药 食 同 源 资 源
FOOD & MEDICINE HOMOLOGY RESOURCES
ISSN 3136-103X (online)
https://doi.org/10.26599/FMHR.2026.9740004

Review Article

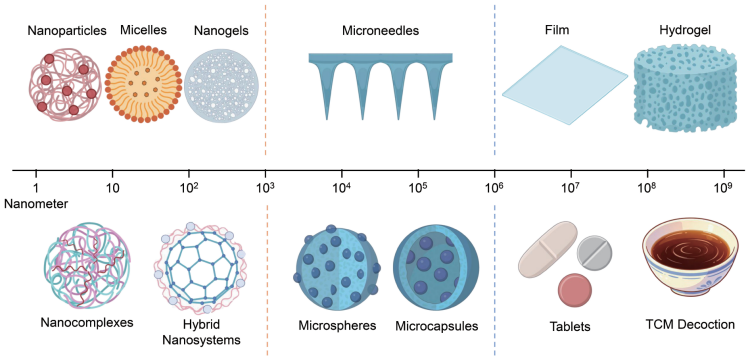
Size-tailored natural polysaccharides for advanced drug delivery: From nano to macro

Yu-Xuan Li[1, †], Jing-Han Zhou[1, †], Meng-Ting Jiang[1, †], Yue-Fan Liu[1, †], Yu-Jie Sun[1], Yi-Xuan Liu[3], Chun-Jie Bao[1, 2] (✉), Jia-Lun Duan[1] (✉)

[1] *Jiangsu Collaborative Innovation Center of Chinese Medicinal Resources Industrialization, National and Local Collaborative Engineering Center of Chinese Medicinal Resources Industrialization and Formulae Innovative Medicine, Jiangsu Provincial Key Laboratory of Functional Substances in Traditional Chinese Medicine Formulae and Innovative Drug Discovery, Key Laboratory of National Forestry and Grassland Administration on Goji, Nanjing University of Chinese Medicine, Nanjing* 210023, *China*
[2] *School of Medicine, Nanjing University of Chinese Medicine, Nanjing* 210023, *China*
[3] *Pharmaceutical Sciences Division, School of Pharmacy, University of Wisconsin-Madison, Madison WI* 53705, *USA*
† *Yu-Xuan Li, Jing-Han Zhou, Meng-Ting Jiang, and Yue-Fan Liu contributed equally to this work.*

Received: 22 August 2026 / **Revised:** 26 August 2026 / **Accepted:** 27 August 2026

Abstract: Natural polysaccharides are valued in drug delivery for their biocompatibility, biodegradability, and low immunogenicity. Many of these polymers, including chitosan, alginate, hyaluronic acid (HA), and pectin (PEC), originate from food-medicine homology resources and have a long history of safe human use. A key advantage of these polymers is their chemical versatility, which allows precise control over molecular assembly and dimensional programmability. This feature enables the construction of carriers ranging from nanoscopic colloids to macroscopic implants. Although polysaccharide-based systems have been intensively studied, most investigations have focused on chemical modifications or encapsulation strategies. The physical size of the carrier has received comparatively less systematic consideration. In this review, we propose a size-tailored classification that organizes polysaccharide delivery platforms into nanoscale, microscale, and macroscale categories, with each defined by its distinct functional role in the delivery process. Nanoscale platforms, including nanoparticles, micelles, and nanogels, are well suited for improving solubility, achieving targeted delivery, and facilitating cellular uptake after intravenous administration. Microscale systems, such as microcapsules, microspheres, and microneedles, act as localized depots that provide sustained release and minimize drug distribution to nontarget tissues. Macroscale constructs, including hydrogels, films, and tablets, accommodate large drug doses and enable site-specific application, often with enhanced patient compliance. By examining how carrier dimensions influence drug transport, tissue retention, and release dynamics, this review establishes size control as a meaningful and accessible design parameter. Therefore, this framework offers a rational basis for engineering next-generation polysaccharide-based delivery systems in the context of precision medicine.



Keywords: polysaccharide carrier; drug delivery; size-tailored platform; assemble; precision medicine; sustained release; site-specific delivery; size-dependent biodistribution

Citation: Li Y X, Zhou J H, Jiang M T, et al. Size-tailored natural polysaccharides for advanced drug delivery: From nano to macro. *Food & Medicine Homology Resources*, 2026, 1: 9740004. https://doi.org/10.26599/FMHR.2026.9740004

1 Introduction

Natural polysaccharides derived from plants, algae, and microbial fermentation are widely used in drug delivery because of their biocompatibility, biodegradability, and low immunogenicity. Many of these materials have a long history of human use and come from food–medicine homology sources with well-established safety records[1]. Compared with synthetic polymers, polysaccharides offer distinct advantages: They are chemically versatile, modifiable under mild conditions, and capable of self-assembly in aqueous media[2]. These properties have prompted extensive investigation of polysaccharide-based carriers for cancer

© National R & D Center for Edible Fungus Processing Technology, China 2026. Published by Tsinghua University Press. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Address correspondence to Chun-Jie Bao, chunjie@njucm.edu.cn; Jia-Lun Duan, jialun.duan@njucm.edu.cn

therapy, anti-infective treatment, vaccine delivery and inflammatory disease management[3].

Despite this broad interest, the majority of reviews have emphasized chemical derivatization, formulation techniques, or therapeutic outcomes, with comparatively less attention devoted to the physical size of the carrier. This oversight is noteworthy because size is not simply a byproduct of fabrication but a primary determinant of how carriers traverse biological barriers, interact with cells and tissues, and release their cargo. For polysaccharides in particular, the inherent tunability of molecular features such as chain length, branching degree, substituent pattern, and conformational flexibility makes dimensional control both feasible and mechanistically informative. Through appropriate design, these polymers can be assembled into structures that span from nanometres to centimetres, each with distinct transport and release characteristics.

The functional implications of carrier size are well illustrated by systems at different scales. Nanoparticles in the range of 10 to 200 nm exploit the enhanced permeation and retention (EPR) effect to accumulate in tumors, increase local drug concentrations, and facilitate cellular uptake for intracellular delivery[4,5]. Microparticles between 1 and 1,000 μm serve as injectable or oral depots that sustain drug release over extended periods and reduce rapid systemic clearance[6,7]. Macroscale forms such as hydrogels, films, and tablets are suited for local administration, offering high drug loading, controlled release, and improved patient adherence[7,8] (**Fig. 1**).

Natural polysaccharides are particularly attractive for the construction of delivery systems across these different dimensional scales. Their molecular characteristics, such as chain length, degree of branching, substitution patterns, and conformational flexibility, can be tailored to regulate drug encapsulation, transport, retention, and release. Through appropriate molecular design and formulation strategies, polysaccharides can be engineered into delivery platforms with distinct structural features and biological functions[9]. Consequently, dimensional control has become an important approach for optimizing the pharmacokinetic properties, biodistribution profiles, and therapeutic outcomes of polysaccharide-based drug delivery systems.

Despite the growing number of studies in this area, the relationship between carrier size and delivery performance remains fragmented across the literature. A unified framework describing how dimensional characteristics influence drug delivery behavior has not yet been established. As a result, it remains unclear how the size of polysaccharide carriers should be rationally selected to address specific biological barriers, administration routes, and therapeutic objectives. Addressing this issue is particularly important in the context of precision medicine, where delivery systems are increasingly required to exhibit well-defined biological behaviors and application-specific performance[10,11].

In this review, we propose a size-tailored framework that classifies polysaccharide-based drug delivery systems into nanoscale, microscale, and macroscale categories according to their characteristic dimensions and corresponding functions. Unlike previous reviews that primarily organized polysaccharide carriers by chemical strategies or therapeutic outcomes, our framework adopts carrier size as a central design variable, offering a functionally oriented and mechanistically informed classification. We focus on the connections between carrier size and biological performance, including transport kinetics, cellular interactions, biodistribution, and release profiles. By synthesizing representative findings across dimensional scales, we aim to establish size as a central design principle rather than a peripheral consideration. Such a perspective may assist the rational selection and engineering of polysaccharide carriers for specific therapeutic applications and contribute to the advancement of precision medicine.

2 The nanoscopic realm: Precision targeting and intracellular trafficking

Nanoscale polysaccharide carriers, ranging from 1 to 1,000 nm, are distinguished by their ability to cross biological barriers and engage cellular machinery with high efficiency. At this scale, carrier size determines not only tissue penetration depth and vascular extravasation but also the mode of cellular uptake and subsequent intracellular routing. Polysaccharides are particularly well suited for constructing nanoscale platforms because their molecular parameters, such as chain length, branching architecture, and charge distribution, can be adjusted to control particle size, surface properties, and drug loading. These features enable precise engineering of carriers that address common challenges in drug delivery, including poor solubility, rapid

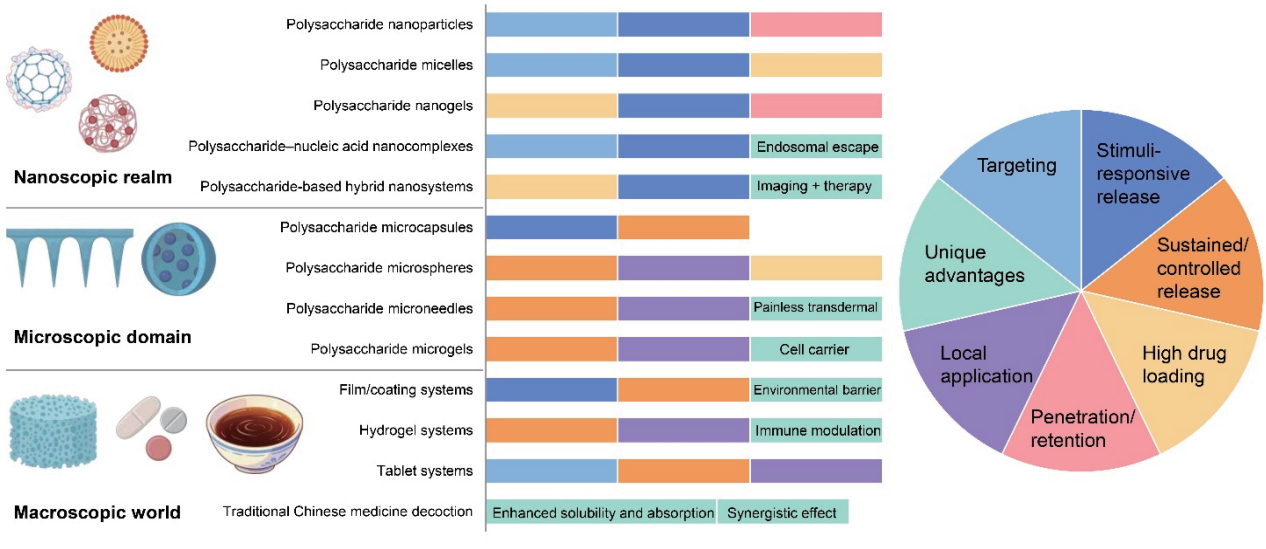


Figure 1 Multiscale natural polysaccharide-based delivery systems graded by their major strengths.

clearance, and insufficient accumulation at target sites (Fig. 2).

A diverse array of polysaccharide-based nanosystems has been developed, including nanoparticles, micelles, nanogels, nanocomplexes, and hybrid structures. Despite their differences in composition and internal architecture, these systems share a common design principle: The size range of 10 to 200 nm favours passive targeting *via* the EPR effect, active targeting through surface-conjugated ligands, and efficient endocytic uptake by target cells. This convergence of size-dependent behaviours provides a strong rationale for treating nanoscale polysaccharide carriers as a coherent category, distinct from their microscale and macroscale counterparts.

The functional advantages of nanoscale polysaccharide systems are rooted in both the inherent properties of the polysaccharide backbone and the engineered structural features of the carrier. The abundant hydroxyl, amino, and carboxyl groups along polysaccharide chains enable high drug loading through electrostatic interactions, hydrogen bonding, or covalent conjugation. The same chemical handles allow for versatile surface modification, including PEGylation for prolonged circulation, ligand conjugation for cell-specific recognition, and crosslinking for stimuli-responsive drug release. Furthermore, the molecular weight and degree of substitution of the polysaccharide directly influence self-assembly behaviour and particle formation, providing a molecular-level handle for dimension control. This molecular-to-macromolecular hierarchy makes polysaccharides especially attractive for building nanosystems in which size and function are intrinsically linked.

These design features have made nanoscale polysaccharide carriers effective in a range of therapeutic contexts (Table 1). Their size-dependent tissue penetration and cellular uptake properties have been exploited in cancer chemotherapy, where enhanced tumor accumulation improves efficacy while reducing off-target toxicity. Similar principles apply to vaccine delivery, where nanoscale carriers facilitate lymph node drainage and antigen presentation, and to gene therapy, where efficient endosomal escape and cytosolic delivery are critical. In each case, the nanoscale dimension is not incidental but a deliberate design choice that shapes the biological outcome. The next section examines the microscale regime, where larger dimensions shift the functional emphasis from systemic targeting to local retention and sustained release.

2.1 Polysaccharide nanoparticles

Polysaccharide nanoparticles represent the most widely investigated category of polysaccharide-based nanocarriers, owing to the relative simplicity of their fabrication and the versatility of drug loading strategies, which include encapsulation, surface adsorption, and covalent conjugation. The biological performance of these nanoparticles is strongly influenced by their size, which is one of the key physicochemical parameters governing *in vivo* fate. Particles between 50 and 200 nm are widely referenced as a general design guideline for systemic administration: They are large enough to avoid rapid renal clearance but small enough to extravasate through leaky vasculature and penetrate tumor tissues *via* the EPR effect. Particles below 5.5 nm may be cleared more rapidly by renal filtration, while those exceeding 200 nm often show reduced tissue penetration and increased uptake by the reticuloendothelial system[12-14]. However, it should be noted that these size-dependent trends represent general observations rather than absolute thresholds, as biological behaviors are also modulated by other physicochemical properties including surface charge, shape, rigidity, and surface modification[15]. This size window therefore serves as a useful primary design guideline for most polysaccharide nanoparticle formulations, with the understanding that optimal performance ultimately depends on the interplay of multiple particle characteristics.

Beyond the size criterion, the intrinsic chemistry of the polysaccharide backbone itself provides an equally critical lever for modulating nanoparticle behavior. The molecular properties of

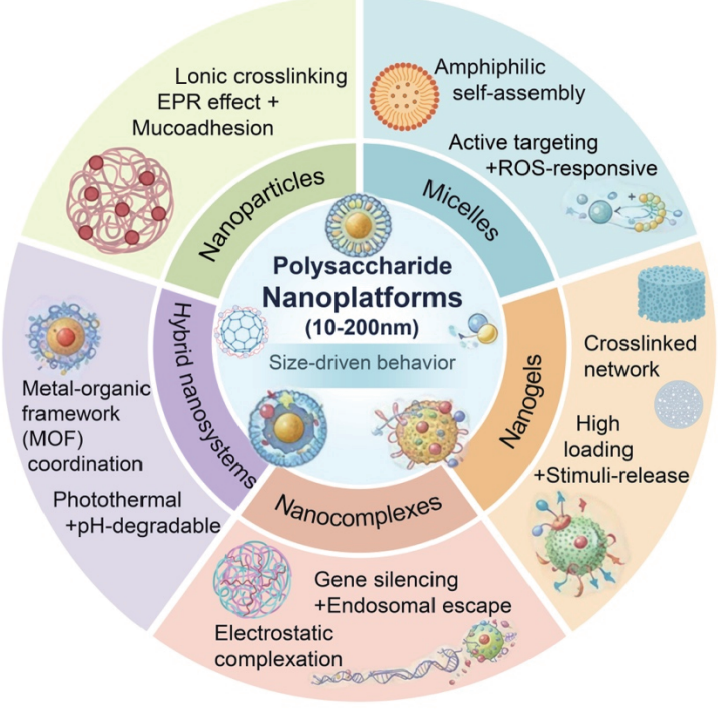


Figure 2 Nanoscale natural polysaccharide-based drug delivery systems.

the constituent polysaccharides directly influence nanoparticle formation and performance. Molecular weight, degree of substitution, and chain conformation affect not only particle size distribution but also drug loading efficiency and release kinetics. For example, high molecular weight chitosan tends to form larger nanoparticles with slower drug release due to more extensive chain entanglement, whereas lower molecular weight variants yield smaller, more rapidly releasing particles. Surface charge, determined by the density of ionizable groups, affects colloidal stability and interactions with biological membranes. These structure–property relationships provide a molecular handle for tailoring nanoparticle dimensions to specific therapeutic needs.

Recent studies have demonstrated the practical utility of polysaccharide nanoparticles across diverse applications. Thiolated chitosan (TCS) nanoparticles have been developed for mucosal vaccine delivery, where the thiol groups form disulfide bonds with mucus glycoproteins, prolonging antigen retention at mucosal surfaces and enhancing immune responses[16]. Amphiphilic carboxymethyl cellulose (CMC) derivatives have been engineered into self-assembled nanoparticles that improve the stability and controlled release of hydrophobic hydrophobic pesticides[17]. In each case, the size of the nanoparticles was carefully tuned to match the intended route of administration and biological barrier to be overcome.

Despite these advances, several challenges persist. Batch-to-batch consistency remains difficult to achieve because natural polysaccharides vary in molecular weight and degree of substitution depending on source and extraction method. Moreover, the relationships among polysaccharide primary structure, nanoparticle architecture, and *in vivo* performance are still incompletely understood, which complicates rational design and clinical translation. Addressing these issues will require more standardized raw materials and a deeper mechanistic understanding of how nanoparticle size and surface properties jointly determine biological fate.

Polysaccharide nanoparticles offer tunable size and high drug loading, however, batch-to-batch consistency remains a challenge owing to natural polymer variability, and the structure–performance relationships governing *in vivo* fate are incompletely understood.

2.2 Polysaccharide micelles

Polysaccharide micelles are self-assembled colloidal systems formed by amphiphilic polysaccharide derivatives in aqueous media. These carriers typically exhibit a core–shell architecture, where the hydrophobic core serves as a reservoir for poorly water-soluble drugs and the hydrophilic shell provides colloidal stability. The amphiphilic character is usually achieved by conjugating hydrophobic moieties, such as deoxycholic acid (DC) or alkyl chains, to hydrophilic polysaccharide backbones *via* ester or amide linkages. Beyond solubilization, the abundant functional groups on polysaccharide chains enable the attachment of targeting ligands and stimuli-responsive elements, making micelles a flexible platform for precision delivery.

The size of polysaccharide micelles is determined by several interrelated factors, including the molecular weight of the polysaccharide backbone, the length and density of hydrophobic grafts, and the assembly conditions. For systemic applications, micelles in the range of 50 to 200 nm are generally preferred, as this range favours passive tumor targeting while avoiding rapid clearance. The molecular weight of the polysaccharide backbone, typically between 20 and 80 kDa, must be sufficient to stabilize the micellar structure during circulation but not so high as to cause prolonged tissue accumulation. Similarly, the degree of hydrophobic modification must be carefully controlled: Insufficient grafting prevents stable self-assembly, whereas excessive grafting may induce aggregation or alter biocompatibility.

Several representative examples illustrate how polysaccharide micelles can be rationally designed for specific therapeutic challenges. For rheumatoid arthritis (RA) therapy, folate-modified *Panax notoginseng* polysaccharide–DC conjugates self-assembled into ~115 nm micelles that actively target folate receptor-β-positive macrophages. The system achieved targeted delivery of polyphyllin I and therapeutic efficacy *via* JAK2/STAT3 pathway inhibition and M2 polarization[18]. Beyond cell-specific targeting, polysaccharide micelles have also been engineered to respond to pathological microenvironments and overcome treatment resistance. A hyaluronic acid/dextran-based micellar system (~138 nm) was designed with an ROS-responsive doxorubicin (DOX) prodrug and a TPP moiety for mitochondrial targeting, further coated with HA for CD44-mediated tumor uptake. Upon internalization, hyaluronidase exposure and ROS triggered drug activation, overcoming P-gp-mediated multidrug resistance (MDR) in breast cancer models[19]. Further advances have integrated multiple functional modules within a single polysaccharide micellar platform to achieve self-amplifying therapeutic responses. A dextran-based micellar system integrated an ROS-responsive paclitaxel (PTX) prodrug with a chemiluminescent agent and photosensitizer, creating a self-amplifying loop wherein tumor H_2O_2 triggers chemiluminescence, amplifies ROS, and accelerates prodrug activation for enhanced antitumor efficacy[20].

From a translational perspective, the design of polysaccharide micelles should consider several practical factors. The choice of linker chemistry between the hydrophobic moiety and the polysaccharide backbone determines both the stability of the conjugate during storage and circulation and the release kinetics of the drug at the target site. Stable amide linkages are suitable for maintaining integrity during systemic circulation, whereas stimuli-responsive linkages such as thioketal (ROS-responsive), hydrazone (pH-sensitive), or disulfide (redox-responsive) bonds enable controlled intracellular release. The selection of linker should match the pathological features of the target disease, such as the oxidative stress environment of tumors or the acidic pH of inflammatory lesions. Equally important is the use of well-defined conjugation chemistries, such as EDC/NHS coupling, to ensure batch-to-batch reproducibility. Finally, systematic evaluation of the safety of synthetic linkers and their degradation products remains essential for clinical development.

Polysaccharide micelles provide high loading capacity for hydrophobic drugs and allow flexible functionalization; however, their dilution-dependent instability and the safety profiles of synthetic grafts warrant careful evaluation for systemic administration.

2.3 Polysaccharide nanogels

Polysaccharide nanogels are three-dimensional hydrogel networks at the nanoscale. They occupy a unique position among polysaccharide carriers: They combine the high water content and soft, tissue-friendly mechanical properties of conventional hydrogels with the transport advantages of nanoscale systems, including stable dispersion, efficient cellular uptake, and the ability to extravasate through biological barriers. Unlike solid

nanoparticles, nanogels possess a porous network that provides ample space for drug loading and allows the accommodation of both hydrophilic and hydrophobic agents. Unlike micelles, they maintain structural integrity upon dilution, avoiding the instability that often plagues self-assembled systems.

Polysaccharide nanogels are typically constructed through either physical crosslinking, driven by electrostatic interactions or hydrogen bonding, or chemical crosslinking, involving covalent bonds or disulfide linkages[21]. The crosslinked structure offers several functional advantages. Drug encapsulation efficiencies for hydrophobic drugs can exceed 80%, substantially higher than the 40%–50% typically observed in conventional hydrogels[22]. The network also protects encapsulated therapeutics from premature release under physiological conditions. Moreover, the crosslinks can be designed to respond to specific stimuli, including pH changes, redox potential shifts, or enzymatic activity, enabling spatiotemporally controlled drug release[23].

The therapeutic utility of polysaccharide nanogels is well illustrated by recent studies. In diabetic wound healing, a quaternized chitosan-based nanogel co-delivering platelet-derived growth factor (PDGF) BB and DNase I was developed to address the dual challenges of impaired angiogenesis and excessive neutrophil extracellular trap (NET) formation. In diabetic mouse models, this dressing achieved a wound closure rate more than 60% higher than that of the blank hydrogel at day 14, demonstrating the benefit of simultaneous pro-healing and anti-inflammatory actions. The nanogel formulation ensured programmable local release of both therapeutics with distinct kinetics, a task that would be difficult to accomplish with simple solution-based administration[24].

HA-based nanogels offer particular advantages for CD44-targeted cancer therapy. A representative example is a self-assembled nanogel in which cisplatin functions simultaneously as a chemotherapeutic agent and a physical crosslinker for HA, with daunorubicin encapsulated within the network. The nanogel, approximately 38.5 nm in diameter, achieved 87.5% encapsulation efficiency for daunorubicin and 9.86% loading, along with 26.2% cisplatin loading. In CD44-positive acute myeloid leukaemia cells, the nanogel enhanced intracellular drug retention, induced lysosomal membrane permeabilization, and promoted differentiation alongside direct cytotoxicity. In relapsed or refractory leukaemia (rrAML) mouse models, the nanogel extended survival beyond 40 days in 75% of treated animals, compared with only 20% for free drug combinations, while significantly reducing cisplatin-associated nephrotoxicity and daunorubicin-associated cardiotoxicity[25]. This example highlights how the nanogel format enables the co-delivery of mechanistically complementary agents with distinct physicochemical properties.

In summary, polysaccharide nanogels combine high water content, structural stability, high drug loading, and stimuli-responsive release; nevertheless, the complexity of multi-stimuli-responsive design and the limited understanding of structure–function relationships remain obstacles to clinical translation.

2.4 Polysaccharide–nucleic acid nanocomplexes

Polysaccharide–nucleic acid nanocomplexes are formed primarily through electrostatic interactions between cationic polysaccharides and negatively charged nucleic acids, including siRNA, mRNA, and plasmid DNA. This mode of assembly is straightforward and mild, avoiding the use of organic solvents or harsh chemical reactions that might damage the nucleic acid cargo. However, most naturally occurring polysaccharides are neutral or negatively charged because of the prevalence of hydroxyl, carboxyl, or sulfate groups. Among common polysaccharides, chitosan is a notable exception, possessing protonatable amino groups that confer cationic character under mildly acidic conditions. Even so, the charge density of chitosan is pH-dependent and often insufficient for stable complexation at physiological pH, necessitating chemical modification strategies to enhance or introduce cationic functionalities.

Several approaches have been developed to increase the cationic charge density of polysaccharides. Amination reactions can introduce primary or secondary amine groups, as in the synthesis of 6-amino-6-deoxychitosan or 6-amino-6-deoxycurdlan, which impart pH-dependent positive charges and improve nucleic acid binding. Naturally occurring polyamines, such as spermine, can be grafted onto polysaccharide backbones, as exemplified by dextran–spermine and pullulan–spermine conjugates, which form stable complexes with nucleic acids through multivalent electrostatic interactions. An alternative strategy involves conjugating synthetic cationic polymers, such as polyethyleneimine, onto polysaccharides like alginate, chitosan, or laminarin. This approach not only enhances charge density but also introduces endosomal buffering capacity that facilitates escape from acidic endosomal compartments. In all these cases, the degree of substitution is a critical parameter: Sufficient modification is required for stable complex formation, but excessive modification may compromise biocompatibility or impede intracellular release[26]. When covalent modification is followed by complexation, targeting ligands such as galactose, folic acid (FA), or transferrin can be attached to the polysaccharide to mediate receptor-specific cellular uptake without affecting the electrostatic binding mode.

The biological advantages of polysaccharide-based nanocomplexes over naked nucleic acids are substantial. Electrostatic condensation protects nucleic acids from nuclease degradation, and the nanoscale size, typically between 100 and 200 nm, reduces renal clearance and prolongs circulation. The polysaccharide shell provides additional benefits: It shields the complex from opsonization, reduces non-specific protein adsorption, and can be decorated with targeting moieties for cell-specific delivery. Furthermore, the incorporation of endosomal escape functionalities, such as the proton sponge effect of polyethyleneimine, enables efficient cytoplasmic delivery of the nucleic acid cargo. The intrinsic biodegradability of polysaccharides also offers an important safety advantage over many synthetic cationic polymers, which often show dose-dependent toxicity due to non-degradable backbones.

Recent studies have demonstrated the versatility of this approach. For hepatocellular carcinoma (HCC) therapy, chitosan was used to form electrostatic nanocomplexes with si-circPAK1, yielding nanoparticles suitable for systemic delivery. *In vivo*, these complexes significantly suppressed tumor growth and lung metastasis compared with naked siRNA, demonstrating enhanced gene silencing efficacy[27]. The improvement was attributed to protection of the siRNA from degradation and improved cellular uptake mediated by the cationic chitosan matrix.

More sophisticated systems have integrated structural and biological functionalities. A natural polysaccharide-based nanoplatform (ZymA@SiR21), combining zymosan A with siRNA through a cationic intermediate, was developed for myocardial infarction (MI) therapy. The optimized nanocomplex exhibited controlled particle size and surface charge, enabling

stable siRNA delivery. Functionally, the system achieved stage-dependent therapeutic regulation, with early inflammatory activation followed by subsequent gene silencing that cooperatively improved cardiac repair. *In vivo* experiments showed significantly improved cardiac function and reduced fibrosis compared with MI model group, highlighting the advantage of polysaccharides in combining delivery functions with intrinsic bioactivity[28].

Further optimization has incorporated biomimetic and stimuli-responsive features. A *β*-glucan-based "virus-mimicking" nanocomplex (CEEPG) was constructed by grafting pH-responsive polymers onto the polysaccharide backbone and subsequently assembling with chitosan/siRNA polyplexes. The resulting nanoparticles had a uniform size of approximately 140 nm with low polydispersity and high siRNA encapsulation efficiency exceeding 90%. The system displayed pH-dependent membrane-disruptive activity, enabling efficient endosomal escape under acidic conditions while remaining inert at neutral pH. In multiple *in vivo* models, including MI and inflammatory diseases, this nanocomplex achieved enhanced lesion accumulation and significantly improved gene silencing efficacy[29]. This design demonstrates how incorporating stimuli-responsive and biomimetic features can substantially enhance the delivery performance of polysaccharide–nucleic acid nanocomplexes.

The formation of these nanocomplexes is primarily governed by electrostatic interactions, wherein cationic polysaccharides self-assemble with negatively charged nucleic acid phosphate backbones through charge neutralization. The degree of polymerization and degree of deacetylation of chitosan are key parameters for regulating complex properties. By optimizing the formulation ratio and processing conditions, precise control over charge properties, particle size, loading capacity, and release behavior can be achieved, thereby addressing the fundamental design tension where strong binding favours stable encapsulation but hinders intracellular release[27,28].

Polysaccharide–nucleic acid nanocomplexes provide a mild, solvent-free platform for gene delivery; however, the pH-dependent charge density of most natural polysaccharides and the inherent trade-off between binding stability and intracellular release require further optimization.

2.5 Polysaccharide-based hybrid nanosystems

Polysaccharide-based hybrid nanosystems integrate natural polysaccharides with inorganic components to create multifunctional platforms that combine the biological adaptability of polysaccharides with the physicochemical functionality of inorganic materials. These systems are typically constructed in core–shell or network architectures, where the polysaccharide provides a biocompatible interface and the inorganic component contributes structural reinforcement, imaging capability, or therapeutic functionality. The rationale for hybridization is straightforward: Many therapeutic challenges require functions that neither organic polymers nor inorganic materials can achieve alone. By combining them, hybrid systems enable properties such as pH-responsive drug release, photothermal therapy, magnetic targeting, or real-time imaging within a single nanoplatform[30].

The structural versatility of polysaccharides facilitates this integration. The abundant hydroxyl, amino, and carboxyl groups on polysaccharide chains allow conjugation, surface modification, and interaction with inorganic nanomaterials through electrostatic attraction, hydrogen bonding, or coordination. This chemical compatibility enables stable hybrid formation while maintaining the biological functionality of the polysaccharide component[31,32].

Among inorganic materials, metal–organic frameworks (MOFs) have attracted considerable interest due to their high porosity, tunable pore structures, and stimulus-responsive degradation. Constructed from metal ions coordinated with organic ligands, MOFs can achieve exceptionally high drug loading and undergo controlled disassembly in acidic environments, enabling site-specific drug release[33,34]. When combined with polysaccharides, MOF-based hybrids benefit from both the structural advantages of the inorganic framework and the targeting and biocompatibility properties of the polysaccharide coating.

A representative example is the fucoidan-loaded ZIF-8 nanoparticle platform designed for antibacterial therapy. In this system, fucoidan is encapsulated within the porous ZIF-8 framework through coordination-assisted self-assembly, and the nanoparticle surface is further coated with HA for active targeting. The hybrid structure enables multiple synergistic effects: The MOF component provides high drug loading and pH-responsive degradation, releasing zinc ions that disrupt bacterial membranes and generate ROS; the polysaccharide components contribute both biological activity and targeting ability, facilitating intracellular delivery to infection sites. Experimental studies have demonstrated that such systems can effectively inhibit methicillin-resistant Staphylococcus aureus, reduce inflammation, and promote tissue regeneration[34].

In addition to MOFs, hydroxyapatite nanoparticles and carbon-based nanomaterials have been incorporated into polysaccharide hybrid systems. Nanocellulose-based hybrids have been developed by integrating cellulose nanocrystals with targeting ligands, carbon nanodots, and chemotherapeutic agents. In these systems, the polysaccharide backbone provides a high surface area and modifiable interface, while the carbon components contribute imaging capability and photodynamic or photothermal therapeutic functions. These hybrids exhibit pH-responsive drug release and light-triggered therapeutic activity, demonstrating the feasibility of integrating multiple treatment modalities within a single nanoplatform[35].

Chitosan-based hybrid systems have been extensively explored because of the unique cationic nature and modifiability of chitosan. By incorporating magnetic nanoparticles or silica components into chitosan matrices, researchers have achieved enhanced stability, sustained drug release, and additional functionalities such as magnetic resonance imaging or hyperthermia. The cationic nature of chitosan also facilitates interactions with negatively charged inorganic nanoparticles, enabling stable hybrid formation without extensive chemical modification[30].

Beyond nanoparticle-based systems, polysaccharide–inorganic hybrids can be incorporated into higher-order delivery platforms such as injectable hydrogels. Chitosan-based hydrogels integrated with hydroxyapatite nanoparticles, for example, have been developed for localized drug delivery in implant-associated infections. These systems exhibit thermosensitive gelation, sustained drug release, and strong antibacterial efficacy, achieving prolonged bacterial growth inhibition and significant biofilm eradication. The incorporation of inorganic nanoparticles enhances mechanical stability and provides additional therapeutic functions, while the polysaccharide matrix ensures biocompatibility and injectability[36].

Overall, polysaccharide-based hybrid nanosystems provide a versatile strategy for constructing multifunctional drug

delivery platforms by integrating the advantages of organic and inorganic components. Through rational design of structure and interactions, these systems enable targeted delivery, stimuli-responsive release, and synergistic therapeutic effects. With continued advances in material engineering, such hybrid systems are expected to play an increasingly important role in antimicrobial therapy, cancer treatment, and tissue regeneration.

Polysaccharide-based hybrid nanosystems uniquely integrate biological adaptability with inorganic functionality for multifunctional therapy; nonetheless, concerns regarding batch-to-batch reproducibility, long-term stability, and the toxicity of degradation product persist.

2.6 Structure–function relationship of polysaccharides in carrier design

The physicochemical properties and delivery performance of polysaccharide-based systems are closely associated with the intrinsic molecular characteristics of polysaccharides. Structural parameters, including molecular weight, degree of substitution, charge density, branching architecture, hydrophobic modification, and crosslinking degree, collectively regulate the self-assembly behavior, structural organization, and functional performance of polysaccharide carriers. Generally, polysaccharides with higher molecular weight exhibit stronger chain entanglement and intermolecular interactions, which can contribute to enhanced structural integrity and stability, while their effects on hydrodynamic size and dispersion behavior may vary depending on polymer concentration, molecular conformation, and assembly conditions. The degree of substitution and hydrophobic modification regulate the amphiphilic balance of polysaccharide chains and facilitate the formation of self-assembled structures, such as micelles or nanoparticles, thereby improving the encapsulation and solubilization of poorly water-soluble bioactive compounds. Meanwhile, surface charge density influences electrostatic interactions, structural stability, and biological interactions with cells and tissues, thereby affecting carrier behavior and biological performance. In addition, branching architecture and crosslinking degree determine chain arrangement, network formation, and molecular diffusion pathways, ultimately modulating drug release profiles. Therefore, rational regulation of polysaccharide molecular architecture provides an effective strategy for tailoring carrier properties and

Table 1 Representative polysaccharide-based nanoscale drug delivery systems

Categories	Vehicle	Payload	Size (nm)	Application	Administration	Effect	Reference
Nanoparticle	Chondroitin sulfate and chitosan or diethylaminoethyl chitosan	Dexamethasone phosphate	100–400	Anti-inflammatory	/	Prolonged Release of dexamethasone phosphate	[37]
Nanoparticle	TCS	Virus-like particles	15–200	Influenza A virus (IAV)	intranasal	+Mucosal immunity	[16]
Nanoparticle	CMC and rosin (RS)	Avermectin (AVM)	150–220	Hydrophobic pesticides	foliar spraying	↑Water dispersibility and stability, loss prevention, pH-controlled release rate	[17]
Nanoparticle	Poly(lactic-co-glycolic acid) (PLGA) and oligomeric chitosan (OCS)	Alpha-cyano-4-hydroxycinnamic acid (CHC) and the monoclonal antibody cetuximab (CTX)	200–900	Glioblastoma	/	↑Cytotoxic and antiangiogenic effects	[38]
Nanoparticle	Chitosan	Carmustine	200–430	Glioblastoma	Intranasal	↑Sustained release, permeability	[39]
Nanoparticle	Chitosan	Non-alkylating agent gemcitabine (GEM)	150–200	Glioblastoma	/	↑GEM antiproliferative activity to sensitize cells to TMZ	[40]
Nanoparticle	Gastrin-releasing peptide (GRP)-conjugated mGOC (mGOCG)	DOX	180–220	Glioblastoma	Intravenous	Dual active/magnetic targeted drug delivery, ↓tumor growth, ↑animal survival time	[41]
Nanoparticle	Chitosan	Curcumin (Cur)	100–260	Breast cancer	/	pH-responsive release	[42]
Nanoparticle	Chitosan	Amoxicillin	150–200	Helicobacter pylori	Oral	Effective amoxicillin delivery, ↑antibacterial activity	[43]
Nanoparticle	Chitosan	Methotrexate (MTX)	~200	Lung cancer	Intravenous	pH-dependent drug release, ↑anticancer activity, tumor Accumulation of methotrexate, ↓Tumor growth, no overt toxicity	[44]
Nanoparticle	Starch	Ovalbumin (OVA)	200–480	Gastrointestinal M-cell targeting	Oral	↑Transport efficiency	[45]
Nanoparticle	Pullulan	Epirubicin (EPI)	200–300	Cervical cancer	Intravenous	↑Half-life, ↑AUC, ↑tumor drug concentration, ↑liver accumulation	[46]

(Continued)

Categories	Vehicle	Payload	Size (nm)	Application	Administration	Effect	Reference
Nanoparticle	Tragacanth gum-gelatin	Cur nanocrystals	~80	RA	Intravenous	↓Oxidative stress, ↑M2 macrophage polarization, ↓Expression of inflammatory cytokines (TNF-α, IL-1β, and IL-6), excellent anti-inflammatory effect and significant alleviation of joint swelling in gouty arthritis treatment.	[47]
Nanoparticle	Zymosan A	siRNA-21 (SiR21)	~80	MI	Intravenous	Dual immunoregulatory and gene-silencing functions	[28]
Micelle	Panax notoginseng polysaccharides (PNP) with DC	Polyphyllin I (PPI)	1–115	RA	Intravenous	FA receptor-mediated cellular uptake, ROS elimination, inflammation reduction, JAK2/STAT3 pathway suppression, M2 polarization, and M1/M2 balance restoration by FA-PPI-Ms	[18]
Micelle	HA/dextran	Ursolic acid (UA) and DOX	~138	Cancer MDR	Intravenous	Enhancing the mitochondria-accumulation, inducing its malfunction, ultimately contributing to the susceptibility restoration of MCF-7/ADR cells to chemotherapeutic agents	[19]
Micelle	Dextran	A chemiluminescence agent luminol, a photosensitizer chlorine e6 (Ce6), and a ROS-activable thioketal-based PTX prodrug	~190	Combination of stimuli-activable prodrug based chemotherapy and photodynamic therapy (PDT)	Intravenous	Direct killing of tumor cells and amplification of oxidative stress to accelerate PTX prodrug activation	[20]
Micelle	Pullulan	DOX and Beclin1-targeting shRNA	120–180	Cervical cancer	Intravenous	FR-mediated targeting of FR-positive cancer cells, and tumor growth inhibition	[48]
Micelle	Natural polysaccharides (chitin, chitosan)	The system itself acts as a macromolecular antibacterial agent	1–50	Multidrug-resistant bacterial infections and wound healing	Topical	Inhibition of bacterial biofilm formation and eradication of mature biofilms, along with anti-infective effects and acceleration of MRSA-infected wound healing *via* bacterial elimination, inflammation alleviation, angiogenesis, and collagen deposition by QCS-2	[49]
Nanogel	HA	DOX	150–200	Glioma	Intravenous	↑Cytotoxicity, ↑cellular uptake efficiency, ↑brain permeability, ↑brain accumulation	[50]
Nanogel	HA	PTX	100–150	Breast cancer	Intravenous	Higher cytotoxicity against breast cancer cells, higher AUC and lower clearance	[51]
Nanogel	Chitosan	PDGF and DNase I	1–150	Diabetic foot ulcer (DFU)	Topical	Neutrophil recruitment, ↑endothelial migration, ↓Excess NETs, prevention of wound infection, ↑wound closure	[24]

(Continued)

Categories	Vehicle	Payload	Size (nm)	Application	Administration	Effect	Reference
Nanogel	HA	Cisplatin and daunorubicin	~38.5	rrAML	Intravenous	Targeted therapeutic intervention into lysosomes, causing lysosomal membrane permeabilization, ROS accumulation, and metabolic reprogramming of rrAML cells	[25]
Polysaccharide-Coated Liposome	Sodium alginate and HA	5-fluorouracil	150–200	Basal cell carcinoma	Topical	Sustained release ↑cytotoxicity	[52]
Polysaccharide-Coated Liposome	Chitosan	Tetrahydrocurcumin (THC)	100–300	Triple-negative breast cancer	Transdermal	↑*In vitro* skin permeation and cellular uptake, ↑significant cytotoxicity	[53]
Nanocomplex	Chitosan	siRNA	100–150	HCC	Intravenous	↓Tumor growth and lung metastasis, gene silencing of circPAK1	[27]

optimizing the therapeutic performance of polysaccharide-based delivery systems.

3 The microscopic domain: Local depots and sustained-release platforms

Carriers with dimensions between 1 and 1,000 μm occupy a distinctive position in drug delivery. Unlike nanoscale systems, which are designed for systemic circulation, cellular uptake, and extravasation, microscale carriers are optimized for local retention, sustained release, and physical protection of their cargo. Their size confers two interrelated advantages: First, they are large enough to remain at the administration site for extended periods, providing a depot effect; second, they can accommodate high drug payloads while maintaining a controlled release profile. These features make microscale polysaccharide carriers particularly suitable for local injection, implantation, and oral delivery, with applications ranging from long-acting therapy and tissue engineering to cell-based treatments.

Four representative architectures are discussed in this section: Microcapsules, which feature a core–shell structure for protected encapsulation; microspheres, in which drugs are uniformly dispersed within a solid matrix; microneedles, which use physical arrays to penetrate biological barriers; and microgels, which combine the properties of particles and hydrogels for responsive delivery. Each architecture exploits the size and structural features of polysaccharides in a distinct manner, yet all share the common design goal of achieving controlled, sustained release at a local site.

3.1 Polysaccharide microcapsules

Polysaccharide microcapsules are microscale carriers with a distinct core–shell architecture. This compartmentalized structure provides a physical barrier that protects encapsulated agents from degradation while allowing controlled release through the shell. Natural polysaccharides, including alginate, PEC, and chitosan, are particularly suitable shell materials because they can form hydrogels under mild conditions and their permeability can be adjusted through crosslinking density.

The most straightforward application of this protective function is oral delivery, where the microcapsule shell shields the cargo from the harsh gastric environment. Alginate, for instance, readily forms stable hydrogels upon crosslinking with divalent cations such as calcium, creating a robust barrier that resists acidic degradation. Metformin-loaded alginate microcapsules have been developed to release the drug selectively in the intestine for the treatment of inflammatory bowel disease (**Fig. 3A**)[54]. The mild, aqueous fabrication conditions are also advantageous for preserving the activity of sensitive protein drugs. Encapsulation of Infliximab in alginate microparticles, for example, maintained the antibody's structural integrity and biological activity upon release[55].

Beyond simple protection, the physicochemical properties of the shell can be precisely tuned to dictate release kinetics. The molecular weight and concentration of the polysaccharide, as well as the crosslinking density, directly affect shell thickness and porosity. Higher alginate concentrations produce denser microcapsules with slower drug dissolution in simulated intestinal fluid, allowing release times to be tailored from minutes to hours[56]. Blending alginate with other polymers can further refine these properties: Incorporating hypromellose improved mucoadhesion and accelerated drug release in acidic environments by enhancing the solubility of the composite matrix[57].

The inherent pH responsiveness of many polysaccharides enables the design of smart microcapsules that release their payload in response to specific physiological cues. The pH-dependent solubility of alginate and PEC is particularly valuable for colonic delivery: The shell remains intact in the acidic stomach but dissolves in the near-neutral environment of the small intestine or colon[58]. This concept has been extended to double-layered core–shell microcapsules, where a probiotic core and a prebiotic shell work synergistically. A centrifuge-driven micro-nozzle system has been used to fabricate such biomimetic microcapsules with an alginate shell and a core containing both Lactiplantibacillus plantarum and prebiotics[59]. This design maintained bacterial viability at approximately 47.8% at pH 2, while the prebiotic shell, upon reaching the colon, served as a nutrient source for the released bacteria[59,60].

The compartmentalized structure also allows for the co-delivery of multiple agents. A PEC- and arabinoxylan (AX)-based microcapsule system was designed for the dual delivery of Clostridium butyricum and prebiotic polysaccharides[58]. The dual-layer structure not only protected the probiotic during gastrointestinal transit but also released prebiotics in the colon, where they promoted the growth of beneficial bacteria and the production of short-chain fatty acids, leading to superior therapeutic outcomes in a colitis model. This example shows how the polysaccharide matrix can transition from a passive carrier to

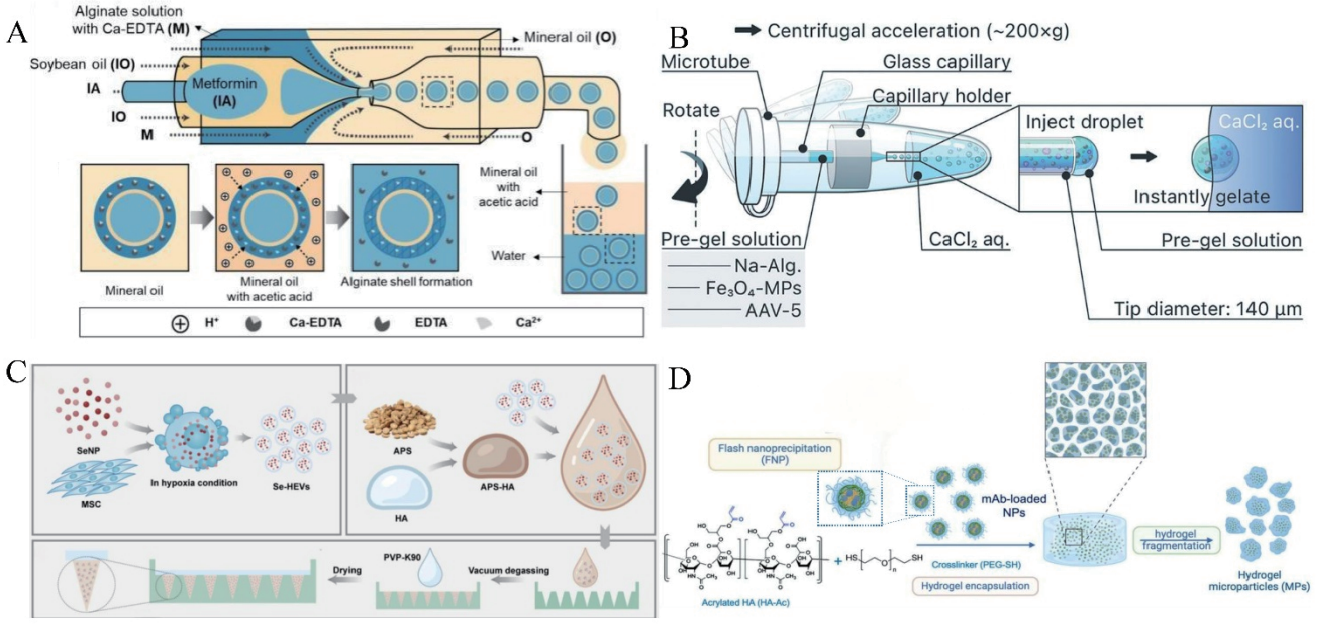


Figure 3 Preparation process of microscopic natural polysaccharide drug delivery system.(A) Metformin-loaded alginate-shelled microcapsules. (B) Alginate hydrogel microspheres. (C) Microneedle-mediated hypoxic extracellular vesicle (EV)-encapsulated selenium nanoparticles delivery. (D) Long-acting injectable nanoparticle formulation.

an active participant in the therapeutic strategy.

Microcapsules provide effective cargo protection and controlled release *via* a core–shell architecture; however, precise control over shell thickness and scalable manufacturing remains challenging.

3.2 Polysaccharide microspheres

Polysaccharide microspheres are solid, roughly spherical particles in which drugs are uniformly dispersed within the polymer matrix. Unlike microcapsules, which have a distinct shell and core, microspheres present a homogeneous structure. This architecture offers high drug loading capacity and a relatively simple fabrication process, but it provides less precise control over release kinetics than the shell–core design. The choice between microcapsules and microspheres therefore depends on whether protection of the cargo or simplicity and payload capacity is the priority.

The size and morphology of polysaccharide microspheres can be tailored through fabrication techniques such as spray-drying and emulsion crosslinking, and these parameters directly influence *in vivo* performance. For inhalation therapy, the aerodynamic diameter must be carefully tuned to achieve deposition in specific regions of the lung. Locust bean gum (LBG) microparticles produced by spray-drying exhibited a mean Feret diameter of approximately 4 μm and an irregular surface, which minimized air resistance and enhanced deep lung deposition[61]. In a related approach, co-spray-drying polymyxin B sulfate (PMBS) with raffinose (a natural oligosaccharide with high lectin affinity) enabled fine control over aerodynamic diameter; the optimal formulation achieved a mass median aerodynamic diameter of 2.54 μm, dramatically improving antibiotic delivery to infected lung tissue[62]. These examples illustrate how microsphere size can be engineered to meet the stringent requirements of specific administration routes.

The abundant functional groups of polysaccharides permit chemical modification and crosslinking, enabling the creation of microspheres with advanced functionalities. Chitosan–melanin complex microspheres, crosslinked with formaldehyde and tripolyphosphate, demonstrated superior drug loading and colon-specific drug release compared with traditional chitosan microspheres, attributed to enhanced hydrophobicity and stronger drug–polymer interactions[63].

The structural versatility of polysaccharide microspheres also allows for the incorporation of multiple components to achieve synergistic therapeutic effects. Manganese-coordinated chitosan (CS-Mn) microparticles were designed to capture DNA fragments released after radiotherapy; the chitosan component facilitated cytosolic delivery of DNA, while manganese cooperated with the delivered DNA to activate the cGAS–STING pathway, thereby potentiating antitumor immunity[64]. Similarly, alginate microspheres encapsulating *Limosilactobacillus reuteri* and a manganese–cerium oxide nanozyme protected the probiotic from gastric degradation and enabled dual targeting to inflamed colonic tissue *via* electrostatic interactions and mannose receptor binding, leading to effective treatment of colitis in mice[65]. Such multifunctional platforms demonstrate the potential of polysaccharide microspheres to integrate diagnostic, targeting, and therapeutic functions within a single carrier.

Several challenges remain for clinical translation. Scalable and reproducible manufacturing processes that preserve the integrity of labile drugs need to be established. The relationships among microsphere size, surface charge, and biological fate across different administration routes require systematic investigation. Moreover, while many polysaccharides are generally regarded as safe, comprehensive toxicological profiles for novel derivatives and composite materials, especially for inhalation and parenteral use, are still lacking. Future efforts should focus on developing standardized characterization protocols and exploring hybrid systems that combine multiple polysaccharides or integrate with synthetic polymers.

Microspheres provide high drug loading and relatively straightforward fabrication; nevertheless, optimizing aerodynamic properties for inhalation and establishing GMP-compliant scale-up processes remain key hurdles.

3.3 Polysaccharide microneedles

Microneedles are microscopic needle-like devices, typically ranging from several hundred to over a thousand micrometres in height. They create transient micropores in the skin or mucosal layers, enabling drug delivery without stimulating pain receptors. Natural polysaccharides are well suited for fabricating microneedle arrays because they are biocompatible, biodegradable, and mechanically robust enough to penetrate the stratum corneum. The dimensions of the microneedle—height, tip sharpness, and spacing—are critical design parameters that determine both the efficiency of skin penetration and the mode of drug release.

A distinct advantage of polysaccharide-based microneedles is their capacity to act not merely as inert carriers but as active contributors to the therapeutic outcome. Microneedles fabricated from carboxymethyl chitosan (CMCS) and *Bletilla striata* polysaccharide (BSP) possess intrinsic hemostatic and antimicrobial properties, actively participating in the initial phases of wound healing while simultaneously delivering anti-inflammatory agents[66]. This multifunctionality can be further amplified by integrating drug-loaded nanoparticles within the polysaccharide matrix. A composite microneedle for diabetic wound healing, for example, encapsulated *Astragalus* polysaccharide (APS) nanoparticles co-loaded with baicalein and berberine within a CMCS and BSP needle tip. The polysaccharide matrix ensured the mechanical integrity needed for skin insertion, while its rapid dissolution facilitated the release of the nanomedicine directly into the wound microenvironment.

The dimensions of the microneedle itself can be strategically designed to achieve either rapid dissolution or sustained release. HA-based dissolving microneedles, with needle lengths typically around 400–900 μm, efficiently penetrate the skin or nasal mucosa and dissolve within minutes, releasing their payload for immediate local or systemic effect (**Fig. 3C**)[67]. This approach has been successfully applied for the rapid delivery of bleomycin (BLM) for haemangioma treatment and for the nose-to-brain delivery of nanoparticles loaded with the Alzheimer's drug huperzine A, where rapid dissolution ensures swift access to the vascular and neuronal networks beneath the mucosa[67,68]. For conditions requiring prolonged therapy, a core–shell microneedle design can be employed. By encapsulating alfacalcidol (ALF)-loaded PLGA microparticles within a water-insoluble ethylcellulose (EC) shell, the polysaccharide-based tip acts as a durable intradermal depot, extending the drug release profile to 14 days and dramatically reducing the required administration frequency[69]. In this construct, HA or other soluble polysaccharide in the core facilitates initial insertion, while the shell material dictates the long-term release kinetics.

Microneedles enable minimally invasive transdermal delivery and can process intrinsic bioactivity, while balancing mechanical strength with drug release kinetics and ensuring uniform fabrication of large-area arrays are ongoing challenges.

3.4 Polysaccharide microgels

Polysaccharide microgels are hydrogel particles with diameters in the micrometre range, typically between 1 and 100 μm. They combine the high water content and soft mechanical properties of macroscopic hydrogels with the injectability and transport advantages of particulate systems. Unlike nanogels, which are designed for systemic circulation and cellular uptake, microgels are optimized for local retention, serving as injectable depots that release therapeutics over extended periods. Their crosslinked network structure provides ample space for drug loading and protects encapsulated agents from enzymatic degradation and premature release.

A key advantage of polysaccharide microgels is their ability to safeguard fragile payloads and control release through stimuli-responsive mechanisms. The layer-by-layer assembly of oppositely charged polysaccharides, such as anionic alginate and cationic chitosan, creates a robust electrostatic barrier that withstands gastric degradation while enabling pH-triggered release in the intestine. This strategy has been used to protect *Lactobacillus reuteri* (L.r@(SA-CS)_2) for targeted CRC therapy[70] and to co-deliver *Lactobacillus casei* Zhang with anti-fibrotic nanoparticles for renal fibrosis treatment[71]. Beyond passive protection, incorporating functional nanomaterials within the polysaccharide network enables externally triggered drug liberation. Alginate hydrogel microbeads co-encapsulating adeno-associated virus (AAV) and photothermal Fe_3O_4 microparticles achieved on-demand gene delivery upon near-infrared irradiation, as the localized heating accelerated viral diffusion through the hydrogel mesh without compromising infectivity (**Fig. 3B**)[72].

The size and composition of polysaccharide microgels can be engineered to influence biological interactions, residence time, and targeting. Microparticles in the 80–120 μm range enabled a long-acting injectable system in which anti-TNF-α antibody-loaded nanoparticles were embedded within an HA hydrogel matrix (**Fig. 3D**). This ensured prolonged intramuscular retention and maintained therapeutic serum levels for over 100 days in healthy mice, while a single injection also demonstrated substantial therapeutic efficacy in a 9-week chronic colitis model[73]. The choice of polysaccharide can also confer targeting capability: HA-based inhalable aerogels exploit the affinity of HA for CD44 receptors overexpressed on activated alveolar macrophages during tuberculosis infection, enabling selective binding to both extracellular *Mycobacterium tuberculosis* and infected host cells while delivering synergistic peptide–antibiotic combinations[74].

Microgels combine high water content with injectability, making them suitable as local depots; however, achieving uniform size distribution and conducting comprehensive long-term safety evaluation *in vivo* require further investigation.

3.5 Multiscale perspectives on polysaccharide gel systems

Polysaccharide-based gel systems exhibit distinct advantages across different size scales, enabling their use in diverse drug delivery applications (**Fig. 4**, **Tables 2 and 3**). Nanogels, with their ultrasmall size and high specific surface area, offer efficient tissue penetration, cellular uptake, and systemic circulation. Their stimuli-responsive properties enable precise and targeted drug release, making them particularly suitable for tumor therapy and nucleic acid delivery. Microgels provide a balance between loading capacity and structural flexibility: Their larger internal space allows higher drug encapsulation, while controllable fabrication methods such as microfluidics enable tunable particle sizes for localized delivery, biosensing, and cell carrier applications[75]. Macroscopic hydrogels, discussed in Section 4, offer superior mechanical strength, structural stability, and long-term retention, making them ideal for tissue engineering, wound dressings, and implantable systems. Together, these multiscale gel platforms illustrate how size engineering can regulate drug transport, release behaviour, and biological interactions, and they provide a conceptual bridge between the microscale and macroscale regimes.

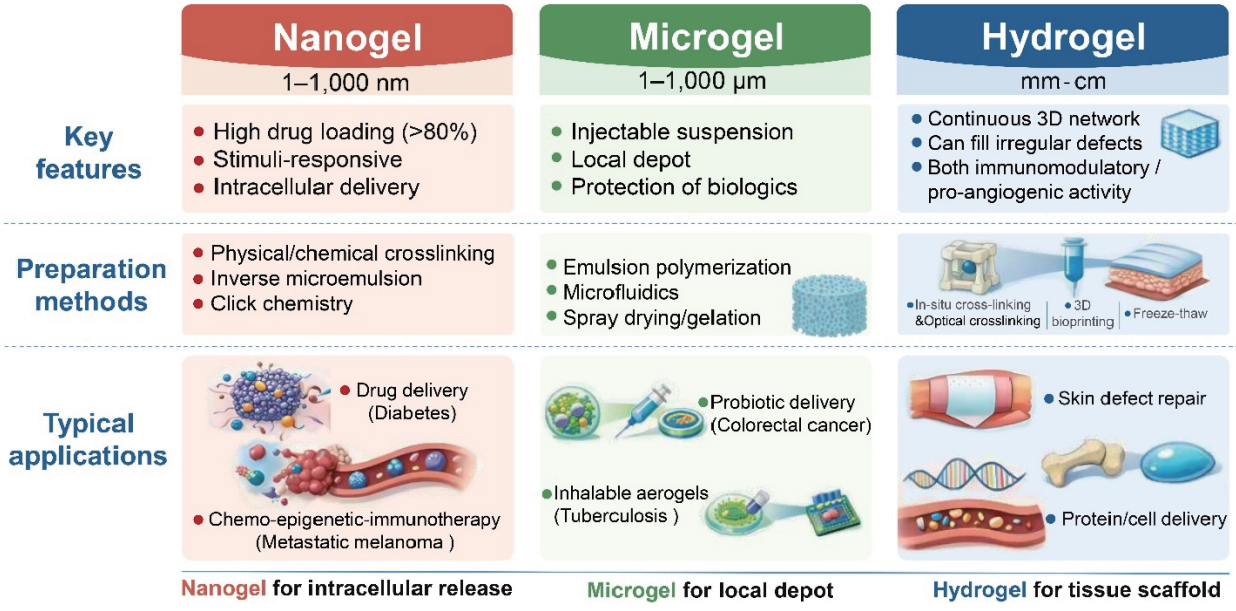


Figure 4 Comparative illustration of nanogel, microgel, and hydrogel.

Table 2 Comparative analysis of nanogels, microgels, and hydrogels (microscale)

	Nanogel	Microgel	Hydrogel (Macroscale)
Size range	20–200 nm (sometimes up to 500 nm)	1–1,000 μm	mm-cm scale (macroscopic bulk)
Structural features	Nanoscale 3D crosslinked network, colloidal dispersion	Micron-sized particulate gels	Continuous 3D network (bulk structure)
Dispersibility	Stable colloidal dispersion (in solution)	Suspended particles or dispersed system	Non-dispersible, exists as a bulk
Preparation methods (Key differences)	-Self-assembly + crosslinking (e.g., ionic crosslinking) -Nanoprecipitation-click chemistry crosslinking	-Emulsion polymerization (W/O, O/W) -Microfluidics (precise size control) -Spray drying/spray gelation	-In situ crosslinking (in situ gelation) -Photo-crosslinking/thermal crosslinking -Freeze–thaw method -3D printing
Preparation difficulty	High; requires control over size and stability	Moderate	Relatively simple
Size controllability	High (precise nanoscale tuning)	Relatively high (best with microfluidics)	Low (primarily bulk structure)
Specific surface area	Very high	High	Low
Drug loading modes	-Encapsulation -Electrostatic adsorption -Covalent conjugation	Similar to nanogels, but with larger loading space	-Mainly physical encapsulation -Limited covalent immobilization
Release behavior	Rapid/stimuli-responsive (pH, enzymes, temperature)	Moderate release rate	Sustained/long-term release
Tissue penetration ability	Excellent (can enter cells/tumor tissues)	Mediocre (local tissue penetration)	Minimal penetration
In vivo distribution	Systemic circulation possible (IV administration)	Local or limited circulation	Primarily local application
Typical applications	-Targeted drug delivery (tumor, gene) -siRNA/mRNA delivery -Blood circulation systems	-Local injectable delivery -Cell carriers -Biosensors	-Tissue engineering scaffolds -Wound dressings -Implantable systems
Biological barrier penetration	Strong (EPR effect)	Moderate	Minimal
Mechanical properties	Very weak (soft particles)	Moderate (tunable)	Strong (designable high strength)
Injectability	Good (solution form)	Good (suspension)	Requires special design for injectability
Degradation behavior	Rapid or tunable	Moderate	Slow (long-term)
Stability	Prone to aggregation; requires surface modification	Relatively stable	Highly stable
Representative materials	HA, chitosan, dextran	Alginate, gelatin microspheres	Alginate gel, PEG hydrogel
Key advantages	High targeting, high responsiveness, high bioavailability	Moderate size, high loading capacity, flexible operation	Structural stability, strong support, suitable for long-term use
Limitations	Complex preparation, stability issues	Larger size limits systemic application	Not suitable for systemic delivery; limited diffusion

Table 3 Representative polysaccharide-based microscale drug delivery systems

Categories	Vehicle	Payload	Size (μm)	Application	Administration	Effect	Reference
Microcapsule	Dextran	Pyraclostrobin	0.5–1.2	Pesticides	Foliar spray	Fungicidal ability, doubled water half-life, ↓acute exposure toxicity of Pyr	[60]
Microcapsule	Alginate	Resistant starch nanoparticles (RSNP, prebiotic) and LP (probiotics)	~420	Colitis	Oral	High encapsulation efficiency, protection against acidic conditions, ↑short-chain fatty acid production, ↓inflammatory cytokines, restoration of intestinal microbial diversity	[59]
Microcapsule	Cellulose	Imidacloprid (IMI)	~60	Pesticide	Foliar spray	Significant thermo-responsiveness, superior spread ability, retention, and flush resistance, with high encapsulation efficiency and loading capability, markedly lower LC_{50} against target organisms, excellent biocompatibility and low toxicity	[76]
Microcapsule	PEC and AX	Clostridium butyricum	~50	IBD	Oral	Enhanced survival and colon-targeted release of C. butyricum, mitigation of weight loss, reduction of inflammation, repair of intestinal barrier function, and restoration of gut microbiota balance	[58]
Microcapsule	lipid nanoparticles (LNPs)	An mRNA encoding a computationally optimized broadly active (COBRA) influenza immunogen	Micrometer-scale	Vaccine platform for SARS-CoV-2	Intramuscular/ Subcutaneous	Production of a broadly neutralizing antibody response and protection after lethal influenza challenge	[77]
Microsphere	CS-Mn	DNA	~1.1	Radioimmunotherapy	Intratumoral injection	Enabling efficient cytosolic DNA delivery in the presence of serum, cooperating with Mn^{2+} to activate the cGAS-STING pathway in dendritic cells, and markedly enhancing radiotherapy efficacy against tumors through collective promotion of tumor-infiltrating $CD8^+$ T-cell stemness and activation of innate immunity	[64]
Microsphere	Sodium alginate and Hydroxypropyl methylcellulose (HPMC)	Posaconazole (POS)	~10–15	Fungal infections	Oral/Vaginal	Modify drug release and to improve their mucoadhesive properties for both oral or vaginal application	[57]
Microsphere	High-lectin-affinity (HLA) sugar	PMBS inhalable microparticles	~3	Pulmonary infections	Dry powder inhaler (DPI)	↑Anti-biofilm efficacy, superior bacterial killing and anti-inflammatory effects	[62]
Microsphere	Dung beetle chitosan-melanin complex (CMC)	Bovine serum albumin (BSA)	< 50	Colon-targeted drug delivery	Oral	Superior drug loading capabilities, optimal swelling behavior, and controlled *in vtro* drug release profiles in the colonic environment, along with excellent adhesion and enzymatic degradation properties within intestinal tract	[63]
Microgel	Chitosan/sodium alginate (CS/SA)	Emodin (EMO) and AA self-assembled nanoparticles (NPYs), along with *Lactobacillus casei* Zhang	~465	Renal fibrosis	Oral	Controlled release of loaded NPYs, ↑EMO and AA levels, regulating the TGF-β/Smad pathway	[71]
Microgel	HA hydrogel microparticles (MPs)	mAb-releasing NPs	80–120	IBDs	Intramuscular injection	↑Tissue retention, ↑duration of mAb release *in vivo*	[73]
Microgel	Alginate hydrogel	AAV	~200	Genetic diseases such as sensorineural deafness	/	Releasing AAV on demand, avoiding immune response, and gene transfection to cells by AAV is confirmed without loss of viral activity	[72]
Microgel	SA and CS	Probiotics	~5.5	CRC	Oral	Improving gut microbiota dysbiosis and enhancing anti-tumor therapeutic effect	[70]

(Continued)

Categories	Vehicle	Payload	Size (μm)	Application	Administration	Effect	Reference
Microgel	HA	Anti-TB peptide	~1	Multidrug-resistant TB (MDR-TB)	Inhalation	Avidly binding and killing both drug-sensitive and drug-resistant mycobacteria, while being efficiently internalized into macrophage host cells *in vtro* and *in vivo* to clear Mtb persisters	[74]
Microneedle	CMCS/BSP composite	APB@Ber nanoparticles	600	Healing of chronic diabetic wounds	Transdermal	Hemostasis, anti-inflammatory, antioxidant, antimicrobial, and induction of angiogenesis	[66]
Microneedle	EC	ALF	~700	Osteoporosis	Transdermal	Sustained-release, lower systemic drug dose, better efficacy in increasing bone mass and improving trabecular microstructure.	[69]
Microsphere	HA	BLM	~830	Hemangioma of infancy	Transdermal	Inhibited hemangioma formation by modulating the P53 pathway	[68]
Microneedle	APS	Hypoxic EV-encapsulated selenium nanozyme (Se-HEVs-AMN)	~800	Androgenetic alopecia (AGA)	Transdermal	Increased hair density and enlarged hair follicle diameter through regulating inflammation, promoting angiogenesis, scavenging ROS, and resisting androgen	[78]

4 The macroscopic world: Engineered scaffolds and interfaces

Macroscale carriers, with dimensions ranging from hundreds of micrometers to several centimetres, occupy a distinct position in the drug delivery cascade. Whereas nanoscale systems are optimized for systemic circulation and cellular entry, and microscale carriers for local depot formation, macroscale platforms are designed to interface directly with tissues, cavities, or mucosal surfaces. Their larger size confers three interrelated advantages: High drug loading capacity, ease of handling and administration, and the ability to provide sustained release at a specific anatomical site[79]. These features make macroscale polysaccharide systems particularly suitable for topical application, implantation, and oral delivery.

Three representative architectures are discussed in this section. Film and coating systems exploit the barrier and adhesive properties of polysaccharides to protect surfaces and control drug release at interfaces[80]. Hydrogel systems, with their three-dimensional networks, provide mechanical support and spatial conformity for tissue repair and local therapy[81]. Tablet systems use polysaccharide matrices to achieve controlled release in the gastrointestinal tract, capitalizing on the hydration and enzymatic degradation properties of these polymers[82]. Together, these architectures illustrate how polysaccharides can be engineered into macroscopic forms that address distinct therapeutic needs through different physical and chemical mechanisms (**Fig. 5**, **Table 4**).

4.1 Film and coating systems

Polysaccharide films and coatings are thin, planar structures in which drugs are dispersed or encapsulated within a continuous polymeric matrix. Their primary function is to serve as a protective or controlled-release barrier at an interface, whether on a tissue surface, a medical device, or a food product[83]. The film-forming ability of polysaccharides arises from hydrogen bonding, electrostatic interactions, or coordination bonds between polymer chains, which create dense networks upon solvent evaporation or crosslinking.

The abundant hydroxyl, amino, and carboxyl groups on polysaccharide chains provide multiple sites for functional modification. These groups enable the incorporation of active components and, in many cases, confer intrinsic biological activities. Chitosan, for example, possesses inherent antibacterial and mucoadhesive properties, which can complement the effects of loaded therapeutics. The same chemical handles allow the introduction of reversible crosslinks, such as Schiff bases or metal–phenolic networks, that impart environmental responsiveness to the film.

The simplest application of polysaccharide films is passive protection. Carboxymethylated cellulose nanofibers (CM-CNFs) crosslinked with divalent cations form dense, hydrophobic coatings that reduce water loss and respiration rates in fresh produce. In strawberry preservation trials, such coatings significantly extended shelf life while maintaining fruit quality[84]. The mechanism relies on the physical barrier created by the crosslinked network, which limits gas exchange and moisture evaporation. More sophisticated designs incorporate stimuli-responsive release.

Chitosan films grafted with benzaldehyde *via* Schiff base reactions release volatile antifungal compounds upon hydrolysis of the imine bond under acidic conditions. This pH-dependent behaviour allows the film to respond to the local environment, releasing its cargo only when conditions are favourable[85]. Such systems have been explored for food packaging applications, where an acidic environment triggers the release of preservatives.

In the context of pharmaceutical tablets, film coatings serve a different purpose: They modulate the hydration and disintegration of the core matrix. Immediate-release film coatings based on PVA or HPMC undergo rapid hydration and dissolution upon contact with aqueous media. The dissolution rate of the coating, which can be tuned by adjusting coating composition, significantly influences water permeation into the core and thus the onset of drug release. A coating approximately 100 μm thick, for example, typically dissolves within several hundred seconds at room temperature, acting as a barrier that delays capillary water transport and thus core disintegration[86].

Future developments in polysaccharide film and coating systems are likely to focus on expanding the range of responsive triggers and improving fabrication precision. Chemical

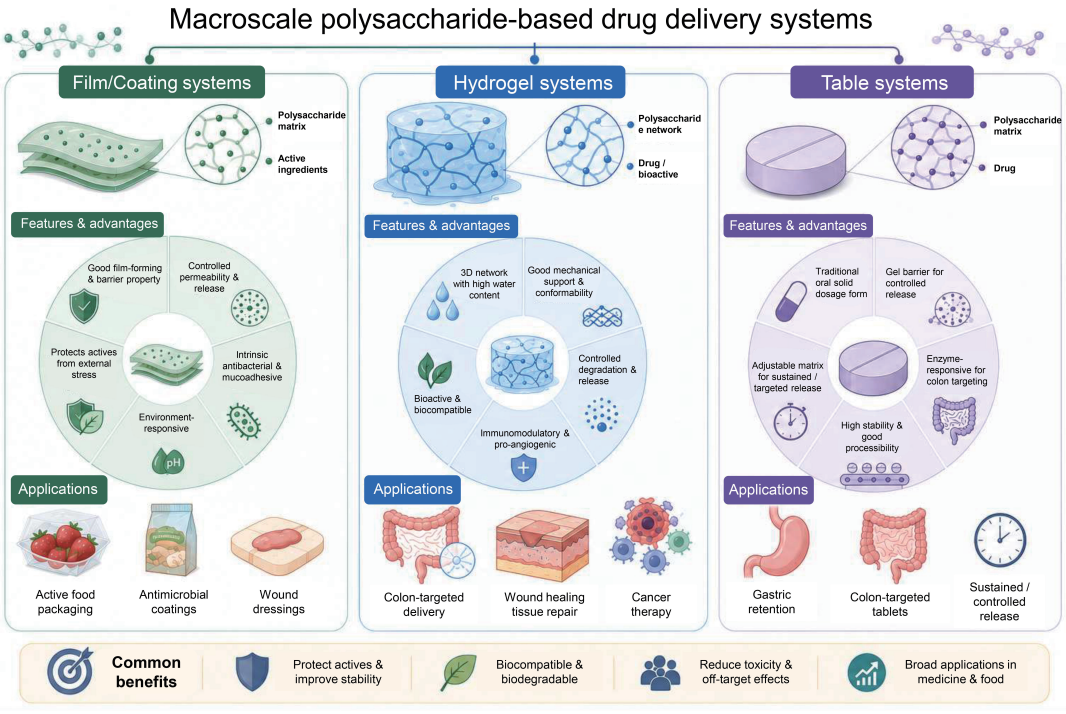


Figure 5 The advantages, characteristics and applications of the macroscopic natural polysaccharide drug delivery systems.

modification strategies, such as carboxymethylation or graft copolymerization, can increase the density of reactive sites, enhancing functional component loading. Introducing multi-stimuli responsiveness, including enzyme, temperature, or redox sensitivity, could enable more precise on-demand release. Integration with additive manufacturing techniques, such as 3D printing, may allow personalized customization of film architectures for wound dressings and implant coatings.

Film and coating systems exploit barrier and adhesive properties for surface-mediated delivery, though controlling uniform thickness control, ensuring long-term storage stability, and preservation of active ingredients during film formation remain concerns.

4.2 Hydrogel systems

Macroscale polysaccharide hydrogels are three-dimensional networks formed by physical or chemical crosslinking of hydrophilic polymer chains. Their defining characteristic is bulk network integrity: Unlike nanogels or microgels, which are dispersed particles, macroscopic hydrogels are continuous structures that can be handled, implanted, or injected as a single entity. This continuous network provides mechanical support, high water content, and spatial conformity to irregular tissue defects, making hydrogels particularly suitable for localized drug delivery and tissue repair[81,87].

The crosslinking chemistry determines the mechanical and release properties of the hydrogel. Ionic crosslinking, exemplified by the "egg-box" structure formed between alginate and calcium ions, is mild and reversible. Covalent crosslinking, including Schiff base formation or photocrosslinking, provides greater mechanical strength and longer persistence. Hydrophobic interactions can also contribute to network stability. The pore size, crosslinking density, and degradation kinetics of the hydrogel can be tuned by adjusting the molecular weight of the polysaccharide, the degree of substitution, and the crosslinking conditions.

The biological activity of the polysaccharide itself can synergize with the therapeutic payload. *Lycium barbarum* polysaccharide (LBP), which has a high galacturonic acid content, forms stable egg-box crosslinks with calcium ions. Exploiting ion exchange-mediated crosslink disruption in the colonic environment, this hydrogel system achieves targeted release of oxaliplatin (Oxa) in CRC models. Beyond drug delivery, the polysaccharide matrix induces macrophage lipid reprogramming through the TLR4–IRF3–LXRα axis, thereby remodelling the immunosuppressive tumor microenvironment and significantly prolonging survival[88].

Composite hydrogels combine multiple polysaccharides to achieve properties that single-component systems cannot provide. An oxidized astragalus polysaccharide and carboxymethyl chitosan/sodium methacrylated alginate and magnesium ions hydrogel (OAPS-CMC/SAMA-Mg^{2+}, OCS) loaded with curcumin (Cur)-encapsulated Achyranthes bidentata supramolecular self-assemblies (NX@Cur) uses dual crosslinking networks (Schiff base and photocrosslinking) to enable injection and in situ curing. In rat full-thickness skin defect models, this hydrogel significantly accelerated wound healing by reducing inflammatory factors and enhancing angiogenesis. The combination of injectability and post-injection stabilization is particularly valuable for filling irregular wounds or surgical defects[89]. Layer-by-layer assembly technology has been used to modify calcium alginate microspheres with ionic agarose derivatives, achieving sustained release of water-soluble ionic drugs for up to 14 days through surface charge modulation. This approach demonstrates how macroscopic hydrogel architectures can be engineered to provide long-term local delivery without the need for repeated administration[90].

In cancer immunotherapy, a hydroxypropyl chitosan/dextran organohydrogel (OHG) encapsulating an EZH2 inhibitor, PTX, and an anti-TIGIT antibody was designed for local injection into post-resection cavities of melanoma. The triple-loaded formulation suppressed tumor growth by approximately 80% and prevented lung metastasis, with some treated mice remaining relapse-free[91]. The macroscopic hydrogel matrix provided

sustained local retention of the three agents with distinct release kinetics, demonstrating the feasibility of combination immunotherapy delivered from a single carrier.

Future directions for polysaccharide hydrogel systems include enhancing drug loading through the incorporation of additional binding sites, such as cyclodextrins or MOFs, within the hydrogel network. Integrating hydrogels with nanotechnology to encapsulate immune checkpoint inhibitors or cytokines could enable synergistic chemo-immunotherapy combinations while minimizing systemic toxicity. Combining pH and enzyme dual responsiveness or mucoadhesive ligands such as lectins could further enhance retention time and targeting precision, particularly for colonic delivery of biomacromolecules.

Macroscopic hydrogels provide mechanical support, spatial conformity, and sustained local release; nonetheless, the trade-off between mechanical strength and injectability, as well as the need of precise control over *in vivo* degradation kinetics, require further refinement.

4.3 Tablet systems

Tablets are the most traditional oral solid dosage form, but when formulated with polysaccharide matrices, they offer sophisticated controlled-release capabilities[92]. The principle is simple: Upon ingestion, the polysaccharide matrix hydrates to form a gel layer at the tablet surface. This gel layer acts as a barrier that controls the diffusion of the drug out of the tablet and the ingress of fluid into the matrix. Drug release occurs either by diffusion through the gel layer or by erosion of the hydrated matrix, depending on the properties of the polysaccharide and the formulation.

The release behaviour of polysaccharide matrix tablets is determined by the molecular characteristics of the polymer. Xanthan gum, xyloglucan, and sodium alginate, all of which are highly hydrophilic, form viscous gel layers upon hydration. The molecular weight, degree of branching, and substituent pattern of the polysaccharide influence the strength of the gel layer and the

Table 4 Representative macroscopic polysaccharide-based drug delivery systems

Categories	Polysaccharide	Payload	Preparation Method	Application	Effect	Reference
Film/Coating	Chitosan	/	Grafting benzaldehyde and citral onto the surface of chitosan films using reversible imine bonds	Food packaging	pH-dependent antifungal system	[85]
Film/Coating	Cellulose	/	CM-CNFs stabilized by cationic salts	Food storage	An edible film coating for the long-term storage and prolonged freshness of strawberries	[84]
Film/Coating	Cellulose	/	10 % *w*/*w* Opadry II (either PVA- or HPMC-based) reconstituted in deionised water under stirring	Film-coated tablets	Protecting the drug from environmental degradation, facilitating the packaging process, and enhancing patient compliance	[86]
Film/Coating	Cellulose, starch	Ibuprofen	Obtained *via* the freeze-thaw technique using an innovative combination of two film-forming polymers of natural origin, i.e. hydroxyethylcellulose and a pea starch derivate (Linecaps®)	Pediatric buccal formulation	Buccal films with good properties showed similar ibuprofen permeation fluxes on synthetic and rabbit mucosa, indicating promising mucoadhesive, taste-masking, and drug release potential	[83]
Film/Coating	Starch	Mesalamine	Chemically modified mandua starch film-coated mesalamine tablets were produced using the wet granulation method followed by dip coating	Colon-targeting release	Low gastric release, high colonic release	[80]
Hydrogel	LBP	Oxa	Utilize LBP as the functional material to encapsulate Oxa, forming the oral colon-targeted drug delivery system (OCTDDS), Oxa@LBP gel	Microsatellite stable colorectal cancer (MSS-CRC)	Achieving higher tumor accumulation than Oxa, regresses tumors, and reverses immunosuppression *via* M2 macrophage repolarization	[88]
Hydrogel	APS, chitosan and alginate	NX@Cur	OCS loaded with NX@Cur	Wound healing	Modulating the inflammatory environment of the wound, thereby promoting the formation of granulation tissue and neovascularization and accelerating collagen deposition and re-epithelialization	[89]
Hydrogel	Agarose	Suramin, methylene blue, etc.	Agarose sulfates (AS) were synthesized in a one-step synthesis, while ammonium-bearing cationic agarose carbamates (AC) were synthesized *via* agarose phenylcarbonates (APC) with subsequent aminolysis	Sustained drug release	Effectively reducing the burst release and sustain the release of adenosine triphosphate (ATP), suramin and methylene blue over a time of 14 days	[90]
Tablet	Xyloglucan	5-ASA and caffeine	Eudragit FS coating with xyloglucan matrix	Colonic drug delivery	Inhibiting drug release after coating removal in the small intestine and to allow microbiome-triggered drug release by enzymatic action in the colon	[93]

rate of drug diffusion. High molecular weight polymers tend to form stronger gels with slower drug release, whereas lower molecular weight variants hydrate more rapidly but provide less sustained release.

A distinctive feature of certain polysaccharides is their specific degradation by colonic microbiota. Xyloglucan, a hemicellulose that is selectively degraded by bacterial enzymes in the colon, serves as a matrix for colon-targeted tablets. When coated with the pH-sensitive polymer Eudragit FS 30D, xyloglucan tablets protect the drug from release in the stomach and small intestine, delivering it specifically to the colon. In porcine pharmacokinetic studies, this formulation extended the time to peak concentration of caffeine from 2.7 h (for immediate-release tablets) to 25.8 h, with approximately 96% of caffeine absorption occurring in the large intestine. This approach provides a reliable strategy for colon-targeted delivery without relying solely on pH changes[93].

Gastric retention tablets represent another application of polysaccharide matrices. Xanthan gum floating tablets form gel barriers upon hydration; when combined with effervescent agents such as sodium bicarbonate, they achieve gastric floating for more than 12 h, significantly enhancing gastric retention time and drug bioavailability. This approach is particularly useful for drugs that are absorbed primarily in the upper gastrointestinal tract or that require prolonged local action in the stomach[94].

The hydration behaviour of polysaccharide matrix tablets can be monitored in real time using low-field nuclear magnetic resonance. T_1-T_2 relaxation mapping reveals changes in polymer mobilization and bound water states during hydration, providing a foundation for the rational design of sustained-release tablets. This analytical approach enables formulation scientists to relate hydration kinetics to drug release profiles[95].

Several practical considerations govern the design of polysaccharide matrix tablets. Blending polysaccharides with other excipients, such as polyvinylpyrrolidone (PVP) or HPMC, enables modulation of the hydrophilic–hydrophobic balance to accommodate drugs with varying solubility. The choice of the polysaccharide and its molecular weight affects not only release kinetics but also the tablet's mechanical properties and manufacturability. Enzyme-responsive matrices such as xyloglucan show some tolerance to individual variations in microbiota composition: Tenfold differences in enzyme concentration induce less than twofold changes in release rate. However, process parameters, including coating thickness and core hardness, require precise control to ensure batch-to-batch reproducibility. Future exploration may combine polysaccharide matrices with multiparticulate systems such as pellets to reduce inter-individual variability in gastrointestinal transit time, or introduce thiol groups through chemical modification to enhance mucoadhesion, further improving colonic retention and absorption efficiency.

Polysaccharide matrix tablets enable controlled gastrointestinal release through hydration and enzymatic degradation, while inter-individual variability in microbiota composition and batch-to-batch consistency of coating processes represent notable limitations.

5 Polysaccharide delivery systems in TCM decoctions

Traditional Chinese medicine (TCM) decoctions are aqueous extracts of herbal formulas, containing a complex mixture of polysaccharides, flavonoids, alkaloids, saponins, and other bioactive constituents. Among these components, polysaccharides have traditionally been regarded primarily as active pharmacological agents. Recent evidence, however, suggests an additional, less obvious role: Polysaccharides in decoctions may function as endogenous delivery carriers that improve the solubility, stability, and gastrointestinal absorption of co-existing active compounds, thereby contributing to the synergistic therapeutic effects characteristic of herbal formulas[1].

From a dimensional perspective, a TCM decoction is a macroscopic liquid formulation. Within this macroscopic system, polysaccharides and small-molecule compounds spontaneously associate through hydrogen bonding, electrostatic interactions, and hydrophobic association, forming supramolecular complexes or colloidal aggregates[96]. These assemblies, typically in the nanometre to sub-micrometre range, improve the dispersion of poorly soluble constituents and protect labile compounds from degradation during gastrointestinal transit. This phenomenon represents a distinct example of size hierarchy in natural polysaccharide systems, one that arises spontaneously without engineering intervention.

Recent studies have begun to provide direct experimental evidence supporting the existence of endogenous supramolecular assemblies in TCM decoctions. Gao *et al.*[97]. summarized accumulating evidence that decoctions should be regarded as complex supramolecular systems rather than simple molecular solutions, in which polysaccharides, proteins, polyphenols, alkaloids, and other constituents spontaneously assemble through multiple non-covalent interactions. More recently, Nie *et al.*[98] demonstrated that naturally formed nanoparticles in the Zhimu–Huangbai herb pair decoction were generated through interactions between endogenous polysaccharides and small-molecule constituents. These nanoparticles were systematically characterized with respect to particle size distribution, gastrointestinal stability, drug release behavior, and formation mechanism, providing direct evidence that polysaccharides contribute to the formation and functional performance of endogenous colloidal assemblies. Furthermore, Chen *et al.*[99] reported that endogenous fructans and triterpenoids in Zexie Tang spontaneously formed thermally driven supramolecular particles during decoction, which significantly contributed to the therapeutic efficacy of the formula. Collectively, these findings provide growing experimental support for the existence of naturally occurring polysaccharide-associated delivery structures in herbal decoctions.

The enhancement of oral bioavailability by polysaccharides involves multiple mechanisms operating at the intestinal mucosal interface. Their mucoadhesive properties prolong residence time at absorption sites, increasing the local concentration of active ingredients and promoting sustained absorption. Polysaccharides can also modulate the expression of tight junction proteins, facilitating paracellular transport of co-existing small molecules[100]. In parallel, certain polysaccharides are metabolized by gut microbiota into bioactive metabolites, which indirectly modulate the intestinal environment and further influence drug absorption[97,101]. These combined effects are particularly relevant in TCM decoctions, where multiple constituents face challenges related to low solubility, poor membrane permeability, and gastrointestinal instability.

Several experimental systems provide evidence for the delivery functions of TCM-derived polysaccharides, although the strength of evidence varies. One direct example involves chitosan–licorice extract hydrogels, which exhibit porous, highly hydrated network

structures with sustained release characteristics. The polysaccharide matrix in this system modulates molecular diffusion in a manner analogous to what might occur in a polysaccharide-rich decoction environment, albeit in a formulated hydrogel rather than a liquid extract[102].

A more indirect but instructive example comes from chemically modified BSP. When conjugated with stearic acid, BSP forms self-assembled micelles that successfully deliver docetaxel with pH-dependent release and enhanced antitumor efficacy[103]. Although this system is artificially prepared rather than naturally occurring in a decoction, it demonstrates the intrinsic amphiphilic potential of TCM polysaccharides and supports the hypothesis that similar assemblies may form spontaneously in decoction environments, where hydrophobic small molecules and hydrophilic polysaccharide chains coexist.

Further evidence comes from BSP–alginate mucoadhesive microspheres loaded with *Panax notoginseng* saponins. This system improved gastric retention and enhanced anti-ulcer efficacy through mucosal adhesion and controlled release provided by the polysaccharide matrix[104, 105]. While this is again a formulated system, it illustrates the bioadhesive potential that polysaccharides naturally possess, suggesting that analogous effects may occur in decoctions where polysaccharides coat the gastrointestinal mucosa and prolong the local residence of co-administered compounds.

Collectively, these observations support the emerging concept that naturally occurring polysaccharides may participate in endogenous delivery processes within TCM decoctions, although further experimental validation is still required. In this conceptual framework, naturally occurring polysaccharides serve not merely as structural or nutritional components but as carriers that enhance the bioavailability and synergistic efficacy of co-existing active constituents. The framework bridges traditional decoction theory with modern drug delivery science, providing a potential explanation for the holistic efficacy of herbal formulas. It also suggests that TCM-derived polysaccharides, with their inherent biocompatibility and assembly properties, may serve as a source of inspiration for the development of novel delivery platforms that mimic the spontaneous assembly and synergistic functions observed in traditional decoctions.

Despite these encouraging findings, direct evidence supporting endogenous polysaccharide-mediated delivery systems remains limited. Most available studies have focused on physicochemical characterization of naturally formed supramolecular particles, whereas their precise structural composition, mucus penetration, intestinal transport, pharmacokinetic behavior, and *in vivo* delivery mechanisms remain largely unexplored. Moreover, whether similar polysaccharide-associated assemblies universally exist across different herbal decoctions and how polysaccharide structural characteristics govern their formation and biological functions require further investigation. Future studies integrating advanced structural characterization, multi-scale imaging, intestinal transport models, and *in vivo* pharmacokinetic evaluation will be essential to validate the endogenous delivery role of polysaccharides in TCM decoctions.

6 Discussion and future perspectives

The size-centric framework proposed in this review offers a coherent way to understand the diverse landscape of polysaccharide-based drug delivery systems. Rather than treating size as a passive formulation parameter, our analysis establishes it as an active design variable that profoundly shapes therapeutic performance. Each size regime—nanoscale, microscale, and macroscale—operates under distinct biophysical principles, encounters different biological barriers, and fulfills complementary therapeutic roles.

The nanoscale domain (10–200 nm) is governed by receptor-mediated interactions and endocytic transport[106, 107]. Nanoparticles navigate the circulatory system, exploit the EPR effect for passive tumor accumulation[108], and deliver payloads to subcellular compartments[109]. This regime is ideal for systemic administration, where prolonged circulation, active targeting[110], and intracellular delivery are paramount[111]. Its inherent limitations include rapid clearance by the mononuclear phagocyte system[112], poor accumulation at non-leaky vasculature, and challenges in crossing the blood–brain barrier or penetrating dense stromal matrices[11]. In contrast, the microscale domain (1–1,000 μm) shifts the paradigm from systemic circulation to local retention. These carriers are too large for efficient endocytosis or transvascular transport, but this limitation becomes an advantage for sustained local action. They serve as injectable or implantable depots, physically entrapping drugs and releasing them over days to weeks[113, 114]. Microneedles further exploit their characteristic height to breach the stratum corneum for painless transdermal delivery[115]. The macroscale (millimetres to centimetres), including films, hydrogels, and tablets, is designed for topical, oral, or surgical applications where high drug loading, ease of handling, and patient compliance are prioritized. Hydrogels fill irregular tissue defects and provide structural support for regenerative medicine[116, 117]; tablets leverage polysaccharide hydration to control gastrointestinal drug release[82, 118]; films serve as conformable wound dressings or protective coatings[119]. This regime sacrifices cellular-level precision for macroscopic practicality. Importantly, these size regimes should not be considered as independent design options. Increasing evidence suggests that hierarchical integration of different size domains can overcome the intrinsic limitations of single-scale carriers by assigning distinct biological functions to different structural levels. In such systems, nanoscale components facilitate cellular uptake and intracellular delivery, microscale structures provide local retention and sustained release, whereas macroscale matrices improve handling, tissue adaptation, and clinical applicability. Representative examples include nanoparticle-loaded microneedles, microsphere-containing hydrogels, and injectable bulk hydrogels incorporating nucleic acid nanocomplexes, where multi-scale organization enables simultaneous control of penetration, retention, and therapeutic localization[120–124]. These advances indicate that future polysaccharide delivery systems may not be optimized toward a single ideal size, but rather through rational combination of multiple size domains to achieve coordinated biological functions.

A key insight is that these three domains are not mutually exclusive but can be integrated into hierarchical systems that combine the advantages of multiple scales. Nanoparticles embedded within a microneedle patch enable rapid skin penetration followed by sustained intracellular delivery[120, 123]. Microspheres dispersed in an injectable hydrogel provide both stimuli-responsive release from the microscopic reservoirs and sustained release from the macroscopic matrix[124]. These hybrid constructs show how deliberate engineering across scales can overcome the limitations of any single regime.

This cross-scale integration logic can be extended to a broader spectrum of hierarchical formulations beyond the commonly cited

microneedle–nanoparticle and hydrogel–microsphere hybrids. The underlying design principle is that different dimensional components can be assigned distinct yet complementary functions: The macroscale or microscale matrix provides structural support, protection against premature clearance, and spatiotemporal control over release initiation, while the nanoscale carriers confer target specificity, cellular internalization, and intracellular trafficking capabilities. By decoupling these otherwise conflicting requirements hierarchical systems enable a "division of labor" that single-scale platforms cannot achieve, as tissue retention favored by larger constructs and versus cellular uptake favored by smaller ones[125].

For instance, injectable hydrogel microspheres encapsulating tetrahedral framework nucleic acid (tFNA)-based nanocomplexes enabled sustained joint retention and subsequent cellular uptake for osteoarthritis therapy[126]. In another example, an oral bilayer microgel system with a guar gum/PEC core and alginate-chitosan shell delivered Cur-loaded nanomicelles to the colon *via* pH and enzyme dual-triggered release for ulcerative colitis treatment[127]. The rational selection of multi-scale over single-scale platforms is further guided by the nature of biological barriers: While nanocarriers alone may suffice for crossing cellular membranes, multi-compartmental challenges—such as enzymatic degradation in the gastrointestinal tract, mucosal penetration, and systemic clearance—often necessitate hierarchical designs that provide sequential protection and triggered release at each stage[128].

Notably, the transitions between dimensional scales are not merely additive but sequential and synergistic—an injectable hydrogel microsphere may degrade locally to release nucleic acid nanocomplexes for cellular entry; an oral macro-tablet may disintegrate in the gut, releasing microgels that adhere to the colonic mucosa and in turn release nanomicelles for uptake. This cascading release logic underpins the design rationale for selecting multi-scale over single-scale platforms: When the delivery challenge is confined to cellular uptake, single-scale nanocarriers suffice; however, when facing multi-compartmental barriers—such as gastrointestinal mucus, epithelial tight junctions, systemic clearance, and target tissue stroma—hierarchical strategies decouple conflicting requirements for tissue penetration, target recognition, and intracellular action, achieving spatiotemporal orchestration beyond the capability of any single-scale system[11].

While chitosan, alginate, HA, dextran, and PEC are considered safe based on historical human use, their safety as purified, chemically modified, or intravenously administered carriers cannot be assumed. Key factors alter their biocompatibility[129]: Molecular-weight (MW) distribution affects biodistribution and clearance (e.g., high-MW chitosan accumulates heavily in the liver, while low-MW fractions show less hepatic retention); impurities from natural sources (e.g., proteins, endotoxins, or mixtures of polysaccharides with similar molecular sizes[130]) can provoke inflammatory or immune responses, especially upon parenteral administration; residual modification reagents (e.g., crosslinkers, preservatives) introduce toxicity risks not associated with the native material; and administration route is critical—oral or topical use tolerates broader quality ranges, whereas intravenous delivery demands rigorous purity, controlled MW, and complete removal of chemical residues. These safety considerations, however, represent only the foundational prerequisites for clinical translation. Beyond biocompatibility, several unresolved challenges concerning the rational design and industrial production of polysaccharide-based carriers warrant further investigation.

Several unresolved challenges warrant further investigation. First, the optimal carrier size depends on a complex interplay of administration route, target tissue, and disease biology, and no single size fits all applications. Balancing competing requirements remains difficult: Efficient extravasation favours smaller particles, whereas prolonged retention benefits from larger dimensions; positive surface charge enhances transcytosis but neutral surfaces are preferred for extended circulation[131]. Second, when chemically modifying polysaccharides to introduce targeting ligands or responsive linkages, it is essential to verify that the molecular structure of the loaded drug remains intact upon release and that such modifications do not compromise therapeutic efficacy[132]. Importantly, as noted above, these very chemical modifications introduce additional safety variables beyond those of the native polymer, further complicating the risk–benefit assessment. Third, Scalable and reproducible manufacturing methods that preserve size monodispersity and batch-to-batch consistency are urgently needed for clinical translation[133]. Recent advances in microfluidics have shown promise for producing polysaccharide-based nanoparticles with controlled size and low polydispersity[134], and continuous manufacturing strategies such as inline sonication combined with tangential flow filtration have been demonstrated at industrial scale for polymeric nanomedicines[135]. Electrospray and 3D bioprinting offer additional promising routes but require optimization for each polysaccharide and size target.

Addressing these interconnected issues—from raw material quality control to formulation design and scalable fabrication—will be essential to unlock the full therapeutic potential of these versatile natural polymers.

Looking ahead, several directions are likely to shape the next generation of size-tailored polysaccharide delivery systems. Personalized medicine will benefit from on-demand fabrication technologies, such as 3D printing of patient-specific hydrogels or microneedle arrays[136], which leverage the processability of polysaccharides. Intelligent systems that integrate sensing, feedback, and closed-loop drug release could be realized by combining polysaccharides with responsive nanomaterials[137]. The convergence of size engineering with advanced manufacturing and artificial intelligence promises to accelerate the discovery of optimal carrier dimensions for specific diseases (**Fig. 6**). The size-centric framework articulated here not only organizes existing knowledge but also provides a heuristic for future innovation. By recognizing that the therapeutic power of polysaccharides arises from their unique ability to be engineered across scales, researchers can move beyond chemical-focused paradigms and embrace dimensional design as a core strategy. The challenge ahead lies in translating this size-aware mindset into clinical realities, where the right carrier at the right size delivers the right drug to the right place at the right time.

7 Conclusion

Natural polysaccharides offer a versatile platform for drug delivery, and their full therapeutic potential is realized when their inherent size-tailorability is systematically exploited. In this review, we have established a hierarchical framework that classifies polysaccharide-based delivery systems into three interconnected domains based on characteristic length scales. The nanoscopic realm enables precision targeting, intracellular trafficking, and stimuli-responsive release, making it the regime of choice for systemic therapies requiring cellular or subcellular delivery. The microscopic domain provides local depots and sustained-release

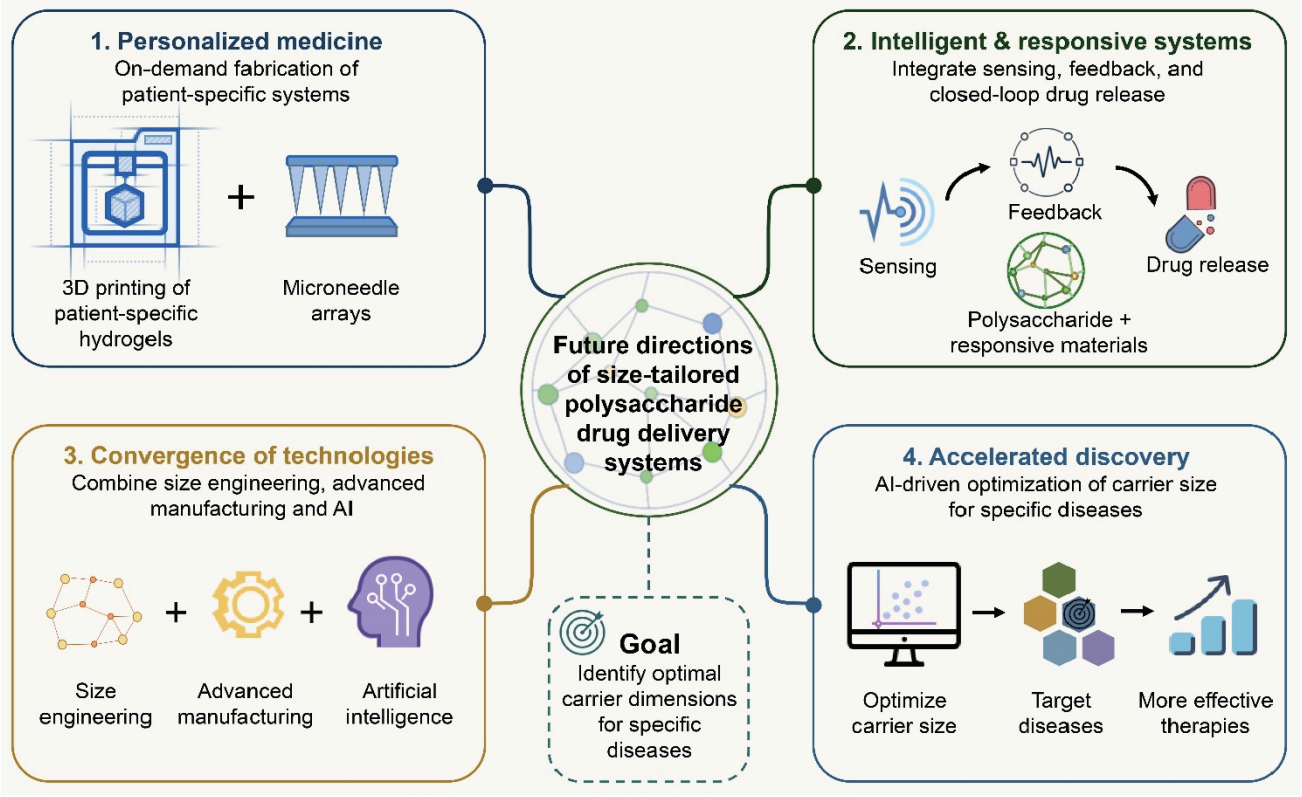


Figure 6 Future Directions of Size-Tailored Polysaccharide Drug Delivery Systems.

platforms, offering prolonged action and minimally invasive administration for applications ranging from vaccine delivery to probiotic therapy. The macroscopic world delivers engineered scaffolds and interfaces for localised treatment, high drug loading, and patient-compliant oral or topical formulations.

By explicitly linking carrier size to biological function, this framework reveals that therapeutic outcomes are not determined solely by chemical composition but are profoundly influenced by physical dimensions. The size of a polysaccharide carrier dictates its transport pathways, the biological barriers it encounters, its clearance mechanisms, its release kinetics, and ultimately its clinical applicability. Recognising this size–function relationship enables rational selection of the appropriate size regime to match the specific demands of a given disease, administration route, and therapeutic goal.

The integration of multiple scales within a single system, such as nanoparticles in microneedles or microspheres in hydrogels, offers synergistic advantages that transcend the limitations of any isolated regime. These hierarchical constructs represent the next frontier in polysaccharide-based drug delivery, where size engineering is combined with chemical versatility and advanced manufacturing to create intelligent, personalised, and clinically translatable therapies.

Beyond the classification of polysaccharide delivery systems according to dimensional scales, rational selection of an appropriate delivery platform should be guided by the specific therapeutic objectives, administration routes, biological barriers, and release requirements. Nanoscale polysaccharide systems are generally advantageous for systemic administration and intracellular delivery due to their small size, high surface area, enhanced biological interactions, and potential to facilitate cellular internalization. These characteristics make them particularly valuable for improving the bioavailability and targeted delivery of poorly soluble drugs and biologically active molecules. Microscale polysaccharide systems provide distinct advantages in sustained release, gastrointestinal retention, and localized delivery, making them promising platforms for oral administration and site-specific therapeutic applications, particularly when prolonged residence time or controlled release is required. In contrast, macroscale polysaccharide platforms, including hydrogels and scaffolds, are more suitable for tissue engineering, implantation, and long-term local therapy owing to their structural integrity, three-dimensional network architecture, and capacity for extracellular matrix-like support. Therefore, the rational design of polysaccharide-based delivery systems should involve a comprehensive consideration of dimensional scale, structural complexity, biological interactions, and therapeutic requirements rather than simply pursuing enhanced delivery efficiency. Such a design-oriented perspective may facilitate the development of more effective and application-specific polysaccharide delivery platforms.

Systematic investigation of structure–size correlations, comparative biological fate studies across size regimes, and scalable manufacturing processes will be essential to translate laboratory innovations into patient benefits. The size-centric perspective presented here not only synthesises decades of research but also provides a roadmap for future discovery. Given that many polysaccharides discussed in this review derive from food–medicine homology sources, their established safety profiles and wide availability may accelerate clinical translation and facilitate the development of accessible, sustainable delivery platforms. In this context, the remarkable dimensional flexibility of natural polysaccharides can be fully exploited to address the most pressing challenges in drug delivery and precision medicine.

Data availability

Not applicable.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work. Jia-Lun Duan is an Associate Editors of Food & Medicine Homology Resources, but was not involved in the processing, peer review or decision making of this article.

Acknowledgements

None.

Funding

The authors acknowledge financial support from National Key Research and Development Program of China (Young Scholars, No. 2025YFC3512200), National Natural Science Foundation of China (Grant No. 82405025), Natural Science Foundation of the Jiangsu Higher Education Institutions (Grant No. 24KJB360017), Natural Science Foundation of Jiangsu Province (Grant No. BK20230462, BK20240749), and the High-Level Key Discipline Construction Project of National Administration of Traditional Chinese Medicine (Grant No. ZYYZDXK-2023083).

Author contribution statement

Yu-Xuan Li: Writing-original draft, investigation. Jing-Han Zhou: Writing-original draft, data curation. Meng-Ting Jiang: Data curation. Yue-Fan Liu: Data curation. Yu-Jie Sun: Methodology. Yi-Xuan Liu: Methodology. Chun-Jie Bao: Writing-review & editing, supervision. Jia-Lun Duan: Writing-review & editing, supervision, project administration.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

During the preparation of this work, the authors used ChatGPT (OpenAI) to improve the clarity, grammar, and readability of the manuscript. After using this tool, the authors carefully reviewed and edited the generated content and take full responsibility for the content of the publication.

References

[1] Wang, B., Wang, X. F., Xiong, Z. W., et al. A review on the applications of traditional Chinese medicine polysaccharides in drug delivery systems. *Chinese Medicine*, **2022**, 17: 12. https://doi.org/10.1186/s13020-021-00567-3

[2] Fan, Y., Liu, Y., Wu, Y., et al. Natural polysaccharides based self-assembled nanoparticles for biomedical applications-a review. *International Journal of Biological Macromolecules*, **2021**, 192: 1240–1255. https://doi.org/10.1016/j.ijbiomac.2021.10.074

[3] Barclay, T. G., Day, C. M., Petrovsky, N., et al. Review of polysaccharide particle-based functional drug delivery. *Carbohydrate Polymers*, **2019**, 221: 94–112. https://doi.org/10.1016/j.carbpol.2019.05.067

[4] Ediriwickrema, A., Saltzman, W. M. Nanotherapy for cancer: Targeting and multifunctionality in the future of cancer therapies. *ACS Biomaterials Science & Engineering*, **2015**, 1: 64–78. https://doi.org/10.1021/ab500084g

[5] Ernsting, M. J., Murakami, M., Roy, A., et al. Factors controlling the pharmacokinetics, biodistribution and intratumoral penetration of nanoparticles. *Journal of Controlled Release*, **2013**, 172: 782–794. https://doi.org/10.1016/j.jconrel.2013.09.013

[6] Pushpamalar, J., Meganathan, P., Tan, H. L., et al. Development of a polysaccharide-based hydrogel drug delivery system (DDS): An update. *Gels*, **2021**, 7: 153. https://doi.org/10.3390/gels7040153

[7] Lima, C. S. A., Balogh, T. S., Varca, J., et al. An updated review of macro, micro, and nanostructured hydrogels for biomedical and pharmaceutical applications. *Pharmaceutics*, **2020**, 12: 970. https://doi.org/10.3390/pharmaceutics12100970

[8] Rial-Hermida, M. I., Rey-Rico, A., Blanco-Fernandez, B., et al. Recent progress on polysaccharide-based hydrogels for controlled delivery of therapeutic biomolecules. *ACS Biomaterials Science & Engineering*, **2021**, 7: 4102–4127. https://doi.org/10.1021/acsbiomaterials.0c01784

[9] Liu, Z. H., Jiao, Y. P., Wang, Y. F., et al. Polysaccharides-based nanoparticles as drug delivery systems. *Advanced Drug Delivery Reviews*, **2008**, 60: 1650–1662. https://doi.org/10.1016/j.addr.2008.09.001

[10] Yu, M. X., Zheng, J. Clearance pathways and tumor targeting of imaging nanoparticles. *ACS Nano*, **2015**, 9: 6655–6674. https://doi.org/10.1021/acsnano.5b01320

[11] Blanco, E., Shen, H., Ferrari, M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnology*, **2015**, 33: 941–951. https://doi.org/10.1038/nbt.3330

[12] Kizhakkanoodan, K. S., Rallapalli, Y., Praveena, J., et al. Cancer nanomedicine: Emergence, expansion, and expectations. *SN Applied Sciences*, **2023**, 5: 385. https://doi.org/10.1007/s42452-023-05593-4

[13] Menge, J. L., Yang, C. J., Weitz, D. A., et al. Engineering the biophysical properties of lipid nanostructures for drug delivery. *Communications Materials*, **2026**, 7: 25. https://doi.org/10.1038/s43246-026-01073-5

[14] Subhan, M. A., Yalamarty, S. S. K., Filipczak, N., et al. Recent advances in tumor targeting *via* EPR effect for cancer treatment. *Journal of Personalized Medicine*, **2021**, 11: 571. https://doi.org/10.3390/jpm11060571

[15] Öztürk, K., Kaplan, M., Çalış, S. Effects of nanoparticle size, shape, and zeta potential on drug delivery. *International Journal of Pharmaceutics*, **2024**, 666: 124799. https://doi.org/10.1016/j.ijpharm.2024.124799

[16] Ding, P. Y., Liu, H. L., Zhu, X., et al. Thiolated chitosan encapsulation constituted mucoadhesive nanovaccine confers broad protection against divergent influenza A viruses. *Carbohydrate Polymers*, **2024**, 328: 121689. https://doi.org/10.1016/j.carbpol.2023.121689

[17] Zhao, M., Zhou, H. J., Hao, L., et al. Natural rosin modified carboxymethyl cellulose delivery system with lowered toxicity for long-term pest control. *Carbohydrate Polymers*, **2021**, 259: 117749. https://doi.org/10.1016/j.carbpol.2021.117749

[18] Yu, Y., Kong, L., Guo, R. B., et al. Engineered *Panax notoginseng* polysaccharide micelles inhibit macrophage polarization and delay the progression of rheumatoid arthritis *via* JAK2-STAT3 signaling pathway. *Journal of Nanobiotechnology*, **2025**, 23: 509. https://doi.org/10.1186/s12951-025-03576-8

[19] Guo, Y. F., Yang, X. R., Zhang, Y. H., et al. Hyaluronic acid/dextran-based polymeric micelles co-delivering ursolic acid and doxorubicin to mitochondria for potentiating chemotherapy in MDR cancer. *Carbohydrate Polymers*, **2024**, 332: 121897. https://doi.org/10.1016/j.carbpol.2024.121897

[20] Ding, C. D., Shi, Z. Q., Ou, M. T., et al. Dextran-based micelles for combinational chemo-photodynamic therapy of tumors *via in vivo* chemiluminescence. *Carbohydrate Polymers*, **2023**, 319: 121192. https://doi.org/10.1016/j.carbpol.2023.121192

[21] Friday, C., Edgar, K. Recent developments in all-polysaccharide hydrogels: Synthesis, properties, and biomedical applications. *Carbohydrate Polymers*, **2026**, 376: 124806. https://doi.org/10.1016/j.carbpol.2025.124806

[22] Al-Hussain, S. A., Sultan, A., Rubab, L., et al. Nanoparticle-reinforced polysaccharide hydrogels in drug delivery systems: A review of recent progress. *International Journal of Biological Macromolecules*, **2026**, 335: 149238. https://doi.org/10.1016/j.ijbiomac.2025.149238

[23] Chen, J. L., Chen, Z. B., Kuang, Y., et al. Advances in the preparation of smart responsive chitosan-based nanohydrogels and their application in functional ingredient delivery. *Journal of Functional Materials*, **2025**, 56: 9049–9065. https://doi.org/10.3969/j.issn.1001-9731.2025.09.007

[24] Zhang, Y., Lin, S. Q., Xu, X., et al. Programmable hierarchical hydrogel dressing for sequential release of growth factor and DNase to accelerate diabetic wound healing. *Journal of Controlled Release*, **2025**, 383: 113825. https://doi.org/10.1016/j.jconrel.2025.113825

[25] Xu, S. L., Wang, T., Hu, X. C., et al. A dual chemodrug-loaded hyaluronan nanogel for differentiation induction therapy of refractory AML *via* disrupting lysosomal homeostasis. *Science Advances*, **2025**, 11: eado3923. https://doi.org/10.1126/sciadv.ado3923

[26] Hong, S. J., Ahn, M. H., Sangshetti, J., et al. Sugar-based gene delivery systems: Current knowledge and new perspectives. *Carbohydrate Polymers*, **2018**, 181: 1180–1193. https://doi.org/10.1016/j.carbpol.2017.11.105

[27] Hao, X. P., Zhang, Y., Shi, X. L., et al. CircPAK1 promotes the progression of hepatocellular carcinoma *via* modulation of YAP nucleus localization by interacting with 14-3-3ζ. *Journal of Experimental & Clinical Cancer Research*, **2022**, 41: 281. https://doi.org/10.1186/s13046-022-02494-z

[28] Guo, X., Zhai, S. D., Zhang, H. D., et al. Natural polysaccharide-nucleic acid nanocomplex alleviates myocardial infarction by driving chronologically programmed macrophage polarization. *Materials Today Bio*, **2026**, 37: 102831. https://doi.org/10.1016/j.mtbio.2026.102831

[29] Gao, H., Wang, S. Q., Long, Q., et al. Rational design of a polysaccharide-based viral mimicry nanocomplex for potent gene silencing in inflammatory tissues. *Journal of Controlled Release*, **2023**, 357: 120–132. https://doi.org/10.1016/j.jconrel.2023.03.037

[30] Nair, R., Paul, P., Maji, I., et al. Exploring the current landscape of chitosan-based hybrid nanoplatforms as cancer theragnostic. *Carbohydrate Polymers*, **2024**, 326: 121644. https://doi.org/10.1016/j.carbpol.2023.121644

[31] Alavi, S. E., Alavi, S. F., Koohi, M., et al. Nanoparticle-integrated metal–organic frameworks: A revolution in next-generation drug delivery systems. *Journal of Pharmaceutical Investigation*, **2024**, 54: 751–783. https://doi.org/10.1007/s40005-024-00691-w

[32] Yang, P. P., Chen, W., Li, J., et al. Hollow CuS nanoparticles equipped with hydroxyapatite/hyaluronic acid coating for NIR/pH dual-responsive drug delivery. *International Journal of Biological Macromolecules*, **2023**, 253: 127150. https://doi.org/10.1016/j.ijbiomac.2023.127150

[33] Furukawa, H., Cordova, K. E., O'Keeffe, M., et al. The chemistry and applications of metal-organic frameworks. *Science*, **2013**, 341: 1230444. https://doi.org/10.1126/science.1230444

[34] Hsu, C. Y., Jasim, S. A., Saleh, E. A. M., et al. Hyaluronic acid and ZIF-8 nanocomposites for wound care. *International Journal of Biological Macromolecules*, **2025**, 315: 144475. https://doi.org/10.1016/j.ijbiomac.2025.144475

[35] Do, T. T. A., Grijalvo, S., Imae, T., et al. A nanocellulose-based platform towards targeted chemo-photodynamic/photothermal cancer therapy. *Carbohydrate Polymers*, **2021**, 270: 118366. https://doi.org/10.1016/j.carbpol.2021.118366

[36] Akhlaghi, N., Najafpour-Darzi, G. Thermosensitive injectable dual drug-loaded chitosan-based hybrid hydrogel for treatment of orthopedic implant infections. *Carbohydrate Polymers*, **2023**, 320: 121138. https://doi.org/10.1016/j.carbpol.2023.121138

[37] Dubashynskaya, N. V., Bokatyi, A. N., Trulioff, A. S., et al. Delivery system for dexamethasone phosphate based on a Zn^{2+}-crosslinked polyelectrolyte complex of diethylaminoethyl chitosan and chondroitin sulfate. *Carbohydrate Polymers*, **2025**, 348: 122899. https://doi.org/10.1016/j.carbpol.2024.122899

[38] Ferreira, N. N., Granja, S., Boni, F. I., et al. Modulating chitosan-PLGA nanoparticle properties to design a co-delivery platform for glioblastoma therapy intended for nose-to-brain route. *Drug Delivery and Translational Research*, **2020**, 10: 1729–1747. https://doi.org/10.1007/s13346-020-00824-2

[39] Ahmad, S., Khan, I., Pandit, J., et al. Brain targeted delivery of carmustine using chitosan coated nanoparticles *via* nasal route for glioblastoma treatment. *International Journal of Biological Macromolecules*, **2022**, 221: 435–445. https://doi.org/10.1016/j.ijbiomac.2022.08.210

[40] Ramalho, M. J., Serra, É., Lima, J., et al. Chitosan-PLGA mucoadhesive nanoparticles for gemcitabine repurposing for glioblastoma therapy. *European Journal of Pharmaceutics and Biopharmaceutics*, **2024**, 200: 114326. https://doi.org/10.1016/j.ejpb.2024.114326

[41] Dash, B. S., Lu, Y. J., Huang, Y. S., et al. Chitosan-coated magnetic graphene oxide for targeted delivery of doxorubicin as a nanomedicine approach to treat glioblastoma. *International Journal of Biological Macromolecules*, **2024**, 260: 129401. https://doi.org/10.1016/j.ijbiomac.2024.129401

[42] Esfandiarpour-Boroujeni, S., Bagheri-Khoulenjani, S., Mirzadeh, H., et al. Fabrication and study of curcumin loaded nanoparticles based on folate-chitosan for breast cancer therapy application. *Carbohydrate Polymers*, **2017**, 168: 14–21. https://doi.org/10.1016/j.carbpol.2017.03.031

[43] Jing, Z. W., Jia, Y. Y., Wan, N., et al. Design and evaluation of novel pH-sensitive ureido-conjugated chitosan/TPP nanoparticles targeted to *Helicobacter pylori*. *Biomaterials*, **2016**, 84: 276–285. https://doi.org/10.1016/j.biomaterials.2016.01.045

[44] Guo, X. L., Zhuang, Q. F., Ji, T. J., et al. Multi-functionalized chitosan nanoparticles for enhanced chemotherapy in lung cancer. *Carbohydrate Polymers*, **2018**, 195: 311–320. https://doi.org/10.1016/j.carbpol.2018.04.087

[45] Xie, L., Zhang, Y. P., Chen, L., et al. Structural changes of layer-by-layer self-assembled starch-based nanocapsules in the gastrointestinal tract: Implications for their M cell-targeting delivery and transport efficiency. *International Journal of Biological Macromolecules*, **2024**, 261: 129786. https://doi.org/10.1016/j.ijbiomac.2024.129786

[46] Tang, H. B., Feng, X., Zhang, T., et al. Stability, pharmacokinetics, biodistribution and safety assessment of folate-conjugated pullulan acetate nanoparticles as cervical cancer targeted drug carriers. *Journal of Biomedical Nanotechnology*, **2015**, 15: 6405–6412. https://doi.org/10.1166/jnn.2015.10752

[47] Sun, J. P., Du, J. Q., Liu, X. B., et al. Chondroitin sulfate-modified tragacanth gum-gelatin composite nanocapsules loaded with curcumin nanocrystals for the treatment of arthritis. *Journal of Nanobiotechnology*, **2024**, 22: 270. https://doi.org/10.1186/s12951-024-02540-2

[48] Chen, L. L., Qian, M., Zhang, L. W., et al. Co-delivery of doxorubicin and shRNA of Beclin1 by folate receptor targeted pullulan-based multifunctional nanomicelles for combinational cancer therapy. *RSC Advances*, **2018**, 8: 17710–17722. https://doi.org/10.1039/c8ra01679h

[49] Xie, F., Jiang, L., Xiao, X. M., et al. Quaternized polysaccharide-based cationic micelles as a macromolecular approach to eradicate multidrug-resistant bacterial infections while mitigating antimicrobial resistance. *Small*, **2022**, 18: e2104885. https://doi.org/10.1002/smll.202104885

[50] Zhang, M., Asghar, S., Tian, C. H., et al. Lactoferrin/phenylboronic acid-functionalized hyaluronic acid nanogels loading doxorubicin hydrochloride for targeting glioma. *Carbohydrate Polymers*, **2021**, 253: 117194. https://doi.org/10.1016/j.carbpol.2020.117194

[51] Gao, D., Asghar, S., Ye, J. X., et al. Dual-targeted enzyme-sensitive hyaluronic acid nanogels loading paclitaxel for the therapy of breast cancer. *Carbohydrate Polymers*, **2022**, 294: 119785. https://doi.org/10.1016/j.carbpol.2022.119785

[52] Cadinoiu, A. N., Rata, D. M., Atanase, L. I., et al. Formulations based on drug loaded aptamer-conjugated liposomes as a viable strategy for the topical treatment of basal cell carcinoma-*in vitro* tests. *Pharmaceutics*, **2021**, 13: 866. https://doi.org/10.3390/pharmaceutics13060866

[53] Truong, T. H., Alcantara, K. P., Bulatao, B. P. I., et al. Chitosan-coated nanostructured lipid carriers for transdermal delivery of tetrahydrocurcumin for breast cancer therapy. *Carbohydrate Polymers*, **2022**, 288: 119401. https://doi.org/10.1016/j.carbpol.2022.119401

[54] Kim, E. J., Jeong, H. S., Park, J. Y., et al. The inflammatory bowel disease and gut microbiome are restored by employing metformin-loaded alginate-shelled microcapsules. *Journal of Controlled Release*, **2025**, 378: 490–502. https://doi.org/10.1016/j.jconrel.2024.12.041

[55] Li, X., Yu, M. L., Zhu, Z., et al. Oral delivery of infliximab using nano-in-microparticles for the treatment of inflammatory bowel disease. *Carbohydrate Polymers*, **2021**, 273: 118556. https://doi.org/10.1016/j.carbpol.2021.118556

[56] Ta, L. P., Corrigan, S., Tselepis, C., et al. Gastrointestinal-inert prebiotic micro-composites improve the growth and community diversity of mucosal-associated bacteria. *Journal of Controlled Release*, **2024**, 375: 495–512. https://doi.org/10.1016/j.jconrel.2024.09.021

[57] Kruk, K., Szekalska, M., Basa, A., et al. The impact of hypromellose on pharmaceutical properties of alginate microparticles as novel drug carriers for posaconazole. *International Journal of Molecular Sciences*, **2023**, 24: 10793. https://doi.org/10.3390/ijms241310793

[58] Wang, W., Tu, F., Yang, Z. H., et al. Pectin/arabinoxylan dietary polysaccharide microcapsule encapsulated with *Clostridium butyricum* for targeted delivery in colitis treatment. *Carbohydrate Polymers*, **2025**, 367: 123971. https://doi.org/10.1016/j.carbpol.2025.123971

[59] Liu, M. Y., Ma, S., Zhi, J. L., et al. Bioinspired core-shell microparticle for dual-delivery of prebiotic and probiotic for the treatment of ulcerative colitis. *Journal of Controlled Release*, **2024**, 376: 566–576. https://doi.org/10.1016/j.jconrel.2024.10.026

[60] Xie, Z. G., Liang, W. L., Xiong, Q. Y., et al. Acetalated dextran microparticles for the smart delivery of pyraclostrobin to control *Sclerotinia* diseases. *Carbohydrate Polymers*, **2022**, 291: 119576. https://doi.org/10.1016/j.carbpol.2022.119576

[61] Pontes, J. F., Guerreiro, F., Silva, J. P., et al. Locust bean gum (LBG) - a potential excipient for inhalation purposes: Excipient characterisation and *in vitro* and *in vivo* toxicological evaluation. *Carbohydrate Polymers*, **2025**, 363: 123729. https://doi.org/10.1016/j.carbpol.2025.123729

[62] Zhou, Y., Huang, J. Y., Wang, G. L., et al. Polymyxin B sulfate inhalable microparticles with high-lectin-affinity sugar carriers for efficient treatment of biofilm-associated pulmonary infections. *Science Bulletin*, **2023**, 68: 3225–3239. https://doi.org/10.1016/j.scib.2023.11.004

[63] Zhao, H. M., He, X., Tan, C. J., et al. Chitosan-melanin complex microsphere: A potential colonic delivery system for protein drugs. *Carbohydrate Polymers*, **2025**, 348: 122886. https://doi.org/10.1016/j.carbpol.2024.122886

[64] Zhang, S., Wang, C. J., Zhu, Y. J., et al. DNA-capturing manganese-coordinated chitosan microparticles potentiate radiotherapy *via* activating the cGAS-STING pathway and maintaining tumor-infiltrating $CD8^+$ T-cell stemness. *Advanced Materials*, **2025**, 37: e2418583. https://doi.org/10.1002/adma.202418583

[65] Zhou, P. W., Sun, Q., Huang, L. C., et al. Dual-targeting Mn@CeO_2 nanozyme-modified probiotic hydrogel microspheres reshape gut homeostasis in inflammatory bowel disease. *ACS Nano*, **2025**, 19: 31619–31642. https://doi.org/10.1021/acsnano.5c08999

[66] Liu, X. W., Guo, C. J., Yang, W. L., et al. Composite microneedles loaded with *Astragalus membranaceus* polysaccharide nanoparticles promote wound healing by curbing the ROS/NF-κB pathway to regulate macrophage polarization. *Carbohydrate Polymers*, **2024**, 345: 122574. https://doi.org/10.1016/j.carbpol.2024.122574

[67] Ruan, S. Y., Li, J. Q., Ruan, H., et al. Microneedle-mediated nose-to-brain drug delivery for improved Alzheimer's disease treatment. *Journal of Controlled Release*, **2024**, 366: 712–731. https://doi.org/10.1016/j.jconrel.2024.01.013

[68] Sun, B., Zhang, T. K., Chen, H. R., et al. Microneedle delivery system with rapid dissolution and sustained release of bleomycin for the treatment of hemangiomas. *Journal of Nanobiotechnology*, **2024**, 22: 372. https://doi.org/10.1186/s12951-024-02557-7

[69] Xu, B., Zhang, S. H., Liu, H., et al. Double-layered core-shell microneedle patch integrated with microparticles for long-acting treatment of osteoporosis. *Journal of Controlled Release*, **2025**, 384: 113898. https://doi.org/10.1016/j.jconrel.2025.113898

[70] Li, N. N., Niu, L. L., Liu, Y., et al. Taking SCFAs produced by *Lactobacillus reuteri* orally reshapes gut microbiota and elicits antitumor responses. *Journal of Nanobiotechnology*, **2024**, 22: 241. https://doi.org/10.1186/s12951-024-02506-4

[71] Hou, Y., Zhu, L., Ye, X. F., et al. Integrated oral microgel system ameliorates renal fibrosis by hitchhiking co-delivery and targeted gut flora modulation. *Journal of Nanobiotechnology*, **2024**, 22: 305. https://doi.org/10.1186/s12951-024-02586-2

[72] Takatsuka, S., Kubota, T., Kurashina, Y., et al. Near-infrared-triggered on-demand controlled release of adeno-associated virus from alginate hydrogel microbeads with heat transducer for gene therapy. *Small*, **2023**, 19: e2204139. https://doi.org/10.1002/smll.202204139

[73] Zhang, Y., Li, L., Kong, J., et al. Long-acting injectable nanoparticle formulation for sustained release of anti-TNF-α antibody therapeutic in ulcerative colitis treatment. *Journal of Controlled Release*, **2025**, 380: 1005–1016. https://doi.org/10.1016/j.jconrel.2025.02.043

[74] Simonson, A. W., Umstead, T. M., Lawanprasert, A., et al. Extracellular matrix-inspired inhalable aerogels for rapid clearance of pulmonary tuberculosis. *Biomaterials*, **2021**, 273: 120848. https://doi.org/10.1016/j.biomaterials.2021.120848

[75] Sartipzadeh, O., Naghib, S. M., Haghiralsadat, F., et al. Microfluidic-assisted synthesis and modeling of stimuli-responsive monodispersed chitosan microgels for drug delivery applications. *Scientific Reports*, **2022**, 12: 8382. https://doi.org/10.1038/s41598-022-12031-9

[76] Li, J., Wu, C., Xu, H. J., et al. Fabrication of thermo-responsive microcapsule pesticide delivery system from maleic anhydride-functionalized cellulose nanocrystals-stabilized pickering emulsion template. *Carbohydrate Polymers*, **2024**, 344: 122531. https://doi.org/10.1016/j.carbpol.2024.122531

[77] Hendy, D. A., Ma, Y., Dixon, T. A., et al. Polymeric cGAMP microparticles affect the immunogenicity of a broadly active influenza mRNA lipid nanoparticle vaccine. *Journal of Controlled Release*, **2024**, 372: 168–175. https://doi.org/10.1016/j.jconrel.2024.06.007

[78] Jing, S. L., Liu, Y. H., Wang, B., et al. Microneedle-mediated hypoxic extracellular vesicle-encapsulated selenium nanoparticles delivery to treat androgenetic alopecia. *Journal of Controlled Release*, **2025**, 381: 113597. https://doi.org/10.1016/j.jconrel.2025.113597

[79] Yuan, Y., He, N., Dong, L. Y., et al. Multiscale shellac-based

delivery systems: From macro- to nanoscale. *ACS Nano*, **2021**, 15: 18794–18821. https://doi.org/10.1021/acsnano.1c07121

[80] Malik, M. K., Kumar, V., Kumarasamy, V., et al. Film coating of phosphorylated mandua starch on matrix tablets for pH-sensitive release of mesalamine. *Molecules*, **2024**, 29: 3208. https://doi.org/10.3390/molecules29133208

[81] Sanjanwala, D., Londhe, V., Trivedi, R., et al. Polysaccharide-based hydrogels for medical devices, implants and tissue engineering: A review. *International Journal of Biological Macromolecules*, **2024**, 256: 128488. https://doi.org/10.1016/j.ijbiomac.2023.128488

[82] Azehaf, H., Benzine, Y., Tagzirt, M., et al. Microbiota-sensitive drug delivery systems based on natural polysaccharides for colon targeting. *Drug Discovery Today*, **2023**, 28: 103606. https://doi.org/10.1016/j.drudis.2023.103606

[83] Magnano, G. C., Scomparin, A., Argenziano, M., et al. Exploring new buccal films based on hydroxyethyl cellulose and Linecaps® combination for the pediatric delivery of hydrophobic molecules. *Carbohydrate Polymers*, **2026**, 371: 124499. https://doi.org/10.1016/j.carbpol.2025.124499

[84] Kwak, H., Shin, S., Kim, J., et al. Protective coating of strawberries with cellulose nanofibers. *Carbohydrate Polymers*, **2021**, 258: 117688. https://doi.org/10.1016/j.carbpol.2021.117688

[85] Heras-Mozos, R., Gavara, R., Hernández-Muñoz, P. Chitosan films as pH-responsive sustained release systems of naturally occurring antifungal volatile compounds. *Carbohydrate Polymers*, **2022**, 283: 119137. https://doi.org/10.1016/j.carbpol.2022.119137

[86] Ma, M. R., Powell, D., Nassar, M., et al. Impact of immediate release film coating on the disintegration process of tablets. *Journal of Controlled Release*, **2024**, 373: 533–546. https://doi.org/10.1016/j.jconrel.2024.07.037

[87] Maiti, S., Maji, B., Yadav, H. Progress on green crosslinking of polysaccharide hydrogels for drug delivery and tissue engineering applications. *Carbohydrate Polymers*, **2024**, 326: 121584. https://doi.org/10.1016/j.carbpol.2023.121584

[88] Zhang, J., Bao, C. J., Zhang, X. L., et al. *Lycium barbarum* polysaccharide-based hydrogel as a novel oral colon-targeted drug delivery system for enhanced MSS-CRC treatment by macrophage lipid reprogramming. *Advanced Functional Materials*, **2026**, 36: e23769. https://doi.org/10.1002/adfm.202523769

[89] Zhao, M. Y., Xiang, J. W., Meng, Y., et al. *Astragalus* polysaccharide hydrogels with drug-carrying super self-assembly from natural herbs promote wound healing. *ACS Nano*, **2025**, 19: 21571–21588. https://doi.org/10.1021/acsnano.5c03744

[90] Witzler, M., Schulze, M., Gericke, M., et al. Ionic agarose derivatives as polyelectrolytic additives for drug release. *Carbohydrate Polymers*, **2026**, 373: 124622. https://doi.org/10.1016/j.carbpol.2025.124622

[91] Tang, Q., Leng, S. L., Tan, Y. Q., et al. Chitosan/dextran-based organohydrogel delivers EZH2 inhibitor to epigenetically reprogram chemo/immuno-resistance in unresectable metastatic melanoma. *Carbohydrate Polymers*, **2024**, 346: 122645. https://doi.org/10.1016/j.carbpol.2024.122645

[92] Veronica, N., Heng, P. W. S., Liew, C. V., et al. Alginate-based matrix tablets for drug delivery. *Expert Opinion on Drug Delivery*, **2023**, 20: 115–130. https://doi.org/10.1080/17425247.2023.2158183

[93] Doggwiler, V., Puorger, C., Paredes, V., et al. Efficient colonic drug delivery in domestic pigs employing a tablet formulation with dual control concept. *Journal of Controlled Release*, **2023**, 358: 420–438. https://doi.org/10.1016/j.jconrel.2023.04.047

[94] Bhardwaj, B. Y., Vihal, S., Pahwa, R., et al. Recent advancements in xanthan gum-based gastroretentive floating formulations: Chemical modification, production and applications. *Carbohydrate Polymers*, **2025**, 348: 122809. https://doi.org/10.1016/j.carbpol.2024.122809

[95] Baran, E., Birczyński, A., Dorożyński, P., et al. Low-field time-domain NMR relaxometry for studying polymer hydration and mobilization in sodium alginate matrix tablets. *Carbohydrate Polymers*, **2023**, 299: 120215. https://doi.org/10.1016/j.carbpol.2022.120215

[96] Yang, B., Xu, Y., Zhang, W. Y., et al. Oral absorption mechanisms of polysaccharides and potential as carriers for the construction of nano-delivery systems: A review. *International Journal of Biological Macromolecules*, **2025**, 310: 143184. https://doi.org/10.1016/j.ijbiomac.2025.143184

[97] Gao, Y., Dong, Y. Y., Guo, Q., et al. Study on supramolecules in traditional Chinese medicine decoction. *Molecules*, **2022**, 27: 3268. https://doi.org/10.3390/molecules27103268

[98] Nie, W. L., Zhang, X. Y., Kang, P., et al. Exploring the influence of polysaccharide on gastrointestinal stability, drug release and formation mechanism of nanoparticles in Zhimu and Huangbai herb pair decoction. *Scientific Reports*, **2025**, 15: 8293. https://doi.org/10.1038/s41598-024-82130-2

[99] Chen, S. J., Xu, Y. B., Liu, D. W., et al. Thermally driven self-assembly of triterpenoid-fructan supramolecular particles contributes significantly to the efficacy of Zexie Tang against MASH. *Carbohydrate Polymers*, **2026**, 386: 125450. https://doi.org/10.1016/j.carbpol.2026.125450

[100] Chen MC, Mi FL, Liao ZX, et al. Recent advances in chitosan-based nanoparticles for oral delivery of macromolecules. *Adv Drug Deliv Rev.*, **2013**, 65(6): 865–879. https://doi.org/10.1016/j.addr.2012.10.010

[101] Yang, Y., Ren, R. R., Chen, Q. Q., et al. *Coptis chinensis* polysaccharides dynamically influence the paracellular absorption pathway in the small intestine by modulating the intestinal mucosal immunity microenvironment. *Phytomedicine*, **2022**, 104: 154322. https://doi.org/10.1016/j.phymed.2022.154322

[102] Mujahid, M., Zubair, M., Yaqoob, A., et al. Formulation and evaluation of licorice-extract-enhanced chitosan, PVA, and gelatin-derived hydrogels for wound dressing. *Bioengineering*, **2025**, 12: 439. https://doi.org/10.3390/bioengineering12050439

[103] Zhao, L. C., Sun, D. D., Lu, H. B., et al. *In vitro* characterization of pH-sensitive *Bletilla striata* polysaccharide copolymer micelles and enhanced tumour suppression *in vivo*. *Journal of Pharmacy and Pharmacology*, **2018**, 70: 797–807. https://doi.org/10.1111/jphp.12888

[104] Zhou, B. Q., Zhang, W., Wu, Y. J., et al. Improved efficacy of *Panax notoginseng* saponin loaded into BSP/alginate microspheres for the treatment of alcoholic gastric ulcers. *International Journal of Pharmaceutics*, **2021**, 596: 120218. https://doi.org/10.1016/j.ijpharm.2021.120218

[105] Wu, Y. J., Zhang, W., Huang, J. Y., et al. Mucoadhesive improvement of alginate microspheres as potential gastroretentive delivery carrier by blending with *Bletilla striata* polysaccharide. *International Journal of Biological Macromolecules*, **2020**, 156: 1191–1201. https://doi.org/10.1016/j.ijbiomac.2019.11.156

[106] Sousa de Almeida, M., Susnik, E., Drasler, B., et al. Understanding nanoparticle endocytosis to improve targeting strategies in nanomedicine. *Chemical Society Reviews*, **2021**, 50: 5397–5434. https://doi.org/10.1039/d0cs01127d

[107] Canton, I., Battaglia, G. Endocytosis at the nanoscale. *Chemical Society Reviews*, **2012**, 41: 2718–2739. https://doi.org/10.1039/c2cs15309b

[108] Makhani, E. Y., Zhang, A., Haun, J. B. Quantifying and controlling bond multivalency for advanced nanoparticle targeting to cells. *Nano Convergence*, **2021**, 8: 38. https://doi.org/10.1186/s40580-021-00288-1

[109] Mazumdar, S., Chitkara, D., Mittal, A. Exploration and insights into the cellular internalization and intracellular fate of amphiphilic polymeric nanocarriers. *Acta Pharmaceutica Sinica B*, **2021**, 11: 903–924. https://doi.org/10.1016/j.apsb.2021.02.019

[110] Lee, N. K., Kim, S. N., Park, C. G. Immune cell targeting nanoparticles: A review. *Biomaterials Research*, **2021**, 25: 44.

https://doi.org/10.1186/s40824-021-00246-2
[111] Sun, Y. Z., Davis, E. Nanoplatforms for targeted stimuli-responsive drug delivery: A review of platform materials and stimuli-responsive release and targeting mechanisms. *Nanomaterials* (*Basel*), **2021**, 11: 746. https://doi.org/10.3390/nano11030746
[112] Zelepukin, I. V., Shevchenko, K. G., Deyev, S. M. Rediscovery of mononuclear phagocyte system blockade for nanoparticle drug delivery. *Nature Communications*, **2024**, 15: 4366. https://doi.org/10.1038/s41467-024-48838-5
[113] Soni, S. S., D'Elia, A. M., Alsasa, A., et al. Sustained release of drug-loaded nanoparticles from injectable hydrogels enables long-term control of macrophage phenotype. *Biomaterials Science*, **2022**, 10: 6951–6967. https://doi.org/10.1039/d2bm01113a
[114] Li, Y., Yang, H. Y., Lee, D. S. Biodegradable and injectable hydrogels in biomedical applications. *Biomacromolecules*, **2022**, 23: 609–618. https://doi.org/10.1021/acs.biomac.1c01552
[115] Ali, M., Namjoshi, S., Benson, H. A. E., et al. Dissolvable polymer microneedles for drug delivery and diagnostics. *Journal of Controlled Release*, **2022**, 347: 561–589. https://doi.org/10.1016/j.jconrel.2022.04.043
[116] Zeng, J. F., Huang, L. P., Xiong, H. Z., et al. Injectable decellularized cartilage matrix hydrogel encapsulating urine-derived stem cells for immunomodulatory and cartilage defect regeneration. *npj Regenerative Medicine*, **2022**, 7: 75. https://doi.org/10.1038/s41536-022-00269-w
[117] Cui, R. W., Zhang, L. H., Ou, R. Y., et al. Polysaccharide-based hydrogels for wound dressing: Design considerations and clinical applications. *Frontiers in Bioengineering and Biotechnology*, **2022**, 10: 845735. https://doi.org/10.3389/fbioe.2022.845735
[118] Doggwiler, V., Lanz, M., Paredes, V., et al. Tablet formulation with dual control concept for efficient colonic drug delivery. *International Journal of Pharmaceutics*, **2023**, 631: 122499. https://doi.org/10.1016/j.ijpharm.2022.122499
[119] Hodge, J. G., Zamierowski, D. S., Robinson, J. L., et al. Evaluating polymeric biomaterials to improve next generation wound dressing design. *Biomaterials Research*, **2022**, 26: 50. https://doi.org/10.1186/s40824-022-00291-5
[120] Chen, Q., Xiao, Z. S., Wang, C., et al. Microneedle patches loaded with nanovesicles for glucose transporter-mediated insulin delivery. *ACS Nano*, **2022**, 16: 18223–18231. https://doi.org/10.1021/acsnano.2c05687
[121] Kurt, E., Segura, T. Nucleic acid delivery from granular hydrogels. *Advanced Healthcare Materials*, **2022**, 11: e2101867. https://doi.org/10.1002/adhm.202101867
[122] Radmanesh, F., Sadeghi Abandansari, H., Ghanian, M. H., et al. Hydrogel-mediated delivery of microRNA-92a inhibitor polyplex nanoparticles induces localized angiogenesis. *Angiogenesis*, **2021**, 24: 657–676. https://doi.org/10.1007/s10456-021-09778-6
[123] Wang, H., Fu, Y. X., Mao, J. Z., et al. Strong and tough supramolecular microneedle patches with ultrafast dissolution and rapid-onset capabilities. *Advanced Materials*, **2022**, 34: e2207832. https://doi.org/10.1002/adma.202207832
[124] Zhao, F. L., Wu, D., Yao, D., et al. An injectable particle-hydrogel hybrid system for glucose-regulatory insulin delivery. *Acta Biomaterialia*, **2017**, 64: 334–345. https://doi.org/10.1016/j.actbio.2017.09.044
[125] Bayer, I. S. Controlled drug release from nanoengineered polysaccharides. *Pharmaceutics*, **2023**, 15: 1364. https://doi.org/10.3390/pharmaceutics15051364
[126] Zhang, Z. C., Fu, L. W., Zheng, Y. Z., et al. Antilipotoxic framework nucleic acid-loaded injectable hydrogel microspheres for the targeted delivery of miR-34a-5p inhibitors to attenuate dietary fat-associated osteoarthritis. *Chemical Engineering Journal*, **2025**, 522: 168281. https://doi.org/10.1016/j.cej.2025.168281
[127] Wen, Z. J., Kang, L., Fu, H. D., et al. Oral delivery of porous starch-loaded bilayer microgels for controlled drug delivery and treatment of ulcerative colitis. *Carbohydrate Polymers*, **2023**, 314: 120887. https://doi.org/10.1016/j.carbpol.2023.120887
[128] Liu, Y. J., Xu, J., Guo, Y. Q. Natural polysaccharide-based nano-drug delivery systems: Innovative strategies and research advances in cancer therapy-a review. *International Journal of Biological Macromolecules*, **2025**, 321: 146081. https://doi.org/10.1016/j.ijbiomac.2025.146081
[129] Wang, J., Viola, M., Migliorini, C., et al. Polysaccharide-based nanogels to overcome mucus, skin, cornea, and blood-brain barriers: A review. *Pharmaceutics*, **2023**, 15: 2508. https://doi.org/10.3390/pharmaceutics15102508
[130] Zhang, X. T., Li, L. F., Fung, H., et al. Critical review of the criterion of polysaccharide purity. *Carbohydrate Polymers*, **2025**, 352: 123187. https://doi.org/10.1016/j.carbpol.2024.123187
[131] Zhang, M., Ma, H., Wang, X. J., et al. Polysaccharide-based nanocarriers for efficient transvascular drug delivery. *Journal of Controlled Release*, **2023**, 354: 167–187. https://doi.org/10.1016/j.jconrel.2022.12.051
[132] Meng, Q. Y., Zhong, S. L., Gao, Y., et al. Advances in polysaccharide-based nano/microcapsules for biomedical applications: A review. *International Journal of Biological Macromolecules*, **2022**, 220: 878–891. https://doi.org/10.1016/j.ijbiomac.2022.08.129
[133] Zoratto, N., Montanari, E., Viola, M., et al. Strategies to load therapeutics into polysaccharide-based nanogels with a focus on microfluidics: A review. *Carbohydrate Polymers*, **2021**, 266: 118119. https://doi.org/10.1016/j.carbpol.2021.118119
[134] Greco, A., Gabold, B., Chen, S., et al. Microfluidic mixing as platform technology for production of chitosan nanoparticles loaded with different macromolecules. *European Journal of Pharmaceutics and Biopharmaceutics*, **2023**, 188: 170–181. https://doi.org/10.1016/j.ejpb.2023.05.010
[135] Operti, M. C., Bernhardt, A., Sincari, V., et al. Industrial scale manufacturing and downstream processing of PLGA-based nanomedicines suitable for fully continuous operation. *Pharmaceutics*, **2022**, 14: 276. https://doi.org/10.3390/pharmaceutics14020276
[136] Loh, J. M., Lim, Y. J. L., Tay, J. T., et al. Design and fabrication of customizable microneedles enabled by 3D printing for biomedical applications. *Bioactive Materials*, **2024**, 32: 222–241. https://doi.org/10.1016/j.bioactmat.2023.09.022
[137] He, Y., Chen, N. X., Zang, M. M., et al. Glucose-responsive insulin microneedle patches for long-acting delivery and release visualization. *Journal of Controlled Release*, **2024**, 368: 430–443. https://doi.org/10.1016/j.jconrel.2024.03.001