymers used in DDSs should be activated at the site of action, to be stable in blood circulation, to have low toxicity and immunogenicity, and to provide protection fromthe degradation of drugs before the target tissue is reached. Additionally, polymer nanocarriers of DDSscan must be easily synthesized without impurities.

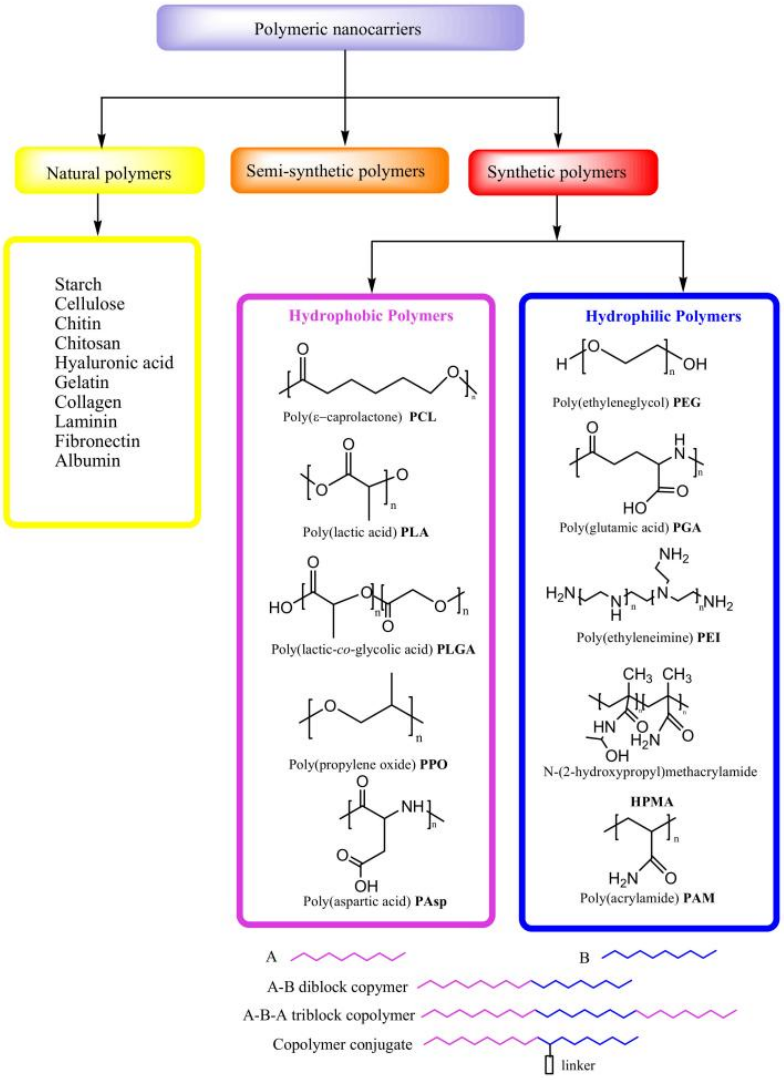

Figure 3: Types of polymeric nanocarriers

Polymer in Drug Delivery

Superabsorbent polymer compositions (SAPCs) based on poly (acrylic acid-co-acrylamide-co-22-acrylamido-2-methyl-1-propanesulfonic acid)-grafted nanocellulose /poly(vinyl alcohol)-P(AA-*co*-AAm-*co*-AMPS)-*g*-NC/PVA, were obtained using graft copolymerization reaction, to create a system for amoxicillin drug delivery. The SAPCs drug delivery vehicle obtained was intended to apply for the treatment of peptic and duodenal ulcers induced by *Helicobacter pylori* [31]. Smart (thermo- and pH-responsive) microgel particles based on HPC-AAc and poly(l-glutamic acid-2-hydroxyethyl methacrylate) were synthetized by emulsion polymerization. The microgel was tested for controlled delivery of insulin, being noted that the system is resistant to gastric pH (1.2) and release insulin in a controlled manner at intestinal pH (6.8) [32]. By NIPAAm/CMC copolymerization were obtained copolymeric (CP) sIPN hydrogels, which were redox crosslinked using *N*,*N*′-methylenebisacrylamide (BIS) and *N*,*N*′-bis(acryloyl)cystamine (CBA). The hydrogels were tested for egg white protein lysozyme delivery at pH 1.2 while the system cross-linked with BIS showed higher swelling and maximum release [33]. A hydrogel system based on CMC and CMPVA grafted copolymer was developed by crosslinking with adipic dihydrazide. This copolymeric hybrid hydrogel was proposed as a carrier for drug delivery and as a scaffold for tissue engineering, based on its

biocompatibility with the living cells and the fact that ensures outstanding survival rate at lower polymer concentration [34]. Hydrogels based on bacterial cellulose-g-poly (acrylic acid) that are stimuli-responsive were fabricated using electron beam irradiation and evaluated as oral delivery system for proteins (e.g., bovine serum albumin (BSA)). This method offers the advantage that no cross-linking agents are involved, thus overcoming the eventual toxic effects related to cross-linkers use.

Hyaluronic acid (HA) is abundant in connective, epithelial, and neural tissues. HA macromolecules showed anti-inflammatory, immunosuppressive properties and block angiogenesis, while cleaved small fragments induce opposite behavior, enabling endothelial cells migration and angiogenesis. Kim et al.obtained PVA/HA hydrogel nanofibers by chemical crosslinking, using HCl and glutaraldehyde. They observed that the swelling ratio of these hydrogels is higher than that corresponding to pure PVA hydrogel. A good biocompatibility of PVA/HA hydrogel nanofibers was evidenced by a higher cell adhesion at their surfaces, independent on the HA presence.

Heparin (Hep) has a high negative charge, the 3-D hydrogels based on it being used in tissue engineering, implantation, biosensor domain, drug delivery. Because Hep poses some safety problems (because it is often obtained from animal sources), analogous Hep-mimicking polymers and hydrogels obtained from synthetic sources were proposed.

Starches Source Starch is the principal carbohydrate reserved material in green plants and it is mainly present in seeds and underground organs. Starch occurs in the form of granules (starch grains). A number of starches are recognized for pharmaceutical use and these include maize (Zea mays), rice (Oryza sativa), wheat (Triticum aestivum), and potato (Solanum tuberosum).16 CompositionStarch or amylum is a carbohydrate consisting of a large number of glucose units joined together by glycosidic bonds. It consists of two polymers, namely amylose (a non-branching helical polymer consisting of α-1, 4 linked D-glucose monomers) and amylopectin (a highly branched polymer consisting of both α-1,4 and α-1,6 linked D-glucose monomers).18Thermoplastic starch is used in packaging, containers, mulch films, textile sizing agents, adhesives19

Inulin: It is a polysaccharide obtained from the bulbs of Dehlia, Inula Helenium (Compositae), roots of Dendelion, Taraxacum officinale (Compositae). Burdock root, Saussurea lappa (Compositae) or chicory roots, Cichonium intybus (Compositae).16 Inulin with a high degree of polymerization was used to prepare biodegradable colon-specific films in combination with Eudragit® RS that could withstand break down by the gastric and intestinal fluids.20

Self-Assembling Hybrid Hydrogels

Self-assembling hybrid hydrogels containing peptides provide the desired biological functionality and biodegradability, are able to mimic biological structures and materials having direct biomedical applications, namely as carriers for drug and cell delivery (e.g., incorporation of bioactive sequences from natural proteins). To control mechanical, biocompatibility and degradation properties, the peptides are combined with polymeric networks by chemical modification, covalently linking or non-covalent interactions between peptides and polymers [35].

Hybrid hydrogels self-assembled from graft copolymers via formation of coiled coil antiparallel heterodimers was also demonstrated based on HPMA copolymers backbone and a pair of oppositely charged peptide grafts. The formation of these hybrid hydrogels was reversible. A DNA/poly(lactic-co-glycolic acid) (PLGA) hybrid hydrogel (HDNA) was prepared for water-insoluble ophthalmic therapeutic delivery of dexamethasone and it may be applied in treatment of various eye diseases.

Polymer in tissue engineering (Scaffolds)

Attempts to find tissue-engineered solutions to cure orthopaedic injuries/diseases have made necessary the development of new polymers that meet a number of demanding requirements. These requirements range from the ability of scaffold to provide mechanical support during tissue growth and gradually degrade to biocompatible products to more demanding requirements such as the ability to incorporate cells, growth factors etc and provide

osteoconductive and osteoinductive environments. Furthermore, the development of in-situ polymerizable compositions that can function as cell delivery systems in the form of an injectable liquid/paste are becoming increasingly attractive in tissue engineering applications. Many of the currently available degradable polymers do not fulfil all of these requirements and significant chemical changes to their structure may be required if they are to be formulated for such applications.

Scaffolds made from synthetic and natural polymers, and ceramics have been investigated extensively for orthopaedic repair. This approach has advantages such as the ability to generate desired pore structures, matching size, shape and mechanical properties to suit a variety of applications. However, shaping these scaffolds to fit cavities/defects with complicated geometries, bonding to the bone tissues, and incorporating cells and growth factors, and requirement of open surgery are a few major disadvantages of this approach [36].Organ failure and tissue loss account for roughly half of the medical cost in the United States, resulting in ~8,000,000 surgical procedures and 40−90 million hospital days/year for treatment[37]. Tissue engineering or regenerative medicine is a multidisciplinary and interdisciplinary field that aims to develop functional biological substitutes that restore, maintain, or improve tissue function by combining a scaffold, cells, and biological molecules.Scaffolds combine several functions including biocompatibility with host tissues, tunable biodegradation rate, nontoxic degradation products, and suitable porosity for the transportation of nutrients and wastes, mechanical strength, and sterilization[38]. Polymers possess great processing flexibility, biocompatibility, and biodegradability and are one of the most widely used scaffolding biomaterials. Natural polymers such as chitosan, gelatin, collage, alginate, and so on and synthetic polymers including polylactide (PLA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), poly(glycerol sebacate), and polyurethane (PU) are the dominant biomaterials as scaffolds for tissue engineering. Biomaterials play a pivotal role during tissue repair. They not only serve as matrices for cellular adhesion but should also improve the interactions between the biomaterials and the seeding cells as well as further control cellular activities, such as cell proliferation and differentiation, and neo-tissue genesis. It is nevertheless still a challenge to develop bioactive biomaterials that can enhance cell proliferation and guide differentiation of cells. Conducting biomaterials based on carbon nanotubes, carbon nanowires, graphene, and metallic particles (e.g., gold nanoparticle) have been widely investigated in biosensor and bone tissue engineering applications due to their high electrical conductivity and tensile strength in recent years[39].However, drawbacks including nonbiodegradability, issues of uncertain long-term in vivo toxicity, and the inhomogeneous distribution of the conducting particles in a composite system have restricted their

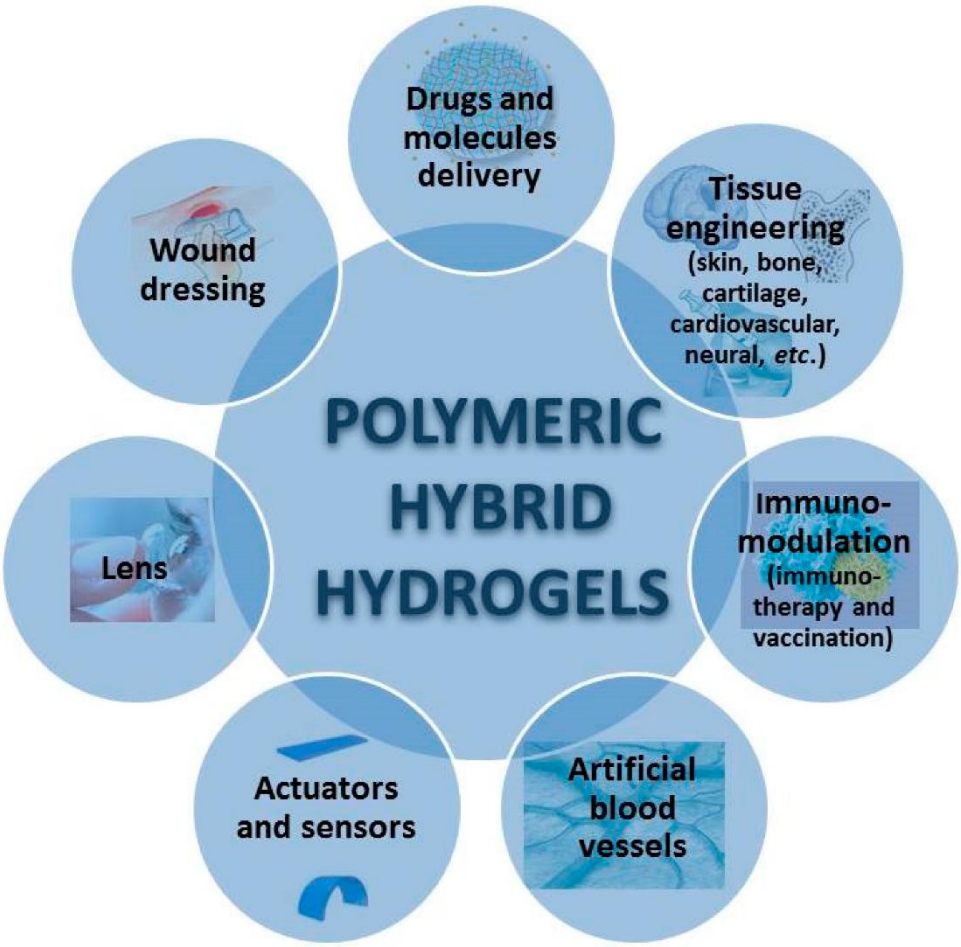

Figure 4: polymeric hybrid hydrogels

widespread and effective use. Conducting polymers (CPs) as a new generation of organic materials exhibit electrical and optical properties resembling metals and inorganic semiconductors but also show properties including ease of synthesis and flexibility in processing. The soft nature of organic conductive polymers provides better mechanical compatibility and structural tunability with cells and organs than conventional electronic inorganic and metal materials. CPs such as polyaniline (PANI), polypyrrole (PPY), and polythiophene and their derivatives and composites are attractive biomaterials due to their biocompatibility, facile

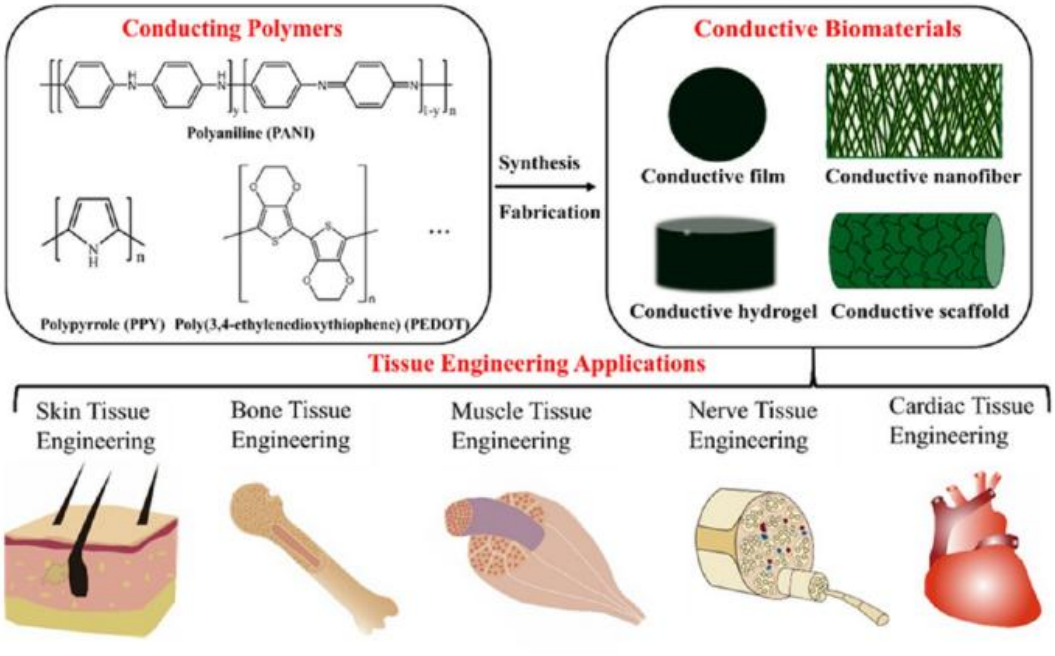

Figure 5: Conducting polymers and conductive biomaterials and their tissue engineering applications

synthesis, simple modification, and ability to electronically control a range of physical and chemical properties by (i) surface functionalization techniques and (ii) the use of a wide range of molecules that can be entrapped or used as dopants. These advantageous properties make them attractive in many biomedical applications, including drugdelivery systems, artificial muscles, bioactuators, biosensors, neural recording, and tissue engineering. CPs are not only biocompatible but also can promote cellular activities, including cell adhesion, migration, proliferation, differentiation, and protein secretion at the polymer−tissue interface with or without electrical stimulation. Biomaterials based on CPs are especially useful in the engineering of electrical-sensitive tissues such as skeletal muscles, cardiac muscles, nerves, skins, and bones[40]. It was found that biomaterials containing CPs can significantly enhance cell adhesion and proliferation of a series of cells such as L929 fibroblasts, C2C12 myoblasts, PC12 cells, RSC96 Schwann cells, H9c2 cardiac cells, primary cardiomyocytes, MC3T3-E1 cells, and mesenchymal stem cells.This review will discuss CPs as bioactive biomaterials for tissue engineering applications. In the first part, we focus on various kinds of conducting biomaterials fabricated by different techniques, and then, we summarize the application of these conductive biomaterials in tissue engineering including bone, skeletal muscle, nerve, cardiac, and wound healing as depicted in Figure 1.

Smart and biodegradable polymer: pH-responsive dendrimers

Dendrimers are potential candidates for a variety of biological applications such as drug delivery, gene therapy, and MRI imaging due to their distinctive dual properties of ultrasoft colloids and structured polymers[41]. These entities improve the penetration and retention properties of the drug. Developing pH-responsive drug delivery systems can also be accomplished by directly conjugating the drug molecules to the dendritic backbone using pH-responsive biodegradable linkers. Their ability to dissolve in water is a key feature that makes them appealing to pH-responsive drug delivery. Some dendrimers must be adjusted to give diverse functions depending on the requirements.123 Dendrimers have excellent qualities; however, their diameters of less than 15 nm make several application processes difficult. pH-responsive polymers like poly (propyleneimine) (PPI) and poly (amidoamine) (PAMAM) have extensively been studied for their use as dendrimers.Zhang et al. developed doxorubicin-conjugated folic acid-modified and partially acetylated PAMAM

dendrimers with a further pH-sensitive cis-aconite linker. This nanosystem being acidresponsive, released the drug at an acidic tumor microenvironment confirmed through in vitro testing on KB-LFAR and KB-HFAR cells[42].

Drug delivery to the malignant tissues

Rapid cancer cell development causes excessive glucose consumption, lactic acid buildup, and limited blood supply at tumor locations, causing the microenvironment to be acidic (pH 5.5–6.8).Solid tumors have altered pH gradients throughout their cell membrane and an acidic extracellular environment. Nanomaterials that respond to pH gradients offer the possibility for the delivery of anti-cancer drugs like angiogenesis inhibitors and monoclonal antibodies. The pH-responsive nanocarriers have ligands or functional groups that respond to a small change in ambient pH. To facilitate cellular targeting and internalization, nanocarriers have been created with functional groups that remain insoluble at basic pH and solubilize at pH 5.6 (tumor extracellular environment)[43]. Nanoparticles rapidly localize 7 via EPR (enhanced permeability and retention), post-IV injection due to leaky arteries, and a lack of lymphatic outflow in tumor tissues. As a result, pH-sensitive drugdelivery platforms have received much attention for utilizing the pH gradient that exists between normal (7.4) and malignant tissue to administer tumortargeted drugs (5.5–6.8).177 Figure 4 presents a schematic mechanism of tumor-targeted drug delivery based on pH-responsive nanocarriers. Polymeric micelles, liposomes, and polymer-drug conjugates often enter the cells via endocytosis.181 The pH gradually decreases from a physiological pH of 7.4 to an endosomal pH of 6 and then to a pH of 5 in the lysosomal compartments during internalization. Nano-formulations capable of responding to acidic endo/lysosomal pH have been extensively researched for intracellular delivery of cytotoxic drugs via the endocytic pathway. Camptothecin encapsulated in PbAEM micelles has been investigated for tumor-specific drug delivery.Apartsin et al. prepared methotrexate-loaded triazine-carbosilane dendrimersomes. These amphiphilic dendrimersomes elicited pH-triggered anticancer effects on the leukemia cell lines [44].In today's technological milieu, it is commonly acknowledged that stimuli-sensitive systems with controlled drug release are feasible. Both exogenous and endogenous stimuli are used for the sake of this objective, however, the most frequent trigger is endogenous pH. Functionalizing the fundamental pH-responsive polymers with chemical moieties that render these polymers dually responsive to a variety of stimuli makes the targeting efficiency more precise. This phenomenon has been investigated by Xu et al. A pH and glutathione-triggered drug delivery system against breast cancer was developed by conjugating doxorubicin with polyethylene glycol linked through disulfide bonds and cis-aconitic anhydride. Nanomicelles were formulated that released more than 80% of drug content in breast tumors triggered by the acidic pH and GSH levels of cancer cells [45].

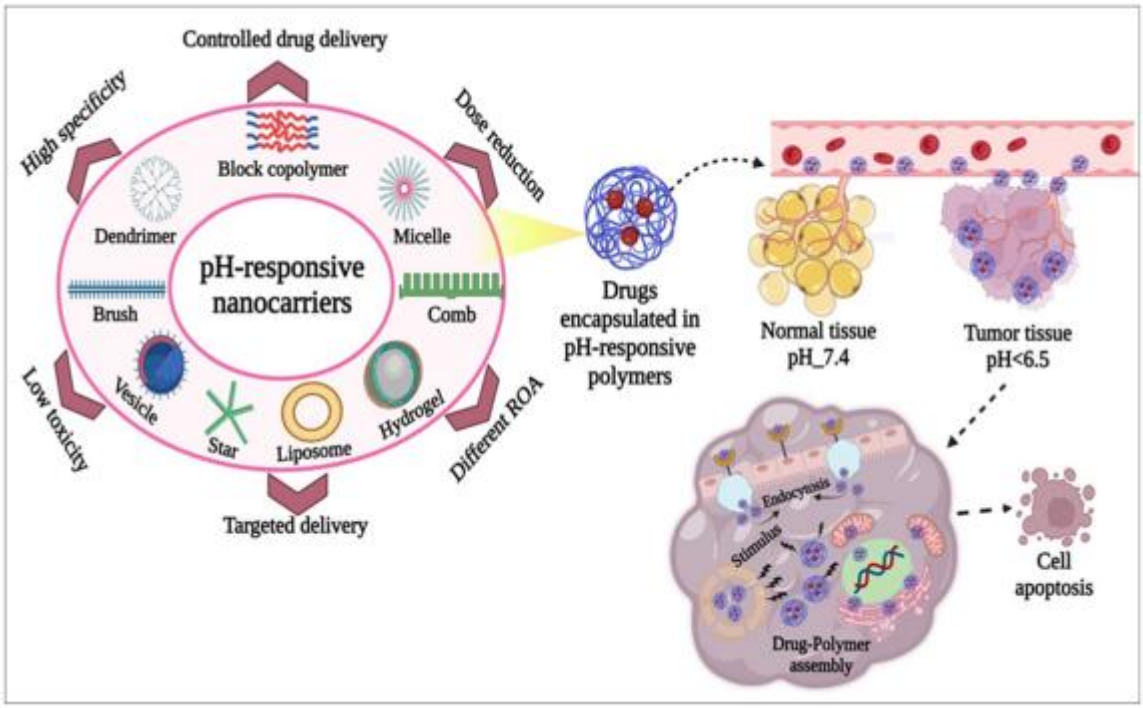

FIGURE 6: Schematic representation of tumor-specific drug delivery employing various pH-responsive polymeric systems.

Polymer Thermosensitive Liposomes (PTSL)

Another approach to sensitizing liposomes to lower mild hyperthermia conditions involves integrating thermosensitive LCST polymers into the liposomal structures. The introduction of polymers also addresses concerns about eventual in vivo and in vitro thermosensitivity-loss of LTSLs, as the lysolipids tend to desorb and leach out from the liposome bilayer, leaving behind fenestrae open to the surrounding biological milieu [46]. Premature drug release from LTSL was demonstrated in vivo, as about 50% of the encapsulated DOX was released within 1 h of administration in mice kept at 36.5–37.5 ◦C . In comparison, up to 80% was released in vitro within half an hour, when tested in serum at physiological conditions . Thus, conjugating or polymerizing the liposomes with thermosensitive polymers is a promising approach that overcomes the drawbacks of older designs. These synthetic polymers can be used to introduce thermosensitivity to the non-thermosensitive formulation or augment the thermo-responsiveness of already thermosensitive formulations. At temperatures below the LCST, the polymers are completely hydrated, hindering interactions with the extra-liposomal environment and preventing cargo release. As the liposomes experience an increase in temperature, the polymers shrink and condense into their dehydrated globular forms, disrupting the membranes' stability and releasing the drug load . These polymers can be easily tuned to respond to the desirable range of temperatures, thereby impacting the liposomal responsivity as well. Such liposomes are commonly referred to as 'polymer thermosensitive liposomes' (PTSLs). As previously discussed, various thermosensitive polymers exist in research and can be modified according to the requirements. Liposomes surface modification with thermosensitive polymers dates to 1991, where Ringsdorf and colleagues [47]. tried inducing reversible conformational transitions in liposomal membranes by incorporating hydrophobic PNIPAAm chains onto them. This study was fundamental in outlining the basis of coil-to-globule chemistry in the science of polymers. Figure 7 illustrates the different ways polymers can be incorporated into liposomes. Hydrophilic thermosensitive polymers can be physically adsorbed on the liposome surface (Figure 7A), polymerized to entrap the liposome inside (Figure 7B), covalently bonded to the phospholipid

heads (Figure 7C left), or polymerized into fused networks on the surface of the liposome (Figure 7C right). Furthermore, amphiphilic thermosensitive polymers can either be separated in segregated domains (Figure 7D left) or homogenously distributed through the liposomal bilayer (Figure 7D right) [89]. Research in this area has blossomed due to the merits of this approach, which include facile synthesis schemes, flexibility in tuning the properties, and highly efficient systems, which can cater to the burst release requirements. Kim et al. [48]. reported that copolymerization of NIPAAm and AAc, then mixing the result into liposomes primarily composed of egg phosphatidylcholine (PC) and DPPC, resulted in a highly-controlled thermoresponsive system. Similarly, Han and colleagues successfully modified DPPC, HSPC, and cholesterol (56:28:17 mol%) based liposomes with PNIPAAm-AAc mixed at a ratio of 83 to 17 (mol/mol%). The PTSLs showed remarkable release of encapsulated DOX, corresponding to almost 65% of the load after 5 min of hyperthermal exposure at 39 ◦C. At temperatures less than that, i.e., 37–38 ◦C, the carriers were able to retain almost 90% of their contents[49]. To summarize, functionalizing liposomes with thermosensitive polymers can yield highly controllable therapeutic platforms with desirable tunable properties. Table 4 presents some studies which investigated the effects of comonomers choice for affecting PNIPAAm polymer thermo-responsiveness, and which extend to the liposome's thermosensitive functionality.

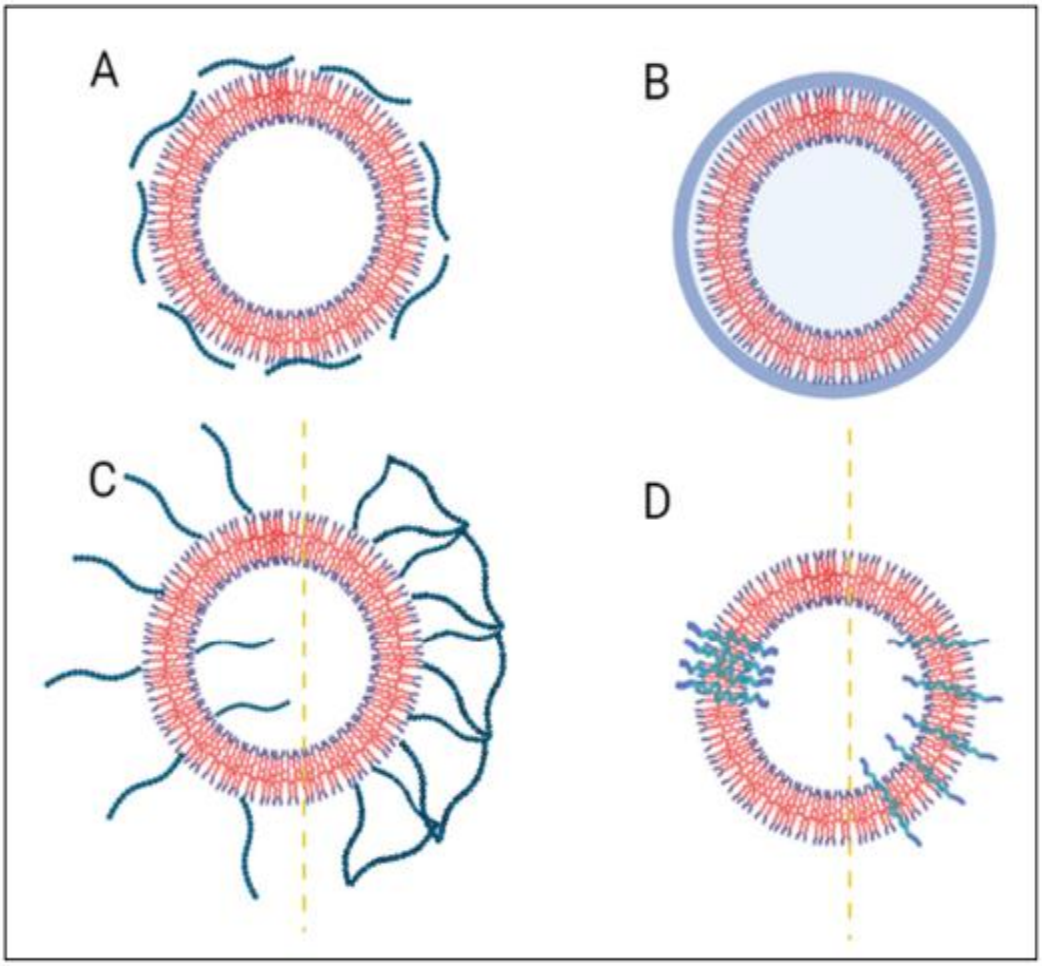

Figure 7: Thermosensitive polymers can (A) adsorb on the liposome surface, (B) encapsulate the liposome, (C, left) be covalently bonded to the polar phospholipid heads, or (C, right) reticulate to form fused networks on the liposome surface. Amphiphilic thermosensitive liposomes either (D, left) segregate in distinct domains, or (D, right) are uniformly distributed in the lipid bilayer [50].

Future perspective:

polymers in medicine is poised for significant advancements, driven by innovations in material science, nanotechnology, and biomedical engineering. In drug delivery, next-generation polymer-based systems will focus on stimuli-responsive and targeted drug release mechanisms, enhancing therapeutic efficacy while minimizing side effects. Smart polymers capable of responding to physiological conditions such as pH, temperature, and enzyme activity are expected to revolutionize personalized medicine by enabling controlled and site-specific drug delivery.In biomaterials, the development of biodegradable and bioresorbable polymers will play a critical role in regenerative medicine, tissue engineering, and wound healing. Advanced 3D printing techniques, combined with biopolymers, will facilitate the fabrication of patient-specific implants and scaffolds with improved biocompatibility and mechanical properties. Furthermore, polymeric hydrogels and nanocomposites will be extensively explored for applications in artificial organs, biosensors, and bioelectronic interfaces.Emerging research also focuses on self-healing and antimicrobial polymers to prevent infections and improve implant longevity. Additionally, integrating polymers with nanomedicine and bioelectronics could lead to breakthroughs in smart drug delivery systems, bioactive implants, and real-time health monitoring. Despite these promising developments, challenges such as polymer toxicity, long-term stability, and large-scale manufacturing must be addressed. Future research should emphasize biocompatibility, sustainability, and cost-effective production to ensure the widespread adoption of polymer-based medical technologies.

Conclusion:

Polymers have revolutionized modern medicine, offering versatile applications ranging from advanced drug delivery systems to biomaterials used in tissue engineering and regenerative medicine. Their tunable properties, including biocompatibility, biodegradability, and mechanical adaptability, have enabled significant progress in controlled drug release, medical implants, and artificial organs. Recent advancements in polymer chemistry have led to the development of smart, stimuli-responsive polymers capable of site-specific drug delivery, minimizing side effects and improving therapeutic outcomes.Looking ahead, the future of polymer-based medical technologies is expected to be driven by innovations in nanotechnology, bioengineering, and digital health. Smart polymers, which respond to external stimuli such as pH, temperature, and enzymes, will pave the way for highly efficient and personalized medicine. In biomaterials, 3D-printed polymer scaffolds, bioresorbable implants, and multifunctional hydrogels will continue to transform tissue engineering and regenerative therapies. Additionally, integrating polymers with bioelectronics and wearable medical devices will enhance real-time health monitoring and therapeutic interventions.Despite these advancements, challenges such as long-term stability, potential cytotoxicity, and large-scale production remain to be addressed. Future research must focus on improving the biocompatibility, sustainability, and cost-effectiveness of polymeric materials to ensure their widespread adoption in healthcare. With continuous advancements, polymers will remain at the forefront of medical innovation, shaping the future of drug delivery, biomaterials, and patient-specific treatments.

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