Scientific Research Publishing

Pharmacology & Pharmacy, 2025, 16(8), 303-322
https://www.scirp.org/journal/pp
ISSN Online: 2157-9431
ISSN Print: 2157-9423

Prodrugs in Modern Medicine: Strategies, Applications, and Future Directions

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How to cite this paper: Lin, J.Y. (2025) Prodrugs in Modern Medicine: Strategies, Applications, and Future Directions. *Pharmacology & Pharmacy*, **16**, 303-322.
https://doi.org/10.4236/pp.2025.168016

Received: July 11, 2025
Accepted: August 26, 2025
Published: August 29, 2025

Abstract

Prodrugs are pharmacologically inactive compounds that undergo enzymatic or chemical transformation in vivo to release active drugs. This strategy has emerged as a powerful tool in modern drug development, addressing key limitations such as poor solubility, limited bioavailability, rapid metabolism, and systemic toxicity. This review provides a comprehensive overview of prodrug classifications, including carrier-linked, bio-precursor, and self-immolative systems, and their applications across therapeutic areas such as oncology, infectious diseases, and cardiovascular disorders. It explores historical developments, rational design strategies (e.g., mutual, co-drugs, double prodrugs), and molecular targeting approaches including enzyme-, pH, and redox-sensitive systems. Additionally, it discusses macromolecular and nanoparticle-based prodrugs and evaluates key challenges in stability, activation variability, and toxicity from released promoieties. Emphasis is also placed on emerging trends such as biorthogonal activation, probiologics, and machine learning-guided design. By integrating advances in nanotechnology, precision medicine, and computational modeling, prodrugs are poised to transform therapeutic delivery in increasingly targeted and patient-specific ways.

Keywords

Prodrug, Drug Delivery, Pharmacokinetics, Activation Mechanism, Precision Medicine

1. Introduction

The term "*prodrug*" was introduced by Adrien Albert in 1958, signifying compounds that require biotransformation to exhibit therapeutic activity [1] [2]. Initially, prodrugs were considered a last resort in drug development. However, advancements in combinatorial chemistry, high-throughput screening, and molec-

ular biology have positioned prodrugs as a central strategy in early-stage drug discovery [2] [3]. This shift has been driven by the ability of prodrugs to optimize physicochemical properties, overcome biological barriers, and achieve site-specific drug delivery [4] [5].

Currently, 5 - 7% of drugs approved worldwide are classified as prodrugs, with an increasing number entering clinical trials and commercial markets annually [1] [3]. Examples such as valacyclovir, oseltamivir, and capecitabine demonstrate the versatility of prodrugs in addressing diverse therapeutic needs, including antiviral, anticancer, and cardiovascular applications [2]-[4]. These successes underscore the potential of the prodrug strategy to revolutionize drug design by reducing toxicity, enhancing bioavailability, and improving patient compliance [1] [3] [4].

This review aims to explore the advancements in prodrug design and applications. It pays close attention to the mechanisms of activation, therapeutic benefits, and prospects. By reviewing the recently developed and marketed prodrugs, this paper highlights lessons learned and outlines the challenges that persist in this evolving field.

2. Historical Perspective

The idea of prodrugs dates to the late 19th and early 20th century when researchers first noted that certain inactive substances could be transformed into active drugs within the body. One of the first examples was aspirin, made from salicylic acid, and methenamine, which liberates formaldehyde in acidic urine as a urinary antiseptic [6]. However, the term "*prodrug*" was not introduced until 1958, when Albert Adrien characterized it as an inactive form that is transformed in vivo into an active form to achieve pharmacological activity [6]. This development highlighted the potential of utilizing metabolic pathways to enhance drug delivery and efficacy.

Prodrugs were initially found serendipitously, with little knowledge at the time about the biochemical pathways that lead to their activation. With advancements in the field of pharmaceutics and drug metabolism, these processes were addressed, and rational approaches to the design of prodrugs were implemented to circumvent the pharmacokinetic (PK) and pharmacodynamic (PD) limitations. These discoveries led to the creation of drugs like codeine, a prodrug that CYP2D6 converts to morphine, and prontosil, a sulfa drug with an active metabolite, sulfanilamide [1].

By the end of the 20th Century, the prodrug strategy was consciously and systematically applied in drug design. Esterification, amidation, and similar strategies were employed by pharmaceutical researchers to improve the solubility, stability, and permeability of parent compounds [6]. The classification of prodrugs into carrier-linked and bio-precursor types also enriched the evolution of prodrugs and their use in therapeutics. Today, nearly 10% of approved drugs are prodrugs worldwide, and their numbers are increasing, owing to their potential ability to overcome problems like poor bioavailability, systemic toxicity, and targeted delivery [1] [6].

Prodrugs have been utilized in a wide range of therapeutic fields, covering oncology, cardiovascular, and infectious diseases. For example, the anticancer prodrug tegafur is metabolized into 5-fluorouracil, which selectively kills tumor cells,

thereby avoiding systemic toxicity [1]. Likewise, the prodrug approach has been the basis for several antiviral drugs (e.g., oseltamivir) and antibiotics (e.g., bacampicillin) that lead to significant gains in therapeutic index by improving the pharmacokinetic properties of agoACDs [6].

The transformation from serendipitous discovery to rational design has solidified the status of prodrugs as a crucial tool in modern medicine, creatively addressing some of the more challenging problems in drug design.

3. Classification of Prodrugs

Prodrugs are broadly classified based on their activation mechanisms and structural features, including carrier-linked, bio-precursor, self-immolative, mutual, and macromolecular prodrugs. Each type leverages distinct triggers—such as enzymatic cleavage, chemical hydrolysis, or external stimuli—to achieve controlled activation and targeted drug delivery. **Table 1** below outlines the key features, activation triggers, advantages, and marketed examples of each prodrug type, providing a concise framework for comparing diverse design strategies in modern drug development.

Table 1. Classification of prodrug types, activation mechanisms, and representative examples.

Prodrug Type	Activation Trigger	Advantages	Marketed Example
Carrier-linked	Enzymatic (e.g., esterase, phosphatases), or chemical (pH)	Improves solubility, permeability, targeting, and stability; customizable promoiety	Oseltamivir (Tamiflu), Enalapril, Adefovir
Bio-precursor	Metabolic transformation (e.g., oxidation, reduction)	Does not require a carrier; simple structural modification of parent drug	Sulindac (oxidized to active sulfide), Prednisone (reduced to prednisolone)
Self-immolative	Trigger-induced cleavage (e.g., redox, enzyme) causing self-elimination cascade	Spatiotemporal control; programmable release for targeting tumor or disease site	Duocarmycin prodrugs, disulfide-linked doxorubicin derivatives
Double Prodrug	Sequential enzymatic/chemical activation of two linkages	Improves stability and site-specific activation; overcomes premature cleavage	6-deoxyacyclovir, pilocarpine
Targeted Prodrug	Stimuli (e.g., pH, enzyme, redox) at disease site, or receptor-mediated targeting	Increased selectivity and reduced systemic toxicity; enhanced targeting	Antibody-drug conjugates (e.g., trastuzumab emtansine), ADEPT systems
Macromolecular Prodrug	Enzymatic or hydrolytic cleavage of polymer-drug bond in specific tissues	Extended circulation time; controlled release; reduced immunogenicity	HPMA-doxorubicin conjugates, PEG-irinotecan

Table 1: This chart illustrates the key differences among prodrug types—including carrier-linked, bio-precursor, self-immolative, double, targeted, and macromolecular strategies—by summarizing their activation triggers, therapeutic advantages, and representative marketed examples

3.1. Carrier-Linked Prodrugs

Carrier-linked prodrugs represent a specialized class of prodrugs in which the active drug is covalently attached to a carrier molecule. These carriers are often designed to have a strong affinity for specific biological targets, enabling the prodrug to bypass biological barriers, such as cell membranes, or to home in on diseased tissues, like tumors. The carrier temporarily masks or alters the parent drug's physicochemical properties, thereby improving solubility, stability, or pharmacokinetics. Once the prodrug reaches its intended site, the linkage between the carrier and the active drug is cleaved—typically via enzymatic or chemical hydrolysis—releasing the active compound and, depending on the system, either an inert or biologically active carrier moiety [7].

An ideal carrier-associated prodrug fulfills several requirements. The prodrug should be less active or inactive in relation to the parent drug to be transported safely. The breakage of the linkage at the target site should be rapid and selective, yielding therapeutic levels of the active drug while minimizing alternative metabolic pathways and avoiding toxicity due to the carrier [7]. Carrier moieties are sometimes lipophilic in nature, such as PEG, fatty chains, macromolecules (albumin, antibody), which increase membrane permeabilization and drug stability.

The successes of carrier-linked prodrugs reflect the capabilities for strategic improvements with molecular transformation. One such example is *Protaxel*, which is a water-soluble carbonate conjugate of paclitaxel that follows pH-dependent intramolecular cyclization for the liberation of the active drug molecule, resulting in enhanced aqueous solubility and in vivo antitumor activity [7]. Buparvaquone derivatives are another example, where derivatization with a phosphate moiety enhances aqueous solubility and skin permeation, making them promising candidates for the treatment of cutaneous leishmaniasis. In this case, the phosphate group does not act as a carrier but rather functions to improve the compound's physicochemical properties. Furthermore, the *ProTide technology* also illustrates the value of carrier-linked design, in the sense that it delivers nucleoside monophosphates into cells and negates the constraining rate-limiting phosphorylation steps, while enhancing antiviral potency to a remarkable degree, seen in drugs such as Sofosbuvir for hepatitis C [7].

This novel concept is developing as it adapts through polymer chemistry, nanotechnology, and enzymatic activation to improve drug delivery and therapeutic effects in various clinical applications.

3.2. Bio-Precursor Prodrugs

Bio-precursor prodrugs are a unique class of prodrugs that are internally con-

verted into active drug molecules by metabolic mechanisms. Unlike carrier-linker prodrugs, bio-precursor prodrugs have no carrier part. Thus, the drug is instead chemically modified into an inactive biochemical precursor of the drug, which is converted to the active drug in a biological system [7] [8]. This method can be especially useful for regulating the lipophilicity, stability, and organotropism of a *pharmakon*.

The bio-precursor prodrug is generally activated by enzymatic reactions such as oxidation, reduction, or hydrolysis. For example, *Sulindac* is a bio-precursor of its active sulfide metabolite, and reductive activation by gut bacteria leads to less gastric irritation than observed with the traditional NSAIDs [8]. Tegafur is an orally administered N-tetrahydrofuran derivative of 5-fluorouracil (5-FU), a fluoropyrimidine. It is converted to 5-FU primarily by cytochrome P450 enzymes, enabling tumor-selective activation and thereby reducing systemic toxicity during cancer chemotherapy [7]. Likewise, *Valacyclovir*, a prodrug of acyclovir, improves oral bioavailability by being hydrolyzed by esterase of the intestinal mucosa; therefore, it is more favored for antiviral therapy [8].

A bio-precursor prodrug is especially useful in overcoming certain pharmacokinetic and pharmacodynamic issues. Their main advantage is *improved bioavailability*, due to avoidance of first-pass metabolism or low absorption, leading to increased plasma levels of the active substance. Furthermore, bio-precursor prodrugs play a role in *reduced toxicity* as they allow for tissue-specific activation, thus reducing side effects—e.g., sulindac and tegafur [8]. The second benefit is *increased stability*: as it can protect the active drug from degradation and further decomposition prior to storage or after release into the body, maintaining the pharmacological activity [7].

The development of prodrug bio-precursors also evolves further with the integration of computational modeling and enzyme engineering for accurate prediction and selection of activation pathways. Therefore, bio-precursor prodrugs will continue to be relied on as an important method in future drug design, as promising concepts to address and solve established problems in pharmacokinetics, targeting therapeutic benefit profiles, as we are able to claim here.

3.3. Self-Immolative Prodrugs

Self-immolative prodrugs are another class of prodrugs that are good for controlled drug release. This type of prodrug uses an unusual mechanism: it triggers a cascade of reactions, ultimately leading to the release of the active drug. The concept was first introduced in 1981 by Katzenellenbogen et al.. His team demonstrated the utility of 1,4- and 1,6-benzyl elimination as a mechanism for controlled drug release [9].

The general design of self-immolative prodrugs includes three key components:

1) A trigger unit, which responds to specific stimuli such as enzymatic activity, redox conditions, or light.

2) A self-immolative spacer, which undergoes an elimination reaction after ac-

tivation of the trigger.

3) An active drug payload, released after the spacer decomposes [10].

The flexibility of self-immolative prodrugs relies on the possibility of responding to diverse bio-stimuli, which allows for regulated and localized drug release. For instance, *hydrogen peroxide responsive systems* exploit the oxidative stress of certain pathological states, such as cancerous tissues, to release a therapeutic with specificity. BDP-NAC is one such case employing an aryl boronic acid pinacol ester trigger to release persulfides with cytoprotective activity that quenches reactive oxygen species (ROS) [10]. Enzyme-activated prodrugs, such as esterase-triggered prodrugs, were developed for cancer therapy that can release anticancer reagents such as carbonyl sulfide (COS) or hydrogen sulfide (H_2S), both with favorable pharmacological effects [10]. Moreover, *light-activated systems* use photocaged thiocarbamates to precisely release COS or H_2S in space and time, allowing for an extremely localized treatment with reduced ability to reach systemic circulation [10].

Self-immolative prodrugs hold some promise for therapeutically selective drug activation for several reasons; perhaps most noteworthy is their ability to generate multiple products from the same triggering event, a characteristic that has been exploited in signal amplification and drug delivery strategies [9]. This method is particularly useful in the release of sulfur-containing compounds such as persulfides that participate in important redox-signaling cascades and cellular protection.

Recent progress in self-immolative prodrug design has aimed at improving trigger specificity and release kinetics. Modular systems, such as BDP-Fluor, have presented selective H_2O_2-triggered activation, showing great therapeutic promise for oxidative stress-related diseases, such as myocardial infarction and neurodegenerative diseases [10].

Being a promising approach, self-immolative prodrugs will be used more widely in oncology, inflammation, and precision medicine as a potential modality to resolve the drawbacks associated with traditional drug delivery systems.

3.4. Type I and Type II Prodrugs

Prodrugs can be generally divided into two types according to the position where they are converted to the drug (Type I and Type II). It provides a perspective on the pharmacokinetics, efficacy, and safety of prodrugs by the consideration of the biological environment in which the activation is done [11]. The prodrugs of type I are activated intracellularly, on the target therapeutic, and/or in the main organ of first pass. In subtype IA, the prodrug(s) are converted to their active metabolites inside the cell, where the therapeutic effect is produced, e.g., 5-fluorouracil and zidovudine. This direct activity on the therapeutic site is responsible for high efficacy and reduced side effects. Type IB prodrugs, such as sulindac or heroin, in contrast, are activated in a metabolic tissue, such as the liver, gastrointestinal mucosa, or lungs. For example, sulindac is metabolized to an active sulfide metabolite

in the liver; thus, it causes less gastrointestinal irritation compared with other NSAIDs. Heroin also undergoes enzymatic hydrolysis in hepatic tissues to morphine, which produces its analgesic effect as well [11].

In contrast, type II prodrugs are bio-reversible prodrugs, which are activated outside biological fluids at or near the site of therapeutic targets. They are also divided into three subtypes. Prodrugs of type IIA, such as sulfasalazine, undergo conversion in the GI fluids. Sulfasalazine is metabolized by colonic bacteria to sulfate pyridine and mesalamine, which both exert their therapeutic effect locally in the colon, thus being useful in the treatment of inflammatory bowel diseases. Type IIB prodrugs, such as fosphenytoin, are hydrolyzed in the systemic circulation or extracellular fluid to achieve fast activation and enhanced solubility. Type IIC prodrugs have been developed for activation in close proximity to target cells or tissues, which commonly require a specific enzymatic action. One of the most notable examples is ADEPT (antibody-directed enzyme prodrug therapy), in which a prodrug is activated at the tumor location when in the conjugated enzyme-antibody complex, while the systemic toxicity can be reduced [11].

Between the two classes, type I prodrugs are particularly dependent on the intracellular metabolism to activate with desirable tissue-specific therapeutic effects, as observed with antiviral nucleosides and lipid-lowering statins. In comparison, Type II prodrugs take advantage of the extracellular space or systemic enzyme activity for activation, which can be especially useful for diseases where the desired drug effect occurs in non-cellular specific or systemic compartments, such as GI and circulatory diseases. Some prodrugs represent a mixed nature of both types, so-called Mixed-Type prodrugs. These compounds are activated at several levels simultaneously or in a step-wise manner. For example, the Sequential Mixed-Type prodrug tenofovir disoproxil fumarate is activated in the gastrointestinal fluids (Type IIA) and in the target cell (Type IA). This double-targeting strategy can achieve effective in vivo delivery and therapeutic performance and bypass the PK barriers [11].

The Type I and Type II classification can define a rational framework to gain insights into the mechanism of action of prodrugs, underlining different approaches to drug design. Type I prodrugs are superior in cellular targeting, whereas Type II prodrugs are suitable for systemic and extracellular applications. A combination of these categories can further enable precision medicine and targeted therapeutics delivery.

4. Rationale for Using Prodrugs

4.1. Improving Pharmacokinetic Profile

4.1.1. Enhancing Bioavailability

Therapeutic plasma concentration is hard to achieve when drugs have poor aqueous solubility. Thus, prodrugs that can increase bioavailability by adding hydrophilic or lipophilic functional groups are very favorable. For example, fosamprenavir, a prodrug of the HIV protease inhibitor amprenavir, increases water solu-

bility and facilitates better oral absorption. After absorption, it is directly converted into Amprenavir by cellular phosphatases, thereby enhancing oral absorption and bioavailability compared to direct administration of Amprenavir [12].

Another example is Valacyclovir, a prodrug of Acyclovir. Acyclovir has limited bioavailability (15% - 30%) due to poor absorption in the gastrointestinal tract. Valacyclovir, an L-valyl ester prodrug of Acyclovir, significantly improves its bioavailability (approximately 55%) by enhancing intestinal absorption via peptide transporters. Once in circulation, it is hydrolyzed to release Acyclovir, providing better antiviral efficacy with lower dosing frequency [1].

Curcumin, a natural compound with extensive pharmacological benefits, suffers from poor bioavailability due to low solubility and rapid metabolism. To address this, curcumin prodrugs have been developed, incorporating promoieties that enhance stability and absorption. Studies indicate that curcumin prodrugs improve systemic circulation levels and prolong curcumin's therapeutic effects [13].

4.1.2. Improving Stability

Certain drugs degrade rapidly in the stomach due to acidic conditions or enzymatic metabolism. Prodrug modifications, such as esterification or phosphate conjugation, protect the active drug from premature degradation. Omeprazole, a proton pump inhibitor, is a classic example where the prodrug formulation allows it to remain stable until activation in the parietal cells [7].

Another example is the development of amino acid prodrugs, which improve stability through strategic linker modifications. Research indicates that prodrugs containing methoxy, ethoxy, and propylene glycol linkers exhibit varying degrees of stability, with propylene glycol-linked prodrugs showing the highest stability at physiological pH [14]. The study further highlights that amino acid side chains influence stability, with aliphatic amino acid-based prodrugs being more stable than their aromatic counterparts.

Ester prodrugs also play a crucial role in improving drug stability by modifying ester linkages. For example, lipid ester prodrugs utilize fatty acid moieties to protect the drug from premature hydrolysis and enhance membrane permeability [15]. Modifications like this can help drugs to resist rapid degradation in the gastrointestinal tract, ensuring that the drug is optimally absorbed.

4.2. Targeted Drug Delivery

Some prodrug design strategies include using tissue-specific enzymes, pH variation, and metabolic pathways. By doing so, site-specific activation can be achieved. In oncology, the goal is to selectively release cytotoxic agents in tumor cells while minimizing systemic toxicity. For instance, capecitabine is a prodrug of 5-fluorouracil that undergoes enzymatic conversion primarily in tumor tissues, reducing off-target effects [1].

Another approach to targeted delivery involves esterase-sensitive prodrugs, which activate in specific tissues where esterase enzymes are overexpressed. For example, esterase-responsive nanoparticles have been utilized to selectively re-

lease anticancer drugs in tumor environments, thereby improving treatment efficacy and reducing systemic toxicity [15].

Similarly, pH-sensitive prodrugs leverage the acidic microenvironment of tumors to trigger drug activation. Doxorubicin-based prodrugs incorporating acid-labile linkers have demonstrated improved tumor selectivity, reducing adverse effects on normal tissues [14].

4.3. Reducing Side Effects and Toxicity

By controlling the release and distribution of active drugs, prodrugs help minimize adverse effects. In NSAIDs, direct administration can lead to gastrointestinal irritation, but prodrug forms such as nabumetone bypass the gastric mucosa and are activated in the liver, reducing gastric toxicity [8].

Another strategy involves enzyme-specific prodrugs, which are activated only in target tissues, thereby limiting systemic exposure and reducing side effects. For example, phosphate-based prodrugs have been used to reduce renal toxicity in antiviral therapies by ensuring drug activation only after absorption [15].

Moreover, site-specific hydrolysable prodrugs have been engineered to remain stable during circulation but undergo enzymatic conversion at the intended site of action. This approach has been particularly effective in reducing hepatotoxicity in chemotherapeutic agents by confining drug activation to tumor tissues [14].

5. Prodrug Design Strategies

5.1. Carrier-Linked Prodrug Design Strategy

Carrier-linked prodrugs are designed by attaching promoieties in the form of a dashboard via a covalent bond, so that undesirable properties, such as poor solubility or a short half-life, can be mitigated. The carrier is cleaved with the help of enzymes or by chemical means to release the active drug. Enalapril is an example of a carrier-linked drug. It is converted to enalaprilat (the active form) through hydrolysis in the liver by enzymes such as carboxylesterase [16].

The design for a carrier-linked prodrug consists of carefully selecting the promoieties. It must be both non-toxic and able to be split enzymatically or chemically by physiological conditions [7]. Commonly available carrier moieties, such as PEG (polyethylene glycol), fatty acid chains, and macromolecules like albumin or antibodies, can enhance bioavailability in addition to allowing for tissue-specific targeting [13].

This is illustrated by a few examples of advanced strategies for prodrug development, which show how different approaches can be used to improve drug efficacy and delivery.

An example is the prodrug of Oseltamivir carboxylate, *Oseltamivir*, which improves oral availability by means of esterification and covers up polar groups. Also, *paclitaxel prodrugs* like Protaxel use carbonate linkages with pH-dependent cleavage, enhancing both solubility and tumor specificity; thus, they offer a more successful means for treating cancer.

For a successful application, the linker between the drug and carrier must demonstrate:

1) Sufficient stability during formulation and circulation,

2) Rapid and site-specific cleavage in the body,

3) Inertness of the released carrier moiety,

4) Improved pharmacokinetics or therapeutic index over the parent drug alone [7].

Overall, carrier-linked prodrugs represent a rational and versatile approach to overcoming the limitations of many lead drug candidates and are a cornerstone in modern prodrug design.

5.1.1. Mutual Prodrug Strategy

Mutual prodrugs are a specialized subgroup of carrier-linker prodrugs in which the carrier is not an inert molecule, but rather another pharmacologically active drug. This design consists of two active drugs linked to one another by covalent bonds. Each drug functions as a prodrug for the other, so that both drugs will be released whenever there is enzymatic or chemical cleavage. This dual-drug approach can enhance therapeutic outcome by delivering drugs with synergistic effects or complementary actions while minimizing side reactions [17].

The mutual prodrug strategy can be especially helpful when one drug plays the role of an adjuvant in targeting or delivering the other, or when both drugs face similar challenges concerning bioavailability and/or toxicity. This approach is also highly advantageous if combination therapy is desired, as it allows two pharmacologically active agents to be combined into a single molecular entity, thereby offering streamlined administration and the potential for enhanced therapeutic synergy.

Mutual prodrug Aspacardin is an example. Aspirin and paracetamol are chemically linked into a single molecule in this case. In this form, it exhibits enhanced gastrointestinal tolerability and improved synergistic analgesic activity. Likewise, sultamicillin is a mutual prodrug combining ampicillin and sulbactam. This combination is designed to overcome β-lactamase-mediated resistance while enhancing oral bioavailability [17].

Overall, mutual prodrugs extend the utility of carrier-linked strategies by incorporating bioactive synergy, targeting potential, and co-delivery benefits, making them a powerful tool in rational prodrug design.

5.1.2. Co-Drug Strategy

Co-drugs are structurally like mutual prodrugs but often do not require complete cleavage into separate active agents. Instead, they function as a single hybrid molecule where pharmacological effects or improved pharmacokinetics are achieved through combination. Co-drugs are frequently used to overcome poor absorption or short half-lives [1].

The terms *co-drug* and *mutual prodrug* are often used interchangeably in the field of prodrug design, as both involve the covalent linkage of two pharmacologically active agents into a single molecular entity. Upon administration, the co-

drug or mutual prodrug is inactive but is designed to release both active components through enzymatic or chemical cleavage in vivo. However, subtle distinctions exist in their conceptual application. Mutual prodrugs are traditionally defined as bio-reversible conjugates where each drug acts as promoieties for the other, typically linked via a cleavable bond such as an ester or amide. These are often designed with site-specific release in mind, sometimes to reduce toxicity or improve absorption. In contrast, the term co-drug is broader and may refer to dual-drug conjugates with or without a cleavable spacer, often emphasizing synergistic therapeutic effects or pharmacokinetic enhancements. Despite these nuances, in most contemporary pharmaceutical contexts, the two terms are functionally equivalent and used interchangeably [18].

5.2. Bio-Precursor Prodrug Design Strategy

Bio-precursor prodrugs are inactive molecules that undergo molecular modification within the body to regenerate the active drug without requiring a distinct carrier moiety. Unlike carrier-linked prodrugs, bio-precursors are derived through structural alteration of the parent drug itself, typically via redox reactions, hydrolysis, or enzymatic cleavage [6] [15].

Bio-precursor prodrugs do not require an additional carrier but undergo metabolic transformation into an active form. These transformations often involve oxidation, reduction, or hydrolysis. Levodopa, a prodrug of dopamine, crosses the blood-brain barrier and is converted enzymatically to dopamine in the CNS, overcoming the poor penetration of direct dopamine administration [1]. The main goal of bio-precursor prodrug design is to overcome challenges such as poor oral bioavailability, rapid metabolism, or selectivity by enabling targeted in vivo activation. This approach is particularly useful for drugs that are otherwise unstable or poorly absorbed in their active form [19].

Sulindac is an example of a bio-precursor prodrug. It is a non-steroidal anti-inflammatory drug. The active sulfide form of the drug is converted through reductive metabolism in the liver. By doing so, the side effects in the gastrointestinal tract are reduced [19]. Another example is Tegafur, which is an oral anticancer agent. It is metabolized by the liver into 5-fluorouracil (5-FU). Tegafur is used as a prodrug instead of 5-FU because it allows for oral administration and provides a slower, more controlled release of the active drug. This helps improve effectiveness and reduce the severe side effects associated with direct 5-FU treatment [15].

This approach prevents the use of bulky and potentially toxic promoieties, but also allows a simpler chemical structure for the prodrug itself. However, their reliance on metabolic enzymes introduces variability based on interindividual differences, which may affect the consistency of drug activation across patient populations [19].

5.3. Double Prodrugs (Pro-Prodrugs)

Beyond carrier-linked and bio-precursor prodrugs, several advanced strategies have been developed to enhance site-selectivity, stability, and therapeutic synergy.

These include double prodrugs, mutual prodrugs, targeted prodrugs, macromolecular prodrugs, self-immolative systems, and co-drugs [1] [6] [19].

Double prodrug strategy, also referred to as cascade latentiation, involves the design of a prodrug that itself is a derivative of another prodrug. In this sequentially activated system, the initial pro-prodrug undergoes an enzymatic or chemical transformation to form an intermediate prodrug, which is subsequently converted to the active parent drug. This approach provides enhanced control over drug release, improved stability, and potential for site-specific activation [20].

This concept is particularly useful when single prodrugs suffer from poor chemical stability or incomplete activation. For instance, a chemically labile prodrug can be stabilized through further derivatization into a double prodrug form, where the first cleavage step is enzymatic, thus offering better in vitro formulation properties (e.g., longer shelf life), while ensuring efficient in vivo activation [20].

The double prodrug strategy offers a powerful means of optimizing drug delivery, particularly in cases where conventional prodrugs are limited by instability or poor pharmacokinetics.

A classic example is 6-*deoxyacyclovir*, a double prodrug of the antiviral agent acyclovir. While acyclovir suffers from poor oral bioavailability due to low solubility, 6-deoxyacyclovir is significantly more water-soluble and undergoes in vivo conversion by xanthine oxidase to release acyclovir, improving absorption from 15 - 20% to over 75% [20].

In ophthalmology, *pilocarpine diesters* represent another successful application. Although pilocarpine acid monoesters improved corneal penetration, they were chemically unstable in solution. The development of a double ester (diester) prodrug provided enhanced aqueous stability and a two-step activation mechanism: enzymatic hydrolysis followed by intramolecular lactonization, resulting in improved shelf life and ocular bioavailability [20].

This strategy is especially valuable for improving prodrug stability during storage and formulation, enabling site-specific drug delivery through transport enhancement and localized activation, extending drug release profiles for compounds with short half-lives, and modulating physicochemical properties such as solubility or lipophilicity via layered promoieties design. Its versatility has been demonstrated across various drug classes, including antivirals, benzodiazepines, and antiglaucoma agents, making it a rational and robust solution when traditional prodrug approaches prove insufficient.

5.4. Targeted Prodrug Strategy

Targeted prodrugs are designed for selective activation at specific biological sites such as tumors, inflamed tissues, or organs with unique enzyme expression. This can be achieved through:

5.4.1. Enzyme-Sensitive Prodrugs (e.g., Glucuronidase-Activated Systems in Tumors)

Enzyme-sensitive prodrugs are designed to be activated by specific enzymes that

are overexpressed or uniquely present in diseased tissues. This approach enables site-specific drug release, thereby enhancing therapeutic efficacy while reducing systemic toxicity. For instance, enzymes such as β-glucuronidase, which are overexpressed in tumor microenvironments, have been used to trigger the release of anticancer agents from glucuronide-linked prodrugs. Similarly, protease-sensitive linkers have been incorporated in prodrugs to target matrix metalloproteinases (MMPs), which are commonly elevated in cancer and inflammatory conditions. Advanced therapeutic systems like Antibody-Directed Enzyme Prodrug Therapy (ADEPT) utilize engineered enzymes conjugated to antibodies that bind selectively to tumor cells. Once localized, the systemically administered prodrug is cleaved by the enzyme, ensuring localized drug activation. The specificity and catalytic efficiency of enzymes make this strategy a powerful tool for precision drug delivery.

5.4.2. pH-Sensitive Prodrugs (e.g., Acid-Labile Linkers in the Stomach or Tumor Microenvironment)

pH-sensitive prodrugs exploit the distinct acidic environments of pathological tissues, such as tumors, sites of inflammation, or intracellular endosomes and lysosomes. These regions often exhibit lower pH values (around pH 6.5 or lower) compared to normal physiological pH (approximately 7.4). By incorporating acid-labile linkers—such as hydrazones, cisaconityl groups, or acetal bonds—into prodrug structures, drug release can be triggered specifically under acidic conditions. For example, doxorubicin has been conjugated via a hydrazone bond to polymeric carriers, resulting in pH-responsive systems that release the active drug in the acidic tumor milieu or within acidic intracellular compartments following endocytosis. This approach minimizes premature drug release in systemic circulation and enhances accumulation at the target site. The simplicity and environmental responsiveness of pH-sensitive designs make them highly attractive for developing safer and more effective therapies.

5.4.3. Redox-Sensitive Prodrugs (e.g., Disulfide Bonds Cleaved by Intracellular Glutathione)

Redox-sensitive prodrugs are engineered to respond to the differences in redox potential between healthy and diseased tissues, particularly in cancer cells, which often exhibit elevated levels of intracellular reducing agents like glutathione (GSH). By incorporating redox-labile linkages—such as disulfide or thioketal bonds—into the prodrug structure, selective activation can be achieved within the reductive cytosol of tumor cells. Upon cellular uptake, the high intracellular GSH concentration cleaves the disulfide bonds, releasing the active drug. This strategy has been successfully applied in various anticancer systems, including nanoparticle-based drug conjugates and polymeric micelles. For example, paclitaxel prodrugs with disulfide linkers have demonstrated improved tumor targeting and reduced systemic toxicity. Redox-sensitive systems offer a dynamic and selective mechanism of drug release, particularly useful in targeting intracellular compartments or oxidative stress-related pathologies [1] [21].

5.5. Macromolecular Prodrug Strategy

Macromolecular prodrugs use polymers, proteins, or antibodies as carriers covalently linked to the active drug. These systems can enhance pharmacokinetics, prolong circulation time, and facilitate passive or active targeting. PEGylated drugs (e.g., PEG-interferon) and polymer-drug conjugates are prominent examples used in cancer and antiviral therapies [19].

Macromolecular prodrugs (MPs) have emerged as an attractive approach in drug delivery, where drugs are covalently linked to high-molecular-mass carriers, which can be synthetic polymers or endogenous proteins. Such macromolecular conjugates typically bear multiple copies of the drugs, resulting in improved pharmacokinetic properties, a prolonged blood half-life, and passive tumor accumulation through the enhanced permeability and retention (EPR) effect. Recent developments of MP designs are based on biodegradable main chain polymers, such as HPMA copolymers with cleavable GFLG linkers or reductive-sensitive backbones containing disulfide bonds. They enable triggered degradation and drug release in response to intracellular or tumor-associated stimuli, thereby decreasing nonspecific toxicity. Furthermore, albumin-polymer conjugates are considered an attractive alternative, leveraging the long half-life and receptor-mediated recycling of albumin to carry high amounts of drugs while retaining biocompatibility. These developments point out MP systems as a flexible and translationally appealing strategy for targeted, efficient, and safer drug delivery [22].

5.6. Self-Immolative Prodrugs Strategy

Self-immolative prodrugs are an advanced construction principle for the controlled liberation of bioactive agents in a stimulus-triggered cascade reaction. At the core of the idea lies a cleavable "trigger" unit, directly attached to the warhead via a self-immolative spacer, in general, minimally comprising a 1,4- or 1,6-benzyl elimination motif, was postulated. When stimulated by a target environment (example: pH, enzymatic or reactive oxygen species), the trigger is extricated, and a spontaneous intramolecular reaction is activated, thus enabling the release of the drug. Dillon et al. exploited this feature to design persulfide-releasing prodrugs triggered only by oxidative stress. Their BDP-NAC system utilizes an aryl boronic ester, which reacts with H_2O_2, causing it to undergo self-immolation and release the NAC-SSH, a powerful antioxidant. Such precision, temporal, and spatial control of drug activation and minimization of off-target effects make self-immolative linkers a highly favorable method for stimulus-responsive drug delivery [10].

Together, these approaches expand the landscape of prodrug design, offering more quantitative and precise control over drug release, targeting, and therapeutic synergy.

6. Challenges in Prodrug Development

Although they offer significant advantages in improving drug solubility, permeability, and site-specific drug targeting, developing new prodrugs is a challenging

process. A major challenge in prodrug design is the reliable and efficient conversion of an inactive prodrug to the active parent compound, an essential process for a successful therapeutic outcome. This conversion is generally enzymatically mediated by hydrolysis, oxidation, or reduction strategies, which present wide interindividual differences due to genetic polymorphisms, disease, age, diet, and coadministered medications [3]. Exceptionally, the prodrug valacyclovir for antiviral therapy needs to be activated by the human valacyclovirase in the intestinal wall and in the liver. Yet diversity in expression of enzyme levels can cause underconversion in individual patients, with subtherapeutic plasma levels of the active drug, acyclovir [4]. Likewise, the anticancer prodrug capecitabine is metabolized through a three-step enzymatic activation pathway and converted into the C drug in the presence of thymidine phosphorylase, which is preferentially overexpressed in tumors relative to normal tissues. Although it enables tumor-targeted activation of drugs, heterogeneous thymidine phosphorylase levels in patients may result in varying responses to drugs and adverse effects.

Additionally, interspecies differences in enzyme expression make it challenging to extrapolate preclinical data from animal models to humans, thereby complicating dose prediction during early-phase clinical trials. To address these challenges, prodrug strategies increasingly incorporate molecular targeting, co-delivery systems, or diagnostic tools that assess enzymatic activity in vivo. Despite such innovations, reliable and reproducible activation across patient populations remains one of the most demanding aspects of prodrug design.

Stability represents a major hurdle in prodrug design, as both chemical and enzymatic degradation pathways must be tightly controlled to ensure consistent therapeutic outcomes. A prodrug must maintain sufficient stability during manufacturing, storage, and transit through the gastrointestinal tract (for oral agents) to avoid premature release of the active drug. However, many prodrugs—particularly ester- and phosphate-based ones—are inherently labile. For example, ester prodrugs like enalapril are designed to be hydrolyzed by ubiquitous esterase in the liver and plasma; yet, they can also undergo unintended hydrolysis during storage, particularly under humid or acidic conditions, compromising product shelf-life and dose accuracy [12]. Phosphate prodrugs, such as fosamprenavir, are prone to hydrolysis in aqueous environments, especially in the presence of trace metal ions or under elevated temperature, necessitating stringent control of formulation pH and excipient selection [3]. Additionally, prodrugs that rely on enzymatic activation face variability due to species- or tissue-specific expression of enzymes, such as carboxylesterases or alkaline phosphatases. This variability can impact not only efficacy but also stability during in vitro testing or preclinical modeling. Some prodrugs, like sulindac (a bio-precursor), require metabolic reduction, and their oxidative instability in light or oxygen-rich environments can complicate formulation. Therefore, achieving the ideal balance between sufficient shelf-stability and efficient bioconversion remains a central challenge in prodrug development. Strategies such as double prodrug design, protective encapsulation, lyophilization,

or co-formulation with stabilizers are often employed to mitigate these issues.

Toxicity remains a critical challenge in prodrug development, particularly due to the presence of promoieties that are released upon bioconversion. Although these chemical groups are frequently engineered to be pharmacologically silent, their metabolism can occasionally disrupt normal physiology. A well-known example thereof is pivaloyloxymethyl (POM) esters, which have been utilized in the synthesis of various antiviral prodrugs, including adefovir dipivoxil and tenofovir disoproxil. They produce pivalic acid on hydrolysis, which is conjugated with carnitine and eliminated. Long-term exposure to the drug can lead to a significant reduction in the systemic carnitine pool, which can then possibly worsen fatty acid metabolism, particularly in children or in malnourished individuals [3]. A related issue is the release of formaldehyde, as is evident in prodrugs of methenamine, that could become mutagenic if not meticulously regulated [6]. Moreover, the in vivo production of the active species of a prodrug as a reactive intermediate (e.g., quinones or aldehydes) could lead to oxidative stress or immune responses, and hence off-target toxicity as a result of any potential formation in vivo of such reactive intermediates. As a result, a comprehensive safety profile evaluation of both the parent compound and the liberated promoieties is essential, often requiring separate toxicological assessments. These problems highlight the need to select chemically stable and rapidly excretable prodrugs in the prospective design of prodrugs, particularly for long-term therapies.

Furthermore, formulation problems frequently occur because of the modified physicochemical characteristics, which complicate drug formulations during prodrug design. For example, increasing lipophilicity to take advantage of improved membrane permeability may lead to decreased aqueous solubility, which may not be suitable for oral and parenteral formulations. Esters of the amino acids, e.g., the valine esters, have better solubility and permeability, but in some cases too high susceptibility for premature hydrolysis to be suitable for all applications, i.e., a poor shelf-life or non-reproducible drug release [12]. Phosphate ester prodrugs, likewise effective for solubility enhancement, tend to suffer stability problems (e.g., pH-dependent hydrolysis, or compatibility with some excipients) [3]. The effects of these changes on drug dissolution rate, stability in the GI fluids, and predictability of bioavailability contribute to making dosage form development difficult. Therefore, further formulation approaches, e.g., protective coatings, buffering systems or complexation agents, are frequently necessary to ensure drug performance and therapeutic benefit.

Despite their utility, the application of prodrugs in oncology remains underexploited, even though cancer therapy would particularly benefit from their targeted activation capabilities. Many chemotherapeutic agents are limited by their narrow therapeutic index and systemic toxicity, which severely restrict dosing and reduce patient quality of life. Prodrugs offer a promising solution by allowing site-specific activation—using tumor-associated enzymes (e.g., β-glucuronidase or matrix metalloproteinases), acidic microenvironments, or hypoxia-triggered systems—

to release cytotoxic agents preferentially at the tumor site while sparing healthy tissues [5]. For instance, synthetic prodrugs based on naphthyl combretastatin scaffolds have been engineered to undergo bond-forming reactions in vivo through transition metal catalysis, achieving selective tumor growth suppression in mouse models [5]. However, challenges such as controlling off-target activation, ensuring sufficient prodrug accumulation at tumor sites, and developing biocompatible activation catalysts have slowed broader clinical adoption [3]. Future research combining prodrug chemistry with biorthogonal catalysis and nanocarrier delivery systems may unlock the full potential of prodrugs in oncology.

In addition to scientific and formulation challenges, prodrug development must also navigate complex regulatory requirements. Agencies such as the U.S. Food and Drug Administration (FDA) mandate comprehensive evaluations of both the active drug and any promoieties released upon activation. This includes toxicological assessments, pharmacokinetic profiling, and demonstration of safety for long-term use. The FDA specifically emphasizes that promoieties should be pharmacologically inert, non-toxic, and rapidly cleared from the body. Furthermore, regulatory pathways can be prolonged if the prodrug introduces a novel mechanism of activation or if human enzymes involved in bioconversion are not well-characterized. These hurdles can complicate Investigational New Drug (IND) applications and delay New Drug Application (NDA) approval, highlighting the importance of incorporating regulatory considerations early in prodrug design.

In summary, while the prodrug approach represents a promising strategy for optimizing drug properties, its success is contingent upon addressing challenges in activation, formulation, and safety through careful molecular design and interdisciplinary collaboration.

7. Future Perspectives in Prodrug Development

The future of prodrug research lies at the intersection of precision medicine, nanotechnology, and biotechnology. As the field evolves, advances in targeted drug delivery and molecular design are opening new avenues for site-specific activation and improved therapeutic outcomes. Technologies such as antibody-drug conjugates (ADCs), stimuli-responsive polymeric carriers, and gene-directed enzyme prodrug therapy (GDEPT) offer unprecedented precision in delivering and activating prodrugs at specific cellular or tissue sites, thereby reducing systemic toxicity and enhancing efficacy [4] [5].

Nanocarrier platforms, including liposomes, dendrimers, and pH-sensitive micelles, can be engineered to co-deliver prodrugs with their activating enzymes or respond to endogenous stimuli such as pH, redox state, or enzymatic gradients. These systems enable spatiotemporal control of activation and are especially valuable in treating heterogeneous diseases like cancer or inflammation.

Simultaneously, computational tools and machine learning algorithms are revolutionizing the rational design of prodrugs. In silico models now assist in pre-

dicting enzymatic cleavage rates, transporter interactions, and physicochemical properties such as solubility and permeability. These approaches significantly accelerate the lead optimization process and reduce reliance on labor-intensive empirical screening [23].

With the rapid expansion of biologics in modern pharmacotherapy, a new frontier is emerging in the form of *probiologics*—engineered protein therapeutics that are biologically inactive until they undergo selective enzymatic activation in diseased tissues. These constructs offer an elegant solution for minimizing off-target effects in sensitive applications such as immuno-oncology, regenerative medicine, and gene therapy.

Furthermore, the integration of omics data, high-throughput screening, and synthetic biology will likely catalyze the development of more intelligent and personalized prodrug systems. As regulatory frameworks evolve to support such innovations, prodrugs are poised to become central tools in the future of precision, adaptive, and systems-based medicine.

In conclusion, the prodrug approach offers a powerful means to optimize drug properties such as solubility, permeability, stability, and site-specific activation. Despite substantial progress, challenges related to bioconversion variability, formulation complexity, toxicity of promoieties, and regulatory constraints continue to hinder widespread application. However, emerging technologies—ranging from antibody-drug conjugates and gene-directed enzyme prodrug therapy to nanocarrier-based delivery systems and probiologics—are redefining what is possible in targeted drug design. Concurrently, computational modeling and machine learning are accelerating the development of prodrugs with enhanced predictability and performance. As precision medicine continues to evolve, the integration of prodrug strategies with systems biology and personalized therapeutics holds great promise for delivering safer, more effective, and patient-tailored treatments.

Acknowledgements

Avoid the stilted expression, “One of us (R. B. G.) thanks...” Instead, try “R. B. G. thanks”. Do NOT put sponsor acknowledgements in the unnumbered footnote on the first page, but at here.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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