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Development of Polymersomes as Macromolecular Platforms for Nanomedicine

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Abstract

The conventional method of drug delivery is plagued with instability, low targeting and low bioavailability. A solution to these shortcomings is the use of polymersomes, artificial vesicles that are produced through self-assembly of amphiphilic block copolymer, and they are suggested as universal nanoscale carriers. They have stiff, tunable membranes (thickness = 2–50 nm) due to accurate control of polymer chemistry, chain length, and hydrophilic mass fraction (f), which allows predictability of the drug loading and programmable release kinetics. Stimuli-responsive Polymersomes. Polymersomes can be designed to be responsive to stimuli (pH, redox/ROS, temperature/LCST) and disease-specific (disease-signal) delivery by modulating block composition (e.g., PEG-b-PCL/PLA, PMOXA-b-PDMS), glass transition (Tg), and critical packing parameter. PEGylation of surfaces or zwitterionic coronas decreases opsonisation and increases circulation, whereas click-chemistry (azide-alkyne, thiol-maleimide) and EDC/NHS-based coupling allow site-specific functionalization with antibodies, peptides, sugars, vitamins or small molecules to result in receptor-mediated targeting and further endosomal escape. The use of degradable polyesters (PLA, PLGA, PCL) or ROS-cleavable blocks (PPS) gives controllable biodegradation and good pharmacokinetics. In contrast, RAFT/ATRP synthesis pathways give low-dispersity (Đ) materials that can be scaled up by microfluidics, dual asymmetric centrifugation, or tangential-flow processing. Polymersomes mimic cellular membranes: they can be loaded with hydrophilic, hydrophobic and macromolecular cargos (proteins, peptides, nucleic acids) and reduce off-target toxicity by the rigidity of the membrane and steric stabilisation. This regulated discharge profile and biomimetic architecture locate polymersomes as second-generation macromolecular platforms in nanomedicine, having the potential to repair and regenerate tissues in systemic environments. Their formation, structure-property-function, and workflow relationships, highly developed surface chemistry, and scalable production make them an important emerging part of developing highly efficient, targeted drug-delivery systems.

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Keywords: Polymersomes, block copolymers, nanocarriers, targeted drug delivery, surface functionalization, stimuli-responsive release

INTRODUCTION

Background on Drug Delivery Challenges

In Figure 1, we see that the development of next generation drug delivery system polymersomes occurs from many factors that are associated one way or the other with a modern-day therapeutic issues, pathological microenvironment, and limitation of a conventional drug carrier and delivery system. In the modern era, the delivery of drugs to diseased tissues at the necessary concentration without damaging the healthy is a challenge in treatment of diseases. Standard carriers – such as liposomes, micelles, and hydrogels –

used to enhance drug solubility and bioavailability, suffer from low stability, rapid clearance from the body, poor encapsulation efficiency, and unpredictable drug-release kinetics [1]. Vicious microenvironments – such as acidic pH, elevated activity of enzymes, and dense extracellular matrices – further reduce the efficacy of therapies by limiting penetration of the drug into tumors and chronic sites of infection and increasing risk of dangerous off-target toxicity and shortening plasma half-life. According to Figure 1, the increasing role of nanotechnology-based delivery systems, particularly polymersomes, has made them an efficient choice for delivering both hydrophilic and hydrophobic drugs along with prolonged circulation time. Furthermore, site-specific or stimulus-responsive drug release could help overcome the therapeutic limitations and tackle antibiotic resistance [2].

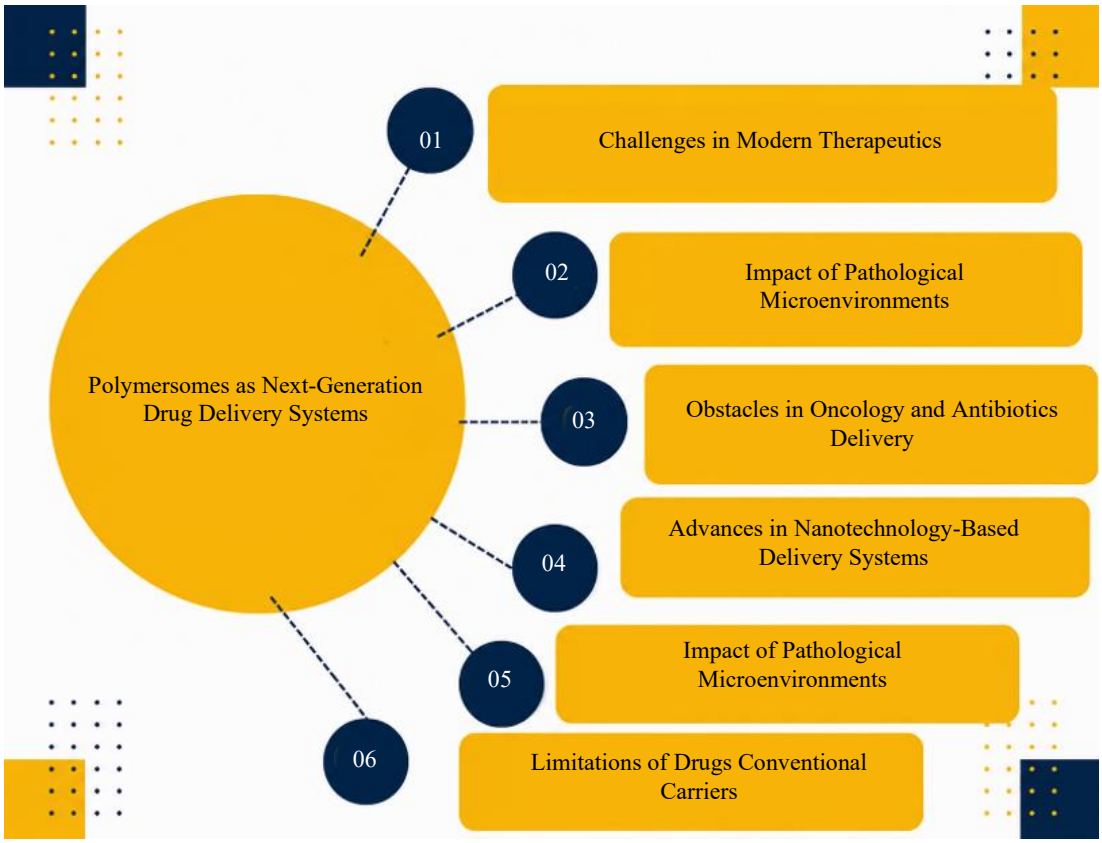

Figure 1. Key factors shaping polymersomes as next-generation drug delivery systems [3].

Liposomes, noisome and polymersomes are the vesicular nanocarriers that resemble the biological membranes and have the capacity of carrying a wide variety of therapeutic cargo. Nevertheless, the lipid bilayers that make up liposomes are relatively fragile and hence restrict their mechanical stability, as well as making it difficult to manufacture them in large quantities. It is on this basis that polymersomes, which are vesicles based on amphiphilic block copolymers, combine the biological mimicry of liposomes and the versatility of synthetic polymers [4].

Rise of Nanoscale Carriers and Polymersomes

As shown in Figure 2, the evolution of polymersomes from simple nanoscale carriers to complex multifunctional drug delivery systems has been driven by the advances of nanomedicine in structural design, targeted drug delivery, stimuli-responsive release and more recently theranostics. Drug delivery systems (DDS) based on nanoscale carriers have made significant advances in drug delivery during the last two decades. These nanocarriers offer control over particle size, surface chemistry, and biological responsiveness.

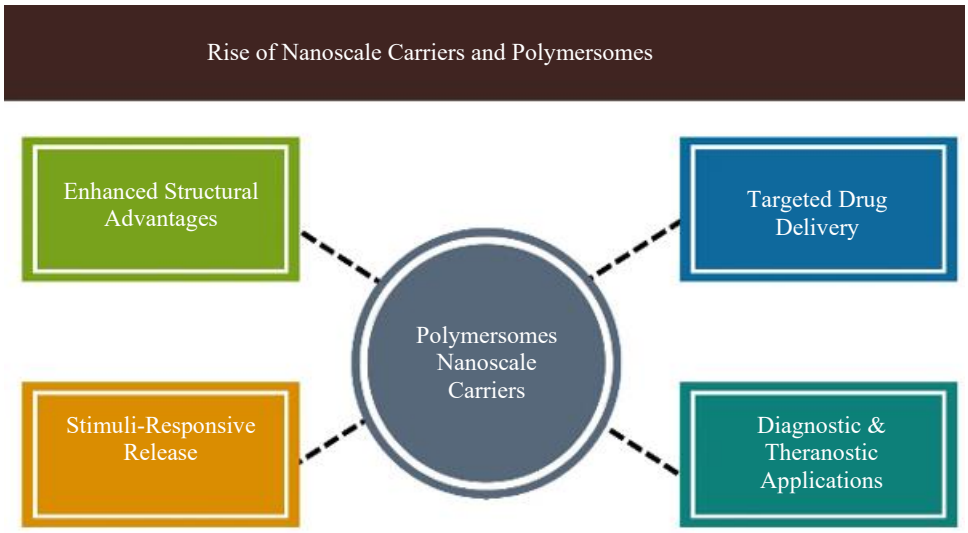

Figure 2. Rise of nanoscale carriers and polymersomes [5].

Discher and colleagues were among the early scientists to develop a pH-responsive polymersome system. The introduction of nanoparticles by Napoli and co-workers for the intracellular delivery of enzymes through encapsulation formed the basis of their work. By 2006, it was shown that polymersomes could co-encapsulate hydrophilic and hydrophobic drug. Moreover, the further introduction of redox-sensitive components allowed for glutathione-triggered release. Che et al.'s follow-up studies enhanced the efficient targeting of anticancer agents and the work of Meng et al. showed that polymersomes can deliver genes efficiently. Lomas et al. used magnetic nanoparticles for the development of theranostic platform, Su et al. designed thermo-responsive carriers while Alibolandi et al. engineered polymersomes for insulin delivery via oral route. Waldemar et al. later proposed strategies to deliver antibiotics to enhance efficacy, while Porges et al. demonstrated intracellular clearance of bacteria. As depicted in Figure 2, there have been two important developments in these areas. Polymersomes are recognized as stable alternatives for liposomes; and versatile nanocarriers delivering cargo – like drugs, genes, proteins, and diagnostic agents – accurately aiding next-gen therapeutics. Discher and colleagues were among the early scientists to develop a pH-responsive polymersome system. The introduction of nanoparticles by Napoli and co-workers for the intracellular delivery of enzymes through encapsulation formed the basis of their work. By 2006, it was shown that polymersomes could co-encapsulate hydrophilic and hydrophobic drug. Moreover, the further introduction of redox-sensitive components allowed for glutathione-triggered release. Che et al.'s follow-up studies enhanced the efficient targeting of anticancer agents and the work of Meng et al. showed that polymersomes can deliver genes efficiently. Lomas et al. used magnetic nanoparticles for the development of theranostic platform, Su et al. designed thermo-responsive carriers while Alibolandi et al. engineered polymersomes for insulin delivery via oral route. Waldemar et al. later proposed strategies to deliver antibiotics to enhance efficacy, while Porges et al. demonstrated intracellular clearance of bacteria. As depicted in Figure 2, there have been two important developments in these areas. Polymersomes are recognized as stable alternatives for liposomes; and versatile nanocarriers delivering cargo – like drugs, genes, proteins, and diagnostic agents – accurately aiding next-gen therapeutics [6].

Scope and Objectives of This Review

The paper presents a critical synthesis of the present research on polymersomes as the next-generation nanocarriers with a particular emphasis on their polymer architecture, fabrication, functionalization, and biomedical uses. Although comparative reviews of liposomes and polymersomes have been done in general terms, few studies have explicitly associated macromolecular design parameters, such as block copolymer composition, chain length, molecular weight ratio, membrane thickness, and ligand

chemistry, with the eventual functional performance of macromolecules in terms of mechanical stability, biodegradability, pharmacokinetics, and receptor-specific targeting. This paper will help bridge the gap between material-science concepts and biomedical behavior by suggesting how rational polymer design is the direct determinant of stability, biocompatibility, and specificity of polymer-dependent drug-delivery systems by focusing on how polymer chemistry, amphiphilicity balance, and membrane mechanics control vesicle performance [7].

Key Objectives Include

- Explaining the structural and physicochemical principles underlying polymer self-assembly and detailing state-of-the-art fabrication and scale-up methods such as microfluidics, dual asymmetric centrifugation, and Passerini three-component chemistry.
- Evaluating surface modification strategies (antibodies, peptides, vitamins, and sugars) that enable receptor-mediated targeting and stimuli-responsive release.
- Reviewing applications across oncology, antimicrobial therapy, protein and gene delivery, and diagnostics.
- Identifying challenges to clinical translation, including pharmacokinetics, immunogenicity, and regulatory considerations.

RELATED LITERATURE ON POLYMERSOMES

In 1999, Discher et al. proposed polymersomes, that is, block copolymer vesicles, which have tenable membranes and are far more stable than liposomes. Not long after this, Ahmed and colleagues developed pH-responsive systems, which were preceded by Napoli, who encapsulated enzymes to transfer them into cells. As early as 2006, polymer Somes could deliver hydrophilic and hydrophobic drugs simultaneously, and redox sensitivity was added to provide glutathione-controlled release. Che et al. enhanced anticancer targeting, and Meng et al. attained effective gene delivery. Lomas et al. used magnetic nanoparticles to serve as a theragnostic, Su et al. suggested thermo-responsive carriers, and Alibolandi et al. coated oral insulin. Waldemar et al. made a step forward towards the development of the antibacterial delivery system, and Porges et al. were able to prove successful clearance of bacteria on an intracellular level. Altogether, these studies outline how polymersomes can be developed as a stable replacement of liposomes into versatile, bioreactive nanocarriers which can be used to convey therapeutic drugs, genes, and proteins to their designated targets, decades of invention in nanomedicine (Table 1).

Table 1. Related literature.

Focus/application	Key findings	IEEE reference
Amphiphilic block copolymer vesicles (polymersomes)	First demonstration of a polymer with some self-assembly, tunable membrane thickness, and improved stability over liposomes.	[8]
pH-sensitive polymersomes	Showed controlled drug release triggered by acidic conditions mimicking tumor environments.	[9]
Enzyme-loaded polymersomes	Encapsulation of enzymes in a biodegradable polymer retained activity and enabled intracellular delivery.	[10]
Polymersomes for dual drug loading	Demonstrated simultaneous encapsulation of hydrophilic and hydrophobic drugs with sustained release.	[11]
Redox-responsive polymersomes	Incorporated disulfide linkages to achieve intracellular glutathione-triggered release.	[12]
Polymersomes for anticancer drug delivery	Enhanced tumor accumulation and reduced off-target toxicity of doxorubicin.	[13]
Polymer-based gene delivery	Cationic surface-modified polymersomes for siRNA and DNA transport with improved transfection efficiency.	[14]
Magnetic nanoparticles inside polymersomes	Created hybrid nanocarriers for combined imaging and drug delivery (“theragnostic”).	[15]

Temperature-sensitive polymersomes	Achieved on-demand release in hyperthermic tumor conditions using thermo-responsive polymers.	[16]
Dextran–poly(lactide-co-glycoside) polymersomes for oral insulin delivery	Protected insulin from GI degradation and enhanced oral bioavailability.	[17]
Oleyl amine–hyaluronic acid grafted polymersomes for vancomycin delivery	Improved antibacterial activity against MRSA and enhanced targeting.	[18]
Block copolymer polymersomes for antibiotic delivery to *Burkholderia Thailanders*	Efficient clearance of intracellular bacterial infections using antibiotic-loaded polymersomes.	[19]

Source: Authors' compilation based on previously published experimental studies on polymersome-based drug delivery systems [8, 19].

STRUCTURE AND SURFACE MODIFICATION OF POLYMERSOMES

Architecture and Types of Block Copolymers

As can be seen from Figure 3, the polymersomes are formed because of self-assembly of amphiphilic block co-polymers in the aqueous medium to form stable bilayer vesicles which have a hydrophilic domain and a hydrophobic domain through a different mode of assembly. Polymersomes are vesicular nanostructures which are like liposomes but more mechanically strong, structurally stable and membrane robust. Polymersomes are stable in a physiological environment, in contrast to typical liposomes – which have a lipid bilayer that is rather fragile, more importantly, polymersomes can be designed to obtain controlled mechanical features, enhanced drug encapsulation, and controlled drug release. A polymersome comprises a hollow aqueous core surrounded by a bilayer membrane composed of polymers. The most extensively studied systems are AB-type diblock copolymers, where the hydrophilic block is in contact with the surrounding aqueous medium and the hydrophobic block is in the core of the membrane. More intricate triblock copolymers consist of extra hydrophilic or hydrophobic segment and facilitate the formation of various nanostructures such as tunable worm-like, cylindrical micelles, and similar structures. The accurate control over molecular weight, block composition, and polymer chemistry provides great flexibility in designing polymersomes for different biomedical applications. The vesicle rigidity, permeability, and cargo retention can be influenced through membrane thickness in the range of 2–50 nm. The thicker membranes have a higher mechanical strength, lower permeability, and enhanced encapsulation of hydrophobic therapeutics in the bilayer. Recent advancements in polymer synthesis, like reversible addition-fragmentation chain transfer (RAFT) polymerisation, atom transfer radical polymerisation (ATRP), and post-functionalisation linkers, have further broadened the potential of polymersomes. Zheng et al. used RAFT polymerisation to prepare fluorescently labelled polymersomes with enhanced in vivo stability and glioblastoma tissue accumulation, for example. Figure 3 illustrates the general self-assembly process leading to polymersome formation. Amphiphilic block copolymers self-organize into polymer vesicles through intermediate bilayer and vesicular structures. This makes polymersomes highly efficient nanocarrier designs for various biomedical applications [20].

Amphiphilic block copolymer is self-assembled in water to form polymersomes. Hydrophilic blocks are oriented towards the aqueous phase; hydrophobic blocks form the membrane. This vesicles structure enables loading of water soluble, lipid soluble therapeutic agents as well as macromolecules.

Surface Functionalization Techniques

Unmodified or "plain" polymersomes can circulate passively, but decorating their surfaces with biological ligands, imaging agents, or responsive moieties turns them into smart, multifunctional nanocarriers. Various conjugation strategies are available to attach such molecules. Among the most widely used are copper-catalysed azide–alkyne cycloaddition biotin–streptavidin interactions, Michael addition, and EDC-assisted carbodiimide coupling. Each method offers advantages and limitations: for example, carboxylated polymersomes often form o-acylisourea intermediates prone to hydrolysis,

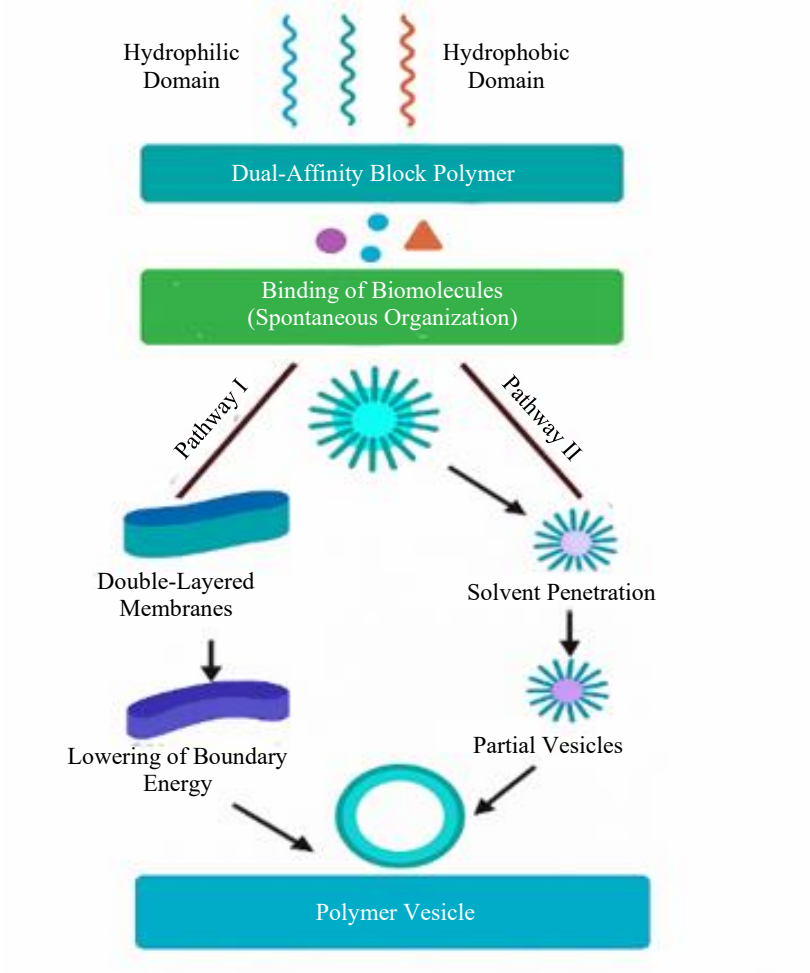

Figure 3. General process to obtain polymersomes [21].

necessitating additional carbodiimide or more stable N-hydroxysuccinimide (NHS) esters to ensure reaction completion. Researchers can also introduce amine, thiol, or other functional groups onto the polymer chains before or after assembly to facilitate coupling with biomolecules. Thiol-maleimide chemistry in near-physiological pH, particularly, is of high interest because it produces stable thiol-ether coupling with the highest selectivity and low side reactions. The Passerini three-component reaction (3CR) is another potent method that enables the synthesis of cytocompatible polymersomes, with the ability to hold drugs in high capacity, in a one-pot reaction. Travanut et al. demonstrated that Passerini-based polymersomes encapsulating doxorubicin achieved superior antitumor activity in malignant breast cancer models compared with traditional formulations. Collectively, these functionalization strategies provide precise control over the polymer's surface properties, including charge, hydrophilicity, and ligand density. This enables receptor-mediated endocytosis, site-specific accumulation, and stimulus-triggered release while maintaining vesicle integrity. However, because these reactions occur at the nanoscale, even minor variations in reaction conditions or purification can significantly impact the final properties. Therefore, careful optimisation of surface chemistry is essential to preserve the structural and functional integrity of the nanocarrier [22].

Impact of Surface Chemistry on Targeting and Stability

As per (Table 2), polymer-engineering strategies have affected positively the targeting efficiency, stability, PK behavior and immunocompatibility of polymersomes on account of advances in polymer-ligand chemistries and hybrid membrane designs. Active targeting strategies use bioconjugated ligands – like antibodies, peptides, aptamers, and small molecules – to selectively bind disease biomarkers leading to enhanced cellular internalisation with lowered off-target effect. Surface

functionalisation likewise enables controlled adjustment of ligand density, orientation and spatial distribution on the vesicle surface, which modulates receptor binding, endocytosis and therapeutic efficacy. According to Table 2, Hybrid lipo-polymersomes (HLPs) are obtained by mixing amphiphilic block copolymers with natural phospholipids to form heterogeneous membranes. These membranes can benefit from the mechanical stability of the polymers and the membrane fluidity of the lipids. The hybrid structure helps in enhancing drug encapsulation, controlled release, colloidal stability, pharmacokinetic performance, and cellular interaction at the same time it tackles purification challenges via superior processes like tangential flow filtration, microfluidic purification, etc. Overall, these surface-engineering approaches have increased the clinical potential of polymersomes as targeted nanocarriers for drug and gene delivery applications [23].

Table 2. Key aspects of surface-engineered polymersomes and hybrid lipo-polymersomes (HLPS) [24].

Aspect	Description	Examples/notes
Targeting	Surface engineering with ligands (antibodies, peptides, aptamers) enables active targeting by binding to overexpressed receptors on diseased cells, improving uptake and reducing off-target effects.	Antibody-targeted polymersomes; aptamer-functionalized vesicles.
Stability & Pharmacokinetics	Surface modifications influence vesicle stability, circulation time, and immunogenicity, requiring optimized design for in vivo performance.	PEGylation to reduce opsonisation; lipid composition tuning.
Hybrid Lipo-Polymersomes (HLPs)	Blend diblock copolymers with natural lipids (e.g., cholesterol) to create heterogeneous membranes with polymer-rich and lipid-rich domains.	Enables mechanical robustness plus membrane fluidity; mimics cell membranes.
Fine-Tuning Properties	Adjust lipid composition, cooling rates, and ratios to control domain size, morphology, and mechanical properties.	Small domain sizes for stability; large domains for responsive release.
Purification Challenges	Centrifugation, dialysis, and filtration may stress vesicles, induce aggregation, or disrupt surface ligands.	Excess ligand removal often compromises colloidal stability.
Potential Solutions	Use milder purification techniques, buffer systems, and gentle handling to preserve vesicle integrity post-functionalization.	Tangential flow filtration; microfluidic purification.
Ligand Example (Biotin–Streptavidin)	High-affinity system enables attachment of antibodies, enzymes, or imaging agents without extensive chemical modification.	Broz et al. [25] – triblock polymersomes functionalized with biotin for macrophage A1 receptor targeting.
Validation Needs	Each added layer of complexity requires testing for stability, reproducibility, and biocompatibility.	In vitro assays and in vivo pharmacokinetic studies are essential.

Source: Compiled by the authors from published studies on surface-engineered polymersomes and hybrid lipo-polymersomes, including Ref. [25].

Hybrid lipid polymer systems allow the mechanical strength to be precisely modulated and have close similarity to natural cell membranes. In changing lipid composition and cooling rates, the size and morphology of membrane domains can be fine-tuned. It is a hybridisation between polymer rigidity and lipid fluidity, and thus it has expanded applications in drug delivery and biosensing. However, purification and processing can be very difficult, since centrifugation, dialysis, filtration, etc., may cause vesicle stress, aggregation or colloidal instability, potentially affecting surface functionality and biological activity. Purification strategies and compatible buffer systems that are environmentally friendly are thus important to maintain structural integrity following functionalisation. Biotin-streptavidin systems are examples of ligand engineering, which allows efficient targeting of ligands without any chemical modification of the ligands. But the fact that the systems have become more complex should be cautiously considered in terms of their stability, reproducibility and biocompatibility to maintain clinical translatability. Surface functionalization converts plain polymersomes into smart carriers. Antibodies, peptides, sugars, vitamins, or imaging agents can be attached using click chemistry, thiol–maleimide coupling, biotin–streptavidin binding, or EDC/NHS reactions to improve targeting and controlled delivery [26].

POLYMERSOMES AS DRUG CARRIERS

Loading Strategies and Release Kinetics

According to Table 3, there have been several polymeric systems, fabrication methods, and therapeutic payloads developed to optimize polymersome based drug delivery for various biomedical applications. Incorporation of therapeutic agents in polymersomes can be done using active or passive loading. Passive loading refers to the incorporation of drugs in the formed vesicles. This can happen by diffusion into the aqueous core or incorporating the drug in the polymeric bilayer. This method is fairly straightforward and is especially applicable for neutral or hydrophobic compounds. The retention of drugs can be improved with the generation of pH gradients that facilitate ionisation and entrapment inside. Active (remote) loading, in contrast, happens after vesicle assembly and takes advantage of gradients already present (pH or ion) for the efficient accumulation of drug into the polymersome, leading to higher encapsulation efficiency and drug retention. Table 3 depicts representative polymersomes made by methods such as solvent exchange, solvent injection, self-assembly, self-aggregation, and dual asymmetric centrifugation (DAC). Their applications include targeted drug delivery, gene delivery, photodynamic therapy, intracellular transport and oral anticancer therapy. The thick polymeric membranes of polymersomes enable the release of an agent at the site of therapy, while preventing leakage and improving drug efficacy. Advancements in fabrication techniques and membrane engineering have further enhanced permeability control, cargo stability, and prolonged therapeutic performance, making polymersomes promising nanocarriers for a wide range of clinical applications [27].

Table 3. Representative polymersomes and their applications in drug delivery [28].

Polymer used	Target molecule/payload	Method of formation	Application
PEG-b-PCL (Polyethylene glycol-block-polycaprolactone)	–	Dual asymmetric centrifugation	General biomedical applications/high-efficiency drug loading.
Poly(lactic acid)–co–poly(ethylene glycol) (PLA–PEG)	Azobenzene	Solvent exchange	Pancreatic adenocarcinoma therapy.
Amphiphilic triblock copolymer (PVb2-b-PEG-b-PVb2)	Avidin, Sialyl Lewis X, anti-MCAM1 antibody	Solvent injection	Intracellular targeted drug release.
Biocytin-terminated copolymer PEO(1300)-b-PBD(2500)	Hypericin, peptides, ceftriaxone	Self-assembly	Targeted drug delivery in inflammation.
Poly(ethylene oxide)-b-poly(acrylic acid)-b-poly(N-isopropylacrylamide)	FITC–dextran, peptides, siRNA, pDNA	Self-assembled	Smart carriers for macromolecules (gene/protein delivery).
Triphenylphosphonium cation-conjugated PLA–PEG	Doxorubicin	Self-assembly	Anticancer drug delivery to mitochondria.
Polymer of didodecyl-substituted o-nitrobenzyl	Folic acid and doxorubicin	Self-assembly	Targeted photo-responsive drug delivery.
Poly(N-nitrobenzyl acrylate)/Poly(N,N-dimethylacrylamide)	Hydrophilic and hydrophobic drugs	Self-assembly	Photo-responsive drug carrier.
Poly(2-hydroxypropyl methacrylamide) analog (HPMA)	Fluorescent dye and siRNA	Solvent switching	Hydrophilic cargo/gene delivery.
Pluronic / Poly(lactic acid) blend	Biotinylated transferrin, folic acid, paclitaxel	Self-aggregation	Dual-targeting drug delivery.
F127–PLA / D-α-Tocopherol polyethene glycol succinate (TPGS)	Folate-conjugated paclitaxel	Self-aggregation + dialysis	Oral anticancer delivery.

Source: Compiled by the authors from published literature on representative polymersomes and their applications in drug delivery [28].

Antibacterial and Antiviral Applications

Polymersomes have shown great possibilities with respect to counteracting the multidrug-resistant bacterial infections and emergent viral diseases. Oleylamine-hyaluronic acid functionalized vancomycin loaded polymersomes have demonstrated a greater anti-methicillin-resistant Staphylococcus aureus activity by increasing the encapsulation of the drug, as well as targeted delivery [29]. Polymersomes

have been developed in diagnostics to detect the viral proteins with a very high amount of sensitivity. Markedly, polymersomes encapsulating dyes designed to detect the SARS-CoV-2 spike protein had a high level of reproducibility and analysis [30]. This combined therapeutic and diagnostic potential, referred to as theranostics, allows polymersomes to increase cellular uptake, avoid efflux pathways, prevent enzyme degradation of antimicrobials, and deliver effective concentrations of drugs to infected tissues, and as such, they are promising solutions to develop next-generation antibacterial and antiviral devices. Polymersomes can be used to enhance the efficacy of antimicrobial treatments, shielding drugs from degradation, boosting drug penetration into antimicrobial treated infected cells, and preventing cells from developing resistance. Vancomycin-loaded and diagnostic polymersomes are potentially effective against MRSA, intracellular bacteria, and viral protein detection such as SARS-CoV-2 assays.

Protein and Gene Delivery

Extremely sensitive biomolecules that polymersomes can easily transport are proteins, peptides, and nucleic acids. Polymers in dextran have been produced to allow oral delivery of insulin to neutralize the hormone against gastrointestinal enzymes and increase intestinal uptake. A transmembrane channel protein is added to enhance membrane permeability to hydrophilic biomolecules, further, to permit the continued enzymatic activity and cascade reactions. The study of membrane mechanics is essential in the delivery of proteins and genes; by adjusting polymer chain length, crosslinking, and hydrophobicity, it is possible to stabilize large biomolecules. Polymersomes' membrane can adaptively structure to accommodate the biopore insertion, even though channel proteins are generated out of lipid systems. Polymersomes are also designed to transport siRNA, pDNA, and CRISPR elements and protect them against nucleases, which is a testament to the flexibility of their use in biomolecular delivery [31].

TARGETED ANTICANCER DRUG DELIVERY

Ligand-Conjugated Polymersomes for Tumor Targeting

Although chemotherapeutic agents have been developed extensively, there exist issues of low selectivity, low half-life of circulation, low bioavailability and resistance to drugs. Polymersomes provide a cell-like structure, consisting of a membrane and lumen, which can absorb hydrophobic and hydrophilic anticancer medications at the same time. In another study, indocyanine green and doxorubicin were covalently linked to polymersomes and anti-HER2 antibodies through the carbodiimide crosslink. The HER2 receptor over-expressing breast cancer cells showed a widespread increase in cell death rate with the dual-drug polymersomes when compared to the single-drug formulations, which is evidence of increased therapeutic activity with decreased chemotoxicity. The traditional antibody–drug conjugates usually experience low drug–antibody ratios, which require a large amount of antibody. Another method is the conjugation of antibodies with drug-loaded polymersomes. Several antibodies – including anti-EGFR (cetuximab, trastuzumab), anti-CD44, anti-PSCA, anti-EpCAM, and AM6 monoclonal antibody – have been used to target specific cancer receptors. For example, Khanna et al. reported paclitaxel-loaded PLGA polymersomes functionalized with AM6 antibody via thiol–maleimide chemistry, which selectively bound to pelican in breast cancer cells and facilitated improved drug release [32]. Beyond antibodies, peptides with high binding specificity can also be conjugated to polymersomes. Oz et al. demonstrated that the tumor-homing peptide WREAAYQRFL, linked to a diblock copolymer using thiol–ene click chemistry, enabled integrin-targeted delivery of doxorubicin in breast cancer cells overexpressing αvβ3 integrin. Other targeting ligands, such as tetraiodothyroacetic acid, triphenyl phosphonium cation, biotin, and anisamide (for sigma receptors), have also been incorporated to enhance tumor localisation. Moreover, folic acid ligands have been attached to PLA–Pluronic F127 polymersomes co-loaded with paclitaxel and Vitamin E TPGS to exploit folate receptor abundance in the gastrointestinal tract. These folate-decorated carriers achieved higher cytotoxicity and bioavailability compared to free drugs, making oral delivery of anticancer agents feasible [33]. By conjugating polymersomes to ligands that target tumor-specific receptors, the cancer therapy is enhanced. Antibodies, folic acid,

peptides, anisamide and biotin improve tumor uptake, decrease systemic toxicity and facilitate delivery of doxorubicin, paclitaxel and combination anti-cancer agents.

Dual/Multitargeted Strategies for BBB and BTB Penetration

Brain tumors – such as gliomas – are challenging to treat because of the restrictive blood–brain barrier (BBB) and blood–tumor barrier (BTB). Polymersomes can be engineered for dual or multitargeted delivery to overcome these barriers. Figueiredo et al. encapsulated doxorubicin in diblock copolymersomes conjugated with angiopep-2, a ligand targeting low-density lipoprotein receptor-related protein 1 (LRP1) overexpressed on the BBB. In vitro tests on glioblastoma cells showed greater cytotoxicity and sustained release than the free drug. Chen et al. developed a dual-targeted system incorporating des-octanoyl ghrelin to promote transport across the BBB and folic acid to bind folate receptors on tumor cells. This combined approach improved drug accumulation and facilitated receptor-mediated endocytosis for enhanced efficacy in brain tumors [34]. Despite the great strides made in recent years, brain tumors are still challenging therapeutic entities as crossing the BBB and BTB is difficult. Angiopep-2, folic acid, and ghrelin derivatives are examples of ligands that can be used to construct dual-targeted polymersomes that show improved barrier crossing, tumor recognition, and receptor-mediated uptake in the context of glioma therapy.

Combination Chemotherapy and Immunotherapy Platforms

Alternatively, polymersomes can be used as multifunctional nano factories that have the capability of co-loading chemotherapy agents and immunomodulators to give synergistic antitumor effects. Japir et al. suggested tumor-dilatable polymer, some nano factories that could be used to deliver long, sustainable intratumoral retention and enzyme-prodrug chemo-immunotherapy, which could have a profound impact on therapeutic outcomes [35]. Polymersomes can be utilized to provide a combination therapy of multiple agents in a single carrier with an improved permeability and retention (EPR) effect to provide a versatile platform of personalized combination therapies, which enhances specificity in drug delivery and reduces systemic toxicity.

SMART AND STIMULI-RESPONSIVE POLYMERSOMES

Internal Stimuli-Responsive Systems

As seen in Table 4, polymersomes that are responsive to internal stimuli are purposely designed to exploit the biomedical properties of the specificity of the tumor microenvironment. For example, acidic PH, high intracellular glutathione (GSH), high reactive oxygen species (ROS), and hypoxia can be used for controlled release.

The use of physiological and biochemical stimuli for smart growth in polymersomes was one of the most used designs. This will affect the cancer tissue abundantly, while healthy cells are scantly affected. Tumors usually exhibit an acidic extracellular environment, high levels of ROS, elevated concentration of intracellular GSH and oxygen-poor regions (hypoxic), because of rapid cell proliferation, aberrant metabolism, oxidative stress, and poor vasculature. These pathological conditions allow polymersomes to stay stable during circulation in the body but undergo membrane destabilisation or enhanced permeability after reaching the site of action thereby causing site-specific release. The various internal stimulus which corresponds to the tumor characteristics, designing strategies and therapeutic benefits of pH-sensitive, redox-responsive, ROS-responsive and hypoxia-responsive multi-responsive polymersomes is shown in Table 4. In answer to disease-specific microenvironments, smart nanocarriers significantly accumulate drugs in tumors and enhance therapeutic efficacy. They also limit early discharge of drugs and off-target toxicity making them promising platforms for precision cancer therapeutic and controlled drug delivery [36].

- *pH-Responsive Systems:* The closest extracellular pH is 7.4, and most healthy tissues have this pH, but the tumor tissues are acidic and have a pH of approximately 6.5 or lower. The difference enables the insertion of pH-sensitive groups in the polymer such as tertiary amines and imidazole rings. These groups themselves are neutral, and under neutral conditions, the vesicle is

Table 4. Internal stimuli-responsive polymersomes [37].

Stimulus	Tumor feature	Design strategy	Key advantage
pH	Acidic environment (pH ≈6.5)	pH-sensitive groups (amines, imidazole, acid-labile linkages)	Stable in the blood, rapid release at the tumor site.
Redox (GSH)	High intracellular glutathione	Disulfide bonds are cleaved inside cells	Selective intracellular drug release.
ROS	Elevated reactive oxygen species	ROS-cleavable linkages (thioketals, boronic esters)	Targeted release in oxidative regions.
Hypoxia	Low oxygen zones in tumors	Azobenzene/nitroimidazole groups, tissue-penetrating peptides	Enhanced delivery and penetration under hypoxia.

Source: Compiled by the authors from published literature on internally stimuli-responsive polymersomes for controlled drug delivery [37].

not dismantled. When protonated in the acidic regions, it thus increases its hydrophilicity and swelling of the membrane, or ruptures acid-sensitive covalent bonds, which releases the drug cargo. Albuquerque et al. prepared doxorubicin-loaded polymersomes using the microfluidic technology, and they were more pH responsive, hence leading to rapid delivery of the drug to the tumor site [38].

- *Redox and ROS-Responsive Systems:* High intracellular GSH levels are another characteristic of cancer cells and can be as much as four times higher than those of normal cells. Reductive cleavage of the vesicle can be achieved by introducing disulfide bonds in the backbone or side chains of the polymer, and then the polymer can cleave when it is present in the cancer cells. This segmentation disrupts the hydrophobic domains and transforms them into hydrophilic ones, leading to the disassembly of vesicles and leakage of drugs. Equally, one can destabilize the polymer in some membranes with ROS-reactive linkages to release drugs specifically in cancerous tissue in the presence of high levels of ROS, which includes thioketals or boronic esters [25].
- *Hypoxia-Responsive Systems:* Solid tumors are often hypoxic (low oxygen) because of the inadequate blood supply. The incorporation of azobenzene, nitroimidazole or any other hypoxia-sensitive moieties into polymersomes can help to exploit hypoxia. Kulkarni et al. developed an echogenic particle with azobenzene and the tissue-penetrating iRGD peptide to improve drug delivery in hypoxic conditions. This system containing gemcitabine showed extensive penetration of the tumor and effective delivery in models of pancreatic adenocarcinoma [39].
- *Advantages of Internal Stimuli Systems:* By harnessing internal stimuli, polymersomes can remain stable during blood circulation, reducing premature drug leakage, and then respond precisely to the tumor microenvironment, minimising off-target effects. These systems can also be designed to carry imaging agents, enabling simultaneous diagnosis and therapy (theragnostic). The figure you provided illustrates how the polymer travels through the bloodstream, accumulates at the tumor site via the EPR effect, and then responds to local conditions – such as pH, ROS, and hypoxia – to release its drug cargo directly inside tumor cells. In summary, internal stimuli-responsive polymersomes offer a powerful and selective mechanism to exploit the inherent biochemical abnormalities of tumors. They represent a key step toward personalized, localized cancer therapy with fewer systemic side effects [40].

External Stimuli-Responsive Systems

According to Table 5, externally stimuli-responsive polymersomes are a new class of smart nanocarriers that can selectively deliver drugs non-invasively and on demand using external physical triggers. Differing from internally responsive systems that function on disease-specific biochemical conditions, these polymersomes undergo activation via externally applied stimuli such as heat, ultrasound, magnetic fields and light, specifically NIR irradiation. The ability to regulate the timing, location and amount of drug release, while limiting systemic exposure and damage to healthy tissues, makes it a powerful strategy. Table 5 outlines the most important external stimuli, the relevant material design strategies, and their associated therapeutic advantages. Thermo-responsive polymers can release their therapeutic payload beyond the desired temperature whereas ultrasound-

Table 5. External stimuli-responsive polymersomes [41].

Stimulus	How it works	Material/design used	Main benefit
Heat	Local heating or focused ultrasound	Heat-sensitive polymers such as PNIPAM or LCST copolymers	The drug is released only when the temperature rises above a set point.
Ultrasound	Sound waves cause mechanical disruption and allow imaging	Tiny gas-filled bubbles or antibody-linked carriers	Combines imaging with treatment and improves delivery to the target area.
Magnetic Field	External magnet guides or heats particles	Magnetic nanoparticles or magnet-responsive polymers	Can steer carriers to the tumor and trigger release at the site.
Light / Near-Infrared (NIR)	Laser or light breaks bonds or heats particles	Gold nanorods or light-cleavable linkers	Penetrates deeper into tissue, allows real-time tracking, and gives rapid release.

Source: Compiled by the authors from published literature on externally stimuli-responsive polymersomes for controlled and targeted drug delivery [41].

responsive systems will present an acoustic energy response which enhances infusion at the tissue and the controlled-release drug element. Polymersomes responsive to magnetic fields contain nanoparticles that allow for directed movement and accumulation at diseased sites, whereas NIR-responsive systems employ photosensitive materials for deep tissue penetration and rapid local release. These externally activated nanocarriers enhance the precision and efficacy of therapies while minimizing off-target toxicity, making them excellent candidates for next-generation targeted drug delivery and precision medicine platforms [42].

- *Temperature-Sensitive Polymersomes:* Localized hyperthermia or high-intensity focused ultrasound (HIFU) are extravagant techniques of heating the tumor site. Thermo-responsive polymers – like poly(N-isopropylacrylamide) (PNIPAM) or a block copolymer – have a lower critical solution temperature (LCST). The polymer is not only hydrated and stable at temperatures lower than the LCST, but it also collapses at temperatures higher than the LCST, which increases the permeability of the membrane and liberates drugs that are encapsulated [43].
- *Ultrasound-Triggered Systems:* Ultrasound waves offer two benefits: (1) mechanical disruption of the polymer some to increase membrane permeability, and (2) imaging capability, since many carriers can be made echogenic (bubble-like) for contrast enhancement. Zhong et al. developed a nanobubble carrier system loaded with paclitaxel and conjugated with Herceptin antibody. When exposed to ultrasound, the system showed enhanced tumor targeting and drug release, functioning as a theragnostic agent in image-guided therapy [44].
- *Magnetic Field-Activated Systems:* Embedding magnetic nanoparticles or using magnetically responsive polymers allows the external application of a magnetic field to guide carriers to a tumor or induce localized heating (magnetic hyperthermia). This not only concentrates the drug at the tumor but can also trigger release through polymer destabilisation [45].
- *Light-Activated and NIR-Responsive Systems:* The light of near-infrared (NIR) (700–900 nm) is very penetrating in tissues, and hence it is the most effective for targeted therapy. Researchers can use the photo-cleavable bonds or photothermal agents incorporated in the polymersomes by embedding them in the polymersomes, such as gold nanorods, and using them locally, upon the application of a laser, to heat or break the chemical bonds of the polymersomes. Application of this method gives the polymer some ability to deliver its therapeutic agent to the places where they are required in areas of illumination, enhancing a significant site-specific drug delivery. The release process can also be monitored together with the imaging technologies, which enable clinicians to integrate therapy and monitoring without any difficulties [46].
- *Advantages of External Stimuli Systems:* The main advantage of external stimuli – like NIR light, ultrasound or temperature – is the high degree of control that they provide on the drug release. The physicians can determine where and when the carrier will be switched on without risking early diffusion and high concentration in the required location. This system also allows two or more repeatable dosing cycles per administration, thus doing away with the necessity of having to be re-injected. This is especially beneficial in tumors that are difficult to reach or oddly shaped, so that the standard carriers do not enter them in a homogenous manner [47].

Dual/Multi-Stimuli Responsive Carriers

Tumors offer an extremely dynamic and changeable micro-environment; one stimulation is usually not sufficient to reach total or prompt drug release. To this effect, scientists are working on polymersomes, which can respond to more than one cue-internal (pH or redox conditions) and external (NIR light or heat) [48]. These dual or multi-trigger systems offer a second degree of flexibility and accuracy and, in particular, promise to be used in difficult-to-cure or therapy-resistant cancers.

RAFT-Fabricated Dual-Responsive Polymersomes

The reversible addition fragmentation chain transfer (RAFT) polymerisation can provide extraordinary control of the polymer structure, where block copolymers of specific functions can be prepared. In this method, triblock polymersomes were developed, which were sensitive to pH changes as well as temperature variations, by Zhou and other team members. The permeability of the vesicle membranes was controllable; that is, the release of the drugs could be controlled or adjusted by changing the environment. This technology has made it possible to release hydrophilic and hydrophobic payloads (e.g., Doxorubicin or PTAX) concurrently or sequentially in the same delivery system [49].

RAFT (Reversible Addition–Fragmentation Chain Transfer) polymerization provides an ability to control precisely polymer architecture, molecular weight, and functionality. With this technique, it is possible to fabricate dual-responsive polymersomes, which respond to two stimuli (e.g., pH and temperature) and which are able to release the drug on-demand, increase the stability of the vesicles, improve the therapeutic efficiency and finally, target the drug to its ideal destination in cancerous tissue.

Combining pH and NIR Responsiveness

Rodriguez et al. incorporated gold nanorods into polymersomes that were pH-responsive to generate signal-responsive carriers. When such vesicles met acidic conditions found in tumor tissues and were also irradiated with NIR light, the gold nanorods would heat the membrane, which significantly enhanced its permeability. The synergistic effect of dual-trigger systems is demonstrated by the observation that this combined stimulus produced a significantly greater release of drugs and death of cells at tumor sites than when either stimulus was used individually [50].

Redox/Acidic Dual-Stimuli Systems

Khan et al. were able to come up with polymers containing disulfide linkages and acid-sensitive functional groups. The polymers would self-assemble into vesicles that were stable under normal physiological conditions and degraded in the reductive and acidic environment of a tumor. This selectivity ensured that the encapsulated drugs were strongly shielded during circulation and liberated where they were most required, thereby causing minimal collateral damage to normal tissue [51].

The ability to alter response properties according to internal and external stimuli permits a large variety of formulations with dual stimulus response (pH, reactive oxygen species, hypoxia, redox conditions and temperature, ultrasound and near-infrared irradiation) highly controlled and site-specific drug delivery as illustrated in Figure 4.

Via the sequential/simultaneous response to multiple stimuli, these intelligent nanocarriers can counter biological barriers, improve tumor penetration and release of therapeutic agents in diseased tissue. The diagnostic and therapeutic dual roles also allow concurrent imaging and treatment monitoring. Dual-stimuli-responsive deal polymersomes allows for platform personalization of combination therapy to improve the EPR effect, enhance therapeutic efficiency and reduce systemic toxicity. Such personalized therapies may be promising strategies for next-generation precision cancer therapies (Table 6) [52].

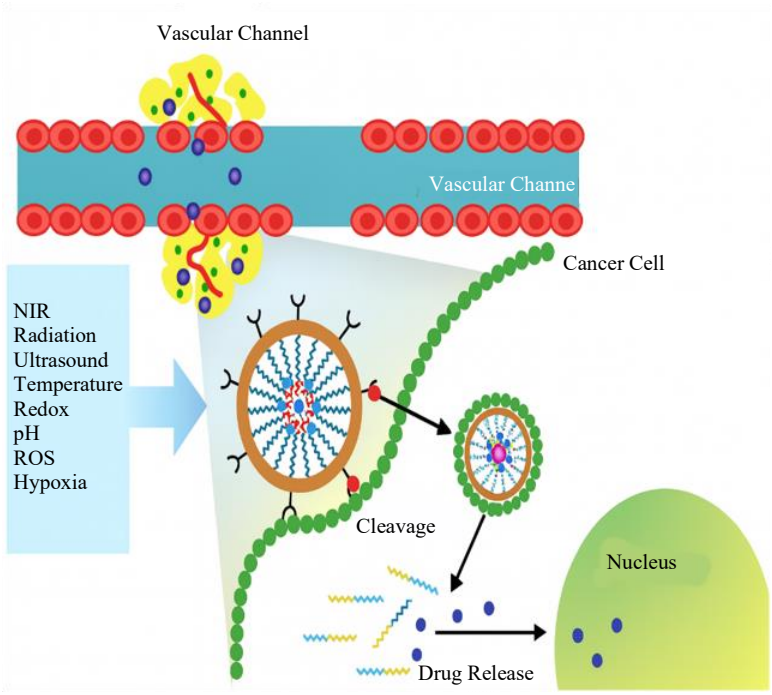

Figure 4. Stimuli-responsive characteristics of polymersomes.

Table 6. Recent research evidence on stimuli-responsive polymersomes (random order + 1–4 added at bottom).

Polymer	Stimuli response	Payload	Application/use	Reference
Poly(N-isopropylacrylamide)-dox-poly (ethylene glycol)-2,4,6-trimethoxy benzylidene pentaerythritol carbonate (PNIPAM-DOX-PEG-TMPBFC)	pH-responsive, Temperature	Doxorubicin	Development of Cancer Therapy.	[53]
Amphiphilic poly (ethylene glycol)-block-poly(β-aminoacrylate)-block-poly (ethylene glycol)	NIR-responsive	Doxorubicin and photosensitizer IR-780	Chemotherapy, Photothermal and Photodynamic therapy.	[54]
Poly (ethylene glycol)-b-poly (N, N-diethylaminomethyl methacrylate) (PEG-b-PDEAEM)	pH-responsive, NIR-irradiation	Gold nanorods, Doxorubicin	Photothermal therapy and targeted drug delivery vehicles.	[55]
Poly (propylene sulfide)-b-poly (ethylene glycol)12 (PPS20-b-PEG12)-ZnPc	ROS, NIR-irradiation	Zinc phthalocyanine (ZnPc), Doxorubicin	Chemo-photodynamic therapy.	[56]
Methoxyl poly (ethylene glycol)-b-poly(N-isopropylacrylamide)-b-poly(2-(diethylamino) ethyl methacrylate-co-2-hydroxy-4-(methacryloyloxy)benzophenone)	pH-responsive, Temperature	Doxorubicin, Paclitaxel	Promising drug carriers for tumor combination chemotherapy.	[57]
Poly(2-(dimethylamino)ethyl methacrylate)-block-polystyrene (PDMAEMA-b-PS)	pH-responsive, Temperature	Ascorbic acid, Cationic EPR probe CAT1	Gene delivery and Nanoreactors.	[58]
Poly(3-methyl-N-vinylcaprolactam)-block-poly(N-vinylpyrrolidone) (PMVC-PVPON)	Temperature	Doxorubicin	Tumor targeting and next-generation drug carriers.	[59, 60]
Poly (ethylene glycol)135-b-P-(CPT methacrylate monomer)-co-2-(pentafluoro phenyl methacrylate)25-b-PEG12-b-P(CPTMMA25-co-P(MA5)2)x2	ROS-responsive, pH-responsive	Calprotectin	Starving therapy, chemodynamic therapy, and chemotherapy.	[61]

Poly (ethylene oxide)-block-poly(2(diethylamino)ethyl methacrylate)-stat-poly (methoxyethyl methacrylate) [PEO-b-PDEA-stat-MEMA]	Ultrasound	Doxorubicin	Chemotherapeutic efficiency.	[62]
Poly(N-vinylcaprolactam)-b-poly(N-vinylisobutylacetamide)-b-poly(N-vinylpyrrolidone)	pH-responsive, Temperature	Doxorubicin	Delivery of hydrophobic and hydrophilic anticancer therapeutics and a controlled drug delivery system.	[63]
PEO-b-PCSSMA copolymer	Dual responsive (Light + Reduction)	Doxorubicin	Synergistic loading and programmed release of therapeutics.	[64]
Poly (ethylene glycol) monomethyl ether-b-methyl methacrylate-ran-2-(dimethyl amino) ethyl methacrylate mPEG-b-(PMMA-ran-PDMAEMA)	pH-responsive	Curcumin, 2-naphthole, Paclitaxel, Ampicillin sodium salt	Intermolecular drug release interactions.	[65]
Poly (ethylene oxide)-b-poly(2-(((5-methyl-2-(2,4,6-trimethoxyphenyl)-1,3-dioxan-5-yl) methoxycarbonyl) amino) methyl methacrylate) (PEO-b-PTTAMA)	pH-responsive	Nile Red, Doxorubicin	Targeted combinational therapeutic drugs.	[66]
Poly(2-(methacryloyloxyethyl) choline phosphate)-b-poly(2-(diisopropylamino)ethyl methacrylate) (PMCP-b-PDPA)	pH-responsive	Doxorubicin	Targeted intracellular delivery system.	[67]

Source: Compiled by the authors from recent published studies on stimuli-responsive polymersomes for randomized and controlled drug-delivery applications, as cited in References [53, 67].

ENGINEERING AND SCALING UP THE LARGE-SCALE PRODUCTION OF POLYMERSOMES

Polymersomes are coming out as one of the most efficient nanocarriers and adaptable microreactors in medicine, diagnostics and biotechnology. They have a strong bilayer membrane and can be chemically tuned, which gives them obvious advantages over traditional liposomes. Nevertheless, there are still major difficulties in the transfer of laboratory-level production into industrial manufacturing. Mass production should be able to maintain quality, be cost-effective and produce large quantities without affecting the quality of vesicles. One of the principles of polymer scale-up is the consistency of materials and processing conditions. The same solvents, operating parameters and polymers at the laboratory or pilot scale should be maintained at the industrial level to ensure reproducibility. Physicochemical parameters – like pH, ionic strength, and temperature – must be kept under strict control since variations may have an impact on vesicle size, membrane thickness and encapsulation efficiency. The design of equipment is also of utmost importance; whereas the industrial systems are expected to be like the laboratory geometries, the shear forces, flow patterns, and mixing rates should be scaled in proportion. These approaches are feasible, as indicated by recent studies. Poschenrieder et al. were able to scale the production of polymersomes in 12 mL laboratory batches to 1.5 L volumes to obtain monodisperse vesicles (~180 nm) with low polydispersity [68]. On the same note, Rameez et al. utilized constant low-pressure extrusion via hollow-fibre membrane to form consistent polymersomes under 200 nm. Collectively, these reports prove that polymersomes, as currently produced at an industrial scale, can maintain nanoscale control that can be subsequently used in large-scale drug delivery and diagnostics [69].

CONCLUSIONS AND FUTURE PERSPECTIVES

Summary of Key Findings

Polymersomes are advanced nanocarriers with thick, stable and highly tunable membranes. They can carry drugs, imaging agents and combination therapies in a single vesicle. Polymersomes offer advantages over conventional liposomes in terms of permeability, surface chemistry, stability and release behavior. These properties make them useful for targeted drug delivery, diagnostic imaging

and theranostic applications. Polymerosomes have the added benefit of responding to disease-specific signals, like acidic pH, enzymes or signals from the tumor microenvironment, and consequently being able to deliver therapeutic agents more selectively. Ligand-based targeting further increases the cellular uptake, treatment effectiveness, and decreases off-target toxicity. Preliminary studies have also shown that they have good biocompatibility and low systemic toxicity which support their potential to be clinically translated [70].

Challenges to Clinical Use

However, the polymersomes has some attractive properties, but their clinical translation is limited by some challenges. They have limited information on their pharmacokinetics, biodistribution, metabolism and long-term safety, leading to a partial knowledge of their in vivo behavior and clearance. In addition, when polymersomes are scaled by increasing laboratory to industrial levels, vesicle size, polydispersity, encapsulation efficiency, and stability of the membrane tend to be changed by polymer composition, solvents and processing conditions. This inconsistency makes it difficult to control the quality and adhere to regulations. To improve its translational potential, standardized datasets of pharmacological, immunogenicity and degradation are required in comparison with known liposomal carriers.

Future Research Priorities

In future, it is important to investigate hybrid polymer–lipid systems and new copolymer chemistries to enhance the efficiency of drug loading, stability of the membrane and biological responsiveness. New developments in polymer synthesis could help control molecular architecture, which could lead to patient-specific, stimuli-responsive therapeutic platforms. Systematic preclinical and clinical studies are required to identify detailed biosafety, pharmacokinetic, biodistribution and degradation profiles for clinical translation. Comparisons to liposomal carriers are also required to determine efficacy, immunogenicity and long-term safety. Low cost, easy replication and scaling up of fabrication techniques are also critical. The multifunctional polymersomes with their targeting, imaging, diagnosis and therapy properties have great potential for future clinical applications.

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