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Polymeric nanomaterials as a drug delivery system for anticancer and antibacterial infections: a review

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Globally, cancer remains the primary cause of mortality. Despite significant progress in cancer research, the efficacy of chemotherapy has diminished in recent decades due to the emergence of multidrug resistance. Conventional cancer treatments such as radiation, chemotherapy, and surgical interventions often result in morbidity and inadequate cure rates for various cancer types. Bacterial infections also pose a growing therapeutic challenge, primarily due to their inherent characteristics, increasing antibiotic resistance, and the increasing number of immunocompromised individuals. Polymeric nanoparticles (NPs) serve as crucial tools for improving targeted drug delivery at the site of action and enhancing drug bioavailability. Polymers may be an optimal choice because of their versatility in meeting the specific requirements of each drug delivery system. This review encompasses polymeric nanoparticles for cancer drug delivery, polymeric nanoparticles for antibacterial drug delivery, types of biodegradable polymeric nanoparticles, and the functions of polymeric nanoparticles in various routes of drug administration.

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1. Introduction

Recently, there has been an increasing focus on the development of novel drug delivery systems to improve the efficacy of pharmaceutical therapies. Compared to other drug delivery systems, polymer-based drug delivery systems have attracted much interest. The need to enhance drug delivery, particularly for drugs that require sustained release or have low bioavailability, has led to this field of research.[1] Owing to their versatility, polymers may be the best choice for fulfilling the requirements of each drug delivery system. Polymers enable researchers to customize them according to specific needs or objectives. Polymeric tailoring can be directly applied to biopolymers through chemical derivations to achieve specific properties. The development of synthetic polymers from their corresponding monomers is an alternative approach that can result in a wide variety of applications and structures. These are the reasons for the growing significance of polymeric materials in nanotechnology and their application as nanoparticle precursors in drug delivery systems.[2]

Paul Ehrlich first introduced the concept of "magic bullets" carrying microscopic drugs over a century ago. Building on this vision, Kumar and Banker (1996) proposed a submicron drug delivery device. Among the different carriers explored, micro/nanoparticles and liposomes have received the most attention. However, liposomes face certain technological limitations, such as poor reproducibility, low stability, and limited drug

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encapsulation efficiency, and they are most effective only with low-molecular weight drugs. To overcome these drawbacks, polymeric nanoparticle-based drug delivery systems have been developed as promising alternatives.[3] Targeted delivery using polymeric nanoparticles has shown particular effectiveness in cancer therapy.[4]

Polymeric nanoparticles offer several advantages, including high surface-to-volume ratio, reproducibility, non-immunogenicity, ease of synthesis and characterization, stability upon administration, and enhanced absorption properties. These unique features make them highly attractive as drug carriers while also enabling low-cost formulations. Importantly, nano drug delivery systems provide sustained and targeted release of therapeutics, in contrast to the less specific release observed in conventional systems, thus marking a shift from macro to nano approaches in drug delivery.[3]

A wide range of polymeric nanoparticulate systems with well-established chemistries are now available. Polymers used in these systems are typically biocompatible, biodegradable, and nontoxic. Notably, certain polymeric nanoparticles also possess the ability to cross the blood–brain barrier, offering protection against chemical degradation and expanding their potential therapeutic applications.[5]

Depending on the preparation technique and the properties of the resulting system, polymeric nanoparticles are classified into two groups. Nanospheres are homogeneous matrix systems in which the drug is uniformly dissolved or dispersed, whereas nanocapsules are reservoir systems in which the drug is enclosed within a cavity surrounded by a single polymer membrane that coats the nanoparticle surface. Drug release from these systems can be regulated by adjusting the polymer composition, thereby achieving the required therapeutic concentration at the target site for the desired duration.[6]

Numerous polymeric nanoparticles have been utilized, and each has its own advantages and disadvantages. Many types of biodegradable polymers have been used as nanoparticle matrices, such as poly(lactide-*co*-glycolide), gelatin, chitosan, dendrimers, and poly(D,L-lactic acid) (PLA). Numerous approaches for using polymer-based nanoparticles in drug delivery are made possible by their broad-spectrum drug encapsulation efficiencies, stimuli-responsive qualities, and targeting moieties. Polyethylene glycol (PEG) is frequently employed to surface-functionalize nanoparticles. This gives oral nanoparticles the ability to penetrate mucus, increasing the entry of drugs into inflamed intestinal regions.[7] This review discusses different types of natural and synthetic biodegradable polymeric nanoparticles used in drug delivery, highlighting their synthesis methods, key physicochemical properties, mechanisms of action, and interactions with cellular membranes and role of polymeric nanoparticles in different routes of drug delivery.

2. Polymeric nanoparticles in cancer drug delivery

Cancer poses a major threat to human health. Cancer is an abnormality that results from genetic or epigenetic modifications of a cell structure. In cancer cells, this negative directional shift occurs rapidly and uncontrollably. Additionally, due to the mutation, cancer cells have the ability to metastasize and escape from physiological suppressors. Cancer is the second most common cause of mortality worldwide owing to the active and rapid growth of tumor cells.[8] For many years, scientists have been particularly interested in early identification and efficient treatment of cancer. Body cells are a source of cancer cells. In order to maintain the body's homeostasis and steady state, healthy cells divide to produce new ones to replace the old ones. However, if a cell's genetic material is altered, the cells may grow abnormally and eventually form a tumor. Through lymphatic and blood vessels, cancer cells spread to many parts of the body and accumulate into tumorigenic masses of cells.[9]

Chemotherapy is one of the most common and well-established cancer treatments. Although it employs different mechanisms of action, its primary goal is to kill rapidly dividing cells, whether cancerous or normal. As a result, chemotherapy often causes severe side effects such as gastrointestinal reactions, hair loss, and bone marrow suppression.[10] Similarly, conventional treatment methods, including chemotherapy and radiation therapy, can eliminate cancer cells but also damage healthy tissues and show variable effectiveness among patients.[11]

The development of innovative and more precise cancer therapies is therefore a pressing global challenge. Advances in treatment strategies and the growing range of therapeutic options have already improved outcomes for several malignant tumors. In this context, polymeric nanoparticles have emerged as highly promising drug delivery systems. They offer key advantages, including low immunogenicity, minimal risk of disease transmission, enhanced systemic circulation stability, and high drug bioavailability. Studies demonstrate that nanoparticles can selectively target cancer cells, provide sustained drug release, and improve therapeutic efficacy.[12] Their hydrophilic character and nanoscale size also help extend circulation time by evading clearance from the reticuloendothelial system.

Furthermore, nanoparticles within the size range of 10–200 nm exploit the enhanced permeability and retention (EPR) effect, enabling them to preferentially accumulate and persist in tumor tissues. This makes them particularly effective for passive tumor targeting. In addition, active targeting strategies further enhance their ability to deliver drugs directly to cancer cells, thereby reducing systemic toxicity. Consequently, polymeric nanoparticles represent a promising platform for anticancer drug delivery.[13] Table 1 illustrates their diverse applications in anticancer drug delivery, highlighting their potential to enhance therapeutic outcomes while minimizing systemic toxicity.

3. Polymeric nanoparticles in antibacterial drug delivery

Bacterial infections have a significant impact on public health. While bacteria are ubiquitous and play an essential role in

Table 1 Application of polymeric nanoparticles in anticancer drug delivery

Types of polymeric nanoparticles	Cancer model	Therapeutic agent (drug)	Outcome
Poly(lactic-*co*-glycolic acid) (PLGA)[14]	White albino rats	Olanzapine	Enhanced drug concentration in the brain
PEG–HPMA (hydroxypropyl methacrylamide)[15]	4T1 and MCF-7 cell lines	Doxorubicin (DOX)	Enhanced cellular uptake and cytotoxicity than free DOX
PLGA–PEG–PLGA NPs[16]	HT29 cell line	5-Fluorouracil and chrysin	Exert high potent synergistic anticancer effect
Polycaprolactone (PCL)[17]	—	5-Fluorouracil and methotrexate	Promising alternative to deliver complex chemotherapies
FA–L–PEG–PCL[18]	MCF-7, HEK-293 and HFF-2 cells	Tamoxifen (TMX)	Non-cytotoxic in high concentration and enhanced the apoptosis of cancer cell
Alginate–chitosan nanoparticles (ACNPs)[19]	H1299 cell lines	Amygdalin	Improved cytotoxic effect
Chitosan nanoparticles (CSNPs)[20]	MCF-7 cancer cell line	Doxorubicin (DOX)	Enhance the tumor cell susceptibility, drug accumulation, and drug efficacy
Chitosan nanoparticles (CCNP)[21]	MCF-7 ATCC human breast cancer cell line	Cisplatin	Increased significant cytotoxicity on cancer cell
Chitosan nanoparticles[22]	Human tongue cancer cell line (SCC-9)	Oxaliplatin	Prolonged the sustained release of drug

environmental balance, only a small proportion are responsible for infections and diseases worldwide.[23] The human microbiome, composed of diverse bacterial communities, occupies various tissues such as the skin and gastrointestinal tract. Under healthy conditions, bacteria and host cells maintain a stable relationship; however, disruption of this balance can lead to bacterial pathogenesis.

Infections often arise when bacteria migrate from their normal sites of colonization (*e.g.*, the mucosal lining of the urethra, intestine, nose, and mouth) to normally sterile regions such as the lungs, blood, kidneys, bladder, pancreas, or brain. This translocation is frequently facilitated by long-term implants (*e.g.*, joint replacements, screws, and cardiac devices) or temporary medical devices (*e.g.*, intubation tubes, urinary catheters, needles, and central lines).[24]

Unlike infectious diseases caused by parasites and viruses, bacterial infections pose an additional challenge due to the rapid emergence of antibiotic resistance, which is becoming a critical global health threat.[23] Furthermore, bacterial invasion can be exacerbated by specific factors, including enhanced virulence through co-colonization with other species and the formation of biofilms. Such infections can escalate into severe outcomes, including amputations, sepsis, or even death.[24]

Various community- and hospital-acquired infections such as chronic wound infections, lung infections, implant- and surgery-related infections, and osteomyelitis are increasingly caused by resistant strains of both Gram-positive and Gram-negative bacteria. The discovery of penicillin in the 20th century revolutionized the treatment of bacterial diseases; however, widespread and often indiscriminate use of antibiotics has led to the emergence of tolerance and resistance. These challenges are further compounded by the need for high antibiotic dosages to eradicate bacteria within biofilms and by the natural process of bacterial evolution.

Of particular concern is the alarming rise of multidrug-resistant Gram-negative pathogens, including carbapenemase-producing Enterobacteriaceae (CPE) and *Pseudomonas aeruginosa*. In many cases, colistin, a peptide based antibiotic, remains the last line of defense, as these bacteria exhibit resistance to most other drugs.[25]

From a pharmacological perspective, complications can emerge due to the low efficacy and transport of antimicrobial drugs across biological barriers. To overcome these drawbacks, antimicrobial drug performance and efficiency have been successfully enhanced using nanoparticle-based drug delivery systems. These systems boast improved physicochemical properties, such as small particle size and an increased surface-to-volume ratio, along with the capability to target functionalizable surface.[26] Table 2 illustrates the extensive applications of these nanocarriers in antibacterial drug delivery, featuring their potential to enhance therapeutic outcomes.

A variety of methods are available for preparing polymeric nanoparticles (Fig. 1), including emulsification, nanoprecipitation, dialysis, and solvent evaporation, each offering unique control over particle size and drug loading. Advanced techniques such as salting out and supercritical fluid processing are well-suited for sensitive biomolecules or environmentally friendly production, while polymerization approaches allow precise tailoring of structural features. Collectively, these techniques are pivotal for designing drug delivery systems that ensure stability, biocompatibility, and customizable drug release profiles.

4. Biodegradable polymeric nanoparticle

When considering biomolecules such as proteins and peptides for oral vaccination, biodegradable polymers play a crucial role

Table 2 Application of polymeric nanoparticles in antibacterial drug delivery

Types of polymeric nanoparticles	Targeting bacteria		Antibacterial agent	Outcome
	Gram-positive	Gram-negative		
Chitosan nanoparticles[28]	*L. monocytogenes*, *S. aureus*	*S. typhi*, *E. coli*	Clove NEOs (Nettle essential oil)	Higher antioxidant activity and increased antibacterial activity against *S. aureus* and *E. coli*
Dextran nanoparticles[29]	—	*P. aeruginosa* (PAO1)	SET-M33 (antimicrobial peptide)	The peptide-functionalized nanoparticles and free peptide had similar MIC values and regrowth happened after 24 h of exposure to the nanosystem
Chitosan nanoparticles[30]	*S. aureus* (ATCC25923)	—	Sophorolipids and rhamnolipids	Increased MIC values for rhamnolipid and sophorolipid containing nanoparticles in comparison to levofloxacin control
Poly-caprolactone[31]	*S. aureus* (ATCC25423)	*E. coli* (ATCC25922)	Chlorhexidine	Suppression of 50% growth of the bacteria up to 15 days
Poly lactic-*co*-glycolic acid[32]	*S. aureus*	*E. coli*	Caffeic acid and juglone	The synergistic action of the active compounds and encapsulation into nanoparticles are both important for increased activity of multifunctional nanoparticles
PEG–PLGA nanoparticles[33]	*S. aureus*	*P. aeruginosa*	Rutin and benzamide	The rutin–benzamide loaded nanocarrier demonstrated strong antibiofilm activity and biocompatibility thereby it offers potential antibiofilm therapy
PEG coated ZnO nanoparticles[34]	*S. aureus*, MRSA, *Enterococcus faecium*	*E. coli*, *P. aeruginosa*, *Klebsiella pneumoniae*, *Salmonella typhi*	Ciprofloxacin	The developed nanocarrier offer improved drug stability, efficacy, and targeted drug delivery

by either protecting these compounds from the harsh acidic environment of the stomach or providing sustained release. This protection can help reduce the frequency of doses, whether maintenance or booster doses.[35]

The rate of degradation of biodegradable polymeric nanoparticles (PNs) is influenced by several factors, including their physicochemical characteristics (molecular weight, structure, and size) and environmental conditions such as pH and temperature.[36] Initially, non-biodegradable polymers such as polystyrene, polyacrylamide, poly(methyl methacrylate) (PMMA), and polyacrylates were used to develop polymeric nanoparticles. These nanosystems showed effective and rapid clearance, but they also elicited inflammatory responses and chronic toxicity. Moreover, non-degradable polymers typically take longer to break down than the duration of their intended application.[37]

Biodegradable polymers, whether synthetic or natural, can be combined or coupled to create colloidal systems known as polymer-based nanoparticles. Polymeric nanoparticles offer unique advantages, including high stability in biological fluids, wide availability of polymers, the ability to functionalize their surface, controlled polymer degradation, and stimulus-responsive release of encapsulated compounds. For example, several chemotherapy drugs have been incorporated into polymeric delivery systems to enhance antitumor activity, reduce effective doses, minimize side effects, and limit metastases. Polymers can either adsorb active components on their surfaces or encapsulate them within their structure. The sustained release of macromolecules *via* polymers was first demonstrated by Langer and Folkman, paving the way for antiangiogenic drug delivery systems in cancer treatment.[35]

Examples of synthetic biodegradable polymers include poly(D,L-lactide) (PLA), co-polymer poly(lactide-*co*-glycolide) (PLGA), poly(D,L-glycolide) (PLG), poly-ε-caprolactone, and polyalkylcyanoacrylate. These polymers are considered safe, and several have received pharmaceutical approval from the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Biodegradable polymeric particles

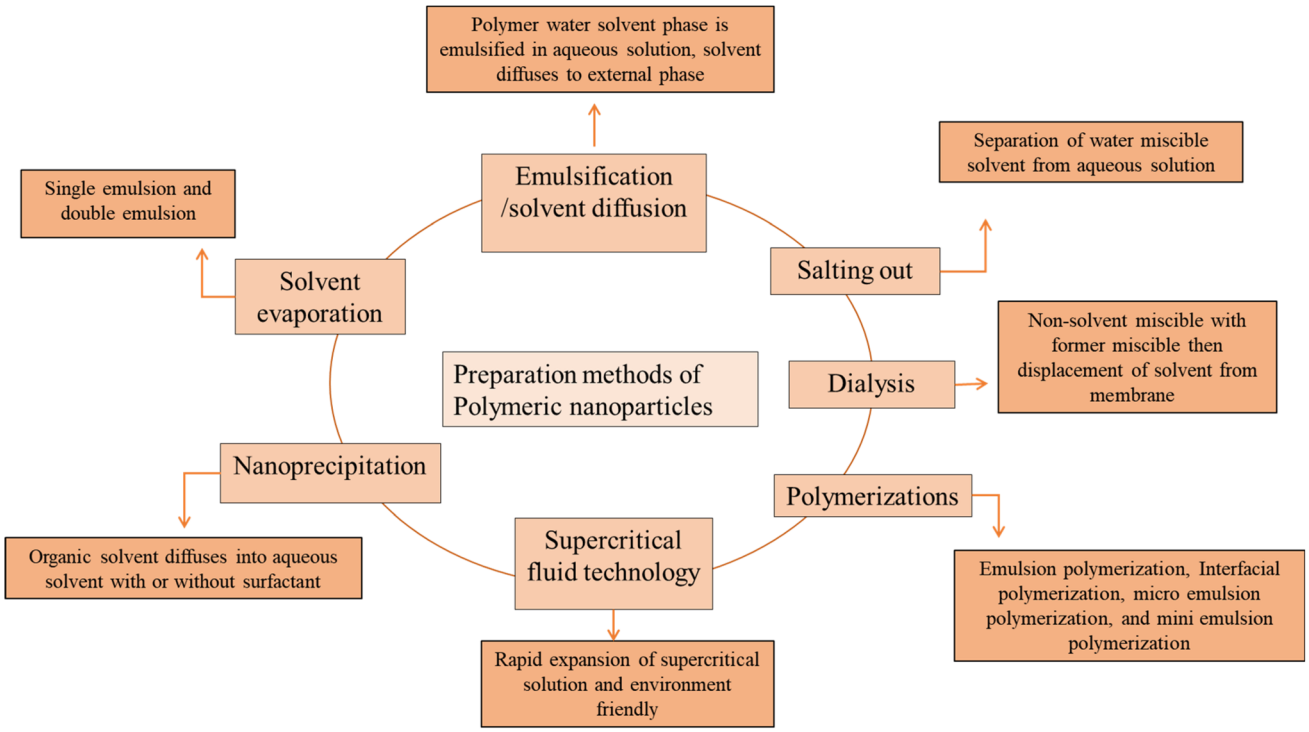

Fig. 1 Preparation methods of polymeric nanoparticles.[27]

generally exhibit high biocompatibility, low systemic toxicity, and tunable drug release kinetics. They are usually degraded into oligomers and monomers, which are metabolized and eliminated *via* normal physiological pathways. Polymeric nanoparticles have also been developed using natural biodegradable polymers such as alginate, zein, chitosan, albumin, and gelatin.[35]

The comparative overview of biodegradable polymeric nanoparticles used in drug delivery system are illustrated in Table 3. Their physicochemical limitations in handling are highlighted in Table 4. Fig. 2 explains the application of biodegradable polymeric nanoparticles.

5. Natural polymeric nanoparticles

Biodegradable and natural polymers have emerged as key materials for the development of advanced drug delivery systems due to their favorable physicochemical and biological properties.[39] Natural polymer-based nanocarriers, characterized by strong drug-binding capacity, low cytotoxicity, abundant surface functional groups, and efficient cellular uptake, offer great potential for effective drug and gene delivery.[40] Despite certain limitations such as batch-to-batch variability and structural complexity, their advantages generally outweigh these drawbacks. Natural polymers can be derived from fungi, bacteria, plants, and other organisms, with polysaccharides and protein-based polymers representing the two major categories.

Both polysaccharides and proteins have been extensively investigated for drug delivery applications, as they mimic extracellular matrix (ECM) components and can be engineered into scaffolds. This allows for minimally invasive delivery with high loading efficiency. Furthermore, the presence of functional groups such as hydroxyl, amino, and carboxyl on their backbones provides opportunities for chemical modification and functionalization.[41]

One of the frontier research is the use of natural polymeric materials to enhance bioavailability, achieve targeted delivery, and improve the therapeutic index, particularly for life-threatening diseases such as cancer. Many natural polymers and their derivatives have been modified chemically or physically to enable the delivery of bioactive compounds *via* targeted or stimuli-responsive systems.[38] Among these, protein- and polysaccharide-based carriers are especially attractive because of their structural similarity to the ECM, reduced invasiveness, and ease of modification.[41] The structures of commonly used natural polymeric nanoparticles, including polysaccharide- and protein-based systems, are illustrated in Fig. 3.

5.1 Polysaccharides based

The unique properties of natural polymers, particularly polysaccharides, make them highly valuable in drug delivery systems. As naturally occurring biopolymers, polysaccharides are stable, non-toxic, biocompatible, and biodegradable. They are also inexpensive, abundantly available, and derived from diverse sources, including plants (cellulose, pectin), animals (chitosan, chondroitin), microorganisms (dextran, pullulan), and algae (alginate).[42] Structurally, polysaccharides are long chains of carbohydrate units composed of more than ten monosaccharides linked by glycosidic bonds.[41]

Table 3 Comparative overview of polymeric nanocarriers for biomedical drug delivery systems

Polymer	Key functional group	Synthesis method	Key properties	Mechanism of action	Interaction with cell membrane & barrier overcoming	Toxicological studies conducted	Animal models & cell lines used	Outcome of toxicological studies
Chitosan[50]	Amine (–NH_2) & hydroxyl (–OH)	Ionic gelation method	Potent antimicrobial and anti-biofilm activities, good biocompatibility, retention in the vaginal environment, and good stability	The cationic nature allows it to form strong electrostatic interactions with the negatively charged glycoprotein components of the vaginal mucosa	The small size and mucoadhesive properties, enable enhanced penetration leading to improved drug delivery, prolonged retention and increased therapeutic effect	Histopatho-logical analysis	Female Swiss albino mice	The developed nanoformulation (MBCSNPs) protects BV infected vaginal epithelium by avoiding hyperemia, hyperplasia, and lymphocyte infiltration
Agarose[55]	Hydroxyl (O–H) & carbonyl (C═O) group, iron–oxygen (Fe–O) & carbon–oxygen (C–O) stretching	Double emulsification technique	pH-responsiveness, increased stability, enhanced drug loading & encapsulation, and biocompatibility	The nanocomposite is engineered to release quercetin more rapidly & efficiently in acidic condition (at pH 4.5)	The nanocomposite possessed a positive charge of 52.8 mV, which facilitated robust electrostatic interactions with negatively charged cell membranes, thereby enhancing attraction and promoting improved absorption of the drug-loaded nanocarrier into the cells	MTT cell viability assay	HepG2 liver cancer cells & L929 fibroblast (normal) cells	The nanocomposite reduced the viability of HepG2 cells by 54% compared to 68% for free QC, whereas 84% of L929 cells survived
Hyaluronic acid[102]	Amine (–NH, NH_2), carboxyl (–COOH), & hydroxyl (–OH)	Electrostatic interaction	Biocompatibility, targeted delivery *via* CD44 receptors, its hydrogel-like property leads to sustained release of drug, and robust stability	GPI (DOX) exhibits acid-sensitive release, as the NH_2 group in GPI are protonated to NH_3 in acidic environment, disrupting the π–π stacking interactions and drug release	The nanosystem is designed for enhanced cellular interaction and barrier overcoming through its targeted delivery to CD44 overexpressing cancer cells, cellular uptake is facilitated by GPI, & its potential to mitigate multidrug resistance and exploit the EPR effect	MTT cell viability assay & *in vivo* mice xenograft experiment	Six-week-old nude mice & HCT116 human colon cancer cells	*In vitro* toxicity study showed <50% cell viability within 24 h, while *in vivo* toxicity study resulted in stable body weight of mice, indicating low systemic toxicity of the nanocarrier
Cyclodextrin[64]	Hydroxyl (O–H) group	Ultrasound-mediated homogenization and lyophilization process	Ability to form inclusion complexes, improved stability, solubility, and bioavailability	The mechanism of drug release is specifically triggered by the unique environmental conditions of the colon, such as pH changes or enzymatic activity	The nanocarrier interact with cell membranes by potentially altering the zeta potential of cancer cells, contributing to their selective cytotoxicity. They overcome various barrier through improved drug solubility and bioavailability due to cyclodextrin, protection from degradation in	MTT cell viability assay	Human colon (HT-29), gastric (AGS) cancer cells, & normal human umbilical vein endothelial cell (HUVEC)	For HT-29 cells the cell viability was approximately 40% (250 μg mL^{-1}), & less than 20% (500 μg mL^{-1}). Whereas for AGS & HUVEC cell the cell viability was above 80% (250 μg mL^{-1}) & 70% (500 μg mL^{-1})

Table 3 (*Contd.*)

Polymer	Key functional group	Synthesis method	Key properties	Mechanism of action	Interaction with cell membrane & barrier overcoming	Toxicological studies conducted	Animal models & cell lines used	Outcome of toxicological studies
					gastrointestinal tract provided by the polymeric structure			
Dextran[69]	Hydroxyl (OH), amine (NH, NH_2), and carboxyl (C=O) group	Ionic gelation method	Biocompatible, biodegradable, pH-sensitive, and prolonged blood circulation	Dextran–spermine is developed as pH-responsive nanocarrier. At neutral pH, drug release follows Fickian diffusion, through the polymer branches. At acidic pH, the mechanism shifts to non-Fickian transport, combining of diffusion, molecular relaxation, and potential network degradation	The nanoparticles possess a positive surface charge (+17.1 mV) which is crucial for their interaction with negatively charged cell membranes. The small size (60–100 nm) and positive charge contributes to the nanoparticles ability to overcome barriers like blood brain barrier	MTT dye reduction method	HUVEC cells	The drug-free nanoparticles did not exhibit any toxic effects on HUVEC cells even at 1 mg mL^{-1} concentration. And the drug loaded nanoparticle leads to reduced toxicity compared to free drug, cell viability remained above 60% in the 24 h incubation period
Albumin[75]	Amine (NH_2)	Desolvation method	Injectability, biocompatibility, biodegradability, strong adhesion, robust mechanical stability, and sustained drug release	Drug release followed the Korsmeyer–Peppas mode, suggesting that the release is influenced by both diffusion through hydrogel matrix and relaxation of the polymer chains, which enhances tumor cell apoptosis	The hydrogel relies on its unique formulation and significant tissue adhesion, where unreacted OPA group in the hydrogel can form chemical bond with the amino groups in the adjacent tissues. This feature is vital for immobilizing the hydrogel and sustaining drug concentration at tumor site	*In vitro* cytotoxicity of hydrogel and drug loaded hydrogel, *in vivo* anti tumor activity, and histo-compatibility assay	Mouse fibroblast L929, colon cancer C26, breast cancer 4T1 cells, and BALB/c mice	The hydrogel showed >80% viability against L929, C26, and 4T1. Drug loaded nanoparticle had higher IC50 value (1.48 μg mL^{-1} for C26, 2.29 μg mL^{-1} for 4T1). Tumor inhibition increased with dosage. Histological analysis showed no pathological changes
Collagen[80]	Carboxyl & amide group	—	Biocompatibility, low immunogenicity, mechanical flexibility, controllable degradation, enhanced stability, and environmental responsiveness	Nanodrug carriers are designed to improve delivery efficiency to specific sites and reduce degradation by adapting to changes in pH within the intracellular microenvironment. The pH changes within cells is crucial in the release of drug from the nanocarrier	The primary mechanisms of nanocarrier internalization into cells are identified as clathrin-mediated endocytosis and autophagy. This was determined by observing a significant decrease in cellular uptake when these pathways were inhibited by chlorpromazine and bafilomycin A1	*In vitro* toxicity studies such as MTT and Calcein AM staining, cell cycle progression, MMP activity and migration. *In vivo* studies such as tissue morphology and particle distribution MTT assay	A549 lung cancer cells, BEAS-2B normal lung cells, and BALB/c mice	The toxicity studies consistently show that the nanocarrier effectively targets and induces apoptosis in lung cancer cells while demonstrating high biocompatibility and minimal toxicity to normal cells and tissues both *in vitro* and *in vivo*
Gelatin[84]								

Table 3 (*Contd.*)

Polymer	Key functional group	Synthesis method	Key properties	Mechanism of action	Interaction with cell membrane & barrier overcoming	Toxicological studies conducted	Animal models & cell lines used	Outcome of toxicological studies
	Hydroxyl, amino, and carboxyl group	Ionic crosslinking technique	High surface loading capacity, drug absorption, increased stability, enzyme-responsive moiety, biocompatibility, and polyelectrolytic complex formation	The nanogel degrade in response to gelatinase (overexpressed in tumor cells). In presence of enzyme, initial burst release observed within 5 h (20.1% at pH 7.4 and 21.65% at pH 5.8). Drug release reached equilibrium at 71.3% and 62.35% after 48 h at pH 7.4 and 5.8 respectively	Cancer cells, such as MCF-7 cells, can take up drug loaded nanogel *via* endocytosis. The presence of enzymes like gelatinase further enhances the degradation of gelatin coating, leading to increase drug release within cells		MCF-7 human breast cancer cells	The drug loaded nanogel with enzyme decreased cell viability compared to free nanogel and drug loaded nanogel. This enhanced cytotoxicity is due to the enzyme-mediated degradation of gelatin coating, which increases the drug release within cells
PLGA[90]	Carboxyl (–COOH) group	Single emulsion-solvent evaporation method	Biocompatibility, biodegradability, protection of encapsulated drugs, controlled drug release, high entrapment efficiency, and bioavailability	Encapsulated drugs within PLGA are released through mechanisms that include diffusion of the drug out of the polymer matrix, swelling of the polymer itself. This controlled release ensures a sustained therapeutic effect	The small size of the nanoparticles (~175 nm) facilitates improved tissue penetration and interaction with cell membranes, leading to enhanced cellular uptake and improved bioavailability of encapsulated drug thereby overcoming significant barriers to drug delivery	MTT assay, apoptosis, and cell cycle analysis	Gastric cancer cell line (AGS)	The maximum inhibition rate for native curcumin and nanocurcumin were 83% and 97% at a 40 μM concentration after 72 h. Lower IC50 values and increased apoptotic cells with nanocurcumin indicate its superior therapeutic potential against cancer cells
PCL[95]	Carbonyl (C=O), hydroxyl (OH) & carboxyl (COOH) group	Emulsion solid-in-oil-in-water evaporation method	Biodegradability, biocompatibility, good physical stability, high permeability, and low toxicity	PCL nanoparticles facilitate sustained drug release through a combination of diffusion and polymer relaxation, with pH-dependent kinetics. At acidic pH, the release of drug is enhanced due to the protonation of polymer chains at lower pH, which favors drug release	The transferrin conjugated to nanoparticles surface can binds to transferrin receptors, which are overexpressed on cancer cells, enhancing cellular uptake. This uptake depends on the optimal transferrin concentration. This receptor mediated transcytosis offers a strategy for drug delivery to challenging sites like blood brain barrier	MTT assay	Human primary glioblastoma cells (U87)	PCL nanoparticles conjugated with transferrin showed no toxicity, with cell viability remaining above 90% at all tested concentrations, indicating no significant toxicity from conjugation

Table 3 (*Contd.*)

Polymer	Key functional group	Synthesis method	Key properties	Mechanism of action	Interaction with cell membrane & barrier overcoming	Toxicological studies conducted	Animal models & cell lines used	Outcome of toxicological studies
PEG[100,101]	Hydroxyl (–OH) group and ether (–O–) linkages	Ring-opening polymerization	Anti-aggregation, enhanced stability, biocompatibility, reduced toxicity, and hydrophilicity	PEG in triblock copolymers enables controlled drug release. Drug release from nanocarriers can be triggered by specific condition at target site, such as acidic pH (5.6) and warmer temperature (40 °C) can significantly accelerate drug release compared to physiological conditions (pH 7.4, 37 °C)	Nanocarrier interact with cell membranes primarily through endocytosis for internalization, while their surface properties and controlled release mechanism enable them to overcome biological barriers, reduce systemic toxicity, and enhance targeted drug delivery	MTT assay	Prostate cancer cell line (PC3)	The nanocarrier itself demonstrated excellent biocompatibility with high cell viability. The drug-loaded nanoparticles, particularly the co-delivery formulation shows significant dose-dependent cytotoxic effects against PC3 cancer cells

Their physicochemical properties enable polysaccharides to form pH-responsive matrices with high drug-loading capacity. Due to their non-toxic nature, polysaccharide-based micro/nanoparticles have been widely investigated as carriers for vaccines, medicines, polypeptides, nucleic acids, genes, and proteins. They are particularly attractive in advanced platforms such as magnetic targeting systems.[43] Recent studies have shown that polysaccharide-based nanoparticles can enhance the therapeutic effectiveness of cytotoxic drugs by improving solubility, stability, and circulation half-life while protecting them from premature degradation and clearance by phagocytes. Moreover, through mechanisms such as the enhanced permeability and retention (EPR) effect, active targeting, or controlled release, these carriers improve the biodistribution of anticancer drugs, thereby increasing tumor-specific efficacy and reducing systemic toxicity.[44]

The performance of polysaccharide-based nanocarriers such as encapsulation efficiency, loading capacity, and release profile is strongly influenced by the type and chemical structure of the polysaccharide. For instance, polysaccharides containing complex monosaccharides provide more cross-linking points, enhancing both drug encapsulation and controlled release compared to those derived from simple monosaccharides.[45] Additionally, electrostatic interactions play a critical role in reinforcing the durability, hydrophilicity, and mechanical strength of these nanocarriers. A deeper understanding of such interaction forces is essential for designing novel polysaccharide-based delivery systems.[46]

5.1.1 Chitosan. Chitosan (CS), a natural amino polysaccharide and the second most abundant biopolymer after cellulose, is one of the most widely studied materials in biomedical research.[47] It is obtained by deacetylating chitin (>50%), yielding a linear cationic polymer of β-D-glucosamine and *N*-acetyl-D-glucosamine units linked *via* 1,4-glycosidic bonds. Chitosan exhibits several favorable properties, including biocompatibility, nontoxicity, mucoadhesivity, antibacterial and antifungal activity, which make it highly attractive for applications in tissue engineering, gene therapy, and drug delivery.[41,47]

Its physicochemical behavior is strongly influenced by molecular weight and degree of deacetylation; lower values enhance solubility and degradation. Mucoadhesivity, particularly valuable for oral drug delivery, arises from electrostatic interactions between the positively charged amino groups of chitosan and negatively charged mucosal membranes, as well as hydrogen bonding with mucus glycoproteins. This interaction prolongs drug residence time, improving absorption and bioavailability.[44] Chitosan drug delivery systems (DDS) can encapsulate proteins, polynucleotides, and small molecules, offering sustained release through ionic crosslinking of free amine groups.[47] Carboxymethyl chitosan, a widely used derivative, improves solubility in water and alkaline media while reducing swelling in acidic conditions.[44]

In oncology, chitosan-based nanocarriers have gained significant attention for improving chemotherapeutic efficacy.[48] They enhance drug stability, prolong release, and target tumor cells through mechanisms such as enzymatic modulation, anti-

Table 4 Physicochemical limitations in the handling of polymeric sample

Polymer	Stability (dry/formulated)	Storage temperature	Optimal pH range	Handling
Chitosan[103]	Stable in dry form, aqueous solutions prone to hydrolysis and microbial growth	2–8 °C for aqueous sample, room temperature for dry sample	4.0–6.0	Store dry in airtight containers
Agarose[104]	Highly stable in dry form, gels swell or shrink at high temperature	4 °C for gel sample, room temperature for dry sample	—	Avoid multiple heating
Hyaluronic acid[105]	Sensitive to enzymatic degradation and extreme pH and temperature	4 °C to −20 °C for dry sample	7–7.5	Avoid extreme pH and temperature, long reaction time
Cyclodextrin[104]	Stable in dry form	Room temperature in airtight container	6.0–8.0	Store in desiccator to prevent moisture uptake
Dextran[106]	Stable in dry form, degrades slowly in aqueous medium	4 °C for aqueous sample, room temperature for dry sample	6.0–8.0	Avoid using strong oxidizing agents
Albumin[107]	Sensitive to heat, pH changes, prone to aggregation	−20 °C for dry sample, protect from light	6.5–7.4	Avoid high pH and heat combination, and agitation
Collagen[108]	Sensitive to temperature, pH	−20 °C (frozen) for long-term, 4 °C for short term	6.0–7.5	Avoid high heat and pH, handle under sterile conditions
Gelatin[84]	Thermo-sensitive, enzyme-responsive degradation	4 °C for aqueous sample, room temperature for dry sample	5.5–7.5	Avoid lack of purification and high temperature, store under sterile conditions
PLGA[109]	Very stable, undergoes slow hydrolytic degradation	4 °C or room temperature for dry sample, 2–8 °C for solution	4.0–8.0	Long storage period, stable in physiological environments
PCL[93]	Highly stable under physiological conditions, reduce renal filtration	4 °C for dispersed sample, room temperature for dry sample	4.0–8.0	Avoid exposure to strong acids or base and excessive moisture
PEG[110]	Excellent chemical and physical stability	4 °C or room temperature	4.0–9.0	Stable in diverse formulation; often used to enhance overall stability

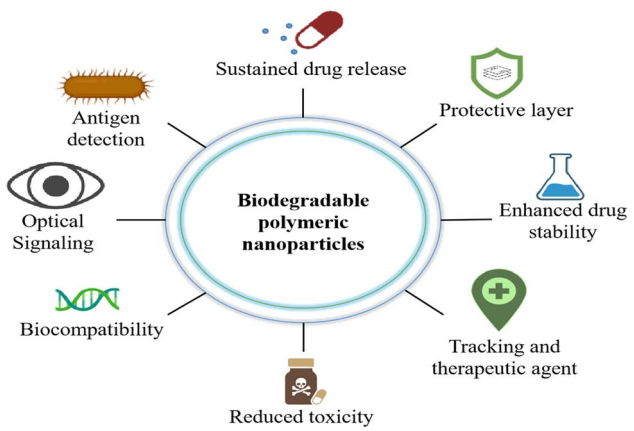

Fig. 2 Application of biodegradable polymeric nanoparticles.[38]

angiogenesis, immunomodulation, antioxidant defense, and apoptosis induction. Low-molecular-weight chitosan nanoparticles, for instance, can trigger apoptosis and arrest tumor growth *via* NF-κB-mediated signaling.[49]

Several studies illustrate the versatility of CS-based nanocarriers. Nayak *et al.* developed metronidazole-loaded CS nanoparticles crosslinked with tannic acid or borax for bacterial vaginosis treatment, achieving strong adhesion to vaginal mucosa, controlled release, and enhanced antimicrobial activity, including biofilm targeting.[50] Similarly, Ahmad *et al.* formulated CS nanoparticles encapsulating cisplatin (CP) and 5-fluorouracil (FA) using ionic gelation with sodium tripolyphosphate. These carriers enabled sustained diffusion-controlled release, enhanced cancer cell targeting, and greater cytotoxicity compared to free drugs.[48]

5.1.2 Agarose. Agarose, a hydrophilic, neutrally charged, and non-pH-sensitive linear polysaccharide derived from red marine algae, consists of repeated disaccharide units of 3,6-anhydro-L-galactose and D-galactose linked *via* α(1 → 4) and β(1 → 3) glycosidic bonds.[51] This marine-derived polysaccharide is well known for its reversible thermogelling behavior, favorable mechanical properties, bioactivity, and ease of functionalization, making it highly attractive for the design of advanced drug delivery systems.

Unlike many polysaccharides that carry high surface charges and thus face circulation barriers such as protein corona formation, agarose maintains a neutral surface charge across physiological pH values. This feature minimizes protein adsorption, enhances circulation stability, and improves drug delivery efficiency.[52] Moreover, agarose-based hydrogels are widely used due to their ability to form crosslinked networks

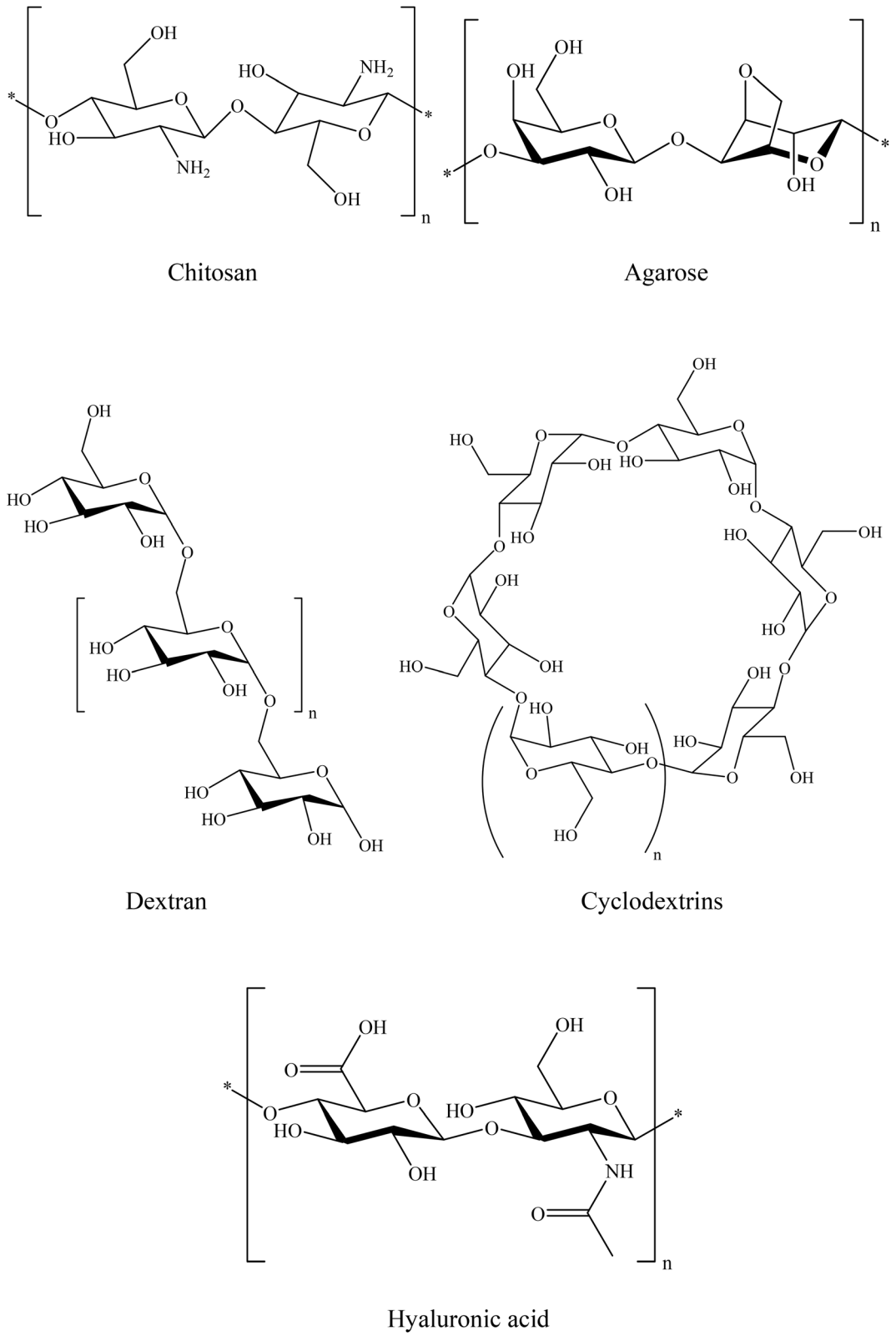

Fig. 3 Structures of natural polymer.

through physical interactions, enabling sustained and controlled drug release.[53] Chemical modifications, such as carboxymethylation, can further impart pH-responsiveness and expand the scope of agarose-based delivery platforms.[54]

Several studies highlight the versatility of agarose in biomedical applications. Najafi *et al.* developed an agarose/α-Fe_2O_3/graphene quantum dot nanocomposite hydrogel for the pH-responsive delivery of quercetin (QC). The positively charged

nanocomposite (+52.8 mV) exhibited strong electrostatic interactions with negatively charged cell membranes, facilitating cellular uptake and enabling sustained QC release, particularly under acidic tumor microenvironments.[55] Similarly, Huang *et al.* reported a macroporous hydrogel dressing based on carboxymethyl agarose combined with silver nitrite ($AgNO_3$). The resulting hydrogel demonstrated antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, anti-inflammatory effects, and controlled Ag^+ release. These mechanisms accelerated wound healing, minimized scarring, and provided prolonged antibacterial protection.[54]

5.1.3 Hyaluronic acid. Hyaluronic acid (HA) is a naturally occurring, nonsulfated glycosaminoglycan with favorable characteristics including biodegradability, biocompatibility, non-immunogenicity, and chemical versatility.[56] Structurally composed of repeating units of *N*-acetyl-D-glucosamine and D-glucuronic acid, HA exhibits strong affinity for CD44 receptors, which are frequently overexpressed in various cancers, particularly colorectal carcinoma.[57] This receptor-mediated targeting ability, combined with its safety profile, makes HA a promising candidate for cancer therapy and advanced drug delivery systems.[56]

Recent studies have highlighted diverse applications of HA-based carriers. Jiang *et al.* developed a manganese–HA hydrogel encapsulating gambogic acid nanoparticles, demonstrating sustained release, biocompatibility, and imaging capability for intratumoral delivery.[45] Raza *et al.* designed a chitosan–HA spongy composite incorporating silver nanoparticles and nystatin, which enhanced antifungal activity and accelerated wound healing.[58] Wu *et al.* synthesized HA-grafted fatty acid monoglyceride nanoparticles loaded with doxorubicin (HGD–DOX), which improved oral bioavailability and selectively targeted CD44-overexpressing cancer cells *via* clathrin-mediated endocytosis, caveolin-mediated endocytosis, and macropinocytosis. This strategy enhanced doxorubicin's therapeutic efficacy while offering controlled uptake pathways.[59]

5.1.4 Cyclodextrin (CDs). Cyclodextrins (CDs) are amphiphilic cyclic oligosaccharides composed of at least six D-(+) glucopyranose units linked by α-(1,4) glycosidic bonds, typically produced by enzymatic degradation of starch from corn, potatoes, and other sources.[60] Structurally, CDs adopt a truncated cone shape with a hydrophobic inner cavity and a hydrophilic outer surface due to the chair conformation of glucopyranose units. This unique architecture enables CDs to encapsulate hydrophobic drugs within their cavities to form reversible host–guest inclusion complexes without the need for chemical modification.[61]

CDs have been extensively applied to enhance drug solubility, permeability, and bioavailability, while also improving stability, safety, and therapeutic efficacy. Their versatility extends to diverse delivery routes, including oral, parenteral, nasal, pulmonary, transdermal, and colon-specific delivery, as well as peptide, protein, and gene delivery.[60] In aqueous solutions, CDs can self-assemble into nanosized particles, offering further potential as carriers for controlled and targeted drug release.[62]

Several studies demonstrate the promise of CD-based nanocarriers in oncology. Alboabdullah *et al.* designed a β-cyclodextrin polymer loaded with Lawson, a nonpolar anticancer phytochemical, which exhibited selective cytotoxicity and apoptotic effects in breast (MCF-7) and gastric (AGS) cancer cells, suggesting potential as an anti-gastric and anti-breast cancer therapy.[63] Similarly, Al Alabdullah *et al.* developed silibinin-loaded zein–β-cyclodextrin nanocarriers (SZBC-NCs) using ultrasound-mediated homogenization. These nanocarriers displayed strong antioxidant activity (ABTS and DPPH assays), reduced IC_{50} values, and induced apoptosis by upregulating caspase-3/9 while downregulating NF-κB expression, confirming their selective cytotoxicity against cancer cells.[64]

5.1.5 Dextran (DEX). Dextran (DEX), first discovered by Louis Pasteur in 1861 from slime-producing bacteria and later associated with *Leuconostoc mesenteroides* by van Tieghem in 1878, is an extracellular polysaccharide synthesized from sucrose by the enzyme dextransucrase in lactic acid bacteria such as *Streptococcus* and *Leuconostoc*.[65] Clinically, dextran has been used for more than five decades as a plasma volume expander to enhance blood flow and prevent post-surgical thrombosis, as well as in antiviral therapies and anemia treatment.[66]

As a biopolymer, dextran offers multiple advantages for nanomedicine, including biodegradability, biocompatibility, non-immunogenicity, and excellent solubility.[65] It is already commercially applied as an iron carrier (ferric hydroxide–dextran complexes for anemia therapy), nanoparticle coating/protective agent, antioxidant, anticoagulant, antithrombotic agent, and inducer of interferon biosynthesis.[66] Its pharmacokinetics are influenced by molecular mass and charge, affecting distribution and clearance.[67] Unlike many polysaccharides, dextran resists degradation by common amylases and is primarily broken down by dextranase in the intestine, liver, spleen, and kidneys. This resistance to premature degradation allows dextran-based nanocarriers to improve oral bioavailability by protecting drugs against enzymatic and chemical elimination.[65]

Recent research highlights its versatility in drug delivery. Bhatnagar *et al.* designed pH-responsive alkylated dextran nanoparticles co-loaded with doxorubicin (DOX) and RITA [2,5-bis([5-hydroxymethyl-2-thienyl]furan)], which acted synergistically to enhance cytotoxicity. The nanoparticles (~132 nm) facilitated cellular uptake, achieved efficient drug accumulation at tumor sites, and triggered apoptosis *via* p53 activation, demonstrating promising anticancer potential.[68] Similarly, Abri *et al.* developed magneto-cationic dextran nanoparticles for pH-responsive antibiotic delivery. With small size (60–100 nm), positive surface charge (+17.1 to +29.0 mV), and good biocompatibility, these carriers promoted cellular internalization and selective drug release in inflamed tissues, highlighting their therapeutic promise for infection treatment.[69]

5.2 Protein based

Protein polymers are naturally occurring macromolecules derived from plants and animals, making them abundant and

renewable resources. Their tunable properties, along with inherent biodegradability and biocompatibility, make them highly suitable for developing protein-based nanoparticles. Due to their unique structure–function relationships, different protein polymers can be tailored for specific biomedical applications.[70]

As natural biomolecules, protein nanoparticles serve as safe and sustainable alternatives to synthetic polymers and can be synthesized under mild conditions without the need for organic solvents or hazardous agents. Common preparation techniques include electrospray, emulsion, and desolvation methods, employing proteins such as 30Kc19, gliadin, ferritin, legumin, albumin, fibroin, and lipoproteins.[71]

5.2.1 Albumin. With a molecular weight of 66.5 kDa, albumin is the most prevalent plasma protein in human serum, ranging from 35 to 50 g L^{-1}. In addition to having minimal immunogenicity, biocompatibility, and biodegradability, albumin is non-toxic. Most importantly, it functions as a transporter for several substances found in blood plasma. Additionally, the amino acids that result from the breakdown of albumin may nourish peripheral tissue.[70] Among the biopolymeric nanoparticles, albumin nanoparticles have attracted considerable interest. They are significant carriers with great potential for tissue engineering, material engineering, nanomedicine, and pharmacology applications. Additionally, it has been demonstrated that albumin has a high affinity for binding different drugs through electrostatic, hydrophobic, or covalent conjugation. Therefore, albumin is a flexible drug carrier.[71]

Albumin nanoparticles also demonstrate tumor-targeting ability through multiple mechanisms. Accumulation at malignant sites occurs primarily *via* the enhanced permeability and retention (EPR) effect, resulting from leaky vasculature and impaired lymphatic drainage. Additionally, overexpressed endothelial receptors facilitate albumin transcytosis from the bloodstream into the tumor microenvironment.[72] These mechanisms collectively enhance tumor selectivity, reduce systemic toxicity, and prolong therapeutic action, enabling lower drug dosages to achieve effective outcomes while minimizing adverse effects.[73]

Several studies highlight the potential of albumin-based carriers. Aziz *et al.* reported that doxorubicin-loaded albumin nanoparticles exhibited four times higher apoptotic activity than free doxorubicin, attributed to sustained release and reduced drug aggregation.[74] Similarly, Wang *et al.* designed an injectable hydrogel for localized cancer therapy, incorporating paclitaxel (PTX)-loaded bovine serum albumin nanoparticles (PTX@BN). The hydrogel, cross-linked with *o*-phthalaldehyde (OPA)-terminated 4-armed poly(ethylene glycol) (4aPEG-OPA), displayed strong tissue adhesion as unreacted OPA groups formed covalent bonds with nearby tissue amines. This property immobilized the hydrogel at the tumor site and sustained local drug concentration. Drug release followed the Korsmeyer–Peppas model, indicating a mechanism governed by both diffusion through the hydrogel matrix and polymer chain relaxation, ultimately enhancing tumor cell apoptosis. This strategy demonstrates considerable promise for effective and localized drug delivery.[75]

5.2.2 Collagen. The human body contains a large amount of collagen, which is present in the muscles, tendons, bones, and skin. It is an important component of tissue engineering and drug delivery systems (DDS) because of its tensile strength, considerable stretchability, biocompatibility, biodegradability, biomimetic nature, vivo capacity, weak antigenicity, and exceptional safety profile.[76] Collagen is composed of three separate polypeptide chains that are bound together by hydrogen bonds between the CO and NH groups, in addition to electrostatic interactions. Moreover, collagen nanoparticles can serve as transporters for therapeutic treatments; therefore, they may potentially aid in the healing process.[77]

Collagen serves as an effective delivery system for a variety of substances including growth hormones, proteins, drugs, and DNA. Collagen is versatile; therefore, it may be altered to develop materials with a wide range of durabilities, forms, and structures. Collagen has applications in drug delivery, such as the development of microneedles, microspheres, and the formulation of nanoparticles for gene delivery. Production of pellets and tablets for gel formation, in combination with liposomes for sustained drug delivery, protein delivery, cancer treatment, and ophthalmology collagen shielding.[78] Collagen and nanoparticles work together to stabilize nanoparticles and aid drug entrapment, resulting in continuous and controlled release of the drug for ideal therapeutic outcomes. Because collagen nanoparticles are small and have high absorptive qualities, they are a good example of a sustained drug-releasing bioscaffold. Collagen is similar to the tumor microenvironment; for example, collagen nanoparticles can facilitate the transport of anti-cancer therapies into tumors.[77]

Hongsa N. *et al.* created a novel gold nanoparticle nanohybrid that was reduced, stabilized, or coated with collagen in the first layer and then modified with biotin-quat188-chitosan in the outer layer for the delivery of 5-fluorouracil to enhance cellular uptake and encourage specific cell targeting. The developed nanocarrier was efficient in delivering 5-fluorouracil into cancer cells. Intermolecular interactions were used to synthesize the nanoparticles. Hongsa *et al.* demonstrated the synthesis of uniformly distributed AuNPs in an environmentally friendly manner utilizing type I collagen. Additionally, the application of modified chitosan to the surface of collagen-coated nanohybrids improves the durability and efficacy of drug encapsulation, which enhances their anticancer ability.[79]

Tang *et al.* fabricated a nanocarrier system that integrates gold nanoparticles (AuNPs), type 1 collagen (Col), and alkaline berberine (BB) to enhance the delivery of the therapeutic agent directly to cancer cells. This Au–Col–BB nanocarrier system enhance the delivery of BB to cancer cells, thereby increasing its efficacy. BB has been demonstrated to triggers apoptosis through various mechanisms, including the activation of pro-apoptotic proteins vital to the apoptosis pathway. In lung cancer cells, BB activates the p53 pathway, resulting in cell cycle arrest and apoptosis. Additionally, BB inhibits telomerase activity, which is crucial cancer cell proliferation and survival. BB also modulates the immune response against tumors by boosting the activity of immune cells, such as $CD8^+$ T cells, which are crucial for targeting and destroying cancer cells.[80]

5.2.3 Gelatin. Natural amphiphilic macromolecules such as gelatins are often produced by hydrolyzing collagen found in fish, mammals, insects, and other sources. There is a good opportunity for gelatin for being identified as a biopolymer for nanomaterials among other natural polymers because it has been used for many years as a plasma expanders.[81] It is a polyampholyte with hydrophilic and cationic groups, in addition to anionic groups. It is generally known that the degree of gelatin crosslinking affects mechanical, thermal, and swelling characteristics.[82] Owing to their biocompatibility and ability to be metabolized, gelatins offer a wide range of combinations with ligands, linkers, drugs, and protective compounds.

Food and Drug Administration (FDA) in the United States has shown great interest in developing gelatin nanoparticles as safe drug delivery systems in the past few years. Their outstanding properties, such as non-immunogenicity, biodegradability, good nutritional value, potential for reduced reticuloendothelial system (RES) opsonization, excellent binding capacity, and high stability, are the fundamental causes.[83]

Recently, Aslzad *et al.* developed effective enzyme-responsive system for delivering doxorubicin, using gold nanoparticles embedded with chitosan/gelatin hybrid nanogels. This nanocarrier releases the drug in response to enzyme, ensuring that the drug is primarily released at the tumor site, thereby minimizing systemic exposure and reducing adverse effects of the drug. The nanogel size (approximately 119.3 nm) and positive zeta potential (31.9 mV) are crucial for its interaction with negatively charged cell membranes. Smaller nanoparticles generally exhibit higher cellular uptake, enhancing their efficiency in delivering drug to cancer cells. The incorporation of biopolymers, such as chitosan and gelatin, not only provides a biocompatible environment but also imitates the extracellular matrix and this allows the nanogel to navigate through biological barriers more effectively.[84]

6. Synthetic polymeric nanoparticles

Synthetic polymers can be engineered with specific features such as charge, hydrophobicity, and degradation profile to optimize delivery routes and target particular diseases. Controlled synthesis ensures low batch-to-batch variability, while large-scale production remains feasible and sustainable. However, synthetic polymers may sometimes exhibit cytotoxicity or immunogenicity due to unintended breakdown products or metabolites.[85]

To minimize such risks, chemical synthesis often employs non-toxic monomers like lactic acid and other natural metabolites to produce nanoparticles. These carriers generally do not cause severe adverse effects upon degradation, though they typically undergo a slower biodegradation process compared to natural polymer-based nanoparticles.[86] The structures of commonly used synthetic polymeric nanoparticles are shown in Fig. 4.

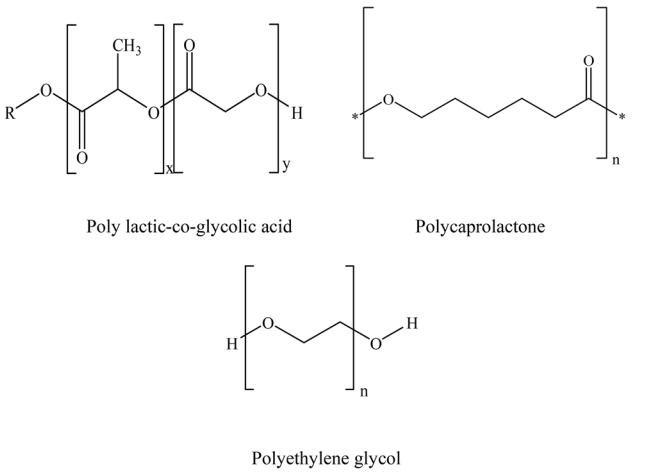

Fig. 4 Structures of synthetic polymers.

6.1 Poly lactic-*co*-glycolic acid (PLGA)

PLGA consists of two distinct blocks, poly(glycolic acid) (PGA) and poly(lactic acid) (PLA). Derived from natural sources, it exhibits unique characteristics such as tunable crystallinity, molecular weight, hydrophilic–hydrophobic balance, and biodegradability.[87] Among polymeric nanoparticles, PLGA is notable for its ability to degrade spontaneously. The US FDA has approved its use in drug delivery systems owing to its low toxicity, biocompatibility with cells and tissues, and capacity for regulated and sustained drug release. With high efficacy and minimal side effects, PLGA nanoparticles hold strong potential for cancer treatment.[88] They enable targeted and sustained delivery of diverse therapeutic agents, including peptides, small molecules, macromolecules, and proteins, and can be further functionalized at the nanoparticle surface. The physicochemical properties of PLGA-based nanoparticles vary depending on the ratio of monomers and the preparation method employed, giving rise to different characteristics and performance profiles.[89]

Alam *et al.* explored the antibacterial and anticancer activity of curcumin encapsulated in PLGA nanoparticles against *Helicobacter pylori* and stomach cancer. Curcumin-loaded PLGA nanoparticles were prepared *via* the single emulsion solvent evaporation method. While native curcumin suffers from low absorption and poor bioavailability, encapsulation within PLGA nanoparticles improves stability, cellular uptake, and therapeutic potential. The small particle size (~175 nm) further enhances tissue penetration and cancer cell interaction, resulting in greater cytotoxicity. Compared with free curcumin, nano-curcumin demonstrated superior antibacterial and anticancer activity, offering a promising strategy to overcome the limitations of conventional therapy.[90]

Taebpour *et al.* formulated berberine-loaded PLGA nanoparticles using a double emulsion (W1/O/W2) technique. These nanoparticles predominantly enter cells, including cancer cells, *via* endocytosis, as confirmed by electron microscopy, which showed nanoparticle adherence and subsequent uptake. Encapsulation significantly enhanced the bioavailability and effectiveness of berberine, with PLGA–berberine nanoparticles showing stronger cytotoxicity against breast cancer cells compared to free berberine. Notably, this formulation did not

harm normal cells, demonstrating selective action and highlighting its promise as a safe and effective cancer treatment strategy.[91]

6.2 Polycaprolactone (PCL)

Poly(ε-caprolactone) (PCL) is a biodegradable aliphatic polyester widely applied in drug delivery systems, wound dressings, and contraceptive devices. Beyond conventional drug delivery, PCL has been adapted for carrying peptides, proteins, vaccines, and other bioactive compounds. In addition to its biodegradability and biocompatibility, PCL is bioresorbable, which is a major advantage in medical applications. Its high permeability to many therapeutic agents with relatively low molecular weights (<400 Da) further enhances its suitability for drug delivery system development.[92]

Targeting agents such as folate, transferrin, arginine–glycine–aspartic acid (RGD), and poloxamers are commonly employed with PCL nanoparticles. Heggannavar *et al.* reported successful outcomes with transferrin-conjugated PCL nanoparticles in an *in vitro* blood–brain barrier (BBB) model, where human brain microvascular endothelial cells (HBMEC) and U-87 MG cells were co-cultured. Paclitaxel-loaded PCL nanoparticles were prepared using an emulsion method and subsequently surface-conjugated with transferrin. Cytotoxicity assays on U-87 MG cells demonstrated enhanced activity, suggesting that controlled transferrin conjugation can make PCL nanoparticles highly effective for brain-targeted delivery.[93–95]

Behl *et al.* developed a nanoformulation (DM–PEG–PCL NPs) using polyethylene glycol–polycaprolactone (PEG–PCL) polymer loaded with doxorubicin and a MUC1 inhibitor. The formulation displayed biodegradability, non-toxicity, and anti-multidrug resistance properties, with prolonged drug release for up to 60 days. Compared with single-drug-loaded nanoparticles, DM–PEG–PCL NPs exhibited stronger cytotoxicity against breast cancer cell lines (MCF-7 and MDA-MB-231), as indicated by lower IC_{50} values. Treatment induced mitochondrial damage, upregulated caspase-3 expression, and downregulated Bcl-2 expression, leading to apoptosis and inhibited proliferation in triple-negative breast cancer cells. This dual-drug nanoformulation highlights the potential of PCL-based carriers for targeted, sustained drug delivery with synergistic therapeutic effects and reduced systemic toxicity.[96]

6.3 Polyethylene glycol (PEG)

Polyethylene glycol (PEG) is a polymeric family with a similar backbone structure but variable molecular weights, making it a versatile material for drug administration. Its key properties such as hydrophilicity, biocompatibility, and biodegradability have established PEG as a promising candidate for developing sustainable, controlled-release systems, particularly for antidiabetic drug delivery. The architecture of PEG molecules allows drug carriers to resist enzymatic degradation and reduce immunogenicity. PEG has been incorporated into diverse delivery platforms, including hydrogels, vesicles, micelles, and nanoparticles.[97]

PEG was first applied in drug delivery by Abuchowski and colleagues, who introduced PEGylation for protein transport.[98] PEGylation enhances drug performance by decreasing toxicity, improving stability, and prolonging the biological half-life of biopharmaceuticals.[99] A major challenge in systemic drug delivery is uneven biodistribution and rapid elimination, both of which can be mitigated by PEGylation. By increasing particle size and forming a hydrophilic protective layer, PEG reduces glomerular filtration, prevents plasma protein adsorption, shields drugs from enzymatic degradation, and extends circulation time, thereby enhancing passive drug targeting.[98]

Expanding its applications, Ibraheem *et al.* developed a novel chemical precipitation method using polyethylene glycol-300 (PEG-300) as an intermediate for synthesizing zinc oxide nanoparticles (ZnONPs). The method enabled stable conjugation of ZnONPs with nystatin (NYS), producing a nanoformulation with strong antibacterial activity. Using the well-diffusion method, the ZnONP–PEG–NYS conjugate demonstrated efficacy against pathogens such as *Streptococcus mutans*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Escherichia coli*. This approach offers a cost-effective and environmentally friendly therapeutic option for infectious diseases.[100]

Yousefnezhad *et al.* investigated the co-delivery of doxorubicin (DOX) and the cholesterol uptake inhibitor ezetimibe (EZ) using biodegradable poly(ε-caprolactone)/poly(ethylene glycol)/poly(ε-caprolactone) (PCEC) nanoparticles in prostate cancer (PC3) cells. The PCEC triblock copolymer was synthesized *via* ring-opening polymerization of ε-caprolactone initiated by PEG2000, and DOX and EZ were encapsulated using double and single emulsion techniques to generate DOX@PCEC, EZ@PCEC, and DOX + EZ@PCEC formulations. Results showed that EZ enhanced the anticancer efficacy of DOX, with the dual-loaded DOX + EZ@PCEC nanoparticles exhibiting superior cytotoxicity compared to single-drug formulations. Mechanistically, DOX targeted cancer cells while EZ reduced cholesterol accumulation—an important factor in prostate cancer progression with PCEC nanoparticles enabling controlled co-delivery for improved therapeutic outcomes.[101]

7. Role of polymeric nanoparticles in different routes of drug delivery

Polymeric nanoparticles play a pivotal role in enhancing drug delivery across various administration routes such as oral, nasal, ocular, rectal, and vaginal. The clinical values and adaptability of polymeric nanoparticles in facilitating precise drug delivery through various physiological routes are shown in Fig. 5.

7.1 Polymeric nanoparticles for nasal drug delivery

Intranasal administration has emerged as a promising route for brain drug delivery because it enables direct transport along neural pathways, making it particularly valuable for central nervous system disorders such as anxiety and depression. Compared with other administration routes, the intranasal pathway offers several advantages: it bypasses the blood–brain

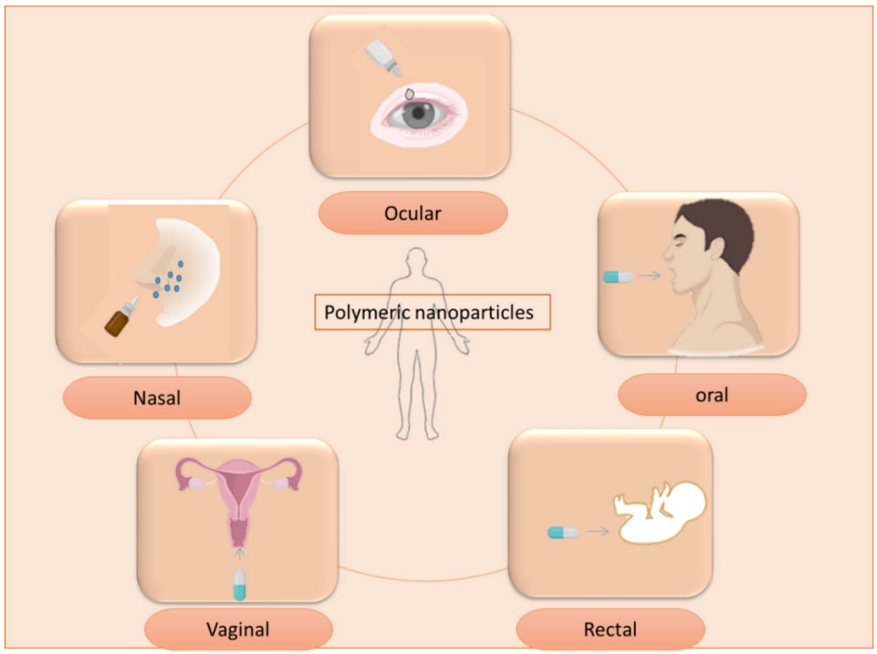

Fig. 5 Polymeric nanoparticles in different routes of drug delivery.

barrier, avoids hepatic first-pass metabolism, facilitates the transport of larger molecules (up to ~1000 Da), reduces systemic side effects and toxicity, and allows lower doses to achieve therapeutically effective concentrations at the target site.[6]

Nanostructured drug carriers, especially polymeric nanoparticles, play a crucial role in enhancing nose-to-brain transport. Their interaction with biological environments increases the amount of drug delivered to the central nervous system, while coatings can impart additional properties such as improved stability or targeting.[111] Polymeric nanoparticles generally provide controlled drug release, often exhibiting a biphasic profile characterized by an initial burst followed by sustained release. Mucoadhesive polymers such as alginate and chitosan are commonly employed to extend residence time in the nasal cavity and improve absorption, thereby enhancing delivery to the site of action.[6]

Sustained-release nanoparticle systems (50–200 nm) further improve oral bioavailability of hydrophobic drugs by enabling prolonged circulation, reduced toxicity, and efficient blood–brain barrier penetration. Smaller nanoparticles (20–200 nm) can traverse both the reticuloendothelial system and the blood–brain barrier, whereas larger nanoparticles are more suitable for gradual drug release. Although smaller nanoparticles possess a high surface-to-volume ratio, they may aggregate and release the drug more rapidly due to surface adhesion. The nasal cavity's olfactory and trigeminal pathways, supported by its lymphatic system, provide direct routes for nanoparticle-mediated transport into the brain.[112]

De Oliveira Junior *et al.* evaluated the effect of PEGylation on the nose-to-brain delivery of polycaprolactone (PCL) nanoparticles (PCL-NPs) encapsulating bexarotene (BEX), a potentially neuroprotective compound. PEGylation at 1, 3, 5, and 10% had no effect on nanoparticle morphology or size; however, 5% PEGylation (PCL–PEG5%) was identified as optimal. Following intranasal administration, PEG–PCL5% NPs displayed enhanced dispersion and retention in the brain, attributed to improved stability and mobility within nasal mucus. Importantly, PEG coating did not reduce absorption by nasal epithelial cells. Compared with drug dispersion and non-PEGylated particles, BEX PCL–PEG5% NPs achieved a higher brain area under the curve (AUC), confirming superior nose-to-brain delivery.[111]

Using a quality-by-design (QbD) framework, process parameters affecting critical quality attributes (CQAs) of intranasal nanoformulations were further optimized. Solid lipid nanoparticles (SLNs) showed improved sustained release, higher encapsulation efficiency (EE), and drug loading (DL) compared with poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles. Moreover, chitosan-coated SLNs achieved more sustained release than meloxicam (MEL)-loaded SLNs without coating. Akel *et al.* provided the first evidence supporting MEL encapsulation in lipid and polymeric nanoparticles for intranasal delivery, with chitosan-coated SLNs demonstrating superior performance.[113]

7.2 Polymeric nanoparticles for ocular drug delivery

According to the World Health Organization (WHO), at least 2.2 billion individuals worldwide suffered from vision impairment or blindness in 2019, of which at least one billion cases could have been prevented with appropriate care.[2] This highlights the urgent need to develop new and effective strategies for ocular therapy. However, drug delivery to the eye is challenging due to its unique anatomy and physiology, which create barriers to effective distribution.

The eye can be divided into two major regions: the anterior and posterior segments. The anterior segment, which includes the aqueous humor, cornea, iris, conjunctiva, ciliary body, and lens, is more accessible and is conventionally targeted by topical instillation of eye drops.[114] In contrast, the posterior segment comprising the choroid, optic nerve, neural retina, retinal pigment epithelium, sclera, and vitreous humor presents greater challenges because drugs remain in the ocular globe for only a short duration, leading to poor bioavailability at the target site.[115]

Systemic administration has also been explored as an alternative, but the blood–retinal barrier severely limits drug availability, necessitating high doses to achieve therapeutic effects. This often results in undesirable systemic side effects.[2] Thus, ocular anatomy and physiology impose significant barriers that complicate the development of effective drug delivery systems for the eye.[116]

Natural polymers have gained attention as promising carriers for ocular drug delivery because of their favorable characteristics, including biodegradability, biocompatibility, non-toxicity, and mucoadhesiveness. They can extend the residence time of drugs on the ocular surface by interacting with mucin and reducing drug elimination, thereby improving absorption at the target site.[116] Moreover, polymers can be tailored to control drug release and address the bioavailability issues associated with conventional ocular therapies.[117]

Among nanosystems, biodegradable polymeric nanoparticles (10–100 nm) are the most widely investigated for ophthalmic applications. Their advantages include enhanced bioavailability, reduced dosage requirements, minimized side effects, and the ability to achieve targeted drug accumulation through passive or ligand-mediated processes. Critical design parameters include nanoparticle size, tissue retention, and the use of mucoadhesive polymers, all of which play a key role in determining therapeutic success in ocular drug delivery.[116]

7.3 Polymeric nanoparticles for oral drug delivery

Oral administration is the most widely used drug delivery route due to its convenience for patients. However, effective absorption can be challenging, particularly for hydrophobic drugs such as SN-38. Oral drugs are exposed to digestive enzymes that can degrade molecules, while the mucus lining of the gastrointestinal (GI) tract further limits absorption.[118] The duodenum and jejunum are the primary sites for drug absorption, whereas the stomach, with its smaller surface area and thicker mucus layer (~1.5 mm), exhibits lower drug absorption capacity. The intestinal epithelial lining represents a key barrier to effective oral drug delivery.[119]

Poor bioavailability is a major limitation of oral administration. Nanocarriers have emerged as an effective strategy to overcome these challenges.[120] Polymeric drug delivery systems, often composed of hydrophilic, viscoelastic networks, enhance the solubility of hydrophobic drugs and reduce rapid clearance by the reticuloendothelial system, thereby improving systemic exposure.[121]

Polymeric nanocarriers can also deliver insoluble drugs, target specific regions of the GI tract, mitigate the effects of food on absorption, facilitate transcytosis across the mucosal barrier, and enable receptor-mediated intracellular delivery.[119] Biodegradable polymers, in particular, offer controlled release, organ- or tissue-specific targeting, and the potential for oral delivery of DNA, peptides, and proteins.[120] Their versatility allows micro- and nanocarriers to transport a broad range of therapeutic and diagnostic agents including small molecules, nucleic acids, and proteins while providing regulated release. Consequently, polymeric nanocarrier-based oral drug delivery systems can enhance specificity, efficacy, and tolerability.[119]

7.4 Polymeric nanoparticles for rectal and vaginal drug delivery

The rectal route is effective for both local and systemic drug delivery, particularly for drugs with extensive first-pass metabolism, poor oral absorption, gastric irritation, instability in the gastric environment, or those requiring localized activity or alternative administration routes. The rectum provides a relatively constant and low-enzymatic environment, making it suitable for such drugs. However, limitations include low patient compliance, a small absorption area, pathological conditions, and interruption of absorption due to defecation.[122]

In a study, poly(ethylene oxide) (PEO) was used to develop polymeric nanoparticles of the anti-HIV drug dapivirine for vaginal and rectal delivery. Both *ex vivo* and *in vivo* experiments demonstrated increased drug retention compared with pure dapivirine. Additionally, PEO modification reduced *in vitro* toxicity.[123]

The vaginal route has long been employed for drug administration, offering advantages such as avoidance of hepatic first-pass metabolism and bypassing the gastrointestinal tract. Its appeal lies in the versatility of drug incorporation whether dissolved, adsorbed onto the surface, encapsulated within a polymeric matrix, or chemically conjugated. Polymeric nanoparticles, which are submicron-sized colloidal particles produced through mechanical or chemical methods, are commonly used for vaginal drug delivery. Polysaccharides such as alginate and chitosan are frequently employed in nanoparticle formulations, targeting cervical cancer prevention and therapy, as well as the delivery of contraceptives, vaccines, and microbicides for sexually transmitted diseases.[124]

8. Future prospective and conclusion

Polymeric nanoparticles are transforming drug delivery systems, offering an advanced and adaptable platform to overcome the limitations of traditional therapies for complex diseases such as cancer and bacterial infections. These engineered nanomaterials provide versatile systems that can be precisely designed to address therapeutic challenges, including overcoming biological barriers, enhancing drug bioavailability, enabling targeted delivery, and facilitating controlled release. The biocompatibility, biodegradability, and tunable properties of both natural and synthetic polymers allow exceptional

customization, resulting in therapies that are more effective and safer.

This review highlights that each type of polymeric nanoparticle possesses distinct properties suited for specific applications, emphasizing the importance of selecting polymers based on therapeutic objectives and drug characteristics. Natural polymers such as chitosan, albumin, and collagen contribute biocompatibility and tissue adhesion, whereas synthetic carriers like PLGA, PCL, and PEG offer tunable release profiles and enhanced barrier penetration. Functionalized polymers, including hyaluronic acid and gelatin, enable receptor-specific targeting and enzymatic responsiveness.

Despite these advantages, current limitations remain. These include inconsistent release kinetics, production scalability challenges, and insufficient long-term safety data. Comparative *in vivo* studies evaluating the safety, degradation behavior, and organ-specific accumulation of different polymer types are scarce. Although many systems show *in vitro* biocompatibility and selective cytotoxicity, standardized data on systemic clearance, immune activation, and metabolite toxicity—particularly for hybrid polymeric systems—are still lacking.

Future research should focus on optimizing nanoparticle formulations for enhanced drug delivery and efficacy, as well as investigating the long-term safety profile of polymeric nanocarriers in clinical settings. *In vivo* experiments, including animal cancer models, are essential to assess safety, efficacy, and potential side effects. In conclusion, polymeric nanoparticles represent promising platforms for antibacterial and anticancer therapy. Their adaptability for targeted drug delivery provides new avenues for developing customized, safe therapies with the potential to significantly improve patients' quality of life.

Author contributions

Harini A.: literature collection and writing – original draft. Ilaiyaraja Perumal: writing – review & editing and supervision.

Conflicts of interest

All authors declare that there are no conflicts of interest regarding this research.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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