Synthetic Biology Innovations in Designing Cellulose-Based Smart Drug Delivery Systems

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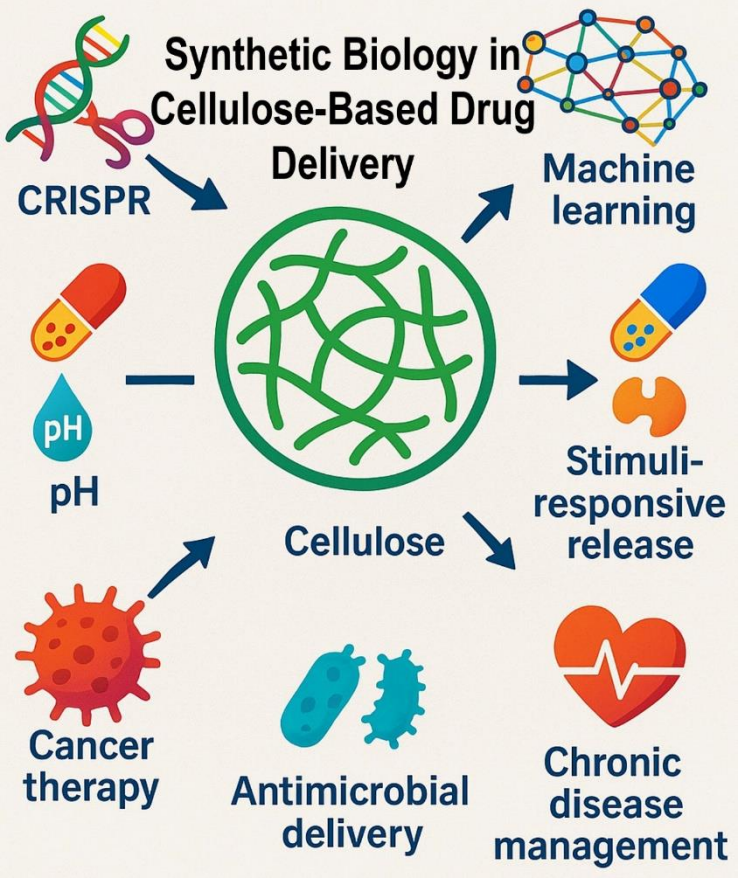
GRAPHICAL ABSTRACT



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The integration of synthetic biology with cellulose-based materials has paved the way for groundbreaking advancements in smart drug release and delivery systems. Synthetic biology, through precise genetic engineering and the creation of programmable biological circuits, enables the development of drug carriers that can respond dynamically to specific physiological cues, such as pH changes. For example, the contrast in pH between the stomach (pH ~1.5 to 3.5) and the intestines (pH ~6 to 7.5) has been exploited in cellulose-based systems to achieve site-specific drug release. Cellulose offers an ideal platform for constructing these responsive drug delivery systems. This review explores recent innovations in genetically engineered cellulose, functionalization strategies *via* synthetic biology, and advanced biofabrication techniques such as 3D bioprinting and microfluidics. Applications of these systems span cancer therapeutics, antimicrobial treatments, chronic disease management, and emerging areas like personalized medicine and gene therapy. Challenges related to biocompatibility, scalability, and regulatory approval persist. Future directions involving CRISPR-Cas9-mediated cellulose modification, machine learning for optimized drug release, and sustainable production strategies highlight the transformative potential of these systems in precision medicine. This review provides comprehensive insights into the current state and future prospects of cellulose-based smart drug delivery, offering a roadmap for advancing next-generation therapeutics.

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Keywords: Synthetic biology; Cellulose-based drug delivery; Smart drug delivery systems; Genetically engineered cellulose; Stimuli-responsive drug release; Biofabrication techniques; Personalized medicine; CRISPR-Cas9 functionalization

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INTRODUCTION

The convergence of synthetic biology and material science has opened unprecedented avenues in the development of smart drug delivery systems. Synthetic biology, in this context, refers to the design and engineering of new biological systems or the modification of existing ones through genetic manipulation, allowing for the creation

of programmable biological circuits that respond to specific cues. Unlike traditional biology, which primarily focuses on understanding and manipulating naturally occurring biological systems, synthetic biology enables the construction of novel systems with enhanced or even artificial capabilities, such as responsive drug release. Through the precise manipulation of genetic circuits and metabolic pathways, synthetic biology offers innovative solutions for creating highly responsive drug delivery platforms. At the forefront of these materials is cellulose, a biopolymer celebrated for its biodegradability, mechanical strength, and biocompatibility. Its structural versatility makes cellulose an ideal candidate for modifications that enable controlled drug release, targeted delivery, and environmental responsiveness (Fazal *et al.* 2023). As synthetic biology techniques, which involve engineered biological systems capable of precise control and adaptation, evolve, they have begun to revolutionize how cellulose can be engineered at the molecular level to develop systems that react to specific biological cues. This fusion promises to enhance the efficacy and safety of therapeutic interventions, especially in treating complex diseases like cancer, where precision in drug targeting is critical (Govindaraj 2021). For example, synthetic biology-driven cellulose nanoparticles have been engineered to respond to the acidic pH of tumors, selectively releasing chemotherapeutic agents at the tumor site, thereby reducing systemic toxicity (Mohammadpanah *et al*. 2025). In addition, Azimi *et al.* (2024) developed a bio-based and bioactive nanofibrous patch composed of bacterial cellulose and chitin nanofibrils for tympanic membrane repair, demonstrating excellent cytocompatibility, non-irritation in vivo, and improved antimicrobial and proinflammatory responses, indicating its potential for tissue regeneration and healing (Azimi *et al*. 2024).

Encapsulation refers to the process of enclosing a therapeutic agent within a protective carrier material, which in this case is cellulose. This technique is vital for controlling the release of drugs in response to various stimuli such as pH, temperature, or enzymatic activity. In cellulose-based systems, the drug is encapsulated within the cellulose matrix, providing protection from degradation before reaching the target site. The encapsulated drug is then gradually released in a controlled manner when the system responds to specific environmental triggers, such as changes in pH or the presence of particular enzymes. This approach ensures that the therapeutic agent is released at the optimal site, enhancing drug efficacy while minimizing side effects.

This review explores recent innovations at the intersection of synthetic biology and cellulose-based smart drug delivery systems, focusing on various modification strategies, including (a) changes to the physical structure of the cellulosic material, (b) chemical derivatization of cellulose molecules, and (c) the use of cellulose in combination with other chemicals that respond to specific stimuli. These approaches enable targeted delivery, controlled release, and stimuli-responsive behavior, addressing key challenges in current drug delivery systems. The review highlights the transformative potential of these technologies and assesses their clinical implications, including therapeutic benefits and limitations. By providing authoritative insights, this review aims to guide future research and advance the development of next-generation cellulose-based drug delivery platforms.

SYNTHETIC BIOLOGY AND CELLULOSE IN DRUG DELIVERY

Synthetic Biology in Smart Drug Delivery

Synthetic biology is revolutionizing biomedical science by enabling the design of biological systems with programmable functions. Through genetic engineering and

molecular manipulation, researchers construct synthetic circuits that control cellular behavior, allowing precise drug delivery in response to physiological cues. These circuits can be tailored to release therapeutic agents in specific environments, such as tumor tissues or inflamed areas, thereby minimizing systemic side effects and enhancing treatment efficacy. A notable example involves engineered bacteria designed to produce anti-cancer compounds directly within tumors, triggered by environmental signals like hypoxia (Cao and Liu 2020). Zhang *et al*. (2022) developed a biomimetic nanoreactor encapsulated self-healing hydrogel with glucose-responsive catalytic activity, combining antibacterial defense and hemostasis through a metal-organic framework-based nanocatalyst loaded with glucose oxidase, which triggers the generation of radical dotOH to kill bacteria while simultaneously promoting hemostasis by utilizing glucose from blood. Ito *et al*. (2024) developed a strategy combining epigenetic data with sequence-based prediction tools to improve CRISPR/Cas9-mediated gene editing efficiency in human T cells, showing that targeting epigenetically closed regions with adjacent gRNAs and pretreatment with IL-7 enhances gene-editing outcomes. Additionally, synthetic gene circuits can be externally regulated by stimuli such as light, temperature, or metabolites, providing dynamic control over drug release (Yi *et al.* 2025).

Cellulose as a Biomaterial in Drug Delivery

Cellulose, the most abundant natural polymer, offers exceptional potential in biomedical applications due to its biocompatibility, biodegradability, and structural versatility. Its capacity to form diverse morphologies—fibers, films, hydrogels, and nanostructures—makes it a highly adaptable platform for drug delivery systems. Furthermore, cellulose's high mechanical strength and non-toxic nature ensure its stability and safety in medical use (Hasanin 2022). Advances in synthetic biology have further expanded the potential of cellulose polymers. Through genetic engineering, bacteria can be modified to produce cellulose with tailored properties, while chemical modifications such as carboxymethylation enhance drug-binding capacities. Nanocellulose, with its large surface area and superior mechanical characteristics, allows for optimized drug encapsulation and controlled release profiles (Mujtaba *et al.* 2023).

The integration of synthetic biology with cellulose materials creates highly responsive drug delivery systems. For instance, engineered bacteria embedded within cellulose matrices can produce therapeutic agents on demand, while synthetic circuits can make cellulose scaffolds sensitive to environmental cues like pH shifts or enzymatic activity (Tang *et al.* 2021). This fusion opens new avenues for personalized, adaptive drug delivery, marking a transformative step in modern therapeutics.

INNOVATIONS IN CELLULOSE-BASED SMART DRUG DELIVERY SYSTEMS

Genetically Engineered Cellulose for Targeted Drug Delivery

Genetically engineered cellulose offers precise control in drug delivery by leveraging bacterial strains such as *Komagataeibacter xylinus* to produce nanofibrous, biocompatible cellulose tailored for therapeutic use. Through synthetic biology, cellulose can be modified to carry functional peptides or binding motifs, targeting specific tissues such as tumors or inflamed areas (Chung *et al.* 2022). For example, pH-responsive cellulose matrices release drugs selectively in acidic tumor microenvironments, enhancing efficacy while reducing systemic toxicity (Ning *et al.* 2021).

Mechanisms of Release in Cellulose-Based Systems

The controlled release of therapeutic agents from cellulose-based drug delivery systems is can be influenced the chemical and physical modifications made to the cellulose matrix. In particular, one common mechanism is pH-induced release. Cellulose materials can be modified with weak acid groups such as carboxyl (-COOH) groups, which are sensitive to pH changes. These modifications are especially useful in creating pH-responsive drug delivery systems.

For instance, in acidic environments such as the stomach (pH 1.5 to 3.5), the carboxyl groups within the cellulose matrix become protonated, decreasing electrostatic repulsion among polymer chains. This reduces the swelling and permeability of the cellulose network, thus limiting drug release and preventing premature delivery in the stomach. Conversely, in more neutral or basic environments, such as the intestines (pH 6 to 7.5), the carboxyl groups become deprotonated and negatively charged. This results in increased electrostatic repulsion and swelling of the cellulose structure, enhancing its porosity and permeability, thereby facilitating the controlled and sustained release of the encapsulated drug specifically in the intestinal region.

These modifications allow for targeted and site-specific release, minimizing side effects and enhancing therapeutic efficacy. The ability to control the release profile by altering the chemical structure of the cellulose matrix is a key advantage of synthetic biology in the development of drug delivery systems.

Functionalization Strategies *via* Synthetic Biology

Synthetic biology enables advanced functionalization of cellulose, introducing reactive groups through enzymatic modifications, and gene circuit designs to control drug attachment and release.

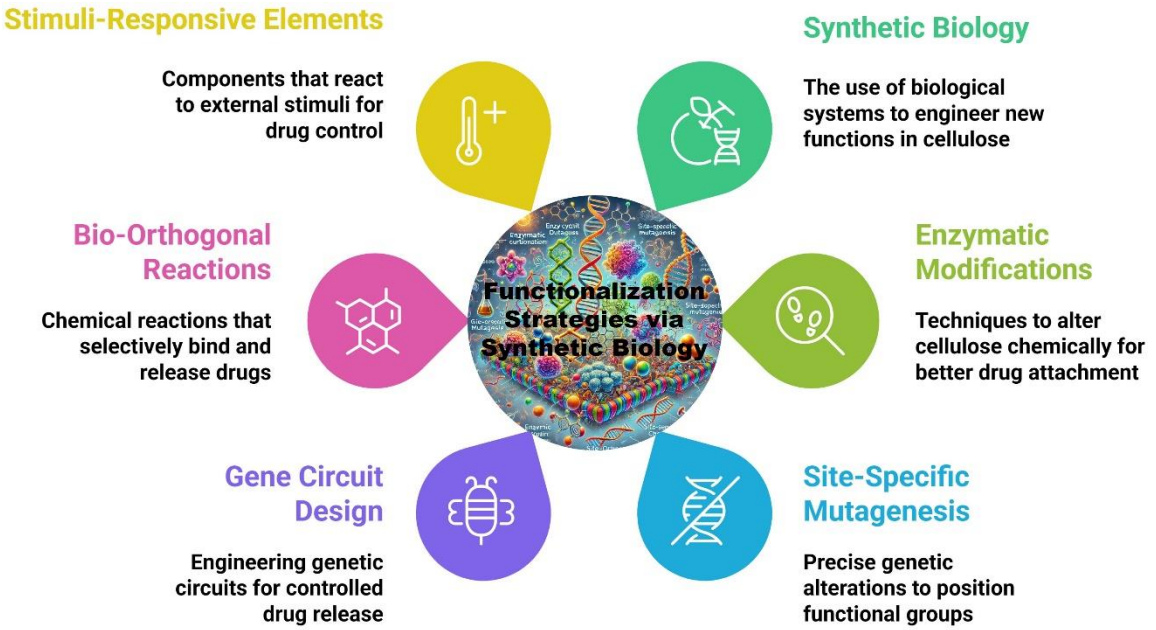

Fig. 1. Functionalization strategies *via* synthetic biology enhance cellulose-based drug delivery systems through stimuli-responsive elements, enzymatic modifications, gene circuit design, and bio-orthogonal reactions for precise and controlled therapeutic release

Techniques such as bio-orthogonal chemistry allow for drug release in response to specific physiological triggers, including enzymes or metabolites (Liu *et al.* 2023). Additionally, stimuli-responsive elements, including light- or temperature-sensitive moieties, are integrated into cellulose structures for external regulation of drug delivery (Sampath Udeni Gunathilake *et al.* 2020; Shi *et al*. 2022). In addition, Ali *et al.* (2024) developed novel near-infrared (NIR)-responsive hydrogels using reactive oxygen species-cleavable thioketal cross-linkers and co-encapsulated indocyanine green (ICG) and doxorubicin (DOX), which demonstrated spatiotemporal drug release and enhanced chemotherapeutic effects on Hela cancer cells upon NIR-irradiation, with minimal toxicity to healthy cells (Ali *et al*. 2024). These strategies broaden the therapeutic potential of cellulose-based systems across diverse medical fields. Figure 1 illustrates key strategies used in synthetic biology to functionalize cellulose for smart drug delivery systems.

Biofabrication Techniques for Advanced Drug Delivery

Biofabrication techniques, such as 3D bioprinting and microfluidics, have revolutionized cellulose-based drug delivery, enabling precise control over structure and function. These methods create porous scaffolds and nanocellulose particles optimized for drug encapsulation and controlled release (Thang and Kim 2025). Zingale *et al.* (2024) developed a soft, biodegradable, and bioadhesive hydrogel scaffold using coaxial 3D printing to deliver curcumin-loaded liposomes and resveratrol for diabetic retinopathy treatment, demonstrating sustained drug release, biocompatibility with retinal cells, and potential for minimally invasive, prolonged drug delivery (Zingale *et al*. 2024). Nanocellulose's high surface area and stability make it ideal for navigating complex biological environments. Furthermore, integrating genetically engineered cells within biofabricated scaffolds leads to living materials capable of dynamic, on-demand therapeutic release (Lu *et al.* 2024), pushing the boundaries of personalized medicine. Figure 2 illustrates the integration of biofabrication techniques, such as microfluidics and 3D bioprinting, with genetic engineering approaches, including engineered cells and therapeutic protein production.

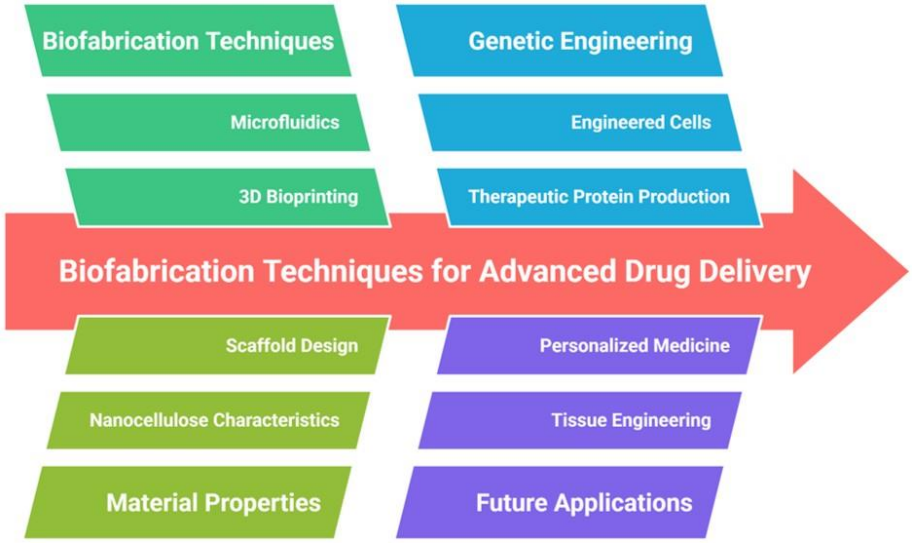

Fig. 2. Integration of biofabrication techniques and genetic engineering for advanced cellulose-based drug delivery, enabling precise scaffold design, controlled drug release, and applications in personalized medicine and tissue engineering

These strategies enhance the design of scaffolds, optimize nanocellulose characteristics, and improve material properties for smart drug delivery systems. The convergence of these technologies opens new avenues for personalized medicine, tissue engineering, and other future applications in precision therapeutics.

APPLICATIONS

Cancer Therapeutics

Cellulose-based smart drug delivery systems, driven by synthetic biology, have shown significant promise in cancer therapeutics by enhancing drug targeting and reducing systemic toxicity. Genetically engineered cellulose materials can be functionalized to respond to specific tumor microenvironment conditions, such as acidic pH or overexpressed enzymes such as matrix metalloproteinases. For example, pH-responsive cellulose nanoparticles have been developed to release chemotherapeutic agents selectively in acidic tumor sites, ensuring minimal impact on healthy tissues (Ehsanimehr *et al.* 2021). In addition to pH-sensitive systems, cellulose scaffolds have been engineered to release anti-cancer drugs in response to specific enzymatic triggers present in the tumor milieu, enhancing site-specific delivery (Wang *et al.* 2022). Furthermore, synthetic gene circuits embedded in bacterial cellulose matrices can regulate the timed release of chemotherapeutics (Omer *et al.* 2022), thus allowing for a sustained and controlled drug release profile.

Antimicrobial and Antiviral Drug Delivery

The use of synthetic biology-driven cellulose systems has significantly advanced the treatment of antimicrobial resistance and viral infections (Zhao *et al.* 2023). These systems can be classified based on their drug delivery mechanisms, which include the use of antimicrobial peptides, antibiotics, and quorum-sensing inhibitors. Engineered cellulose hydrogels infused with antimicrobial peptides or antibiotics respond dynamically to the presence of bacterial or viral pathogens, releasing their therapeutic payload only when needed. This targeted release mechanism minimizes the development of resistance and ensures precise action at the infection site (Gong *et al.* 2024). For example, cellulose matrices functionalized with quorum-sensing inhibitors can disrupt bacterial communication, curbing biofilm formation and improving antibiotic efficacy (Qu *et al.* 2024). In antiviral applications, cellulose nanofibers carrying antiviral agents release their payload in response to specific viral proteins or environmental cues including pH or temperature fluctuations associated with viral replication (Homaeigohar *et al.* 2023). A direct comparison of cellulose-based carriers with traditional materials such as synthetic polymers highlights cellulose's superior biodegradability and biocompatibility, making it an ideal candidate for environmentally friendly and effective drug delivery systems.

Chronic Disease Management

Synthetic biology and cellulose-based drug delivery systems have shown great promise in managing chronic diseases such as diabetes, cardiovascular conditions, and neurodegenerative diseases. These systems can be categorized based on the disease type and delivery mechanisms, such as glucose-responsive insulin delivery for diabetes, biomarker-responsive drug release for cardiovascular diseases, and brain-targeted release for neurodegenerative disorders. In diabetes management, cellulose hydrogels embedded

with glucose-responsive elements release insulin in response to fluctuating blood sugar levels, providing real-time control without the need for continuous patient intervention (Zhang *et al.* 2022). This system improves patient compliance and reduces the risk of hypoglycemia. For cardiovascular diseases, cellulose-based carriers have been designed to deliver drugs such as statins or antihypertensive agents in response to biomarkers like cholesterol levels or blood pressure fluctuations, offering targeted and sustained therapy (Silva *et al.* 2022). Additionally, in neurodegenerative disorders, cellulose nanoparticles can cross the blood-brain barrier and release neuroprotective agents in response to oxidative stress or amyloid-beta accumulation, addressing the underlying pathology of diseases such as Alzheimer's (Fang *et al.* 2025). Compared to traditional drug delivery materials, cellulose-based carriers offer enhanced biocompatibility, reduced toxicity, and the potential for controlled, on-demand drug release tailored to the patient's specific needs.

Emerging Areas: Personalized Medicine and Gene Therapy

The intersection of synthetic biology and cellulose-based systems is unlocking new possibilities in personalized medicine and gene therapy. By incorporating patient-specific genetic or biochemical markers, cellulose matrices can be tailored to release therapeutics in a highly individualized manner. For instance, personalized cellulose scaffolds have been engineered to release drugs or genetic material based on a patient's unique metabolic profile, ensuring optimized therapeutic outcomes (Geraili *et al.* 2021).

In gene therapy, cellulose-based carriers are being explored for the safe and efficient delivery of nucleic acids, such as siRNA, mRNA, or CRISPR-Cas components. These carriers can be designed to release their genetic payload in response to intracellular cues, enhancing gene-editing precision, and reducing off-target effects (Dubey and Mostafavi 2023).

CHALLENGES AND FUTURE PERSPECTIVES

Current Limitations in Design and Application

Despite their promise, cellulose-based smart drug delivery systems face critical challenges. Precise molecular-level functionalization is difficult to control, hindering scalability and product consistency. Functional modifications can compromise biocompatibility, triggering immune responses, or toxicity. Stability under physiological conditions, such as in the bloodstream or gastrointestinal tract, also limits long-term efficacy. Additionally, navigating regulatory approval for biologically engineered materials, especially those involving genetically modified organisms, remains complex. The key challenges, current mitigation strategies, and future research opportunities in synthetic biology-driven cellulose-based smart drug delivery systems are summarized in Table 1.

Future Directions and Opportunities

The future of cellulose-based smart drug delivery systems is promising, driven by advances in synthetic biology and emerging technologies. CRISPR-Cas9-mediated genetic engineering and high-throughput screening are expected to refine cellulose modifications, improving their precision and reliability in therapeutic applications (Mathieu *et al.* 2023). Additionally, integrating machine learning and computational modeling can optimize synthetic circuit design, tailoring drug release profiles to individual patient needs (Gormley

2024). The development of multi-functional cellulose materials that can sense, respond to, and modulate biological environments is an exciting frontier. Hybrid materials combining cellulose with other biopolymers or nanomaterials can enhance mechanical strength and broaden functional applications in drug delivery, tissue engineering, and biosensing (Ramezani *et al*. 2024). Moreover, bio-orthogonal chemistry offers potential for *in situ* functionalization, enabling dynamic, post-administration adaptability in therapeutic systems.

Table 1. Challenges, Current Solutions, and Future Directions in Synthetic Biology-Driven Cellulose-Based Smart Drug Delivery Systems

Challenge	Description	Current Solutions/Strategies	Future Opportunities
Precision in Cellulose Functionalization	Difficulty in achieving uniform and reproducible modifications at the molecular level.	Use of enzymatic modifications and site-specific mutagenesis for improved precision.	Integration of CRISPR-based tools for highly targeted cellulose engineering (Li *et al.* 2024).
Biocompatibility and Immunogenicity	Modified cellulose may elicit unexpected immune responses or toxicity in sensitive tissues.	Surface passivation and bio-inert coatings to reduce immunogenicity.	Development of personalized biocompatibility screening platforms (McBride *et al.* 2024).
Stability in Physiological Conditions	Engineered cellulose may degrade or lose functionality in complex biological environments.	Cross-linking strategies and composite material formulations to enhance stability.	Creation of dynamic, self-healing cellulose materials responsive to physiological stress (Ashammakhi *et al.* 2021).
Regulatory Challenges	Complex approval processes for biologically engineered materials integrating living systems.	Early collaboration with regulatory bodies and preclinical standardization protocols.	Development of global regulatory frameworks for synthetic biology-based therapeutics (Li *et al.* 2021).
Scalability and Manufacturing	Difficulties in scaling up production while maintaining material consistency and functionality.	Optimization of bacterial cellulose production and automation of synthesis processes.	Adoption of sustainable, eco-friendly manufacturing pipelines with bio-reactors (Makurat-Kasprolewicz *et al.* 2024).
Controlled Drug Release Dynamics	Achieving precise, responsive, and sustained drug release profiles across different applications.	Design of synthetic gene circuits and stimuli-responsive elements for controlled release.	Integration of AI and machine learning for predictive modeling of release kinetics (Visan and Negut 2024).
Cost-Effectiveness and Commercialization	High production costs limiting broad clinical and commercial application.	Utilization of low-cost genetic tools and scalable bioprocessing techniques.	Public-private partnerships for cost-sharing and market expansion strategies (Zaheer *et al.* 2021).

Vision for Clinical Translation and Commercialization

Translating cellulose-based smart drug delivery systems from the lab to clinical use requires standardized manufacturing protocols and rigorous quality control to ensure reproducibility and safety. Interdisciplinary collaboration among researchers, clinicians, and regulatory bodies is crucial for establishing evaluation and approval guidelines for these advanced systems. Commercialization will hinge on cost-effective production methods, such as sustainable bacterial cellulose sourcing and affordable genetic engineering tools, to facilitate large-scale pharmaceutical applications (Ciolacu *et al.* 2020). Partnerships with industry can expedite the development of disease-specific delivery platforms, expanding market potential and improving patient outcomes.

Looking forward, the integration of cellulose-based systems into personalized medicine holds transformative potential. Designing carriers tailored to individual genetic and biochemical profiles will revolutionize healthcare, delivering more precise, effective, and safer therapies, thereby realizing the full promise of synthetic biology in modern medicine (Bigham *et al.* 2024).

CONCLUSIONS

The fusion of synthetic biology with cellulose-based materials has driven significant advancements in smart drug delivery systems. Genetically engineered cellulose, particularly from *Komagataeibacter xylinus*, offers precise control over drug release, responding to specific biological cues like pH changes and enzymatic activity. This targeted approach enhances therapeutic efficacy while minimizing systemic toxicity, making it particularly effective in cancer treatments and chronic disease management. Synthetic biology techniques, such as gene circuit design and bio-orthogonal chemistry, have enabled the functionalization of cellulose for dynamic, stimuli-responsive drug delivery.

Biofabrication methods, including 3D bioprinting and microfluidics, have further refined the structural and functional capabilities of cellulose-based carriers, expanding their applications to personalized medicine and gene therapy. Despite these innovations, challenges remain, particularly in ensuring consistent biocompatibility, scaling up production, and meeting regulatory standards for synthetic biology-based therapeutics.

Future directions point toward the integration of CRISPR-Cas9 for precise cellulose modifications and machine learning to optimize drug release profiles. Sustainable production methods and interdisciplinary collaborations will be critical for clinical translation. Ultimately, these innovations hold the potential to transform precision medicine, offering more effective, safer, and personalized therapeutic solutions that align with the evolving needs of modern healthcare.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest regarding the publication of this review article. No financial, personal, or professional relationships influenced the research, writing, or conclusions presented in this manuscript.

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