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## Review Article

# Polymeric innovations in drug delivery: Enhancing therapeutic efficacy

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## ABSTRACT

Drug delivery is the method or process of administering pharmaceutical compounds to achieve a therapeutic effect in humans or animals. Drug delivery technologies are designed to modify the release, absorption, distribution, and elimination of drugs to enhance therapeutic effectiveness, safety, and patient adherence. Innovative drug delivery systems provide a variety of approaches, such as oral, injectable, implantable, pulmonary, nasal, transmucosal, transdermal, and topical routes, along with options for delivering proteins and peptides. Polymers, due to their large molecular structure and diverse functional groups, play a pivotal role in these systems. Progress in polymer science has paved the way for the development of advanced drug delivery platforms. To optimize polymer-based drug delivery, it is essential to carefully evaluate both surface and bulk properties during the design process. This review explores the use of natural and synthetic polymers in oral drug delivery systems. Natural polymers include protein-based polymers like collagen, albumin, and gelatin, and polysaccharides such as alginate, chitosan, dextran, gums, hyaluronic acid, starch, and cellulose. Synthetic polymers are classified into biodegradable types, which include polyesters such as polylactic acid (PLA), polyglycolic acid (PGA), polyhydroxybutyrate-co-valerate (PHBV), polycaprolactone (PCL), and poly(lactide-co-glycolide) (PLGA). Additionally, they encompass poly anhydrides like poly sebacic acid and poly adipic acid. Non-biodegradable synthetic polymers include silicones, cellulose derivatives, synthetic carbonates, acrylics, and others like vinyl chloride polymer and copolymers, styrene acrylonitrile polymer (SAN), acrylonitrile butadiene styrene polymer (ABS), and polystyrenes. This review focuses on summarizing recent progress in polymer-based drug delivery systems, emphasizing their capability to improve therapeutic effectiveness and promote patient adherence.

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## 1. Introduction

### 1.1. Drug delivery overview

Drug delivery is the process of administering pharmaceutical compounds to produce a therapeutic effect in humans or animals. The effectiveness of treatment depends on delivering the medication to the right location in the body, at the right time, and in the correct dosage. Drug delivery technologies are specifically designed to

alter how a drug is released, absorbed, distributed, and eliminated within the body. These adjustments aim to maximize therapeutic benefits while minimizing potential side effects. Additionally, these technologies improve patient compliance by making medications easier to use and more effective over extended periods. Ultimately, drug delivery systems play a critical role in ensuring the success of medical treatments.<sup>1,2</sup>

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## 2. Novel Drug Delivery Systems

Innovative drug delivery systems provide various approaches to enhance the efficiency of drug administration. Some key solutions include:<sup>3</sup>

1. Oral Drug Delivery Systems
2. Parenteral and Implantable Drug Delivery Systems
3. Pulmonary and Nasal Drug Delivery
4. Transmucosal Drug Delivery
5. Transdermal and Topical Drug Delivery
6. Delivery of Proteins and Peptides
7. Drug Delivery Pipelines and Partnerships

## 3. Role of Polymers in Drug Delivery

Polymers are large molecules made up of repeating units, characterized by their long chains and diverse functional groups. Their ability to blend with materials of varying molecular weights makes them highly adaptable. In pharmaceutical applications, polymers play an essential role in enhancing the performance and delivery of drugs. Recent advances in polymer science have enabled the development of innovative drug delivery platforms. By carefully engineering the surface and bulk properties of polymers, researchers can create materials tailored to specific drug delivery needs, ultimately improving treatment outcomes and patient adherence.

### 3.1. List of polymers used in oral drug delivery<sup>4–8</sup>

#### 3.1.1. Natural polymers

- **Protein-based Polymers:** Collagen, Albumin, Gelatin
- **Polysaccharides:**
  1. Alginate
  2. Chitosan
  3. Dextran
  4. Gums
  5. Hyaluronic Acid
  6. Starch
  7. Cellulose

**Others:** Polyisoprenoids

#### 3.1.2. Synthetic polymers

- **Biodegradable Polymers:**
- **Polyester:**
  1. Poly Lactic Acid
  2. Poly Glycolic Acid
  3. Poly Hydroxybutyrate-co-Valerate (PHBV)
  4. Polycaprolactone (PCL)
  5. Poly(lactide-co-glycolide) (PLGA)

#### 3.1.3. Poly anhydride

1. Poly Sebacic Acid
2. Poly Adipic Acid
3. Various Copolymers
4. *Others:* Poly anhydrides

## 4. Non-Biodegradable Polymers:

1. Silicones: Siloxanes
2. Cellulose Derivatives: Cellulose Acetate Propionate, Cellulose Acetate Butyrate
3. Other Synthetic Carbonates: Polycarbonate
4. Acrylics: Polymethyl Methacrylate (PMMA), Ethylene-Vinyl Acetate Copolymer (EVA)

## 5. Others

Vinyl Chloride Polymer and Copolymers, Styrene Acrylonitrile Polymer (SAN) Acrylonitrile Butadiene Styrene Polymer (ABS), Polystyrenes. Recent technological advancements in drug delivery include chemical modification of drugs, carrier-based delivery systems, and drug entrapment within polymeric matrices or pumps placed in specific bodily compartments. These innovations enhance drug therapy efficacy and improve human health. The use of polymeric materials in novel drug delivery systems has garnered significant scientific interest.<sup>9,10</sup>

The application of polymers for medical purposes is rapidly expanding. Polymers are now integral to various biomedical fields, including drug delivery systems, tissue engineering scaffolds, medical device implants, artificial organs, prosthetics, ophthalmology, dentistry, bone repair, and more.<sup>11</sup> Polymers are essential for controlling drug release rates from formulations, offering unique properties unmatched by other materials. The progress in polymer science has resulted in the creation of innovative drug delivery systems. Proper consideration of surface and bulk properties is crucial in designing polymers for diverse drug delivery applications.<sup>11,12</sup>

Advancements in drug delivery technologies, such as chemical drug modifications, carrier-based delivery, and drug encapsulation within polymer matrices or pumps, have greatly enhanced therapeutic effectiveness and improved patient outcomes.<sup>13</sup> Polymer chemists, chemical engineers, and pharmaceutical scientists are actively developing controlled delivery systems to release bioactive agents with precision. Biodegradable polymers are especially valued in biomedical applications due to their compatibility with biological systems and ability to degrade safely over time. These polymers are frequently used in implants, where they are expected to function reliably over long periods, contributing to more effective treatments with fewer side effects and greater patient comfort.<sup>14</sup>

Polymers play a versatile role in pharmaceutical formulations, serving as binders in tablets, viscosity

enhancers in liquids, and emulsifying agents in suspensions. They are also applied as film coatings to mask unpleasant drug tastes, improve stability, and control drug release. These materials enable functions such as taste masking, controlled release (including extended, pulsatile, and targeted delivery), improved stability, and enhanced bioavailability. One example is monolithic delivery devices, where a drug is dispersed within a polymer matrix and released gradually through diffusion. The release rate from such systems depends on factors like the initial drug concentration and the relaxation of polymer chains, ensuring a sustained therapeutic effect.<sup>15</sup>

Polymers can also be modified to expand their applications. Adjusting water solubility by increasing chain length, cross-linking, or incorporating hydrophobic or hydrophilic copolymers creates materials with a wide range of properties. These modifications enable polymers to perform various drug-enhancing functions, supporting more effective and targeted therapies.<sup>16</sup>

## 6. Functions of Polymers in Drug Delivery<sup>17,18</sup>

Polymers offer several benefits in drug delivery, including:

1. Extending drug availability when formulated as hydrogels or microparticles
2. Improving biodistribution through dense nanoparticle formulations
3. Facilitating hydrophobic drug delivery via micelles
4. Targeting inaccessible areas by acting as carriers in gene therapies
5. Releasing drugs in response to specific stimuli for precision therapy

Polymers are produced on an industrial scale, ensuring efficient solubilization of pharmaceuticals for safe administration. Ongoing efforts focus on optimizing clinical doses and dosing schedules to improve the safety and effectiveness of treatments, reducing side effects and enhancing patient comfort.

## 7. Polymer Therapeutics and PEGylation<sup>19,20</sup>

The development of polymer therapeutics has evolved significantly, with notable contributions by Davis and colleagues in the late 1970s through their work on PEGylation. This technique involves covalently attaching polyethylene glycol (PEG) to proteins or peptides to enhance their pharmacokinetic and pharmacodynamic properties. Over the past two decades, PEGylation has become a preferred method in pharmaceutical development because PEG is non-toxic, non-immunogenic, and non-antigenic. The U.S. FDA has approved PEG for various pharmaceutical applications, including injectables, topical products, rectal preparations, and nasal formulations.<sup>21–23</sup>

The hydrophilic nature of PEG shields therapeutic proteins from immune recognition and allows targeted conjugation without crosslinking. While PEGylation may reduce the activity of some proteins, the increased circulation time helps maintain effective drug levels in the bloodstream. The success of PEGylation in enhancing drug efficacy and safety is well-documented, with its impact continuing to shape pharmaceutical innovation.<sup>24,25</sup>

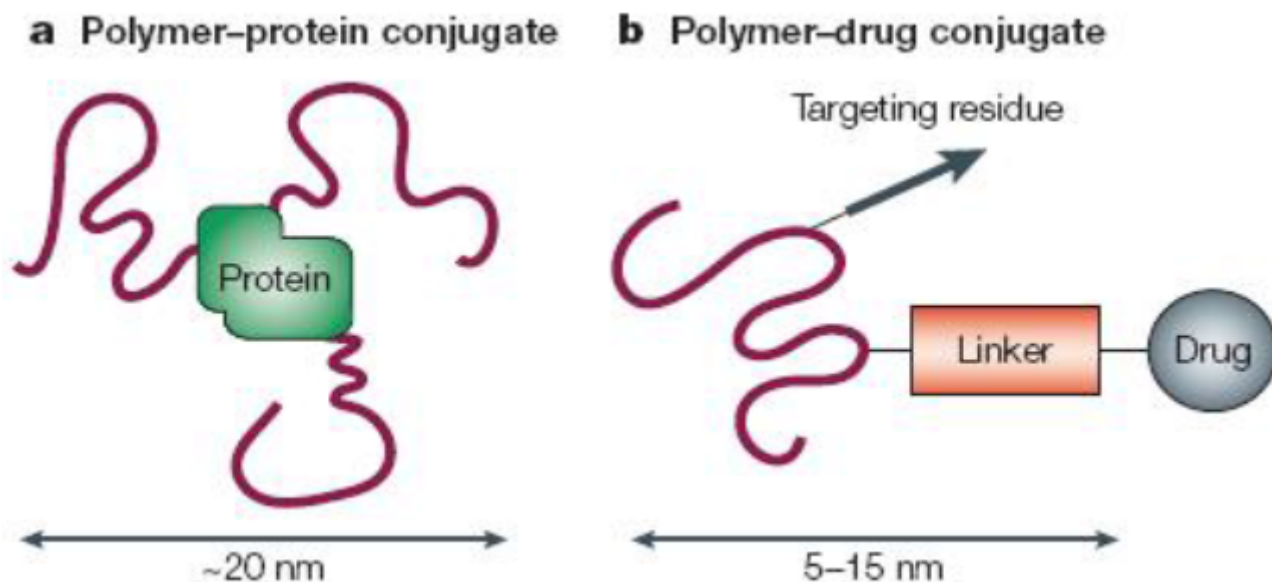
## 8. Limitations of PEGylation and Innovations in Protein Delivery<sup>26–28</sup>

Although PEGylation has proven effective in enhancing the pharmacokinetics of protein-based therapeutics, it has some drawbacks, including limited biodegradability and the potential to alter or reduce protein activity. In response, Duncan et al. introduced *polymer-masking-unmasking protein therapy (PUMPT)*, a novel method that uses biodegradable dextrin, a natural polysaccharide, to mask protein activity during transit and restore it at the target site through controlled degradation. In this approach, dextrin is chemically modified via succinylation to provide reactive sites for covalent attachment. During degradation, the non-toxic byproducts maltose and isomaltose are generated in the presence of  $\alpha$ -amylase. Testing showed that dextrin conjugation reduced trypsin activity by 34–69%, depending on molecular weight and modification level, but incubation with  $\alpha$ -amylase restored 92–115% of the enzyme's activity. PUMPT presents a promising solution for delivering proteins that are prone to inactivation or toxicity during transport, though further research is required to optimize the process and fully understand the degradation products to ensure safety.

## 9. Polymer-Drug Conjugates: Advancing Therapeutics<sup>29–31</sup>

Polymer-drug conjugates, where small-molecule drugs are attached to polymer carriers, represent a significant advancement in drug delivery, particularly in cancer treatment. This field began with the pioneering work of Ringsdorf in 1975 and was further developed by Duncan and Kopecek, who designed the first polymer-based anticancer drug conjugates to enter clinical trials. Unlike conventional drugs, which may cause widespread side effects by dispersing throughout the body, polymer-drug conjugates improve targeting by enhancing circulation time and using *endocytosis* for cellular uptake. Additionally, these conjugates leverage the *enhanced permeability and retention (EPR) effect* to accumulate selectively in tumors.

A notable study by Satchi-Fainaro et al. explored an *HPMA-TNP-470 conjugate*, where the antiangiogenic drug TNP-470 was linked to an HPMA copolymer through an enzyme-cleavable GFLG tetrapeptide bond. This bond allows the drug to be released inside lysosomes by cysteine



**Figure 1:** Categories of polymer constructs known as polymer therapeutics

proteases, such as cathepsin B, which are abundant in many tumors. In animal studies, the conjugate accumulated in tumor tissues via the EPR effect and prolonged TNP-470's therapeutic activity without the neurotoxic effects observed with the free drug, likely due to the conjugate's inability to cross the blood-brain barrier. The HPMA-TNP-470 conjugate, currently in preclinical development under the name *caplostatin* by SynDevRx, has shown significant promise in cancer therapy.<sup>32–34</sup>

## 10. Emerging Polymer Architectures for Drug Delivery

Innovations in polymer chemistry have led to new architectures, such as *dendrimers*, *star-shaped polymers*, and *grafted systems*, for future drug delivery applications. For example, researchers studied the conjugation of *paclitaxel*, a poorly soluble chemotherapy drug, with linear bis-PEG and *dendritic polyamidoamine (PAMAM) G4* to assess the impact of carrier structure on drug performance. Both PEG and PAMAM improved the solubility of paclitaxel compared to its free form (0.3 mg/ml). However, the PAMAM-based conjugate achieved a solubility of 3.2 mg/ml, outperforming the PEG-based system at 2.5 mg/ml. Confocal microscopy revealed that both conjugates achieved more uniform distribution within cells compared to free paclitaxel. While PEG reduced paclitaxel's efficacy by 25-fold, the PAMAM-G4 dendrimer enhanced its anticancer activity by more than ten times, demonstrating the potential of dendrimers as superior carriers for intracellular delivery of poorly soluble drugs.

## 11. Classification of Polymers<sup>35</sup>

Polymers used in pharmaceutical applications can be categorized as follows:

### 11.1. Based on interaction with water

1. Non-biodegradable hydrophobic polymers (e.g., polyvinyl chloride)
2. Soluble polymers (e.g., HPMC, PEG)
3. Hydrogels (e.g., polyvinylpyrrolidone)

### 11.2. Based on polymerization method

1. Addition polymers (e.g., alkane polymers)
2. Condensation polymers (e.g., polystyrene, polyamides)

### 11.3. Based on polymerization mechanism

1. Chain polymerization
2. Step-growth polymerization

### 11.4. Based on chemical structure

1. Activated carbon-carbon polymers
2. Inorganic polymers
3. Natural polymers

### 11.5. Based on occurrence

1. Natural polymers (e.g., collagen, keratin, cellulose)
2. Synthetic polymers (e.g., polyesters, polyamides)

## 12. Based on bio-stability

1. Biodegradable polymers (e.g., lactides, glycolides, polyanhydrides)
2. Non-biodegradable polymers (e.g., acrolein, epoxy polymers)

## 13. Role of Polymers in Pharmaceutical Drug Delivery<sup>36</sup>

Polymers are essential components in *immediate-release dosage forms*, such as tablets, where they act as excipients to aid manufacturing and protect drugs from degradation during storage. *Microcrystalline cellulose* is commonly used as a diluent in low-dose tablet formulations, offering an alternative to carbohydrate-based fillers. Polymers also serve critical roles in controlling drug release, enhancing solubility, and improving the stability of pharmaceutical formulations, making them indispensable for modern drug delivery systems.

## 14. Role of Polymers in Immediate-Release Dosage Forms<sup>37,38</sup>

In tablet formulations, *starch and cellulose* function as disintegrants. Upon contact with water, these materials swell, causing the tablet to break apart and expose a larger surface area of the drug, improving its dissolution. *Polyvinylpyrrolidone (PVP)* and *hydroxypropyl methylcellulose (HPMC)* act as binders, facilitating the formation of granules that enhance the flow and compressibility of the tablet mixture before compression. In some cases, tablets are coated with non-functional polymer films to protect the drug from degradation, mask unpleasant tastes, or improve the visual appearance of the product without altering the drug release profile.

## 15. Capsules as an Alternative Dosage Form<sup>39–42</sup>

Capsules offer an alternative to tablets, particularly for drugs that are difficult to compress or have a bitter taste. They may also enhance *bioavailability* for certain drugs. Many polymeric excipients used in capsule formulations are the same as those found in immediate-release tablets. Traditionally, *gelatin* has been the primary material for both hard (two-piece) and soft (one-piece) capsules, but *HPMC* is now being widely adopted for hard capsules as a plant-based alternative.

## 16. Modified-Release Dosage Forms<sup>43</sup>

Immediate-release formulations can sometimes lead to ineffective treatment or unwanted side effects. To address these limitations, pharmaceutical scientists have developed *modified-release systems*, which improve therapeutic outcomes by controlling the release rate of the drug.

## 17. Extended-Release Dosage Forms<sup>44</sup>

For drugs with short half-lives, extended-release formulations help maintain therapeutic drug levels over an extended period, reducing dosing frequency and improving patient adherence. Common polymers used for extended-release systems include *ammonium ethacrylate copolymers (Eudragit RS and RL)*, *ethyl cellulose*, *cellulose acetate*, and *polyvinyl acetate*. Eudragit RS is less water-permeable due to its higher content of quaternary ammonium groups. Additionally, ethyl cellulose is available in various viscosity grades, with higher viscosities forming stronger, more durable coatings.

## 18. Gastroretentive Dosage Forms<sup>44</sup>

*Gastroretentive systems* provide an alternative method for extended drug release by remaining in the stomach for longer periods. This approach ensures the drug dissolves in the stomach's contents and gradually moves into the small intestine. Unlike traditional extended-release formulations, which release the drug throughout the gastrointestinal (GI) tract, gastroretentive systems are particularly useful for drugs absorbed primarily in specific GI regions. For example, some drugs are poorly absorbed from the distal gut, where conventional extended-release formulations may spend a significant amount of time. Researchers are exploring *mucoadhesive* and *low-density polymers* to increase gastric retention by either adhering to the stomach lining or floating on the stomach's contents, but these strategies still face challenges in achieving consistent results.

## 19. Characteristics of an Ideal Polymer<sup>43,44</sup>

1. Versatility: Should exhibit diverse mechanical, physical, and chemical properties
2. Non-Toxicity: Must be safe for administration with adequate mechanical strength
3. Cost-Effectiveness: Should be affordable and easy to manufacture
4. Biocompatibility: Must be inert and compatible with biological tissues and the environment

## 20. Criteria for Polymer Selection<sup>44</sup>

1. Solubility and Synthesis: The polymer should dissolve easily and be straightforward to synthesize
2. Molecular Weight: Must have a specific molecular weight to ensure desired functionality
3. Biocompatibility: Should not elicit adverse biological responses
4. Biodegradability: The polymer should break down safely in the body
5. Drug Linkage: Must offer stable and effective drug-polymer binding

## 21. Conclusion

Drug delivery systems are essential for the effective and safe administration of pharmaceutical compounds, playing a critical role in optimizing the release profile, absorption, distribution, and elimination of drugs. These systems not only enhance therapeutic efficacy but also minimize side effects, making them pivotal in modern medicine. The integration of various drug delivery solutions, such as oral, parenteral, pulmonary, nasal, transmucosal, and transdermal systems, further improves patient compliance and convenience.

Polymers play a crucial role in these developments thanks to their versatility and flexibility, enabling the creation of cutting-edge drug delivery systems. A variety of both natural and synthetic polymers, encompassing both biodegradable and non-biodegradable varieties, have broadened the scope for controlled and targeted drug release. Recent progress in polymer science and drug delivery methods has resulted in the emergence of more effective and patient-centric therapeutic solutions.

By meticulously selecting and engineering polymers, researchers can significantly enhance the performance of pharmaceutical compounds, ultimately leading to better patient outcomes and the continued advancement of the medical field.

## 22. Source of Funding

None.

## 23. Conflict of Interest

None.

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