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REVIEW

Polymer paradigm: revolutionizing drug delivery

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The present review paper addresses using different polymers to deliver medicinal drugs. It deals with different forms of dosage like tablets, films, patches, semi-solids, tapes, powders, etc. It also discussed dyslipidemia and the management of statins, binding resins, and niacin for lowering LDL-cholesterol levels; and fibrates for reducing triglycerides while raising HDL cholesterol. It focused on the polymers that have been used in drug-delivery systems for example natural polymers like chito, alginate, collagen, etc. and synthetic polymers like polyethylene glycol, poly (vinyl alcohol) or PVA in addition to their advantages, mechanism of action with their recent development. Drug-delivery systems (DDS) are based on polymers—they determine how drugs are released from the drug-delivery devices. Recent advances in polymer science have led to a wide variety of novel drug-delivering systems. Polymer-based DDS has revolutionized medical therapy by enabling precise regulation of drug release and targeting. The advancement of polymer science has specifically led to the fabrication of many new drug-delivery systems. Polymer-based DDS has proven to be the favorite choice in drug-delivery systems providing controlled and targeted built-in control over drug release. However, many aspects are yet to be covered. Polymer science has seen a lot of development in the field with various innovative drug-delivery systems developed over time. The polymer-based DDS changed radically existing therapeutic strategies because it gives control of the drug release and delivery. Polymers are commonly used as biomedical implants and have been long-lived. Since the onset of action is fast, rapid dissolving polymers are often used to create oral dispersing films and nanoparticles. These advancements increase the effectiveness of treatments and minimize unwanted side effects or other issues for patients.

Keywords: polymer, novel delivery of drug, nanoparticles, polymer-based delivery, sustained release drug administration, hydrogels, novel polymer, pullulan

Introduction

Polymers are large, long chains that contain diverse functional groups and are essential in drug-delivery systems because of their excellent pharmacokinetic properties. They control medication release through various devices and are used as stabilizers, flavor masking agents, and protective agents in oral drug administration. Their unique characteristics make them a valuable tool in managing drug release rates and formulations (1). Synthetic polymers are widely used due to their diverse properties and longevity in circulation. They can bond with solid dosage particles, improving liquid formulation flow characteristics (2).

Understanding drug-delivering methods is fundamental to investigating the function of polymers in enhancing therapeutic efficacy and patient compliance. Polymers play a significant part in assessing the design and effectiveness of delivery systems. The use of polymers in drug-delivery systems enables regulated release kinetics, targeted delivery, and enhanced bioavailability (2). Polymers are suitable for coating, matrices, or carriers also polymers contribute to the modulation of drug release rates, protection of active therapeutic components and improved medication stability. The significance of polymers in medication delivery systems arises from their ability to overcome the inherent problems of administering medicinal substances. The polymeric materials can be programmed to control the release kinetics of drugs, and consequently, sustainable and personalized drug delivery can be achieved. A film coating for pharmaceutical preparation is one of the most effective approaches for stabilizing drugs, altering drug release rates, and masking taste (1).

Objective

This review's objective is to provide a comprehensive, elaborate description of drug-delivery techniques based on polymers. To realize the relevance of polymers in drug-delivery systems, it is important to understand how polymers affect the efficiency of treatments and the compliance of patients to their antieducation medication regimen (3).

Classification of polymer (Figure 1)

(A) Depending on sources:

a. Natural: Alginate, dextran, gelatine, albumin, chitosan, collagen
b. Semi-synthetic: Hydroxy Propyl Methyl Cellulose (HPMC), Methyl Cellulose (MC)
c. Synthetic: Polyethylene, Polylactic acid, Polyglycolic acid, Poly hydroxybutyrate

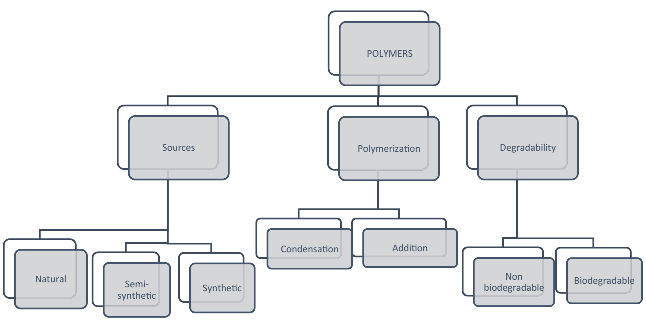

FIGURE 1 | Classification of polymers (2, 7).

TABLE 1 | Types of polymers.

Natural polymers	Semi-synthetic	Synthetic polymers
Chitosan	HPMC	Polylactic acid
Dextrin	Methylcellulose	Polyglycolic acid
Gelatine	HPC	Polyethylene
Pullulan	–	–

(B) Polymerization-based:

a. Condensation polymers: Polyester, Polyurethane
b. Addition Polymers: polypropylene, polyethylene, and polyvinyl chloride

(C) Degradability-based:

a. Non-biodegradable: Ethyl Cellulose PDE, Polyether urethane, and Polymethyl Siloxane.
b. Biodegradable: polylactic acid, polyglycolic acid, and polycaprolactone

The significance of polymers in medication delivery:

- Formulations for immediate-release dosages:

Tablet: Polymer compounds are commonly used in immediate-release oral dosage formulations to facilitate production and protect medicines from degradation. Microcrystalline cellulose is used as a diluent in tablets for low-dosage medicines, replacing carbohydrates. Cellulose and starch act as disintegrants, expanding when water meets them, and improving dissolving properties. Polymers like HPMC and polyvinyl-pyrrolidone create granules, enhancing tablet flow and compaction (4).

Capsules: Capsules are more effective than tablets for poorly malleable substances, efficiently masking the unpleasant taste of some medications, and greatly increasing bioavailability. The polymeric additives used to "bulk up" capsule fillings are quite like those used in immediate-release tablets. Gelatine had traditionally been the most common substance employed in both hard (two-piece) and soft (one-piece) capsules. Nevertheless, HPMC has currently developed as a promising alternative option for a hard (two-piece) capsule production (1, 2, 5).

- **Modified-release dosage formulations**

It has been accepted that many therapeutic agent deliveries of immediate-release dosage result in various side effects (6). Investigators have attempted to address the restrictions of standard doses by inventing modified-release dosages.

- **Extended-release dosage formulations**

Extended-release formulations of therapeutic agents with short half-life can improve their efficacy. It enhances the duration of the drug's systemic release, maintains the therapeutic window, and reduces the number of doses. Water-insoluble polymers often used for extended-release applications include polyvinyl acetate methacrylate copolymers, cellulose derivatives (ethyl cellulose, cellulose acetate), and ammonium methacrylate copolymers. Eudragit RL and RS differ in the percentage of quaternary ammonium groups, making Eudragit RS impermeable/low permeable to water, while ethyl cellulose is accessible in a variety of viscosity grades, resulting in stronger and more lasting films.

- **Gastro-retentive dosage formulations**

Gastroprotective dose formulations provide an alternate technique for attaining a prolonged release profile. These formulations stay in the stomach for a longer period, allowing the medicine to be released in place. The medication then dissolves in the liquid material before gently passing into the intestine (8).

Different kinds of polymer drug-delivery systems

(1) Microsphere

The term MICROSPHERE refers to a small sphere having an interior porous matrix and a surface that can be modified. If a medicine is encapsulated, it diffuses throughout the internal matrix. Microspheres vary in size between 1 and 500 μm in diameter and possess great importance in the field of science.

(2) Nanoparticles as drug carrier

Drug delivery has undergone game-changing development through polymer nanoparticles. These have a wide range of advantages including higher solubility of the drug, better bioavailability, and targeted distribution. The use of polymeric nanoparticles for cancer treatment is marred by the great dependence on poly (lactic-co-glycolic acid) and polyethylene glycol. These nanoparticles can be drugged solutions non-target specific to tumors and get the EPR effect that opens for the nanoparticles to penetrate through the tumor and get trapped in the tissues. Such a medication delivery approach minimizes healthy tissue damage, lowers systemic adverse effects, and improves the overall success of cancer treatment.

(3) Polymers used in gene-therapy

Certain polymers with a cationic charge at physiological pH levels are interesting candidates for gene transfer over the several biological barriers discussed in the preceding article. A perfect gene delivery mechanism should be capable of transferring the gene safely to the targeted tissue's nucleus while limiting the gene's exposure to damaging factors (6).

(4) Polymeric vesicles

Nanoparticles are used in the delivery of vaccines for example, The incorporation of a vaccine into biodegradable and biocompatible polymer nanoparticles greatly enhance the comfort of administration and responsiveness.

The vaccine is released from the encapsulated particle which, it is assumed, provides a constant level of antigen for a more consistent and prolonged immune response. This tells us about Vaccine Delivery and there arises a potentiality for a more effective and durable system that could promote adherence (9).

(5) Polymeric micelles

There are several advantages to using polymeric micelles as therapeutic carriers. These particles are stable in vitro and in vivo, can carry a broad spectrum of poorly soluble drugs, rapidly accumulate at sites where the vasculature is compromised (e.g., tumors and infarctions) and can be end-targeted by tethering specific ligands to their surface. Polymers, arbitrary graft copolymers, and polymers containing hydrophobic low-molecular-weight pendants or terminal groups are examples of large-molecule architectures that can be employed to effectively build polymeric vesicles. These hardy particles come in a diversity of sizes, from nanometers to micrometers, and play a significant role in medication delivery systems, stimulus-responsive release systems, and drug targeting.

General mechanisms of drug release from polymer

Active agents can be released from a delivery system in three main ways:

- **Degradation**

The body's inherent physiological operations lead biodegradable polymers to start breaking down, so there is no requirement to remove the drug-delivery system after the active component is entirely discharged. Most compostable polymers are intended to break through the process of polymer chains hydrolyzing into increasingly smaller and physiologically suitable molecules (10).

- **Diffusion**

In a controlled-release device, the medication moves from the matrix of polymer into the surrounding environment via diffusion. At increasing distances to the active agent, the rate of release slowly decreases and longer diffusion time is required. The selection of bioactive compounds and biocompatible polymer matrices that allow the diffusion of drugs without changing the polymer once they meet the biological milieu is very important (2).

- **Swelling**

These materials expand when set within the body because they retain water or other bodily elements while they are dry (12). The medicine can permeate into the external environment through the inflated network of polymer meshes because of the considerable increase in liquid content that results from this swelling.

Delivery of drug using polymers

Rosin

Rosin is a versatile biological polymer used in film covering, dental varnishes, chewing gum, and cosmetics. Spherical microcapsules can be made with rosin using phase separation. Adding dibutyl phthalate and polyvinyl pyrrolidone improves tensile strength and elongation of the film (**Figure 2**) (14, 15).

Chitosan and chitin

Chitin is a naturally occurring polymer made up of two acetamido-2-deoxy-β-D-glucose molecules. Chitin's tough structure gives it great strength, and its lightweight makes it an excellent component of arthropod shells. Chitin is broken down by chitinase, an enzyme in the digestive system. Chitosan, a similar substance manufactured by humans, has several of the same distinguished attributes, including a lightweight property and the ability to form strong, addictive bonds (16–18) Chitosan has been used in drug administration because it carries a certain charge when in the presence of acidic conditions—a charge that acts as a sort of hook, holding it, and whatever it has bound to it, in the vicinity of the cells that line the inside of a space, be it a digestive or a respiratory space (**Figure 3**) (19, 20).

Collagen

Mammals are mostly composed of collagen, which gives tissue endurance. It has been investigated for application in tissue engineering and bioprosthetic implants of many organs, medication delivery, and other forms of surgery (21)

Starch

In green plants- in particular seeds and subterranean organs- Starch is the principal glucose reserve. Starch comes in granules, every species with its type of form and size (1, 21, 22). The ratio of amylopectin to amylose varies from species to species (16). It improves the protein and peptide availability.

Pullulan

Pullulan is an alpha-1,4 and alpha-1,6-glucan polysaccharide polymer of maltose (triose) units. The α-1,4 glycosidic bonds link three glucose units whereas the α-1,6 glycosidic bonds are present in malt triose units. Common in the environment, these fungi use pullulan as a way of creating reliable cellular protection and structure to guide molecules through their cell packet. The use of the palatable and significantly tasteless polymer, pullulan, in producing edible films presents a promising alternative for several food-related applications

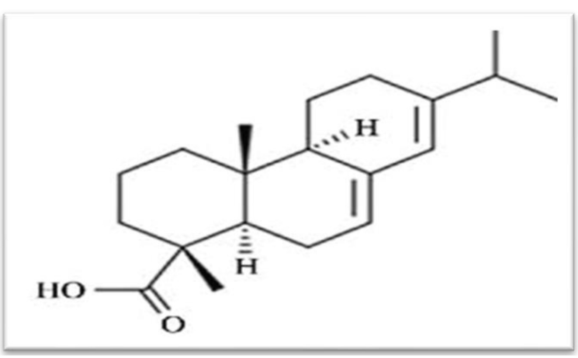

FIGURE 2 | ROSIN (9).

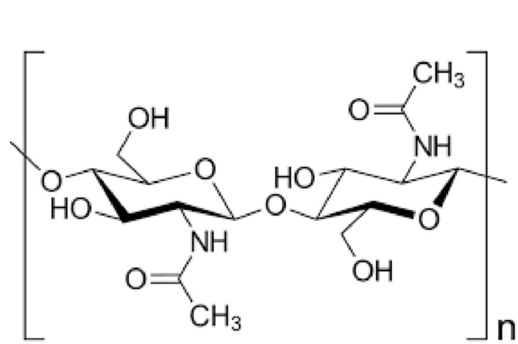

FIGURE 3 | CHITIN (4, 10).

(23–25). Pullulan was also analyzed as a natural polymeric biomaterial for injectable scaffolds in bone tissue engineering and intervertebral disc enthesis (**Figure 4**).

Polycaprolactone

The poly-caprolactone or PCL has a high melting point which should be classified as a synthetic polymer that will melt above 60 + 5°C but just below this range the material has a low melting point of about 70 + 5°C also. One kind of it is generally used to create special polyurethane materials that are highly reactive to moisture, petrol chemicals and chlorine.

Plant-derived polymers for drug delivery

Polymers are valuable for designing drug release systems. They can produce solid, liquid, and semi-solid medications. Both synthetic and natural polymers are evaluated, natural polymers are more popular in the pharmaceutical industry (26).

Cellulose

Cellulose is an organic molecule, a polysaccharide of plant cell walls composed mostly of cellulose, pectin, and hemicelluloses, utilized in pharmaceuticals such as tablet filler. Microcrystalline cellulose serves as a unique and highly usable cellulose powder (7). Microcrystalline material is primarily utilized in the pharmaceutical sector as a binder or diluent in tablets for both granulation and direct compression operations. Microcrystalline, a free-flowing non-fibrous material, is created from high-quality cellulose by treating it with hydrochloric acid, resulting in partly depolymerized cellulose particles (**Figure 5**).

Pectin

Pectin is a type of heteropolysaccharide, found in the main lamella, middle lamella, and cell walls of terrestrial plants.

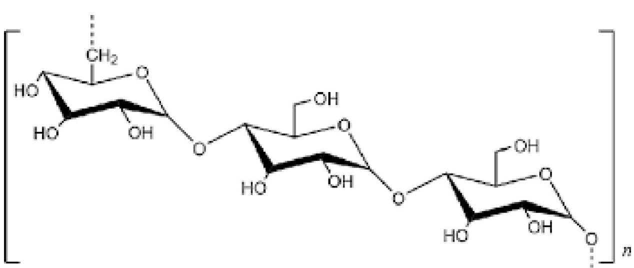

FIGURE 4 | Pullulan (1, 11).

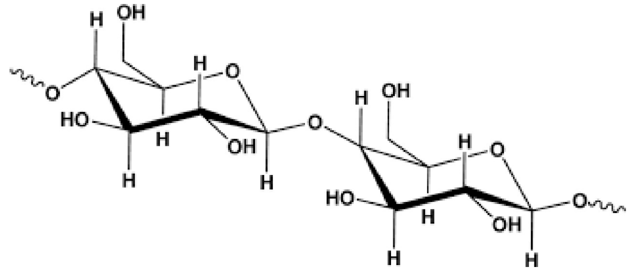

FIGURE 5 | Cellulose (6, 8).

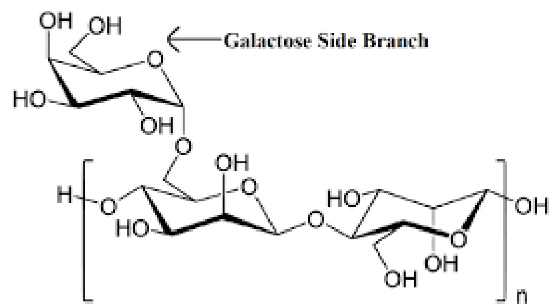

FIGURE 6 | Guar gum (13).

It also prevails in the junctional domains of cells within secondary cell walls, such as the xylem and fiber cells in woody tissue. Pectin has been used as an excipient in many dosage forms, including film coating for colon-specific drug administration with ethyl cellulose, microparticulate delivery for ophthalmic preparations, and matrix-type transdermal patches. Pectin composition can vary according to botanical source; textile pectin from citrus contains fewer neutral sugars and has a lower molecular weight than apple pectin (26).

Guar-Gum

A galactomannan extracted from guar beans, guar gum, or guaran, is a type of natural polymer that has extensive thickening and stabilizing properties. Due to its cost-effectiveness and flexibility, it has now gained attention as one versatile vehicle for oral sustained-release drug delivery. The enzymatic destruction of guar gum in its specific environment, namely the digestive tract, makes it particularly useful for colon administration. What is more, it acts as a favorable thickener for lotions and creams, a binder for tablets, and an emulsion stabilizer (**Figure 6**) (13, 27).

Recent Advances and Emerging Trends

The oral drug-delivery system, a widely used route of administration, has been beneficial for systemic medication distribution. Different pharmaceutical products are used for various dose forms, with synthetic and natural materials being researched for medication delivery systems. Polymers, like polyvinylpyrrolidone and polyethene glycol acrylate-based hydrogels, are commonly used due to their biodegradability and ability to create copolymers. Natural polymers, such as gelatine and collagen, are more biocompatible and less immunogenic, playing a significant role in medication delivery systems (17). Other polymers that are natural include chitosan, alginate, pectin, casein, starch, and cellulose derivatives. Combining many of the mentioned natural polymers with synthetic polymers gives further benefits as drug-delivery transporters since they complement each other's properties.

(A) Smart polymers in drug delivery

Extensive research in drug-delivery methods includes smart polymers that respond to environmental signals like pH and temperature, enabling precise and controlled release of medication.

In addition, the developing trends of drug delivery in smart polymers have aimed to develop novel approaches and applications that improve therapeutic efficacy with fewer adverse effects.

- Personalize medicine
- Advances in the responsive drug release
- Incorporation of nanotechnology

Recent advances in smart polymers for drug delivery illustrate an area of emphasis that is dynamic and in a constant state of flux: precision, responsivity, and versatility. How intelligent polymers are incorporated into these emerging technologies, nanotechnology, and personalized medicine, among others, can become the next generation's therapeutic strategy, with both effectiveness and patient specificity.

(B) Nanotechnology and polymers

It is due to similarities that nanotechnology and polymers have revolutionized drug-delivery systems (24, 27–29). Nanoparticles are biocompatible polymers that can encapsulate drugs and shield them from degradation, enabling controlled release at specific sites in the body. Consequently, drug efficacy is enhanced, and unwanted effects are minimized, leading to better patient compliance. A new study has developed stimulus-responsive polymer nanoparticles with on-demand drug release triggered by environmental factors such as PH Temperature or specific Enzymes (30).

Among the primary drivers in recent trends toward the development of environmentally friendly nanopolymers is sustainability. It remains on the agenda of scientists who continue to discover and develop biodegradable and biocompatible polymers at the nanoscale to eliminate the concerns of toxicity of nanoparticles and their impact on the environment. Sustainable nanopolymers open the field to various applications, starting with packaging materials and water purification up to agricultural technologies.

(C) Personalized medicine and polymer

Due to ongoing development in both technology and polymers, there is personalized medicine that acts according to the genes, habits, and environment of an individual. By enabling highly targeted drug-releasing systems, diagnostic tools or tissue engineering scaffolds according to patient-specific data, polymers substantiate the concept of tailored medicine.

I. Personalized Implantable Devices: The use of polymers is not a novel technology for implantable medical devices anymore. Future medicine tends to adopt the production of custom implants for every person's unique anatomy and health condition. 3D printer technology makes feasible the development of the implants using only the patient-specific data. These biocompatible polymer-based implants are thus a specific solution that is in practice replacing other procedures like bone replacements of the joints, craniofacial reconstruction, and cardiovascular interventions.

II. Precision Drug-Delivery Systems: Polymers have now become a vital part of the drug-delivery system designs that are individualized to the needs of each patient. Customizing drug-loaded polymers allows for precise medication delivery, enhancing effectiveness and reducing side effects. This method guarantees that patients will receive the appropriate medicine, dosage, and timing, therefore, it will decrease side effects and result in better treatment effectiveness (14, 15, 24).

III. Diagnostics and imaging agents based on polymers: Polymers play a pivotal role in creating customized medicine through diagnostic technologies. Polymer-based contrast agents, designed as nanoparticles, enhance sensitivity and specificity in medical imaging. These molecules can adhere to specific biomarkers or tissues, crucial for therapy planning and disease monitoring.

Challenges and Future Directions

The area of polymer drug delivery presents exciting possibilities for creating innovative delivery systems. These systems could administer medication either through implantable devices based on blood levels or target specific drug delivery sites accurately (12, 17, 21). Much of the development of novel materials in controlled drug delivery focuses on the preparation and use of these responsive polymers with specifically designed macroscopic and microscopic structural and chemical features. Such systems include:

- Copolymers with desirable hydrophilic/hydrophobic interactions.

- Dendrimers or star polymers are nanoparticles for immobilizing enzymes, drugs, or other biological agents.
- Block or graft copolymers.
- New biodegradable polymers.
- Complexation networks respond via hydrogen or ionic bonding.
- New blends of hydrocolloids and carbohydrate-based polymers.

Scientists have developed altered copolymers containing various functional groups, anticipating uses outside of drug-delivery systems. These applications consist of artificial linings for organs, testing immunology, targeting drugs, reactors, and substrates for cell growth. There is a significant potential for controlled drug delivery using these polymers with responsive delivery systems. It is anticipated that biodegradable polymer-based products will speed up patient healing and lessen the requirement for more surgeries. The advancement of drug delivery depends on creating and producing novel polymer blends while having a thorough knowledge of their chemical and physical characteristics. Scientists and engineers are dedicating more attention to decreasing the environmental effects of polymer production by examining the product life cycle and creating environmentally friendly materials and processes to promote a sustainable society.

Conclusion

Polymer-based medications are being more recognized as effective treatments for deadly illnesses including cancer and hepatitis. As most of the newly formed drugs possess undesirable physicochemical and pharmacokinetic characteristics, excipients are gradually introduced into preparations not only to occupy the volume and facilitating the process of preparation manufacturing but also to carry out certain specific functions for medication releasing. Natural pharmaceutical excipients, on the other hand, include compounds derived from natural sources which can be formulated in their pure state or in combination with other compounds and are biocompatible, nontoxic, noncarcinogenic, nonmutagenic and conform to antibody to the earth's ecology and they are economical. When building a delivery system, it is critical to carefully choose polymers.

The main goal is to use cost-effective, biocompatible, and multifunctional polymers that are less toxic. This will help the delivery systems pass through different phases of clinical trials and ultimately benefit society. Many polymers have been successfully used, and others are currently being investigated as excipients in the design of dosage forms for effective drug delivery.

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