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Enhancing prodrug development, strategies and challenges

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Abstract

To enhance their pharmacokinetic and pharmacodynamic characteristics, prodrugs are bio reversible derivatives of active medicinal ingredients. Prodrug creation, despite its potential, is a complicated process that involves factors like membrane permeability, enzymatic activation, and chemical stability. Different prodrug development approaches, such as mutual prodrugs, bio precursor prodrugs, and carrier-linked prodrugs, are covered in this review. We also draw attention to the difficulties in prodrug development, including addressing formulation problems, guaranteeing safety and efficacy, and forecasting metabolic destiny. Through comprehension of these tactics and obstacles, scientists can create more potent prodrugs that improve the therapeutic effectiveness and safety of medications. A viable approach to overcoming the drawbacks of drug delivery, such as low bioavailability, toxicity, and lack of selectivity, is prodrug creation. Researchers can enhance the pharmacokinetic and pharmacodynamic characteristics of medicinal medicines by creating prodrugs that can be activated in vivo. Recent developments in prodrug development, such as creative activation mechanisms, targeted delivery methods, and revolutionary prodrug design tactics, are highlighted in this abstract. We'll talk about the prospects and difficulties in prodrug development, with an emphasis on how prodrugs could improve the safety and effectiveness of a variety of medicinal medicines.

Keywords: drug development, bio reversible derivatives, pharmacokinetics, prodrugs, therapeutic efficacy, and bioactive pathways.

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Introduction

A key component of modern pharmaceutical innovation is the strategic development of prodrugs, which aims to minimize side effects while improving the pharmacokinetics and pharmacodynamics characteristics of therapeutic agents. In order to improve clinical efficacy and patient outcomes, a well-thought-out prodrug strategy requires precise chemical alterations that improve drug absorption, distribution, metabolism, and excretion (ADME) properties. Achieving site-specific activation, resolving inter-individual heterogeneity in enzymatic bioactivation pathways, and preserving chemical and metabolic stability during storage and systemic circulation are just a few of the complex hurdles involved in creating the perfect prodrug [1].

Derivatives of active drug moieties, prodrugs are intended to be converted by the body and release the active parent drug. The prodrug strategy is used to get around problems with pharmaceuticals, pharmacokinetics, or pharmacodynamics, like poor stability, low oral absorption, or insufficient site specificity. Prodrugs have grown in popularity and success in recent years; currently, they make up about 10% of all medications sold worldwide, 20% of all small molecular medicines approved between 2000 and 2008, and, when looking specifically at 2008, more than 30% of all approved drugs were prodrugs [2].

The pharmaceutical sciences have seen a molecular revolution in recent years; instead of depending solely on empirical fitting based on plasma levels, modern ADME

(absorption, distribution, metabolism, and excretion) research takes into account molecular/cellular factors like membrane transporters and the expression and distribution of cellular enzymes. As will be discussed in this essay, the prodrug method in particular, as well as drug design and delivery generally, were significantly impacted by this molecular revolution. After oral delivery, the prodrug method is commonly used to improve drug absorption. This can be achieved by using the traditional/classic prodrug method, such as masking charged moieties and improving drug lipophilicity and passive diffusion through the use of different carboxylic acid esters that, upon hydrolysis, release the active carboxylic acid [3].

Prodrugs are substances that are physiologically inactive but become pharmacologically active after being administered. Prodrugs are frequently designed to get past pharmacokinetic obstacles including poor absorption and solubility, high first-pass metabolism, or quick excretion, as well as pharmacodynamic obstacles like toxicity, adverse effects, and low efficacy. Prodrugs are typically activated by chemical reactions (inter- or intra-molecular) like hydrolysis and oxidation, or by enzymatic mechanisms like those involving cytochrome enzymes, amidases, and esterases. Numerous prodrugs have shown promise in the treatment of both acute and chronic diseases [4].

Numerous prodrugs have shown promise in the treatment of both acute and chronic illnesses. Prodrugs designed to treat hypertension, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), are among the effective examples. Others include clopidogrel and prasugrel, which are used to prevent platelet aggregation in clotting problems and heart attacks. One popular prodrug for the treatment of Crohn's disease and ulcerative colitis is sulfasalazine. The prodrug methodology is still being investigated, and new prodrugs are continually being created, despite the fact that the manufacturing of biological therapeutics, such as monoclonal antibodies, is thought to be a promising method of creating new medications. Of all new molecular entities approved by the FDA between 2008 and 2017, prodrugs accounted for 12.4% (31 out of 249) [5].

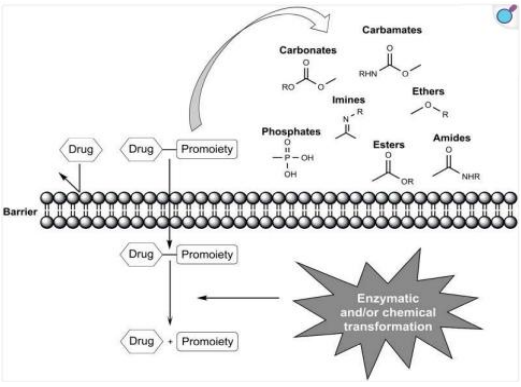

Fig 01: Invivo Bioactivation of Prodrugs by Enzymatic Transformation

Prodrugs continue to be a fundamental component of medicinal chemistry, providing a flexible approach to the creation of new therapeutic molecules. The physicochemical characteristics of drug candidates can be improved with this drug discovery approach, especially when it comes to overcoming obstacles that arise during the switch from preclinical to clinical trials. Although new chemical entities with strong pharmacological activity are produced by contemporary drug discovery methods such as combinatorial chemistry and high-throughput screening, many of these entities have suboptimal physicochemical properties, requiring formulation technologies or chemical modification for proper performance. Therefore, the prodrug approach offers a simplified method of overcoming drug development obstacles while facilitating the enhancement of various pharmacokinetic properties, such as absorption, distribution, metabolism, and excretion (ADME), optimizing dissolution rates, and lipophilicity without changing the drug target or indication or compromising pharmacological efficacy [6].

In vitro, prodrugs are inactive; but, in vivo, they undergo enzymatic or chemical metabolism to become active parent drugs. Before prodrugs can begin to have therapeutic benefits, they must go through a controlled or predictable chemical or enzymatic biotransformation into active forms. [7, 8]. The phrase "prodrug" refers to a circumstance in which the active ingredient of a drug and a "promoiety" create a chemical connection. Prodrugs are necessary to lessen the adverse pharmacodynamic or pharmacokinetic effects of active pharmaceuticals.

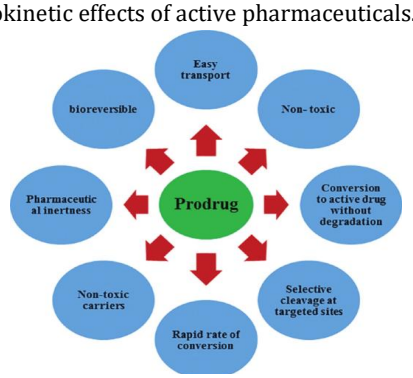

Fig 02: Prodrug Characteristics

A prodrug is a chemical molecule that, when transformed in live organisms, creates metabolites or original pharmaceuticals with pharmacological activity or greatly improved pharmacological activity because it has no or weak activity on its own. In 1958, Adrien Albert introduced the idea of a prodrug, defining a biologically active precursor as a derivative form of a drug molecule that is not pharmacologically active in and of itself but can be transformed into a parent drug with pharmacological effects through in vivo chemical transformations or enzymatic reactions .Through the creation of prodrugs, this approach seeks to maximize the ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of medications in order to increase their efficacy and safety. A prodrug's release method can be

divided into three categories: either the active drug is released from its inert state prior to, during, or following absorption in order to achieve precise action on the target location [7].

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It has been shown that the prodrug strategy has been extremely successful in recent years. Prodrugs are thought to make up 10% of all marketed medications, 20% of small molecular weight medications licensed between 2000 and 2008, and 12% of the drug market between 2008 and 2017.

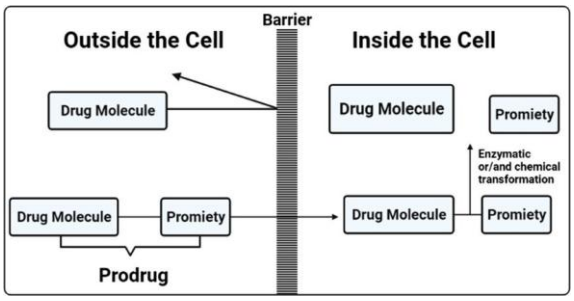


Fig 03 Prod rug Illustration

Various strategies are employed in the prodrug approach. The most common of which is making a prodrug susceptible to abundant enzymes by functionalization with a group that can be cleaved to produce the active form of the drug. The prodrug approach to drug optimization offers chemical stability such as an inactive oral prodrug can be stable in the gastrointestinal tract and only be bio converted by CYP450 in the liver, plasma, or GIT mucosal esterase, or other enzymes. The word Prodrug was introduced by Adrien Albert in 1951 and the concept was identified by Harper in 1959.Harper claims that the term "latentiated" refers to medications that require bioactivation. According to the International Union of Pure and Applied Chemistry (IUPAC), a prodrug is defined as a biologically inactive molecule that undergoes a chemical or enzymatic transformation to become an energetic active drug. This definition remains the most appropriate to this day [9].

Classification

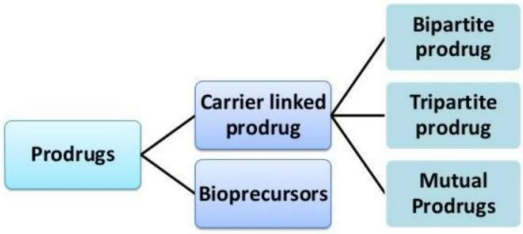


Fig 04: Prodrug Classification

Prodrugs are categorized into two classes based on their constitution, lipophilicity, bioactivation mechanism, and catalyst.

A. Carrier – linked prodrugs.

B. Bio precursor prodrug.

1. Carrier Linked Prodrug

It has a group (like an ester) that is easily broken down by enzymes to expose the actual medicines. For effective activation in vivo, the linking bond needs to be labile, and the group that is eliminated should ideally be pharmacologically inactive and harmless. A carrier group is attached to the active drug to change its physicochemical characteristics, creating a carrier-linked prodrug.

It can be divided into the following categories based on the kind of carrier

A) Bipartite Prodrug, Double Prodrugs, or Cascade-Latentiated Prodrug

The active ingredient in this prodrug is covalently bound to an inert transport or carrier moiety, usually an amide or ester. Because of the connected carrier, these prodrugs have significantly altered lipophilicity. Either chemically or enzymatically, hydrolytic cleavage releases the active medication. Following an in vivo enzymatic or non-enzymatic assault, the prodrug and carrier must be harmless.

B) Tripartate Prodrug

In this case, the medication and carrier moiety are not joined directly. Initially, the linker is connected to the drug moiety, and then, the linker is coupled to the carrier.

c. Macromolecular prodrugs:

Wherein macromolecules such as proteins, peptides, polymers, cyclodextrins, dextrans, and polysaccharides are employed as carriers. d. spot-specific prodrugs: When an active medication is transported to a particular targeted spot by a carrier.

e. Mutual prodrug:

where a different physiologically active medication is utilized as the carrier rather than an inert molecule. A mutual prodrug is made up of two pharmacologically active substances that work together to promote the other substance and vice versa. The chosen carrier may provide synergistic activity if its biological action is identical to that of the parent medication, or it may provide additional

biological action that the parent medication does not provide, guaranteeing an extra benefit.

The carrier could also be a medication that helps direct the parent medication to a particular organ, cell, or site, or it could enhance a medication's site specificity. Some of the parent medications' negative effects may also be mitigated by the carrier medication.

2. Bioprecursor/Metabolic Precursor

No carrier molecule is used in this method. In this case, an inactive medication is being chemically modified to become an active compound or further metabolized into an active form with the intended therapeutic efficacy. This process involves chemical reactions, such as oxidation or reduction (for instance, amine to carboxylic acid to aldehyde) [10].

Classification according to activation mechanisms and chemical structure

Carrier-Linked Prodrugs:

A biologically active drug is conjugated with a transient promoiety (carrier molecule) to create these prodrugs, which control the drug's release rate, metabolic stability, and site-specific activation. To release the active medication at the intended location, the carrier moiety is broken down chemically or enzymatically.

Ester Bonds

Rapidly hydrolysed in the bloodstream, assuring fast activation (e.g., aspirin hydrolyzed to salicylic acid).

Amide bonds:

Amide bonds allow for slower and longer drug release since they are more stable in circulation (e.g., L-dopa, a prodrug of dopamine).

Carbamate bond

Offers enhanced metabolic stability and regulated activation (e.g., fosphenytoin, a prodrug of phenytoin). By interacting with endogenous transporters, such as glucose or amino acid transporters, certain carrier-linked prodrugs take advantage of tissue-specific activation, which guarantees selective uptake and bioactivation at the target location. Bio precursor prodrugs don't need an external promoiety, in contrast to carrier-linked prodrugs. Rather, the active medication is produced by enzymatic or chemical modification via intracellular mechanisms [11].

Oxidative activation

Releases the active form through hepatic enzymes such cytochrome P450 (CYP450)(eg., codeine converted into. morphine).

Activation by reduction

Mitomycin C, an anticancer drug that is selectively activated under hypoxic conditions, is one example of an agent that is activated in hypoxic environments, such as tumor micron.

Application of Specialized Prodrugs

Some prodrugs are made especially to activate specific targets in complex diseases like cancer, infectious diseases, and neurological disorders. In order to maximize effectiveness and reduce systemic toxicity, these prodrugs are designed to stay dormant until they reach the diseased site. vironments, where enzymatic reduction promotes bioactivation.

Examples include:

Antitumor prodrugs, such as capecitabine, a prodrug of 5-fluorouracil, are activated by tumor-specific enzymes or acidic microenvironments.

Neuroprotective Prodrugs

These medications, such as levodopa, a dopamine precursor for Parkinson's disease, are designed to penetrate the blood-brain barrier (BBB) [12].

3. Dual and Mutual Prodrugs

Dual-action prodrugs:

By combining two pharmacophores into a single molecule, these prodrugs maximize medication absorption and metabolism while providing synergistic therapeutic effects. They improve patient adherence and decrease drug-drug interactions, which is especially beneficial in polypharmacy. For instance, a prodrug that combines an anti-inflammatory and an analgesic to treat pain.

Mutual prodrugs:

Two pharmacologically active medications are covalently joined to form mutual prodrugs, which are intended to increase therapeutic stability and efficacy. Both components are produced during bioconversion, which increases pharmacological efficacy. To combat bacterial resistance mechanisms, for instance, β-lactamase inhibitors are used in conjunction with antibiotics (such as sulbactam + ampicillin) (Adeboye, A book of Remington the science of Practice of Pharmacy) [13].

Development

In recent years, prodrug technologya crucial drug delivery method-has advanced significantly. The use of prodrugs in clinical trials and the enhancement of patient treatment outcomes are examples of these advancements, in addition to the innovation of drug design and synthesis technology. Prodrugs are undoubtedly very popular in the realm of cancer treatment because of the unique internal environment found inside tumor cells. The use of radiopharmaceuticals to activate prodrugs has emerged as a successful cancer treatment strategy .This method lessens systemic negative effects while simultaneously improving drug targeting. Significant advancements have also been made in the design of acid-sensitive prodrugs and particular fluorescent prodrugs for tumor-specific medication delivery. For instance, certain prodrugs that are made to release medications at pH 5 and stabilize at pH 7.4 have been demonstrated to give prolonged drug release for over 15 days and reduce inflammation symptoms in animal models (European Journal of Medicinal Chemistry, 276, 116699) [14].

Advanced science. These characteristics offer a fresh approach to tumor treatment by facilitating the effective accumulation of prodrugs in tumor cells of various organs. The high glutathione concentration environment in tumor cells has also drawn attention to glutathione-triggered

prodrugs because of their quick release of active medications in tumor cells. For instance, polysulfide-based prodrug nanodrugs exhibit enhanced therapeutic potential by selectively releasing glutathione from tumor cells at high doses .Through thiol-polysulfide exchange processes, these prodrugs allow the release of medications into tumor cells, producing very potent local therapeutic effects. Furthermore, it is possible to stably bind lipophilic small molecule prodrugs produced using drug modification techniques to LNPs, offering the chance to co-encapsulate several therapies in a single formulation and achieve the results of combination therapy. To combat bacterial resistance, antimicrobial prodrugs are also developing. Prodrugs are anticipated to become increasingly significant in clinical practice in the future [15].

Reason for prodrugs

Developing a prodrug strategy in drug design may be desired for a number of reasons. Prodrugs can be created from drugs with poor solubility, inefficient distribution and absorption, lack of target site specificity, extended release, decreased toxicity, instability, poor acceptability, and formulation problems.

Improves Solubility

Inadequate bioavailability is frequently caused by poorly water-soluble medications' weak solubility and slow rate of dissolution in aqueous gastrointestinal fluids. Because of their low bioavailability, oral dose forms present a significant design issue. Imagine an active medication that cannot be injected in a modest dose because it is not adequately soluble in water. Making active drug molecules into prodrugs of phosphates and esters improves their solubility Fig 05 [16].

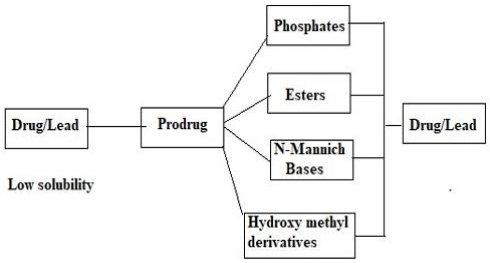


Fig 05: Enhances the Solubility Of Drug Molecule By Prodrug of Phosphate, Esters, N-Manninch Bases, Hydroxy Methyl, Derivatives

Ideal Prodrug Quality

A prodrug should meet the following specifications. In comparison to the parent substance, it is either inactive or less effective. The prodrug must be eliminated from the body along with the pro-moiety.The pro-moiety ought to be innocuous and eliminated from the body.

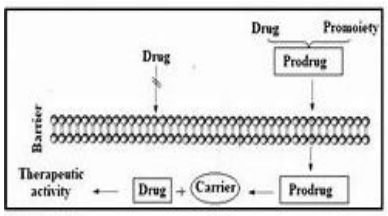
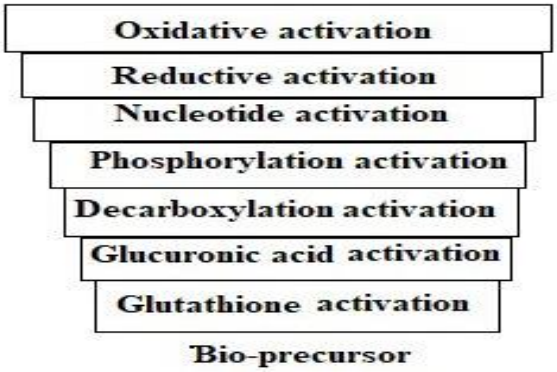


Fig 06: Concept of Carrier Linked Prodrugs

Designing of prodrugs:

Depending on the content, lipophilicity parameter, bioactive pathway, and catalyst used in bio-activation, prodrug design is separated into two categories: bioprecursors and carrier-linked prodrugs . The carrier-connected prodrugs are covalently attached to a nontoxic moiety or carrier to modify or mitigate their unwanted properties. These prodrug molecules undergo chemical or enzymatic cleavage to liberate the real drug molecule Fig 06 [17]. Upon biotransformation, a bioprecursor that lacks a moiety or carrier yields an active drug molecule. Oxidation, phosphorylation, reduction, nucleotide, glucuronic acid, decarboxylation, and glutathione activation, among other processes, transform it into an active medication (fig 07).Prodrugs play a crucial role in contemporary drug development, accounting for around 10% of all pharmaceuticals that are sold commercially. Prodrugs improve therapeutic efficacy and patient compliance by facilitating targeted drug administration, optimized pharmacokinetics, and increased bioavailability by strategic structural alterations. With a focus on design techniques, activation mechanisms, and commercial impact, this section offers a thorough overview of



successful prodrug uses throughout antiviral treatments [18].

Fig 07: Activation of Bioprecursor by Various Method

Successful Prodrug Development: Prodrugs play a crucial role in contemporary drug development, accounting for around 10% of all pharmaceuticals that are sold commercially. Prodrugs improve therapeutic efficacy and patient compliance by facilitating targeted drug administration, optimized pharmacokinetics, and increased bioavailability by strategic structural alterations. With a focus on design techniques, activation mechanisms, and commercial impact, this section offers a thorough overview of successful prodrug uses throughout antiviral treatments.

Strategies of Prodrug

The deliberate chemical alteration of pharmacologically active substances to address intrinsic constraints pertaining to solubility, membrane permeability, metabolic stability, and systemic bioavailability is known

as prodrug development. The goal of rational prodrug design is to ensure selective activation at the targeted site of action while optimizing pharmacokinetic and pharmacodynamic properties. Solubility augmentation is a primary emphasis area for prodrug synthesis techniques, which are systematically grouped according to their functional objectives.

Strategies for Enhancing Aqueous Solubility

A key factor in determining drug absorption, bioavailability, and therapeutic efficacy is aqueous solubility, especially for medications that are taken orally and parenterally. Numerous medicinal substances have poor solubility, which results in inconsistent absorption patterns and less than ideal systemic exposure. Improved pharmacokinetics and higher dissolution rates are made possible by prodrug techniques that increase hydrophilicity [19].

Fig 08: Prodrug Strategy

Strategies for Improving Permeability

Drugs with low membrane permeability often have poor systemic absorption, which calls for structural changes to improve transporter-mediated uptake or passive diffusion. Increasing lipophilicity or altering metabolic activation pathways to promote effective transmembrane transport are the main goals of prodrug techniques meant to increase permeability.

location-Specific Delivery Strategies

By guaranteeing localized drug release at the designated therapeutic location, site-specific prodrug activation reduces systemic toxicity and improves treatment effectiveness. In infectious diseases, inflammatory disorders, and oncology, where non-specific drug distribution frequently results in dose-limiting side effects, such techniques are especially pertinent [20].

The purpose of sustained-release prodrug

Methods is to increase therapeutic efficacy, decrease the frequency of doses, and improve patient adherence by extending the duration of drug release. In the treatment of chronic diseases, where stable plasma medication levels are necessary to sustain therapeutic results, these strategies are very helpful.

Strategies for Targeting

Increased drug selectivity, accurate localization at the therapeutic location, and reduced systemic toxicity are the goals of targeted prodrug methods. Receptor-mediated targeting is one of these strategies that use specialized ligand-receptor interactions to improve cellular uptake and bioavailability, especially in oncology and site-specific drug delivery [21].

Innovative Methods of Delivery

To improve site-specific activation, maximize pharmacokinetics, and reduce systemic toxicity, novel prodrug delivery techniques are being created. Precise activation at the targeted therapeutic site is ensured by photochemical internalization (PCI), which provides spatiotemporal control over drug release.

Bio Conjugation Strategies

Itinvolves the covalent linkage of drugs to biomolecules such as proteins, peptides, or antibodies to enhance selectivity, stability, and bioavailability. These approaches are particularly valuable in oncology, immunotherapy, and site-specific drug delivery, where targeted therapeutic action is required to minimize systemic toxicity and improve pharmacokinetics [22].

Advanced Design Strategies in Prodrug Development

Prodrug design has been transformed by developments in molecular engineering, computational modeling, and predictive analytics, which have made it possible to create optimized drug candidates with better therapeutic efficacy, targeted activation, and pharmacokinetics .In order to improve prodrug selection, synthesis, and activation processes and speed up drug discovery and development, these methods combine in silico modeling, logical structural alterations, and physiologically relevant simulations [23].

Challenges of Prodrug Development

Prodrug research still faces a number of obstacles that prevent broad acceptance and success, despite notable progress. These problems, which call for interdisciplinary solutions, range from regulatory obstacles to pharmacokinetic unpredictability.

Toxicity and Off-Target Activation

The possibility of unintentional activation, which could result in off-target toxicity, is one of the main issues with prodrugs. Unpredictable drug release can result in negative consequences due to factors such non-specific hydrolysis, patient-specific enzymatic variability, and interactions with unexpected metabolic pathways. For instance, several ester-based prodrugs may convert to hazardous metabolites, which would make their clinical use more difficult [24].

Problems with Stability and Shelf-Life

Prodrugs frequently have stability issues, especially those that depend on enzyme- or pH-sensitive activation processes. Prodrugs that are unstable may break down too quickly in the bloodstream or during storage, which could result in unfavorable side effects or decreased effectiveness. The therapeutic potential of certain peptide-based prodrugs is limited, for example, by their propensity to hydrolyze before reaching the desired location.

High Production Costs and Complex Synthesis

creating prodrugs requires complex chemical alterations that frequently call for multi-step validation, purification, and synthesis. These procedures impede large-scale production and raise manufacturing costs. Furthermore, maintaining uniformity from batch to batch in prodrug production is a major problem, especially for formulations based on nanotechnology [25].

Regulatory and Approval Barriers

Because prodrugs have intricate activation mechanisms, regulatory bodies like the FDA and EMA place strict restrictions on them. Development timescales are prolonged by the requirement for comprehensive preclinical and clinical research to assess efficacy, safety, and metabolism (European Journal of Pharmaceutical and Medical Research). Prodrugs need to have better therapeutic profiles than the parent medication, consistent conversion rates, and low toxicity.

Considerations for Personalized Medicine and Inter-Patient Variability

Prodrug activation and efficacy are impacted by metabolic enzyme variability, which is determined by age, disease circumstances, and genetic variations. Cytochrome P450 enzyme polymorphisms, for example, can change how drugs are metabolized, causing suboptimal or inflated reactions in some patient groups. To maximize therapy results, pharmacogenomics must be incorporated into prodrug development [26].

Drug-Drug and Food-Drug Interactions

Co-administered medications that inhibit or induce metabolic enzymes may have an impact on prodrugs that need enzymatic conversion. Enzyme inhibitors, for instance, may hinder prodrug activation when used in combination therapy, resulting in decreased efficacy. Prodrug metabolism can also be changed by dietary factors like grapefruit juice, which is known to impact cytochrome P450 enzymes.

Targeting Specificity and Delivery Difficulties

Getting accurate targeting is still quite difficult, especially for prodrugs intended for site-specific activation. Although delivery has been enhanced by nanotechnology-based methods, issues like immune detection, biodistribution, and removal from circulation still require attention. One important area of continuing research is making sure that prodrugs only activate in sick tissues and stay away from healthy cells. Developments in computer modeling, personalized medicine strategies, and regulatory frameworks that encourage creative medication design are necessary to meet these problems. To expedite prodrug creation, future studies should concentrate on enhancing stability, optimizing activation mechanisms, and incorporating AI-driven drug development techniques [27].

Toxicity and Off-Target Activation: Negative consequences could result from unchecked prodrug conversion.

Problems with stability and shelf life: Some prodrugs lose their effectiveness due to early degradation.

Complex Synthesis and Expensive Production: The process of development is frequently costly and time-consuming.

Regulatory obstacles: To guarantee safety, effectiveness, and predictable bioconversion, prodrugs need to undergo thorough validation.

Limitations of Prodrugs

Prodrug design can lead to a lot of new challenges, particularly when it comes to evaluating pharmacological, pharmacokinetic, toxicological, and clinical features, even though it has been very helpful in overcoming many of the negative aspects of medications [28].

Pharmacological Issues

Because bioactivation to their active species is required, these drugs cannot be submitted to initial in vitro screening procedures such as binding studies, neurotransmitter reuptake, and enzyme inhibition measurement. Some toxicity mechanisms of prodrugs that are not produced by the parent drugs include the formation of toxic metabolites, the consumption of essential components during the prodrug activation process, and the release of a pharmacokinetic modifier that may cause enzyme induction or alter drug excretion. The mutual prodrug might not be the best substrate for the activating enzymes, according to issues with the pharmacokinetic studies. Many misunderstandings can result from pharmacokinetic studies. It is important to consider the variations in the time courses of action of parent molecules andmutual prodrugs when comparing them. AUC is a superior measure for comparison because the maximum activity for mutual prodrugs may manifest later than for parent compounds [29].

Clinical Issues

There is also doubt about the predictive power of animal studies. In rats, the active dosages of two mutual prodrugs of the same parent medication may seem to be the same, but in clinical studies, they may differ significantly.

Future Persepctives

Prodrug development is expected to make major strides in the future. New drug delivery methods, technologies, and personalized medicine. The future generation of prodrugs is anticipated to be shaped by a number of important areas.

Computational Drug Design and Artificial Intelligence (AI)

By predicting prodrug activation pathways, improving molecular structures, and reducing unwanted side effects, AI-driven modeling and machine learning algorithms are revolutionizing drug development. AI can save time and money in drug development by helping to uncover novel promoieties, mimic metabolic changes, and increase the effectiveness of prodrug screening [30].

Personalized and Precision Medicine

Drug design and pharmacogenomics are making it possible to create prodrug therapies that are specific to a person's genetic composition, metabolism, and illness condition. Clinicians can forecast patient-specific reactions to prodrugs by using genetic analysis, which maximizes therapy effectiveness and reduces side effects [31].

Smart and Stimuli-Responsive Prodrugs

To achieve highly controlled and localized drug release, future prodrugs will make use of stimuli-responsive activation mechanisms, including pH, temperature, enzyme levels, and light exposure. For instance:

Redox-sensitive prodrugs

These are activated in conditions of oxidative stress, especially in neurodegenerative and cancerous illnesses.

Light-Activated Prodrugs

Made to be activated at specified sites using laser or UV light in a non-invasive manner. Prodrugs that are magnetically or ultrasound-triggered, these provide exact control over drug activation through the use of outside stimuli [32].

Nanotechnology-Enhanced Prodrug Delivery

Prodrug solubility, stability, and bioavailability will be enhanced by nanocarrier-based delivery systems, such as liposomes, micelles, and dendrimers. Targeted and prolonged drug release is made possible by combining prodrugs with nanoparticle platforms, especially in the cases of cancer, infectious diseases, and central nervous system disorders.

CRISPR and Gene-Directed Prodrug Therapy

By facilitating the creation of gene-activated prodrugs, CRISPR-Cas9 gene-editing technology holds the potential to completely transform prodrug design. For extremely selective and effective drug activation in genetic disorders and customized cancer treatments, gene therapy techniques can be combined with prodrug tactics [33].

Regulatory Innovations and Accelerated Approval Pathways

With new standards for assessing metabolism, bioactivation, and safety, regulatory bodies are changing to meet the complexity of contemporary prodrugs. Faster market access may be made possible by the use of accelerated approval routes for innovative prodrugs with substantial therapeutic potential.

Integration of omics technologies

Prodrug metabolism is being better understood thanks to developments in proteomics, metabolomics, and genomes, which enables more accurate drug design. A key component of next-generation treatments will be tailored prodrug activation plans based on individual patient metabolic profiles [34].

Conclusion

The prodrug strategy is one of the most promising ways to improve the pharmacologically active agents' therapeutic efficacy and/or lessen their side effects through a variety of mechanisms, such as tissue-targeted delivery, enhanced permeability and bioavailability, stability, and solubility. Prodrugs are therefore emerging as a new paradigm for drug discovery. Even though prodrug design has advanced remarkably, additional research is obviously required, particularly in the early phases of drug development, in order for prodrugs to reach the desired state of art and establish themselves in contemporary pharmacotherapy. Prodrugs are a key alternative to address pharmacological and pharmacokinetic issues with drug molecules and have found numerous beneficial therapeutic uses. The increasing percentage of prodrugs suggests that they play a vital role in contemporary medicine. Enzymes or chemical processes can activate these prodrugs. To the best of our knowledge, every detail of prodrugs including their design, synthesis, development, bioactive route, and new therapeutic applications has been thoroughly examined in this study.

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Conflict of Interest

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Author Contribution

All authors are contributed equally.

References

1. Testa B, Mayer JM. Hydrolysis in Drug and Prodrug Metabolism: Chemistry, Biochemistry, and Enzymology. 2003. p. 55–59.
2. Stella VJ, Nti-Addae KW. Prodrug strategies to overcome poor water solubility. Adv Drug Deliv Rev. 2007;59(7):677–94.
3. Bildstein L, Dubernet C, Couvreur P. Prodrug-based intracellular delivery of anticancer agents: Advantages. Adv Drug Deliv Rev. 2011;63:3–23.
4. Huttunen KM, Raunio H, Rautio J. Prodrugs from serendipity to rational design. Pharmacol Rev. 2011;63:750–71.
5. Najjar A, Karaman R. Successes, failures, and future prospects of prodrugs and their clinical impact. Expert Opin Drug Discov. 2019;14:199–220.
6. Najjar A, Karaman R. The prodrug approach in the era of drug design. Expert Opin Drug Discov. 2019;16:1–5.
7. Najjar A, Karaman R. Newly developed prodrugs and prodrugs in development: an insight of the recent years. Molecules. 2020;25(4):884.
8. Rautio J, Kumpulainen H, Heimbach T, Oliyai R, Oh D, Järvinen T, et al. Prodrugs: Design and clinical applications. Nat Rev Drug Discov. 2008;7(4):255–70.
9. Huttunen KM, Raunio H, Rautio J. Prodrugs: Design and clinical applications. Pharmacol Rev. 2011;63(3):750–71.
10. Peppercorn MA. Sulfasalazine: pharmacology, clinical use, toxicity, and related new drug development. Ann Intern Med. 1984;101(3):377–86.
11. Rautio J, Meanwell NA, Di L, et al. The expanding role of prodrugs in contemporary drug design and development. Nat Rev Drug Discov. 2018;17(8):559–87.
12. Najjar A, Rajabi N, Karaman R. Recent approaches to platinum (IV) prodrugs: a variety of strategies for enhanced delivery and efficacy. Curr Pharm Des. 2017;23(16):2366–76.
13. Stella VJ. Prodrugs: My initial exploration and where it led. J Pharm Sci. 2020;109(12):3514–23.
14. Parise Filho R, Polli MC, Barberato Filho S, Garcia M, Ferreira EI. Prodrugs available on the Brazilian pharmaceutical market and their corresponding bioactivation pathways. Braz J Pharm Sci. 2010;46:393–420.
15. Mishra AP, Chandra S, Tiwari R, Srivastava A, Tiwari G. Therapeutic potential of prodrugs towards targeted drug delivery. Int J Pharm Sci Res. 2018;12:111.
16. Kalluri B, Ramesh Y, Venugopalaiah P, Chandra YP. Nanocapsules: a novel drug delivery system – a review. World J Adv Res Rev. 2023;20(2):1240–9.
17. Stella VJ, Himmelstein KJ. Pharmaceutical and biochemical considerations in prodrug design and evaluation. Adv Drug Deliv Rev. 1980;4(1):1–32.
18. Fleisher D, Li C, Zhou Y, Pao LH. Drug–enzyme interactions in prodrug therapy. Adv Drug Deliv Rev. 1996;19(2):115–30.
19. Kumar SV, Kumar SP, Dudhe R, Kumar N. Immunomodulatory effects of some traditional medicinal plants. J Chem Pharm Res. 2011;3(1):675–84.
20. Kumar N, Bhatnagar A, Dudhe R. Synthesis of 3-(4,5-dihydro-1-phenyl-5-substituted phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one derivatives and evaluation of their anticancer activity. Arab J Chem. 2013;1–10.
21. Kwon IK, Lee SC, Han B, Park K. Analysis on the current status of targeted drug delivery using nanomaterials. J Control Release. 2012;164(2):108–14.
22. Ahad HA, Kumar LS. Harnessing nanoemulsion technology and QbD software for improvement of solubility and bioavailability issues of quercetin hydrate. Future J Pharm Health Sci. 2023;5(1):1–7.
23. Nazli A, Khan MZI, Rácz Á, Béni S. Advanced drug delivery review. Adv Drug Deliv Rev. 2024;556–650.
24. Neelima S, Kumar PM, Mounika B. Wound healing potential of ethanolic extract of roots of Glycyrrhiza glabra L. in diabetes-induced rats. Future J Pharm Health Sci. 2022;2(4):269–75.
25. Bildstein L, Pili B, Marsaud V, Wack S, Meneau F, Lepêtre-Mouelhi S, et al. Interaction of an amphiphilic squalenoyl prodrug of gemcitabine with cellular membranes. Eur J Pharm Biopharm. 2011;79(3):612–20.
26. Markovic M, Ben-Shabat S, Dahan A. Prodrugs for improved drug delivery: Lessons learned from recently developed and marketed products. Pharmaceutics. 2020;12(11):1031.
27. Jornada DH, dos Santos Fernandes GF, Chiba DE, de Melo TR, Dos Santos JL, Chung MC. The prodrug approach: A successful tool for improving drug solubility. Molecules. 2015;21(1):42.
28. Penabaka VP, Sireesha E, Ramesh Y, Sarvepalli R. Advancement in drug delivery systems. Int J Clin Pharmacokinet Med Sci. 2015;5(1):36–51.
29. Sravya Sree K, Ramesh Y, Venugopalaiah P, Prapurna Chandra Y. Nanoparticles containing anticancer drugs – a review. Int J Exp Biomed Res. 2013;2(3):91–102.
30. Rao VM, Mandal TK, Palem CR. Transdermal prodrug delivery strategies: recent advances and future

perspectives. J Control Release. 2013;172(3):849–65.

31. Suchitra M, Pratibha GS, Sindhura CL, Cheriyan BV, Gondhale P. Stem cell therapy in progression of breast cancer – an overview. EC Pharmacol Toxicol. 2025;13(3):1–12.
32. Reimer D, Bode HB. A natural prodrug activation mechanism in the biosynthesis of nonribosomal peptides. Nat Prod Rep. 2014;31(2):154–9.
33. Rizvi I, Anbil S, Alagic N. Photochemical internalization-based enhancement of chemotherapeutic drug efficacy. Front Pharmacol. 2018;9:587–91.
34. Chavan NR, Dhaygude VN, Kshirsagar SP, Borkar NN, Devade PB, Pawar S. Microsphere technology: a comprehensive review on recent developments. Future J Pharm Health Sci. 2024;4(4):118–26.