

ROLE OF POLYMER IN PHARMACEUTICAL DRUG DELIVERY

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ABSTRACT

Polymers play a crucial role in pharmaceutical drug delivery systems, acting as a protective barrier to prevent adverse reactions with the body's environment. They release drugs through diffusion, degradation, and swelling processes. Natural polymers are preferred due to their biodegradability and consistent rate of drug release. They are often biocompatible and can be broken down into non-toxic byproducts, making them safer for medical applications. Their unique physicochemical properties and availability make them advantageous for drug delivery systems. Recent advancements aim to improve drug delivery systems' effectiveness, leading to more efficient treatments and reduced side effects. Advanced polymer technologies can optimize drug delivery mechanisms, reducing potential complications and improving patient outcomes. Overall, polymers are essential in advancing medical technologies and improving patient outcomes.

KEYWORD: Novel drug delivery, Controlled drug delivery, Classification, Natural polymer, Biodegradable, Mechanism.

INTRODUCTION

The utilization of polymeric materials within the medical sector is experiencing rapid expansion and innovation. These versatile substances have established a significant presence across a variety of biomedical applications, showcasing their adaptability and effectiveness in addressing complex medical challenges. Polymers are employed in numerous areas including drug delivery systems, where they serve as vital components to ensure the targeted release of therapeutic agents at controlled rates. Additionally, they play a crucial role in tissue engineering, where custom-developed scaffolds support cell growth and tissue regeneration.

In the domain of medical device implantation, polymers are utilized to create biocompatible materials that integrate seamlessly with human tissues, facilitating the acceptance and functionality of devices such as stents and artificial organs. Their application extends to prosthetic devices, where polymers contribute to the development of lightweight yet strong materials that enhance the comfort and mobility of users. Furthermore, in specialized fields such as ophthalmology and dentistry, polymers are used to produce products ranging from contact lenses to dental fillings, underscoring their versatility.

Furthermore, the field of bone repair has also greatly benefited from polymer applications, with these materials providing effective solutions for bone regeneration and repair. The ability of polymers to be tailored for specific medical needs has made them

indispensable across a wide spectrum of healthcare applications. The extensive use of polymers in drug delivery systems has emerged largely due to their distinctive properties, which are not easily replicated by other types of materials.^[1]

Recent advancements in polymer science have paved the way for the emergence of novel drug delivery systems that enhance therapeutic efficacy and improve patient outcomes. These advancements are largely attributed to a profound understanding of both surface and bulk properties of polymers, which are crucial in the design and development process for targeted drug delivery applications. By focusing on these properties, researchers and developers can create polymers that meet the specific requirements of various medical interventions, further advancing the capability and effectiveness of polymer-based solutions in healthcare.^[2]

Polymers have various pharmaceutical applications, such as serving as binders in tablets, regulating viscosity and flow in liquids, suspensions, and emulsions. They can be used as film coatings to hide the unpleasant taste of drugs, enhance drug stability, and modify drug release. Pharmaceutical polymers are extensively used for taste masking, controlled release (e.g., extended, pulsatile, and targeted), improved stability, and enhanced bioavailability. Monolithic delivery devices are systems where a drug is dispersed within a polymer matrix and released through diffusion. The drug release rate from a matrix product depends on the initial drug concentration and the relaxation of the polymer chains, resulting in a

sustained release characteristic.^[3]

Polymers can be made more interesting by changing the water solubility through linear increase in their length by cross-linking or through incorporation of such components as hydrophobic or hydrophilic.

These materials can enhance the activity of drugs in several ways. For instance, they may be used as hydrogels or microparticles to improve drug retention, in the form of large dense nanoparticles to change the distribution of the drug, in the form of micelles to solubilize hydrophobic drugs, to enhance the delivery of the gene therapy agents, and for the control over the release of drugs.^[4,5,6]

History

The origin of the term "polymer" can be traced back to 1833 when Swedish chemist Jöns Jacob Berzelius first introduced it to the scientific community. During the nineteenth century, chemists engaged with macromolecules, though they lacked a comprehensive understanding of the structural complexities inherent to these substances. A number of modified natural polymers began to be commercialized during this time. An example of such a polymer is nitrated cellulose, which was marketed under various names, including celluloid and guncotton. The polymerization of styrene was documented as early as 1839, marking significant early steps in the exploration of synthetic materials. Historically, humans have relied on naturally occurring polymers for a variety of essential purposes, including the creation of clothing, tools, weapons, decorative items, shelter, and writing materials.

The first semi-synthetic polymer, guncotton (or cellulose nitrate), was synthesized by Christian Frederick Schönbein in 1845. Over the years, the production process for guncotton has undergone numerous refinements due to its challenges, including poor solubility, difficulty in processability, and the inherent

explosiveness of the material. A landmark development occurred in 1872 with the invention of Bakelite, a synthetic polymer characterized by its strength and durability, composed of phenol and formaldehyde.

This innovation paved the way for the emergence of polycondensation-based polymer products, such as Bakelite, as well as those derived from phenoxy, epoxy, acrylic, and ketone resins. These polymers became popular substitutes in various industries, particularly automotive and electronics, where they are valued for their cost-effectiveness and performance. The ongoing research and advancements in polymer science continue to foster the growth of their applications in medicine and beyond, driving innovation in numerous fields.^[7,8]

During the 1970s and 1980s, there emerged a significant and increasing interest in the application of polymers in the field of controlled drug delivery systems. These systems were designed to administer medication in a more sophisticated manner, allowing for the gradual release of drugs over an extended period of time, as opposed to traditional methods that delivered the entire dose all at once. This innovative approach to drug delivery had the potential to enhance the therapeutic effects of certain medications by maintaining more consistent drug levels in the bloodstream over time, thereby improving the overall efficacy of treatment. Furthermore, controlled drug delivery systems can significantly enhance patient safety by minimizing the risks associated with high peak concentrations of medication, which can lead to adverse effects. In addition to these benefits, such systems can also reduce the frequency of dosing, which not only improves patient compliance but also contributes to a more stable and effective treatment regimen. The exploration and development of polymer-based controlled drug delivery during this period marked an important step forward in pharmaceutical sciences, opening new avenues for treatment options and ultimately benefiting patients seeking off effective healthcare solutions.^[9,10,11,12]

Table. 01: The historical development of polymer's in pharmaceuticals

Decade	Historical significance development of the use of polymers in pharmaceuticals
1920s	Cellulose acetate is used as a coating for tablets.
1930s	PEG is first used as a lubricant and binder in tablet formulations.
1950s	Poly (lactic acid) (PLA) is first synthesized.
1960s	Poly (glycolic acid) (PGA) is first synthesized.
1970s	Poly (lactic-co-glycolic acid) (PLGA) is first synthesized. PLGA is a biodegradable polymer that is now widely used in controlled drug delivery systems.
1980s	The first controlled release drug delivery systems based on polymers are developed.
1990s	Polymers are used to develop new and innovative drug delivery systems, such as transdermal patches and micelles.
2000s and beyond	Research continues into the development of new and improved polymer-based drug delivery systems [1-4].

Classification Based on origin

Natural Polymer: The polymers, which occur in nature are called natural polymer also known as biopolymers.

e.g. Proteins – Collagen, Keratin, Albumin Carbohydrates – starch, cellulose, glycogen. DNA, RNA.^[13]

Synthetic Polymers: The polymer that was synthesized

in the laboratory is known as a synthetic polymer. These are also known as artificial polymers. e.g. Polyesters, polyanhydrides and polyamides.^[13]

Semi-synthetic polymer: These are natural chemically modified polymers, such as hydrogenated rubber, natural rubber, cellulose, cellulose nitrate, methyl cellulose, etc.^[13]

Based on Bio-stability

Bio-degradable Polymer

These polymers gradually disappear from the site of administration in response to a chemical reaction such as hydrolysis e.g. proteins, carbohydrates, polyesters etc.^[13]

Non – biodegradable Polymers.

These are inert compounds and are eliminated intact from the site of application e.g. ethyl cellulose, HPMC, acrylic polymers, silicones.^[13]

Based on Reaction mode of Polymerization

Addition Polymers

They are produced from olefin, diolefin, vinyl and related monomers. These polymers are formed by the addition of monomeric molecules to one another in rapid succession by a chain mechanism. Examples of such polymers are polyethylene, polypropylene, polystyrene.^[13]

Condensation Polymers

They are formed by the intermolecular reaction between bifunctional and multifunctional monomeric molecules having reactive functional groups such as -OH, -COOH, -NH₂, -NCO, etc.^[13]

Based on Interaction with Water

Hydrogels

They swell but do not dissolve when brought in contact with water. e.g. polyvinylpyrrolidone.

Soluble Polymers

These are moderate molecular weight uncross-linked polymers that dissolve in water. e.g. HPMC, PEG. 4 Mechanism of Polymerization.^[14]

Ideal Properties of Polymer

Biocompatible: The polymer using biocompatible structure should be nontoxic and not eliciting any immune response from the body.

Biodegradable: The polymer should be capable of being gradually broken down by the body. This holds significance for polymers utilized in implants and other drug delivery systems that require prolonged systemic presence.

Good mechanical characteristics: The polymer should to possess qualities like elasticity, toughness, and strength. This carries significance for polymers utilized in implants and medical equipment.

Good barrier properties: The polymer should have good barrier properties to protect the drug from moisture, oxygen, and other environmental factors. This is important for polymers that are used in packaging and drug delivery systems.^[15-17]

Polymerization

It is a significant chemical process characterized by the linking together of smaller molecules, referred to as monomers, to form larger and more complex structures known as polymers. These polymers can manifest as long-chain formations or intricate three-dimensional network structures, offering a wide variety of properties and applications. The importance of polymerization cannot be overstated, as it is fundamental in the manufacturing of numerous synthetic polymers and plastics, which are integral to modern life, as well as contributing to the creation of various natural materials found in nature.

The process of polymerization can occur through several distinct mechanisms, with each mechanism presenting unique characteristics and requirements. These mechanisms include addition polymerization, condensation polymerization, and other specialized types that may involve various catalysts, temperature conditions, and pressure levels. Such variability allows for a diverse range of polymer structures and compositions, each tailored to meet specific functional needs.

The conditions under which polymerization occurs are crucial in determining the resulting polymer's properties, such as strength, flexibility, and thermal stability. By manipulating factors such as the type of monomers used, the presence of additives, and the environmental conditions, chemists and material scientists can effectively control the polymerization process to produce materials with desired features and capabilities.

The visual representation provided in the accompanying figure illustrates the various stages and mechanisms involved in the polymerization process, highlighting the systematic transformation of monomers into complex polymer structures. This depiction serves to enhance understanding of the intricate nature of polymer synthesis and the foundational role it plays in both industrial applications and the natural world. Through ongoing research and development, advancements in polymerization continue to inspire innovations across a multitude of sectors, from packaging and textiles to medical devices and beyond.

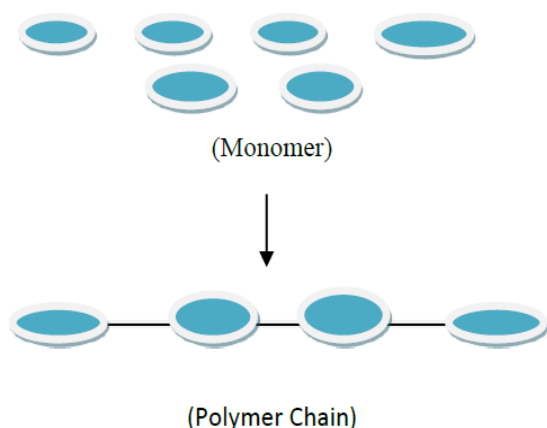


Figure: 01. The schematic representation of polymerization step in the formation of polymer.

ROLE OF POLYMER IN PHARMACEUTICAL DRUG DELIVERY SYSTEM

Immediate Release dosage form

Tablet

The use of polymers in the pharmaceutical field is not a novel concept as these materials have been effective excipients in immediate release oral dosage forms for many years. These multipurpose agents either facilitate the formulation process or provide protective measures for drugs exposed to environmental conditions for extended durations. In tablet formulations, microcrystalline cellulose stands out as a carbohydrate substitute in instances of bulky, low dosage, high-potency medications. Starch and cellulose, on the other hand, are common disintegrants which aid in the disintegration of the tablets in water. This latter activity triggers a “bursting” of the tablet which increases the surface area of the solid dosage form which has the active drug for better dissolution rates.^[19]

Further, the other polymers such as polyvinyl-pyrrolidone and hydroxypropyl methylcellulose (HPMC) are used as binders in the granules formation steps in order to improve the flowability and compactability of the formulations prior to the final tablet compression stage. At times, there is no obvious therapeutic purpose for the coating applied to dosage forms which is in the form of a polymeric film as it provides anti-degradation, mild masking of unpleasant-tasting drugs or excipients and formulation beautification without interfering the drug release kinetics. In this way, polymers remain as important materials in en.^[19]

Capsule

The polymeric excipients that are generally added to dry powder ‘bulks’ to increase the volume are the same as those used in immediate release tablets. Gelatination was mainly practiced in hard (two-shell) and soft (one-piece) capsules for shell fabrication. HPMC has also emerged and has been embraced as a new material for the production of hard (two-piece) capsules.^[20]

Modified-release dosage forms

Pharmaceutical researchers and experts across the medical field have come to a consensus regarding the efficacy of drug delivery methods, particularly in the context of therapeutic agents. Over time, it has been widely acknowledged that utilizing immediate release dosage forms often leads to outcomes that are less than ideal, resulting in either suboptimal therapy for patients or the onset of systemic side effects. To address these concerns and improve patient care, the field of pharmaceutical science has seen a wave of innovation and experimentation. One of the key strategies employed by pharmaceutical scientists has focused on overcoming the limitations associated with traditional oral dosage forms. A notable approach that has gained traction in recent years involves the development and utilization of modified release dosage forms. By extending the release profile of medications or altering the way they are absorbed by the body, these modified forms offer a promising solution for optimizing treatment outcomes and reducing the incidence of systemic side effects. Through a combination of research, clinical trials, and technological advancements, the field continues to push boundaries and explore new possibilities in drug delivery systems. As the quest for enhanced treatment options intensifies, the development of modified release dosage forms stands out as a testament to the ongoing commitment of pharmaceutical scientists to improve patient care and revolutionize the way therapeutic agents are administered.^[21]

Extended Release Dosage Form

Drugs that have a short biological half-life can have their therapeutic effects improved by creating extended or sustained release forms. These types of dosage forms help keep drug levels in the body within the therapeutic range for a longer time, which means patients don’t have to take as many doses to achieve the desired effect, making it easier for them to stick to their medication schedule. Some of the most commonly used water-insoluble polymers for these extended-release applications include ammonium ethacrylate copolymers like Eudragit RS and RL, as well as cellulose derivatives such as ethylcellulose and cellulose acetate, and polyvinyl acetate. Eudragit RS and RL vary in the amount of quaternary ammonium groups they contain, which makes Eudragit RS less permeable to water. Ethylcellulose comes in various grades with different viscosities, and the higher-viscosity grades create stronger and more durable films.^[21]

Gastroretentive Dosage Forms

Gastroretentive dosage forms provide a different approach for achieving a long-lasting release of medication. These formulations stay in the stomach for an extended time, releasing the drug directly where it can dissolve in the stomach’s liquid and gradually move into the small intestine. Unlike traditional extended-release forms that release the drug while moving through the gastrointestinal tract, this system addresses issues with

drugs that are better absorbed in specific areas of the tract. For instance, many drugs do not absorb well in the lower gut, where extended-release forms may spend most of their time, leading to uneven delivery in the bloodstream. Current delivery systems do not rely on polymers to maintain gastroretention. Some mucoadhesive and low-density polymers have been tested for their ability to increase the time the drug stays in the stomach by sticking to the stomach's mucus lining or floating on the gastric contents, but they have not been very successful so far.^[22-26]

TYPES OF POLYMERS IN PHARMACEUTICAL DRUG DELIVERY

Polymers as floating drug delivery system

Polymers are commonly utilized in floating drug delivery systems to facilitate the targeted administration of pharmaceuticals to specific areas within the gastrointestinal tract, particularly the stomach. Various natural polymers have been investigated for their significant potential in stomach-specific drug delivery, including chitosan, pectin, xanthan gum, guar gum, gellan gum, karaya gum, psyllium husk, starch, and alginates etc.^[27]

Polymers used in mucoadhesive drug delivery system

The latest mucoadhesive polymers designed for buccal drug delivery offer several benefits, including longer retention time, improved penetration, targeted adhesion, and the ability to inhibit enzymes. These specialized mucoadhesive polymers are sure to be used for delivering a range of therapeutic substances through the mouth. This type of polymer holds great promise for delivering large therapeutic molecules. Current research is particularly focused on using lectins and "lectinomimetics," which seem to be the most exciting area for safely and effectively delivering drugs through the buccal mucosa.^[28]

Polymers used as Colon Targeted Drug Delivery

Polymers are crucial in the development of colon-targeted drug delivery systems. They serve to shield the drug from degradation or premature release in the stomach and small intestine, while facilitating either an abrupt or controlled release in the proximal colon. For instance, Wong et al. investigated the dissolution profiles of dexamethasone and budesonide from formulations based on guar gum, finding that the release of the drug in simulated colonic fluid significantly increased at galactomannanase concentrations exceeding 0.01 mg/ml. Additionally, a novel tablet formulation aimed at colon targeting was created using pectin as a carrier, with diltiazem hydrochloride and indomethacin serving as model drugs. In vitro studies demonstrated that these dosage forms exhibited minimal drug release in the stomach and small intestine, while maximizing drug release in the colon. Furthermore, McLeod et al. developed glucocorticoid-dextran conjugates, linking dexamethasone and methylprednisolone to dextran via dicarboxylic acid linkers such as succinate and glutarate.

These dextran conjugates showed resistance to hydrolysis in the upper gastrointestinal tract but were rapidly degraded in the cecal and colonic environments, where bacterial populations are elevated. Chitosan capsules were also employed for the colonic delivery of a drug intended for treating ulcerative colitis, specifically using 5-aminosalicylic acid (5-ASA) as the model drug. A significant increase in drug release from the chitosan capsules was noted in the presence of rat cecal content.^[29]

The study involves the utilization of polymers in a sustained release system through the formulation of biodegradable microspheres that encapsulate a novel and potent osteogenic agent. To facilitate the sustained release of 3-ethyl-4-(4-methylisoxazol-5-yl)-5-(methylthio) thiophene-2-carboxamide, an innovative osteogenic compound aimed at addressing bone disorders, microspheres containing BFB0261 were developed. This process incorporated three newly synthesized poly (D, L-lactic acid) (PLA) variants, four poly (D, L-lactic acid-co-glycolic acid) (PLGA) variants, and eight poly (D, L-lactic acid)-block-poly(ethylene glycol) (PLAPEG) biodegradable polymers or copolymers. The release kinetics of the microspheres were subsequently assessed.^[30]

Polymers in tissue engineering

A diverse array of natural-origin polymers, particularly proteins and polysaccharides, holds significant promise as carrier systems for active biomolecules or as cellular carriers within the realm of tissue engineering, aimed at various biological tissues. The protein-based materials utilized in tissue engineering include:

- collagen,
- gelatin,
- silk fibroin, fibrin (fibrinogen), and
- other proteins such as elastin and soybean-derived proteins.

In addition, several polysaccharide-based polymers are employed in tissue engineering, including:

- chitosan,
- starch,
- alginate, and
- chondroitin sulfate.^[31]

Polymeric Nanoparticles as Drug Carriers

Certain chemical compounds, such as peptides, proteins, and nucleic acids, are subject to rapid degradation and/or metabolism following administration. This phenomenon has led to the exploration of nanotechnologies as a means to modify or regulate drug distribution at various biological levels, including tissue, cellular, and subcellular. Among the various technologies employed for targeted drug delivery, polymer-based nanoparticles have gained prominence since their inception in the early 1980s, a period marked by significant advancements in polymer chemistry that facilitated the creation of biodegradable and biocompatible materials. Nanoparticles

are characterized as submicron (<1 µm) colloidal systems predominantly composed of polymers. Their dimensions are typically 7 to 70 times smaller than red blood cells, allowing for intravenous administration without the associated risk of embolization. Depending on the preparation technique, nanoparticles can be classified into either nanospheres or nanocapsules. Nanospheres are defined as matrix systems where the drug is uniformly dispersed within the polymer throughout the particle, whereas nanocapsules are vesicular systems consisting of a drug-containing liquid core—either aqueous or lipophilic—encased by a single polymeric membrane.

Polymeric Micelles as Pharmaceutical Carriers

Polymeric micelles offer numerous appealing characteristics as drug delivery systems. They maintain stability in both laboratory and living systems, can encapsulate a diverse range of poorly soluble drugs, effectively concentrate in areas of the body with damaged blood vessels (such as tumors and infarcts), and can be directed to specific sites by adding various ligands to their surface. Both therapeutic and diagnostic micelles can be produced in large amounts with relative ease. It seems that micellar carriers hold significant potential for the future.

Polymeric Vesicle

Polymeric vesicles can be constructed from diverse macromolecular amphiphile structures, such as block copolymers, random graft copolymers, and polymers that possess hydrophobic low-molecular-weight pendant or terminal groups. These resilient particles, which exist within the nanometer and micrometer size ranges, have potential applications in drug targeting, the development of responsive release systems, and various drug delivery strategies.

Polymer Drug Conjugates

Current investigations in the area of polymer anticancer drug conjugates focus on elucidating the mechanisms by which both free and polymer-bound drugs operate at cellular and subcellular levels. Additionally, novel applications for polymer-drug conjugates are under exploration. Inflammatory diseases exhibit heightened vascular permeability, akin to tumors. While there may be reduced retention due to unobstructed lymphatics, the conjugation of drugs to polymer backbones could provide a therapeutic benefit. This presents new and promising research opportunities for scientists specializing in polymeric drug delivery.

MECHANISM OF DRUG RELEASE FROM POLYMERS

Diffusion

Diffusion is the process by which a drug or other active substance traverses the polymer matrix that constitutes the controlled-release device. This phenomenon occurs as the drug migrates from the polymeric structure into the surrounding environment. Typically, as the release

progresses, the rate of diffusion diminishes in such systems, as the active agent must cover an increasingly longer distance, necessitating an extended diffusion time for its release. In these systems, it is essential that the selected combinations of polymer matrices and bioactive agents facilitate the drug's passage through the polymer's pores or macromolecular framework upon the introduction of the delivery system into the biological milieu, all while maintaining the integrity of the polymer itself.^[32]

Degradation

Biodegradable polymers undergo degradation within the body through natural biological mechanisms, thereby negating the necessity for the removal of a drug delivery system once the active agent has been fully released. Typically, these polymers are engineered to break down via hydrolysis, leading to the formation of biologically compatible and increasingly smaller molecules. In certain degradable polymers, particularly polyanhydrides and polyorthoesters, the degradation process is confined to the polymer's surface, which results in a release rate that correlates directly with the surface area of the drug delivery system.^[33]

Swelling

Initially, these substances are in a dry state; however, upon introduction into the body, they take up water or other bodily fluids, leading to an increase in volume. This swelling not only enhances the aqueous solvent content within the formulation but also enlarges the polymer mesh size, facilitating the diffusion of the drug through the expanded network into the surrounding environment.^[33]

Future Prospects

Numerous researchers are actively engaged in this field, having created a variety of modified copolymers featuring desirable functional groups. They envision applications that extend beyond controlled drug delivery systems, including uses in artificial organ linings, immunology testing, drug targeting agents, chemical reactors, and substrates for cell growth. (R) The biggest chances for these polymers in controlled drug delivery are in responsive delivery systems. In the future, researchers and doctors are likely to have even more biodegradable polymer products at their disposal, which will aid in quicker patient recovery and reduce the need for follow-up surgeries. (R) Looking to present scenario and a wide range of research, total use of these biodegradable polymers in drug delivery applications is within reach in the near future.^[35-36]

CONCLUSION

The introduction of innovative polymers brings both advantages and potential risks due to their associated toxicity and incompatibilities. These polymers exhibit exceptional strength in drug delivery applications, facilitating advancements in the development of new drug delivery systems that enhance therapeutic

outcomes. The primary objective is to create cost-effective, biocompatible, multifunctional, and less toxic polymers, ensuring that these delivery systems successfully navigate the various stages of clinical trials and ultimately benefit society. This review article highlights the crucial and diverse role of polymers in the pharmaceutical industry, demonstrating how they have transformed drug delivery, formulation, and a range of therapeutic applications.

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