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Advanced mechanisms of polymer-based drug delivery systems for clinical applications

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Polymer-based drug delivery technologies have revolutionized modern therapeutics by enabling controlled, sustained, and targeted drug release. These systems employ diverse natural and synthetic polymers that engage with biological environments to exert therapeutic effects. The history of polymeric drug delivery systems, their classification, formulation techniques, mechanisms of action, and diverse applications across various disease conditions are essential for future advancements. Polymer chemistry has led to the development of stimuli-responsive polymers that release drugs in response to external triggers, such as pH, temperature, electricity, light, or ultrasound. Moreover, 3D printing technologies are increasingly employed to develop more complex, multifunctional, layered, polymer-based drug delivery systems. While polymer-based technologies have demonstrated remarkable potential in drug delivery, challenges like scalability, biocompatibility, and regulatory compliance persist. Interdisciplinary collaboration and multifaceted strategies can advance targeted treatments for life-threatening diseases and enhance quality of life through tissue regeneration.

1. Introduction

Polymers have long been central to drug delivery technologies and continue to advance through the creation of new materials by crosslinking or integrating different polymers, resulting in systems with distinct, tunable properties.[1] Polymeric drug delivery systems have been an integral method for enhancing the effectiveness, efficacy, controlled release, and targetability of active pharmaceutical ingredients (APIs) in the body.[2] Polymers utilized as drug carriers are formed into micelles, microspheres, nanoparticles, thin films, microneedles, and hydrogels. Encapsulating or absorbing drugs within a polymer matrix protects them from rapid release and enzymatic degradation in the body.[3] In addition to providing protection, polymers significantly enhance the solubility and bioavailability of drugs that are otherwise difficult to dissolve. Some polymers are specially designed or naturally capable of responding to specific physiological conditions, allowing for the precise release of drugs at targeted sites within the body.[4] Furthermore, these polymers are susceptible to surface modification, enabling diverse functionalities that enhance the system for efficient, controlled, and targeted release to the intended organ.[5] Nowadays, ligands that can exclusively bind to the receptor of interest that is overexpressed in disease conditions can be attached to polymeric drug delivery systems, reducing the distribution of drugs to off-target locations. In cancer treatment, polymeric nanoparticles are currently functionalized with ligands that target drug molecules to cancer cells, significantly enhancing therapeutic efficacy.[6,7]

The diversity, versatility, and biocompatibility of polymeric carriers are key properties that continue to drive research and ensure their relevance for decades to come. Their adaptable nature allows polymers to encapsulate a wide range of therapeutics, including hydrophobic and hydrophilic drugs, proteins, peptides, and nucleic acids. By doing so, polymers enhance the stability of these agents and protect them from unwanted interactions within the physiological environment.[2] Polymeric drug delivery has excellent mechanical characteristics, flexibility, and durability, making it a desirable drug carrier for various medical conditions.[8] Research has also investigated biodegradable polymers that release drugs without leaving damaging polymer residues as they decompose into non-toxic monomers for multiple applications.[8]

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Therefore, a comprehensive evaluation of the long-term toxicity of these polymers remains necessary for their clinical applications. Although numerous studies have reported advanced techniques for synthesizing polymeric carriers, relatively few have focused on systematically confirming their long-term *in vivo* toxicity.[9]

The mechanism of polymer-based drug delivery systems relies on the inherent relation between the polymer networks and the biological environment, including cells, tissues, and the extracellular matrix. These interactions are influenced by factors such as molecular weight, degradation rate, and stimulus responsiveness, all of which play critical roles in determining drug release kinetics and bioavailability.[5,10] Recent research has developed and synthesized polymeric micelles that are stimuli-responsive, also called "smart polymers". These polymers can undergo dynamic alterations in response to certain stimuli such as pH, temperature, light, and redox reaction, thereby facilitating a highly controlled and precise drug release mechanism.[11] Another advancement to polymeric drug delivery was the application of nanotechnology. Polymeric nanoparticles have significantly improved the surface area of drugs, enhanced permeability, better drug loading capacity, and surface modification, which have ultimately enhanced cellular uptake and precise delivery to target organs.[12]

The potential of polymeric drug delivery to create effective delivery systems for personalized therapeutics lies in an interdisciplinary framework that integrates concepts of materials science, pharmacokinetics, pharmacodynamics, and advanced engineering techniques.[13] Innovations in these regards, like bioinspired polymers that mimic natural cellular functions and multifunctional polymeric systems designed for the co-delivery of numerous medicinal agents, are advancing the pursuit of personalized medicine.[14] Furthermore, optimizing drug loading capacity and predicting drug targets in biological systems for polymeric drug delivery using computational modeling, machine learning, and artificial intelligence are enhancing the design of next-generation drug carriers with precise, timely, and targeted drug release with the appropriate dosage.[15]

This review article aims to provide a comprehensive overview of polymeric drug delivery, covering key aspects such as classification, characteristics, formulation, release mechanisms, applications in various diseases, and clinically established polymeric delivery systems. Emphasis is also laid on the recent application of polymeric drug delivery in multiple diseases, including cancer, antimicrobial resistance, vaccines, and gene delivery, among others. These applications have been demonstrated *in vitro*, *in vivo*, in clinical trials, and in FDA-approved polymeric delivery systems.

2. Classification of polymeric drug delivery

Based on their origin or source, polymers used in drug delivery are classified into two categories: natural and synthetic polymers. Also based on inherent properties that support their role in drug delivery, these polymers are modified into various drug carriers. Additionally, polymers can be categorized according to their structure, molecular forces, and polymerization; these characteristics also determine how they are used in drug delivery. Natural polymers derived from biological source such as chitosan, alginate, and gelatin, are highly biocompatible and biodegradable, making them ideal for controlled drug release. For instance, chitosan, which has good mucoadhesive properties and enhances drug permeation, has been investigated for oral insulin delivery using its nanoparticles,[16] while alginate nanoparticles have shown promise for sustained release of anticancer drugs.[17] On the other hand, synthetic polymers that offer superior mechanical stability, tunable degradation rates, and controlled drug release profiles include poly(lactic-*co*-glycolic acid) (PLGA), polyethylene glycol (PEG), and polycaprolactone (PCL). For example, leuprolide acetate, a hormone therapy drug for prostate cancer, has been effectively released over an extended period of time using PLGA-based microspheres.[18] Additionally, PEG is frequently used in stealth nanoparticles because it enhances the circulation time of drugs in the bloodstream, and this is demonstrated by the FDA-approved PEGylated liposomal doxorubicin (Doxil®) for cancer treatment.[19] PCL is also known to offer long-term drug-release capabilities, making it suitable for implants and regenerative medicine.[20] To ensure optimal therapeutic efficacy for a range of drug delivery applications, the choice of natural and synthetic polymers depends on the necessary biocompatibility, degradation rate, and drug release kinetics. Fig. 1 illustrates the classification of polymers based on their origin (natural and synthetic), structure, molecular forces, and polymerization, with various examples for each.

2.1 Natural polymers

These polymers are derived from natural sources, such as plants or animals. They are classified into polysaccharides and protein polymers. Natural polymers offer biocompatibility, biodegradability, low toxicity, and the ability to mimic the extracellular matrix, making them ideal for controlled and sustained drug delivery applications. Table 1 demonstrates the type of natural polymer used in drug delivery, its source, advantages, disadvantages, and approximate degradation time at 37 °C and pH 7.2–7.4.

2.2 Synthetic polymers

These polymers are synthesized in the laboratory from the polymerization of chemical compounds. Synthetic polymers provide high mechanical stability, tunable degradation rates, controlled drug release profiles, and ease of functionalization, making them highly versatile for targeted and sustained drug delivery applications. Table 2 illustrates the advantages and disadvantages of synthesized polymers and the monomers from which they are derived.

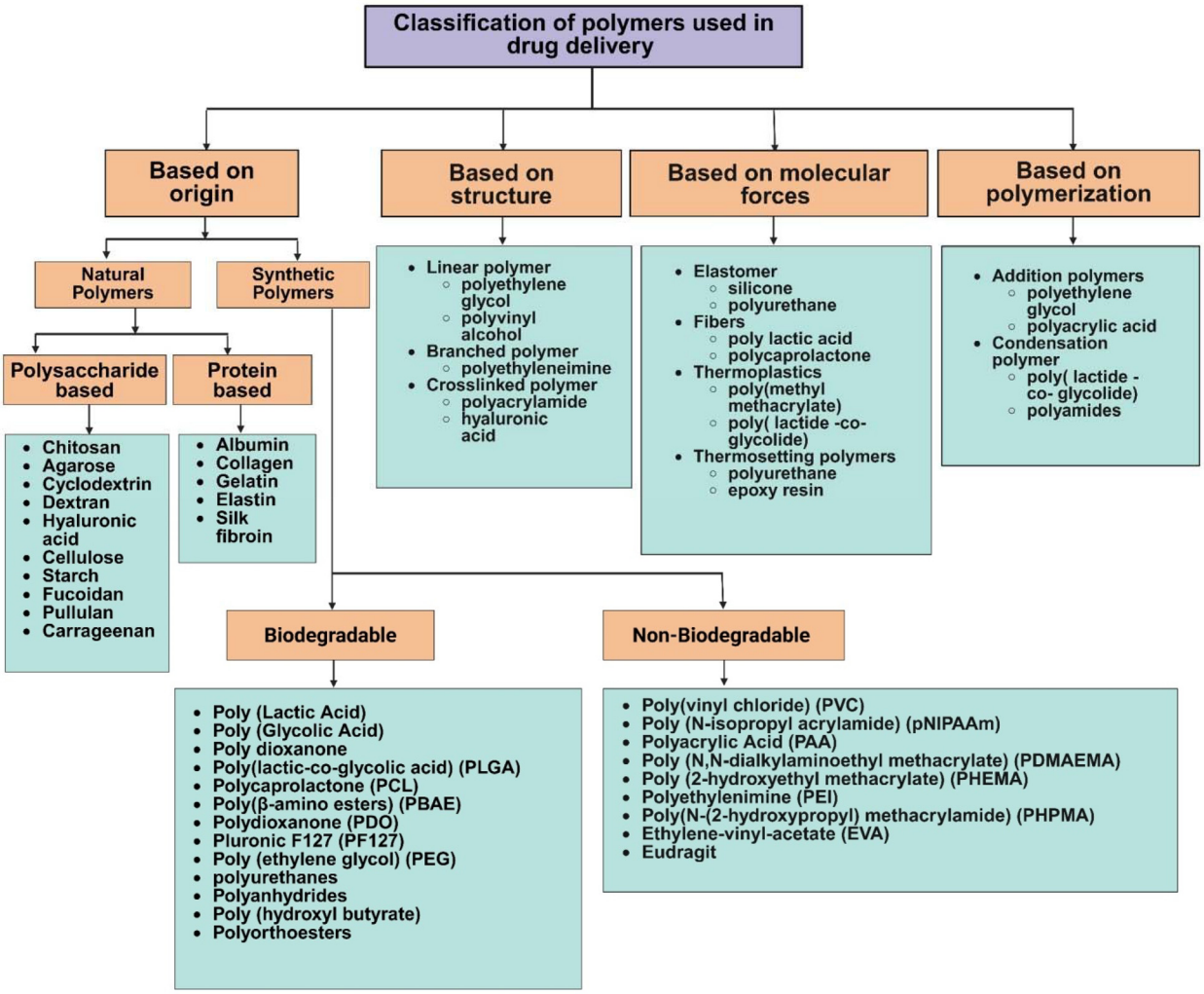

Fig. 1 Classification of polymers in drug delivery. Polymeric drug delivery systems are categorized based on four criteria: (1) origin, including natural polymers (*e.g.*, chitosan, agarose, hyaluronic acid) and synthetic polymers (*e.g.*, albumin, collagen, silk fibroin); (2) structure, such as linear, branched, and crosslinked polymers; (3) molecular forces, comprising elastomers, fibers, thermoplastics, and thermosetting polymers; and (4) polymerization methods, including addition and condensation polymerization. The classification also differentiates between biodegradable polymers (*e.g.*, PLA, PLGA, PCL) and non-biodegradable polymers (*e.g.*, PVC, pNIPAAm, PEI), highlighting their relevance in drug delivery applications.

3. Characteristics of polymeric drug delivery systems

3.1 Biocompatibility

Biocompatibility is the ability of a material to perform its intended function in a biological system without eliciting adverse reactions in surrounding tissues. In drug delivery, polymers serve as excipients for active pharmaceutical ingredients to manufacture a drug dosage form. These polymers must be biocompatible so they do not trigger immune responses, allergic reactions, cytotoxicity, or mutagenesis in the body.[12] Natural polymers used in drug delivery are the ones with the highest biocompatibility. Polymers such as chitosan, alginate, and gelatin are highly compatible and widely used for administering drugs *via* various routes. In addition, certain synthetic polymers can be considered biocompatible excipients for drug delivery when engineered to have specific features and properties. Polymers such as PLGA and PEG are highly biocompatible with biological systems.[6] For instance, PEG has been used extensively in coating nanoparticles and as a co-polymer to extend drug circulation time, reduce the immune system's recognition of nanoparticles, and increase the solubility of other polymers.[42] Chitosan has shown excellent biocompatibility, attributed to its muco-adhesiveness and anti-microbial properties.[51] These biocompatible polymers have found applications beyond conventional drug delivery, including gene delivery, wound healing, long-acting injectables, and vaccine development.

3.2 Biodegradability

In drug delivery, the ability of polymers used as excipients to break down into byproducts or metabolites, which will be

Table 1 Types of natural polymers in drug delivery with the source, advantages, and disadvantages

Polymer	Source	Advantages	Disadvantages	Degradation time	Ref.
Chitosan	Crustacean exoskeleton	- Muco-adhesion properties - Biocompatibility - Biodegradable - Anti-microbial properties - *In situ* gelation - Bind both hydrophobic and hydrophilic drugs	- Limited stability - Low solubility at neutral pH - Low flexibility	1 to 8 weeks, depending on the lysozyme presence	21 and 22
Alginate	Brown algae	- Readily accessible and inexpensive - Biocompatibility - Controlled release - High solubility - Stable in low pH - Biodegradability	- Instability in the room temperature - Low mechanical properties	Days to weeks for ionically (Ca^{2+}) crosslinked	23
Cyclodextrin	Cyclic oligosaccharides of glucose	- Increase the water solubility of a hydrophobic drug - Improve bioavailability - Biocompatibility - Biodegradability	- Premature release of drugs - Complexation Inefficiency - High production cost	Weeks to months, depending on hydrolysable linkers	24
Dextran	Polysaccharides from lactic acid bacteria	- Good thermal and rheological properties - Non-toxicity - Good solubility - Easy functionalization - Biodegradability	- Premature release of drugs - Not easily accessible	~3–12+ weeks	25
Hyaluronic acid	Connective tissues, synovial fluid, and the extracellular matrix of the body	- High water binding capacity - Use in a hydrogel for sustained release - Forms electrostatic complexes with cationic drugs	- Low stability - Short biological half-life - Poor mechanical properties	Hours to 2 days in tissues	26
Cellulose	Cellulose is an abundant polysaccharide derived from plant cell walls	- Abundance in nature - Low cost - Excellent water retention and swelling Properties - Provide structural support for drugs	- Insoluble in many solvents - Limited flexibility - High degradation rate in the body	Oxidized cellulose resorbs in about 2–8 weeks	27
Starch	Natural polysaccharide	- Biocompatibility - Biodegradability - Low cost and easy accessibility - Swelling properties	- Low flexibility - Low stability - High viscosity - Prone to enzymatic degradation	Hours to days with α-amylase	28
Fucoidan	Sulfated polysaccharide derived from brown seaweed	- Anti-coagulant and anti-inflammatory properties - Biocompatibility - Enhance drug absorption - Targeted delivery	- Quality depends on the source - Complex manufacturing process	Days to weeks (formulation-dependent)	29

Table 1 *(Contd.)*

Polymer	Source	Advantages	Disadvantages	Degradation time	Ref.
Pullulan	Polysaccharide from the fungus Aureobasidium pullulans	- Biocompatibility - Good adhesion properties - High water solubility - Biodegradability - Forms a stable viscous solution - Films forming ability	- Poor mechanical properties - Not suitable for c ontrolled release - Expensive to process	Days to weeks	30
Carrageenan	Red seaweed	- Biocompatibility - Forms a viscous and elastic gel - Good adhesion properties - Stabilizes emulsion	- Limited solubility - Quality depends on the source variation - Inflammatory response	Days to weeks by ion exchange	31
Agarose	Red algae or seaweed	- Highly stable in various pH levels - Forms a strong elastic gel - Biocompatibility - Controlled release	- Temperature sensitive - Limited drug loading - Complex extraction process	Weeks to months	32
Albumin	Protein found abundantly in blood plasma	- Biocompatibility and Non-Immunogenicity - Controlled and targeted delivery - Highly abundant - Good water solubility - Non-cytotoxic	- Less stability - Prone to denaturation	Hours to days	33
Elastin	Structural protein found in connective tissues of animals	- Biocompatibility - Good elastic properties - Biodegradability -Forms a thermally stable hydrogel	- Low drug loading - Difficult to modify	Weeks to months	34
Silk fibroin	Cocoons of the silkworm	- Thermal stability - Good mechanical strength - Biocompatibility - Stimuli responsive - Controlled degradation	- Immunogenic response - Less availability	Months to 1 year (tunable)	35
Collagen	Protein in the human body	- Biocompatibility - Low immunogenicity - Good mechanical properties - Good cell adhesion - Abundant and easily accessible	- Low stability - Variation from the source - Low solubility	~3 to 12 weeks	36 and 37
Gelatin	Hydrolysis of collagen	- Biocompatibility - Biodegradability - Non-immunogenic - Great stability - Easily accessible - Easy modification at the isoelectric point	- Fast degradation in the body - Poor mechanical properties	Hours to days	4

Table 2 Various types of synthesized polymers in drug delivery, their sources (monomer), advantages, and disadvantages

Polymers	Sources	Advantages	Disadvantages	Degradation time	Ref.
Poly Glycolic Acid (PGA)	Polymerization of glycolide	- Biodegradability - High mechanical strength - High crystallinity - High melting point - High stability	- Fast degradation rate - Premature drug release - Low biocompatibility - Hydrophobicity	~60 to 90 days	38
Polylactic acid (PLA)	Polymerization of lactic acid from corn	- Slow degradation - Controlled release - Good mechanical properties - Biocompatibility	- Low thermal stability - Hydrophobicity - Accumulation of acid byproduct	Months to years	39
Poly(lactic-*co*-glycolic acid) (PLGA)	Co-polymerization of PLA and PGA	- High stability - Low toxicity - Biocompatibility - Biodegradability	- Accumulation because of long circulation in the body	50 : 50 1 to 2 months 75 : 25 4 to 5 months	39 and 40
Pluronic F127 (PF127)	Triblock copolymer of poly (ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide)	- Thermal responsivity - Biocompatible and low toxicity - Good water solubility - *In situ* gel formation - Controlled and sustained release of the drug	- Poor mechanical strength - Accumulation in the body	Non-biodegradable *in vivo*	41
Poly(ethylene glycol) (PEG)	Polymerization of ethylene oxide.	- High water solubility - Increase circulation - Biocompatible and Non-immunogenic - Enable controlled and targeted delivery	- Slow degradation - Could cause an allergic reaction	Months to years	42 and 43
Poly(*N*-isopropyl acrylamide) (PNIPAm)	Radical polymerization of *N*-isopropyl acrylamide monomers	- pH-responsive characteristics - Zero-order drug release patterns - Gel formation close to body temperature - Controlled release - Biocompatible	- Limited stability - Potential cytotoxicity - Slow degradation	Non-biodegradable *in vivo*	44
Polyacrylic acid (PAA)	Radical polymerization of acrylic acid	- Controlled delivery of proteins and peptide drugs - Response to basic pH - Suitable for drug release in the intestine - Mucoadhesive properties	- Non-biodegradable - Poor structural integrity - Potential tissue irritation	Non-biodegradable *in vivo*	45
Poly(*N*,*N*-dialkylaminoethyl methacrylate) (PDAEMA)	Polymerization of *N*,*N*-dialkylaminoethyl methacrylate.	- pH-responsive polymer - Bind a negatively charged molecule - Good drug loading - Reversible swelling properties	- Limited biocompatibility - Non-biodegradable - Accumulation and cytotoxic	Non-biodegradable *in vivo*	46
Poly(2-hydroxyethyl methacrylate) (PHEMA)	From 2-hydroxyethyl methacrylate monomers.	- High water retention capacity - Biocompatibility - Good hydrophilic properties - Form a stable structure matrix	- Not biodegradable - Potential monomer leaching - Potential cytotoxicity	Non-biodegradable *in vivo*	44
Polyethylenimine (PEI)	Polymerization of ethylenimine monomers	- Enhance cellular uptake of drugs - Provide endosomal escape for drugs - Essential for gene delivery - High drug loading	- High cytotoxicity - Non-biodegradable - Low biocompatibility	Non-biodegradable *in vivo*	47

Table 2 *(Contd.)*

Polymers	Sources	Advantages	Disadvantages	Degradation time	Ref.
Poly(*N*-(2-hydroxypropyl) methacrylamide) (PHPMA)	*N*-(2-Hydroxypropyl) methacrylamide monomers.	- Good water solubility - Biocompatible - Easy modification for controlled release - Non-toxic and non-immunogenic	- Non-biodegradable - Low drug loading capacity	Non-biodegradable *in vivo*	1
Eudragit	From various acrylic and methacrylic acid esters	- pH-responsive polymer - Controlled Release - Good stability	- High production cost - Non-biodegradable - Cytotoxicity - Low bioactivity	Non-biodegradable *in vivo*	48
Poly caprolactone	Ring-opening polymerization of ε-caprolactone, which is chemically derived from petroleum sources.	- Good rheological properties - Good mechanical properties - Biocompatible - Slow degradation for controlled release - Very flexible	- Hydrophobicity - Poor cellular adhesion properties	~2 to 4 years	49
Dendritic Polymers	Synthesized through step-growth polymerization to form a highly branched structure	- High drug loading capacity Precise and controlled molecular weight - Targeted delivery	- Very complex to synthesize - High production cost - Potential cytotoxicity	Varies by chemistry	50

easily disintegrated or excreted by the body, is crucial to avoid long-term accumulation and potential toxicity of drug carriers. Highly biodegradable polymers, such as PLA, PGA, and PLGA. These polymers have wide application in biomedical sciences, especially in drug delivery, tissue engineering, and wound healing. They degrade through hydrolysis of their ester bonds into their monomer unit (lactic acid and glycolic acid), which the body degrades or metabolizes naturally.[12] The degradation rate of PLGA can be precisely tuned by adjusting the ratio of PLA to PGA, providing a valuable engineering strategy for controlling both polymer breakdown and drug release.[40] The PLGA polymer is the only FDA-approved biodegradable polymer for biomedical applications. The controlled release of drugs is influenced by their excellent degradation properties, which can be adjusted by the ratio of PLA to PGA monomers.[52] Studies have demonstrated the effectiveness and biodegradability of PLGA nanoparticles in delivering anticancer agents, which minimizes the risk of long-term toxicity. In microsphere technology, PLGA is frequently used to enable long-term, regulated delivery of drugs for a variety of diseases.[53]

3.3 Versatility

Polymers used as excipients are versatile because of their ability to adapt to various therapeutic needs, such as the type of drugs they carry, the release profile of drugs, and the routes of administration. Most of these polymers can be designed to encapsulate hydrophobic and hydrophilic drugs as well as macromolecules in the form of proteins or nucleic acids.[54] Another versatile ability of polymers is their ability to be formulated in different forms to fit the desired method of administration. These polymers can be formulated into micelles, implants, nanoparticles, hydrogels, and microparticles.[55] This characteristic of polymers allows them to be used in various diseases, including cancer, diabetes, neurodegenerative diseases, wound healing, cardiovascular disease, and infections. Chitosan polymer as microparticles and nanoparticles has been reported for its usage in oral, nasal, and transdermal drug delivery, indicating its versatility.[56] Negut *et al.* highlighted the potential of carrier imaging moieties for cancer theragnostic and emphasized the versatility of polymeric micelles in the delivery of lipophilic drugs and proteins for effective cancer treatment.[57] Another study reported the versatile flexible PEGylated micelles that could integrate mucosal penetration and intestinal targeting for the drug paclitaxel for effective oral delivery.[58]

3.4 Controlled and targeted drug release

The primary advantage of polymeric drug delivery is the ability to control the rate and location of drug release. Polymers also ensure drug release specifically at the disease's target, thereby reducing side effects in other tissues in the body. Controlled release of drugs encapsulated in polymers allows drugs to be delivered over extended periods, thereby improving patient compliance and therapeutic efficacy.[59] The physicochemical properties of these polymers enable them to achieve this feat. Polymers like chitosan, PLGA, PEG, and poly(methyl acrylate)

(PMA) have the features of responding to variations in the biological system, such as PH, temperature, enzymes, or immune cells.[60] This allows polymers to form a delivery system that responds to variation, releases drugs in a controlled manner, and targets specific tissues.[61] Aside from response to biological parameters, polymeric nanoparticles can also be functionalized with ligands to bind cell receptors and enable targeted delivery, especially in cancer therapy.[62]

4. Formulation of polymeric drug delivery

In the development of polymeric drug delivery systems, pharmaceuticals are incorporated into or onto polymers to regulate their release, enhance stability, and improve targeting precision. Various forms of polymeric drug formulations and delivery systems are depicted in Fig. 2. Detailed explanations of some formulation techniques are discussed in the following subsections.

4.1 Interfacial polymerization

The process involves two reactive monomers soluble in two immiscible solutions, such as oil and water; the two monomers are brought together to form an interface where polymerization occurs, creating a thin film of polymer. The resulting polymer film entraps the drug in solid or liquid form within its membrane to serve as a capsule or shell for the drug.[63] The polymer formed at the interphase can also be optimized to control drug release by degradation or diffusion. Interfacial polymerization can be applied to produce nanofiltration membranes (NFM), which can be used in drug delivery devices for selective filtration of therapeutic agents. For example, piperazine and trimesoyl chloride can undergo interfacial polymerization to form thin-film composite membranes used in nanofiltration.[64] The controlled nature of this technique allows the creation of drug carriers with desired thickness, permeability, porosity, and strength, which optimize them for specific drug release profiles.[65]

4.2 Solvent evaporation

This formulation is accomplished by using a volatile organic solvent to dissolve a biodegradable polymer. Drugs are then dispersed into this polymer solution to form a suspension, which is subsequently emulsified in an aqueous phase.[66] The organic solvent in the solution is removed through evaporation at high temperatures or with continuous stirring, leaving solid particles with the drugs encapsulated. The drug loading capacity and the particle size of the polymer are determined by the composition of the solvent, stirring speed, and evaporation conditions. This method of formulating polymer drug delivery is simple and offers great drug-loading efficiency.[67] Biodegradable polymers such as poly lactic-*co*-glycolic acid (PLGA) or polycaprolactone (PCL) are frequently used in this method to encapsulate hydrophobic drugs, which protect them and regulate their release over time.[68] Solvent evaporation is a very useful technique for creating controlled or sustained release drug delivery systems. For instance, nanoparticles produced from solvent evaporation were used to deliver anti-cancer therapy in a controlled manner, which reduces adverse effects and enhances therapeutic efficacy.[69]

4.3 Solvent casting

The solvent casting method is particularly used in transdermal drug delivery systems (TDDS) because it is a simple and common method for producing thin polymeric films.[70] In this procedure, a solvent is used to dissolve the drug and polymer, and the solution is spread onto a level surface (a glass or metal plate). The solvent is then evaporated to produce a thin polymeric layer that contains the drug.[71] Drug-loaded patches can be developed using this technique because it gives exact control over the drug distribution and film thickness.[66] Biocompatible and flexible polymers are typically used, which include: hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and chitosan.[72] Solvent casting is an effective technique for producing thin films with a consistent drug load, and it is a preferred method for producing buccal films, wound dressings, and transdermal patches. Enhancing the mechanical properties of thin films involves incorporating stabilizers and plasticizers in the formulation.[73] A recent study reported a solvent-casting technique in formulating collagen and Carboxymethylcellulose into a novel film for wound healing.[74]

4.4 Nanoprecipitation

Nanoparticles are created with desired characteristics and function using this simple and cost-effective method called nanoprecipitation. In this formulation technique, the polymer and drug are mixed in an organic solvent (ethanol or acetone), then the resulting polymer–drug solution is mixed again in an aqueous solution (water).[75] Upon mixing with water, the polymer precipitates out of the solution and traps drugs within the nanoparticle structure in a controlled and reproducible manner without surfactants or high-shear force methods like ultrasonication.[76] This method has important features in drug delivery, such as consistent nanoparticles with uniform size distribution and encapsulation of hydrophobic and hydrophilic drugs to generate polymeric nanoparticles.[76] Nanoprecipitation relies on diffusion and solvent exchange. The rapid solvent diffusion at the interface of the solvent and water gives rise to defined and functional nanoparticles. In 2020, a study reported a new sequential nanoprecipitation technique to load PEG-PLGA with ketamine for sustained release.[77]

4.5 Emulsion method

The emulsion is a common technique for preparing drug-loaded particles like microparticles and nanoparticles. In a polymeric drug carrier, the polymer and drug are mixed with an organic solvent, which typically forms an oil-phase solution; the aqueous solution is formed by water and an emulsifying agent.[78] The method here involves the mixture of the two

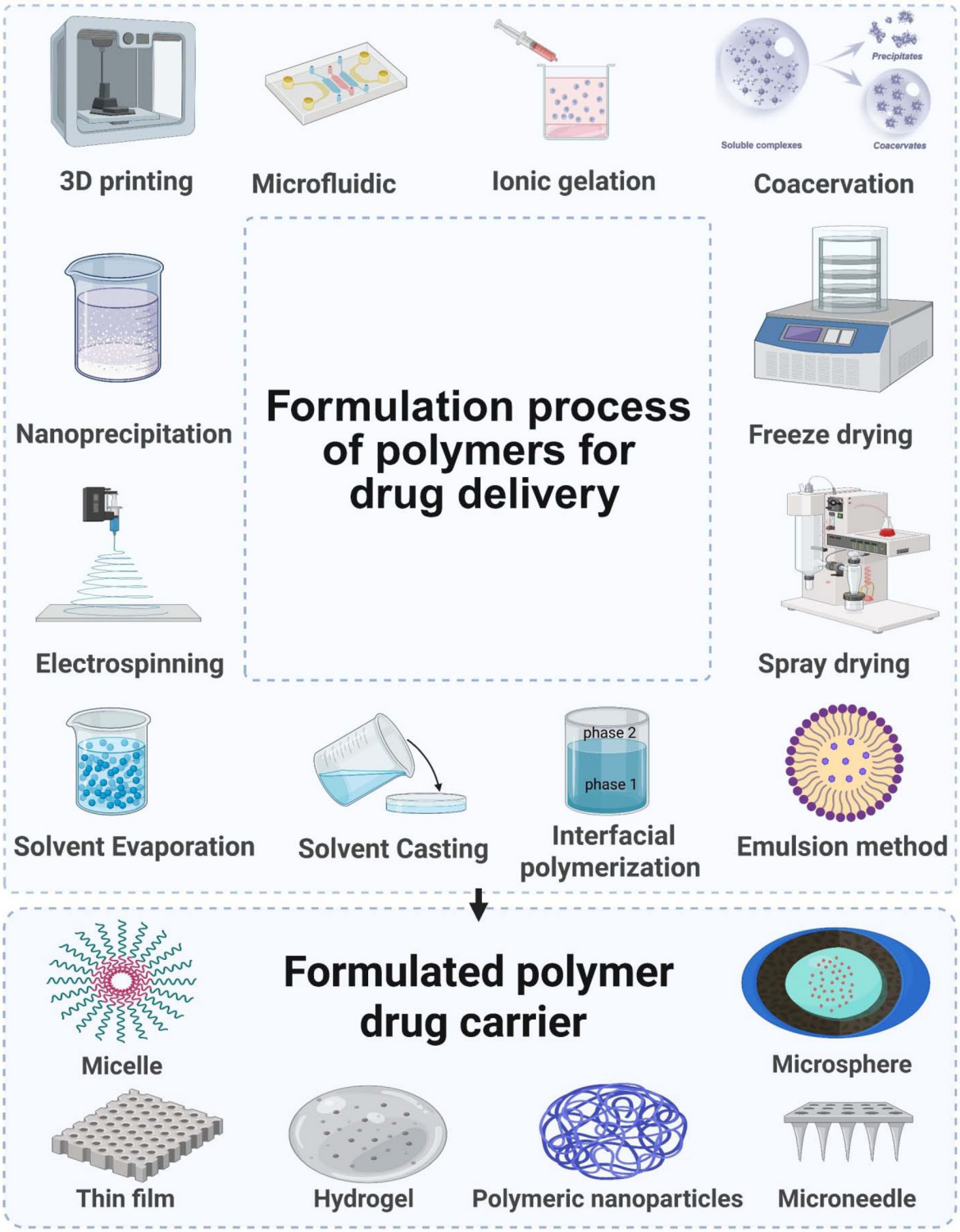

Fig. 2 Formulation processes of polymers for drug delivery and their resulting drug carriers. Various techniques are used to formulate polymer-based drug delivery systems, including 3D printing, microfluidics, ionic gelation, coacervation, freeze-drying, spray-drying, emulsion methods, interfacial polymerization, solvent casting, solvent evaporation, electrospinning, nanoprecipitation, and ultrasonic-assisted techniques. These processes yield various polymer-based drug carriers, such as micelles, thin films, hydrogels, polymeric nanoparticles, microspheres, and microneedles, enabling controlled, sustained, and targeted drug release.

immiscible solutions to form one homogenous solution with the addition of a surfactant or emulsifier to stabilize it under high-speed stirring or sonication that forms an emulsion of small droplets.[79] There are two types of emulsion: single emulsion (Oil-in-Water, O/W) for encapsulating hydrophobic drugs and double emulsion (Water-in-Oil-in-Water, W/O/W) used for trapping hydrophilic drugs.[78] Solid polymeric particles encasing the drugs are created when the organic solvent in the droplets evaporates under low pressure or mild heating. Similar steps are taken with two aqueous phases in the double emulsion to stabilize the water-in-oil droplets further. The drug-loaded microparticles or nanoparticles are gathered after centrifugation or filtration to remove remaining solvents and surfactants.[79] A study used a non-aqueous emulsion method to encapsulate cisplatin with PCL to enhance drug release kinetics.[49]

4.6 Ionic gelation

It is a phenomenon where ionic polymers (anions) react with oppositely charged molecules (cations) through crosslinking, thereby creating structured physical materials such as films, beads, hydrogels, and nanoparticles. Ionic gelation is one of the techniques for encapsulating biomolecules like proteins, peptides, and nucleic acids due to their inherent charge.[80] Electrostatic interactions between a polymer with ionic (often negatively charged) functional groups and a counterion or ionic cross-linker with the opposite charge cause the polymer chains to aggregate, forming a gel network or particle that can encapsulate the drug. Ionic gelation can be achieved with internal, external, or inverse gelation techniques. In the external method, the polymer solution is infused into a crosslinking solution, which causes an instantaneous gel formation and a quick sol–gel transition.[81] Internal gelation is also called *in situ* gelling, and it is frequently applied while preparing polymer particles. The insoluble calcium salt ($CaCO_3$ or $CaSO_4$) is mixed with the polymer solution, and the mixture is then extruded into an acid crosslinking bath. The polymer forms a gel network as a result of the calcium salt being more soluble and expelled due to the unstable circumstances. Optimizing this technique involves adjusting the gelling medium's pH and the quantity of calcium ion donors used.[80] In reverse gelation, the polymer solution is mixed with a medium that contains gelling agents. Small amounts of ionic polymers are used in this process to create the soft molecular shell that encapsulates the drugs.[81]

4.7 Microfluidics

This formulation method in polymeric drug delivery involves precise fluid manipulation at the microscale level using only a few micrometers-wide channels. This method is ideal for developing drug delivery systems with consistent size, shape, and composition, as it involves a highly regulated manufacturing process for polymeric nanoparticles and microparticles.[82] Drugs can be trapped in tiny particles created by microfluidic procedures using microscale channels and droplets. The process involves two or more immiscible liquids (such as water and an organic solvent), which are pushed through small channels of a conventional microfluidic device to create a desired particle size.[83] Optimizing the size and encapsulation efficiency of the polymer particles is achieved by carefully regulating the flow rates and channel dimensions. The organic solvent used is mainly to dissolve the drugs and polymer, which form the dispersed phase in the microfluidic inner channel. In the microfluidic device, the drug–polymer solution is injected with a continuous phase, which is usually an aqueous phase that contains a stabilizer or surfactant. This continuous phase surrounds and stabilizes the droplets that the drug–polymer solution forms. The drug–polymer solution is broken up into uniform droplets by capillary or shear pressures at the junction of the immiscible phases inside the microfluidic device.[84]

4.8 Coacervation

This is a phase separation method in which the drug and polymer precipitate as coacervate droplets. These polymer droplets subsequently coat the drug, forming microcapsules or nanocapsules. This technique is a very effective and flexible method for encapsulating large molecules like proteins and peptides into microspheres or nanoparticles of polymers.[85] It is divided into two primary categories: simple coacervation and complex coacervation. Simple coacervation involves altering the solution's parameters, which is usually done by adding a non-solvent, adjusting the pH, or adjusting the temperature to cause a single polymer to undergo phase separation. The polymer then creates a covering or shell around the drug by forming coacervate droplets.[86] Gelatin, PVA, and PLGA are examples of frequently used polymers. Two oppositely charged polymers are employed in complex coacervation; these polymers undergo phase separation when mixed because of electrostatic interactions. The drug is encapsulated by the coacervate phase that forms when the two polymers precipitate due to their electrostatic affinity. Gelatin, a positively charged protein, and gum arabic or alginate, which are negatively charged polysaccharides, are common polymers employed in complex coacervation.[86]

5. Mechanism of drug release in polymeric system

This refers to the drug release kinetics in polymeric drug carriers. The mechanism and rate of drug delivery depend on the intrinsic properties of the polymers and the interaction of the physiological fluids in the body. The different types of controlled release for polymeric drugs are discussed in the subsequent section. In Fig. 3, various mechanisms for polymeric drug delivery are illustrated with different types of polymers involved in each mechanism.

5.1 Diffusion controlled release

Diffusion represents a mass transfer process propelled by the dynamics of a concentration gradient. In a delivery system gov-

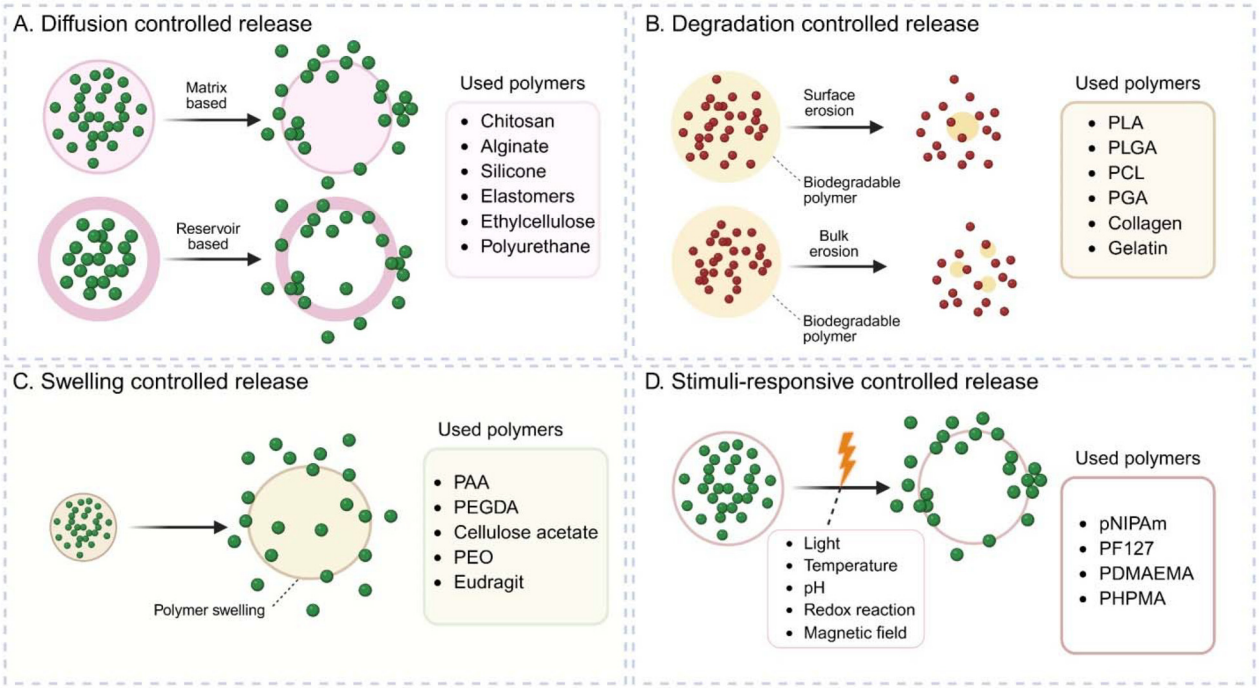

Fig. 3 Mechanism of polymeric drug delivery system. Illustration of the diffusion control mechanism in some polymeric drug delivery and some polymers used (A). The control mechanism in some polymeric drug delivery systems and some polymers used (B). Depiction of the swelling and osmotic-controlled mechanism in some polymeric drug delivery and some polymers used (C). Lastly, the illustration of a stimuli-responsive mechanism in some polymeric drug delivery and the polymers involved (D).

erned by diffusion control, the kinetics of diffusion for a drug molecule become the main factor determining how quickly the drug is released. The concentration gradient between the inside of the delivery system (high concentration) and the outside environment (low concentration) drives this diffusion process.[87] In a matrix-based polymeric release system, the drug may be dispersed or dissolved within the polymeric matrix, and the presence of the drug already dissolved within the matrix may result in an initial burst release from the surface. Moreover, the average diffusion distance before release lengthens over time in polymer matrix systems.[5] Conversely, in a reservoir system, the release rate is dictated by the diffusion process through the polymeric membrane that encases the drug-saturated core. Pharmaceutical compounds may exist in a dispersed or dissolved state within the reservoir. A steady concentration gradient is upheld across the membrane until the reservoir is exhausted, ensuring zero-order release kinetics. The limitation of this reservoir system is the risk of unfavorable dose dumping if the membrane is damaged.[88] The permeability of polymers in relation to drug delivery is crucial for the efficacy of both matrix and reservoir-based controlled release systems.[89] The diffusivity is influenced by various factors, including temperature alterations, the polymer matrix's composition, especially if additives are present, the molecular weight of drugs, and the presence of water molecules. This release mechanism is modelled by Fick's first and second laws of diffusion, and solving these equations can provide an estimate of drug diffusion in a polymer.[89] The formation of a sustained release profile, which results in prolonged absorption and comparatively constant plasma concentrations throughout time, is the main pharmacokinetics (PK) effect of diffusion drug delivery systems. The sharp peaks and troughs connected with immediate-release dosage are avoided. The peak concentration (*C*max) is decreased, and the time above the minimum effective concentration is prolonged when the drug level is more stable.[73] Clinically, this results in better patient compliance and fewer dose administrations. Moreover, maintaining stable medication levels in terms of pharmacodynamics (PD) frequently results in more consistent therapeutic outcomes with a lower likelihood of concentration-related side effects. High transient peaks that can cause toxicity are reduced when plasma levels are sustained.[90]

5.2 Degradation controlled release

A drug molecule incorporated in a degrading polymer matrix is only released when the matrix undergoes hydrolytic disintegration. Polymer matrix degradation is influenced by water penetration rate and the rate of hydrolytic cleavage.[91] One of the advantages of degradable matrices is their capacity to deliver substantially large macromolecules through an implantable system.[4] Surface erosion behavior is observed when water cannot easily infiltrate the matrix (such as polyanhydrides). Quick water penetration into the matrix, more than the degradation rate, will lead to bulk erosion and the collapse of the polymer network.[12] For some polymers, such as PLA and PLGA, the acidic degradation products stimulate hydrolysis, resulting in autocatalytic degradation. The kinetics of con-

trolled release from a degradable system can be effectively attained through the appropriate structural design of polymers. A rectangular design surface of a degradable polymer matrix exhibits approximately zero-order release.[92] This degradation release introduces a time-delayed response, which significantly increases the drug duration in the body, typically from days to months, and modifies the PK profile. The rate of polymer disintegration becomes a limiting factor for drug release, and pharmacokinetically, a medication administered through a degrading polymer (like PLGA microspheres) usually shows a multi-phase release: a diffusion-driven first phase, followed by a sustained zero-order or first-order release controlled by polymer erosion.[10] This frequently leads to a longer drug's effective half-life and prolonged plasma level maintenance. One common example is injectable PLGA depot formulations for peptides, such as monthly depot injections of risperidone or leuprolide, which produce therapeutic levels from a single dose for weeks.[93] The benefit of PD is evident; patients receive continuous therapy without a daily dose, managing symptoms and significantly enhancing compliance and quality of life.

5.3 Swelling controlled release

Swelling-controlled drug release systems employ polymers that expand when exposed to physiological fluids or water. The drug can migrate out of the polymer matrix as the polymer swells. The drug release rate depends on the polymer enlargement rate and the drug's capacity to diffuse through the swollen polymer.[94] The mechanism of drug release through swelling applies to both crosslinked polymer networks, like hydrogels, and polymer matrices. Drugs are dispersed or dissolved in a polymer matrix with restricted diffusivity. The polymeric matrix changes volume due to the solvent penetration when surrounded by a suitable solvent.[95] Solvent penetration into the polymer network is influenced by forces such as entropy changes, osmotic stress, ionic interactions, and hydrophilic/hydrophobic interactions, which result in dissolution, disentanglement of the polymer network, and polymer enlargement.[1] In the case of a crystalline polymeric network, water penetration causes a transition from a glassy state to an expanded elastic state, which is referred to as a gel. The expansion in polymer volume creates gaps between polymer chains, which increase the mass flow of the solvent and the drug diffusivity. Drug release caused by dynamic swelling from a polymeric system can be effectively controlled by incorporating crosslinks, additives, and amorphous polymers.[96] Another controlled release mediated by osmosis is another mechanism in drug delivery that resembles the swelling controlled. It is mostly used in osmotic pumps; the device's main compartment consists of a drug and an osmogen enclosed by a semipermeable membrane.[97] The membrane permits the inward flow of the solvent exclusively, driven by the osmotic gradient. The inward flow of the solvent facilitates the dissolution of the drug molecules, which are subsequently released from the system under hydrostatic pressure at a consistent rate through an orifice within the system.[98] The PK profile of a swelling-controlled release may show an initial lag phase followed by a continuous release phase. This technique is particularly useful for site-specific release or delayed commencement of the drug. For instance, certain oral hydrogel-based formulations will remain compact in the stomach and only swell to release medications when they reach the intestine with a higher pH, thereby effectively delaying absorption until the drug reaches the target.[90] The delayed release translates to a shifted *T*max (time to peak concentration) and concentrates drug effects where needed, which improves local PD while sparing the effect of the drugs on other sites.[97] Although a critical study reveals a major challenge, which is the initial burst that creates a surge in drug levels that deviates from the intended release profile when a significant portion of the drugs is present close to the polymer surface. Because of the early delivery of an excessive amount of drugs, this burst may jeopardize safety or efficacy. Researchers have developed strategies to reduce this, such as increasing cross-linking density, adding diffusion barriers, or utilizing multilayer coatings to limit the initial burst.[99]

5.4 Stimuli responsive release

In this controlled delivery system, polymers used are termed smart polymers because they can undergo a structural or chemical change in response to the stimulus. These polymer matrices are designed to respond to specific triggers such as temperature, pH, light, redox, and magnetic field. Drugs are released when these polymers come into contact with the favorable stimulus.[11] The impact of pharmacokinetics on stimulus-responsive release is often linked to the spatiotemporal control of drug release, which influences the place and time of drug action with high specificity. This consequently improves PD because the drug is delivered at the right time and site, thereby maximizing therapeutic effect and minimizing off-target actions.[100]

5.4.1 pH sensitive release. The pH gradient within human intracellular and extracellular spaces has been investigated for controlled drug release in targeted organs, intracellular components, or environments linked to specific pathologies. Typically, these drug carriers are synthesized using polymers that contain ionizable functional groups. These polymers undergo conformational or solubility changes in response to variations in environmental pH, leading to the decomposition or degradation of the polymer, thereby releasing the drugs entrapped.[101]

5.4.2 Temperature-sensitive release. The rapid metabolic activity and cell proliferation in inflamed tissues cause tumors and other inflammatory disorders to have different temperatures, which can benefit controlled release. Heat-responsive polymers, such as hydrogel, can alter their physical and chemical properties in response to heat, releasing drugs when drug carriers undergo a small temperature change. Exogenous factors can change the temperature in certain areas of the body in addition to the temperature changes caused by diseased tissue.[102] Different temperatures can cause structural changes in polymers, which can change their solubility or hydrophobicity. Below a certain temperature, they become hydrophilic, and above a certain temperature, they become hydrophobic.[103]

5.4.3 Light-sensitive, magnetic-sensitive, and redox-sensitive release. These drug delivery systems ensure that the medicine is only released when activated by an external radiation source, which provides exact control over the time and position of the triggered event. The polymers used to create this delivery system must have functional groups that are sensitive to light or radiation in order to cause conformational changes in the structure and guarantee a successful release of medicine. The external light source must not be harmful to the surrounding cells in *in vivo* application.[103] In a magnetic sensitive response, the polymer is conjugated with magnetic nanoparticles. The delivery system comprises a core–shell structure containing magnetic nanoparticles enveloped by polymers. Permanent or alternating magnetic fields are necessary for drug release, and they can be modified based on the particular application requirements. The time and repeated release of charge doses from the delivery can be controlled with the help of alternating magnetic fields, and it is mostly applied in thernostic applications for diseases.[104] Certain drug delivery systems integrate redox-sensitive functional groups such as disulfides and ferrocenes. The functional groups can respond to variations in redox potential and cause modification to the overall polymeric structure that triggers drug release. Naturally occurring reducing agents, including glutathione, or the presence of reactive oxygen species like hydrogen peroxide, can facilitate the release of encapsulated or covalently modified drugs.[105]

6. Targeted drug delivery approaches

Targeted drug delivery aims to optimize the therapeutic efficacy of drugs by accurately administering them to the affected tissue

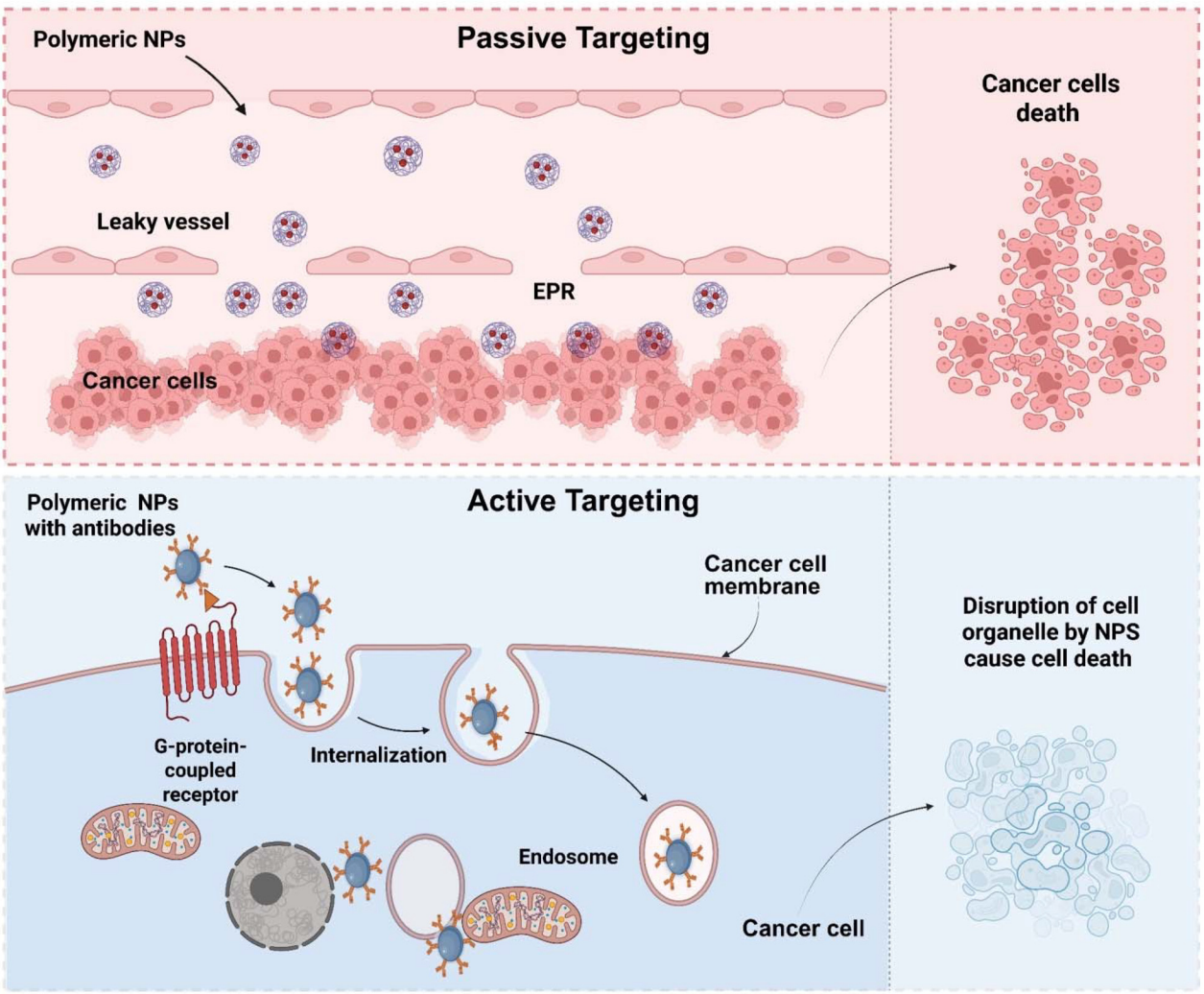

Fig. 4 Illustration of the passive and active targeting mechanisms of polymeric nanoparticles (NPs) for cancer treatment. In passive targeting, polymeric NPs accumulate in tumor tissues through the Enhanced Permeability and Retention (EPR) effect, where leaky blood vessels allow NPs to penetrate and concentrate around cancer cells, ultimately leading to cell death (up). In active targeting, polymeric NPs are functionalized with antibodies that bind to G protein-coupled receptors on the cancer cell membrane, thereby facilitating internalization *via* endocytosis. Once inside, the NPs are enclosed by endosomes, where they release their therapeutic payload, disrupting organelles and inducing cell death (down).

or cells, minimizing adverse side effects. This method can be categorized into three main types: passive targeting, active targeting, and nanoparticle-based systems. The primary objective is to overcome challenges such as systemic toxicity and limited bioavailability to provide regulated and localized medication release. The targeting mechanism is shown in Fig. 4.

6.1 Passive targeting

Drug-loaded nanoparticles accumulate at the target site through passive targeting, leveraging the unique physiological characteristics of specific tissues, particularly neoplasms. The Enhanced Permeability and Retention (EPR) effect is the most commonly utilized passive targeting technique.[106] Nanoparticles can infiltrate tumor tissue and persist longer than healthy tissues due to the tumors' often compromised vasculature and insufficient lymphatic drainage. The dimensions, morphology, surface characteristics of nanoparticles, and the local tumor microenvironment (such as pH and vascularization) are critical factors influencing passive targeting (Fig. 4-up).

6.2 Active targeting

In contrast to passive targeting, active targeting employs a significantly more advanced methodology. Antibody or ligand-conjugated polymeric nanoparticles that specifically bind to antigens generated by tumor cells are used for active targeting, as shown in Fig. 4-down. The active targeting technique utilizing ligand-conjugated nanoparticles emphasizes enhanced selectivity and efficiency in drug delivery.[107] Active targeting employs the interactions between targeting moieties and their corresponding receptors. These targeting moieties regulate the binding of the conjugated ligand to the tumor cells' variably expressed surface receptors. Furthermore, the many binding sites of the targeting moiety ensure enhanced biorecognition and receptor-mediated endocytosis.[108] Due to recent breakthroughs in molecular biology and genetic engineering, the utilization of antibodies as targeting moieties is often desired. Monoclonal antibodies are the predominant ligands utilized in active targeting techniques. The targeting moieties may include small compounds, peptides, carbohydrates, or antibodies, and the interactions facilitating active targeting can be categorized into three primary classes: ligand–receptor, antibody–antigen, and carbohydrate-lectin.[109]

6.3 Nanoparticle-based systems

Nanoparticle-based delivery systems have emerged as an efficient approach for targeted and precise drug delivery. Various types of nanoparticles, such as polymeric nanoparticles, liposomes, dendrimers, and metallic nanoparticles, are utilized to encapsulate and deliver drugs to the target organ. The distinct properties of each type mentioned above can be modified to optimize drug loading, release patterns, and targeting abilities. The bilayer structure (hydrophobic and hydrophilic layers) of liposomes facilitates controlled drug release.[110] Polymeric nanoparticles are engineered to be responsive to certain stimuli in the target environment, such as changes in pH, temperature, or light, providing a more regulated release of the therapeutic ingredient that eventually increases bioavailability.[106] The mechanism involved can be a stimulus-responsive controlled release or passive targeting.

7. Pharmaceutical application of polymers in drug delivery

The application of polymers in pharmacology is diverse, as they are used to treat various disease conditions. Polymers used for this application are formulated into microspheres, micelles, hydrogel, and thin film. With the advent of nanotechnology, natural or synthetic polymers can be modified into nanoparticle sizes ranging from 1 nm to 1000 nm. These modifications increase the surface areas of polymers that can encapsulate more hydrophobic or hydrophilic drugs.[111] Polymeric drug delivery has been applied in cancer treatment, antimicrobial resistance, and neurodegenerative disease, amongst others, as illustrated in Fig. 5. The applications of polymeric drug delivery illustrated in Fig. 5 are further discussed in detail in the following subsections, with examples from recent studies summarized in the accompanying Table 3. Evidence from *in vitro* and *in vivo* research highlights both the importance of polymer-based drug delivery and the continual innovations driving it forward.

7.1 Application in long-acting injectables

Polymers are essential in formulating long-acting injectables (LAIs), enhancing therapeutic efficacy by facilitating drug-controlled release over extended durations. Long-acting injectables (LAIs) can maintain drug levels within the therapeutic range over weeks or months, reduce dosing frequency, and enhance patient adherence.[93] To tackle contemporary drug delivery challenges, recent developments have focused on integrating novel polymer-based systems, including hydrogels, PLGA microspheres, and hybrid block polymers.[112] Polymeric Microspheres with PLGA-based delivery systems are the most often employed polymer in long-acting injectable formulations because lactic and glycolic acids generated during the degradation of PLGA are metabolically assimilated. The microsphere-based long-acting injectable formulations prolong therapeutic effectiveness by gradually releasing the active ingredient through diffusion and polymer degradation.[113] Injectable Hydrogels are highly hydrated polymer networks that form *in situ* hydrogels. These hydrogels, because of their shear-thinning properties, facilitate smooth injection and subsequent gelation within the body that is essential for drug delivery in complex tissues.[94] Another delivery system in LAI is the PEG-PLA block copolymers, which combine the biodegradability of PLA with the biocompatibility of polyethylene glycol (PEG) for intra-articular administration. Poor water-soluble drugs are improved for better solubility and bioavailability using these polymers.[114] Table 3 summarizes recent *in vitro* and *in vivo* research with these polymers.

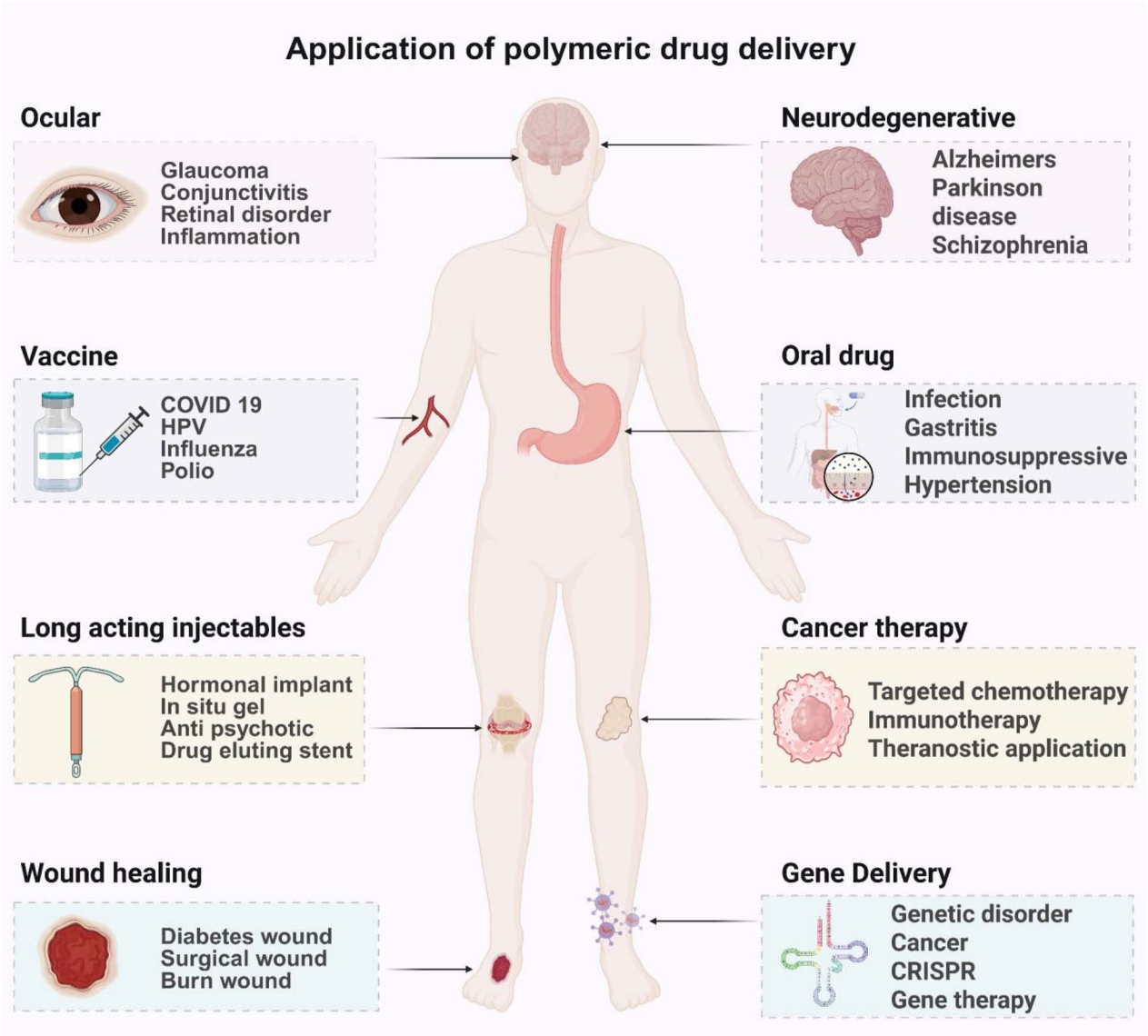

Fig. 5 Applications of polymeric drug delivery across various medical fields. Ocular delivery is used to treat glaucoma, conjunctivitis, retinal disorders, and inflammation with localized therapy. Neurodegenerative applications aid in managing Alzheimer's, Parkinson's disease, and schizophrenia through controlled drug release. By enhancing bioavailability, oral drug delivery improves therapies for infections, gastritis, immunosuppression, and hypertension. Cancer therapy utilizes polymeric carriers for targeted chemotherapy, immunotherapy, and theranostics, improving precision and minimizing side effects. Gene delivery applications include treatments for genetic disorders and cancer, as well as CRISPR-based gene editing. Long-acting injectables, such as hormonal implants and drug-eluting stents, ensure sustained drug release. Polymer-based vaccines enhance immunization for COVID-19, HPV, and influenza. Lastly, wound-healing applications address diabetic, surgical, and burn wounds, promoting tissue regeneration and controlling infection.

7.2 Application in wound healing

The wound healing process is complex and requires a regulated environment for optimal recovery. Polymeric materials enhance this process by controlling drug release, infection management, and cellular proliferation. Advanced polymers are employed in hydrogels, electrospun fibers, and nanoparticles to promote long-term healing.[115] Hydrogels for drug and moisture delivery. Hydrogels collect wound exudates and release encapsulated pharmaceuticals in a controlled manner. Electrospun nanofibers provide a scaffold for tissue formation and cellular migration. Growth factors like EGF incorporated with polycaprolactone (PCL) fibers have demonstrated the ability to improve tissue regeneration.[116]

7.3 Application in oral drug delivery

Polymeric drug delivery technologies are revolutionizing oral medication delivery by enhancing drug stability, bioavailability, and targeting efficacy. These approaches circumvent conventional oral drug delivery challenges, such as

Table 3 Recent research on the application of polymeric drug delivery

Applications	Polymers used	Loaded drugs	Formulation type	Diseases treated	Study type	Key findings	Ref.
Long-acting injectables	PLA, PLGA, PEG	Donepezil	Microspheres	Alzheimer's disease	*In vivo*	- Sustained drug release for two months - Improved therapeutic effects with reduced dosing frequency.	141 and 142
	PLGA	Ivacaftor	Microparticles	Cystic Fibrosis	*In vivo*	- Stable plasma concentrations over 28 days - Controlled drug release *in vivo*.	143
	Carboxymethyl cellulose (CMC) and hyaluronic acid	Ropivacaine	Hydrogel	Anesthetic delivery	*In vivo*	- Prolonged retention and drug release *in vivo* - Achieved sensory and motor blockage for 48 and 36 hours, respectively	94
	Pluronic F127, PEG	Dexamethasone	Hydrogel	Allergic rhinitis	*In vivo*	- Sustained release - Constant drug in plasma concentration	144
Wound healing	Sodium alginate and poly(*N*-vinylcaprolactam)	Rifampicin	Hydrogel	Wound Healing	*In vitro*	- Promoted wound closure and cell migration *in vitro* - Cytocompatibility and effective for wound healing.	145
	Fucoidan		Electrospun nanofibers	Wound Healing	*In vivo*	- Improved nanofiber diameter - Good water absorption capacity and entrapment efficiency - Significant potential for advanced wound dressing applications.	146
Oral drug delivery	Eudragit RS 100	Glibenclamide	Microspheres	Diabetes	*In vitro*	- Controlled and sustained release of glibenclamide. - Enhanced drug efficacy	147
	PLGA, Pluronic F127	Rifampicin	Microsphere	Tuberculosis	*In vitro*	- Showed suitable mucoadhesion property - Controlled release in simulated gastrointestinal conditions	148
Ocular drugs	Carrageenans	Echinochrome	Nanoparticles	Eye diseases	*In vitro*	- Enhanced stability of the drug - Prevent rapid elimination of drugs by tears - Prolonged retention and controlled release of the drug	149
	Poloxamer 407, Hyaluronic Acid	HPβCD-solubilized testosterone	*In situ* hydrogel	Ocular Disorders	*In vivo*/ *ex vivo*	- Enhanced ocular drug retention and reduced loss *via* sol–gel transition at physiological temperature	121
	PLGA-PEG	Anti-VEGF	Nanoparticles	Macular Degeneration	*In vitro*	- Sustained drug release - Reduces the frequency of intravitreal injections	150
Vaccine	PLGA	SARS-CoV-2 Spike Protein	Nanoparticles	COVID-19 Vaccine	*In vitro*/ *In vivo*	- Improved antigen stability and delivery to lymph nodes - Enhances vaccine efficacy	151
	Chitosan-Alginate	Influenza virus	Nanoparticles	Influenza vaccine	*In vivo*	- Elicited more robust immune responses by delivering antigens for 21 days	126
Cancer	PLGA	Paclitaxel	Nanoparticles	Cancer	*In vitro*/ *In vivo*	- Targeted delivery *via* the EPR effect - Reduced tumor growth - Lower systemic toxicity in murine models	58
	Chitosan	5-Fluorouracil	Nanoparticles	Cancer	*In vitro*	- Sustained drug release with enhanced cytotoxicity against cancer cells - Increased accumulation at the target site	152
	pH-Sensitive Poly (β-amino ester)	Camptothecin	pH-responsive Nanoparticles	Colon Cancer	*In vitro*	- An acidic tumor microenvironment triggered drug release, ensuring localized delivery and improved tumor reduction	153

Table 3 *(Contd.)*

Applications	Polymers used	Loaded drugs	Formulation type	Diseases treated	Study type	Key findings	Ref.
	PEG/PEI	Fludarabine	Hydrogels	Cancer	*In vitro*/*In vivo*	- pH-responsive release of 35% of the encapsulated drug in 24 hours at pH 4 - Sustained release increased cytotoxicity against cancer cells.	154
	Amphiphilic Polyurethane	Anti-cancer drugs	Nanoparticles	Breast Cancer	*In vitro*/*In vivo*	- The drug carrier disassembled in redox environments (GSH) due to polymer degradation - pH-responsive amine-facilitated targeted drug delivery in acidic tumor environments.	155
Antimicrobial resistance	PLGA	CiprofloxacinVancomycin	Nanoparticles	Antimicrobial Resistance	*In vitro*	- Enhanced efficacy against MRSA through anti-biofilm and antibacterial action. - Drug release for 168 hours	156
	Mixed Polymeric Micelles	Ciprofloxacin	Micelles	Antimicrobial Resistance	*In vitro*	- High encapsulation efficiency - Prolonged release and significant biofilm disruption against Gram-positive and Gram-negative bacteria	136
	Protein Polymer	Triclosan	Zwitterionic Micelles	Multi-Drug Resistant Bacteria	*In vitro*	- Micelles showed pH-sensitive charge transformation in acidic microenvironments. - Synergistic effect with lipase to enhance biofilm penetration	157
	Pluronic F127	Quercetin and Vancomycin	Micelles Functionalized with APTES	Antibacterial Resistance	*In vitro*	- Dual-drug micelle demonstrated prolonged release of quercetin and vancomycin for 168 hours	137
Neurodegenerative	PEG-PLGA	Fucoxanthin	Nanoparticles	Alzheimer Diseases	*In vivo*	- Improved BBB penetration - Reduced neuroinflammation - Inhibited β-amyloid aggregation	158
	N-Trimethyl Chitosan (TMC)	Green Fluorescent Protein (GFP)-Tagged Plasmid	Nanoparticles	Neurodegenerative Diseases	*In vitro*/*In vivo*	- Enhanced transfection efficiency - BBB crossing, better cell viability in brain cancer cells - Efficient *in vivo* targeting	159
Gene delivery	PLGA	siRNA	Nanoparticles	Gene Therapy	*In vitro*	- Improved stability and siRNA delivery to target cells - Demonstrated therapeutic potential in silencing genes	160
	Poly(β-amino ester)	Plasmid DNA	Nanoparticles	Gene Therapy	*In vitro*/*In vivo*	- Efficient binding with nucleic acids; enhanced endosomal escape - Stimuli-responsive degradation for targeted delivery	161
	PLA-*b*-PAPMA Diblock Copolymers	Nucleic acids	Cationic micelles	Gene delivery	*In vitro*	- Cationic micelles exhibited a low critical micelle concentration (CMC) - High stability, efficient nucleic acid condensation, and good transfection efficiency	129
	Hyaluronic acid, dextran, cyclodextrin	siRNA miRNA	Hydrogel	Gene therapy	*In vitro*/*In vivo*	- Controlled and prolonged release of siRNA - Enhanced therapeutic effects *in vitro* and *in vivo*	162

limited solubility, enzymatic degradation, and first-pass metabolism. Several essential concepts support the polymer-based oral drug delivery mechanism, including absorption enhancement, targeting, controlled release, and protection.[117] Polymers enable a regulated and sustained release mechanism, ensuring that a therapeutic drug concentration is preserved in the plasma for an extended duration. The small intestine exhibits a neutral to slightly alkaline pH range of 6 to 7.5, in contrast to the stomach, which maintains an acidic pH of 1.5 to 3.5.[16] Eudragit and other pH-sensitive polymers degrade in the alkaline medium of the small intestine, facilitating targeted release. Pharmaceuticals vulnerable to gastric degradation exhibit enhanced bioavailability through intestinal targeting.[48] Moreover, mucoadhesive hydrogels engineered from chitosan, hyaluronic acid, alginate, and gelatin can adhere to the mucous layer of the gastrointestinal tract due to their mucoadhesive properties and become better alternatives to conventional oral medication delivery.[25] The introduction of smart stimuli-responsive hydrogels particularly facilitates better-controlled drug release in oral.

Furthermore, the multi-layer delivery systems for sequential drug release using polymers to encapsulate multiple drugs or dosages and releasing them at different sites within the gastrointestinal tract or at distinct time intervals will improve patients' compliance and enhance quality of life. This approach ensures enhanced control over the drug's pharmacokinetics. Various polymers employed in constructing each layer dissolve at specific pH levels or durations, facilitating successive drug release. 3D printing is employed to create this drug distribution system.[118] An example is the encapsulation of probiotics with polysaccharide polymers, which facilitates intestinal colonization by safeguarding live probiotics throughout gastrointestinal transit.[119]

7.4 Application in ocular drugs

The eye's unique physiological barriers, including the corneal epithelium, tear film, blood-aqueous barrier, and rapid tear fluid drainage, complicate ocular pharmaceutical delivery. Polymeric systems have emerged as a promising strategy to enhance pharmaceutical retention, bioavailability, and controlled release within ocular tissues while ensuring improved therapeutic outcomes with reduced dosing.[120] Mucoadhesive polymers such as carrageenan and hyaluronic acid adhere to the mucus layer on the ocular surface by forming hydrogen bonds with mucin. This extends drug retention by reducing rapid elimination by tear clearance and improves the medication's therapeutic effect by facilitating a sustained release and fewer dosages.[120]

Another type of polymer in ocular drug delivery is *in situ* gels from ion-sensitive or thermo-responsive polymeric systems that remain liquid during application and transition to a gel upon contact with the ocular surface. This alteration prolongs the drug's retention time and reduces nasolacrimal duct discharge. At physiological temperature, thermo-responsive polymers, such as poloxamers, undergo a sol–gel transition. The liquid formulation reduces medication loss by transforming into a gel upon application to the eye.[121] Unlike conventional topical eye drops, nanoparticles and micelles are designed to traverse ocular barriers and provide drugs to deeper tissues such as the retina and choroid.[121] These nanosystems ensure effective therapeutic administration by improving pharmaceutical stability and solubility. Hydrophobic pharmaceuticals are enclosed and conveyed over the corneal epithelium by polymeric nanoparticles, including PLGA carriers.[122] Micelles enhance the delivery of lipophilic drugs by encapsulating them within their hydrophobic core, facilitating their passage across the lipid membranes of ocular cells.[122] Most recently, dendrimers have been used for enhanced drug loading capacity at the nanoscale, facilitating precise targeting and augmented drug loading capacity. Dendrimers, administered intravitally, offer a feasible therapeutic approach for retinal problems.[123]

7.5 Application in vaccines

Polymer drug delivery technologies are transforming vaccine development through alternative administration routes, enhanced immune responses, and regulated antigen release. Traditional vaccinations face challenges such as restricted immune activation, dependence on cold chain logistics, and antigen instability. Encapsulating antigens in biocompatible and biodegradable polymers allows effective solutions to overcome these limitations, ensuring continuous antigen release and targeted immune activation.[124]

The encapsulation and protection of antigens are among the primary objectives of polymer-based delivery methods, which are to prevent the degradation of antigens during storage and transportation. PLGA nanoparticles encapsulate antigens, preventing degradation and ensuring intact delivery to immune cells.[125] Before their release in the target location, pH-sensitive polymers, such as chitosan, ensure that the antigens are protected within the acidic environment of the stomach or nasal cavity.[126] The spike protein was protected from degradation by PLGA-encapsulated SARS-CoV-2 antigens, enhancing its distribution to lymph nodes and hence increasing the efficacy of the COVID-19 vaccine.[125] Polymeric systems mimic the natural infection process by delivering antigens in a controlled manner over time, enhancing and extending immune responses. Booster dosages are less essential as this regulated release promotes the development of memory T and B cells. Specific polymers, such as PLGA and chitosan, directly activate the immune system to function as adjuvants. This attribute enhances vaccination efficacy by augmenting both innate and adaptive immune responses. Chitosan nanoparticles enhance the mobilization of immune cells to the vaccination site by stimulating the synthesis of cytokines and chemokines. Due to these adjuvant properties, a reduced quantity of antigen is necessary for the formulation, hence decreasing production expenses.[127]

7.6 Application in gene delivery

Gene therapy, which involves injecting genetic material (DNA, RNA, or gene-editing tools) into cells, is promising for treating infectious diseases, cancers, and genetic disorders. Polymeric

drug delivery technologies, including nanoparticles, hydrogels, and micelles, have significantly advanced gene delivery due to their biocompatibility, non-virality, efficient encapsulation, genetic material protection, and targeted cell administration. Non-viral gene delivery vector development necessitates thoroughly investigating their intracellular and cellular absorption mechanisms to enhance selective cell attachment and internalization.[128] Catalytic polymers can solve problems like cytotoxicity and inadequate endosomal escape. Functionalized polymers can be applied to small interfering RNA, oligonucleotides, and plasmid DNA to increase gene expression. These carriers provide minimal immunogenicity, biocompatibility, *in vivo* biodegradability, and ease of integration.[129]

The core of polymeric micelles, composed of amphiphilic block copolymers, protects hydrophobic drugs or nucleic acids throughout circulation. Distributing siRNA or mRNA for targeted therapy.[129] Encapsulating nucleic acids or gene-editing components in hydrogels enables long-term genetic material delivery for targeted gene therapy and tissue regeneration in organs such as the liver and heart. Positively charged hydrogel forms an ionic interaction with negatively charged DNA or RNA to protect and control the release of nucleic acid. Genetic material can also be covalently attached to hydrogel polymers, and hydrophobic-modified DNA or RNA can be encapsulated in hydrogels' hydrophobic cores.[130]

7.7 Application in cancer

Polymeric nanoparticles (PNPs) have enhanced cancer treatment by increasing drug stability, targeted delivery, and therapeutic efficacy. Their revolutionary potential in oncology is demonstrated by drug release strategies and examples of successful *in vivo* studies. Polymeric nanoparticles are essential for the precise and efficient delivery of pharmaceuticals, so they are extensively used in contemporary cancer treatment.[131] Targeting tumor sites with leaky vasculature using PNPs can be customized to take advantage of the enhanced permeability and retention (EPR) effect, which allows nanoparticles to cluster preferentially in cancer tissues. Active targeting is achieved by functionalizing nanoparticles with ligands such as peptides or antibodies that bind to specific receptors overexpressed on cancer cells.[132] Polymers with stealth properties, such as polyethylene glycol (PEG), aid in avoiding immunological detection. Drug Release in Response to Stimulation PNPs can release drugs in response to internal cues such as pH, redox gradients, and enzymes in the tumor microenvironment. pH-responsive nanoparticles can release medicines in the acidic tumor microenvironment (pH ~3.5–6.8).[69,133]

7.8 Application in antimicrobial resistance

Antibiotic usage and abuse create multidrug-resistant (MDR) bacteria, generating antimicrobial resistance (AMR), a major global health concern. Polymeric nanoparticles offer a potential solution to this problem by enhancing drug administration, bypassing microbial resistance pathways, and disrupting biofilms.[134] PNPs designed for MDR Bacteria encapsulate antibiotics to ensure their delivery to the infection site and protect them from enzymatic degradation. Bacterial lysis and membrane breakdown are caused by cationic PNPs' electrostatic interactions with negatively charged bacterium membranes. PNPs enhance the efficacy of antibiotics at infection sites by releasing them in response to pH, temperature, or lipase activity.[135] Another type is the polymeric micelles that can encapsulate suitable antibacterial drugs, and their stability enhances their efficacy for bacterial and biofilm disruption. In a study shown in Table 3, mixed polymeric micelles (MPMs) recorded high encapsulation efficiency and prolonged release kinetics.[136]

In a 2024 study, the antibacterial effect of pluronic F127 polymer (FQA) was also reported for prolonged release of drugs for 168 h.[137]

7.9 Application in neurodegenerative diseases

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are particularly difficult to treat due to the complexity of the central nervous system (CNS) and the impermeability of the blood–brain barrier (BBB). Polymeric nanoparticles (PNPs) offer solutions to these challenges by providing controlled release, increased bioavailability, and targeted drug delivery.[138] PNPs, because of their small size, allow the delivery of drugs across the BBB through retention and absorption to brain capillaries, which increases PNP transport across endothelial cells. Functionalized PNPs use receptor-mediated transcytosis routes and low-density lipoprotein receptor-related protein (LRP) pathways to cross the BBB and increase the bioavailability of drugs. PNPs can successfully encapsulate hydrophilic and hydrophobic drugs, siRNA, CRISPR components, and growth factors, enhancing their delivery to the brain.[139] Chitosan is one of the polymers used extensively for neurodegenerative diseases because of its high entrapment, adsorption efficacy, mucoadhesive properties, and biodegradability, which increase its potential to cross the blood–brain barrier. For anti-AD research, *N*-trimethyl chitosan (TMC), a type of chitosan, has been used because the positive charges of TMC and anionic sialic acid glycoprotein present in the BBB undergo electrostatic interactions.[140] Recent studies on the polymeric application of neurodegenerative diseases are also given in Table 3.

8. Clinically established polymeric Drug delivery systems

Advancement in polymer drug delivery research is still very active, with many candidates in Phases I–IV clinical trials. Numerous active research studies seek to use polymers for longer-acting therapies, better solubility, or targeted drug delivery. Notably, polymeric delivery formats are being used to study both new therapeutic agents and reformulations of current medications.[163] This suggests that polymer administration is not only facilitating the development of new medications but also prolonging the life cycle of well-established drugs by improving their efficacy or extending their indications.[164] Table 4 shows a selection of polymeric drug delivery

Table 4 Recent research on the polymeric delivery system in clinical trials

Polymer formulation	Target drugs	Target indication	Trial phase	Trial ref
Chitosan nanoparticles	Miconazole	Oral thrush	Phase I	NCT06072716
Chitosan nanoparticles	Chitosan	Periodontal diseases	Phase I	NCT06525363
Hyaluronic acid	Sodium bicarbonate	Oral mucositis	Phase IV	NCT05818007
Pluronic	Amitriptyline 2%, ketamine 1%, and lidocaine 5%	Neuropathic pain	Phase III	NCT00798083
Poloxamer	Raltegravir	HIV infection	Phase I and II	NCT00485264
Polymeric Micelles	Docetaxel	Solid tumors	Phase II	NCT05254665
PEGylated Hyaluronidase (PEGPH20)	Pembrolizumab	Non-small cell lung cancer (NSCLC)	Phase I	NCT02563548
Chitosan hydrogels	Isosorbide Dinitrate	Diabetic foot ulcers	Phase III	NCT02789033
Poloxamer, gelatin, And chitosan	Mediclore	Breast cancer	Phase III	NCT02967146
Laxative polyethylene glycol	Probiotic clostridium butyricum	Irritable bowel syndrome	Phase II	NCT02254629

Table 5 Recent FDA-approved drugs with polymeric delivery systems for different applications

Polymer formulation	Product/drug	Therapeutic indication	FDA approval year	Delivery mechanism/action	Ref.
TransCon PEG-carrier prodrug	Yorvipath™ (palopegteriparatide-tgyl)	Hypoparathyroidism	2024	Slow release of drugs over 24 hours	167
PEGylated macrocyclic peptide	Zilbrysq® (zilucoplan)	Generalized myasthenia gravis	2023	Extended exposure to drugs	168
PEGylated aptamer	Izervay™ (avacincaptad pegol)	Geographic atrophy (AMD)	2023	Increased ocular durability of drugs	169
PEGylated enzyme	Elfabrio® (pegunigalsidase alfa-iabs)	Fabry disease	2023	Prolonged systemic $t_{\frac{1}{2}}$	170
PEGylated protein	Fylnetra® (pegfilgrastim-pbbk)	Neutropenia prophylaxis in cancer	2022	Extended $t_{\frac{1}{2}}$	171
PEGylated interferon (IFN)	Besremi® (ropeginterferon alfa-2b-njft)	Polycythemia vera	2021	Sustained IFN levels	172
In situ PLGA depot (ATRIGEL®)	Fensolvi® (leuprolide acetate, 45 mg)	Central precocious puberty	2020	~6-Month release	173
In situ PLGA depot (ATRIGEL®)	Perseris® (risperidone ER)	Schizophrenia (maintenance)	2018	Monthly *in situ* PLGA depot	174
PEGylated enzyme	Palynziq® (pegvaliase-pqpz)	Phenylketonuria	2018	PEGylated enzyme; prolonged exposure	175
PEGylated enzyme	Revcovi® (elapegademase-lvr)	ADA-SCID	2018	Extended $t_{\frac{1}{2}}$ and reduced clearance	176
PEGylated enzyme	Asparlas® (calaspargase pegol-mknl)	Acute lymphoblastic leukemia	2018	long-acting	177
PLGA microspheres (IA injection)	Zilretta® (triamcinolone acetonide ER)	Osteoarthritis knee pain	2017	Intra-articular PLGA microsphere depot	178
In situ PLGA depot (ATRIGEL®)	Sublocade® (buprenorphine ER)	Opioid use disorder	2017	*In situ* PLGA gel → solid depot; diffusion/erosion	179
GlycoPEGylated protein	Rebinyn® (nonacog beta pegol)	Hemophilia B	2017	Extended $t_{\frac{1}{2}}$	180
PEGylated protein	Adynovate® (rurioctocog alfa pegol)	Hemophilia A	2015	PEGylated FVIII; extended $t_{\frac{1}{2}}$	181
PLGA intravitreal implant (rod)	Ozurdex® (dexamethasone)	Macular edema/uveitis	2009	Biodegradable ocular implant; months-long release	182
PLGA microspheres (injectable depot)	Risperdal Consta® (risperidone)	Schizophrenia; bipolar disorder	2003	Biweekly PLGA depot; diffusion/erosion	183
PEG–protein conjugate	Pegasys® (peginterferon-α2a)	Hepatitis B/C	2002	PEGylation; extended systemic $t_{\frac{1}{2}}$	184
In situ PLGA depot (injectable gel)	Eligard® (leuprolide)	Prostate cancer	2002	Liquid-to-solid PLGA depot; slow erosion	185
PLGA microspheres (topical periodontal)	Arestin® (minocycline)	Periodontitis	2001	Local PLGA microsphere depot; sustained release	186

systems that are currently in clinical trials, spanning various stages and disease areas from the clinicaltrials.gov. Furthermore, some polymers are clinically established after going through rigorous research stages, which demonstrate their efficacy and safety in humans. Numerous drugs across multiple therapeutic areas are formulated with polymeric carriers or matrices, resulting in FDA-approved products that enhance efficacy and patient compliance. These include biodegradable microsphere injectables for sustained release, implantable polymer wafers for localized therapy, and polymer–drug conjugates that prolong circulation time.[164] In Table 5, we summarize some FDA-approved polymeric drug delivery systems. Each case highlights how polymeric formulations might enhance drug delivery, such as by lowering the frequency of doses, limiting systemic toxicity, or facilitating the administration of medications to locations that would otherwise be inaccessible.

According to these ongoing trials, polymeric drug delivery has been recognized by the clinical community as a critical channel for therapeutic advancement. Polymers are becoming increasingly important in drug delivery since they represent the basis of many next-generation medicines that aim to be safer, more effective, and more patient-friendly.[165] If current trials are successful, new FDA approvals for polymeric nanomedicines, especially in oncology, and long-acting injectable therapies for chronic disorders are anticipated in the coming years. Every success will encourage investment in novel polymers, such as biodegradable or stimuli-responsive materials that are appropriate for specific medical needs and help the validation of polymer techniques.[166]

These products' success demonstrates how polymeric delivery systems overcome important drawbacks of traditional drugs. By adjusting the polymer composition and framework, formulators can improve the pharmacokinetic and safety profile of drugs and achieve desired release profiles, ranging from immediate release to months-long release. Patients benefit from more consistent therapeutic effects, fewer injections (better compliance), and frequently fewer side effects.[187] Clinically, polymeric systems have made previously unattainable treatments possible, for instance, high-dose chemotherapy with decreased toxicity *via* PEG conjugates or direct brain chemotherapy. These achievements also support polymer science techniques, assuring investments in novel polymeric delivery technologies.

9. Barriers to clinical translation

A persistent translation gap separates the attractive laboratory science of polymeric drug delivery from clinical benefit. One of the critical considerations that can significantly impact therapeutic outcomes is the biocompatibility and potential toxicity of polymers used in drug delivery systems. Degradation products generated during polymer breakdown, as well as residual unreacted monomers from the synthesis process, may induce immunological responses, cytotoxicity, or chronic inflammation. These adverse effects are highly dependent on the polymer's chemical structure, molecular weight, degradation rate, and the nature of its byproducts. For instance, while polymers such as poly(lactic-*co*-glycolic acid) (PLGA) and polyethylene glycol (PEG) are widely regarded as biocompatible and produce non-toxic metabolites, other synthetic polymers may release acidic or reactive intermediates that could disrupt local tissue homeostasis.[188]

Another challenge is the *in vivo* efficacy in humans based on the drug release mechanism experimented on animals in pre-clinical studies. For instance, advanced delivery mechanisms, such as redox-sensitive polymers, typically require a uniform increase in intracellular glutathione (or oxidative stress) to release the drugs. However, human tissues vary greatly between patients and within lesions, thus accurate activation may be inadequate or occur at the wrong moment.[189] Magnetic-responsive systems, on the other hand, have a unique problem. The field strengths, gradients, and focal accuracy that work in rodents are difficult to replicate in humans without complicating the workflow or causing off-target heating. More so, they have a limited ability to accurately administer therapeutics to specific tissues or cells in complex biological environments. Currently, most advancements are confined to *in vitro* research, with few successful demonstrations *in vivo*. This limitation is particularly evident in challenging systems such as central nervous system (CNS) tumors, where precise targeting remains a significant obstacle.[190]

Manufacturing and scalability further present significant barriers to the widespread clinical adoption of polymeric drug delivery systems. Producing polymers with consistent drug loading efficiency, particle size distribution, morphology, and mechanical properties remains challenging and often cost-intensive. Variations in polymer batch quality can directly influence drug release profiles and therapeutic efficacy, necessitating stringent quality control during manufacturing. Advanced techniques such as microfluidic synthesis and process analytical technology (PAT) are being explored to improve reproducibility at industrial scales. Polymeric drug delivery systems face significant cost restrictions, as their development and manufacturing processes remain expensive, limiting their widespread availability.[191]

Storage and stability issues also remain major concerns, particularly for polymer systems encapsulating sensitive biomolecules such as proteins, peptides, and nucleic acids. Polymers may undergo hydrolysis, oxidation, or other degradation processes during storage, leading to a loss of structural integrity and therapeutic activity. Hydrogels can squeeze out water (syneresis), altering how fast drugs diffuse, and PEG–drug conjugates can lose their PEG chains or oxidize, thereby shortening half-life and changing exposure. Encapsulated pharmaceuticals are similarly vulnerable, with sensitive payloads potentially undergoing denaturation or aggregation. The selection of appropriate polymer matrices with high chemical and thermal stability, along with optimized formulation strategies such as lyophilization and the incorporation of stabilizing excipients, is crucial to preserve the functionality of both the carrier and the drug over extended storage periods.[188]

Regulatory evaluation for complex polymers is often a hurdle as they must overcome various regulatory hurdles related to safety, repeatability, and polymer degradation. Ensuring regulated release over time while attaining considerable medication loading without jeopardizing the polymer's stability. Agencies increasingly expect an evidence framework that connects material attributes to clinically relevant release and exposure, and not just empirical analogy. For instance, regulators want researchers to explain how the material properties (like molecular-weight distribution, end-group chemistry, residual monomers, and moisture) and the process conditions (like mixing and solvent removal) affect the microstructure, particle size, porosity, and phase separation, and how all that affects the clinically relevant release profile. These steps must be clear and not implied for long-acting injectables, implants, micelles, and polymer conjugates. One common mode of failure in regulation is empirical consistency without a mechanistic relationship to pharmacokinetics. Regulators demand credible evidence that relates *in vitro* release and structure to *in vivo* exposure.[192]

Additionally, these delivery systems encounter challenges related to complex pharmacokinetics. The *in vivo* behavior of polymeric carriers, including biodistribution, clearance, and interactions with biological barriers such as the liver and kidneys, is often unpredictable. This variability complicates the design of consistent and effective delivery platforms and poses hurdles for clinical translation.[190] More research on *in vivo* and preclinical studies is needed to accelerate the approval of previously discovered smart polymers. Furthermore, very sensitive smart polymers are being developed to release drugs in a controlled manner in response to certain stimuli such as pH, temperature, enzymes, or light. Multi-functional polymeric nanocarriers can deliver multiple therapeutic substances simultaneously, such as a drug or a gene-editing tool. Biodegradable and bioinspired polymers, such as alginate, chitosan, and silk fibroin, mimic the body's natural physiology. Customized healthcare for individual genetics by developing polymeric carriers based on each patient's clinical and genetic characteristics. Polymer design, drug loading, release kinetics, and targeting approaches are optimized using AI and machine intelligence.

10. Conclusion

Polymeric drug delivery systems represent a paradigm shift in therapeutic applications, combining material science, molecular engineering, and pharmacokinetics to achieve precise and efficient drug delivery. Advances in biocompatible and biodegradable polymers have enabled the design of systems tailored for controlled release and targeted therapy. While natural polymers provide inherent compatibility, synthetic alternatives offer superior tunability and functionality. Despite the progress, scalability, stability, and regulatory hurdles remain critical barriers to clinical translation. The future of polymeric drug delivery lies in integrating smart polymers, computational modeling, and bio-inspired designs to address these limitations. These developments will enable the creation of multifunctional systems capable of co-delivering drugs, genes, and large molecules.

Author contributions

Barakat Olamide Ishola and Khandoker Asiqur Rahaman are involved in conceptualization, drafting the original manuscript, and figure preparation. Shaikh Abdur Razzak, Md Mahamudul Hasan Rumon and Md Salman Shakil critically revised and edited the original manuscript. Shihab Uddin is involved in the conceptualization, review, and editing of the original manuscript; supervision; project administration; and resource management.

Abbreviations

APIs	Active pharmaceutical ingredients
CFTR	Cystic fibrosis transmembrane conductance regulator
CMC	Carboxymethylcellulose
PLGA	Poly(lactic-*co*-glycolic acid)
PGA	Polyglycolic acid
PLA	Polylactic acid
PEG	Poly(ethylene glycol)
PNIPAm	Poly(*N*-isopropyl acrylamide)
PAA	Polyacrylic acid
PDAEMA	Poly(*N*,*N*-dialkylaminoethyl methacrylate)
PHEMA	Poly (2-hydroxyethyl methacrylate)
PEI	Polyethylenimine
PHPMA	Poly(*N*-(2-hydroxypropyl) methacrylamide)
PMA	Poly(methyl acrylate)
NFM	Nanofiltration membranes
PCL	Polycaprolactone
TDDS	Transdermal drug delivery systems
HPMC	Hydroxypropyl methylcellulose
PVA	Polyvinyl alcohol
EPR	Enhanced Permeability and Retention
LAIs	Long-acting injectables
PMMA	Poly(methyl methacrylate)
IPEC	Inter-polyelectrolyte complexes
GRDDS	Gastroretentive drug delivery systems
PNPs	Polymeric nanoparticles

Conflicts of interest

The authors assert that they have no identifiable conflicts.

Data availability

No data was used for the research described in the article.

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