Prodrugs and Unsaturated Fatty Acid Prodrugs in Drug Delivery Systems: A Survey

Abstract

This survey paper explores the innovative role of prodrugs, particularly unsaturated fatty acid prodrugs, in enhancing drug delivery systems for chronic inflammation treatment. Prodrugs, designed to undergo metabolic conversion to release active drugs, address challenges of poor solubility, stability, and bioavailability, thus optimizing therapeutic efficacy. The integration of microplatform technologies, including nano-assembled microcapsules and enzyme-based capping systems, further enhances targeted delivery and controlled release. These advancements are crucial for managing chronic inflammation, where conventional drugs often face limitations such as rapid metabolism and systemic toxicity. The paper systematically reviews the design, development, and activation mechanisms of prodrugs, emphasizing their potential to improve bioavailability and therapeutic outcomes. Additionally, the survey highlights the significance of nanotechnology in drug delivery, offering innovative solutions for solubility enhancement and precise targeting. Despite the promising advancements, challenges persist in the production and regulatory landscape, necessitating continued research to optimize drug delivery systems and ensure clinical applicability. Overall, this comprehensive exploration underscores the transformative potential of prodrugs in pharmaceutical sciences, paving the way for more effective and personalized therapeutic strategies.

1 Introduction

1.1 Concept of Prodrugs

Prodrugs are engineered to enhance the pharmacokinetic and pharmacodynamic properties of therapeutic agents, addressing limitations such as poor solubility, stability, and bioavailability. These compounds undergo metabolic conversion to release active drugs, improving efficacy and reducing toxicity in therapeutic interventions [1]. The design often involves chemical modifications, such as PUFAylation, where nucleoside analogs are conjugated with polyunsaturated fatty acids to create amphiphilic prodrugs, thus enhancing stability and therapeutic potential [1].

Prodrugs are pivotal in modern drug delivery systems, overcoming physiological barriers to improve the delivery of therapeutic agents to target sites. They have revitalized existing antibiotics, enhancing pharmacokinetic properties and addressing previously discarded drugs due to poor performance [2]. Furthermore, prodrugs enhance the solubility and stability of compounds with unfavorable chemical-physical properties, facilitating their application across various therapeutic contexts [3].

The versatility of prodrugs extends to their integration into advanced drug delivery systems, such as exosomes, which efficiently deliver diverse therapeutic cargoes to target cells [4]. This integration illustrates the potential of prodrugs to optimize therapeutic outcomes by ensuring effective delivery of active compounds to intended targets, marking a significant innovation in pharmaceutical sciences that enhances the efficacy and safety of drug treatments.

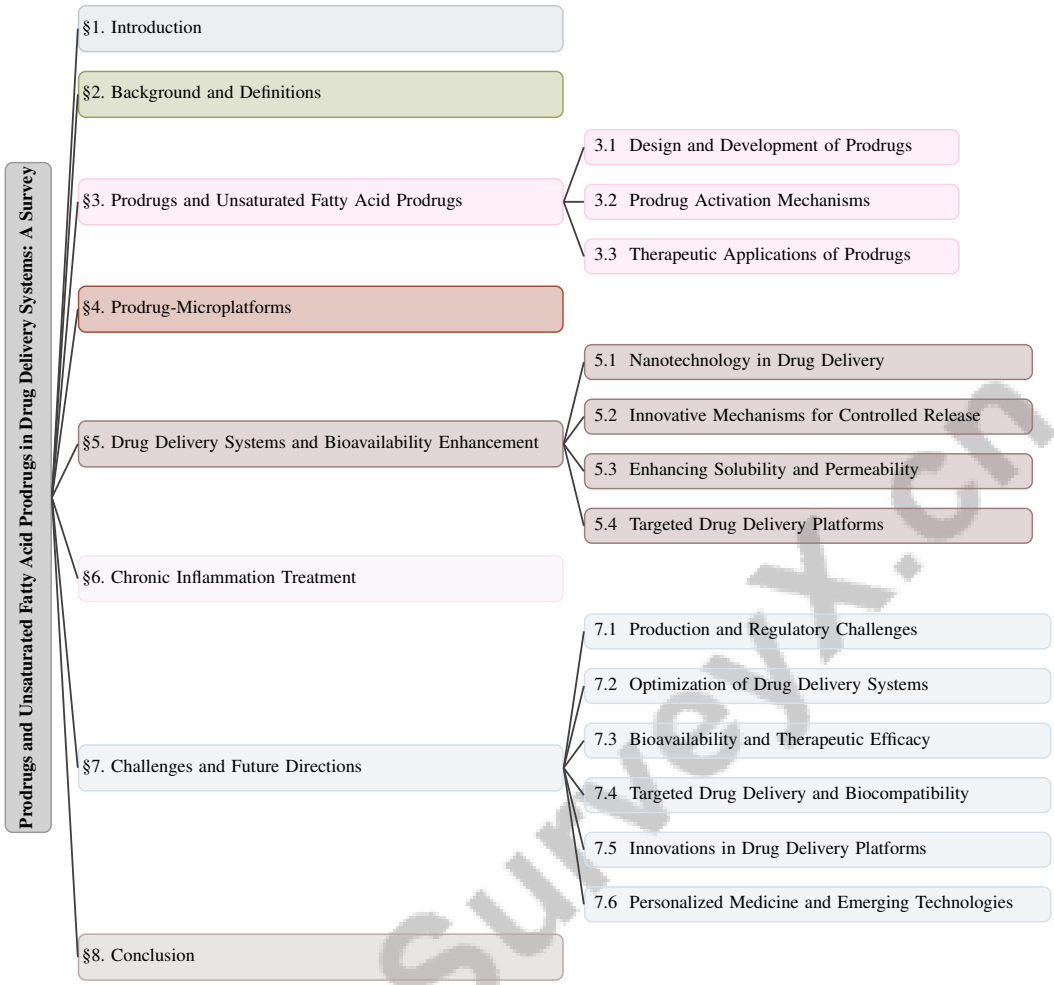


Figure 1: chapter structure

1.2 Relevance to Chronic Inflammation

Prodrugs are particularly relevant in treating chronic inflammation due to their ability to enhance therapeutic outcomes by overcoming conventional drug limitations. Chronic inflammation presents therapeutic challenges like poor bioavailability, rapid metabolism, and systemic toxicity, which undermine treatment efficacy. Factors such as inadequate absorption and swift clearance contribute to suboptimal plasma and tissue levels of therapeutic agents, such as curcumin. Innovative strategies, including complexed or encapsulated formulations and nanoparticles, are being explored to enhance drug delivery and bioavailability, thereby improving the potential of bioactive compounds to mitigate chronic inflammatory conditions [5, 6]. By improving solubility, stability, and permeability, prodrugs are designed to address these barriers, enhancing therapeutic efficacy.

A notable advantage of prodrugs in managing chronic inflammation is their potential to reduce gastrointestinal toxicity associated with nonsteroidal anti-inflammatory drugs (NSAIDs) while preserving therapeutic effects [7]. This is crucial as NSAIDs are commonly used for inflammatory conditions but are often limited by adverse side effects. Prodrugs can be tailored to release active agents specifically at inflammation sites, enhancing efficacy and minimizing systemic side effects.

Integrating prodrugs with advanced drug delivery systems, such as nanomaterials, further enhances their relevance by enabling precise targeting of inflamed sites, maximizing therapeutic effects, and minimizing adverse reactions [8]. This targeted approach is essential for managing chronic inflammation, allowing modulation of the inflammatory response while sparing healthy tissues [9]. The survey also highlights the role of endogenous bioactive lipids in the transition from acute

to chronic inflammation, indicating that prodrugs could modulate these lipids to develop novel therapeutic strategies [5].

The increasing prevalence of bacterial resistance complicates treatment options for chronic inflammation caused by resistant infections, underscoring the relevance of prodrugs in this context [2]. Prodrugs represent a versatile and promising approach to enhance drug delivery and therapeutic outcomes in chronic inflammation treatment [10]. Their application in chronic wounds, which fail to heal due to disrupted physiological processes, further illustrates their potential in addressing complex inflammatory conditions [11].

1.3 Structure of the Survey

This survey is meticulously organized to provide a comprehensive exploration of prodrugs, focusing on unsaturated fatty acid prodrugs and their integration into advanced drug delivery systems. The paper begins with an introduction to prodrugs, emphasizing their significance in pharmaceutical sciences and relevance to chronic inflammation treatment. The background and definitions section delves into fundamental concepts, mechanisms, and the importance of prodrugs, unsaturated fatty acid prodrugs, and prodrug-microplatforms.

The survey progresses to a detailed analysis of prodrug design and development, particularly unsaturated fatty acid prodrugs and their unique activation mechanisms, which enhance bioavailability and therapeutic delivery while minimizing toxicity [10, 12, 13, 14, 15]. It further explores the therapeutic applications of these prodrugs, emphasizing their role in managing chronic inflammation. Subsequently, the integration of prodrugs with microplatform technologies is analyzed, focusing on nano-assembled microcapsules, copolymeric nanoparticles, enzyme-based capping systems, and self-immolative chemistry.

The discussion then shifts to drug delivery systems and bioavailability enhancement, examining the role of nanotechnology, innovative mechanisms for controlled release, and strategies for enhancing solubility and permeability. This section also covers targeted drug delivery platforms. The paper addresses the specific role of prodrugs in treating chronic inflammation, identifying challenges and opportunities in current treatment strategies.

Finally, the survey concludes with a discussion on challenges and future directions in the field, including production and regulatory challenges, optimization of drug delivery systems, and the importance of bioavailability and therapeutic efficacy. The paper provides an in-depth examination of recent advancements in drug delivery platforms, emphasizing the transformative role of personalized medicine and emerging technologies, such as nanomaterials and exosomes. These innovations have significantly enhanced the efficacy and safety of drug delivery systems by enabling targeted, localized, and long-term delivery, addressing critical physicochemical challenges and improving patient outcomes in treating various diseases [8, 4, 16].The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Prodrugs: Definition and Mechanisms

Prodrugs are pharmacologically inactive compounds designed to convert into active pharmaceutical ingredients (APIs) through metabolic processes, thereby enhancing drug delivery and efficacy. This strategy addresses issues like poor solubility, low bioavailability, and inadequate targeting, broadening the therapeutic window and improving outcomes [2]. Activation mechanisms, including enzyme-responsive, redox-responsive, and hypoxia-responsive strategies, ensure precise drug release at target sites, crucial for therapies in chronic conditions [4]. pH-sensitive systems further optimize efficacy in environments with altered pH levels [11].

Advanced systems like bottlebrush prodrugs (BPDs) facilitate encapsulation and controlled release of multiple drugs, while diffusion-based spherical matrix-type drug carrier modeling (DMSM) refines drug delivery by accurately predicting molecular concentrations at receptor sites. This modeling, considering probabilistic absorbers, enhances drug transmission rates, minimizes toxicity, and improves therapeutic outcomes [10, 17, 18, 19, 20]. Prodrugs, as bioreversible derivatives of

APIs, enhance bioavailability and enable selective tissue targeting, optimizing absorption, distribution, metabolism, and elimination (ADME) to reduce toxicity and improve patient compliance [10, 15].

2.2 Unsaturated Fatty Acid Prodrugs

Unsaturated fatty acid prodrugs significantly advance pharmaceutical sciences by enhancing solubility, stability, and bioavailability of therapeutic agents. These prodrugs, synthesized by conjugating APIs with unsaturated fatty acids, improve pharmacokinetic profiles of drugs with poor solubility and stability [1]. This conjugation enhances permeability across biological membranes, crucial for effective drug delivery, particularly in chronic disease treatment where sustained release and targeted delivery are essential. Polyunsaturated fatty acids (PUFAs) in PUFAylation facilitate self-assembly into nanoparticles, maximizing therapeutic effects while minimizing systemic side effects [1].

These prodrugs can be integrated into various macromolecular architectures, optimizing drug delivery and therapeutic efficacy by enhancing intestinal absorption and minimizing toxicity [1]. Their versatility extends to potential use with exosomes, efficiently delivering diverse therapeutic cargoes to target cells [4]. This integration exemplifies how unsaturated fatty acid prodrugs optimize therapeutic outcomes by ensuring effective delivery of active compounds to intended targets.

2.3 Prodrug-Microplatforms

Prodrug-microplatforms integrate prodrug technology with advanced drug delivery systems, enhancing therapeutic efficacy through improved stability, bioavailability, and targeted delivery. These platforms utilize self-assembling prodrugs forming supramolecular nanostructures, optimizing absorption and distribution, facilitating site-specific targeting, and reducing toxicity [10, 16, 13, 15]. Self-emulsifying drug delivery systems (SEDDS) enhance oral bioavailability by creating stable emulsions that improve solubility and absorption of lipophilic drugs [21].

Diffusion-based spherical matrix-type drug carriers modulate drug release profiles for sustained effects while minimizing fluctuations. Incorporating binding reactions into diffusion models is crucial for understanding interactions between prodrugs and microplatforms, significantly altering drug release profiles and necessitating analytical predictions [17]. Mixed-charge pseudo-zwitterionic mesoporous silica nanoparticles (ZMSNs) exemplify the potential of prodrug-microplatforms, reducing protein adsorption and macrophage uptake, enhancing effectiveness as drug delivery systems [22].

Prodrug-microplatforms represent a cutting-edge advancement, providing sophisticated solutions to complex drug delivery challenges. They enhance pharmacokinetic properties, improve bioavailability, and enable targeted therapy through bioreversible modifications, facilitating optimal ADME of therapeutic agents [10, 14, 16, 13]. Their significance lies in integrating the benefits of prodrugs with advanced delivery technologies, enhancing therapeutic potential and safety across various medical applications.

3 Prodrugs and Unsaturated Fatty Acid Prodrugs

The exploration of prodrugs and their therapeutic applications requires a deep understanding of their design, development, and activation mechanisms, as well as the contexts in which they are utilized. Prodrugs enhance drug bioavailability, optimize pharmacokinetics, and improve site-specific targeting, leading to more effective treatments across various clinical scenarios [10, 23, 15, 14, 13]. They address limitations in traditional drug formulations by improving solubility, stability, and bioavailability, making prodrug design and development crucial in modifying APIs to enhance their pharmacokinetic and pharmacodynamic profiles.

This section explores the complexities of prodrug design and development, highlighting innovative strategies that optimize drug delivery systems. As illustrated in Figure 2, the hierarchical structure of prodrugs and unsaturated fatty acid prodrugs is detailed, showcasing their design and development, activation mechanisms, and therapeutic applications. The figure categorizes challenges and strategies in prodrug design, innovative approaches to enhance drug delivery, mechanisms for precise activation, and emerging techniques to improve therapeutic efficacy. By examining various methodologies in prodrug development, we can understand their role in enhancing therapeutic efficacy and addressing

drug formulation and delivery challenges, as well as the significant potential of prodrugs in addressing various medical conditions.

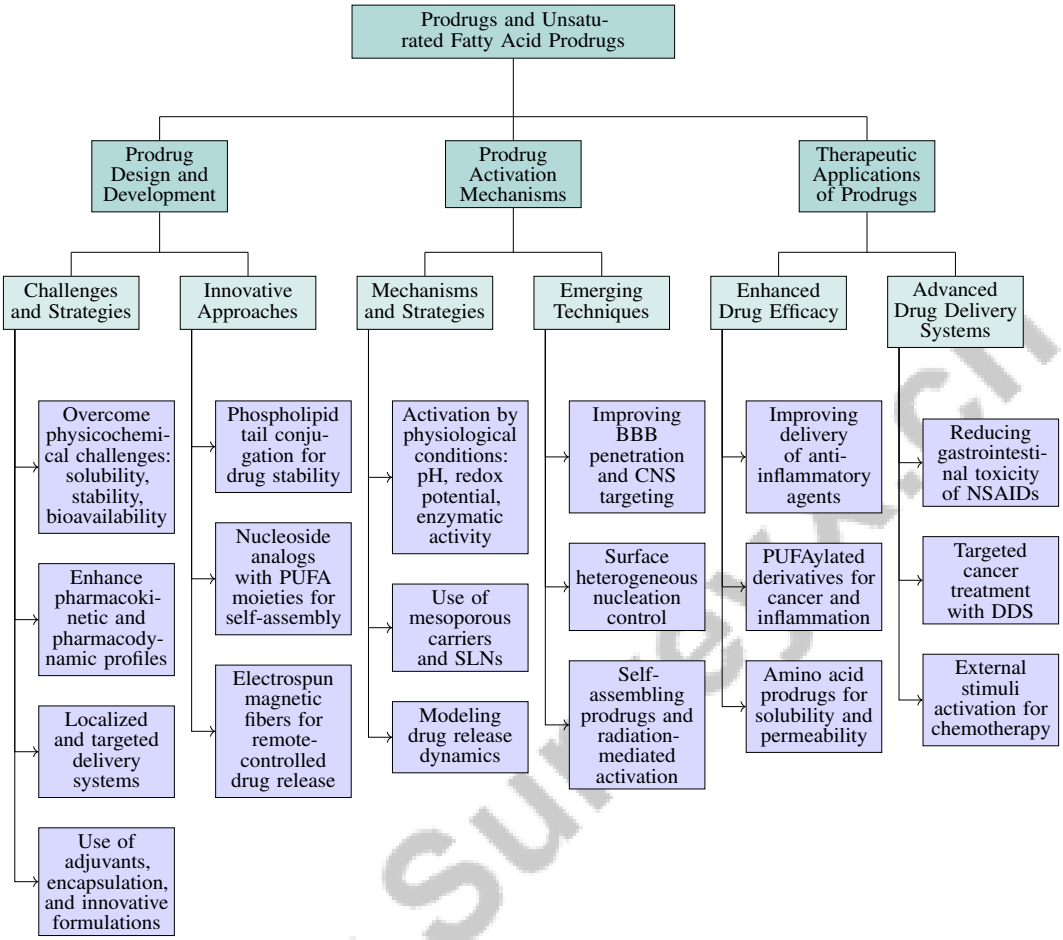


Figure 2: This figure illustrates the hierarchical structure of prodrugs and unsaturated fatty acid prodrugs, detailing their design and development, activation mechanisms, and therapeutic applications. It categorizes challenges and strategies in prodrug design, innovative approaches to enhance drug delivery, mechanisms for precise activation, and emerging techniques to improve therapeutic efficacy. Additionally, it highlights the role of prodrugs in enhancing drug efficacy and advanced drug delivery systems, showcasing their potential in addressing various medical conditions.

3.1 Design and Development of Prodrugs

The design and development of prodrugs are critical for overcoming physicochemical challenges that limit drug formulation, such as poor solubility, stability, and bioavailability. Enhancing the pharmacokinetic and pharmacodynamic profiles of APIs begins with identifying those needing modification, crucial for effective drug delivery systems that maximize efficacy and minimize side effects. Recent advancements, including long-term, localized, and targeted delivery systems, highlight the importance of overcoming physicochemical barriers and biological challenges in new therapies. Strategies like adjuvants, encapsulation techniques, and innovative formulations, especially for compounds like curcumin, are being explored to improve bioavailability and therapeutic outcomes. A focus on translatable research and self-emulsifying drug delivery systems (SEDDS) is essential for creating safer, more effective treatments [16, 21, 6]. Traditional prodrug approaches have evolved to incorporate modern strategies utilizing enzyme targeting and external stimuli for activation, ensuring precise release at targeted sites.

A notable strategy involves conjugating phospholipid tails to parent compounds, significantly improving drug loading efficiency and stability [24]. Additionally, synthesizing nucleoside analogs

with PUFA moieties allows self-assembly in aqueous media, forming nanoparticles that enhance solubility and permeability [1]. The integration of solid lipid nanoparticles (SLNs) further augments bioavailability by modulating interfacial properties during gastrointestinal digestion, as demonstrated with curcumin [25].

Innovative systems, such as electrospun magnetic fibers, enable remote-controlled activation and release of encapsulated drugs via alternating magnetic fields, providing a versatile platform for hydrophilic and hydrophobic drugs [26]. Advanced mathematical modeling, including the generalized random sequential adsorption (gRSA) model, studies the effects of polydispersity and macromolecule overlap on viral surfaces, contributing to optimizing drug delivery systems [27].

Analytical models like the Spherical Homogeneous Matrix Model and the M/M/1/1 queue model are instrumental in understanding drug release dynamics and receptor interactions, allowing for precise predictions and optimizations of drug delivery systems. This multidisciplinary approach, integrating principles from chemistry, biology, and engineering, is crucial for effective prodrug design and development. Strategies such as covalent modification and self-assembly enhance drug delivery, improve pharmacokinetic properties, and increase therapeutic efficacy. Specifically, integrating amino acids as prodrug moieties significantly boosts bioavailability, targets delivery to diseased tissues while minimizing toxicity, and circumvents rapid metabolism, addressing common limitations of existing therapeutic agents [13, 15].

As depicted in Figure 3, this figure illustrates the hierarchical structure of prodrug design and development, focusing on overcoming physicochemical challenges, employing innovative strategies, and utilizing advanced systems to enhance drug delivery and efficacy.

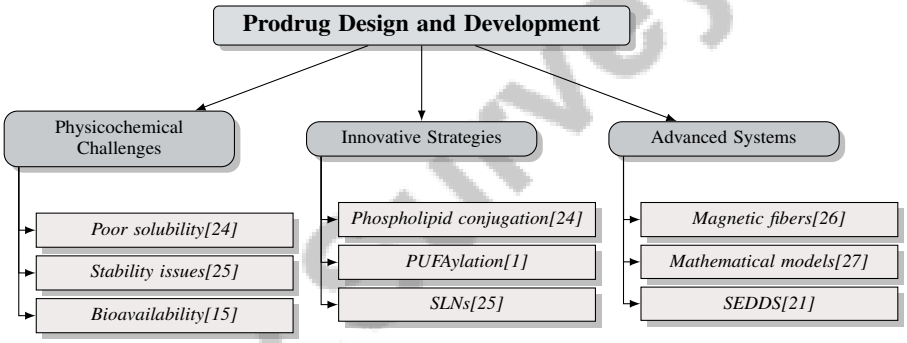


Figure 3: This figure illustrates the hierarchical structure of prodrug design and development, focusing on overcoming physicochemical challenges, employing innovative strategies, and utilizing advanced systems to enhance drug delivery and efficacy.

3.2 Prodrug Activation Mechanisms

Prodrug activation mechanisms are vital for ensuring the precise release of APIs at targeted sites, enhancing therapeutic efficacy while minimizing systemic side effects. These mechanisms often respond to specific physiological conditions, such as pH, redox potential, and enzymatic activity, prevalent in pathological sites like tumors and inflamed tissues [28]. The DA-TAT-PECL system, for instance, employs a reduction-sensitive drug dimer for activation, released in response to the acidic conditions of tumors, showcasing prodrugs' potential to exploit the unique microenvironment of diseased tissues for selective activation.

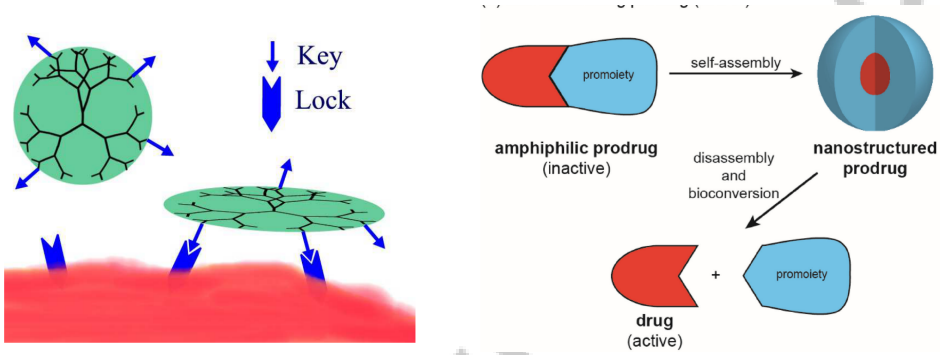
A prominent strategy involves mesoporous carriers, such as mesoporous carbon nanoparticles (MCNs), designed to encapsulate and release therapeutic agents effectively, enhancing solubility and cellular uptake of compounds like curcumin [29]. Similarly, SLNs serve as biocompatible carriers that encapsulate curcumin, modulating its release and absorption during gastrointestinal digestion to enhance stability and bioavailability [25].

Modeling drug release dynamics is crucial for optimizing prodrug systems. The Spherical Homogeneous Matrix Model effectively represents drug release and absorption dynamics, allowing for precise predictions and adjustments to improve delivery systems [18]. Additionally, methodologies

that model the diffusion process and drug molecule interactions with the surrounding medium ensure controlled drug delivery [20].

Recent advancements in non-invasive drug delivery systems focus on improving blood-brain barrier (BBB) penetration and targeted delivery to the central nervous system (CNS), showcasing prodrugs' potential in addressing challenging therapeutic areas [30]. Furthermore, the role of surface heterogeneous nucleation in influencing drug release behavior from nanoporous materials necessitates innovative approaches to monitor and control this phenomenon, ensuring consistent and effective drug activation [31].

Prodrug activation mechanisms are crucial for clinical effectiveness, enabling the development of innovative drug delivery systems tailored for specific therapeutic applications. These mechanisms enhance the pharmacokinetic properties of drugs, allowing for improved absorption, distribution, metabolism, and elimination (ADMET), while facilitating site-specific targeting. Emerging strategies, such as self-assembling prodrugs and radiation-mediated activation, underscore the versatility of prodrug design in overcoming traditional drug delivery barriers, paving the way for more efficient and targeted therapies [10, 23, 13].



(a) Key Lock[32]

(b) Amphiphilic Prodrug Self-Assembly into Nanostructured Prodrug[13]

Figure 4: Examples of Prodrug Activation Mechanisms

In Figure 4, prodrugs, particularly those involving unsaturated fatty acids, exemplify a sophisticated strategy to enhance drug delivery and efficacy. The "Key Lock" mechanism illustrates the structural intricacies of this approach, emphasizing the precision of prodrug activation. In contrast, the "Amphiphilic Prodrug Self-Assembly into Nanostructured Prodrug" mechanism depicts a dynamic process where an amphiphilic prodrug transitions from an inactive form to an active nanostructured entity through self-assembly, ensuring targeted drug delivery. Together, these examples underscore innovative approaches to optimize prodrug activation and enhance therapeutic outcomes [32, 13].

3.3 Therapeutic Applications of Prodrugs

Prodrugs have diverse therapeutic applications, significantly enhancing drug efficacy and minimizing adverse effects across various medical conditions. In chronic inflammation, prodrugs improve the delivery and therapeutic outcomes of anti-inflammatory agents. PUFAylated derivatives exemplify this potential, effectively managing cancer and inflammatory diseases by enhancing solubility, stability, and controlled release, thereby improving the therapeutic potential of nucleoside analogs [1]. This is particularly critical in conditions where conventional drugs suffer from poor bioavailability and rapid degradation.

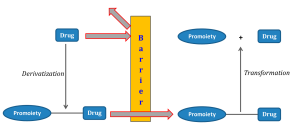
Amino acid prodrugs significantly improve drug solubility, permeability, and targeted delivery, which are crucial for optimizing therapeutic outcomes [13]. This approach is vital in chronic diseases where targeted delivery enhances efficacy and minimizes systemic side effects. Phospholipid prodrug conjugates further highlight the potential for enhanced delivery of hydrophobic chemotherapeutic agents, potentially improving treatment outcomes in cancer therapy [24].

Moreover, prodrugs can reduce gastrointestinal toxicity associated with nonsteroidal anti-inflammatory drugs (NSAIDs) while maintaining efficacy [7]. This is particularly beneficial in

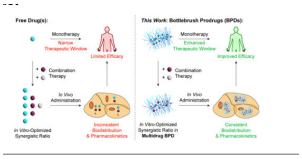
managing chronic inflammatory conditions where long-term NSAID use is common. Advanced drug delivery systems (DDS) incorporating prodrugs have been developed for targeted cancer treatment, emphasizing the importance of selective drug delivery to enhance therapeutic outcomes [9].

In chronic inflammation, prodrugs effectively deliver anti-inflammatory agents, modulating the inflammatory response while minimizing impact on healthy tissues [16]. The integration of bioactive lipids into prodrug strategies further enhances their therapeutic potential, offering novel approaches to manage inflammation and related chronic diseases [5].

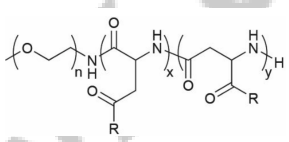
Furthermore, developing prodrugs activated by external stimuli, such as gamma/X-ray irradiation, represents a new strategy for targeted chemotherapy, minimizing systemic toxicity and enhancing treatment efficacy [23]. This innovative approach showcases prodrugs' versatility in advancing treatment strategies for chronic conditions, including osteoporosis and resistant bacterial infections, where enhanced drug delivery mechanisms can significantly improve therapeutic efficacy. The strategic design of prodrugs to enhance therapeutic efficacy while reducing side effects, particularly in targeting the tumor microenvironment and inflamed tissues, underscores their pivotal role in advancing treatment strategies for chronic conditions.



(a) Drug Derivatization and Transformation: Promoiety and Barrier[15]



(b) Improving Therapeutic Efficacy through Bottlebrush Prodrugs (BPDs): A Novel Approach to Enhancing Synergistic Ratio in Multidrug Administration[33]



(c) The image depicts a chemical structure of a polymer.[13]

Figure 5: Examples of Therapeutic Applications of Prodrugs

As shown in Figure 5, the exploration of prodrugs and their applications in therapeutic contexts significantly impacts pharmaceutical research, offering innovative solutions to enhance drug efficacy and safety. The figures illustrate various strategies central to prodrug development, including a flowchart elucidating drug derivatization and transformation processes, emphasizing promoiety and barriers. Another figure introduces Bottlebrush Prodrugs (BPDs), showcasing a novel approach aimed at improving therapeutic efficacy by enhancing the synergistic ratio in multidrug administration, contrasting with traditional monotherapy methods. Additionally, a depiction of a polymer's chemical structure emphasizes the intricate design of materials used in prodrug development. Together, these elements underscore diverse and innovative approaches to harness the full potential of prodrugs in medical treatments [15, 33, 13].

4 Prodrug-Microplatforms

4.1 Nano-assembled Microcapsules for Controlled Drug Release

Method Name	Structural Features	Mechanism of Action	Application Potential
NAM-GNP[34]	Polyelectrolyte Layers	Ultrasound-triggered Release	Targeted Therapies
BPD[33]	Polymer-based Nanocarrier	Controlled Release	Targeted Therapies
DA-TAT-PECL[28]	Polymeric Micelle System	Controlled Drug Release	Effective Cancer Therapy
GDBCS[35]	Polyelectrolyte Layers	Magnetic Fields	Targeted Therapies
CeF3-MTX[9]	Cef3 Nanoparticles	Ph-sensitive Release	Cancer Treatment
EMFs[26]	Polyelectrolyte Layers	Magnetic Fields	Targeted Therapies

Table 1: Overview of various nano-assembled microcapsule methods, highlighting their structural features, mechanisms of action, and application potential in targeted therapies and cancer treatment. The table summarizes innovative approaches such as polyelectrolyte layers, polymer-based nanocarriers, and polymeric micelle systems, emphasizing their role in enhancing drug delivery efficacy.

Nano-assembled microcapsules represent a significant advancement in nanotechnology for drug delivery, allowing for precise control and targeting through polyelectrolyte layers surrounding drug-

loaded nanoparticle cores. The incorporation of gold nanoparticles enhances these microcapsules' stability and responsiveness to external stimuli [34]. Bottlebrush prodrug (BPD) architectures further stabilize drug encapsulation, facilitating the delivery of synergistic drug combinations [33]. Techniques like the DA-TAT-PECL method, using self-assembled polymeric micelles, highlight the potential of these systems in cancer treatment [28].

Genetically engineered biomolecular capping systems, such as those using carbonic anhydrase, enable reversible binding to mesoporous silica nanoparticles (MSNs) for drug release in acidic tumor environments [35]. Nano-assembled cerium fluoride nanoparticles also demonstrate effective controlled drug release [9]. Advances in nano-bio drug delivery systems (NBDDS) show improvements in drug stability, solubility, and targeted delivery [8]. Additionally, electrospun magnetic fibers (EMFs) with magnetic nanoparticles and MSNs offer a novel method for controlled drug release via alternating magnetic fields [26].

These innovations in nano-assembled microcapsules address the limitations of traditional drug delivery by enhancing stability, solubility, and therapeutic efficacy, particularly in targeted therapies for coronary artery disease and vascular disorders. Ongoing research focuses on improving the safety and performance of these systems for clinical applications [34, 8]. Table 1 provides a comprehensive summary of the key methods in nano-assembled microcapsules for controlled drug release, detailing their structural features, mechanisms of action, and potential applications in targeted therapies.

4.2 Copolymeric Nanoparticles and External Potential Dynamics

Copolymeric nanoparticles are pivotal in modern drug delivery, offering enhanced control over drug release and targeting. These nanoparticles self-assemble into defined structures, encapsulating therapeutic agents for controlled release at specific sites. External Potential Dynamics (EPD) effectively models the phase separation dynamics of copolymers, providing insights into their behavior with co-solvents [36].

EPD accurately simulates the impact of mixing rates on particle size and morphology, clarifying the physical mechanisms of self-assembly, such as flow rates during spinodal decomposition [36, 21, 27]. This modeling capability allows for predictions of self-assembly behavior and optimization of nanoparticle properties for specific drug delivery applications.

The inclusion of copolymeric nanoparticles in drug delivery systems enhances solubility, stability, and circulation time of therapeutic agents, enabling precise targeting of diseased tissues. These advancements overcome traditional therapy limitations, such as inadequate stability and solubility, transmembrane transport challenges, and side effects, leading to safer and more effective treatments [8, 37, 34, 36, 38]. Leveraging EPD principles enables fine-tuning of copolymeric nanoparticles, paving the way for next-generation drug delivery platforms.

4.3 Enzyme-based Capping Systems for Mesoporous Silica Nanoparticles

Enzyme-based capping systems for mesoporous silica nanoparticles (MSNs) utilize enzymes' unique properties for controlled drug release, employing bio-orthogonal click chemistry to attach targeting ligands directly to nanoparticles. This design allows selective therapeutic agent release in response to biological stimuli, enhancing MSNs' targeting capabilities and overcoming conventional drug-eluting technologies' limitations [35, 34].

These systems respond to local biochemical environments, ensuring precise delivery to targeted sites while minimizing systemic exposure and adverse effects. Advanced drug delivery systems, including diffusion-controlled mechanisms, optimize release profiles to enhance therapeutic efficacy and patient safety. Such targeted approaches are crucial in complex scenarios like chronic wound healing, where precise delivery is essential to ensure therapeutic agents reach their intended site [11, 16, 17]. Enzyme-based systems can be tailored to release cargo in response to various triggers, making them versatile tools for precision medicine.

Advanced modeling techniques, such as EPD, support these systems' development by capturing early-stage dynamics of particle formation, enabling precise control over nanoparticle size and morphology [36]. By manipulating mixing rates and other parameters, researchers can optimize nanoparticle properties for therapeutic applications.

Enzyme-based capping systems for MSNs represent a transformative advancement in drug delivery technologies, providing precise control over drug release mechanisms and enabling targeted therapeutic interventions. Utilizing bio-orthogonal click chemistry to attach targeting ligands, such as folic acid, facilitates receptor-mediated uptake in specific cell types. This innovative approach enhances encapsulated drugs' stability and solubility while addressing conventional delivery challenges, such as insufficient transmembrane transport and side effects. Furthermore, integrating enzymes like carbonic anhydrase allows pH-responsive release of therapeutic agents, exemplified by successful delivery of Actinomycin D to cancer cells, paving the way for modular and controllable theranostic systems [8, 35, 16, 11, 38].

4.4 Self-immolative Chemistry and Nanoparticle Drug Delivery

Self-immolative chemistry provides a transformative approach in nanoparticle drug delivery, characterized by structural disassembly triggered by specific environmental stimuli. This mechanism is crucial for responsive drug delivery systems, where therapeutic agent release is controlled by triggers such as pH changes, enzymatic activity, and redox conditions, essential for responsive behavior in nanomedicine [39].

These systems are designed to encapsulate therapeutic agents within stable matrices that disassemble upon encountering specific stimuli, triggering sequential release of smaller components and enhancing drug targeting and efficacy. Self-immolative chemistry presents promising avenues for advancing nanomedicine by optimizing drug pharmacokinetics and therapeutic outcomes [13, 39]. Upon activation, self-immolative linkers undergo rapid disassembly, enabling controlled release of encapsulated drugs, enhancing targeting of diseased tissues, reducing systemic toxicity, and improving therapeutic efficacy.

Integrating self-immolative chemistry into nanoparticle systems allows for the design of sophisticated drug delivery platforms that respond to unique microenvironments of pathological sites, such as tumors or inflamed tissues. This approach enhances therapeutic efficacy by ensuring drugs are released in response to specific stimuli while minimizing adverse effects by targeting release to appropriate sites. The sequential disassembly reactions provide a versatile platform for developing prodrugs and nanoparticles tailored for various medical applications, including chronic wound management, optimizing treatment outcomes [13, 11, 17, 39].

As illustrated in Figure 6, the hierarchical structure of self-immolative chemistry in nanoparticle drug delivery highlights key mechanisms and triggers, applications and benefits, as well as research challenges. Self-immolative chemistry represents a multifaceted approach in nanomedicine, leveraging disassembly reactions triggered by specific stimuli to enable sequential release of smaller components. This innovative chemistry enhances prodrug and nanoparticle design for drug delivery, addressing challenges like improving pharmacokinetic properties and enabling targeted, responsive therapeutic strategies. By harnessing self-assembling prodrugs and nanomaterial-based systems' unique properties, researchers can develop more effective therapies that overcome traditional drug delivery barriers, paving the way for advanced, tailored therapeutic interventions in nanomedicine [8, 39, 37, 21, 13].

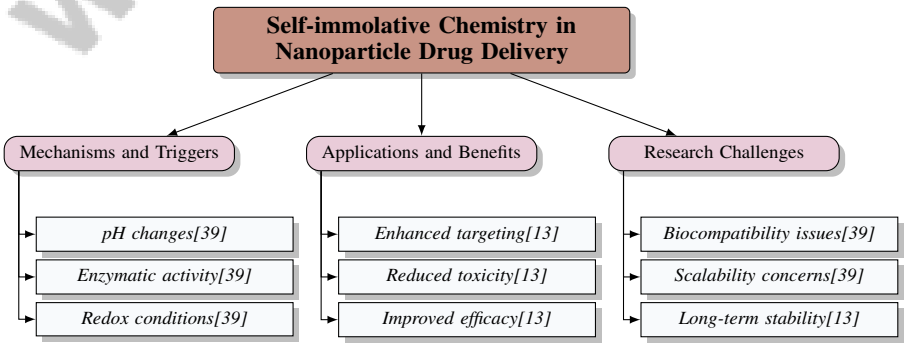


Figure 6: This figure illustrates the hierarchical structure of self-immolative chemistry in nanoparticle drug delivery, highlighting key mechanisms and triggers, applications and benefits, as well as research challenges.

5 Drug Delivery Systems and Bioavailability Enhancement

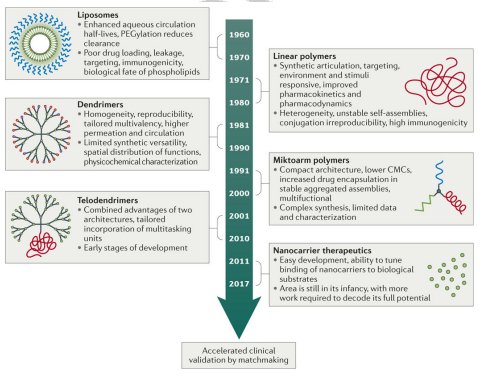
Recent advancements in drug delivery systems focus on enhancing bioavailability and therapeutic efficacy, with nanotechnology playing a crucial role in optimizing drug solubility, stability, and targeting capabilities.

5.1 Nanotechnology in Drug Delivery

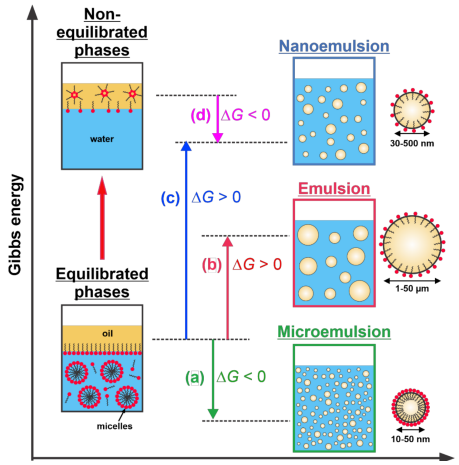
Nanotechnology has transformed drug delivery by improving the solubility, stability, and targeting of therapeutic agents. Magnetic nanoparticles in electrospun fibers exemplify this progress, facilitating precise modulation of drug release kinetics, especially for hydrophobic drugs [26]. Phospholipid prodrugs in lipid membranes further highlight nanotechnology's role in targeted delivery, enhancing bioavailability and efficacy [24]. The Heterogeneous Nucleation Monitoring Method (HNMM) provides insights into drug release processes in nanoporous carriers, crucial for consistent delivery [31]. Combining the Bernoulli equation with Fick's laws of diffusion enhances drug diffusion predictions, improving delivery precision [40]. Advanced modeling techniques, such as simulations for diblock copolymer micelles, tailor nanoparticles to specific therapeutic needs [18]. Mixed-charge pseudozwitterionic mesoporous silica nanoparticles (ZMSNs) exhibit low-fouling properties, enhancing drug stability and bioavailability [22]. Exosomes, due to their natural origin and biocompatibility, are promising vehicles, enhancing drug stability and half-life while enabling targeted delivery [4]. Collectively, these advancements underscore nanotechnology's multifaceted contributions to drug delivery systems, paving the way for personalized treatments and improved clinical outcomes [8, 16, 38].

5.2 Innovative Mechanisms for Controlled Release

Controlled drug release mechanisms are vital for optimizing therapeutic efficacy and minimizing side effects. Revising the Bernoulli equation to work with Fick's diffusion equation enhances drug diffusion predictions, allowing targeted and efficient release [40]. Advanced modeling techniques, like simulations of diblock copolymer micelles, improve nanoparticle design for high-efficiency encapsulation and controlled release [18]. Self-immolative chemistry in nanoparticle systems enables drug release in response to environmental stimuli, enhancing targeted delivery and reducing toxicity, particularly for complex conditions like chronic wounds [11, 39]. Progress in drug delivery technologies over the past seven decades has focused on developing localized and targeted systems for chronic conditions [16, 11].



(a) Timeline of Nanocarrier Therapeutics Development[38]



(b) Phase Behavior of Non-Equilibrium and Equilibrium Phases in Nanoemulsions[21]

Figure 7: Examples of Innovative Mechanisms for Controlled Release

As shown in Figure 7, advancements in drug delivery systems and bioavailability enhancement are critical in pharmaceutical sciences. The "Timeline of Nanocarrier Therapeutics Development" and the

"Phase Behavior of Non-Equilibrium and Equilibrium Phases in Nanoemulsions" illustrate innovative strides in controlled release mechanisms aimed at optimizing therapeutic outcomes [38, 21].

5.3 Enhancing Solubility and Permeability

Enhancing drug solubility and permeability is crucial for improving bioavailability and efficacy. CLEN achieves a 1.4×10^6 increase in curcumin solubility, addressing poor bioavailability due to low solubility and rapid metabolism [41, 6]. Lipid bilayer-coated mesoporous carbon nanoparticles (MCNs) enhance solubility and stability, maintaining integrity in simulated body fluid for up to 28 days [29]. Overcoming low solubility and permeability is vital for prodrugs, ensuring effective delivery of active ingredients [42]. Combretastatin A-4, for example, faces challenges due to low solubility and transformation to an inactive form [43]. Recent nanomaterial-based systems show promise in enhancing bioavailability and efficacy by addressing limitations like poor stability and rapid clearance [8, 16, 6].

5.4 Targeted Drug Delivery Platforms

Targeted drug delivery platforms enhance therapeutic precision by delivering medications directly to specific sites, minimizing systemic exposure and adverse effects. Recent advancements in nanomaterial-based systems optimize this process, addressing challenges like stability, solubility, and biological barriers [8, 16, 11, 6, 13]. Maintaining bioactivity and safety during food processing and digestion is crucial, necessitating effective incorporation into food matrices [44]. Advanced systems, like lipid bilayer-coated nanoparticles, provide stable environments that enhance solubility and stability. In cancer therapy, targeted delivery platforms reduce systemic toxicity and enable precise chemotherapy delivery, enhancing efficacy while minimizing adverse effects [23]. Prodrugs activated by specific triggers, like pH changes, exemplify targeted delivery systems' potential to improve treatment outcomes in cancer and chronic diseases. Advanced nanomaterials in targeted drug delivery represent a breakthrough in pharmaceutical sciences, enhancing efficacy and safety by improving drug stability, solubility, and transport. Ongoing research into diverse delivery technologies is essential for developing effective treatments that maximize patient safety and comfort [8, 45, 16, 11, 4].

6 Chronic Inflammation Treatment

6.1 Role of Prodrugs in Chronic Inflammation

Prodrugs play a pivotal role in treating chronic inflammation by optimizing drug delivery, enhancing bioavailability, and reducing systemic side effects. Phospholipid prodrugs significantly enhance the solubility and stability of hydrophobic drugs, facilitating efficient delivery to target tissues, as exemplified by curcumin's improved solubility and bioavailability [24, 25]. Prodrugs are designed to overcome challenges in delivering anti-inflammatory agents by enhancing absorption and minimizing side effects, which is essential in chronic inflammation management [10]. Strategies like PUFAylation enhance nucleoside analogs' therapeutic potential by improving bioavailability and reducing toxicity [1].

Advanced drug delivery systems, such as electrospun magnetic fibers (EMFs), illustrate the potential of prodrugs by enabling controlled release of both hydrophilic and hydrophobic drugs, thus enhancing permeation and providing a promising platform for drug delivery [26]. Exosomes are also emerging as promising candidates for targeted drug delivery, with potential modifications increasing their therapeutic efficacy and specificity [4]. Additionally, prodrugs are crucial in targeting resistant bacteria associated with chronic inflammation, thereby improving treatment outcomes for persistent infections [2]. The development of mixed-charge pseudo-zwitterionic mesoporous silica nanoparticles (ZMSNs) supports this strategy by showing promise in addressing bacterial infections linked to chronic inflammation [22].

The advancement and application of prodrugs in chronic inflammation treatment underscore their ability to optimize drug delivery, enhance therapeutic outcomes, and reduce systemic side effects, contributing significantly to managing complex inflammatory diseases [10].

6.2 Challenges and Opportunities in Treatment Strategies

The evolution of prodrugs and advanced drug delivery systems presents both challenges and opportunities in chronic inflammation treatment. A major challenge is navigating complex biological interactions that can impede clinical translation, as understanding these interactions remains limited [38]. Achieving reproducible and controlled drug release is another hurdle, with slowly soluble aggregates formed through heterogeneous nucleation leading to inconsistent release profiles and affecting therapeutic efficacy [31]. This highlights the need for innovative strategies to monitor and control nucleation processes for reliable drug release.

In gene therapy, obstacles such as neutralizing antibodies and viral infections of non-target cells lead to off-target effects and toxicity, complicating therapeutic gene delivery and necessitating more selective and efficient mechanisms [27]. Despite these challenges, significant opportunities exist for advancing treatment strategies. Integrating nanotechnology with self-immolative chemistry in drug delivery platforms can enable highly targeted and responsive therapeutic interventions. This approach leverages nanomaterial properties to enhance drug stability, solubility, and bioavailability while enabling precise release through stimuli-responsive mechanisms. By utilizing self-immolative chemistry, researchers can design advanced nanocarriers that improve treatment efficacy and minimize side effects, facilitating sequential release in response to specific triggers [8, 13, 21, 39].

Ongoing research into prodrug-microplatforms and advancements in drug delivery systems aim to address existing challenges in drug efficacy and safety. Prodrugs engineered to enhance absorption, distribution, metabolism, and elimination (ADME) are increasingly integrated into early drug development phases, targeting improved site-specific delivery and reduced toxicity. The evolution of nanomaterial-based drug delivery systems seeks to overcome barriers related to stability, solubility, and targeted delivery, enhancing therapeutic outcomes for various diseases. Collectively, these innovative approaches have the potential to revolutionize drug delivery, making therapies safer and more effective for patients [10, 8, 16, 14, 13]. Continued research and development in this domain are crucial for realizing these opportunities and addressing existing challenges in treatment strategies.

7 Challenges and Future Directions

The transition of prodrugs from laboratory research to clinical application is fraught with production and regulatory complexities. This section delves into the synthesis, safety, and regulatory hurdles that need to be addressed to advance drug delivery technologies.

7.1 Production and Regulatory Challenges

The clinical application of prodrugs faces significant hurdles, particularly concerning nanoparticle toxicity in drug delivery systems, necessitating rigorous safety evaluations [9]. The toxicity of chemotherapeutic agents, coupled with poor selectivity for cancer cells and rapid drug resistance, complicates prodrug formulation [12]. Challenges also arise in controlling drug loading and synthesis complexity, especially in active targeting strategies [13]. Enhancing reproducibility in drug release, particularly for hydrophobic molecules, is critical due to the impact of surface heterogeneous nucleation on release profiles [31].

The regulatory landscape is further complicated by insufficient studies on the biocompatibility of self-immolative by-products [39]. Rapid immune clearance of traditional delivery systems due to protein corona formation necessitates innovative stability approaches [22]. In antibacterial therapies, resistance mechanisms such as enzymatic degradation pose significant challenges [2]. Additionally, synthesizing magnetic nanoparticles (MNPs) with consistent quality and biocompatibility, while addressing environmental concerns, remains a research priority [37].

Addressing these production and regulatory challenges is crucial for advancing prodrug development. Continued research is vital to overcome obstacles in drug delivery systems, enhancing efficacy and safety. Collaborative efforts across research domains are essential to develop more effective systems, such as nanomaterial-based targeted delivery and prodrugs that improve solubility and targeting, optimizing therapeutic outcomes and patient care [8, 16, 10, 11].

7.2 Optimization of Drug Delivery Systems

Optimizing drug delivery systems is essential for enhancing therapeutic efficacy, focusing on stability, scalability, and targeted delivery. Refining prodrug structures to improve stability and evaluating pharmacokinetics are priorities for future research [3]. Lipid bilayer-coated mesoporous carbon nanoparticles (MCNs) show promise for drug delivery, though release profile optimization is needed for broader applications [29].

Developing stable emulsions and understanding self-emulsification mechanisms are crucial for optimizing self-emulsifying drug delivery systems (SEDDS), which face challenges related to cost and stability [21]. Optimizing amino acid structures for transport efficiency and stability represents a promising avenue for improving drug delivery [15]. Ensuring the stability of nano-assembled microcapsules during storage and conducting rigorous safety testing are critical challenges [34].

Research should focus on the influence of shear flow on copolymeric nanoparticle self-assembly, extending models to accommodate complex architectures [36]. Incorporating effects such as swelling and erosion, and the impact of porous matrix structures on release dynamics, can enhance drug delivery systems [18]. Addressing inflammatory responses and thrombosis associated with biomaterials is pivotal to ensuring safety and efficacy in clinical applications [46].

Future research should optimize electrospun magnetic fibers (EMFs) for targeted therapy and personalized medicine [26]. Optimizing drug delivery involves addressing formulation complexity and enhancing permeability, focusing on the roles of bioactive lipids in inflammation and therapeutic strategies targeting these pathways [5]. The integration of exosomes as delivery vehicles shows promise, although standardizing isolation and characterization methods remains a challenge [4]. Optimizing delivery systems is crucial for advancing therapeutic strategies and improving patient outcomes.

7.3 Bioavailability and Therapeutic Efficacy

Enhancing bioavailability and therapeutic efficacy is crucial in advancing drug delivery systems, particularly for prodrugs targeting chronic inflammation. Improving bioavailability ensures therapeutic agents effectively reach their intended sites, enhancing treatment outcomes [45]. The PUFAylation approach exemplifies this by significantly enhancing nucleoside analogs' effectiveness [1].

Advanced delivery technologies, such as pH-sensitive release mechanisms and active targeting capabilities, enhance bioavailability and efficacy by allowing controlled release at specific sites, maximizing benefits while minimizing systemic side effects [9]. Mixed-charge pseudo-zwitterionic mesoporous silica nanoparticles (ZMSNs) highlight their effectiveness in enhancing bioavailability and efficacy, particularly against resistant bacteria [22].

Bioavailability and therapeutic efficacy are also crucial for prodrugs improving existing antibiotics, addressing bacterial resistance challenges [2]. Revising the Bernoulli equation to control drug diffusion dynamics emphasizes considering physiological conditions for precise delivery [40]. Focusing on bioavailability and efficacy is essential for maximizing therapeutic agents' potential, improving treatment outcomes across medical applications. Recent advancements, including targeted delivery systems, show promise in overcoming barriers and enhancing bioavailability of compounds like curcumin, aiming to enhance patient safety and therapeutic success [10, 16, 6].

7.4 Targeted Drug Delivery and Biocompatibility

Targeted drug delivery systems enhance therapeutic precision, ensuring drugs are delivered specifically to pathological sites while minimizing systemic exposure. These systems utilize nanoparticles engineered to improve solubility, stability, and bioavailability [22]. Incorporating targeting ligands and stimuli-responsive materials enables selective binding to diseased tissues and release in response to environmental triggers [35].

Biocompatibility is critical, ensuring materials do not elicit adverse immune responses. Mixed-charge pseudo-zwitterionic mesoporous silica nanoparticles (ZMSNs) exemplify advancements in biocompatibility, reducing protein adsorption and immune clearance [22]. Integrating natural biomaterials, such as phospholipids, enhances biocompatibility by providing a natural interface with tissues [24].

Combining targeted delivery and biocompatibility optimizes therapeutic potential by ensuring precise delivery and well-tolerated vehicles, improving safety and efficacy. This approach enhances patient outcomes by improving drug efficacy and comfort while mitigating systemic exposure risks. Advancements in localized and targeted delivery systems propel pharmaceutical sciences and personalized medicine, addressing disease complexities and optimizing interventions [45, 16, 11, 6].

7.5 Innovations in Drug Delivery Platforms

Recent innovations in drug delivery platforms focus on enhancing bioavailability and therapeutic efficacy through advanced design and material science. Future research aims to improve delivery system design, explore new biobased materials, and conduct extensive safety evaluations [44]. Integrating stimuli-responsive elements into self-assembled prodrug systems (SAPDs) is an emerging trend, facilitating enhanced release in specific environments [13].

Nanoparticle-based systems show promise in improving combretastatin derivatives' therapeutic potential, particularly in cancer treatment [43]. These systems facilitate targeted delivery and controlled release, enhancing efficacy and reducing toxicity. Utilizing differential evolution (DE) algorithms in optimizing delivery system designs proves more robust than traditional algorithms, achieving better solutions and maintaining diversity [47].

Advancements in computational modeling are crucial for the future of drug delivery platforms. Enhanced modeling can improve efficacy and targeting by exploring new chemical linkers and refining approaches [10]. Extending the generalized random sequential adsorption (gRSA) model and incorporating experimental data refine adsorption dynamics predictions, optimizing delivery systems [27].

Recent advancements, including complex macromolecular architectures and extracellular vesicles like exosomes, highlight multidisciplinary approaches' critical role in pharmaceutical sciences. These innovations enhance efficacy and safety by enabling targeted delivery, paving the way for personalized treatment strategies addressing patient needs. As the field evolves, overcoming physicochemical barriers and biological challenges is essential to translate technologies into clinical applications [4, 16, 38].

7.6 Personalized Medicine and Emerging Technologies

Personalized medicine influences drug delivery by customizing interventions to align with patient profiles, enhancing efficacy and minimizing effects. Integrating personalized strategies requires understanding tumor biology and developing smart polymers that respond to stimuli, facilitating precise delivery [38]. This approach is advantageous in oncology, where tumor heterogeneity necessitates tailored treatment plans.

Machine learning in prodrug design marks a significant advancement, offering potential for more selective bioconversion systems enhancing delivery precision [14]. Algorithms analyze datasets to identify optimal candidates and predict behavior, streamlining development and improving success likelihood. Emerging technologies, such as nanoparticle-based systems, are at the forefront of personalized medicine, overcoming barriers and enhancing delivery to specific tissues [8].

Future research should focus on optimizing nanoparticle design, exploring new materials, and improving bioavailability and efficacy of encapsulated drugs. Micro and nano-engineered systems show promise in improving delivery for wound care, indicating a direction for personalized medicine [11]. The development of multi-biomarker responsive prodrugs and advancements in imaging enhance visualization and tracking, providing real-time feedback on treatment and allowing adjustments [12].

Exploring new stimuli-responsive materials and optimizing self-immolative systems is critical for improving targeting and addressing biocompatibility challenges [39]. These innovations hold promise for advancing platforms by providing precise control over release and minimizing effects. The convergence of personalized medicine and emerging technologies is poised to revolutionize strategies, offering more effective, tailored treatments improving outcomes. Future research should continue exploring these avenues, focusing on optimizing formulations for clinical applications and conducting long-term studies to realize advancements' potential, particularly in addressing antibiotic resistance [2].

8 Conclusion

This survey highlights the pivotal role of prodrugs in transforming drug delivery systems by enhancing bioavailability, stability, and targeted delivery. Innovations such as the incorporation of unsaturated fatty acids and advanced microplatform technologies have been instrumental in overcoming physiological barriers, thereby boosting drug efficacy. The exploration into low-energy methods for increasing prodrug bioavailability further extends their applicability across diverse therapeutic areas. The potential of Differential Evolution in optimizing drug delivery systems, especially in cancer treatment, underscores the importance of precise targeting and controlled release mechanisms. The ongoing development of exosome engineering, alongside the establishment of standardized isolation and characterization protocols, is crucial for advancing clinical applications. Tailored drug delivery systems are essential for addressing complex challenges such as chronic wounds and inflammatory conditions, emphasizing the need for continuous innovation in prodrug formulations and delivery platforms. These advancements hold the promise of revolutionizing treatment strategies, significantly improving therapeutic outcomes and patient care across various medical fields.

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