

Review | Received 17 July 2026; Revised 3 September 2026; Accepted 3 September 2026; Published 30 September 2026
<https://doi.org/10.55092/bm20260009>

Functional, next-generation, polymeric materials for targeted and controlled drug delivery applications



Rahul Choudhary¹, Monideepa Roy¹, Vivek Puri¹, Divya Dheer¹, Manju Nagpal¹, Ameya Sharma^{1,*} and Pradeep Kumar^{2,*}

¹ Chitkara University School of Pharmacy, Chitkara University, Baddi, India

² Wits Advanced Drug Delivery Platform Research Unit, Department of Pharmacy and Pharmacology, School of Therapeutic Sciences, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

* Correspondence authors; E-mails: ameya.sharma@chitkarauniversity.edu.in (A.S.); pradeep.kumar@wits.ac.za (P.K.).

Highlights:

- Next-generation polymers enable targeted, controlled, and stimuli-responsive drug delivery.
- Molecular design, nanoengineering, and advanced fabrication govern therapeutic precision and performance.
- Emerging AI, sustainable polymer chemistry, and 4D printing can accelerate clinical translation and personalized therapy

Abstract: Despite their broad clinical use, conventional drug delivery technologies are still limited by inadequate bioavailability, non-specific biodistribution, and uncontrolled drug release, which compromise therapeutic efficacy and safety. With their customizable molecular architecture, physicochemical adaptability, and multifunctional, stimuli-responsive design, next-generation polymeric materials overcome these constraints and allow for precise, site-specific, and regulated therapeutic action. In addition to stimuli-responsive platforms and structurally diverse nanocarriers such as nanoparticles, micelles, dendrimers, polymerases, and nanogels, this review critically examines the molecular and physicochemical design principles, nanoengineering and fabrication strategies, such as self-assembly, microfluidics, and emerging 3D/4D printing. Moreover, the passive, active, and organelle-level targeting mechanisms that govern these systems. In addition to clinical translation challenges, existing research gaps, and emerging directions like sustainable polymer chemistry, AI-driven design, adaptive 4D-printed systems, and personalized therapeutics, their disease-specific applications in cancer, neurological, cardiovascular, and infectious diseases, chronic wound healing, and regenerative medicine are critically evaluated. When taken as a whole, next-generation polymeric materials provide a flexible, clinically translatable platform for accurate, effective, and safe therapeutic intervention. However, they also highlight the crucial issues that need to be addressed in order to expedite clinical translation.



Copyright©2026 by the authors. Published by ELSP. This work is licensed under Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium provided the original work is properly cited.

Keywords: next-generation polymers; polymeric nanocarriers; stimuli-responsive drug delivery; targeted delivery; controlled release; nanoengineering; 3D/4D printing; AI-driven design; personalized therapeutics; clinical translation; regenerative medicine; sustainable polymer chemistry

1. Introduction

1.1. Conventional drug delivery: limitations and the rationale for polymeric systems

Optimizing therapeutic outcomes while reducing side effects has been the primary goal guiding the development of drug delivery systems for more than 50 years [1]. However, the oral and parenteral formulations that now serve as the foundation for the majority of pharmacotherapy still have the same drawbacks as they did decades ago: poor water solubility, rapid systemic clearance, low bioavailability, and non-specific biodistribution [2]. These defects have proved amazingly persistent in incremental are not simply formulation irritations but are a direct consequence of the materials and excipients that underlie them. This tenacity has led to a lot of research on alternative delivery methods. Systems that are able to overcome biological barriers and enhance the effectiveness of medications [3]. The most significant of these constraints is still the lack of site-specific targeting [4]. Healthy tissue is exposed to amounts that are both subtherapeutic at the disease site and harmful elsewhere, when not needed. Drugs are systemically distributed using conventional methods [5]. In the case of treatments that have a narrow therapeutic window, such anticancer medications, where non-specific dispersion often results in unfavourable side effects, this liability is especially important [6]. This is compounded by the fact that poor bioavailability is often encountered, and oral delivery of active ingredients has been found to be affected by the excipients used, not the medicine itself: To resist the first pass enzymatic digestion, limited intestinal permeability and the acidic gastric environment. In contrast, the mononuclear phagocyte system is usually responsible for the clearance and opsonization of intravenous, before they even reach their target, formulations are created [7]. Another structural defect in the first generation of carriers materials is that they are not advanced enough to modify release based on physiological indicators, this leads to either uncontrolled burst release or partial delivery [8]. When non-biodegradable polymers are used, the material itself (not just the formulation) becomes liable for aggregation, immunogenicity and long-term toxicity [9]. The net clinical cost of conventional materials is compounding, not additive, since poor targeting compounds the systemic toxicity already exacerbated by uncontrolled release. The diseases these materials are intended to treat diseases, such as cancer, neurological diseases, and chronic infections, are dynamic and heterogeneous. Static excipients are not architecturally suited to deal with microenvironments [10]. The enduring trend, the gap between polymeric drug delivery and the other approaches has been a driving force for the advancement of polymeric drug delivery in the last few decades. The material capabilities and physiological requirement. Due to their diverse chemical composition and polymer is a very versatile structure for adjusting physicochemical properties, controlled-release carriers [11]. The most of the initial research was macroscopic: hydrogels, polymeric, this is because matrix and microspheres are designed to improve compliance by extended release and extended dose intervals [12]. Hydrogels are potential materials for targeted drug delivery and wound healing due to their high water content and biocompatibility [13]. As the research developed, focus switched to with the progress of research,

emphasis shifted to nanoscale designs, including as micelles, dendrimers, nanogels, and polymeric nanoparticles, which can improve stability, prevent the degradation of labile medicines, and pass biological barriers like the blood–brain barrier [14]. The immunogenicity and increasing toxicity issues of previous non-biodegradable materials were directly addressed by the coexisting introduction of biodegradable polymers, such as the (lactic-co-glycolic acid) (PLGA), PEG and chitosan also helped to achieve regulatory approval [15]. When considered collectively, this step, from macroscopic stores to nanoscale, disposable carriers, demonstrates more than just incremental improvement. It is a foundation for individualized, focused treatment approaches that Currently, complicated diseases require [16]. In order to fully realize this need, materials must be able to They should not simply carry a medicine, but should be platforms that respond to particular biological stimuli and deliver specific, regulated therapeutic responses as necessary [17].

1.2. Emergence of next-generation smart polymeric materials

Beyond the drawbacks of traditional platforms, next-generation polymeric platforms—the stimulation-responsive or intentionally “smart” behavior has given rise to a number of distinguished types in the field of drug delivery. These systems are designed to withstand expected physicochemical changes in response to which can be controlled by specific internal/external stimuli, for a controlled drug release kinetics, localization [18]. Depending on the kind of trigger they react to, polymeric materials that react to stimuli can be broadly categorized. Internal stimuli include physiological factors such as pH, redox potential, enzyme activity, and ionic strength [19]. For example, pH-responsive polymers selectively start medication release at the target region by taking advantage of the acidic milieu of tumors or inflammatory tissues. Similarly, redox-responsive devices achieve regulated drug release in cells by taking advantage of the increased intracellular concentrations of reducing agents like glutathione [20]. In order to enable site-specific medication activation, enzyme-responsive polymers are designed to break down in the presence of particular enzymes that are overexpressed in particular disease states [21]. External stimuli-responsive systems, on another hand, rely on triggers that are applied outside, such as light, temperature, magnetic fields, and ultrasound. Temperature-sensitive polymers, such as those with lower critical solution temperature (LCST) behavior, can withstand phase transitions in response to temperature changes, allowing for regulated drug release. Because certain light wavelengths can trigger medication release, light-responsive polymers have the advantage of both spatial and temporal accuracy. Magnetic and ultrasound-responsive technologies, which enable non-invasive drug release modification, significantly broaden the field of regulated delivery [22,23]. Next-generation polymeric materials incorporate sophisticated targeting techniques in addition to stimuli responsiveness. The enhanced permeability and retention (EPR) effect, which is the basis for passive targeting, was initially defined by Matsumura and Maeda as the aberrant, leaky vasculature and impaired lymphatic drainage of solid tumors that permit nanosized carriers to accumulate preferentially in tumor tissue [24,25]. A recent quantitative reevaluation of liposomal intratumoral microdistribution revealed that only about 4% of the injected dose reached the tumor after 24 hours, against significant sequestration by the liver and spleen, and demonstrated that carriers penetrating the tumor interstitium frequently released their payload before it reached target cells [26]. Even in cases where EPR-mediated accumulation does occur, its efficacy is far more modest than the paradigm suggests. More than any one biological aspect, this heterogeneity has emerged as the principal cause of

the uneven clinical performance of EPR-dependent nanomedicines and the main reason passive targeting is no longer that to be sufficient to ensure the best possible therapeutic results [27]. As a result, active targeting techniques have been used to improve the specificity of polymeric drug delivery systems. These methods include the modification of the surface of the carrier with ligands that bind to excessive numbers of receptors on target cells. One of the most commonly used targeting ligands are aptamers, tiny molecules such as folic acid, peptides and monoclonal antibodies. When the carrier binds to the target receptor, it is internalized thru receptor-mediated endocytosis, allowing for effective intracellular drug delivery. This targeted approach minimizes systemic toxicity and off-target effects as well as increasing therapeutic efficacy [28].

1.3. Scope and objectives of the review

In the wake of the fast development of nanotechnology and polymer science, the research area is called. The field of “next-generation polymeric drug delivery systems” is now very dynamic and interdisciplinary. These systems offer unparalleled opportunities to improve the accuracy, effectiveness and safety of Therapeutic interventions in a wide range of disease states. The main aim of this review is to provide a critical and comprehensive analysis of next generation polymeric systems for targeted and Applications in controlled drug delivery. The goal of the review is to critically assess the design in a systematic way. Focus on principles, classification and functional mechanisms of advanced polymeric carriers, particularly. Focus on stimulus responsive and targeted delivery strategies. It also endeavours to emphasize recent progressive developments in the field, including the development of multifunctional platforms that can carry out simultaneous imaging, medication delivery and diagnostics (theranostics) [29]. Additionally, this review talks about the main challenges associated with the clinical translation of polymeric drug delivery systems. These challenges include issues with long-term safety, regulatory approval, reproducibility, and mass production. The commercialization of these technologies is still in its early stages. significantly impeded by the complexity of polymer synthesis and characterization, as well as the need for uniform assessment procedures. Moreover, the review explores future prospects and emerging developments in the area such as the incorporation of AI into drug delivery design, Bioinspired and precision medicine approaches, as well as the development of personalized and precision medicine approaches in biomimetic materials. This book attempts to be a useful resource for researchers and clinicians. who are working on next-generation drug delivery systems, offering a detailed account of the latest developments and problems [30].

There is no reliable method to date to measure the EPR effect for passive targeting in this study. to gage a patient’s EPR strength prior to starting treatment. Instead, therefore, it is better to use indirect evidence. that a specific tumour will absorb the carrier, doctors select nanomedicine candidates for use. the type of tumour. The selection of patients for EPR-dependent medicines will continue to be a population-level educated guess. Instead of a customised decision, until a readily available pre-treatment biomarker or imaging test is available. developed [31].

2. Design principles of next-generation polymeric systems

The so-called “next-generation polymeric systems” are designed to be advanced drug delivery platforms. Improve the effectiveness, accuracy and security of therapeutic interventions. To achieve specific and

sustained drug release, these systems make use of smart polymers with customizable characteristics such as Biodegradability, stimuli-responsiveness and controlled architecture. They enhance site-specific delivery while reducing systemic adverse effects by reacting to particular biological cues such as pH, temperature, or enzymes. Their flexible structures can be used to encapsulate different medications, such as: Hydrogels, micelles, nanoparticles and dendrimers. All things considered, these technologies mark a significant improvement in the way medications are administered.

2.1. Molecular architecture and polymer chemistry

The primary way by which next generation polymeric materials achieve targeted and controlled the molecular architecture of medication delivery is the medication. The medication is the molecular architecture of medication delivery. The traditional approach to organizing design is around four best ways. Polymer types: linear, branched, dendritic and crosslinked network polymers. Each of these classes, offers a combination of drug loading capacity, degradation behavior, and stimuli-responsiveness that is unique. The choice of these categories is determined by comparing the structure of a polymer to the site-specific The properties and release kinetics needed for a specific application. Many controlled-release systems remain. Use linear, biodegradable polymers as their structural base. For example, bio-ceramic-reinforced PLA hybrid nanocomposites are made of linear poly (lactic acid) chains and nanoparticles. To enhance mechanical properties and wear resistance, such as electrospun fibers, hydroxyapatite, and TiO₂ are introduced. even at higher loads and speeds, as well as providing antibacterial activity, PET_IM and This type of PHT_IM formulations are suitable for internal bone-fixation applications [32]. By packing a high density of functional groups in a compact, self-assembling and easily adjustable structure, hyperbranched polymers (HBPs) deviate from this linear topology thru highly branched, non-linear development [33]. The targeting potential of this architecture was demonstrated by hPDPA, a pH-responsive hyperbranched polymer that was synthesized from a novel inimer (ABMA) and functionalized with PEG and poly-arginine via β -cyclodextrin recognition. It self-assembled into micelles and vesicles and, when loaded with doxorubicin, achieved effective internalization and induced apoptosis in HeLa cells [34]. More generally, HBPs produced using single-, double-, and coupling-monomer methods produce multi-cavity, multifunctional structures appropriate for tissue engineering, drug delivery, antibiosis, bioimaging, and bioadhesive applications, demonstrating the close relationship between molecular design and biomedical function in this architectural class [33]. In contrast to HBPs, which have more random branching, dendrimers are precisely branched, monodisperse, tree-like macromolecules with a well-defined size and surface valency due to their generation-controlled, repeated synthesis. The structural precision has shown versatility in gene delivery, diagnostics, and antimicrobial and antiviral applications including activity against COVID-19 and STDs. This is particularly the case of stimuli-responsive designs such as pH-, redox or tumor-microenvironment-sensitive, used to enhance release specificity and hemocompatibility [35]. The core structural benefits of the architecture are maintained while the surface functionalization enhances the targeting, stability, and biomimetic nature. Consequently, the significant drawbacks of traditional dendrimers, particularly toxicity and rapid systemic clearance, have been efficiently alleviated [36]. The fourth architectural class consists of crosslinked polymer networks, such as hydrogels, which are three-dimensional, covalently or physically crosslinked structures, which exhibit rapid water uptake and more stimuli-responsive activity. Hydrogel design has advanced from simple passive carriers to the same intelligent, responsive behavior

already attained in the micellar and dendritic systems mentioned above. Recent work using controlled RAFT polymerization has produced stimuli-responsive polymeric hydrogels engineered with precise structural and functional control, yielding biocompatible networks that function efficiently as carriers for hydrophilic drugs [37].

2.2. Physicochemical determinants

Three different, systematically related levels of physicochemical determinants control the performance of next-generation polymeric materials for targeted and controlled drug delivery: interaction parameters that determine how tightly the drug is held within the carrier, interfacial parameters that control how the assembled carrier is perceived by its biological environment, and molecular parameters inherent to the polymer chain itself. The two molecular factors that have the most downstream impact are molecular weight and polydispersity index (PDI), which affect circulation half-life, renal clearance thresholds, biodegradation kinetics, and the carrier's overall drug-loading and release profile. Unusual control over molecular weight and polydispersity has been made possible by the development of reversible deactivation radical polymerization (RDRP) techniques, such as RAFT, ATRP, and NMP. A result of this has been the development of nanocarriers that have a very uniform and consistent size and outcome, which translates the way in which they would behave within the body in its pharmacokinetics activities [38]. The relationship between molecular weight and how it is relevant in this study intuitively reveals the connection between porosity and molecular weight of different polymers, which have been proven to be very influential in terms of drug encapsulation efficiency, diffusion rates in the polymer matrix, and ability to respond to different stimuli [39]. Particle size is particularly relevant in the application area since it communicates molecular properties of a compound, which directly affect its later performance in particular processes: smaller nanoparticles (less than 200nm) allow for better tissue penetration and longer circulation time in the human body [40]. The definition of the physical dimension of the carrier is largely determined by its molecular properties and characteristics, however, the carrier's further development depends on other very important factors, which can be rather unrelated, and may dictate how the individual particles interact with the environment [38]. Zwitterionic surface chemistries are notably acting in response to the aforementioned hierarchy, where the cohesive properties of polymers containing any of the following moieties: sulfobetaine, phosphorylcholine, and carboxybetaine can form a stable hydration shell enabling great hemocompatibility and preventing bacteria fouling, platelet adhesion, and protein adsorption due to surface charge balance [41]. A similar interfacial trade-off can be referred to as surface hydrophobicity; while hydrophobic surfaces of nanoparticles facilitate encapsulation of non-water soluble drugs, they also promote plasma protein adsorption and consequently clearance by RES, both functions that recently turned out to be rather difficult to balance in carrier design [42]. The above-mentioned parameters enable a rational and application-specific selection of a polymer for certain therapeutic tasks as the molecular weight, hydrophobicity, and surface charge can be controlled at the same time [43]. The third level of interactions is concerned with direct physicochemical interaction between drug and polymer in term of whether the drug remains in place until needed. Together molecular and interfacial parameters determine the design of the carrier and its perception in the body. This drug-polymer interaction, whether covalent conjugation, hydrophobic entrapment, hydrogen bonding, or electrostatic complexation, collectively determines encapsulation efficiency, drug stability within the carrier, and

the rate and mechanism of payload release under physiological conditions. [44] The concept is demonstrated practically by PLGA-based co-delivery systems: spatial separation of drug cargoes with various physicochemical characteristics within core-shell architectures allows for programmed sequential release, while hybridizing PLGA with pH-, redox-, or enzyme-responsive polymers introduces stimulus-triggered release profiles controlled by the underlying drug–polymer interaction dynamics [40].

2.3. Nanoengineering and fabrication strategies

Whether a next-generation polymeric carrier can be reliably produced at a scale appropriate for clinical translation ultimately depends on nanoengineering and fabrication strategy rather than molecular design alone; the three technique families that currently rule this field are self-assembly, emulsion-based synthesis, and microfluidic production [40,45]. Self-assembly provides a bottom-up production path to structural uniformity without high-energy processing by taking use of the spontaneous, thermodynamically driven arrangement of amphiphilic polymer chains into distinct nanostructures. Instead, emulsion-based methods provide a versatile, easily scaled path to polymeric nanoparticles with adjustable size and form by imposing structure thru regulated interfacial and mechanical energy input. Instead, emulsion-based methods provide a versatile, easily scaled path to polymeric nanoparticles with adjustable size and form by imposing structure thru regulated interfacial and mechanical energy input [38]. By limiting mixing to certain channel geometries, microfluidic manufacturing directly controls reaction and diffusion durations, resulting in batch-to-batch consistency and repeatability that are difficult for traditional bulk technologies to match as shown in Figure 1 [46]. It has been demonstrated that switching from bulk to microfluidic production yields optimal aerosol droplet sizes of 38 μm and 64 μm at operating pressures of 14.7 and 7.4 bar and flow rates of 0.4 and 1.1 mL/s, respectively. Smaller droplets mean better dispersion of particles, a level of process control that cannot be achieved by bulk emulsification. By identifying the crucial flow conditions and reaction zones that control nucleation, growth, and morphology, CFD-guided microfluidic design enhances reproducibility and offers a direct, simulation-driven route to industrial-scale manufacturing. This precision is further extended upstream when microfluidics and CFD are combined [47]. Since three-dimensional printing is now used to create the microfluidic devices themselves, fabrication techniques and manufacturing equipment have also started to converge. This results in highly accurate, repeatable, and customizable synthesis platforms that enhance control over particle size, drug loading, and fluid dynamics while reducing material waste and enabling continuous, as opposed to batch-wise, manufacturing [46].

Exhibits a similar pattern: drug-polymer interactions, molecular weight, and surface charge are nearly always changed separately rather than in tandem [39,41,44]. Although this type of combinatorial mapping is uncommon in the current literature, a carrier's ideal molecular weight may change based on its hydrophobicity or surface charge. Instead of focusing on individual data points, design-of-experiments approaches that change many factors simultaneously would enable the discipline to develop predictive structure-performance models [39,43].

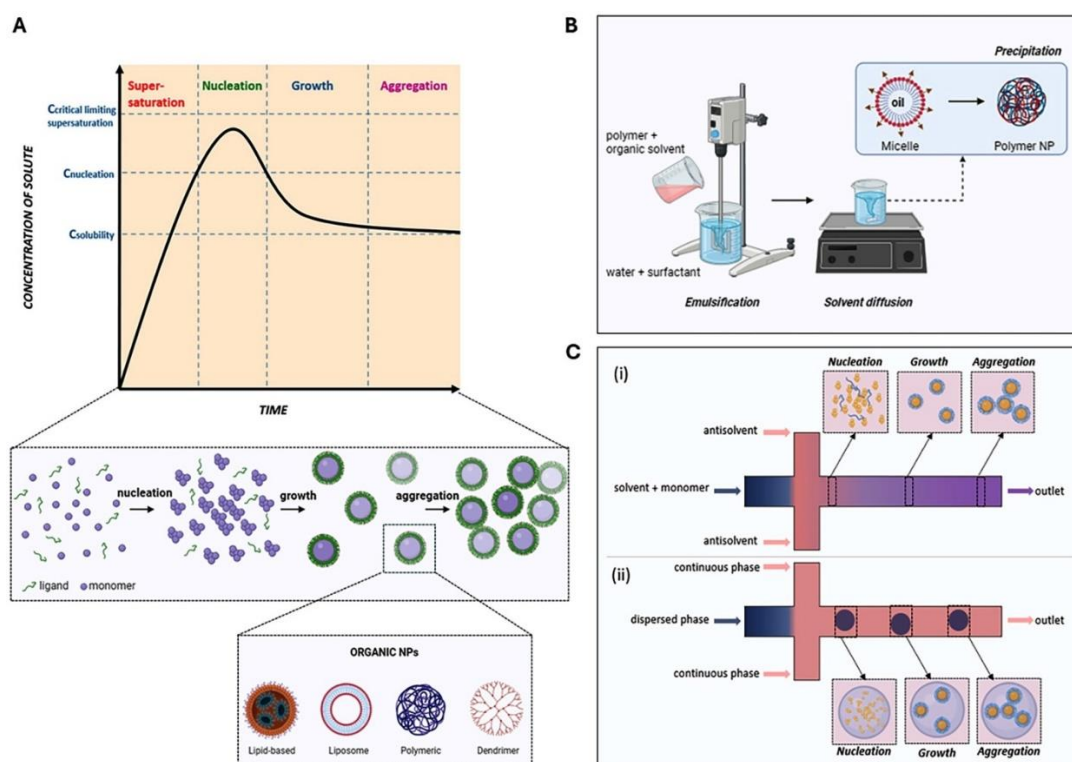


Figure 1. Schematic illustration of nanoparticle synthesis via nucleation and growth, showing (A) Diagram of the nanoprecipitation process, depicting changes in solute concentration during the formation of organic nanostructures; (B) Schematic of batch manufacturing for polymer nanoparticles applying the emulsion diffusion approach; (C) Mechanisms of nanoparticle synthesis within microfluidic devices using (i) single-phase and (ii) multiphase systems. Reproduced from tsitouridou *et al.* [46].

3. Targeted drug delivery strategies

Targeted drug delivery aims to selectively direct therapeutics to diseased tissues, enhancing efficacy while minimizing systemic toxicity. By exploiting biological markers and physiological differences, these systems improve drug accumulation at target sites and reduce adverse effects, representing a major advancement over conventional therapies [48,49].

3.1. Passive targeting

In passive targeting, diseases' pathological features like abnormal blood vessels and impaired lymphatic drainage are exploited in order to improve drug delivery to diseased tissues [50]. For instance, ROS-responsive mPEG-TK-PCL (methoxypolyethylene glycol-thioketal-polycaprolactone) micelles provide significantly better results in terms of cytotoxicity and effectiveness of anticancer treatment compared to other methods used in the past, demonstrating the effectiveness of hypoxic tumor targeting and achieving the efficacy of pH/ROS-induced drug delivery [51]. In addition, paclitaxel-loaded polymeric micelles provide effective pharmacokinetics as the distribution is improved, with complete clearance within 48 hours and free drug plasma levels reduced to 27% of C_0 /dose [52]. It was also established during liposomal pharmacokinetics studies that these types of micelles can accumulate in the liver (approximately 16.3% ID/g) and spleen (maximal numbers of ID/g

being 70.5%) while tumor accumulation is rather low (approximately 4% ID/g indicates the effectiveness of these drugs in tumor area 24 hours after injection of the drug) [53]. Tumor microenvironment-responsive RPP (Ruthenium-Polyphenol-Phloretin) nanozymes enhanced radiation by reducing glucose absorption and hypoxia, which led to about two times more radiosensitivity and increased ROS generation in tumor cells [54]. Similar to this, GSH (glutathione)-responsive POMs-SS-CPT (polyoxometalates and camptothecin) vesicles showed successful redox-responsive chemotherapy by facilitating targeted drug release that reduced off-target damage and suppressed tumor growth by roughly 65%–75% [55]. Even with these promising preclinical results, the clinical efficacy of passive targeting has long been described as much more myth than clinical reality, with EPR-mediated tumor accumulation consistently shown in preclinical models but much less consistently realized in patients as shown in Figure 2 [56]. The fundamental cause is now well established: human tumors exhibit a significantly more heterogeneous EPR effect than the rapidly expanding, highly vascularized preclinical models used to produce data of the type described above. These differences occur along axes like growth kinetics, stromal density, and interstitial fluid pressure, which undermine passive-targeting efficacy in ways that preclinical models do not capture [57]. Even a technically successful passive-targeting formulation delivers only a small, variable fraction of its payload to the intended site, with only about 4% of the injected dose reaching the tumor and the substantial majority sequestered by the liver and spleen, as demonstrated by the liposomal microdistribution data presented earlier in this section [53]. When considered collectively, these data show that passive targeting, although an essential basis for the creation of nanomedicines, is not a sufficient or trustworthy therapeutic approach on its own. This conclusion serves as the basis for the active-targeted techniques covered in the section that follows [56].

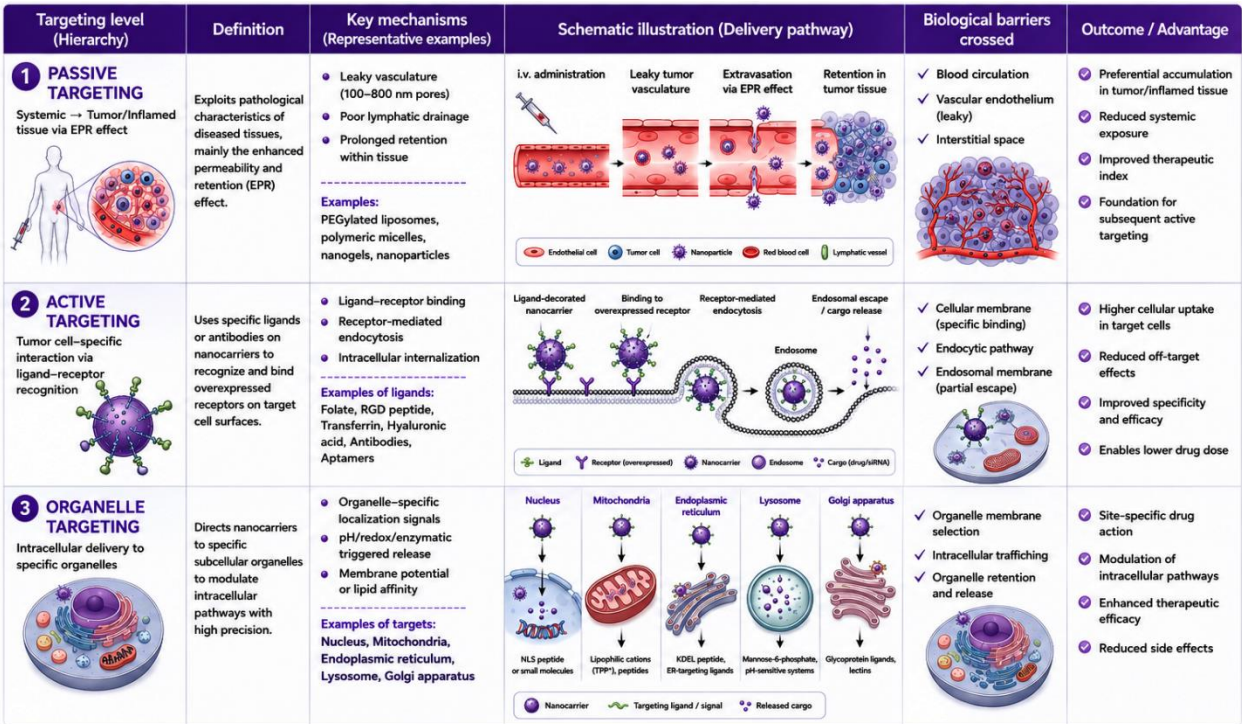


Figure 2. Diagrammatic illustration of passive (EPR effect), active (receptor-mediated endocytosis), and intracellular targeting approaches for drug delivery using nanocarriers (created using AI tool ChatGPT (GPT-5)).

3.2. Active targeting

Carriers functionalized with one of four ligand classes antibodies and antibody fragments, peptides, small compounds, and aptamers are most frequently used in active targeting, which makes use of particular ligand–receptor interactions to improve selective drug delivery and cellular absorption at sick areas [56]. Because of its developed, high-affinity identification of a single cognate antigen, antibody-based ligands provide the most target specificity of the four groups. Antibody-guided MOF-PQDs (Metal-Organic Framework–Perovskite Quantum Dots) nanocomposites enabled dual HER2/PD-L1 (Human Epidermal Growth Factor Receptor 2/Programd Death-Ligand 1) targeting with controlled drug release and multimodal imaging, enhancing tumor-specific delivery and therapeutic precision [58]. Similarly, a conjugation-free scFv-PLGA nanoplatfrom demonstrated its scalability and efficacy in targeted chemotherapy by outperforming clinical Nab-PTX (Nanoparticle Albumin-Bound Paclitaxel) in terms of stability and tumor accumulation, leading to enhanced anticancer activity [59]. In exchange for smaller size, reduced immunogenicity, and easier, more scalable conjugation chemistry, peptide ligands give up some of this selectivity. In comparison to the non-targeted prodrug, a cyclic RGD (Arg-Gly-Asp) peptide that was directly conjugated to a reduction-responsive camptothecin prodrug that self-assembled into polymeric nanoparticles took advantage of the peptide's high affinity for the $\alpha v \beta 3$ integrin receptor overexpressed on tumor cells to achieve greater intracellular drug accumulation, improved tumor-cell affinity, and prolonged systemic circulation [60]. Compared to antibodies and aptamers, small-molecule ligands are even smaller and offer good chemical stability and low production costs at the expense of binding specificity. Folate-functionalized Zein-PEI (Polyethyleneimine) nanoparticles showed reduced size (about 96 nm), selective cytotoxicity ($IC_{50} / IC_{20} = 52.5 \mu\text{g/mL}$; it's important to check which against your source; the manuscript currently states IC_{20}), and conjugation efficiency of about 45%, enabling efficient tumor-specific delivery [61]. The synthetic scalability of small molecules is combined with much of the specificity of antibodies in aptamers, which are single-stranded DNA or RNA sequences chosen for high-affinity target binding. The excellent specificity of aptamer-functionalized nanocarriers in targeted delivery was proven by GPC3 (Glypican-3)-targeted liposomes, which showed significant binding affinity ($K_D = 15.2 \text{ nM}$) and enhanced tumor suppression in hepatocellular carcinoma models [62]. Similarly, nuclear delivery was enhanced by AS1411 aptamer-modified nanoparticles, which decreased GFP (Green Fluorescent Protein)-positive cells to 30.0% from 40.8%, increasing gene-editing effectiveness and anticancer action [63].

3.3. Organelle and intracellular targeting

By guiding drug-loaded carriers to particular intracellular compartments for precise action, organelle targeting improves therapeutic efficacy. It is most effectively arranged around the three destinations and associated barriers that current strategies address: the nucleus, the mitochondria, and the endosomal compartment carriers must escape to reach either [64]. By delivering therapeutic cargo across the nuclear envelope, nuclear targeting directly affects transcriptional or genomic machinery. Aptamer-modified polymer–lipid nanoparticles enabled efficient nuclear transport of CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9), which reduced GFP-positive cells to 30.0% from 40.8% and enhanced the efficacy of gene editing in cancer

cells. Similarly, the nuclear-targeted photodynamic probe 1HA4CD (1-Hydroxy-Anthraquinone 4-Cyano-Dihydroxanthene) increased ROS levels, damaging DNA and inducing immunological reactions that resulted in significant tumor suppression and improved treatment outcomes [63,65]. Instead, mitochondrial targeting takes use of the organelle's crucial function in metabolism and apoptosis by driving selective carrier accumulation thru its distinctive negative membrane potential. MXene @ MnO₂-TPP (Transition Metal Carbide @ Manganese Dioxide–Triphenylphosphonium) nanoplateforms targeting mitochondria in osteosarcoma models induced ferroptosis and activated the cGAS–STING (cyclic GMP–AMP Synthase–Stimulator of Interferon Genes) pathway, generating ROS and significantly enhancing tumor suppression and survival [66]. Similarly, by raising CD8⁺ (Cluster of Differentiation 8-positive) T cell infiltration, increasing mitochondrial apoptosis, and reducing metastases, FU@TPP/PTE Mn²⁺ (Fucoidan @ Triphenylphosphine/Pterostilbene Manganese(II)) nanoparticles achieved dual targeting in breast cancer [67]. The majority of internalized carriers become trapped in endosomes and are degraded before ever reaching the nucleus, mitochondria, or cytosol, so escape from this compartment is often the rate-limiting step for both of the targeting strategies mentioned above. Endosomal escape tackles a unique, upstream issue shared by almost all nanocarrier types. pH-responsive copolymer nanovaccines that enhanced endosomal escape, enabled efficient cytosolic antigen distribution, and significantly enhanced CD8⁺ T-cell activation produced strong tumor suppression with good biocompatibility [68]. Lipid nanoparticles also illustrated the importance of controlled intracellular delivery pathways, demonstrating that enhanced endolysosomal trafficking and perinuclear accumulation greatly increase cytosolic release and transgene expression [68,69]. This allows targeting of the intracellular and organelle compartments using advanced nanoplateforms. By integrating the mitochondria-targeting peptides with the photosensitizers, a trimodular nanoplateform selectively targeted the mitochondria, with 0.98 colocalization, and triggered mitochondrial ROS, pyroptosis, and apoptosis, leading to nearly 100-fold higher killing of cancer cells and potent antitumor immune responses [70].

All three of the targeting strategies discussed in this section are connected by a structural gap: passive, active, and organelle-level targeting are nearly always studied separately, with one mechanism per carrier [58,62,65]. Although hierarchical targeting, that is, targeting of barriers at the tissue, cellular, intracellular and organelle levels sequentially has the potential to enhance targeting, few studies have integrated two or three levels of targeting in one platform and directly compared the efficacy of the combination with that of individual targeting. It is unclear if stacking targeting techniques add cost or provide a proportionate gain in the absence of head-to-head data comparing single- and multi-mechanism carriers [58,59,70].

4. Stimuli-responsive and smart polymeric systems

Stimuli-responsive polymeric systems, also known as smart polymers, enable controlled and site-specific drug release by responding to internal (pH, redox, enzymes) or external (temperature, light) stimuli. These systems enable precise spatiotemporal control of drug release, thereby enhancing therapeutic efficacy and minimizing off-target effects in targeted drug delivery applications (Figure 3 & Table 1) [71,72].

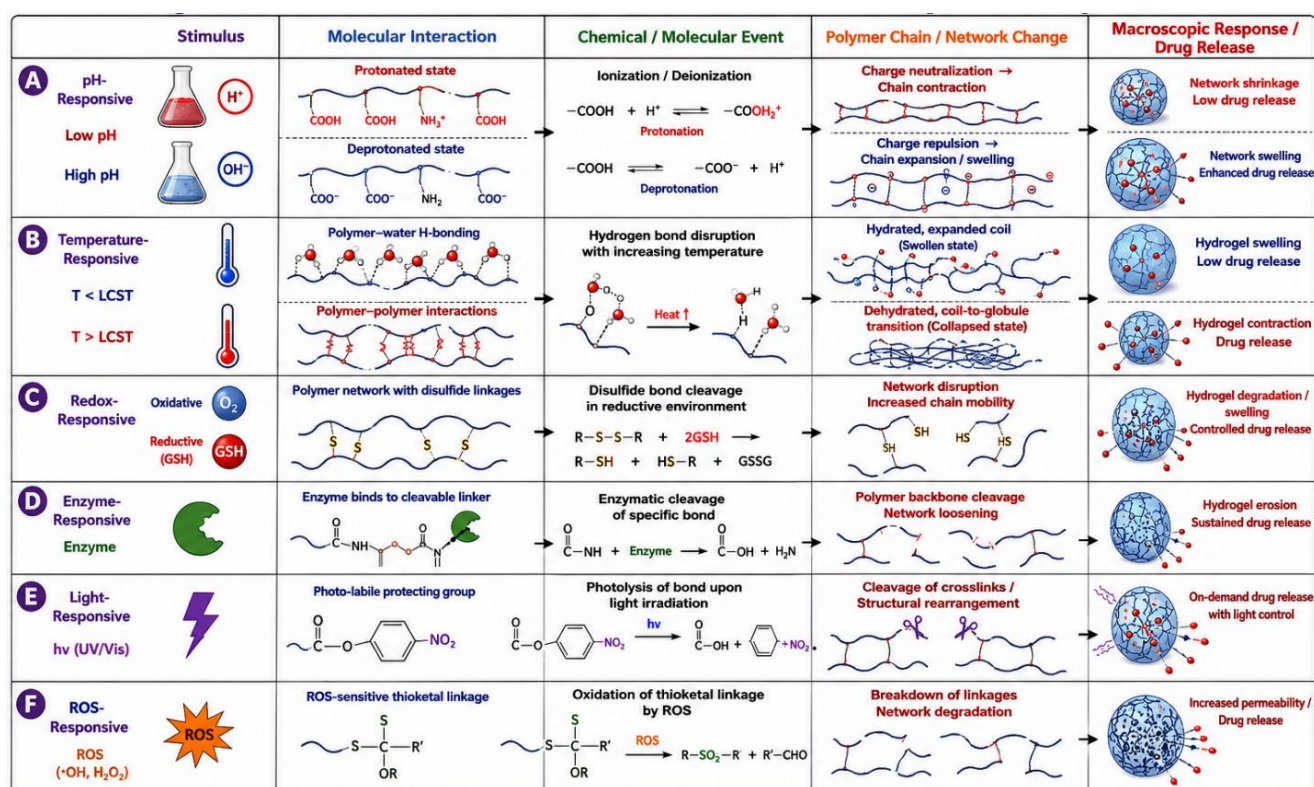


Figure 3. Stimuli responsive and smart polymeric system for targeted and controlled drug delivery (created using AI tool ChatGPT (GPT-5)).

4.1. pH-responsive polymers

A hydrogel composed of PVA-FBA/PEI (Aldehyde Polyvinyl Alcohol–Fluorobenzene Aldehyde/Polyethyleneimine) crosslinked by benzoic-imine linkages demonstrated good cytocompatibility and self-healing qualities, as well as negligible drug leakage at pH 7.4 and significantly increased doxorubicin (DOX) release at pH 6.8 [73]. These developments in pH-responsive polymeric materials have shown great promise for customized medication delivery in cancer treatment. In a similar vein, another research team developed a polycarbonate-based nanoplatfrom (PEDHNPs) with hydrazone and ketal linkages to achieve sequential erlotinib–DOX release, which led to a remarkable 71.54% suppression of A549 cell growth and a 95.1% reduction in tumor volume *in vivo* [71]. The pH-responsive PEDHNP nanoplatfrom exhibited 95.1% reduction in tumor volume *in vivo* in a non-small-cell lung cancer mouse model due to sequential erlotinib and doxorubicin delivery and synergistic antitumor effect [74]. Additionally, one study found that hollow molecularly imprinted polymers (H-MIPs) using Cu-MOF (Copper-based Metal-Organic Framework) scaffolds delivered DOX with an IC₅₀ of 2 µg/mL against MCF-7 breast cancer cells in acidic tumor conditions (pH 5, 41 °C) [75]. Another study created a biopolymeric formulation that simulated the tumor microenvironment by using injectable hydrogels based on hyaluronic acid and crosslinked by dynamic Schiff base linkages to produce bioadhesive, self-healing, and pH-triggered DOX release [76]. Another research team has studied and developed an injectable ROS/pH-dual-responsive hydrogel made by thioketal-aldehyde cross-linking that enables co-delivery of 5-fluorouracil and 5-aminolevulinic acid in order to achieve synergistic chemo-photodynamic tumor suppression along with wound healing [77].

4.2. Temperature-responsive systems

As shown by *in vivo* wound closure and epidermal regeneration significantly accelerated by a PNIPAM/MA- β -CD hydrogel dressing that demonstrated a precisely tuned phase transition at 37 °C, achieving a 55.6% volume shrinkage and 95.34% drug release efficiency—a 10.5-fold increase in shrinkage and a 2.7-fold enhancement in release compared to unmodified PNIPAM [78]. Similarly, PNIPAAm-based injectable nanocomposite hydrogels crosslinked with ROS-cleavable thioketal linkers showed an LCST of 33.6 °C–36.3 °C, extending this concept to oncology and allowing for selective drug release after 670 nm laser irradiation for PDT/PTT synergistic cancer treatment [79]. Similarly, a dual pH/thermo-responsive PNIPAM-g-dextran/sodium alginate hydrogel (DSPD-Hg) demonstrated better tumor suppression against oral squamous cell carcinoma and prolonged doxorubicin release under NIR irradiation without causing systemic toxicity [80]. In a different study, a tissue-adhesive PNI-SA @ Cur hydrogel for wound healing promoted suture-free wound closure, reduced inflammatory infiltration, and enhanced angiogenesis and collagen deposition by combining thermoresponsive PNI with chitin/lignin-curcumin micelles [81]. Additionally, a chitosan/ β -glycerophosphate/gelatin thermosensitive micelle-hydrogel composite (BPA @ Gel) allowed for sustained localized delivery of bempedoic acid, which significantly decreased pro-inflammatory cytokines and alveolar bone loss in a rat model of periodontitis by activating AMPK [82].

4.3. Redox-responsive systems

Redox-responsive polymeric materials that exploit intracellular glutathione (GSH) gradients have enabled targeted delivery of cancer drugs. Amphiphilic polyurethane nanocarriers containing monosulfide, disulfide, and trisulfide bonds gradually increased GSH sensitivity; trisulfide bonds demonstrated the strongest redox-responsive behavior and the best *in vivo* antitumor efficacy against DOX-loaded nano micelles [83]. Building on this concept, a hyaluronic acid-based glycopeptide nanocarrier (HCTK, 88.43 $\pm$ 1.96 nm) was able to achieve GSH-triggered release of 80% payload under tumor-mimicking conditions (10 mM GSH), which led to a 23.78-fold increase in tumor uptake via CD44 targeting and an 80.32% tumor *in vivo* [84]. Similarly, an injectable WPU-GSH/HA hybrid hydrogel enabled sustained DOX release (< 20% at pH 7.4 over 28 days) in patient-derived pancreatic cancer organoids, which increased to 65% under combined acidic-reductive stimuli, leading to a > 97% viability loss [85]. Additionally, a pH/GSH dual-responsive copolyprodrug (P(DSH-DOX-Fc)-PEG) containing ferrocene (14.0%) and DOX (65.5%) induced synergistic chemo-ferroptosis with a combination index of 0.68 in 56 hours with only 7.2% premature leakage [86]. Furthermore, a biotin-disulfide-artesunate combination (Bio-SS-ART, 158.6 nm) demonstrated 3.92-fold higher cellular absorption and 11.85-fold improved cytotoxicity against MCF-7 cells in comparison to free artesunate [87].

4.4. Enzyme-responsive polymers

Enzyme-responsive polymeric materials have become precision platforms for tumor-specific drug delivery by using overexpressed intracellular enzymes as selective triggers. For example, when combined with anti-PD-1 (Programmed Cell Death Protein 1) treatment, enzyme-powered GOD (Glucose Oxidase)-encapsulated micellar nanoreactors used the acidity of the tumor to trigger cascade

ROS amplification and pro-paclitaxel activation, which led to a significant tumor regression in orthotopic pancreatic cancer [88]. A recent study found that while a cathepsin B/pH cascade-responsive peptide nanoplatfrom improved endo/lysosomal escape via *in situ* nanofiber synthesis, HR/siBcl-2 complexes (Histidine-Arginine/small interfering B-cell lymphoma) significantly suppressed 4T1 tumor development *in vivo* [89]. Furthermore, cathepsin B-cleavable ciprofloxacin prodrug nanoparticles (MTCP-NPs) targeted the intramacrophage *Fusobacterium nucleatum* in colorectal cancer when combined with anti-PD-L1 therapy, eradicating bacteria and enhancing anti-tumor immunity [90]. Additionally, self-assembling FRRL-DOX (Phe-Arg-Arg-Leu-Doxorubicin) nanoparticles (165.1 ± 24.7 nm) demonstrated Cathepsin B-specific ICD (Immunogenic Cell Death) induction, eliminating DOX-associated cardiotoxicity and achieving 100% total tumor regression when combined with anti-PD-L1 [91]. Finally, the theranostic prodrug NM-001 (Nuclear-targeted Monomer-001), which used cathepsin B-triggered GFLG (Glycine-Phenylalanine-Leucine-Glycine) cleavage to release chlorambucil with a concurrent green-to-NIR fluorescence shift, enabled real-time dual-channel monitoring of drug delivery dynamics *in vivo*. Despite these promising outcomes, enzyme-responsive systems have a translational vulnerability that the aforementioned case studies do not address: the therapeutic consistency these systems are intended to provide is directly threatened by the inter-individual and intra-tumoral variability in enzyme activity [92].

The trigger enzymes themselves, cathepsin B foremost among them given its use in four of the five platforms described here, are not expressed uniformly across patients or even across regions of the same tumor. Therefore, in patients with abnormally high expression, a carrier calibrated to trigger at population-average cathepsin B activity may release its payload prematurely, risking systemic toxicity, or fail to release enough drug in patients with low expression, resulting in subtherapeutic dosing an asymmetric risk that preclinical models using a single, genetically homogeneous cell line or xenograft are structurally unable to reveal. To overcome this problem, it will probably be necessary to stratify patients by enzyme-activity biomarkers prior to treatment or to design carriers with configurable, self-adjusting trigger thresholds, rather than assuming a fixed enzyme-expression profile that is the same for the entire treated population [93].

4.5. Multi-stimuli responsive platforms

The development of stimuli-responsive nanocarriers, such as dual-responsive diblock copolymers, which disintegrate at pH 5 but form stable nanoparticles at physiological temperatures (27–31 °C) and achieve 40% acetal hydrolysis in 20 hours to promote cargo release, has revolutionized targeted medication delivery by matching polymer architecture to specific disease microenvironments [94].

Similarly, under mild heat stress or acidic circumstances, PISA-synthesised PTEGMA-b-PDPA nano-objects show morphological plasticity, enabling the encapsulation and triggered release of hydrophobic compounds [95]. In a different study, redox-responsive protein nanoparticles (RR-PAL-NPs) employ glutathione-mediated triggers in addition to pH and temperature. They cause significant G0/G1 phase arrest and mitochondrial depolarization while achieving high entrapment efficiency (91.23%) and releasing up to 88.98% of Palbociclib in 10 mM glutathione [96]. Furthermore, for adaptive biosensing, PISA-generated nanogels offer reversible, tunable swelling. Finally, meta-analyses of preclinical data show that therapeutic efficacy is maximized when polymer functional motifs, such as

oxidation-sensitive polyethers or enzyme-degradable matrices, are carefully matched to disease-specific biochemical signatures, such as oxidative stress or protease overexpression [97,98].

One particular shortcoming of the stimuli-responsive literature is that trigger conditions are typically set at a single idealized level, such as a flat 10 mM glutathione concentration that represents the tumor cytosol [84]. As previously mentioned for enzyme-responsive systems in particular, real tumors exhibit a distribution of trigger levels rather than a single value, and that distribution varies between patients and within a single tumor. In contrast to one assumed value, very few systems in Sections 4.1 to 4.5 describe how release performance varies over a realistic range of trigger strengths [86,96].

Table 1. Stimulus-responsive polymeric drug delivery systems: mechanisms, trigger conditions, representative therapeutic efficacy, and disease applications.

System	Trigger conditions	Representative efficacy	Applicable diseases
pH-responsive (4.1)	Acidic tumor/endosomal pH (5.0–6.8) vs. physiological pH 7.4	Negligible drug release at pH 7.4; enhanced DOX release at pH 6.8 [73]. Sequential erlotinib–DOX delivery achieved 95.1% tumor-volume reduction [74].	Breast cancer, NSCLC, postoperative cancer therapy, wound healing
Temperature-responsive (4.2)	LCST transition ~33–37 °C; NIR/laser irradiation	PNIPAM-based hydrogel showed 55.6% shrinkage and 95.34% drug release [78]. NIR-triggered systems enabled selective drug release [79,80].	Wound healing, oral squamous cell carcinoma, periodontitis
Redox-responsive (4.3)	Elevated intracellular GSH (~10 mM) vs. low extracellular GSH	Up to 80% payload release at 10 mM GSH [84]; combined acidic/reductive stimuli increased release from < 20% to 65% [85].	Breast cancer, pancreatic cancer, colorectal cancer
Enzyme-responsive (4.4)	Overexpressed tumor-associated enzymes, mainly cathepsin B and glucose oxidase-related tumor conditions	Enzyme-triggered systems produced cascade ROS amplification [88]; cathepsin B-responsive nanoparticles achieved complete tumor regression when combined with anti-PD-L1 [91].	Pancreatic, breast (4T1), colorectal cancer
Multi-stimuli responsive (4.5)	2–3 combined triggers: pH + temperature ± redox	Dual-responsive polymers showed 40% acetal hydrolysis in 20h [94]; redox/pH/temperature-responsive protein nanoparticles achieved 88.98% palbociclib release at 10 mM GSH [96].	Cancer therapy, targeted drug delivery, adaptive biosensing

5. Advanced polymeric nanocarriers

Polymeric nanocarriers such as nano micelles, nanogels, and dendrimers play an important role in nanomedicine by improving drug delivery, imaging, and biosensing. They enhance solubility, enable targeted and controlled release, cross biological barriers like the BBB, and improve diagnostic imaging and analyte detection. Although challenges in large-scale production and clinical use remain, they show strong potential for personalized medicine [99]. Dissolving microneedles efficiently release nanocarriers transdermally by avoiding the stratum corneum barrier. Nevertheless, interactions between the

nanocarriers and the DMN polymer matrix result in a “polymer modification effect” (PME), which may inadvertently change the physicochemical characteristics of the nanocarriers. *In vivo* drug release behavior, biodistribution, clearance, and cellular uptake are all impacted by these modifications. Optimizing next-generation nanocarrier-loaded DMN systems requires an understanding of and control over PME [100]. As biocompatible and biodegradable nanocarriers, food-derived biopolymers show great promise for improving the stability, bioavailability, and controlled release of bioactive substances. Additionally, more advanced technologies such pH-sensitive systems and customized delivery platforms are also contributing to improving their functional efficacy. In general, these polymers appear to be suitable for use in oral vaccines, nutraceuticals, and smart food systems which fit the direction of personalized nutrition [101].

5.1. Polymeric nanoparticles

Polymeric nanoparticles (PNPs) can range from chitosan, polyethylene glycol (PEG), to poly PLGA, and are known to be physiochemical structures that are biodegradable, biocompatible, and that can encapsulate different therapeutic agents. The release of the drug takes place via diffusion and physical degradation of the polymeric host, unrelated to the ways that substances can be targeted as discussed in Section 3 and 4. Whether the PNPs are targeted intentionally or not has an effect on the treatment success, lower toxicity for the patient associated with the usage of PNPs [102]. The advantages of using stimuli-responsive PNPs capable of reacting to pH, redox, and mixed triggers in terms of release increase were significantly enhanced [103,104]. Hybrid lipid-polymer nanoparticles made it possible to apply the structural principle to the area of nucleic acids, such that the effective mRNA delivery with the great immunogenicity and anticancer activity was observed almost the same as with the classical lipid nanoparticles. This fact serves as the proof of the applicability of hybrid polymer structures in practice [105]. The same trend could be noticed in the case of osteomyelitis when the targeted design of the surface chemistry enabled effective accumulation of the drug in the bone where the reduction of germ quantity was seen as a result of such an activity and the accumulation of local drug [106]. In addition, the polymeric hybrid nanoparticles have become the efficient vehicle for the delivery of poorly soluble drugs, like ursolic acid, due to their hybrid structure which combined the merits of both types of nanoparticles and provided prolonged release and enhanced performance in the leishmaniasis [107].

5.2. Polymeric micelles

These are composed of amphiphilic block copolymers and represent nanoscale self-assembling carriers with a hydrophobic core to encapsulate poorly water soluble drugs and a hydrophilic shell that provides colloidal stability and prolonged circulation. Section 4 discusses stimuli-responsive release as a structural add-on. Section 3 discusses ligand-mediated active targeting as a structural add-on. This core-shell structure results in concrete loading and release performance. Thiomeric poly (MAA-CA-Cyst) micelles stabilized gold and silver nanoparticles with significant anti-Alzheimer's activity. Silver nanoparticles showed higher apoptosis induction. Mucoadhesion (47%) and sustained drug release (21% over 180 min) were efficient [108]. The synthesis based on RAFT (Reversible Addition-Fragmentation Chain-Transfer) polymerization permitted accurate structural control of

the micelle size (80–200 nm), thus permitting tunable drug release and multipurpose uses such as co-delivery and haemostasis [109]. High encapsulation effectiveness (around 90%), better solubility (up to 335-fold), and extended release (72 hours) were all achieved by structurally modified micelles for bicalutamide, which immediately translated into increased cytotoxicity against cancer cells [110]. Chitosan-based micelles (Cela/GCTR PMs) circumvented P-glycoprotein (P-gp) efflux, thereby enhancing oral bioavailability and reducing celestrol systemic toxicity while allowing controlled release. The effectiveness of this technology in targeting tumor using Section 3, which provides evidence for any tumor-targeting property of chitosan micelles [111]. Additionally, in acidic tumor circumstances, microfluidics-fabricated micelles (fabrication procedure described in Section 2.3) showed regulated size distribution and faster drug release, supporting effective delivery of chemotherapeutics such as docetaxel [112].

5.3. Dendrimers

Dendrimers are highly branched, nanoscale polymers with a unique, tree-like structure that make them perfect drug delivery vehicles: a multivalent surface allows conjugation of both medicines and targeting ligands, the mechanisms of which are described in Section 3, while interior holes improve drug solubility and stability. In comparison to free drug, HA (hyaluronic acid)-decorated PAMAM (polyamidoamine) dendrimers (G4-HA+5ASA) significantly enhanced colonic drug accumulation, reduced inflammation, and improved pharmacokinetics in TNBS-induced colitis; the CD44-mediated targeting mechanism underlying this accumulation is discussed in Section 3 [113]. Similarly, designed dendritic systems (1218D/pDNA) generated complexes of about 255–371 nm with a charge of +21 to +23 mV, which showed about 6-fold higher transfection efficiency, sustained drug release, and antibacterial action directly attributable to this structural design [114]. OA-G4 dendrimers demonstrated structural performance metrics in brain targeting that allowed for effective nose-to-brain transport and decreased cognitive decline: 78.59% $\pm$ 5.52% drug loading, 62.12% $\pm$ 0.67% entrapment, and 68.44% $\pm$ 1.88% release in 24 hours [115]. While polyester bis-MPA-COOH dendrimers showed structurally similar pH-responsive drug association and controlled release behaviour, with the underlying stimuli-responsive design principles described in Section 4, glucose-responsive PPI (Polypropylenimine) dendrimers achieved insulin release up to 65% under hyperglycaemic conditions with encapsulation efficiencies of 73.6% and 85.8% and roughly 100% cell viability as shown in Figure 4 [116,117].

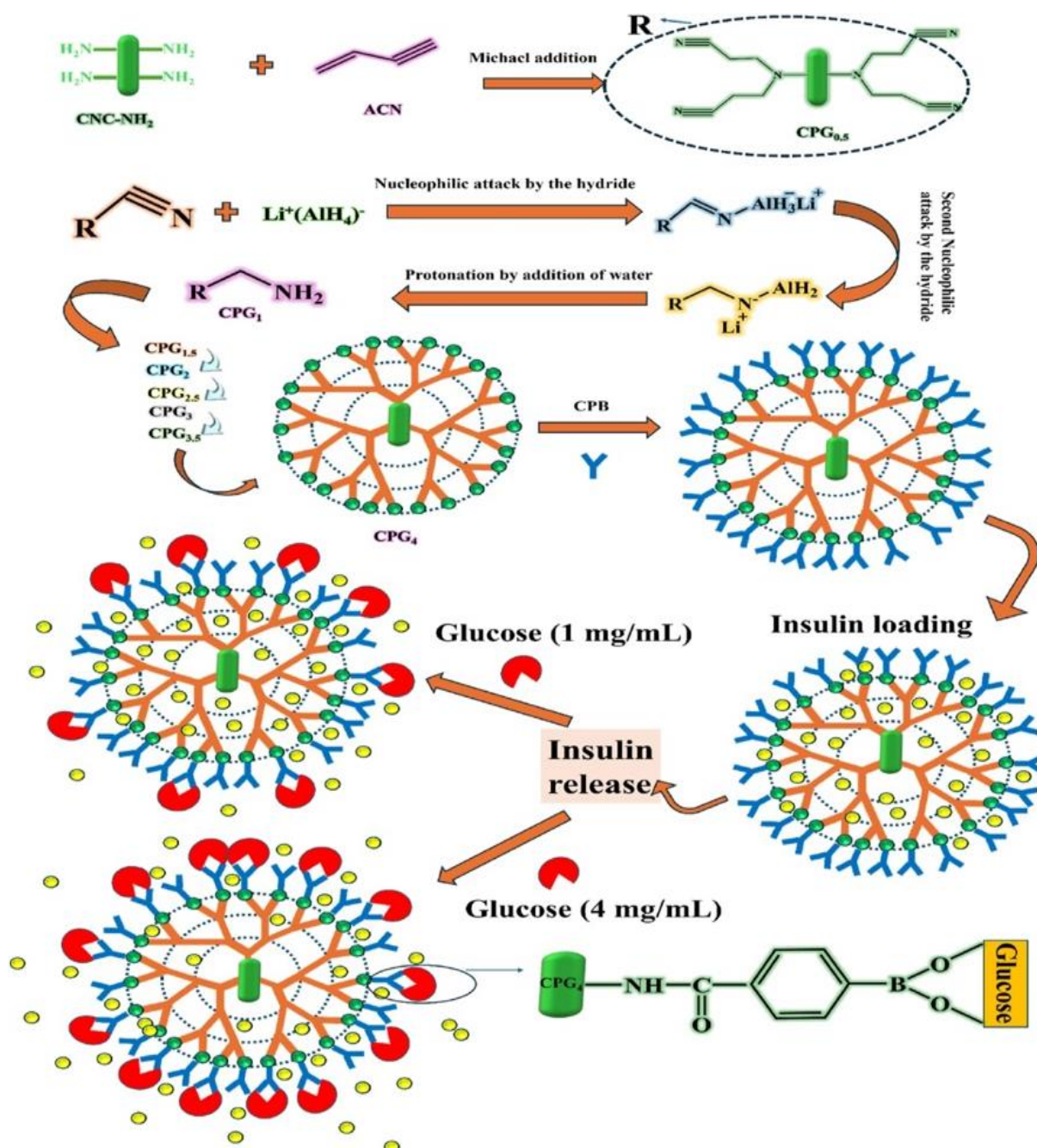


Figure 4. Schematic representation of the CPG dendrimer synthesis and its subsequent functionalization with CPB. The diagram further demonstrates the process of insulin encapsulation and its controlled, glucose-responsive release at concentrations of 1 and 4 mg/mL. Reproduced from sharifabad *et al.* [117].

5.4. Polymersomes

Numerous studies show how the structural design of polymersomes, which self-assemble from amphiphilic block copolymers, translates into loading and release performance, making them highly versatile nanocarriers for targeted and regulated drug administration. With the underlying stimuli-responsive chemistry described in Section 4, structurally hypoxia-sensitive doxorubicin (DOX)-loaded polymersomes showed increased cytotoxicity and apoptosis under hypoxic conditions, achieving *in vivo* tumor suppression comparable to free DOX while significantly reducing systemic toxicity, as evidenced by decreased weight loss in

treated mice [118]. Similarly, in OVX rat models, teriparatide (PTH 1–34) delivered by bone-targeted PLGA-PEG-Su-Asp polymersomes (targeting mechanism in Section 3) showed strong hydroxyapatite affinity (64.86%) and optimized structural properties (size 245.78 ± 8.2 nm, PDI 0.352 ± 0.12 , zeta potential -18.89 ± 0.1 mV, and $72.20\% \pm 2.9\%$ entrapment efficiency) [119]. In a different approach, HSA (Human Serum Albumin)-coated PLLA-Cys-melittin polymersomes (PMH NPs) demonstrated enhanced toxicity in cancer cells, reduced hemolysis, and significant tumor volume reduction *in vivo* without altering body weight or causing organ damage, a direct result of the coating's structural design [120]. Additionally, GSH-responsive prodrug polymersomes (PED @ ICG; responsive chemistry in Section 4) produced substantial anticancer efficacy by synergistic photothermal therapy without requiring exogenous copper by achieving customized intracellular drug release and deep tumor penetration [121]. Urease-coupled ammonia-sensing polymersomes showed high selectivity and real-time monitoring by rapidly and linearly detecting urea in blood, successfully differentiating clinically relevant concentrations in less than a minute. Polymersome-based microreactors also showed diagnostic potential structurally different from drug delivery [122].

5.5. Nanogels

Nanogels are discrete, nanoscale, crosslinked colloidal polymer particles, distinct in both scale and morphology from the bulk, macroscale networks that define hydrogel nanocomposites (Section 5.6), and their small size and customizable crosslink density translate directly into tunable drug encapsulation and release. Effective drug encapsulation (74.52%) and controlled release were shown by chitosan-based nanogels (CS-g-PDEAEA/AA @ ER), which structurally translated into considerable cytotoxicity against A549 tumor cells, reducing cell viability to 11.56% at 200 $\mu\text{g/mL}$ [123]. Similarly, for the treatment of osteoarthritis, a dual-responsive nanohydrogel system (KPP @ PLEL) produced enhanced cartilage penetration, prolonged retention, and effective kartogenin delivery—a penetration profile only possible at nanogel-scale dimensions—which resulted in significant cartilage regeneration and slowed disease progression *in vivo* [124]. Additionally, as a direct structural result of the functionalized nanogel network, lysine-functionalized silver nanoparticle nanogels demonstrated superior hemostatic performance in comparison to conventional treatments, with a shorter hemostatic time ($117 \text{ s} \pm 2.99 \text{ s}$) and less blood loss ($0.332 \pm 0.03 \text{ g}$), all while maintaining good biocompatibility and low toxicity [125].

5.6. Hydrogel nanocomposites

In contrast to the free-standing colloidal particles that characterize nanogels (Section 5.5), hydrogel nanocomposites are bulk, macroscale, crosslinked polymer networks that incorporate discrete nanoscale fillers, such as metal nanoparticles or carbon nanomaterials, throughout their matrix. This composite structure enables the bulk gel to inherit functional properties from its embedded nanomaterial. Accurate spatiotemporal drug release was obtained using an injectable second near-infrared (NIR-II)-responsive nanocomposite hydrogel comprising carbon nanotubes coated with gold nanoparticles, leading to synergistic chemo-photothermal treatment with enhanced *in vivo* antitumor efficacy [126]. Similarly, in a breast cancer mouse model, a composite hydrogel that combined a gelatin-oxidized alginate (Gel-OA) matrix with chitosan-coated zein nanoparticles allowed for structurally compartmentalized dual-drug delivery, with doxorubicin contained within the bulk hydrogel and quercetin contained

within the embedded nanoparticles. This resulted in significant tumor growth inhibition and decreased lung metastasis [127].

Performance is nearly often provided as a single point estimate, such as one particle size, one encapsulation efficiency, or one release curve, rather than as a swept range among the nanocarrier types in this section [110,115]. It is much less frequent to find true structure-performance relationships that demonstrate how loading or release vary with size, crosslink density, or surface chemistry [109,124]. Because it is frequently unclear which structural element truly caused the stated performance, results are difficult to apply to a different medication or target [110,119].

6. Applications in disease-specific therapy

Applications in disease-specific therapy entail creating therapies that specifically address a disease's fundamental cause as opposed to only relieving its symptoms. This method makes use of cutting-edge techniques including gene therapy, targeted drug delivery, and personalized treatment based on a person's genetic and molecular profile. It lessens adverse effects while increasing the effectiveness of treatment. In diseases including cancer, genetic disorders, and autoimmune diseases, disease-specific therapy is frequently used. Therapies are designed to block specific pathways or mutations, resulting in better quality of life and clinical outcomes for patients.

6.1. Cancer therapy

The use of many different polymers such as chitosan, polycaprolactone (PCL), and poly PLGA makes polymeric nanoparticles (PNPs) highly effective in the delivery of cancer drugs, adding stability to drugs and improving their bioavailability and therapeutic efficiency while minimizing toxicity to the body. Drug accumulation in tumours and patient survival outcomes have been greatly enhanced by their capacity to accomplish both passive targeting through increased permeability and retention and active targeting through ligand functionalization [128]. By enhancing peptide stability and delivery, advanced systems such as pH-responsive peptide-loaded nanoparticles (P-NPs) based on PEO-PC7A further demonstrate improved immunotherapy. They exhibit uniform particle size (91.2 ± 3.5 nm), increased T-cell cytotoxicity, elevated interleukin-2 secretion, and superior tumor inhibition with higher interferon- γ levels *in vivo*, without significant toxicity as shown in Figure 5 [129]. In a comparable manner pH-sensitive polymeric photosensitizer nanoparticles (Pc4-NPs and TT1-NPs) exhibit improved tumor penetration, high photocytotoxicity, selective action on cancer cells, and effective induction of apoptosis via reactive oxygen species generation and inhibition of Akt phosphorylation [130]. Despite these developments, obstacles like quick clearance, little tumour accumulation, and biological barriers still exist. Nevertheless, improving physicochemical characteristics like size, shape, and surface chemistry has shown promise in getting around these restrictions and improving delivery effectiveness [131]. Additionally, in the treatment of colorectal cancer, nanocarrier systems such as PNPs, quantum dots, and lipid-based nanoparticles have shown up to 70% improved therapeutic efficacy, a 50% increase in bioavailability, decreased systemic toxicity, and improved imaging capabilities for accurate tumour targeting [132].

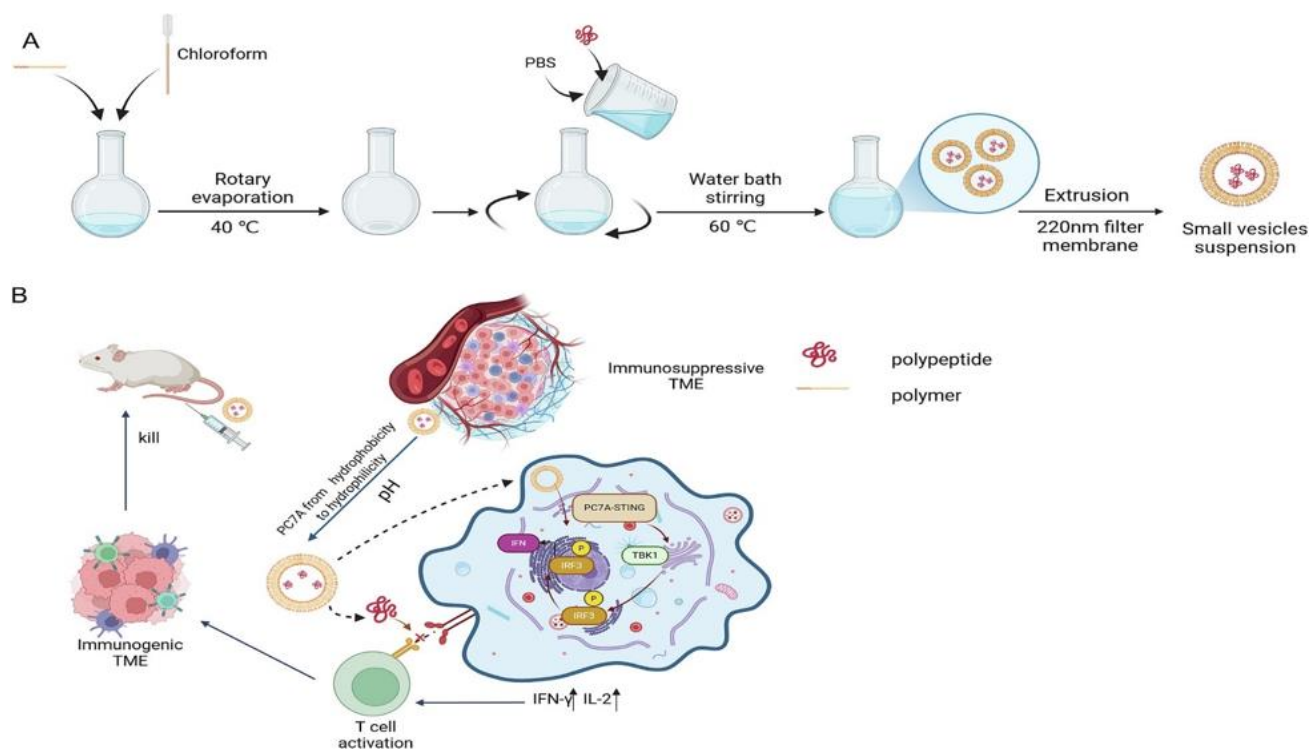


Figure 5. Design and function of peptide-loaded, pH-responsive nanoparticles (P-NPs). The schematic highlights the nanoparticle assembly process, subsequent morphological and charge-reversal transitions upon stimulation, and their underlying role in mediating synergistic immunotherapy. Reproduced from Rui *et al.* [129].

6.2. Neurological disorders

As opposed to only treating symptoms, disease-specific therapy for neurological illnesses aims to address the underlying causes of diseases. Precise treatments for diseases like Alzheimer's, Parkinson's, epilepsy, and multiple sclerosis are now possible because to developments in molecular biology, gene therapy, and targeted medication delivery. Gene silencing, neuroprotective drugs, and blood-brain barrier-crossing drug delivery systems based on nanoparticles are some of these strategies. Medications specific to the condition lead to improved efficiency and reduced adverse effects and open new avenues for personalized therapy in neurology, which focuses on the unique disease process of the patient.

Parkinson's disease (PD) is a progressive neurological illness characterized by degeneration of the dopamine-producing neurons in the substantia nigra pars compacta, whose process leads to motor disorders that include tremors, bradykinesia, and rigidity. A set of dysfunctions, such as the occurrence of abnormal proteins formed from alpha-synuclein aggregation, oxidative stress, neuroinflammation, and mitochondrial dysfunction, leads to the occurrence of PD [133]. Thus, interestingly, nanotechnology-driven solutions have produced positive results. For instance, it was found that idebenone nanoprodrug micelles (IDBP NMs) significantly altered the oxidative stress markers, IL-6, TNF- α , IL-1 β cytokines and α -syn in rotenone-based PC12 cells. Reactive oxygen species were modified accordingly, and a longer life span was registered in the *Drosophila* PD model after the application of the above-mentioned nanocarrier. Correspondingly, a study revealed that the gamma irradiated chitosan-based PLGA nanoparticles (CS γ NPs) were characterized by great compatibility, decreased cytotoxicity, and the most optimal size ($\sim 211.9 \pm 14.04$ nm) and charge ($+7.1 \pm 2.3$ mV), thus being relevant for drug

delivery systems, providing for effective uptake by neurons and maintaining the integrity of the blood-brain barrier [134]. Apart from drug delivery, advanced indicators such as microneedles biomimetic devices have demonstrated a sensitivity to dopamine of that 0.58 nM with a wide range from 5 nM to 100 μ M, providing real-time monitoring, which is an important factor for targeted therapy [135]. Moreover, natural compounds such as epigallocatechin gallate exhibited the potential for therapeutic application while maintaining functional activity and reducing neurodegenerative diseases thanks to lowering the polymerization of neuroserpin and ensuring its stabilization [136]. Furthermore, the application of innovative nanosensors made of polydopamine-pyrrole composites allowed for *in vivo* monitoring of fluctuations in ionic concentrations in cerebrospinal fluid within the models of PD, establishing new avenues for monitoring the disease's progress and implementing precision-targeted treatment approaches [137].

6.3. Cardiovascular diseases

The future role of such advanced biomaterials and nanotechnology in the sensitive diagnosis and personalized therapy is increasingly recognized. For example, the analytical performance of a newly designed biosensing platform based on the molecularly imprinted polymer nanoparticles was found to be compared to high-sensitivity ELISA ($R^2 = 0.893$) and correlated with clinical relevant parameters ($R^2 = 0.855$). This method allows for the sensitive and rapid detection of cardiac troponin I with high sensitivity from a single drop of blood, enabling affordable and portable point-of-care testing [138]. A totally biodegradable poly (L-lactic acid) (PLLA) atrial septal defect (ASD) occluder demonstrated effective implantation and near-complete degradation over 36 months without problems in therapeutic applications, proving its safety and viability in clinical use [139]. In a similar vein, the advances in drug delivery such as sirolimus-coated balloons (SCBs) showed comparable clinical outcome between the phospholipid nanocarriers Magic Touch and biodegradable polymeric microsphere SELUTION SLR without significant difference in target lesion failure at 12 months (7.4% *versus* 10.5%, AHR 0.67) that could be utilized in local drug delivery during percutaneous coronary intervention [140]. Additionally, the PTX-PEG-coated magnesium alloy-based drug-eluting stents showed enhanced blood compatibility (hemolysis rate 0.6%), prolonged drug release, and increased corrosion resistance which can be used for the site-specific and controlled drug delivery [141]. Finally, the response to disease-associated biomarker such as GPVI, PDGF-B, ROS, and shear stress, the polymeric anti-platelet carriers were able to provide a targeting strategy with reduced systemic exposure and side effects like bleeding while delivering the drug specifically and triggered by different stimuli [142].

6.4. Infectious diseases

Recent advances in antimicrobial and infectious disease therapy highlight the growing importance of intelligent, targeted drug delivery systems in overcoming resistance and improving therapeutic outcomes. For example, the multifunctional Fe(III)-TAML bonded cyclodextrin polymer (Fe(III)-TAML-CDP) showed strong potential in targeted antimicrobial water treatment, achieving a 7.9 log reduction of *Escherichia coli* within 1 h and maintaining > 90% inactivation efficiency against natural microbial communities while increasing bacterial sensitivity to reactive species by 1.3–5.9 fold [143]. Similarly, a cascade multimodal therapy that combined photothermal disruption, hypoxia-alleviated singlet

oxygen generation, and enzyme-like catalytic activity was made possible by a conformation-adaptive porous organic polymer (DFP-POP), which demonstrated precise microenvironment-responsive targeting by nearly completely epithelializing infected wounds by day 9 in murine models [144]. Another research shows PLGA nanoparticles improved site-specific drug delivery in bacterial, viral, and parasite infections by preferentially accumulating in infected alveolar macrophages with noticeably greater intracellular drug concentrations than uninfected cells [145]. In addition, a pH/ROS-responsive hydrogel technology allowed for the sequential and prolonged release of quercetin and antimicrobial peptide, which successfully reduced oxidative stress and promoted M2 macrophage polarization for better healing in chronic diabetic wounds [146]. Additionally, by evaluating vast datasets, AI-driven medication repurposing methodologies speed up the identification of targeted treatments and minimize development time while optimizing safety and efficacy profiles [147]. Furthermore, considerable antiviral efficacy against IBV was demonstrated by copper-based medications, which confirmed their targeted antiviral potential by considerably enhancing cell viability, decreasing viral gene expression, and raising survival rates in infected chicks and embryos [148].

6.5. Chronic wound healing and regenerative medicine

Chronic wound healing remains a major therapeutic challenge due to inadequate tissue regeneration, infection, and persistent inflammation. By using stem cells, biomaterials, and growth factors to repair damaged tissues, speed up the healing process, and improve patient outcomes through cutting-edge, focused therapy approaches, regenerative medicine provides creative solutions. Polymeric hydrogels are hydrophilic, three-dimensional networks of polymers that can absorb a lot of biological fluids. Because of this, they are highly valuable for biomedical applications, particularly in the treatment of wounds and the delivery of targeted medications. Swelling behavior, biocompatibility, biodegradability, mechanical strength, cross-linking density, and stimuli-responsiveness are their main attributes that impact their clinical performance and enable regulated and site-specific therapeutic action [149]. Recent advances show how bioactive and bioadhesive hydrogels can promote strong adhesion, rapid tissue regeneration, and localized drug release to enhance wound healing. This lessens complications and enhances treatment outcomes [150]. The multifunctionality of injectable hydrogels, such as alanine-modified cellulose nanofibril-based systems (Ala-CNFs @ PVA/PBCD), includes injectability, self-healing, and biodegradability. Additionally, they achieve quick hemostasis in 38 seconds for cardiac wounds and 34 seconds for femoral artery injuries, both of which are critical features supporting localized therapeutic delivery [151]. Similarly, curcumin-loaded silver metal-organic framework hydrogels (CUR-Ag-MOFs) show improved wound healing ($p < 0.05$) and sustained drug release ($13\% \pm 2.7\%$ in the first hour and $77\% \pm 3.61\%$ over 48 hours), with improved collagen deposition, cytokine modulation, and tissue remodeling by day 14 [152]. Additionally, dual-responsive hydrogels, like PVA/CGG/CPBA @ ZnO systems, react to changes in pH and glucose in diabetic wounds, allowing for accurate, environment-triggered release of antimicrobial agents while retaining superior mechanical stability, biocompatibility, and self-healing capacity, ultimately speeding up wound healing in infected diabetic models [153].

Across the disease domains examined here, translational maturity varies significantly, and it is important to state this clearly. A fully degradable atrial septal occlude monitored for 36 months and a 12-month clinical trial comparing drug-coated balloons head-to-head are already examples of

cardiovascular applications [139,140]. Applications for cancer, neurological disorders, infections, and wound healing, on the other hand, are still primarily preclinical and are tested in cell lines, rodents, or, in the case of Parkinson's disease models, *Drosophila* [129,136,143]. This is a reason why the timeline discussed elsewhere in this review should not be assumed to be consistent across disease areas, but it is not a critique of the underlying science. Compared to the majority of the neurology and oncology platforms mentioned above, cardiovascular polymeric devices simply sit closer to patients [139,142].

7. Translational challenges and clinical perspectives

One of the biggest translational bottlenecks in advanced polymeric drug delivery is still the shift from laboratory research to clinical application. This is caused by a combination of biological barriers, immune responses, biocompatibility, and the tumor microenvironment, as well as non-biological constraints like manufacturing scale-up and different regulatory requirements across regions like the U.S., EU, and China. This problem is particularly severe for cancer and other complex diseases [154]. Polymer-based nanotherapeutics (PNs) have demonstrated significant promise in targeted drug delivery by enabling controlled release, improved pharmacokinetics, and site-specific action; however, their structural complexity and insufficient physicochemical characterization often result in inconsistent *in vivo* performance and regulatory uncertainty, necessitating standardized evaluation frameworks [155]. Similarly, by maintaining drug release and improving patient compliance, polymer microparticles—particularly PLGA-based systems—have demonstrated clinical success in long-acting injectable formulations. Though new machine learning techniques are now increasing design efficiency and predictability, formulation complexity and scalability issues have impeded their development [156]. Despite these developments, studies show that the toxicity of DDS based on nanoparticles is closely linked to physicochemical characteristics, leading to consequences like genotoxicity, oxidative stress, and inflammation. This emphasizes the need for standardized nanotoxicity assessment models and sophisticated *in vitro/in vivo* testing techniques [157]. In this regard, PLGA nanoparticles are especially promising carriers because of their tunable and biodegradable characteristics. While decreasing burst release and opsonization, recent advancements like surface modification, hybrid polymer systems, and microfluidic fabrication have greatly improved drug loading, stability, and targeting efficiency [158]. The first aimed polymeric nanoparticle to be tested in human trials, BIND-014, a PSMA-targeted, PLGA-based docetaxel nanoparticle, showed encouraging Phase I pharmacokinetic and safety data but was eventually discontinued after Phase II trials in non-small cell lung cancer and other tumor types failed to achieve the overall response rate required to justify further development. This failure was widely attributed to over-reliance on the EPR effect, whose accumulation and efficacy proved far more heterogeneous and unpredictable in human tumors than the preclinical models used to design the trial. An investigator-initiated Phase Ib/IIa trial combining CRLX101 with bevacizumab in metastatic renal cell carcinoma reported encouraging activity, with 55% of patients achieving progression-free survival beyond four months. However, the subsequent randomized Phase II trial found no benefit over standard of care, with a median progression-free survival of 3.7 months for CRLX101 *versus* 3.9 months for standard therapy (hazard ratio 1.25, $p = 0.822$). A common structural lesson between the two cases is that neither trial used a predictive biomarker to preselect patients who would benefit from increased drug release or nanoparticle accumulation. As a result, the average population-level effect diluted what might have been genuine benefit in a molecularly defined subgroup, a gap that is increasingly

recognized as a key, treatable cause of nanomedicine trial failure. With 55% of patients achieving progression-free survival beyond four months, an investigator-initiated Phase Ib/IIa trial that combined CRLX101 with bevacizumab in metastatic renal cell carcinoma reported encouraging activity. With a median progression-free survival of 3.7 months for CRLX101 compared to 3.9 months for standard therapy (hazard ratio 1.25, $p = 0.822$), the subsequent randomized Phase II trial, however, found 46no benefit over standard of care. Due to the absence of a predictive biomarker in either study to identify patients who would likely experience increased nanoparticle accumulation or drug release, the overall impact at the population level obscured a potential advantage in a molecularly characterized subset. This gap is becoming more widely acknowledged as a major, curable factor in the failure of nanomedicine trials [159,160].

Regulatory pathways increase this translational uncertainty because the US and the EU have different approaches to nanomedicine oversight. While the European Medicines Agency has published a number of product-class-specific reflection papers addressing liposomes, block copolymer micelles, iron-carbohydrate colloids, and related nanomedicines, the Food and Drug Administration does not maintain a separate regulatory category for nanomedicines; instead, it applies existing drug, biologic, or device frameworks with heightened, product-specific scrutiny of nanoscale physicochemical properties on a case-by-case basis. While both agencies agree that rigorous characterization of particle size distribution, chemical composition, drug loading, and release kinetics should be required as minimum quality parameters, they diverge significantly when it comes to follow-on products: proving regulatory sameness for a generic or biosimilar-like nanomedicine is significantly more difficult than for a conventional small-molecule generic because small variations in nanoparticle size, surface chemistry, or drug-release profile can measurably alter safety and efficacy. This difficulty is demonstrated by the extensive comparability testing necessary before generic liposomal doxorubicin products were deemed therapeutically equivalent to the innovator formulation [161]. Because of this regulatory divergence, a polymeric nanomedicine that has been optimized for one jurisdiction's evidentiary requirements may need more characterization and, in certain situations, more clinical data before a second jurisdiction will authorize it, which would prolong the time and expense of international development initiatives. The microfluidic and CFD-guided fabrication techniques covered in Section 2.3 significantly improve control over nucleation, particle size, and morphology at laboratory scale, but translating these same flow conditions to industrial throughput without reintroducing the size and polydispersity variability that plagues bulk emulsification requires extensive re-optimization of channel geometry, flow rate, and mixing time, which many academic formulations never undergo before entering trials [162].

Clinical translation is still hampered by these technical bottlenecks in scale-up production. A second bottleneck that is primarily unique to nanoscale carriers is sterilization and long-term storage: aseptic manufacturing is expensive and challenging to validate at scale; many polymeric nanocarriers require lyophilization to achieve acceptable shelf life, which can cause particle aggregation; and terminal sterilization techniques like autoclaving or gamma irradiation can degrade polymer backbones or cause premature drug release [162]. Last but not least, the cost of goods scales negatively for many next-generation polymeric systems when compared to conventional formulations because specialized excipients, multi-step conjugation chemistry, and the analytical burden of nanoscale quality control which includes dynamic light scattering and electron microscopy for every batch add significantly to

manufacturing costs without a corresponding increase in reimbursement. This economic bottleneck has stopped the development of technically successful nanomedicine candidates regardless of any scientific limitations [159]. A separate insight is added by two further cases, both of which are polymeric micelle reformulations of paclitaxel. Together, they demonstrate that success or failure frequently depends on resolving a single issue with the original medication rather than focusing on sophistication [163,164]. Approved in South Korea in 2007, Genexol-PM is a paclitaxel micelle devoid of Cremophor EL. A higher, better-tolerated dose was made possible by the removal of the hazardous solvent that produces hypersensitivity reactions in traditional paclitaxel. Genexol-PM considerably outperformed standard paclitaxel in a randomized Phase III trial, with a response rate of 39.1% *versus* 24.3% ($p = 0.016$). In preclinical tests, NK105, a comparable paclitaxel micelle composed of PEG and a polyamino acid, demonstrated robust tumor accumulation and reduced neurotoxicity. In contrast, the Phase III trial revealed that NK105 did not achieve its primary objective in 436 patients, with progression-free survival of 8.4 months as opposed to 8.5 months for conventional paclitaxel (hazard ratio 1.255). One of the biggest side effects of paclitaxel, severe nerve damage, was considerably lessened [163,164]. A subsequent study discovered a plausible explanation for the deficiency: approximately 73% of patients had anti-PEG antibodies prior to the start of treatment. Pre-existing immunity to PEG may be subtly eroding PEGylated nanocarriers in a significant proportion of patients because PEG is now widely used in food, cosmetics, and other medications [165]. These four incidents, together with BIND-014 and CRLX101, all lead to the same conclusion: failures in nanomedicine rarely have a single reason. The promise these carriers exhibit in preclinical models is undermined by EPR heterogeneity, insufficient biomarkers, and now anti-PEG immunity [159].

8. Emerging trends and future directions

The trajectory of next-generation polymeric drug delivery is best understood as two distinct horizons: short-term objectives that expand and improve capabilities already shown in the aforementioned sections, and long-term visions that call for fundamental advancements not yet attained. The most obvious of the short-term objectives is the transition of artificial intelligence and machine learning, which are already used to predictively model important formulation quality attributes like stability, release behaviour, encapsulation efficiency, and particle size, from a research accelerant into a standard, prospective formulation-design step integrated directly into quality-by-design workflows within the next three to five years [166,167]. Over the same time frame, three-dimensional printing of dosage forms which is currently in the early stages of clinical translation for a number of drug classes is also poised to develop into a scalable pathway to patient-specific dosing, structure, and pharmacokinetic profiles, especially for polypharmacy and paediatric or geriatric populations where standard dosing is not well matched to individual needs [168]. Green and biodegradable nanocarrier chemistries, which are made from natural polymers and lipids rather than synthetic precursors, are also close to practical deployment on this timescale because they can be substituted directly into existing formulation and manufacturing pipelines while improving biocompatibility, reducing toxicity, and lowering the environmental footprint of large-scale production [169]. A decade or more of parallel advancements in biocompatible actuator materials, long-term implant stability, and regulatory frameworks that do not yet exist for devices whose structure changes after implantation are probably needed for clinical maturation. Beyond this horizon, the field's more ambitious, ten-plus visions require materials

science and manufacturing advances that do not yet exist at clinical scale, most notably four-dimensional printing, which produces materials capable of autonomously changing structure or function over time in response to physiological indications [170]. In order to achieve this, biodegradable materials, additive manufacturing, and AI-driven design must be deeply integrated into a single, closed-loop pipeline that can produce customized therapeutics on demand at the point of care. Although this convergence has been conceptually established, it still requires the manufacturing infrastructure, regulatory pathways, and cost reductions required to make on-demand, truly personalized production commonplace rather than exceptional [171].

9. Conclusion

This conclusion summarizes the review's conclusions into what is truly unresolved and what the evidence collected here supports as consensus, rather than restating the review's scope. With a fair degree of certainty, three conclusions can be made. First, rather than being a materials science curiosity, molecular architecture is a true, practical design lever. The structure–performance relationships shown across linear, branched, dendritic, and crosslinked polymers, as well as across nanoparticles, micelles, dendrimers, polymersomes, and nanogels, are now sufficiently understood to guide rational carrier selection for a given drug and disease rather than empirical trial-and-error. Second, the enhanced permeability and retention effect is still a fundamental mechanism, but due to its well-documented heterogeneity across human tumors, active targeting, stimuli-responsiveness, and organelle-level precision are now required complements rather than optional enhancements. As a result, passive targeting is no longer justified as a stand-alone clinical strategy. Third, the field's future advancement will come from more sophisticated matching of design to application rather than from the discovery of a single superior platform because no single architecture, carrier type, or stimulus dominates universally; instead, the appropriate design choice depends on the particular combination of disease, target tissue, and required release kinetics. There are still three valid open questions. First, in order to prevent carriers calibrated to population averages from consistently under-treating or over-treating significant subsets of patients, how should stimuli- and enzyme-responsive systems account for the significant inter-patient and intra-tumoral variability in trigger expression documented throughout this review? Second, will clinical translation continue to lag years behind laboratory design, as it did with BIND-014 and CRLX101, or will manufacturing scale-up, sterilization, and batch-to-batch reproducibility keep up with the increasing structural sophistication of next-generation carriers? Third, as more advanced, multi-mechanism systems enter human trials, what mix of predictive biomarkers, adaptive regulatory pathways, and harmonized international standards will be required to stop this trend of late-stage clinical failure from happening again? Whether next-generation polymeric drug delivery meets its therapeutic promise over the next ten years will depend more on the answers to these challenges than on any one novel material or method.

Data availability statement

No supplementary or additional data were generated in this study.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used ChatGPT to create the Graphical Abstract and Figures 2 and 3. The authors take full responsibility for the content of the manuscript.

Authors' contribution

Conceptualization, data curation, writing—original draft preparation, R.C.; literature review, methodology, and validation, M.R.; formal analysis, visualization, and manuscript editing V.P.; investigation, supervision, and review of the manuscript: D.D.; formal analysis, visualization, and manuscript editing, M.N.; conceptualization, supervision, project administration, and final review and editing of the manuscript, A.S.; conceptualization, mentoring, and final review and editing, P.K. All authors have read and approved the final version of the manuscript.

Conflicts of interest

Pradeep Kumar holds the position of Associate Editor for *Biofunctional Materials* and has not peer reviewed or made any editorial decisions for this paper. The authors declare no conflicts of interest.

Abbreviations

AI—Artificial Intelligence
 AMPK—Adenosine Monophosphate-Activated Protein Kinase
 ASD—Atrial Septal Defect
 ATRP—Atom Transfer Radical Polymerization
 BBB—Blood–Brain Barrier
 CFD—Computational Fluid Dynamics
 cGAS–STING—Cyclic GMP–AMP Synthase–Stimulator of Interferon Genes
 CD8—Cluster of Differentiation 8
 CD44—Cluster of Differentiation 44
 Co—Initial Drug Concentration
 CRISPR/Cas9—Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated Protein 9
 DDS—Drug Delivery System
 DMN—Dissolving Microneedles
 DOX—Doxorubicin
 EPR—Enhanced Permeability and Retention
 GFP—Green Fluorescent Protein
 GPC3—Glypican-3
 GSH—Glutathione
 H-MIPs—Hollow Molecularly Imprinted Polymers
 HBP/HBPs—Hyperbranched Polymer/Hyperbranched Polymers
 HER2—Human Epidermal Growth Factor Receptor 2
 hPDPA—Hyperbranched Poly(2-(diisopropylamino)ethyl Methacrylate)

IBV—Infectious Bronchitis Virus
IC₅₀/IC₂₀—Half/Partial Maximal Inhibitory Concentration
ICD—Immunogenic Cell Death
ICG—Indocyanine Green
ID/g—Injected Dose per Gram of Tissue
IL-6—Interleukin-6
LCST—Lower Critical Solution Temperature
MAA—Methacrylic Acid
MCF-7—Michigan Cancer Foundation-7
MOF—Metal-Organic Framework
MRSA—Methicillin-Resistant Staphylococcus aureus
MXene—Transition Metal Carbide Nanomaterial
Nab-PTX—Nanoparticle Albumin-Bound Paclitaxel
NDDS—Nanoparticulate Drug Delivery System
NIR—Near-Infrared
NIR-II—Near-Infrared-II
NMP—Nitroxide-Mediated Polymerization
PAMAM—Poly(amidoamine)
PCL—Polycaprolactone
PD-1—Programmed Cell Death Protein 1
PD-L1—Programmed Death-Ligand 1
PDGF-B—Platelet-Derived Growth Factor-B
PDI—Polydispersity Index
PEDHNPs—Polycarbonate-Based Drug Delivery Nanoparticles
PEG—Polyethylene Glycol
PEI—Polyethyleneimine
PISA—Polymerization-Induced Self-Assembly
PNIPAM/PNIPAAm—Poly(N-isopropylacrylamide)
PNPs—Polymeric Nanoparticles
POMs—Polyoxometalates
PQDs—Perovskite Quantum Dots
PPI—Poly (propylene imine)
PSMA—Prostate-Specific Membrane Antigen
PDT—Photodynamic Therapy
PTT—Photothermal Therapy
PVA—Polyvinyl Alcohol
RAFT—Reversible Addition–Fragmentation Chain Transfer
RDRP—Reversible Deactivation Radical Polymerization
RES—Reticuloendothelial System
RGD—Arginyl-Glycyl-Aspartic Acid
ROS—Reactive Oxygen Species
RPP—Ruthenium-Polyphenol-Phloretin

RR-PAL-NPs—Redox-Responsive Palbociclib Nanoparticles
SCBs—Sirolimus-Coated Balloons
SRPNs—Stimuli-Responsive Polymeric Nanoparticles
TNBS—Trinitrobenzene Sulfonic Acid

References

- [1] Suksaeree J, Maneewattanapinyo P, Monton C. AI-enabled, QbD-aligned predictive, and sustainable design of natural polymer-based drug delivery systems. *AAPS PharmSciTech*. 2026, 27(2):90.
- [2] Tahir H, Alanazi AK, Ahmad Z. Exploring the functional diversity of hypoxia-responsive polymers in drug delivery: a comparative analysis. *J. Drug. Delivery Sci. Technol*. 2026, 117:108026.
- [3] Singh D, Krishna V, Kumari N, Banerjee A, Kapoor P. Thermodynamics of polymer drug interactions: an influential factor for the development of a stable drug delivery system. *J. Macromol. Sci. B* 2026, 65(2):303–313.
- [4] Hasan N, Aftab M, Ullah M, Nguyen PT, Agustina R, *et al*. Nanoparticle-based drug delivery system for oral cancer: mechanism, challenges, and therapeutic potential. *Results. Chem*. 2025, 14:102068.
- [5] Bairagi RD, Reon RR, Hasan MM, Sarker S, Debnath D, *et al*. Ocular drug delivery systems based on nanotechnology: a comprehensive review for the treatment of eye diseases. *Discov. Nano*. 2025, 20(1):75.
- [6] Shah SW, Li X, Yuan H, Shen H, Quan S, *et al*. Innovative transdermal drug delivery systems: benefits, challenges, and emerging application. *BMEMat*. 2025, 3(4):e70001.
- [7] Chenxi Z, Hemmat A, Thi NH, Afrand M. Nanoparticle-enhanced drug delivery systems: an up-to-date review. *J. Mol. Liq*. 2025, 424:126999.
- [8] Liu S, Deng T, Cheng H, Lu J, Wu J. Advances in transdermal drug delivery systems and clinical applications in inflammatory skin diseases. *Pharmaceutics*. 2025, 17(6):746.
- [9] Mamidi N, Silva FFD, Mahmoudsalehi AO. Advanced disease therapeutics using engineered living drug delivery systems. *Nanoscale* 2025, 17(13):7673–7696.
- [10] Reddy KT, Reddy AS. Recent breakthroughs in drug delivery systems for targeted cancer therapy: an overview. *Cell. Mol. Biomed. Rep*. 2025, 5(1):13–27.
- [11] Gao P, Jiang X, Li J, Nicolas J, Ha-Duong T. Molecular simulations of polymer-based drug nanocarriers: from physical and structural properties to controlled release. *Adv. Healthc. Mater*. 2026, 15(4):e03503.
- [12] Lal N, Rastogi V, Mishra R, Jahan S, Ali H, *et al*. Polymeric nanoparticles: a promising pharmaceutical approach for advanced drug delivery systems. *Pharm. Nanotechnol*. 2026, 14(5):634–651.
- [13] Jangra N, Singla A, Puri V, Dheer D, Chopra H, *et al*. Herbal bioactive-loaded biopolymeric formulations for wound healing applications. *RSC Adv*. 2025, 15(16):12402–12442.
- [14] Jyothika M, Gowda SJ, Kumar GK, Rakshitha KB, Srikruthi KS, *et al*. Innovative polymer modifications: unlocking new horizons in drug delivery applications. *Biomed. Mater. Devices*. 2024, 4(1):62–77.

- [15] Puri V, Sharma A, Kumar P. Mechanically dynamic and immuno-instructive biomaterials: converging strategies to direct cell fate in regenerative microenvironments. *Eur. Cell. Mater.* 2026,58:4–24.
- [16] Manna S, Nath NC, Sarkar P, Karmakar S, Gupta P, *et al.* Alginate-based target specific bioadhesive drug delivery systems: a review. *Int. J. Polym. Mater. Polym. Biomater.* 2026, 75(2):212–238.
- [17] Alburyhi MM, El-Shaibany A, Al-Wajih AM, Almlhani AN, Alqadhi AA. Innovative approaches in herbal drug delivery systems enhancing efficacy and reducing side effects. *World. J. Pharm. Pharm. Sci.* 2025, 14(1):916–929.
- [18] Al Alim M, Hore S, Zohora F, Ghosh D, Hore R. Advances in smart polymeric materials for sustainable and next-generation applications. *Civil. Eng. Build. Sci.* 2025, 2(1):1–8.
- [19] Mubasshira, Rahman MM, Uddin MN, Rhaman M, Roy S, *et al.* Next-generation smart carbon-polymer nanocomposites: advances in sensing and actuation technologies. *Processes.* 2025, 13(9):2991.
- [20] Riaz Z, Khan KA. Next-generation programmable materials: multifunctionality, smart integration, and industrial frontiers. *ES. Mater. Manuf.* 2025, 29:1755.
- [21] Slamani M, Louhichi B, Amroune S, Jawaid M. Next-generation composite materials and manufacturing: a review of smart, sustainable, and digital advancements. *Adv. Mater. Technol.* 2026, 11(9):e01409.
- [22] Sahu B, Maity S, Jain A, Banerjee S. Next-generation stimuli-responsive polymers for a sustainable tomorrow. *Chem. Commun.* 2025, 61(66):12265–12282.
- [23] Singh N, Sinha P, Sinha DK, Banerjee S. Smart polymers for 3D printing applications: current status and future outlook. *Polym. Chem.* 2025, 16(41):4479–4523.
- [24] Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumorotropic accumulation of proteins and the antitumor agent SMANCS. *Cancer. Res.* 1986, 46(12 Pt 1):6387–6392.
- [25] Ma X, Ma H, Shen Y, Yang F, He M, *et al.* A ROS-responsive TPZ prodrug micelle for co-delivery with doxorubicin in synergistic cancer therapy. *Chin. Chem. Lett.* 2026:112466.
- [26] Cai Y, Zhang Z, Lu Y, Shen S, Lu H, *et al.* Liposomal particokinetics and intratumoral microdistribution: a quantitative reassessment of the enhanced permeability and retention effect. *J. Control. Release.* 2026, 393:114759.
- [27] Kim J, Cho H, Lim DK, Joo MK, Kim K. Perspectives for improving the tumor targeting of nanomedicine via the epr effect in clinical tumors. *Int. J. Mol. Sci.* 2023, 24(12):10082
- [28] Saleem MS, Nair LV, Thomas V. Scope of biomaterials for theranostics application. In: *Nanomedicine in Translational Research: Status and Future Challenges*. Academic Press; 2024. pp. 209–228.
- [29] Veres C, Tănase M, Szabo DA. Polymeric materials in biomedical engineering: a bibliometric mapping. *Polymers (Basel).* 2025, 17(21):2886.
- [30] Lohani A, Saxena R, Duarte JG, Khan S, Figueiras A, *et al.* Tailored polymeric hydrogels for regenerative medicine and drug delivery: from material design to clinical applications. *Int. J. Pharm.* 2025, 681:125818.

- [31] Herdiana Y. Bridging the gap: the role of advanced formulation strategies in the clinical translation of nanoparticle-based drug delivery systems. *Int. J. Nanomedicine*. 2025, 20:13039-13053.
- [32] Sharma R, Singh I, Pal K. Mechanical, tribological, and antibacterial performance of bio-ceramic reinforced PLA hybrid nanocomposites for biomedical applications: an experimental and machine learning approach. *Tribol. Int.* 2026, 217:111626.
- [33] Jiang H, Zhang Z, Liu Y, Li Y, Hu Y, *et al.* The hyperbranched polymers as a medical rising star: from synthesis to biomedical applications. *Mater. Today. Chem.* 2025, 48:102937.
- [34] Zhang Y, Tian L, Zhang J, Zhong M. pH-responsive hyperbranched polymer scaffolds for polymer and peptide conjugation through molecular recognition: synthesis and self-assembly. *Biomacromolecules*. 2025, 26(5):2960–2970.
- [35] Fadaei MR, Fadaei MS, Kheirieh AE, Hatami H, Rahmanian-Devin P, *et al.* Overview of dendrimers as promising drug delivery systems with insight into anticancer and anti-microbial applications. *Int. J. Pharm X*. 2025, 10:100390.
- [36] Omolo CA, Ismail EA, Amuhaya EK, Fasiku V, Nwabuife JC, *et al.* Revolutionizing drug delivery: The promise of surface functionalized dendrimers in overcoming conventional limitations. *Eur. Polym. J.* 2025, 235:114079.
- [37] Manna K, Roy A, Pal S. Polymeric micelles and hydrogels: tailored synthesis strategies and biomedical applications. *Polymer* 2026, 346:129650.
- [38] Beach MA, Nayanathara U, Gao Y, Zhang C, Xiong Y, *et al.* Polymeric nanoparticles for drug delivery. *Chem. Rev.* 2024, 124(9):5505–5616.
- [39] Floyd TG, Gurnani P, Rho JY. Characterisation of polymeric nanoparticles for drug delivery. *Nanoscale* 2025, 17(13):7738–7752.
- [40] Stevanović MM, Qian K, Huang L, Vukomanović M. PLGA-Based co-delivery nanoformulations: overview, strategies, and recent advances. *Pharmaceutics*. 2025, 17(12):1613.
- [41] Moayedi S, Xia W, Lundergan L, Yuan H, Xu J. Zwitterionic polymers for biomedical applications: antimicrobial and antifouling strategies toward implantable medical devices and drug delivery. *Langmuir*. 2024, 40(44):23125–23145.
- [42] Ly P, Ly K, Phan H, Nguyen HHT, Duong V, *et al.* Recent advances in surface decoration of nanoparticles in drug delivery. *Front. Nanotechnol.* 2024, 6:1456939.
- [43] Rescignano N, Kenny JM. Physicochemical properties of nanosized polymeric drug carrier systems. In: *Core-Shell Nanostructures for Drug Delivery and Theranostics*. 2018. pp. 7–17.
- [44] Ishola BO, Rahaman KA, Razzak SA, Rumon MM, Shakil MS, *et al.* Advanced mechanisms of polymer-based drug delivery systems for clinical applications. *Pharmaceutics*. 2026, 3(2): 331–360.
- [45] Kara A, Ongoren B, Anaya BJ, Lalatsa A, Serrano DR. Continuous manufacturing of nanomedicines using 3D-printed microfluidic devices. *Appl. Mater. Today*. 2025, 43:102672.
- [46] Tsitouridou A, Parhizkar M, Wu CY, Chen T, Tsaoulidis D. CFD approaches in microfluidics for the development of polymeric, lipid-based and inorganic nanoparticles for drug delivery. *Chem. Eng. J. Adv.* 2025:100853.
- [47] Catania G, Guerriero G, Bakrin N, Pourchez J, Kaouane G, *et al.* Generation of continuous production of polymeric nanoparticles via microfluidics for aerosolised localised drug delivery. *Int. J. Pharm.* 2025, 675:125532.

- [48] Janakiraman K, Sethuraman V, Krishnaswami V, Sampath G. Recent advances in polymer-based nanoparticles: current strategies and translational challenges in cancer therapy. *J. Chemother.* 2025;1–22.
- [49] Lin X, Li Z, Huang Y, Li Y, Li Y, *et al.* Polymer nanoparticles advancements for gynecological cancers. *Int. J. Nanomedicine.* 2025, 20:6721–6742.
- [50] Rahim MA, Jan N, Khan S, Shah H, Madni A, *et al.* Recent advancements in stimuli responsive drug delivery platforms for active and passive cancer targeting. *Cancers* 2021, 13(4):670.
- [51] Ayyanaar S, Kumar GG, Rajagopal G, Sampath M, Sumathi G, *et al.* Multifunctional niosome–chitosan–gold nanohybrids for pH/ROS-triggered camptothecin release in breast cancer treatment. *Bioorg. Chem.* 2026:109866.
- [52] Yu L, Guo Y, Liu T, Sheng Y, Liu M, *et al.* *In vivo* fate mapping of a paclitaxel-loaded polymeric micelle and its components. *Acta. Pharm. Sin. B* 2026.
- [53] Wang J, Mao W, Lock LL, Tang J, Sui M, *et al.* The role of micelle size in tumor accumulation, penetration, and treatment. *ACS Nano.* 2015, 9(7):7195–7206.
- [54] Ren J, Wen Q, Du S, Ge X, Li L, *et al.* Tumor microenvironment-responsive metal-natural polyphenol nanozyme for radiosensitization by interfering glucose metabolism and redox homeostasis. *J. Control. Release.* 2025, 388(Pt 2):114219.
- [55] Li L, Li S, Gao L, Chen S, Zang D, *et al.* A GSH-responsive drug delivery system based on self-assembly of polyoxometalates modified camptothecin for chemotherapy. *Mater. Today. Adv.* 2026, 29:100679.
- [56] Bae YH, Park K. Targeted drug delivery to tumors: myths, reality and possibility. *J. Control. Release.* 2011, 153(3):198–205.
- [57] Joo KS, Sym SJ, Kim K, Khang D. Strategies for pancreatic cancer-responsive nanodrug platforms targeting tumor hypoxic environments. *Int. J. Nanomedicine.* 2025, 20:13457–13488.
- [58] Han X, Chen J, Zhao Y, Kang R, Wei Y, *et al.* Dual antibody-guided drug delivery systems using MOF-PQDs nanocomposites for precise tumor diagnosis and combination therapy. *Chem. Eng. J.* 2025, 505:159275.
- [59] Tian T, Zhao D, Fan Y, Li X, Zhong Z, *et al.* A genetically programmable, conjugation-free nanomedicine platform for modular antibody-guided drug delivery. *Cell. Biomater.* 2026, 100410.
- [60] Zhou R, Zhang M, He J, Liu J, Sun X, *et al.* Functional cRGD-conjugated polymer prodrug for targeted drug delivery to liver cancer cells. *ACS Omega.* 2022, 7(24):21325–21336.
- [61] Pourhossein A, Rezaei S, Shojaosadati SA. Folate-functionalized Zein-PEI nanoparticles for targeted cancer therapy: integrated experimental and molecular dynamics insights into stability, uptake, and cytotoxicity. *Int. J. Biol. Macromol.* 2025:145954.
- [62] Zhou H, Dong S, Si Z, Niu H, Mao J, *et al.* Aptamer-based nanoparticle drug delivery system designed for targeting GPC3-positive liver cancer. *J. Pharm. Anal.* 2026:101614.
- [63] Xu Z, Haghighat M, Shafiabady N, Wu R, Sang R, *et al.* Nuclear-targeted CRISPR/Cas delivery by using aptamer-modified polymer lipid nanoparticles. *Nanomedicine.* 2026:102928
- [64] Torchilin V. Multifunctional and stimuli-sensitive pharmaceutical nanocarriers. *Eur. J. Pharm. Biopharm.* 2009, 71(3):431–444.

- [65] Liu R, Tan Y, Jiang Y, Zheng J, Ni W, *et al.* DNA damage-driven cgas-sting activation via a nuclear-targeted probe enables potent near-infrared theranostics in breast cancer. *Acta Biomater.* 2026.
- [66] Zeng J, Yan Z, Wang D, He T, Tong Z, *et al.* Mitochondria-targeted MXene\@MnO₂-TPP nanoheterostructures for synergistic enhancement of sonodynamic therapy and immunotherapy in osteosarcoma. *Bioact. Mater.* 2025, 54:450–465.
- [67] Xue P, Yu Z, Shang Y, Liu S, Zhang M, *et al.* Dual-targeted fucoidan-TPP nanoparticles delivery system potently inhibit breast cancer via mitochondrial dysfunction and cGAS-STING activation. *Colloids. Surf. B. Biointerfaces.* 2026, 258:115279.
- [68] Zhang S, Su Y, Jin G, Yu B, Yang Z, *et al.* A pH-responsive polymeric nanovaccine with efficient endosomal escape and potent antitumor immunity for cancer treatment. *Acta Biomater.* 2026, 216:348–361.
- [69] Cheng Y, Zhao E, Yang X, Luo C, Zi G, *et al.* Entrapment of lipid nanoparticles in peripheral endosomes but not lysosomes impairs intracellular trafficking and endosomal escape. *Int. J. Pharm.* 2025, 669:125024.
- [70] Liu J, Yan Y, Zhang Y, Chen B, X Pan, H Xia, *et al.* Lysosome-mitochondria cascade targeting nanoparticle drives robust pyroptosis for cancer immunotherapy. *J. Am. Chem. Soc.* 2024, 146(50):34568–34582.
- [71] Zheng J, Yang Z, Shi J, Zhang X, Zhang F. Targeted polymeric drug delivery systems with stimuli-responsive release capabilities: status and future perspectives. *Nanomedicine (Lond.)* 2025, 20(21):2609–2612.
- [72] Singh D, Thakur A. Spatiotemporal nanocarriers for circadian-aligned drug delivery: advances, challenges, and future directions. *Assay. Drug. Dev. Technol.* 2026, 24(3):189–205.
- [73] Yu Y, Zhao Y, Zou Y, Lu C, Li N, *et al.* Ultra-sensitive pH responsive hydrogels with injectable and self-healing performance for controlled drug delivery. *Int. J. Pharm X.* 2025, 9:100334.
- [74] Li J, Liao H, Tian S, Liu L, Xu H, *et al.* A pH-responsive polycarbonate nanoplatform enables sequential drug release for enhanced apoptotic cascade synergy in non-small cell lung cancer therapy. *Acta Biomater.* 2025.
- [75] Hosseinzadeh H, Vahdatkhah A, Javanbakht S, Mohammadi R. Synthesis of pH-responsive hollow molecularly imprinted polymers for enhanced doxorubicin delivery in cancer therapy. *J. Pharm. Sci.* 2025:103993.
- [76] Cancilla F, Martorana A, Fiorica C, Pitarresi G, Craparo EF, *et al.* Development and characterization of injectable, bioadhesive, pH-responsive hyaluronic acid-based hydrogels for enhanced postoperative cancer therapy. *Int. J. Pharm.* 2025:126233.
- [77] Yi D, Wang T, Xu S, Liu Y, Wang Z, *et al.* Injectable ROS/pH-Responsive hydrogel for synergistic chemo-photodynamic tumor therapy and enhanced wound healing. *Adv. Healthc. Mater.* 2026, 15(1):e02349.
- [78] Cui Q, Zhang K, Fei X, Wang C, Cheng S, *et al.* Thermoresponsive hydrogel dressings for precision drug release under physiological conditions. *Eur. Polym. J.* 2025:114178.

- [79] Kim M, in Lee J, Choi J, Kim SY. Reactive oxygen species-responsive nanocomposite hydrogels for accurate drug delivery and localized PDT/PTT/chemo synergistic cancer therapy. *Eur. Polym. J.* 2025, 224:113683.
- [80] Shi C, Liu B, Feng L, Wei B, Yu S, *et al.* Design and evaluation of multi-responsive PNIPAM-g-dextran-sodium alginate blended smart hydrogel for enhanced chemo-photodynamic therapy against oral squamous cell carcinoma. *Colloids. Surf. B. Biointerfaces* 2026, 259:115293.
- [81] Zhang Y, Wen S, Zheng K, Zhou X, Huang C, *et al.* Fabricating a curcumin-loaded chitin/lignin micelle thermoresponsive hydrogel with dynamic contractility and tissue-adhesive properties for enhanced wound regeneration. *Biomacromolecules.* 2025, 26(9):5778–5790.
- [82] Liu Y, Zhao Y, Wang Y, Qin Q, Zi H, *et al.* Engineering a thermosensitive micelle-hydrogel composite for controlled delivery of bempedoic acid in periodontitis therapy. *Colloids. Surf. B. Biointerfaces* 2025, 115217.
- [83] Wu J, Yang S, Xiong Y, Liu J, Wu Z, *et al.* Comparative study on the redox-responsive properties and antitumor efficacy of polyurethane nanocarriers with mono-, Di-, and trisulfide bonds. *J. Control. Release.* 2025, 385:114035.
- [84] Tang W, Liu Z, Lu N, Hou H, Wang H, *et al.* Redox-sensitive hyaluronic acid-based glycopeptide nanoparticles: dual-action platform for mitochondrial disruption and tumor suppression. *Int. J. Biol. Macromol.* 2025, 331(Pt 2):148544.
- [85] Cancilla F, Cimino M, Martorana A, Fiorica C, Craparo EF, *et al.* Injectable redox-responsive glutathione-polyurethane/hyaluronic acid hybrid hydrogel for controlled chemotherapy in patient-derived pancreatic cancer organoids. *Mater. Today. Chem.* 2025, 50:103211.
- [86] Zhao X, Zhao R, Liu P. Facile design of amphiphilic multi-functional copolyprodrug for pH/GSH dual-responsive tumor chemotherapy and self-enhanced ferroptosis. *Polymer* 2025, 339:129186.
- [87] Liu J, Mei K, Dai X, Song Y, Deng L, *et al.* Carrier free nano-assembled redox dual-responsive biotin-artesunate conjugate for enhanced tumor therapy. *Eur. J. Pharm. Biopharm.* 2025, 215:114841.
- [88] Li X, Sun L, Liu X, Wen P, Zhang Y, *et al.* Enzyme-powered micellar nanoreactors enable tumor-specific, cascade-amplified prodrug activation for synergistic oxidation-chemo-immunotherapy. *J. Control. Release.* 2026, 389:114363.
- [89] Sun Y, Xi Y, Yu Y, Huang L, Li Y, *et al.* Cathepsin B/pH cascade-responsive transformable peptide: Orchestrating endo/lysosomal escape and cytoplasmic release of siRNA to enhance tumor therapy. *Chem. Eng. J.* 2025, 522:167455.
- [90] Yu Y, Jin Y, Zhou Y, Cui Z, Xin Y, *et al.* Nanoprodrug targeting tumor-associated intracellular bacteria enhances colorectal cancer immunotherapy. *J. Control. Release.* 2025:114512.
- [91] Shim N, Kim J, Song S, Yoo H, Kim Y, *et al.* Cathepsin B-Cleavable doxorubicin prodrug nanoparticles for eliciting cancer-specific immunogenic cell death and minimizing systemic toxicity. *Adv. Healthc. Mater.* 2026, 15(9):e04414.

- [92] Zhai W, Li J, Zhao D, Xu K, Liu Y, *et al.* Cathepsin B-activated prodrug for precision tumor theranostics. *J. Med. Chem.* 2025, 68(20):21829–21839.
- [93] Li X, Lu X, Tang J, Patel-Burrows F, Fielding LA. Highly swellable pH-responsive nanogels generated by polymerisation-induced self-assembly. *Polym. Chem.* 2026, 17(9):897–902.
- [94] Pytlíková S, Konefał R, Pola R, Braunová A, Lobaz V, *et al.* Dual thermo- and pH-responsive polymer nanoparticle assemblies for potential stimuli-controlled drug delivery. *ACS Appl. Bio Mater.* 2025, 8(1):271–284.
- [95] Lukáš Petrova S, Vragović M, Pavlova E, Hrubý M, Pokorný V. Dual pH- and thermoresponsive nano-objects with tunable morphologies and dye encapsulation prepared via aqueous emulsion polymerization-induced self-assembly. *R Soc. Open. Sci.* 2026, 13(3):252454.
- [96] Gupta U, Kumar R, Sharma A, Aalhate M, Maji I, *et al.* Redox-responsive palbociclib-loaded self-assembled protein nanoparticles in breast cancer therapy—quality by design approach and efficacy assessment in 2D and 3D in vitro culture systems. *Pharm. Dev. Technol.* 2025, 30(10):1609–1635.
- [97] Yu W, Yu S, Zhang X, Kong J. Polymerization-induced self-assembly: engineered nanomaterials for advanced biomolecule detection and multifaceted biomedical applications. *J. Polym. Res.* 2025, 32(8):271.
- [98] Dinya M, Dinya E, Mórotz GM. From pathology to formulation: designing biodegradable polymers for personalized drug delivery. *Pharmaceutics* 2026, 18(3):330.
- [99] Rajabi M, Feyzbakhsh H. Polymeric nanocarriers in drug delivery, bioimaging, and biosensing: advances and perspectives on nanomicelles, nanogels, and dendrimers. *RSC Adv.* 2025, 15(48):40400–40438.
- [100] Wu Y, Jeong H, Wang W, Wu C, Lu A, *et al.* Polymer modification effects in nanocarrier-loaded dissolving microneedles: implications for transdermal drug delivery. *Chin. Chem. Lett.* 2026, 37(3):111944.
- [101] Munawar MA, Christopher Moses A, Sakthivel P, Chandrasekar J, Bharathy P. Functional food polymers as nanocarriers: advances in encapsulation and targeted delivery of nutraceuticals. *Grain Oil Sci. Technol.* 2025.
- [102] Sheykholeslami SE, Halimi S, Ahangari F, Mohammadgholi A, Mansouri A, *et al.* Emerging roles of polymeric nanoparticles in cancer therapy: design, targeting, and clinical integration. *Eur. Polym. J.* 2026, 244:114447.
- [103] Zhu R, Yu X, Zhang Y, Zhang J, Li S, *et al.* Smart stimuli-responsive polymeric nanoparticles in precision cancer therapy: from tumor microenvironment triggers to controlled release. *Chem. Eng. J.* 2026, 534:175025.
- [104] Chang K, Xue K, Zou M, Gao Z, Lin P, *et al.* Near-infrared-II/glutathione-dual responsive multifunctional conjugated polymer nanoparticles for synergistic photothermal/chemotherapy of tumors. *J. Photochem. Photobiol. A Chem.* 2025:116998.
- [105] Huang M, Wang C, Wang X, Chen D, Ling J, *et al.* Two-step screening of lipid-polymer nanoparticles for efficient mRNA vaccine delivery and cancer immunotherapy. *Nano Today* 2026, 67:102943.

- [106] Guo P, Buttar BA, Xue HY, Tran NT, Wong HL. Bone-targeting lipid-polymer hybrid nanoparticles for less invasive, injectable local antibiotic treatment of bone infections by methicillin-resistant *Staphylococcus aureus* (MRSA). *Int. J. Pharm.* 2026, 690:126539.
- [107] Gollapalli S, Bajad G, Brahma U, Chandanapalli DK, Veerabomma H, *et al.* Stearylamine enriched lipid-polymer hybrid nanoparticles of ursolic acid for targeting *Leishmania donovani*: In vitro studies. *Glycosci. Ther.* 2026:100024.
- [108] Baskaran A, Nagaraj G, Abdin ZS, Velu N, Kasthuri J, *et al.* Self assembled cholic acid derivative based polymeric micelles for mucoadhesive drug delivery applications and their stabilised gold and silver nanoparticles mediated Alzheimer's therapy. *J. Mol. Liq.* 2026, 447:129371.
- [109] Stenzel MH. RAFT polymerization: an avenue to functional polymeric micelles for drug delivery. *Chem. Commun.* 2008, 44(30):3486–3503.
- [110] Ozaksun NT, Tayyar T, Ozdemir A, Ark M, Incecayir T. Development and optimization of Soluplus®/Pluronic-based polymeric micelles for bicalutamide delivery: characterization, lyophilization, stability, and cellular studies. *Eur. J. Pharm. Sci.* 2025.
- [111] Lin Y, Cai L, Lin L, Zhang H, Xu W, *et al.* Hepatoma-targeted chitosan-based polymeric micelles for oral delivery of celastrol for liver cancer treatment. *Int. J. Biol. Macromol.* 2026, 338(Pt 2):149774.
- [112] Ebrahimi N, Ahmadpour-Samani P, Sakhaee K, Keshavarzsaedi M, Zahedi P. Interfacial effects of microfluidics versus bulk method on drug delivery of pH-responsive micelles based on docetaxel-loaded oxazoline triblock copolymer: a molecular dynamics study. *Mater. Today Chem.* 2026, 53:103479.
- [113] Mairal A, Kumar A. Multifunctional hyaluronic acid-decorated polyamidoamine dendrimers enhance drug solubility and enable precision therapy for ulcerative colitis. *Int. J. Biol. Macromol.* 2026, 344(Pt 1):150503.
- [114] Ahmadi Z, Jena H, Gautam HK, Kumar P. Polyethylenimine-based starburst dendrimer nanoarchitecture as potential gene and drug delivery vectors with inherent antimicrobial properties. *J. Mol. Struct.* 2026, 1352(Pt 1):144418.
- [115] Suthar T, Maurya R, Sonwani A, Upadhyay P, Datusalia AK, *et al.* Nose-to-brain delivery of donepezil hydrochloride via oleic acid-conjugated PAMAM G4 dendrimers for the treatment of Alzheimer's-like dementia. *Mol. Pharm.* 2026, 23(1):177–195.
- [116] Cho Y, Moon J, Han H, Park S, Lim YS, *et al.* Nanoarchitectonics of melittin-based polymersomes inducing lysosomal rupture for anticancer therapy. *J. Ind. Eng. Chem.* 2026, 155:639–648.
- [117] Sharifabad AH, Behzad T, Salami-Kalajahi M. Boronic acid-modified cellulose nanocrystal-cored poly (propylene imine) dendrimers as biocompatible glucose-responsive nanocarriers for intelligent insulin delivery and sensing. *Adv. Sens. Energy Mater.* 2026.
- [118] Ciepla J, Jelonek K, Musiał-Kulik M, Jaworska J, Czapla J, *et al.* Minimizing systemic toxicity of doxorubicin via targeted delivery of hypoxia-sensitive polymersomes. *Nanomedicine* 2026:102902.
- [119] Poorirani S, Mirian M, Hassanzadeh F, Kamali AN, Alipour AM, *et al.* Smart polymersome carriers for osteoporosis treatment: enhanced bone regeneration via targeted teriparatide delivery. *Nanomedicine* 2025.

- [120] Guo Y, Zhang X, Wang S, Feng H, Wu S, Wu F. Metal–phenolic network-facilitated “foe-to-friend” conversion of melittin for cancer immunotherapy with boosted abscopal effect. *Research* 2023, 6:0052.
- [121] Tan F, Zeng Y, Dong D, Deng Y, Tang Z, *et al.* GSH-responsive prodrug polymersomes for copper-free cuproptosis and synergistic photothermal cancer therapy. *Biomacromolecules* 2025, 27(1):608–623.
- [122] Belin C, Lenglet E, Al-Hawat ML, Caron J, Bartumeu EG, *et al.* Enzyme-coupled polymersome microreactor for point-of-care blood urea sensing. *J. Controlled Release* 2025.
- [123] Karaçoban YE, Işıklan N. Design, development, and characterization of pH-responsive chitosan-graft-poly (2-(diethylamino) ethyl acrylamide/acrylic acid) copolymeric nanogels for controlled and sustained erlotinib release. *Mater. Today Chem.* 2026, 52:103345.
- [124] Zhou K, He X, Shi K, Hu D, Yang C, *et al.* A dual responsive nanohydrogel system for sustained drug delivery and cartilage penetration in osteoarthritis therapy. *J. Controlled Release* 2025:114494.
- [125] Haq NU, Mazhar D, Ahmed N, Rehman AU, Naz SS. Synthesis, characterization, and in vivo evaluation of lysine functionalized silver nanogel: an efficient approach to enhanced hemostasis. *J. Drug Delivery Sci. Technol.* 2025.
- [126] Lai YJ, Ting PJ, Yang SJ, Chen G, Tsai CM, *et al.* Injectable NIR-II-responsive nanocomposite hydrogels containing gold nanoparticle-decorated carbon nanotubes for controllable drug delivery and tumor therapy. *Acta Biomater.* 2025.
- [127] Nascimento SD, de Souza RR, Sobral MV, Xavier-Junior FH, da Silva MV, *et al.* Gelatin-Oxidized alginate and chitosan-coated zein nanoparticle hydrogel composite to enhance breast cancer cytotoxicity in dual-drug delivery. *ACS Omega* 2024, 9(45):45190–202.
- [128] Joseph S, Chakrabarty R, Paira P. Advances in nano-drug delivery systems for metallic compounds in cancer therapy: challenges and future perspectives. *Dalton Trans.* 2025, 54(37):13820–13850.
- [129] Rui M, Tang H, Gao L, Hu Y, Liang W, *et al.* pH-responsive polymeric nanoparticles for peptide delivery: Synergistic STING pathway activation enhances tumor immunotherapy. *Int. J. Pharm X* 2025.
- [130] Malarz K, Borzęcka W, Ziola P, Domiński A, Rawicka P, *et al.* pH-sensitive phthalocyanine-loaded polymeric nanoparticles as a novel treatment strategy for breast cancer. *Bioorg. Chem.* 2025, 155:108127.
- [131] Austria Jr E, Bilek M, Varamini P, Akhavan B. Breaking biological barriers: engineering polymeric nanoparticles for cancer therapy. *Nano Today* 2025, 60:102552.
- [132] Noreen S, Maqbool I, Saleem A, Mahmood H, Rai N. Recent insights and applications of nanocarriers-based drug delivery systems for colonic drug delivery and cancer therapy: an updated review. *Crit. Rev. Oncol. Hematol.* 2025, 208:104646.
- [133] Sharma R, Bhate L, Agrawal Y, Aspatwar A. Advanced nutraceutical approaches to Parkinson’s disease: bridging nutrition and neuroprotection. *Nutr. Neurosci.* 2025, 28(9):1134–1150.
- [134] Yan X, Mao M, Feng S, Lan F, Li T, *et al.* Nanotechnology-enhanced neuroprotection: a novel idebenone nanoprodug conjugate strategy for Parkinson's disease. *Bioorg. Chem.* 2025:108777.

- [135] Panicker LR, Joy A, Anusree PR, Kadian S, Narayan R, *et al.* Molecular imprinted polymer based microneedle-strip electrochemical sensor for label-free dopamine monitoring: advancing neurological disorder diagnostics. *Chem. Eng. J.* 2025, 516:163870.
- [136] Ahmad T, Zaidi FK, Siddiqui U, Gupta S, Sheikh A, *et al.* Structural targeting of a familial variant of neuroserpin (Ser52Arg) by epigallocatechin gallate binding that reduces polymerization and enhances the tissue plasminogen activator inhibition. *Biochim. Biophys. Acta Proteins Proteomics.* 2026, 1874(4):141140.
- [137] Liu C, Cheng Y, Wang Z, Lu L. Bionic radical-polymerization tailored nanofilm sensor for long-term *in vivo* monitoring ionic dynamics in cerebrospinal fluid. *Adv. Sens. Energy Mater.* 2026:100181.
- [138] Saczek J, Jamieson O, McClements J, Dann A, Johnson RE, *et al.* Troponin I biomarker sensing from clinical patient samples using molecularly imprinted polymer nanoparticles for advancing healthcare approaches in cardiovascular disease. *Biosens. Bioelectron.* 2025, 282:117467.
- [139] Li B, Xie Z, Wang Q, Chen X, Liu Q, *et al.* Biodegradable polymeric occluder for closure of atrial septal defect with interventional treatment of cardiovascular disease. *Biomaterials* 2021, 274:120851.
- [140] Leone PP, Gitto M, Regazzoli D, Calamita G, Tartaglia F, *et al.* Sirolimus-coated balloon with phospholipid nanocarriers or biodegradable polymer microspheres for treatment of coronary artery disease. *Am. J. Cardiol.* 2026.
- [141] Liu K, Cheng A, You J, Chang Y, Tseng CC, *et al.* Biocompatibility and corrosion resistance of drug coatings with different polymers for magnesium alloy cardiovascular stents. *Colloids Surf., B* 2025, 245:114202.
- [142] Fa J, Chen Y, Pan W, Zhang J, Cheng W, *et al.* Polymeric anti-platelet carriers for the precision-targeting of age-related cardiovascular and cerebrovascular diseases. *Mater. Today Bio* 2026:102920.
- [143] Lu Z, Zhao D, Wang K, Liu Q, Li M, *et al.* Preparations of multifunctional iron (III)-TAML bonded cyclodextrin polymers to efficiently inactivate diverse waterborne pathogenic microorganisms. *Chem. Eng. J.* 2025:169418.
- [144] Du M, Zhang Z, Gao F, Qin Y, Gao F, *et al.* Interleaving-twisted nanoarchitected porous organic polymer synergizes photoactivity enhancement and nanozyme-powered microenvironment remodeling for advanced infected wound therapy. *RSC. Adv.* 2025, 15(57):49474–49487.
- [145] Pochet A, Bourguignon T, Grandé A, Godinez-Leon JA, Li X, *et al.* Selective accumulation of nanoparticles in infected cells for targeted drug delivery. *J. Controlled Release* 2025:114415.
- [146] Li Y, Gong H, Gan T, Ma X, Geng Q, *et al.* Smart hydrogel dressing enhances the healing of chronic infectious diabetic wounds through dual-barrier drug delivery action. *Biomacromolecules* 2024, 25(10):6814–6829.
- [147] Singh A. Artificial intelligence for drug repurposing against infectious diseases. *Artif. Intell. Chem.* 2024, 2(2):100071.
- [148] Lin L, Li J, Shang C, Li D, Sun M, *et al.* Copper-based drugs inhibit infectious bronchitis virus (IBV) *in vitro* and *in vivo*. *Vet. Microbiol.* 2025:110857.

- [149] Dong S, An S, Saiding Q, Chen Q, Liu B, *et al.* Therapeutic hydrogels: properties and biomedical applications. *Chem. Rev.* 2025, 125(18):8835-8920.
- [150] Kim Y, Kim SE, Park KD, Park KM. Bioadhesives and bioactive hydrogels for wound management. *J. Controlled Release* 2025, 379:285-302.
- [151] Zhao X, Chen Y, Cao K, Song H, Yasz Y, *et al.* Alanine-modified cellulose nanofibril hydrogel bioadhesives: an injectable angiogenic platform for promoting wound healing. *Int. J. Biol. Macromol.* 2026, 368:152124.
- [152] Sarfaraz S, Zaidi MB, Jabbar A, Khalid M, Shafeeq S, *et al.* Enhancement of wound healing via conjugated polymeric serum of curcumin, silver, and metal-organic frameworks. *J. Drug. Delivery Sci. Technol.* 2025:107577.
- [153] Ma S, Jia P, Yin Z, Zhang X, Han B, *et al.* CGG-strengthened PVA hydrogel enables pH/glucose-responsive ZnO delivery for diabetic wound healing. *Mater. Chem. Phys.* 2026, 359:132472.
- [154] Balash M, Boucetta H, He W. Factors affecting drug delivery system translation: a focus on advanced technologies, biological barriers, and regulatory challenges. *J. Controlled Release* 2025, 387:114167.
- [155] Stucchi F, Li M, Castellano G, Cellesi F. Regulatory framework for polymer-based nanotherapeutics in clinical translation. *Front. Bioeng. Biotechnol.* 2026, 14:1735885.
- [156] Bao Z, Kim J, Devedec FL, Clasky A, Allen C. Polymer microparticles in an evolving drug delivery landscape: challenges and the role of machine learning. *Int. J. Pharm.* 2025, 682:125906.
- [157] Thomas J, Kumar V, Sharma N, John N, Umesh M, *et al.* Recent approaches in nanotoxicity assessment for drug delivery applications: challenges and prospects. *Med. Drug. Discovery* 2025, 25:100204.
- [158] Chhetri P. Polymeric nanocarriers: advances, challenges, and future perspectives in targeted drug delivery. *Nanomedicine.* 2026, 72:102896.
- [159] Đorđević S, Gonzalez MM, Conejos-Sánchez I, Carreira B, Pozzi S, *et al.* Current hurdles to the translation of nanomedicines from bench to the clinic. *Drug. Deliv. Transl Res.* 2022, 12(3):500–525.
- [160] Voss MH, Hussain A, Vogelzang N, Lee JL, Keam B, *et al.* A randomized phase II trial of CRLX101 in combination with bevacizumab versus standard of care in patients with advanced renal cell carcinoma. *Ann. Oncol.* 2017, 28(11):2754–2760.
- [161] Desai N, Rana D, Patel M, Bajwa N, Prasad R, *et al.* Nanoparticle therapeutics in clinical perspective: classification, marketed products, and regulatory landscape. *Small* 2025, 21(29):e2502315.
- [162] de Souza Cardoso Delfino C, de Paula Pereira MC, dos Santos Oliveira M, de Carvalho Favareto I, Valladão VS, *et al.* Scaling nanopharmaceutical production for personalized medicine: challenges and strategies. *J. Nanopart. Res.* 2025, 27:108.
- [163] Park IH, Sohn JH, Kim SB, Lee KS, Chung JS, *et al.* An open-label, randomized, parallel, phase III trial evaluating the efficacy and safety of polymeric micelle-formulated paclitaxel compared to conventional Cremophor EL-based paclitaxel for recurrent or metastatic HER2-negative breast cancer. *Cancer. Res. Treat.* 2017, 49(3):569–577.

- [164] Fujiwara Y, Mukai H, Saeki T, Ro J, Lin YC, *et al.* A multi-national, randomised, open-label, parallel, phase III non-inferiority study comparing NK105 and paclitaxel in metastatic or recurrent breast cancer patients. *Br. J. Cancer*. 2019, 120(5):475–480.
- [165] Kosaka Y, Saeki T, Takano T, Aruga T, Yamashita T, *et al.* Multicenter randomized open-label phase II clinical study comparing outcomes of NK105 and paclitaxel in advanced or recurrent breast cancer. *Int. J. Nanomedicine*. 2022, 17:4567-4578.
- [166] Shen C, Zhang M, Lu M, Chang E, Gao Z, *et al.* Machine learning empowered formulation design, optimization and characterization of nanoparticulate drug delivery systems: current applications, challenges, and future perspectives. *Acta. Pharm. Sin. B*. 2026, 16(2):665–685.
- [167] Azimi S. Intelligent nanoparticle design: unlocking the potential of AI for transformative drug delivery. *Curr. Opin. Biomed. Eng.* 2025, 36:100625.
- [168] Sharma A, Puri V, Huanbutta K, Sangnim T. The role of 3D printing in regenerative medicine: a game-changer in tissue engineering. *Int. J. Mol. Sci.* 2026, 27(6):2589.
- [169] Sharma A, Puri V, Dheer D, Kaur M, Huanbutta K, *et al.* Cutting-edge smart hydrogel platforms for improved wound healing. *Pharmaceutics*. 2026, 18(4):406.
- [170] Yousefi MA, Rahmatabadi D, Ahmadi M, Bayati A, Baniassadi M, *et al.* 4D printing for minimally invasive biomedical applications: programmable smart materials for deployable devices, drug delivery, and tissue regeneration. *Mater. Des.* 2026, 263:115555.
- [171] Kannan G, Kurien RA, Khoklang K, Srimornsak P, Suttiruengwong S. Biodegradable polymers and biocomposites in sustainable additive manufacturing: a review. *Int. J. Biol. Macromol.* 2026, 333(Pt 1):148611.