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Recent Advances in Prodrug Design: Chemical Strategies and Pharmaceutical Applications

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ABSTRACT
As a crucial molecular modification strategy, prodrugs enable the release of active pharmaceutical ingredients through enzymatic or chemical reactions within the body, thereby playing a pivotal role in enhancing drug solubility, stability, bioavailability, and safety. With advances in medicinal chemistry, nanotechnology, and biomedicine, prodrug research has expanded beyond mere physicochemical optimization to encompass targeted therapy and personalized medicine. This paper systematically reviews the fundamental principles, classification, primary applications, development challenges, and future directions of prodrugs. It highlights emerging trends such as drug-auxiliary prodrugs, microenvironment-responsive prodrugs, AI-assisted design, and enzyme-mediated prodrug therapies.

KEYWORDS
Prodrug; Drug design; Pharmacokinetics; Targeted delivery; Nanomedicine; Tumor microenvironment; Artificial intelligence; Enzyme prodrug therapy

1 Introduction

Prodrugs represent a masked form of active pharmaceutical ingredients that undergo activation via enzymatic or chemical reactions following administration. They possess little to no intrinsic pharmacological activity and are converted into active parent drugs through enzymatic or chemical transformations within the body. As a molecular modification strategy, the core objective of prodrug design lies in optimizing a drug's physicochemical and pharmacological properties to enhance solubility, stability, absorption rates, and pharmacokinetic characteristics.

During drug development, many candidate compounds face challenges in clinical application due to poor water solubility, low oral bioavailability, rapid first-pass metabolism, or significant systemic toxicity. The prodrug strategy effectively addresses these issues, enabling the successful commercialization of drugs that were previously difficult to develop. Over the past three decades, prodrug development has significantly advanced medicinal chemistry and pharmaceutical science. Currently, an estimated 10% of all marketed drugs globally are classified as prodrugs [1], underscoring the success of this approach.

In recent years, driven by advances in organic synthesis, nanodelivery systems, and biotechnology, prodrug research has expanded beyond simple physicochemical enhancement into more complex drug delivery and precision medicine domains. This review outlines the fundamental principles, classification, typical applications, development challenges, and future directions of prodrugs, aiming to provide guidance for subsequent research and clinical translation.

2 Basic concepts and principles

Prodrug design strategies primarily depend on the structural characteristics of the parent drug molecule, particularly whether suitable chemical functional groups can serve as modification sites. Introducing cleavable modifying groups onto these functional groups temporarily masks the drug's pharmacodynamic activity. Another critical factor is the prodrug's biotransformation mechanism—how the active drug is released in vivo through enzymatic or chemical reactions. Thus, prodrug design centers on dual optimization: molecular structural modification and in vivo conversion pathways.

In modern drug development, prodrug strategies primarily address physicochemical and biopharmaceutical limitations of parent drugs, such as poor solubility, instability, pronounced first-pass effects, or short half-lives. Through appropriate modifications, prodrugs can: improve water solubility and lipid solubility; enhance oral bioavailability; reduce toxic side effects; enable targeted delivery; and protect the drug from premature inactivation. An ideal prodrug typically possesses the following characteristics: (a) resistance to hydrolysis during absorption; (b) exhibit weak or no activity; (c) possess some water solubility; (d) demonstrate good bio-membrane permeability; (e) maintain chemical stability across varying pH conditions; (f) exhibit reasonable conversion kinetics for effective parent drug release.

Based on structure and conversion mechanisms, prodrugs are primarily categorized into two types: carrier-linked prodrugs and bio-precursor prodrugs.

(1) Carrier-linked prodrugs: These couple the active drug with a temporary carrier (typically non-toxic and

pharmacologically inactive) via a cleavable chemical bond. Upon systemic administration, the prodrug is absorbed by cells and tissues, where it is activated to release both the active drug and the carrier.

(2) Bioprecursor prodrugs: These are inactive compounds, often lacking a carrier moiety. They are metabolic analogues of the parent drug and require in vivo metabolic processes such as oxidation or reduction to convert into the active compound. This modification may result from oxidation or reduction, yielding a new compound that can be further metabolized or chemically transformed into the active drug.

3 Primary applications of prodrug strategies

3.1 Improving pharmaceutical properties of drugs

Many drugs exhibit undesirable characteristics, including poor water solubility, chemical instability, inadequate oral or topical absorption, rapid systemic first-pass metabolism, short half-lives, toxicity, and local irritation. These issues severely limit clinical application and can often be addressed using prodrug approaches. Additionally, this strategy can overcome challenges related to drug formulation and administration.

Take paclitaxel (PTX) as an example. This widely used chemotherapeutic agent treats various cancers—including breast, ovarian, lung, and pancreatic cancers—by inhibiting the assembly-disassembly kinetics of microtubule polymerization. However, its poor water solubility severely hinders clinical application. Consequently, attaching hydrophilic groups to PTX represents a rational strategy for modifying its physicochemical properties. Thus, PTX modified with amino, carboxyl, hydroxyl, or amino acid moieties exhibited 6- to 140-fold enhanced water solubility [2], along with superior in vitro anticancer activity and significantly improved bioavailability in mice compared to PTX alone.

Furthermore, self-assembling prodrugs have garnered extensive attention in recent years as therapeutic agents. These prodrugs spontaneously aggregate into well-organized supramolecular structures in aqueous solutions, overcoming limitations of traditional solubilization methods—such as reducing particle size, employing solubilizing excipients, complexing agents, or surfactants—which fail to enhance water solubility while simultaneously lowering toxicity to desirable levels. A study examining the top 200 oral drug products in Japan, the UK, the US, and Spain revealed that approximately 37% of drugs exhibit solubility below 0.1 mg/mL [3]. This finding underscores the critical role of prodrugs in improving pharmaceutical properties.

3.2 Improving pharmacokinetic properties

Another common issue is rapid metabolism within the body, resulting in short half-lives and pronounced first-pass effects that diminish clinical efficacy. Prodrug design enables sustained presence of the drug in a stable form, followed by gradual release of the active ingredient. This prolongs duration of action and enhances pharmacokinetic characteristics.

For example, enalaprilat is the active metabolite of the oral prodrug enalapril maleate. Enalaprilat exhibits poor oral absorption and requires intravenous administration. Enalaprilat competitively inhibits angiotensin-converting enzyme (ACE), blocking the conversion of angiotensin I to angiotensin II, and demonstrates superior oral absorption and clinical utility [4].

3.3 Enhancing targeting and reducing systemic toxicity

In treating tumors and central nervous system disorders, drugs lacking tissue selectivity often cause significant systemic side effects. Prodrug strategies achieve targeted delivery through chemical modifications or enable selective drug release in specific pathological environments (e.g., the acidic tumor microenvironment).

A classic example is unsaturated fatty acid (UFA) prodrugs, which exhibit biocompatibility and tumor targeting [5]. These molecules are typically formed by covalently coupling anticancer drugs with biocompatible fatty acids. Although fatty acids themselves lack direct therapeutic effects, they promote nanoparticle formation and confer tumor targeting to drugs, demonstrating promising applications in cancer chemotherapy. Consequently, they are widely considered for designing chemotherapy agent UFA (CA-UFA) prodrugs in cancer treatment.

3.4 Other applications

Beyond enhancing physicochemical properties, pharmacokinetics, and targeting, prodrug strategies also show potential in overcoming drug resistance and enabling combination therapy.

Particularly noteworthy is the integration of self-assembling prodrugs with nanomedicine delivery systems (DDS). This approach not only improves drug loading efficiency but also enables disease-environment-specific drug release, prolongs circulation time, and enhances overall therapeutic efficacy. Typical self-assembling prodrugs comprise three components: the active drug, linker, and auxiliary fragment [6]. The linker characteristics dictate drug release kinetics, while the physicochemical properties of the auxiliary fragment govern self-assembly behavior. This strategy shows promising prospects in both cancer therapy and antiviral research.

4 Challenges and limitations in R&D

Despite significant advances in improving physicochemical properties, pharmacokinetics, and targeting through prodrug strategies, numerous challenges and limitations persist in practical R&D and clinical translation:

4.1 Complexity of molecular design

Designing molecules with predictable and beneficial properties represents one of the most critical objectives in organic synthesis. Particularly in polymer prodrug design, while the underlying principles are well-established, selecting appropriate linkers that balance stability and degradability remains challenging. The heterogeneity of drugs within complex biological environments—such as tumor microenvironments and metastatic characteristics—further compounds design unpredictability.

4.2 Conversion efficiency and interindividual variability

The efficacy of prodrugs depends on in vivo conversion, a process significantly influenced by enzyme activity, genetic differences, and pathological states. This leads to individualized clinical outcomes, complicating R&D and evaluation.

4.3 Safety and metabolic risks

The conversion of prodrugs may generate unknown or toxic metabolites, posing challenges to their clinical feasibility and long-term safety. Additionally, incomplete release of the active ingredient after drug-carrier conjugation may compromise therapeutic efficacy.

4.4 Pharmaceutical and pharmacokinetic issues of nanoparticle prodrugs

Although several prodrug-based nanomedicines have entered clinical trials with preliminary efficacy, further research is needed on their pharmaceutical and pharmacokinetic properties, solubility, stability, biosafety, biocompatibility, and biodegradability [7]. This will enhance their feasibility and optimize their clinical application.

5 Future development directions

With the rapid advancement of medicinal chemistry, materials science, and biotechnology, prodrug research is expanding beyond traditional improvements in physicochemical properties and pharmacokinetics toward more precise and intelligent approaches. Future trends in prodrug development are primarily reflected in the following aspects:

5.1 Combination of prodrugs with adjuvants

The concept of drug-adjuvant prodrugs has garnered significant attention in recent years. These are typically obtained through covalent coupling of the drug with a biocompatible adjuvant moiety. Such prodrugs are typically created by covalently coupling the active pharmaceutical ingredient to a biocompatible adjuvant moiety (e.g., fatty acids, polymers, or hydrophilic molecules). The adjuvant itself lacks direct therapeutic efficacy but facilitates the formation of prodrug nanoparticles or confers other beneficial properties [8], improving physicochemical characteristics or imparting novel functions such as enhanced solubility, prolonged circulation time, or targeted delivery.

Notably, prodrugs/prodrug formulations inevitably impede the release of the parent drug. Drug-supporting prodrug formulations often exhibit relatively slow active drug release processes due to physical entrapment or chemical conjugation of the drug molecule. This controlled-release characteristic can be advantageous in certain diseases, such as antiviral therapy, where prolonged release profiles facilitate sustained suppression of viral replication and reduce dosing frequency.

5.2 Tumor microenvironment-sensitive prodrugs

Tumor tissues typically exhibit characteristics such as low pH, hypoxia, and high glutathione concentrations. Microenvironment-sensitive prodrugs designed based on these pathological features can be activated specifically at tumor sites, minimizing toxicity to normal tissues. For instance, pH-sensitive and redox-sensitive prodrugs have demonstrated enhanced selectivity and therapeutic efficacy in experimental studies [9]. Such strategies offer novel approaches to addressing the high toxicity and low selectivity challenges of conventional chemotherapy.

5.3 Artificial intelligence-assisted prodrug design

Artificial Intelligence (AI) is demonstrating immense potential in drug discovery. In prodrug design, AI can predict physicochemical properties, metabolic pathways, and in vivo conversion efficiency based on big data, significantly shortening development cycles and reducing costs. In the future, intelligent prodrug design integrating molecular modeling, machine learning, and virtual screening may become a crucial component of new drug development.

5.4 Enzyme-mediated prodrug therapy

Enzyme-mediated prodrug therapy represents a precision medicine strategy gaining considerable attention in recent years. Its core principle involves utilizing exogenous or specifically delivered enzymes to selectively convert non-toxic prodrugs into pharmacologically active compounds at the target site. Compared to traditional systemic administration, this approach enables spatially concentrated drug effects, significantly reducing systemic toxicity and side effects. Typical approaches include ADEPT (antibody-mediated), GDEPT (gene-mediated), and VDEPT (virus-mediated). ADEPT employs specific antibodies to deliver enzymes to tumor tissues, followed by intravenous administration of prodrugs for local activation. GDEPT/VDEPT, meanwhile, introduces exogenous enzyme genes via genetic or viral vectors, enabling tumor cells to metabolize prodrugs autonomously [10].

Although enzyme prodrug therapy shows promising prospects in tumor chemotherapy and certain anti-infective treatments, it still faces several challenges, such as enzyme delivery efficiency, immunogenicity, prodrug conversion rates, and difficulties in clinical translation. With advances in synthetic biology, antibody engineering, and nanomedicine delivery technologies, this strategy holds promise for broader clinical application in the future.

6 Conclusion

The development of prodrugs fulfills patient expectations and, as a crucial molecular modification strategy, has demonstrated immense value in modern drug discovery and clinical applications. By enhancing physicochemical properties, pharmacokinetics, and reducing adverse effects, prodrugs not only broaden the applicability of drugs but also enable clinical translation for certain molecules that were previously challenging to develop. Currently, a significant number of prodrugs have successfully reached the market, with their clinical efficacy and safety validating the feasibility and importance of this strategy.

Advances in medicinal chemistry, polymer science, recombinant methods, and biotechnology are propelling prodrug research toward greater precision and intelligence. Particularly through integration with emerging technologies like nanomedicine delivery systems, tumor microenvironment-responsive mechanisms, and gene/enzyme prodrug therapies, prodrugs are evolving beyond mere "auxiliary tools" into essential pathways for targeted therapy and personalized medicine.

Future advancements in prodrug development are anticipated to achieve breakthroughs in target specificity, reduced host toxicity, and optimized pharmacokinetics. It is foreseeable that multidisciplinary integration will continue to drive the widespread application of prodrug strategies in drug discovery and clinical therapy, further cementing their central role in modern pharmaceutical R&D.

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