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Review Article

Utilizing Biomimetic Polymers for Innovations in Drug and Gene Delivery

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ABSTRACT

Biomimetic polymers are increasingly being explored in advanced drug and gene delivery research due to their ability to imitate the structure and function of natural biological systems. Increased biocompatibility, targeted delivery, and controlled release (with time-dependent release kinetics) make them ideally suited for therapeutic applications. These polymers imitate the features of cell membranes, proteins and other biological entities, and have shown greater biocompatibility, targeted delivery, and controlled release kinetics widely tunable to allow for a variety of therapeutic applications; including cancer therapy, regenerative medicine, and gene therapy, biomimetic polymers can facilitate the targeted and efficient transport of therapeutic agents, including small molecules (e.g., drugs), nucleic acids and proteins, in a manner that has helped overcome barriers associated with existing delivery systems. The materials design and synthesis of biomimetic polymers have become much better recent years, allowing their full potential as therapeutics to be realized, even though issues related to stability, targeting, and ways to efficiently manufacture it to scale for clinical application remain. Biomimetic polymers possess considerable potential to change drug and gene delivery paradigms, with opportunities to enhance clinical outcomes and personalize medicine. Given these challenges, we can only begin to imagine what we can achieve with biomimetic polymers in the future, and continue effort into addressing existing limitations while continuing to realize their promise will be necessary to allow their transformation of chemotherapy delivery vehicles and other therapeutic delivery systems. This review highlights recent advancements biomimetic polymer technologies, and highlights their considerable ability to impact the improvement of efficacy, targeting and safety of drug and gene delivery technologies. It also explores current obstacles and prospective advancements in the field, emphasizing the significant potential of these materials to revolutionize drug delivery systems and improve clinical outcomes.

Keywords: Biological Molecule and amp, Biomimetic Polymer, Gene Delivery, Structure.

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INTRODUCTION

Overview of Biomimetic Polymers in Drug and Gene Delivery

Biomimetic polymers, inspired by naturally occurring biological systems, have become valuable in the field of drug and gene delivery. These innovative materials mimic the structures, behavior, and function of nature's molecules, resulting in better therapeutic efficacy. Now, the design incorporates biocompatibility and biodegradability parameters that are necessary to ensure safe and effective treatment. These polymers draw on nature's biological structures for comparative enhancements to therapeutics' targeted delivery and controlled release. Overall, biomimetic polymer-based drug and gene delivery systems show great promise as an alternative to traditional drug delivery systems by solving a variety of problems relating to bioavailability, off target side effects, and systemic toxicity. The biomimetic polymer systems include special features that include: target precision, drug specificity, drug delivery with potential long-term savings.[1,2]

Nature offers vast amounts of inspiration to produce polymers that exhibit the properties needed for biomedical uses. Cell membranes, proteins, nucleic acids and so forth are all structurally and functionally complex systems, the qualities of which can be recapitulated in synthetic polymeric systems. Utilizing patterns learned from these biological features, scientists have proposed the use of biomimetic polymers with improved potential in therapeutic agent delivery.[3] These polymers can be tailored to target biological processes, which increases their efficacy and

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reduces potential side effects. Biomimetic polymers are widely utilized in biomedical fields such as controlled drug delivery, gene therapy, tissue engineering, and regenerative medicine due to their adaptable and multifunctional nature. Due to their potential for molecular recognition, self-assembly, and responsive behavior to environmental stimuli, nanocarriers serve as ideal candidates in contemporary drug and gene delivery systems.[4]

Design Strategies for Biomimetic Polymers

Biomimetic polymers are engineered with structural and functional features that mimic natural biological systems, improving their interaction with living tissues, enhancing drug delivery, and ensuring biocompatibility. Several key strategies are utilized in their design, incorporating principles from molecular recognition, self-assembly, stimuli responsiveness, biodegradability, and functionalization with bioactive molecules.

Molecular Recognition and Selectivity

Biomimetic polymers are designed to recognize and attach to biological molecules like enzymes, receptors, or antigens allowing for precise drug delivery while reducing off-target effects. This extreme degree of specificity can often be accomplished using Molecularly Imprinted Polymers (MIPs). The synthesis of MIPs involves creating a polymer matrix around a template molecule; after the template is removed a cavity is left behind those mimics the shape and chemical properties of the former target. The result is specific binding sites that mimic the natural processes of receptors and ligands. MIPs are widely used in drug delivery, biosensors and diagnostics due to their unmatched stability and selectivity. For instance, polymeric nanoparticles functionalized with folic acid can very specifically target folate receptors that are expressed on the surface of cancer cells and promote enhanced delivery and therapeutic efficacy of anticancer drugs, or glycopolymer-based drug carriers can mimic carbohydrate interactions on the surfaces of cells to enhance recognition by other immune or cancer cells and achieve specificity.[5,6]

Stimuli-Responsive Behavior for Smart Drug Delivery

Biomimetic polymers are able to be engineered to respond to external signals including changes in pH, temperature, light exposure, presence of enzymes, redox environment, magnetic fields, or ultrasound; allowing for localized delivery of drugs in a controlled manner so that a precise and targeted therapy can be achieved.

pH-Responsive Polymers

Diseased regions (ex. tumors or inflamed tissues) typically have lower pH than healthy tissues. pH-sensitive polymers can either change their structure or degrade in the low pH of the diseased environment promoting localized drug release while limiting exposure to healthy environments. Poly Beta Amino Acids (PBAA) are biodegradable, and can release small-molecule drugs like paclitaxel, at an acidic pH like that of the tumor microenvironment (pH ~6.5-7.0), allowing for improved outcomes in cancer therapy. Hydrazone-linked polymers are able to degrade in the low pH of a endosomes and following this, provide spatiotemporal control of drug or gene release from the tumor, endosomes and lysosomes.

Temperature-Responsive Polymers

The polymeric materials Poly (N-Isopropylacrylamide) (PNIPAM) and Poly (Ethylene Oxide)-Poly (Propylene Oxide) (PEO-PPO) are temperature responsive, which means they will alter their solubility with changes in the temperature. These polymeric materials can be utilized to release drugs in response to therapeutic temperatures such as body temperature or fever, enabling temperature controlled therapeutic delivery in various disease states such as cancer, infection and glaucoma. For example, in the case of PEO-PPO copolymers they will form hydrogels at body temperature leading to prolonged drug residence time in the eye, which is valuable for ocular drug delivery.

Enzyme-Responsive Polymers

Certain disease states also have elevated levels of various enzymes, Matrix Metalloproteinases (MMPs), found in cancerous tissue. Polymers can be designed to degrade in the presence of specific enzymes, to allow for highly selective drug delivery to the target site for a disease, such as cancer, diabetes, wound healing and more recently infection detection. For example, micelle type assemblies made from peptide based amphiphiles with sequences sensitive to MMP have been used to deliver cisplatin to breast cancers, and liposome type assemblies with enzyme sensitive coatings have been designed to deliver methotrexate to the site of rheumatoid arthritis based on the action of Phospholipase A2 (PLA2).

Light-Responsive Polymers

Biomimicry polymers that are photoresponsive can be designed to allow for controlled, on-demand drug delivery using light. These advanced materials can be initiated by different wavelengths of light to allow for operations at spatially and temporally precise times and locations. Collectively, light activated delivery will allow unique control over your therapeutic delivery that has both spatial and temporal precision to minimize side effects and improve effectiveness. Near-Infrared (NIR)-based systems can penetrate more deeply into tissues making them attractive for photothermal therapy including cancer treatment, diabetes delivery, and ocular diseases. For instance, using gold nanorods embedded into light-responsive polymers can photothermally ablate cancer cells.[5,6]

Redox-Sensitive Polymers

Tumor cells have higher levels of Glutathione (GSH) than normal controls, and there exist redox responsive Biomimetic Polymers (BioMP) including thioketal based polymers and poly (methacrylic acid) based systems that are degraded at increased levels of GSH. These polymers ensure that drug release occurs in a selective manner by releasing a payload specifically in the presence of cancerous tissue. Redox-sensitive micelles, vesicles, and polymersomes enhance specificity of delivery based on disintegration of NPs in the high-GSH tumor environment. For example, thioketal based nanoparticles have been tested to deliver curcumin (biomimetic) for inflammatory bowel disease, and poly (methacrylic acid)-based micelles as a delivery vehicle to release siRNA gene silencing in lung cancer.

Magnetic Field-Responsive Polymers

These polymers incorporate magnetic nanoparticles (e.g., iron oxide) to enable remote-controlled drug release or targeting using external magnetic fields. They are used in cancer therapy for hyperthermia-induced drug release.

Ultrasound-Responsive Polymers: These polymers release drugs in response to ultrasound waves, offering non-invasive control. They are explored for insulin delivery in diabetes management.

Biocompatibility and Biodegradability

One of the most important considerations in the design of biomimetic polymers is the usability of the material and the polymer platform to be biologically compatible and biodegradable so the material can be safely metabolized and excreted out of the body. Natural polymer-based biomaterials such as polysaccharides (e.g., chitosan, alginates, hyaluronic acid, dextran, agar, agarose, starch) and proteins (e.g., collagen, gelatin, silk fibroin, elastin, resilin, keratin, zein) are chosen, because they show inherent biological compatibility.

Polysaccharide-based Biomimetic Polymers

Chitosan, hyaluronic acid, dextran, agar, agarose, and starch-based carriers are great for drug delivery and tissue engineering, because they have great biocompatibility and biodegradability, even when undergoing natural enzymes. The only reason Dextran has made it a drug delivery platform is because it is water soluble and can form hydrogels that result in some levelling out effect like the extracellular matrix (ECM) to facilitate tissue repair. Agar and agarose form gels with properties like biological tissues, used in wound healing and cartilage scaffolds. Starch, with its biocompatibility, is employed in controlled-release systems for oral drug delivery, responding to temperature or pH changes.

Protein-based Biomimetic Polymers

Collagen and gelatin provide structural support and promote cell adhesion, making them useful for regenerative medicine. Elastin offers elasticity for vascular tissue engineering, resilin provides resilience for soft tissue applications, keratin is used in wound healing for its mechanical strength, and zein is employed in drug delivery for its biodegradability and film-forming properties. Elastin-Like Polypeptides (ELPs) form temperature-responsive hydrogels for cancer therapy.

Biodegradable Synthetic Polymers

Biodegradable polymers like Poly (Lactic-co-Glycolic Acid) (PLGA), Polycaprolactone (PCL), Polyglycolic Acid (PGA), and Polyhydroxyalkanoates (PHAs) degrade into non-toxic byproducts, and provide predictable and controlled drug delivery with adjustable degradation rates.

These biocompatible substances have the additional advantage of limiting or reducing the possibility of negative immune response and providing a safe means of complete clearance from the body after the delivery of a drug.[7]

Mechanisms of Drug and Gene Delivery Using Biomimetic Polymers

Biomimetic polymers use different methods to enable efficient drug and gene delivery as they enhance accurate targeting of therapeutics while minimizing detrimental systemic effects. These strategies include encapsulating therapeutic agents within polymer matrices, facilitating cellular uptake through receptor-mediated endocytosis, enabling membrane translocation, and triggering release in response to specific stimuli. By imitating natural biological pathways, these polymers improve the stability, targeting accuracy, and availability of drugs or genetic material, positioning them as valuable tools in advanced delivery platforms.

Polymer-Based Encapsulation and Controlled Release

Biomimetic polymers are carriers that are designed to sequester drugs / genetic material by encapsulation and protect them from break down or degradation, while also increasing stability.[5,7] Biomimetic carriers are designed for controlled release over time so that the drug and therapeutic effect can last longer. There are many ways biomimetic polymers can provide a controlled release of a drug:

Diffusion-Controlled Release

The drug is released from a polymeric matrix and can do so at a constant rate. This allows for steady state levels of the drug in the blood while minimizing number of doses.

Swelling-Controlled Release

Some biomimetic polymers, e.g., hydrogels, can absorb water to generate a swollen volume that can then provide slow release of a

therapeutic agent embedded in it. These polymers are very useful for tissue engineering and wound healing applications.

Degradation-Controlled Release

Biodegradable polymers are typically degraded by enzymatic or hydrolytic means, and they typically degrade over time, and can provide localized drug release. For example, Poly (Lactic-co-Glycolic Acid) (PLGA)-based drug delivery systems degrade into non-toxic byproducts while providing prolonged drug release.

This mechanism not only enhances drug stability but also prolongs therapeutic efficacy, making it an effective strategy for chronic disease management.

Receptor-Mediated Endocytosis

Biomimetic polymers frequently utilize receptor-ligand interactions to facilitate targeted cellular uptake.[4,6] These polymers are functionalized with ligands that specifically bind to receptors overexpressed on diseased cells, allowing selective delivery of therapeutic agents. This targeted approach enhances drug efficacy while minimizing systemic toxicity.

Ligand-Based Targeting Method

Ligands, which are proteins or other biological molecules such as folic acid, transferrin, and antibodies, can be attached to biomimetic polymers to promote site-specific binding to cancer or other disease related receptors. In the case folic acid functionalized nanoparticles, the nanoparticles can specifically bind to the folate receptors expressed in cancer cells, resulting in localized accumulation of drug at the cancer site. Another method for targeting specific disease routes are inflammatory diseases such as rheumatoid arthritis, where ligands such as anti-TNF-α antibodies can promote uptake by inflamed tissues or joints.

Antibody- Conjugated Polymers

Monoclonal antibodies conjugated with biomimetic polymeric carriers increases the specificity of drug delivery, especially within immunotherapy applications. Antibody-Drug Conjugates (ADCs) allow a high degree of localization of chemotherapeutic agents targeting tumor cells which decrease unwanted off-target effects.

Aptamer-Based Targeting

Aptamers are short sequences, single-stranded DNA or RNA that can bind a specific molecular target with high affinity. When linked to biomimetic polymers, the aptamer can direct drug carriers to diseased cells with high specificity.

All of these examples communicate the efficiency of receptor-mediated endocytosis that cell will go through to mediate the intracellular delivery of therapeutic agents with maximum therapeutic effect and a minimum adverse effect.

Membrane Penetration and Intracellular Transport

Certain biomimetic polymers are capable of directly entering cells and bypassing standard endocytic delivery pathways.[10] This feature is particularly useful to gene therapy applications that require nucleic acids to enter the nucleus for effective gene expression.

Cell-Penetrating Peptides (CPPs)

Short peptides derived from naturally occurring proteins can facilitate intracellular drug delivery by translocating across the plasma membrane. When conjugated with biomimetic polymers, CPPs improve the cellular uptake of nucleic acids, proteins, and small-molecule drugs.

Fusogenic Polymers

Drawing inspiration from viral fusion proteins, fusogenic polymers have the ability to integrate with cell membranes, allowing therapeutic agents to be delivered directly into the cytoplasm. This will be especially beneficial for gene editing applications with CRISPR/Cas9 because this will help to protect the gene editing materials from being degraded in endosomes.

Cationic polymers for gene delivery

The ability of a cationic (positively charged) biomimetic polymer, such as Polyethylenimine (PEI) or chitosan, to create electrostatic complexes with negatively charged DNA or RNA enables them to form polyplexes that add the ability to escape from an endosome and successfully transfect and express genes. Membrane-penetrating biomimetic polymers are going to significantly improve the intracellular distribution of therapeutics, and it is clear they must play an integral role in the development of sophisticated drug and gene delivery systems.

Stimuli-Responsive Drug Release

One major advancement in biomimetic polymer-based drug delivery is their ability to detect physiological signals, allowing for drug activation at the target site. These smart delivery systems have higher treatment specificity and less collateral effects on healthy tissue.[8,9]

pH-Responsive Polymers

Most tumors and inflamed tissues have a slightly acidic microenvironment. pH sensitive polymers, such as poly (β-amino acid) and hydrazone-linked polymers, are stable at physiological pH (~7.4), but are able to change conformationally or degrade at acidic pH (~6.5, or lower) to release drugs specifically at the diseased site. Poly (β-amino acid) is advantageous for cancer therapy for its quick degradation in acidic tumor environments, while hydrazone-linked polymers are utilized for the management of diabetes through pH-triggered insulin release. For example, Poly(N-isopropylacrylamide) (PNIPAAm)-based systems have

received considerable attention in terms of pH sensitive delivery of drugs.

Enzyme-Triggered Drug Release

There are pathological tissues that have high levels of certain enzymes such as Matrix Metalloproteinases (MMPs) that are commonly found in cancers. Biomimetic polymers capable of breaking-down when encountering an enzyme will allow targeted drug release only at the diseased geographic locations. Peptide-based micelles and liposomes which have coatings that are enzyme-dependent are applied in cancer and wound healing studies where enzymes like MMPs or elastases initiate drug release. As an example, some carriers could be inhibited by the action of hyaluronidase (an enzyme that is frequently found in a tumor's microenvironment) if made from Hyaluronic Acid (HA). That would allow for specific and localized delivery of therapeutics.

Temperature-Sensitive Polymers

Temperature-sensitive polymers are capable of drug release via exposure to temperature changes. Certain biomimetic hydrogels like Poly(N-Isopropylacrylamide) (PNIPAAm) and temperature-sensitive liposomes or starch-based dual responsive polymers can retain a gel form at low temperatures and change to liquid at body temperature. These systems can be used in cancer therapies in instances where drug release was initiated following hyperthermia and also for wound healing by temperature control of delivery. This thermosensitive delivery characteristic provides for something effectively regulated and accurate inside the body.

Redox Responsive systems

Cancer cells have elevated levels of the antioxidant Glutathione (GSH) when compared to normal cells. Redox-triggered BioMPs such as thioketal-based polymers and poly (methacrylic acid)-based systems degrade in the presence of the high concentration of GSH selectively releasing the drug payloads in the tumor tissue. Redox-sensitive micelles, vesicles, and polymersomes improve drug delivery and infection suppression by disassembling in a high GSH tumor microenvironment, thus increasing specificity for cancer treatments.

The instructive mechanisms for these stimuli can transform biomimetic polymers into strategically controlled drug cargo systems to effectuate desired therapeutic outcomes, while minimizing the adverse effects.

Materials Used for Biomimetic Polymers

Biomimetic polymers, created to imitate the structures and functions found in natural biological systems, are ideal for applications in drug and gene delivery. These polymers can be categorized based on their origin-either natural or synthetic-and by their functional properties such as biocompatibility, biodegradability, and responsiveness to physiological stimuli. These properties enhance their usefulness in targeted and controlled therapeutic uses.

Natural Biomimetic Polymers

Natural biomimetic polymers are made from biological materials, and are highly biocompatible and degrade easily in the body. Natural biomimetic polymers have very similar structure and functions to Extracellular Matrix (ECM) parts, making them beneficial for constructs in tissue engineering and regenerative medicine, and for use in drug delivery systems.[10-12]

Polysaccharide-Based Biomimetic Polymers

Polysaccharides are used extensively due to their hydrophilicity, biocompatibility, and their ability to bind with biological molecules.

Chitosan: Chitosan is a cationic polymer derived from chitin and is regularly used in drug delivery applications due to its ability to adhere to biological tissues (mucoadhesion). Chitosan can also form polyplexes with negatively charged nucleic acids providing a way for gene delivery.

(Hyaluronic acid-Ha)

HA is a major component of the extracellular matrix and can be used in targeted drug delivery systems, especially for cancer therapy. Its utility stems from its specific binding affinity to CD44 receptors, which are frequently found in high amounts on cancer cell surfaces.

Alginate: Alginate, a polysaccharide derived from brown seaweed, is biocompatible, forms hydrogels under mild conditions, and is degradable by enzymatic processes. It is commonly used in drug delivery, such as insulin-loaded alginate microspheres for diabetes management, protecting sensitive therapeutics and providing controlled release.

Formulation Example

Alginate-based microbeads for insulin delivery in diabetes mellitus

Alginate-insulin microbeads or alginate-chitosan nanoparticles have been developed as oral insulin delivery systems. These formulations encapsulate insulin within alginate hydrogel matrices that protect the drug from gastric degradation and allow controlled release in the intestine.[10,11]

In addition to chitosan, hyaluronic acid, and alginate, several other naturally derived polysaccharides have demonstrated significant biomimetic potential in drug and gene delivery applications:

Dextran: A branched glucan polymer with excellent biocompatibility and water solubility. Dextran-based nanoparticles have been explored for targeted cancer therapy and

imaging due to their long circulation times and ability to evade immune recognition.

Agar and Agarose: Derived from red algae, these gel-forming polysaccharides are frequently used to fabricate hydrogels for tissue engineering and controlled drug release. Agarose gels exhibit excellent biocompatibility and structural stability, making them ideal for sustained release formulations and scaffolding materials.

Starch: A naturally abundant polysaccharide composed of amylose and amylopectin, starch has been used to prepare biodegradable microparticles and hydrogels for oral drug delivery. Its enzymatic degradability and non-toxic profile enable its application in controlled-release systems, especially for gastrointestinal targeting.

Protein-Based Biomimetic Polymers

Proteins exhibit excellent biodegradability and natural bioactive properties, making them highly suitable for applications in biomimetic systems.

Collagen: As a major structural element of the extracellular matrix, collagen-based materials are widely employed in wound healing and drug delivery applications because of their superior biocompatibility.

Gelatin: A hydrolyzed form of collagen, gelatin is used for drug-loaded hydrogels and nanoparticle formulations.

Silk Fibroin: Silk fibroin, derived from silkworms, achieves very high mechanical strength and is biodegradable, making it a compelling choice to use for drug delivery and become a part of tissue engineering.[12]

Synthetic Biomimetic Polymers

Synthetic biomimetic polymers provide the opportunity to better control their molecular structure, mechanical properties, and degradation behavior. They can be designed wholly to mimic the function of a natural biomolecule while providing more durability, stability, and performance in many biomedical applications.[13-15]

Polyesters

Polyesters are biodegradable and use in biomimetic drug delivery systems.[16-19]

PLGA (Poly (lactic-co-glycolic acid)): This is a biodegradable polymer that has been approved by the FDA and is used in drug delivery systems such as nanoparticles, microspheres, and implantable devices.

Polylactic Acid (PLA): This biocompatible polyester is typically used in drug delivery and to some extent tissue engineering. PLA breaks down into lactic acid, which is naturally produced in the body.

Polycaprolactone (PCL): PCL has a very slow rate of degradation and can be utilized to maintain extended drug release, and is often employed in the production of tissue engineering scaffolds.

Poly(Ethylene Glycol) (PEG) and PEGylated Polymers

The ability of PEGylation is to increase the solubility, circulation time, and stability of biomimetic polymers.

PEGylated Nanoparticles: Increased bioavailability of drugs through inhibition of opsonization and decreased immune-mediated drug clearance.

PEGylated Hydrogels: Polyethylene Glycol (PEG) modified hydrogels are some of the most studied biomimetic polymers in regenerative medicine and controlled drug delivery due to their tunable properties and compatibility with biological systems.

Smart and Stimuli-Responsive Polymers

Using these polymers, drugs release in a site-specific manner and in response to an external stimulus (i.e. pH, temperature, enzymes, and/or redox condition).

pH-Responsive Polymers: For example, poly(N-isopropylacrylamide) (PNIPAAm) and poly (β-amino esters) release drugs in the acidic environment of tumors.

Enzyme-Degradable Polymers: For instance, peptide-functionalized hydrogels degrade upon contact with disease-specific enzymes.[16-19]

Redox-Sensitive Polymers: Such as polymers that contain disulfide bonds that will be cleaved upon high levels of intracellular glutathione.[15]

APPLICATIONS OF BIOMIMETIC POLYMERS IN DRUG AND GENE DELIVERY

Targeted drug delivery systems employ biomimetic polymers that deliver drugs to diseased cells and agents selectively without exposing healthy cells to the effects of the same drug. Instead of getting drugs throughout the body using conventional drug delivery methods, the targeted approach has its treatment concentrated to the disease and approach it selectively. This concentrated delivery increases efficacy and reduces toxicity. The major components of these methods are biomimetic polymers that can replicate biological processes that describe a wide variety of biological processes like receptor-ligand interaction, cellular membrane interaction, and drug transport via a nanosized carrier.[20,21]

Ligand-receptor interactions are a common method of targeting, where biomimetic polymers are functionalized with ligands that bind severely to receptor expressed on diseased cells.[22,23] In particular, if the polymer is functionalized with folic acid, it has the ability to target folate receptors synthesized in specific cancer cells. Antibody-conjugated polymers also target earliest stage

means of specific drug localization via exploiting the specificity between antigen and antibody interactions. The important aspect of local drug delivery from the perspective of safety is to localize the effect specifically on the diseased cells and should avoid damaging the healthy cells.

Apart from utilizing directed targeting in oncology, ligand-based targeting has explored promising applications in inflammatory diseases like rheumatoid arthritis and inflammatory bowel disease. For example, nanoparticles functionalized with hyaluronic acid have selectively bound to CD44 receptors that are overexpressed on activated macrophages located in inflamed tissues. In addition, folate-conjugated carriers have also been used to bind folate receptors present on inflammatory monocytes. These ligand-based targeting approaches allow localization and greater and more specific delivery of anti-inflammatory therapeutic agents, such as methotrexate or corticosteroids, which improve their therapeutic potential while reducing systemic side effects.

Many ligand-based targeting approaches have been developed focusing on Cell-Penetrating Peptides (CPPs), which provide a means of assisting drug carriers in penetrating cellular membranes.[24,25] Cell-Penetrating Peptides (CPPs) are short peptide units derived from naturally-occurring proteins that enhance the intracellular uptake of poly-meric drug carriers. When used with biomimetic polymers, CPPs enable the direct delivery of drugs that bypass endosomal trapping occurring inside endosomes, making it ideal for forms of treatment that require intracellular action like bioactive/chemoactive, and some gene therapies.

Controlled Release Systems

Controlled release systems are developed to deliver medications steadily and reliably over an extended period, improving therapeutic outcomes and promoting greater patient compliance.[1,3] Biomimetic polymers are essential in the design and development of advanced controlled release systems. platforms that react to biological signals, allowing for site-specific and time-regulated drug delivery.[23,25]

A sophisticated method for controlled drug delivery utilizes stimuli-sensitive polymers that respond to changes in physiological conditions like variations in pH, temperature fluctuations, or enzyme presence.[21,26] Since the tumor microenvironment tends to be acidic, the pH-responsive biomimetic polymers can only release the drug specifically at the tumor site, which will provide localized therapy and decrease side effects throughout the body. In the same way, temperature-responsive polymers will release their drugs if there are changes in body temperature, which could, theoretically, provide external control of the delivery process.[27-29]

Hydrogels, a special class of biomimetic polymer, have attracted considerable research interest because of their ability to regulate drug delivery, particularly in applications related to tissue engineering and wound healing.[24,29] Their water-rich content and tunable properties provide excellent qualities for delivering therapeutic agents in a controlled and prolonged manner. The hydrophilic polymers swell in response to physiological conditions and release their drugs in a sustained manner. Hydrogels provide a moist environment and a regulation of how a drug will be delivered. Once again, injected hydrogels are particularly useful options for localized drug treatment in surgical or post-surgical settings or for chronic disease management.[22,25]

Polymer-drug conjugates, in which therapeutic agents are covalently linked to biomimetic polymers, are a more advanced delivery vehicle.[23,26] Polymer-drug conjugates can be designed to degrade enzymatically or hydrolytically *in vivo* to provide a drug release that is both controlled and spatially-targeted. PEGylated polymers improve drug availability through increased solubility and circulation time. Enzyme-responsive polymer systems degrade following enzymatic degradation by enzymes that are overexpressed in some diseased tissues.[27,28] These strategies work together to improve specificity and efficacy of treatments while minimizing dosing frequency and side effects.

Non-Viral Gene Delivery Vectors

The timely, effective Delivery of Nucleic Acids (DNA, RNA) to target cells is a major consideration in gene therapy. Virus vectored delivery is highly effective at gene therapy *in vitro* and *in vivo* but often poses several risks, including immunogenicity and insertional mutagenesis. A safer and more effective option, biomimetic polymers offer a clean and precise method for gene delivery that is non-toxic and involves several mechanisms that allow for transfection such as electrostatic interactions, membrane fusion, and nuclear localization.[20, 23, 25]

Polyplexes are one of the most used non-viral polymer based delivery systems for gene delivery 21, 24, 28. Polyplexes are complexes that form when positively charged biomimetic polymers (e.g., polyethylenimine or chitosan) electrostically interact with negatively charged nucleic acids (DNA or RNA) to create a complex that releases and protects genetic material from enzymatic degradation and promotes cellular uptake through endocytosis. Once inside the cell, the polymers promote endosomal escape that allows for efficient gene transfection.[22,26,28]

Another new delivery technologies include fusogenic polymers which function as viral fusion proteins to improve intracellular delivery of genetic material.[25, 28] The advantage of utilizing fusogenic polymers is their ability to into and fuse with cell membranes, allowing for genetic material to be released directly into the cytoplasm. This offers impressive advantage compared to conventional approaches, as it eliminates endosomal entrapment, leading to enhanced gene transfection effectiveness, particularly for applications that require rapid and targeted gene delivery.[21,30]

One strategy to enhance nuclear targeting is to construct biomimetic polymers with Nuclear Localization Signals (NLS).[23,27] The NLS offers signaling features that help navigate genetic cargo towards the nucleus, thereby heightening the potential for successful and efficient gene expression. A system like this would be particularly beneficial for DNA therapies as nuclear entry of DNA is important for transgene integration and expression.[26,28]

SYNTHESIS OF BIOMIMETIC POLYMERS FOR DRUG AND GENE DELIVERY

The biomimetic polymer synthesis is an important part of drug and gene delivery system design. By mimicking the structure and function of natural biological macromolecules, the biomimetic polymers provide greater therapeutic advantages such as targeted therapy, controlled release of drugs, and improved stability.

The ability to dictate the polymer structure at the molecular level allows one to fine-tune the physicochemical properties, such as hydrophilicity, hydrophobicity, biodegradability, and bioactivity, so that such polymers become not only biocompatible but also responsive to various physiological signals. This paper discusses the important processes in the synthesis of biomimetic polymers, their capabilities for drug and gene delivery, and challenges and future directions in the field (Refer Figure 1). [31]

Figure 1 Legend: Biomimetic carriers encapsulate therapeutic agents and are designed to mimic natural biological structures. These carriers undergo a series of steps to achieve efficient therapy: (i) Targeting - recognition of specific receptors or diseased cells; (ii) Cellular uptake - internalization of the biomimetic carrier by endocytosis or related pathways; (iii) Drug release -controlled liberation of the therapeutic payload in response to intracellular conditions; and (iv) Recycling of the carrier system to enable sustained delivery.

Ring Opening Polymerization (ROP)

Ring-Opening Polymerization (ROP) is a flexible biomimetic polymer synthesis method with careful control over molecular weight, polymer identity, polymer architecture and functional groups for specific applications. ROP is based on the ring-opening polymerization of cyclic monomers to give a polymer chain. The process can be used for the synthesis of well-defined polymers of predetermined physicochemical properties, which are crucial to their stability and bioactivity in biological systems.[32] ROP also allows the process to be precisely controlled so that resulting polymers are highly purified and have very narrow molecular weight distributions, something which is wanted in biomedical application for drug as well as gene delivery.[33]

ROP is particularly relevant in the synthesis of biodegradable polymers like Poly (Lactic Acid) (PLA) and Poly (Caprolactone) (PCL), which are main drugs for drug delivery.[34] The materials degrade to non-toxic by-products upon long-term use, minimizing the risk of chronic toxicity in the body. Moreover, ROP can be used to copolymerize various monomers, which offers a special opportunity to create polymers with varied properties, including increased solubility, stability, and degradation rates in certain biological environments.[35]

Some recent investigations have also focused on applying ROP to form copolymeric systems consisting of synthetic and natural monomers with additional prospects for drug delivery application. Copolymers of Poly (Lactic Acid) (PLA) and Poly (Ethylene Glycol) (PEG), for example, have been studied extensively because of their ability to provide increased solubility, increased circulation half-lives and reduced immunogenicity to target drug delivery systems.[36,37]

Bio-conjugation Methods

With bioconjugation techniques, researcher is able to link biologically active molecules to synthetic polymer backbones; and thus, prepare biomimetic polymers by attaching peptides, proteins, and nucleic acids, or other biologically active molecules that add biological functionality and specificity (targeting capabilities) to the synthetic polymer backbone. With all of these methods and bioconjugation in general, bioconjugation techniques can enhance and improve the specificity for drug delivery, promote selective binding for specific cell types, and ultimately can improve therapeutic efficacies.

For example, attaching targeting ligands to polymers is a method used to fabricate newer generations of drug delivery systems. By utilizing targeting ligands therapeutic agents can be directed to certain cells and tissues, for example, tumor or infected cells, with reduced engagement of healthy tissue; and therefore, reducing off-target effects while promoting the efficacy of treatment regimens.[35,38]

This chemistry is special among bioconjugation methods because it is one of the most efficient, specific bioconjugation methods and it can occur under mild conditions. Click chemistry reactions, including the CuAAC reaction, enable the rapid and selective functional group bonding onto polymeric systems, resulting in the most appropriate methodology for biomimetic polymer formation with the desired properties for drug and gene delivery. In addition, thiol-Michael addition and Schiff base reactions have been used successfully for the conjugation of functional molecules onto polymer backbones.[39]

Bioconjugation methods are used to incorporate Cell-Penetrating Peptides (CPPs) into polymeric carriers for enhancing intracellular delivery of drugs and genes by many folds. CPPs are short peptides that facilitate macromolecules' crossing through biological membranes, thus making the gene delivery systems more efficient and overcoming cellular uptake obstacles.[35,37]

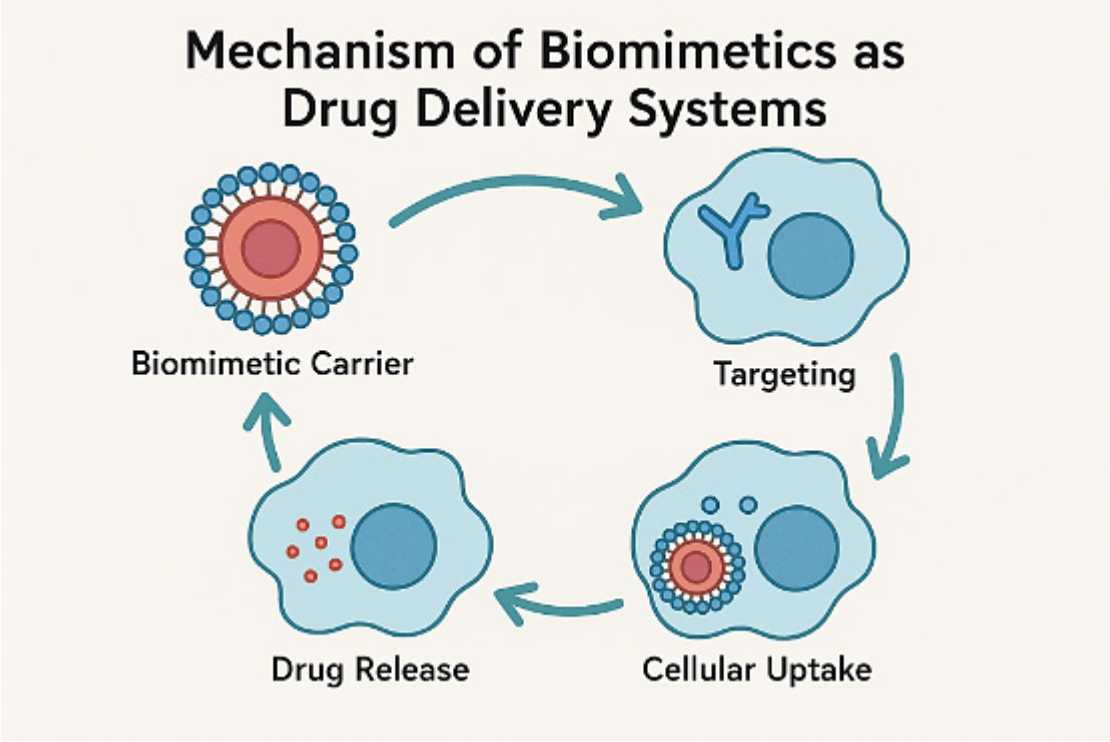

Figure 1: Mechanism of Biomimetics.[32]

CASE STUDIES AND CLINICAL APPLICATIONS

Cancer Therapy and Biomimetic Polymers

Treatment of cancer is often through chemotherapy, which, though effective, carries major complications because of the non-specific nature of the drugs. Biomimetic polymers such as nanoparticles and dendrimers offer significant potential to address the drawbacks of traditional treatments by providing targeted drug delivery, controlled drug release, and reduced toxicity. These advanced systems can be designed to transport chemotherapy drugs directly to cancer cells, limiting their impact on healthy tissues and enhancing treatment effectiveness while decreasing side effects.

Case Study

A study demonstrated the effectiveness of surface-engineered PLGA nanoparticles with folic acid for targeting doxorubicin to cancer cells. Targeting greatly enhanced drug efficacy and diminished side effects, as there was a primary emphasis in targeting with drugs delivered through nanoparticles.

The study pointed out the importance of macroscale delivery platforms, such as PLGA nanoparticles, for transport of both molecular and cellular agents. These delivery systems significantly contribute to enhancing drug delivery efficiency and enable the controlled release of therapeutics precisely at the target site. The research suggests that functionalizing PLGA nanoparticles for targeted therapy offers substantial potential to improve treatment outcomes, especially in challenging cancer types.[40]

Gene Therapy and Biomimetic Polymers

Gene therapy, which involves the insertion or modification of genetic material within a patient's cells, has shown significant promise in treating genetic disorders that currently have limited or no effective cures. Biomimetic polymers are becoming non-viral vectors with a safer and more effective way of delivering genes. Biomimetic polymers have the capability to encapsulate and deliver genetic material to target cells, penetrate in biological barriers, and facilitate controlled release for prolonged therapeutic responses. Two of the more well-known applications of gene therapy where biomimetic polymers are being applied are cystic fibrosis and muscular dystrophy.[41]

Gene Delivery for Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD) is a genetic disorder caused by mutations within the gene for dystrophin that leads to degeneration and weakness of muscles. Gene therapy for DMD is directed towards rescue of dystrophin expression either by the introduction of a healthy dystrophin gene or by exon-skipping processes to bypass the gene mutations. Biomimetic polymers, for example, PEGylated liposomes, have been utilized to deliver exon-skipping oligonucleotides, which have the capability to restore production of a truncated but functional isoform of dystrophin.[42]

Case Study

Employed PEGylated liposomes for the delivery of exon-skipping oligonucleotides to the mouse model of DMD. The liposomes were able to deliver oligonucleotides into muscle cells, which resulted

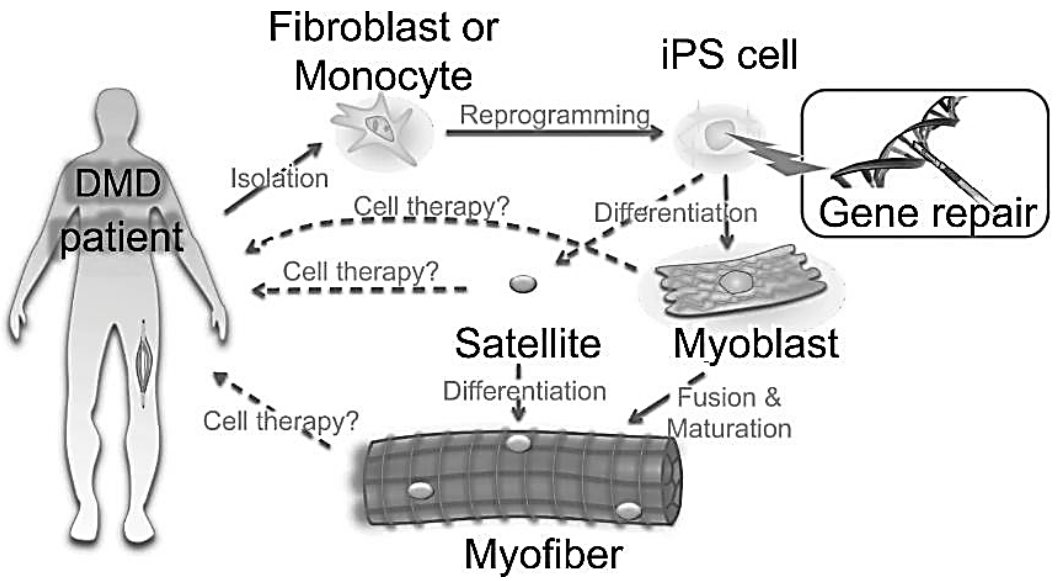

Figure 2: Gene Delivery for Muscular Dystrophy.[40]

in the production of normal dystrophin and the restoration of muscle function.[42,43]

It is shown in this study that biomimetic polymers can be used for the gene therapy of muscular dystrophy because they can deliver therapeutic factors to the desired site with very high efficiency.[42]

Use of liposomal systems in gene delivery has been highlighted, who refers to their advantages regarding biocompatibility, ability to encapsulate genetic molecules, and reduction in immune response. In Figure 2 shown Gene Delivery for Muscular Dystrophy. Ligands for targeting can be conjugated to liposomes, or they can be conjugated with other polymers, in order to further enhance their delivery efficacy and specificity, providing a better platform for the therapy of genetic disorders such as DMD.[42,43]

Figure 2 Legend: Patient-derived fibroblasts or monocytes can be reprogrammed into iPS cells for gene repair and myogenic differentiation, while satellite cells or myoblasts may be used directly for cell therapy. Myoblasts fuse and mature into myofibers, supporting muscle regeneration.

CONCLUSION

Biomimetic polymers, isolated from natural biological systems, are proven reagents for drug and gene delivery that hold revolutionary promises for contemporary medicine. Biomimetic polymers reproduce the natural structure and processes of biomolecules, and there are numerous advantages associated with biomimetic polymers such as biocompatibility, biodegradability, and specific targeting of biological systems. Biomimetic polymers, with all these properties, are apt for resolving long-term issues in therapeutic delivery such as low bioavailability, off-target activity, and clearance of the drug. One of the significant benefits of biomimetic polymers is their biocompatibility and biodegradability, which will ensure that they will not cause unnecessary immune response or leave toxic residues behind after penetrating the body. They are designed to degrade into non-toxic by-products, hence being safer delivery system alternatives than the conventional method. This is the major property to allow drugs and genes to be delivered effectively and safely to target sites of interest without the possibility of inducing side effects in healthy tissues. Having the ability to mimic the properties of biological molecules, biomimetic polymers offer more controlled and targeted interaction with the body to increase therapy effectiveness. Biomimetic polymers are best in targeted delivery in drug delivery. Specific ligands can be functionalized to these polymers so that they bind selectively to the overexpressed receptors present on the diseased cells, e.g., cancer cells. Targeted delivery increases the level of therapeutic agents at the point of action while minimizing the healthy tissue exposure to toxic drugs. Moreover, the inclusion of Cell-Penetrating Peptides (CPPs) improves the capacity of these polymers to penetrate cellular membranes, allowing for the direct delivery of drugs into the cytoplasm. These strategies play a crucial role in improving drug effectiveness while minimizing adverse effects, particularly in the treatment of cancer and long-term illnesses. Biomimetic polymers in gene delivery provide a less risky, more manageable option over viral vectors with risks of immunogenicity and insertional mutagenesis. Polyplexes, created by electrostatic attraction between polymers and nucleic acids, shield genetic content from enzymatic degradation and enable cellular uptake. This non-viral system has opened up new routes for gene therapy, including the delivery of CRISPR/Cas9 components for genome editing. Polymers can encapsulate CRISPR components such as ribonucleoproteins, which are shielded and can be delivered into cells. Stimuli-responsive polymers also enable controlled release of genetic material upon intracellular or physiological stimuli, increasing specificity and reducing off-target effects. The clinical use of biomimetic polymers has already shown promising results in treating complex diseases. In cancer therapy,

PLGA nanoparticles are used to deliver chemotherapeutic drugs specifically to tumor cells, improving the drug's efficiency and reducing damage to healthy tissues. In the field of gene therapy, biomimetic polymers are applied to address genetic disorders such as cystic fibrosis and muscular dystrophy by delivering therapeutic genes or exon-skipping oligonucleotides, aiming to restore normal function in the affected tissues. Biomimetic polymer's clinical uses have already started to be productive in the treatment of multifactorial diseases. Gazing into the future, multifunctional biomimetic polymers hold promises to improve further the efficiency of drug and gene delivery systems. Through integration of imaging, targeting, and therapeutic functionalities in one polymer, these systems have the potential to monitor in real time responses to treatment and offer more personalized therapies. Yet regulatory barriers, safety issues, and scalability must be overcome before such polymers become a standard part of clinical practice. In summary, biomimetic polymers are the next big hope for the drug and gene delivery systems of tomorrow. Their versatility to replicate Nature's processes as well as being targeted, effective, and control-driven in terms of delivering medication is what sets them apart for their potential therapeutic uses in virtually every disease ever known. While further research has yet to continue, biomimetic polymers are poised to revolutionize medical practices today in a safer and more effective yet less reactive, breaking grounds for even personalized and precision-medicine therapeutic strategies.

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ABBREVIATIONS

ATP: Adenosine Triphosphate; **ATRP:** Atom Transfer Radical Polymerization; **ADCs:** Antibody-Drug Conjugates; **CPPs:** Cell-Penetrating Peptides; **CRISPR/Cas9:** Clustered Regularly Interspaced Short Palindromic Repeats / CRISPR-Associated Protein 9; **CuAAC:** Copper-Catalyzed Azide-Alkyne Cycloaddition; **DMD:** Duchenne Muscular Dystrophy; **DNA:** Deoxyribonucleic Acid; **ECM:** Extracellular Matrix; **FDA:** Food and Drug Administration; **GSH:** Glutathione; **HA:** Hyaluronic Acid; **MIPs:** Molecularly Imprinted Polymers; **MMPs:** Matrix Metalloproteinases; **MRI:** Magnetic Resonance Imaging; **NIR:** Near-Infrared; **NLS:** Nuclear Localization Signal; **NPs:** Nanoparticles; **PCL:** Polycaprolactone; **PEG:** Polyethylene Glycol; **PEI:** Polyethylenimine; **PLGA:** Poly(Lactic-co-Glycolic Acid); **PNIPAAm:** Poly(N-isopropylacrylamide); **RAFT:** Reversible Addition-Fragmentation Chain-Transfer Polymerization; **RNA:** Ribonucleic Acid.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUMMARY

Biomimetic polymers are gaining significant attention in drug and gene delivery due to their ability to imitate biological systems, offering enhanced biocompatibility, targeted delivery, and controlled release of therapeutic agents. These polymers replicate characteristics of natural structures like cell membranes and proteins, allowing efficient transport of small molecules, nucleic acids, and proteins. Their tunable nature enables applications across a broad range of treatments, including cancer, regenerative medicine, and gene therapy. Recent innovations in their design and synthesis have led to improved therapeutic performance and safety. Despite these advances, challenges such as achieving optimal stability, precise targeting, and scalable production remain. This review discusses the evolution of biomimetic polymer-based delivery systems, highlighting how they overcome limitations of conventional methods. It also explores future directions aimed at refining their design for clinical use. Overall, biomimetic polymers hold immense promise in revolutionizing therapeutic delivery, contributing to improved clinical outcomes and the advancement of personalized medicine.

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