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Polymers as Versatile Excipients: Drug Delivery in Pharmaceutical Formulations: Innovations, Challenges, and Future Prospects

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ABSTRACT. Polymers have become essential excipients in pharmaceutical formulations, significantly enhancing drug delivery systems due to their versatility, biocompatibility, and specialized properties. This review discusses the role of natural and synthetic polymers, which are favored for their biodegradability and ability to improve drug stability and controlled release. The paper highlights innovations in polymer-based drug delivery, including the development of stimuli-responsive polymers that release drugs in response to specific environmental triggers and the integration of natural and synthetic polymers to create hybrid systems. Despite the advantages, challenges such as variability in natural polymer sources, potential toxicity of synthetic polymers, and regulatory hurdles remain. Future prospects include advancements in green and sustainable polymers, personalized medicine, and the use of nanotechnology to enhance drug delivery efficacy. This comprehensive examination underscores the importance of interdisciplinary research in overcoming existing barriers and advancing polymer-based drug delivery systems to improve patient outcomes.

1. INTRODUCTION

Polymers have emerged as indispensable excipients in pharmaceutical formulations, playing a pivotal role in drug delivery systems due to their versatility, biocompatibility, and tunable properties. Natural polymers, such as alginate, pectin, and carrageenan, are particularly favored for their biodegradability, non-toxicity, and ability to enhance drug stability and controlled release. These polymers can be modified through physical or chemical cross-linking to form hydrogels, microbeads, or films, enabling targeted drug delivery and improved therapeutic outcomes [1]. For instance, chitosan-based systems have demonstrated remarkable potential in targeted delivery and chemotherapeutic agent, while synergistic combinations with other materials, such as nanoparticles, further optimize drug release profiles and sensitivity. The growing emphasis on sustainable and patient-centric formulations has driven innovation in polymer-based excipients, addressing challenges such as dose frequency reduction and enhanced bioavailability [2].

Despite their advantages, the application of polymers in pharmaceuticals is not without challenges [3]. Variability in natural polymer sources, batch-to-batch inconsistencies, and the need for precise crosslinking techniques pose significant hurdles in large-scale production. Additionally, while synthetic polymers offer reproducibility, their potential toxicity and environmental impact raise concerns. Future prospects lie in advancing hybrid systems that combine natural and synthetic polymers, leveraging technologies like 3D printing and nanotechnology to create multifunctional drug carriers [4]. Research into stimuli-responsive polymers, which release drugs in response to pH, temperature, or enzymatic triggers, also holds promise for personalized medicine. As the pharmaceutical industry moves toward greener and more efficient solutions, polymers will continue to be at the forefront of excipient innovation, bridging the gap between formulation science and clinical application.

This review aims to provide a thorough and current understanding of the types, manufacturing processes, difficulties, and potential applications of polymeric materials in drug delivery. We aim to clarify the ways in which material composition and structure affect polymer performance, as well as to critically assess present issues and potential paths forward for effective clinical translation.

2. POLYMER-BASED DRUG DELIVERY INNOVATION

2.1 Type of Polymer in Drug Delivery

2.1.1 Natural Polymers

The use of natural polymers in drug delivery systems continues to expand because of their capacity to create structures that can be tailored for a range of pharmaceutical uses. High biocompatibility, natural degradability, and minimum immune system contact are among its benefits, which lower the possibility of adverse effects [5]. Furthermore, it is possible to modify natural polymers like chitosan and alginate to enhance drug solubility, controlled drug release, and targeted specificity to particular tissues [6].

Natural polymers such as chitosan, alginate, gelatin, and pectin are increasingly used in controlled drug release applications. Chitosan has a positive charge that allows it to interact with cell membranes to improve drug absorption. Alginate and gelatin are used in gel-based drug delivery systems due to its ability to form a hydrogel matrix. It can minimize the side effects of drug release [7,8]. While, pectin is usually used in oral drug formulations targeted to the colon [9].

Compared to synthetic polymers and other non-biodegradable materials, natural polymers are more environmentally friendly and sustainable since they are frequently sourced from renewable resources. Their abundance and simplicity of separation from many sources make them important for creating cost-effective drug delivery systems, particularly in low-resource scenarios.

2.1.2 Synthetic Polymers

Synthetic polymers are chemically prepared macromolecules with customized structures for various applications in pharmaceuticals. Synthetic polymers are designed to have specific properties that favour stability and controlled drug release. Synthetic polymers can be modified. Compared to natural polymers, synthetic polymers are more resistant to enzymatic degradation and can be designed to respond to specific environmental conditions, such as pH or temperature. Synthetic polymers may be created to provide exact control over drug delivery. Numerous parameters, including the kind, concentration, properties of crosslinkers, the physical and chemical characteristics of hydrogels, and the type of medication being employed, are crucial in ensuring targeted, consistent, and predictable drug release [10].

An overview of commonly used natural and synthetic polymers in drug delivery applications is shown in Table 1.

Table 1. Overview of commonly used natural and synthetic polymers in drug delivery applications

	Polymer	Source	Key Properties	Eco-Friendliness	Ref.
Natural Polymers	Chitosan	Chitin from crustaceans	Biodegradable, mucoadhesive, antimicrobial	Biodegradable, renewable	[12]
	Alginate	Brown seaweed	Antimicrobial, antiviral, biocompatible, gel-forming	Highly eco-friendly	[12]
	Starch	Plant starch	Favorable physicochemical properties	Biodegradability and biocompatibility	[13]
	Pectin	Fruit and vegetable pomaces	Antimicrobial and antiviral	Biocompatibility and biodegradibility	[9]
	Lignin	Woods, grasses, crops stalks	Good mechanical strength	Biodegradable	[14]
Synthetic Polymers	Poly(ethylene-glycol) (PEG)	Synthetic	Non-immunogenic, hydrophilic, modifiable	Non biodegradable but low toxicity	[15]
	Poly(vinyl alcohol)	Synthetic	High mechanical strength, film-forming, stable	Limited biodegradability	[15]
	Polyacrylamide	Synthetic	Highly hydrophilic, tunable porosity, non-biodegradable	Not eco-friendly	[16]
	Poloxamer	Synthetic	Thermosensitive, reversible gelation, amphiphilic	Biodegradable to some extent	[17]

Several types of synthesized polymers have been developed for a long time, such as Poly(lactide) (PLA) and Poly(lactide-co-glycolid) (PLGA), biodegradable polymers that are widely used in nanoparticle delivery systems [11]. Degrade through hydrolysis into lactic acid and glycolic acid, which can be metabolized by the body. Polyethylene glycol (PEG), used to improve the solubility and stability of drugs in the body. Plays a role in PEGylation, a technique that binds PEG to drugs or proteins to extend their half-life in the blood. PEG is a polymer that has the ability to absorb large amounts of water and form a gel-like structure.

2.1.3 Stimuli-responsive Polymers

Stimuli-responsive polymers, also known as "smart polymers", are polymers that can change their physical or chemical properties in response to an external stimulus such as pH, temperature, light, or the presence of enzymes [18]. The main advantage of these polymers in drug delivery is their ability to release drugs in a controlled and specific manner at the target site, thereby increasing therapeutic effectiveness and reducing side effects [6].

pH-responsive polymers such as eudragit (methacrylate copolymer) is used in enteric-coated tablets to ensure drug release in the gut instead of the stomach, and Polymethacrylate is used for targeted drug delivery to tumors, as the tumor environment is more acidic. These polymers undergo changes in solubility or structure based on changes in environmental pH. Thermosensitive polymers will change solubility or shape (sol-gel transition) based on ambient temperature. One type of thermossensitive polymer is poloxamer (Pluronic) It changes from solution to gel at body temperature, used in ophthalmic drug delivery and injection. Poly(N-isopropylacrylamide) (PNIPAM) undergoes a solution-to-gel transition at certain temperatures. Enzyme-sensitive polymers, polymers are degraded by certain enzymes found in the target environment, such as cancerous tissue or inflammatory areas. Examples of enzyme-sensitive polymer types are peptide-linker-based polymers that are degraded by protease enzymes in cancer cells and hyaluronic acid-based polymers that are degraded by hyaluronidase enzymes in tumors [19]. Some types and stimuli-responsive polymera are depicted in Table 2.

Table 2. Type and Properties of Polymers for Drug Delivery Applications

Polymer	Properties	Application	Ref
Polyethylene glycol (PEG), polyvinyl alcohol (PVA), and zinc oxide nanoparticles (ZnO NPs)	pH-sensitive, improved cytotoxic activity	Cancer treatment	[15]
Folic acid (FA), chitosan (CS), and Silver nanoparticles (Ag)	pH-sensitive	Colon cancer treatment	[20]
k-carrageenan and chitosan	pH-responsive	Antibacterial and anticancer carrier	[21]
Chitosan	Inhibition of breast cancer cell growth a d reducing their viability	Chemotherapeutic agent	[22]
Carboxymethyl tamarind kernel gum and polyacrylamide	pH-sensitive, limited degradability	Colon cancer treatment	[23]
Chitosan, gold nanoparticles, and copper sulfide	pH and temperature responsive	Breast cancer treatment	[2]

2.2 Types of Polymer Fabrication Methods for Drug Delivery Applications

2.2.1 Polymerization-Induced Self-Assembly (PISA)

Polymerization-induced self-assembly (PISA) is a polymerization technique based on addition polymerization, which produces block copolymers capable of forming nanostructures spontaneously in a solution. This method typically uses reversible addition-fragmentation chain transfer (RAFT) polymerization, which allows precise control over polymer size and structure. In this process, a hydrophobic monomer such as methacrylate or styrene is dissolved in a hydrophilic monomer like PEG or poly(acrylamide). The polymerization reaction occurs at 50-80°C in either aqueous or oil-based solutions, depending on the monomer properties.

The resulting polymer is a block copolymer-based nanoparticle that can automatically form micelles or vesicles in solution. The main advantage of this method is its ability to create highly stable structures that can encapsulate poorly water-soluble drugs. However, strict control over reaction conditions is necessary to ensure successful polymerization and maintain the desired molecular architecture [24,25].

2.2.2 Hydrogel Encapsulation

Hydrogel encapsulation is a technique in which hydrophilic polymers form a three-dimensional network capable of absorbing water and storing drugs within its matrix. The hydrogel formation process typically occurs

through crosslinking reactions. In drug delivery systems, crosslinking polymers are frequently used to increase the stability, regulate the release profile, and boost the bioavailability of medicinal medicines. Many techniques can be used to crosslink both synthetic and natural polymers, producing materials like hydrogels with specific characteristics for use in biomedical applications [26–28].

Drug delivery systems frequently use natural polymers such chitosan, alginate, and starch, however they need to be crosslinked to enhance their mechanical qualities and functionality. In order to create hybrid systems with improved responsiveness, synthetic polymers like polyacrylamide, poly-NIPAM, and PEG are frequently crosslinked with natural polymers [29]. Chemical and physical crosslinking are the two different kinds of crosslinking mechanisms. Dialdehyde starch, formaldehyde, glyoxal, genipin, epichlorohydrin, and glutaraldehyde are examples of chemical crosslinkers that are used to create covalent connections between polymer chains [29]. However, non-covalent interactions such as hydrogen bonding, van der Waals forces, electrostatic contacts, hydrophobic interactions, dipole interactions, host-guest interactions, π-π stacking, and metal coordination can produce physical crosslinking [28].

The final product is a porous hydrogel that can retain drugs and release them gradually in response to pH changes, temperature fluctuations, or enzymatic reactions in the body. Hydrogels are highly useful for long-term drug delivery due to their soft, biocompatible nature. The hydrogel-based drug delivery possessed a low swelling ratio and a slow degradation process. Composite hydrogel demonstrated a higher compressive modulus and the ability to sustain structures under external pressure, according to compressive and rheological testing. Additionally, the composite hydrogel showed good self-healing features in the compressive and rheological testing [12].

2.2.3 Polymeric Micelles

Polymeric micelles are nanoscale structures that form spontaneously when amphiphilic polymers (having both hydrophilic and hydrophobic segments) are dissolved in water. This process is based on self-assembly rather than polymerization, though the polymer itself is usually synthesized via addition polymerization. Commonly used polymers include Pluronic (poloxamer), poly(lactide-co-glycolide) (PLGA), and poly(ε-caprolactone) (PCL). The micelles form with a hydrophobic core that can encapsulate oil-soluble drugs, while the hydrophilic shell enhances solubility in water.

The resulting product is nanosized micelles (10-100 nm) capable of solubilizing poorly water-soluble drugs and improving their bioavailability. The key advantage of polymeric micelles is their ability to enhance drug stability and provide controlled release. However, one of the main challenges is that micelles may disassemble in the body, particularly if the polymer concentration falls below the critical micelle concentration (CMC), requiring careful formulation to maintain stability [30].

2.2.4 Polymeric Nanoparticles

Polymeric nanoparticles are produced through various methods, including emulsion-solvent evaporation, nanoprecipitation, and spray drying, depending on the desired properties. The polymerization mechanism involved can be addition or condensation polymerization, depending on the polymer type. In the emulsion-solvent evaporation method, a polymer such as PLGA, PCL, or chitosan is dissolved in an organic solvent like dichloromethane and then mixed with an aqueous phase containing surfactants under strong agitation. The solvent is then evaporated at 30-50°C, leading to the formation of nanoparticles encapsulating the drug.

The final product consists of nanoparticles with a size range from 50 to 500 nm with controlled drug release properties. Particle size significantly influences the potential delivery of bioactive compounds to cancer sites, as various properties of nanocarriers, such as chemo-physical stability in serum, effective drug dosage, evasion of immune system barriers, and efficient cellular internalization, are known to be dependent on particle size [20]. The major advantage of this method is that it enables precise control over drug release, enhances drug stability, and allows for targeted delivery. However, one of the drawbacks is that complex characterization techniques are required to optimize particle size, drug loading efficiency, and release kinetics [31].

2.2.5 Polymer-Drug Conjugation

Polymer-drug conjugation involves the direct chemical attachment of drug molecules to polymers, typically through condensation reactions or covalent bonding with active functional groups. This method commonly uses natural or synthetic polymers such as PEG, poly(glutamate), or dendrimers, which contain reactive groups like carboxyl (-COOH) or amine ($-NH_2$) that can form stable bonds with drug molecules. The conjugation reaction occurs in aqueous or organic solvents at 20-50°C, often using catalysts or activation agents such as carbodiimides to facilitate bonding.

The resulting polymer-drug conjugate allows for controlled drug release via enzymatic cleavage or pH changes in the body. This method is particularly beneficial for enhancing drug half-life, reducing side effects, and enabling

targeted delivery. However, a key challenge is the complexity in designing polymer structures that balance stability and degradability while ensuring efficient drug release at the target site [32].

Comparison of all methods of polymer fabrication for drug delivery is depicted in Table 3.

Table 3. Comparison of Polymer Fabrication for Drug Delivery

Polymer	Method	Application	Properties	Ref
Bisphosphonate, acrylamide	Polymerization-Induced Self-Assembly (PISA)	Bone-targeted drug delivery	Weak pH-responsive, high loading capacity for hydrophilic drug, sustained drug release	[33]
Carboxyethyl chitosan and oxidized alginate	Hydrogel Encapsulation	Anti-cancer drug delivery	Excellent self-healing ability under physiological condition, sustained drug release	[12]
PLGA-PEG-PLGA	Polymeric Micelles	Tumor-targeted drug delivery	pH and irradiation-responsive	[34]
Carboxymethyl guar gum and chitosan	Polymeric Nanoparticles	Therapeutic agent delivery	Sustained drug release	[35]
N-(2-Hydroxypropyl)meth acrylamide (HPMA)	Polymer-Drug Conjugation	Targeted chemotherapy delivery	Tumor-stimuli sensitive	[36]

3. CHALLENGES AND FUTURE PROSPECT

Ensuring the biocompatibility of polymer-based drug delivery systems requires a thorough understanding of their interactions with biological tissues. Some polymers, despite being initially biocompatible, may degrade into harmful byproducts that trigger adverse effects [37]. For example, PLGA, a commonly used biodegradable polymer, breaks down into lactic and glycolic acid, which can lead to localized acidosis and inflammation if not properly buffered. Similarly, PEG, although widely used to improve drug solubility and circulation time, has been associated with hypersensitivity reactions and immune recognition, limiting its long-term use. To mitigate these risks, researchers are exploring polymer modifications, such as surface functionalization or the incorporation of bioinert coatings, to enhance compatibility with human tissues [11].

In addition to chemical degradation concerns, the structural and physicochemical properties of polymers must be carefully tailored to minimize cytotoxicity. Smart polymers like PNIPAAm or poly(N-isopropylacrylamide), which undergo temperature-induced phase transitions, can potentially disrupt cellular homeostasis if their transition temperatures overlap with physiological conditions [1]. Likewise, the incorporation of magnetic nanoparticles in polymer matrices, although useful for targeted drug delivery, poses risks of oxidative stress and cellular damage if the nanoparticles aggregate or leach into surrounding tissues. These concerns highlight the need for comprehensive preclinical evaluations, including cytotoxicity assays, hemocompatibility studies, and long-term biodistribution analyses. Advances in nanotechnology and biomaterial engineering are helping to address these challenges by enabling the development of safer, more biocompatible polymeric drug carriers tailored for specific medical applications [38].

The regulatory approval process for polymer-based drug delivery systems is particularly stringent due to the complexity of these materials and their interactions with biological systems. This includes detailed studies on drug release kinetics, polymer stability, and long-term toxicity assessments. For instance, stimuli-responsive polymers, which change properties based on environmental conditions (e.g., pH-sensitive hydrogels), must consistently demonstrate predictable and reproducible behaviours under physiological conditions. Variability in polymer synthesis and drug release profiles can lead to inconsistent therapeutic effects, making it difficult for these systems to meet regulatory standards [39]. Another major challenge is the lack of standardized testing protocols for emerging polymeric drug carriers, particularly those incorporating nanotechnology or biodegradable materials. Unlike traditional excipients, novel polymers often require customized evaluation methods to assess their safety and efficacy, which can prolong the approval process. Additionally, regulatory agencies mandate extensive preclinical and clinical trials, significantly increasing the cost and timeline for product development. These hurdles can discourage pharmaceutical companies from investing in polymer-based delivery technologies. To overcome these challenges, collaboration between researchers, industry leaders, and regulatory bodies is crucial in establishing clearer guidelines and streamlined approval pathways. Regulatory advancements, such as adaptive

licensing frameworks and harmonized global standards, could accelerate the introduction of innovative polymer-based drug delivery systems into clinical practice while ensuring patient safety [7].

Scaling up the production of polymer-based drug delivery systems presents multiple technical and economic challenges, primarily due to the need for high precision in polymer synthesis and formulation stability. Many fabrication techniques, such as electrospraying, nanoprecipitation, and ultrasonication, are effective at the laboratory scale but often suffer from batch-to-batch variability and low production yields when applied to industrial manufacturing [40]. The integration of continuous manufacturing and process automation offers a promising solution to improve the scalability and reproducibility of polymer-based drug delivery systems. Unlike batch processes, continuous manufacturing allows for real-time monitoring and control of polymer synthesis, leading to more consistent product quality and reduced material waste.

Moving forward, advancements in green chemistry approaches and solvent-free polymerization techniques could also enhance the sustainability and cost-effectiveness of polymer-based drug manufacturing. By incorporating biodegradable and non-toxic materials, researchers are paving the way for more effective and eco-friendly drug delivery solutions. The focus on green polymers in the fabrication of nanofibers is essential for advancing drug delivery system while ensuring safety and sustainability in biomedical applications [41]. Advancements in 3D printing technology enable the customization of drug delivery devices, supporting personalized treatment strategies. These innovations hold the promise of revolutionizing the management of chronic illnesses and improving patient outcomes [3].

Recent advancements in nanotechnology have significantly enhanced the development of polymer-based drug delivery systems for anticancer therapies, positioning them as pivotal tools in personalized and precision medicine. These systems leverage the unique properties of polymers, such as biocompatibility, biodegradability, and the ability to control drug release, to optimize therapeutic outcomes. By encapsulating anticancer agents within polymeric nanoparticles (PNPs), these DDSs can effectively target tumor sites, thereby minimizing the cytotoxic effects typically associated with conventional chemotherapy. This targeted approach not only reduces the adverse side effects on healthy tissues but also enhances the solubility and bioavailability of hydrophobic drugs, leading to improved therapeutic efficacy. As a result, polymer-based drug delivery system are emerging as a promising strategy in the biopharmaceutical industry, offering a reliable means to advance personalized treatment regimens for cancer patients [42].

4. CONCLUSION

This review defines a thorough examination of the evolving landscape of polymer-based drug delivery systems, underscoring their critical role in enhancing therapeutic efficacy and patient safety. The research highlights the diverse types of polymers—natural, synthetic, and stimuli-responsive—each offering unique advantages for drug encapsulation and release. It identifies significant challenges, including biocompatibility, toxicity, and regulatory hurdles, that must be addressed to ensure the successful implementation of these systems in clinical settings. The exploration of various fabrication methods, such as hydrogel encapsulation and polymer-drug conjugation, reveals innovative strategies to optimize drug delivery. Furthermore, the article emphasizes the future potential of green and sustainable polymers, personalized medicine, and hybrid systems, which could lead to more effective and environmentally friendly therapeutic solutions. Overall, the findings advocate for continued interdisciplinary research and collaboration to overcome existing barriers and advance the field of polymer-based drug delivery, ultimately improving patient outcomes in healthcare.

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