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TARGETED PRODRUG IN CLINICAL PRACTICE

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ABSTRACT

Prodrugs are pharmacologically inactive derivatives that are converted into active drugs in the body through enzymatic or chemical transformation. This approach is widely used in pharmaceutical research to address challenges such as poor water solubility, low oral bioavailability, chemical instability, lack of site specificity and adverse side effects. By modifying drug molecules, prodrug design enhances pharmacokinetic and pharmacodynamic properties, ensuring better therapeutic outcomes. Various strategies, including carrier-linked systems, bioprecursors, mutual prodrugs and nanotechnology-based conjugates, have been successfully applied. Activation mechanisms generally rely on pH-sensitive or redox-responsive chemical triggers, as well as enzymatic processes like hydrolysis, reduction, or phosphorylation. Clinically successful examples include aspirin, enalapril, valacyclovir and capecitabine. In cancer therapy, targeted prodrugs offer selective delivery, reducing systemic toxicity and improving efficacy. Innovative techniques such as gene-directed enzyme prodrug therapy (GDEPT) and antibody-directed enzyme prodrug therapy (ADEPT) are progressing into clinical trials. Looking ahead, the integration of nanotechnology with artificial intelligence is expected to enable more precise, personalized and safer prodrug-based treatments, making them a promising frontier in modern drug development.

KEYWORDS

Prodrug, Pharmacokinetics, Solubility, Bioavailability, pH-dependent, Interpatient variability, AI-driven design and Clinical practice.

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INTRODUCTION

Adrian Albert first introduced the concept of a "prodrug" or "pro-agent" in 1958¹. Prodrugs are substances that become active parent drugs in the body through enzymatic or chemical metabolism. They are reversible derivatives of drug molecules that release the active parent drug, which has the intended pharmacological action. Prodrugs are

designed to overcome pharmacokinetic, pharmacodynamic and formulation restrictions^{2,3}.

History

The history of prodrugs dates back to the introduction of aspirin in 1899 by Bayer. The field expanded in the 1970s-1980s, with systematic approaches to improving solubility, absorption, and site-specific delivery². In the 1990s, the prodrug strategy focused on targeted drug delivery, with L-DOPA for Parkinson's disease emerging as a classical example³.

Importance

Prodrugs are crucial in modern pharmaceutical research and development, providing innovative solutions to overcome limitations associated with conventional drug molecules. They enhance physicochemical properties, optimize pharmacokinetics and bioavailability, and enable targeted drug delivery^{2,4}. They also minimize adverse effects by masking reactive groups or reducing systemic exposure. Long-acting prodrugs or those with reduced dosing frequency enhance patient compliance⁵.

Rationale of prodrug

Prodrug design is a crucial tool in drug discovery to overcome the issue of poor water solubility, which restricts absorption, oral bioavailability, and clinical efficacy². Prodrugs can be converted into phosphate esters, carbonate/carbamate, amino acid and sulfate conjugates, polymers and nanotechnology-powered drugs⁶.

Poor oral bioavailability is a major barrier in drug development, often caused by low permeability, poor solubility, substantial first-pass metabolism, or quick clearance^{4,5}. Prodrugs are often employed to improve absorption, shield the medication from early metabolism, or make it easier for it to pass through biological membranes³.

Classification of prodrugs

Carrier linked prodrugs

Carrier-linked prodrugs are drugs that contain an active drug covalently linked to a promoiety (carrier), improving solubility, stability, absorption, or targeting. These prodrugs are converted into the active drug through hydrolysis. Subclasses include esters, amides, carbonates, phosphates, glycosides

and carbamates. Esters improve lipophilicity and hydrophilicity, while amides are more stable and hydrolyzed by amidases or peptidases. Carbonates and carbamates increase stability and are used for masking hydroxyl or amine groups. Phosphates and phosphonates improve solubility and use transporters^{3,5}.

Bioprecursor

Bioprecursor prodrugs are chemically altered inactive versions of drugs that need to undergo enzymatic or chemical modification in the body to release the active parent substance. These drugs are activated by metabolic enzymes catalyzing oxidative, reductive, or hydrolytic reactions. Oxidation conversions involve oxidation caused by oxidases or cytochrome P450 enzymes, revealing necessary functional groups for action. Reductive conversions occur in tissues with low oxygen tension, such as tumors and liver, converting inactive precursors into active drugs. Hydrolytic conversions involve enzymatic cleavage of functional groups, such as esters, amides, or carbamates, and are common activation pathways for prodrugs^{3,4}.

Mutual prodrug

Mutual prodrugs, also known as codrugs, are formed when two pharmacologically active medications are covalently joined to form a single molecule. Both halves of a mutual prodrug are physiologically active and serve as carriers to enhance the delivery of the other. These drugs can improve patient compliance by combining two therapies into one molecule. Examples of mutual prodrugs include sultamicillin and ampicillin, which offer dual therapeutic action in a single molecule³.

Polymer based prodrug

Polymer-based prodrugs are macromolecular conjugates with a cleavable bond binding an active drug to a biodegradable polymer backbone. They offer enhanced solubility, extended circulation time, targeted distribution and decreased toxicity. Examples of polymer-based prodrugs include PEGylated medications, HPMA conjugates, drug-dextran conjugates, and conjugates of polymers and platinum. These drugs offer enhanced solubility, reduced dose frequency, tailored delivery and

improved resistance against enzymatic deterioration⁶.

Nano technology

Nanotechnology has revolutionized the design of prescription drugs, enabling site-specific release of active ingredients and improving physicochemical characteristics. These nanocarriers, such as liposomes, polymeric micelles, dendrimers, nanoparticles, or nanogels, allow for passive targeting through increased permeability and retention (EPR) or active targeting by attaching ligands to specific receptors on sick cells. Stimuli-responsive nanoprodrugs release their active drug in response to pH changes, redox conditions, or enzymatic activity at the disease site. Advantages include increased stability, solubility, targeted delivery, continuous and regulated release, reduced adverse effects, and the ability to combat cancer's multidrug resistance⁶.

Mechanism of prodrug

Prodrugs are pharmacologically inactive compounds that undergo enzymatic or chemical transformation within the body to release the active drug^{3,4}. This strategy enhances the drug's absorption, distribution, metabolism, excretion and toxicity (ADMET) properties. Enzymation activation is a primary mechanism, involving specific enzymes that cleave the prodrug to release the active agent. Examples of enzyme-activated prodrugs include telotristatetiprate, plasma esterases, phosphatases, and reductases. Chemical activation is the process of transforming an inactive substance into its active drug form by means of redox processes, pH-dependent reactions, and hydrolysis. These mechanisms provide improved therapeutic profiles and controlled medication release. Hydrolysis activation is often carried out by enzymes such as hydrolases, phosphatases, and esterases, while pH-sensitive prodrugs selectively cleave in acidic environments. Redox-sensitive prodrugs use different redox potentials present in both healthy and diseased conditions, such as increased intracellular glutathione levels in cancer cells⁶.

Application

Prodrugs are inactive drug forms designed to improve pharmacokinetics-enhancing absorption, distribution, metabolism, and elimination. They can increase solubility and membrane permeability for better oral delivery and reduce side effects by targeting specific tissues^{2,4}. Prodrugs are often activated at specific sites or by enzymes, improving treatment accuracy and safety. In targeted therapies, they help treat diseases like cancer or neurological disorders by delivering drugs to precise locations, such as across the blood-brain barrier using nanoparticles or biological carriers. Prodrugs also boost patient compliance by improving taste, reducing side effects and lowering dosing frequency-especially helpful in chronic disease management³.

Successful prodrugs examples

Successful prodrugs include aspirin, enalapril, valacyclovir and capecitabine. Aspirin is an ester prodrug of salicylic acid, which reduces gastric irritation and improves tolerability. Enalapril is an ACE inhibitor with improved oral bioavailability and is effective for antihypertensive therapy. Valacyclovir is an L-valyl ester prodrug of acyclovir, with improved oral bioavailability and effective treatment for herpes simplex and varicella-zoster infections. Capecitabine is a carbamate prodrug of 5-fluorouracil, which allows tumor-selective activation and reduces systemic toxicity compared to direct 5-FU infusion^{3,4}.

Prodrug Strategies in Clinical Practice

Cancer therapy

Tumor targeted

Cancer chemotherapy has been limited by poor tumor selectivity, systemic toxicity, and resistance mechanisms. Prodrug strategies offer solutions by releasing active agents preferentially in tumors or delivering cytotoxins through targeted carriers. Two advanced approaches are tumor-targeting prodrugs, designed to exploit tumor-specific enzymes, hypoxia, or micro-environmental conditions, and antibody-drug conjugates (ADCs), which deliver ultra-potent cytotoxins to tumor cells via prodrug-like linkers. These approaches have advantages

such as high tumor selectivity, improved therapeutic index and improved therapeutic index.

Antibody-Drug Conjugates (ADC)

Antibody-Drug Conjugates (ADCs) are targeted prodrugs that deliver potent cytotoxins via a cleavable linker. They are composed of high-specific antibodies, cleavable or non-cleavable linkers and highly potent payloads. ADCs have been successful in oncology, with several clinical approvals. Challenges include antigen heterogeneity, off-target toxicity and resistance. Future improvements include site-specific conjugation, bispecific ADCs, bystander-active payloads, and ADC-immunotherapy combinations^{7,8}.

CNS

Levodopa (L-DOPA), a metabolic precursor of dopamine and the cornerstone of Parkinson's disease therapy, is a key drug in the treatment of Parkinson's disease. It is a metabolic precursor of dopamine and is used in Parkinson's disease therapy. L-DOPA is administered systemically, typically combined with peripheral AADC inhibitors to reduce peripheral decarboxylation and increase CNS availability. However, oral L-DOPA is associated with pharmacokinetic variability, meal-dependent fluctuations, motor complications, and peripheral side effects, which motivate improved delivery strategies.

Optimizing systemic administration involves controlled-release oral formulations, continuous intrajejunal infusion of levodopa-carbidopa intestinal gel (LCIG) and subcutaneous continuous infusion systems. LAT1-utilizing prodrugs can improve brain selectivity by designing LAT1-recognizable promoieties that favor BBB transport and protect against peripheral metabolism until brain entry. Intranasal delivery seeks to bypass systemic circulation and deliver drug along olfactory/trigeminal pathways to the CNS. Intranasal formulations have demonstrated faster onset and sometimes higher brain exposure in preclinical and early clinical studies.

Nanoparticles, polymeric prodrugs and hybrid systems are being developed to optimize CNS delivery of L-DOPA. These systems can protect

against peripheral metabolism, modulate release and enhance residence time for intranasal deposition. However, translation requires attention to scale-up, sterility and mucosal toxicity^{3,4}.

Anti-viral therapy

Antiviral drug development faces challenges such as poor oral bioavailability, low cellular permeability and rapid degradation. Prodrug strategies have been crucial in overcoming these issues, particularly for nucleoside/nucleotide analogues. Tenofovir prodrugs and remdesivir demonstrate how rational prodrug design can enhance absorption, intracellular activation, and therapeutic efficacy against viral infections like HIV, HBV and SARS-CoV-2. Tenofovir disoproxilfumarate (TDF) improves oral bioavailability by masking the phosphonate moiety. Tenofovir alafenamide (TAF) addresses renal toxicity and bone mineral density loss by enhancing lymphoid cell uptake and stability in plasma. Remdesivir, originally developed for Ebola, is a monophosphoramidate prodrug of an adenosine analogue. These prodrugs demonstrate the power of prodrug chemistry in pandemic response and demonstrate the potential of prodrug design in drug development⁹.

Challenges in prodrug development

Prodrug development faces challenges such as enzyme variability, species differences, competing metabolism, plasma stability vs target activation, drug-drug interactions, transport and distribution, *in vitro* to *in vivo* limitations, lack of biomarkers, patient-specific factors, and analytical limitations. Enzymes vary across tissues and individuals, and animal models often underestimate human activation. Competing metabolism and first-pass effects can also affect drug release. *In vitro* assays often miss tissue exposure, and *in vivo* systems lack full physiological context^{3,4,5}.

Inter patient variability

Inter-patient variability in enzyme activity in drugs leads to unpredictable efficacy and toxicity, influenced by genetics, age, disease, co-medications, microbiome and environment. This complexity complicates dose selection, safety margins, and patient stratification. Major sources of

variability include genetic polymorphisms, age and ontogeny, disease and organ dysfunction, ethnic and population differences and microbiome and environmental factors. Regulating prodrugs is more complex than standard drugs due to unpredictable metabolism, variable activation and potential toxic intermediates. Key challenges include unpredictable activation, metabolism characterization, species differences in preclinical models, off-target or incomplete activation, complex pharmacokinetics, drug-drug interactions, regulatory classification ambiguity and long-term monitoring.

Future perspectives

AI and machine learning are revolutionizing prodrug design by enabling faster, smarter and more precise prediction of activation, safety and efficacy. This includes predicting activation pathways, designing novel promotions, improving *in silico* → *in vivo* translation, predicting toxic or reactive metabolites early, integrating with multi-omics and precision medicine, and automating synthesis and optimization. This move moves beyond traditional trial-and-error methods¹⁰.

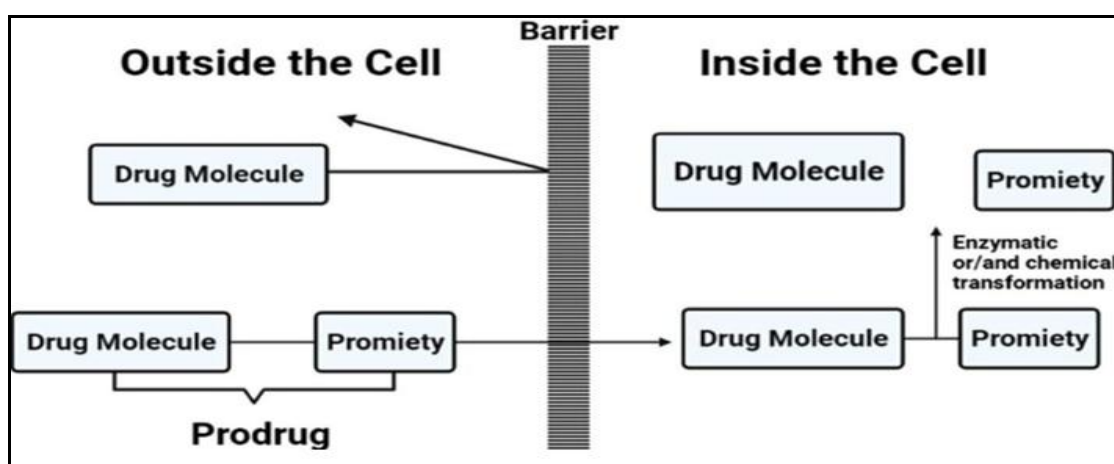


Figure No.1: Schematic representation of prodrug concept

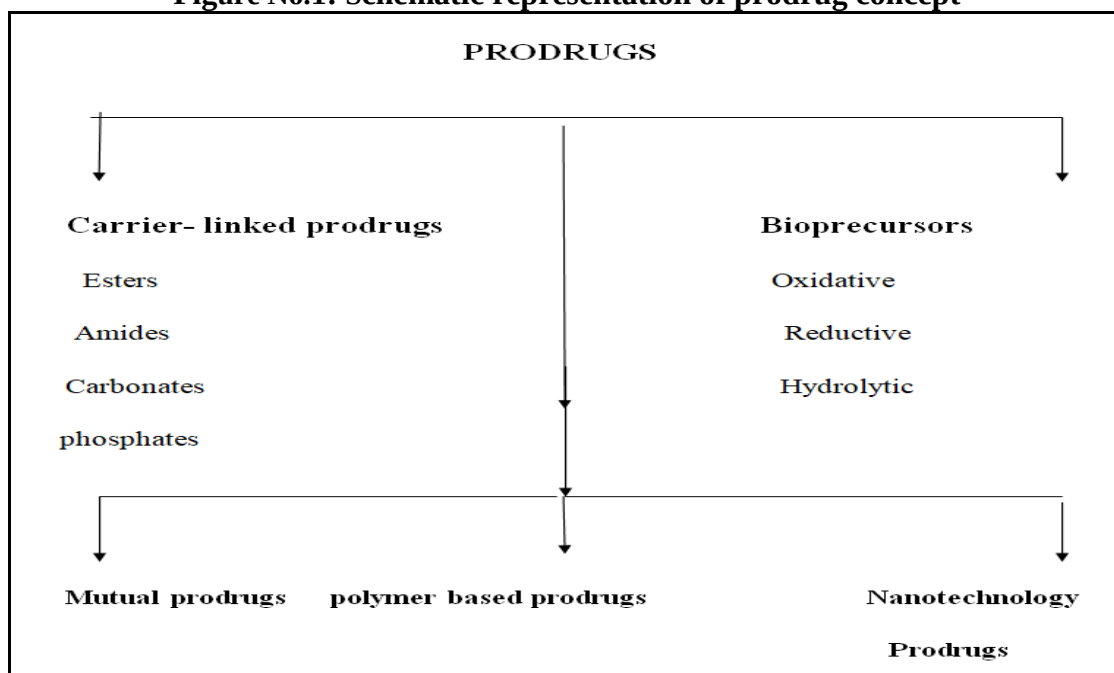


Figure No.2: Classification of Prodrugs

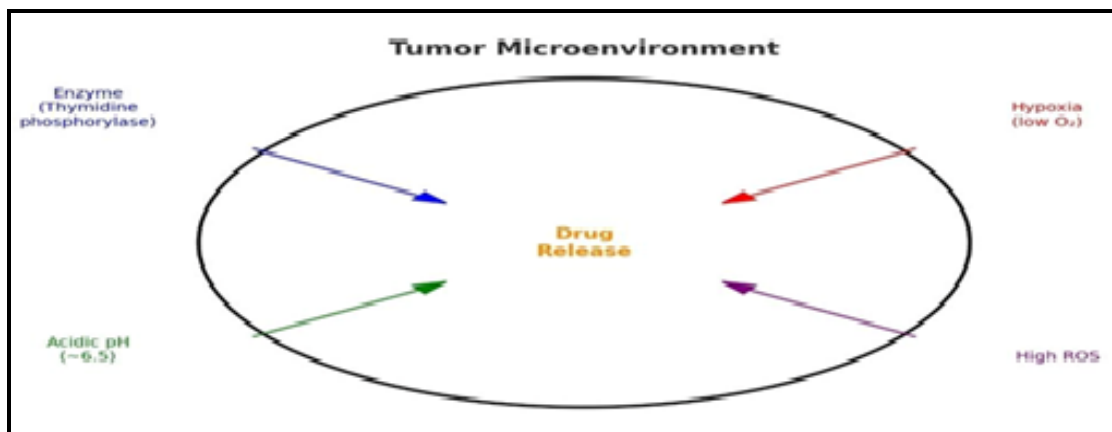


Figure No.3: Mechanism of Tumor -Targeting prodrug activation

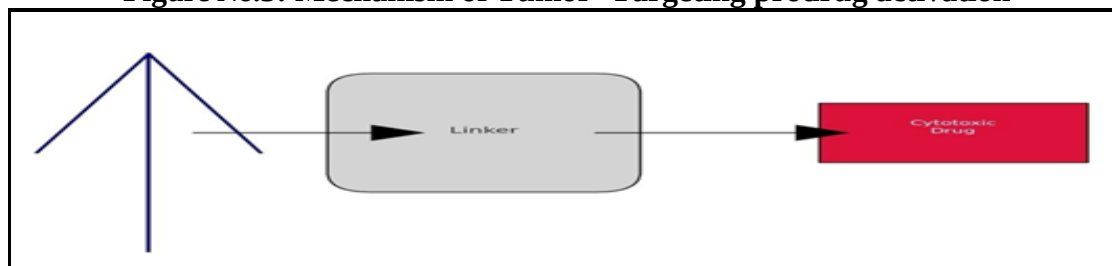


Figure No.4: General structure of an antibody – Drug Conjugate (ADC)

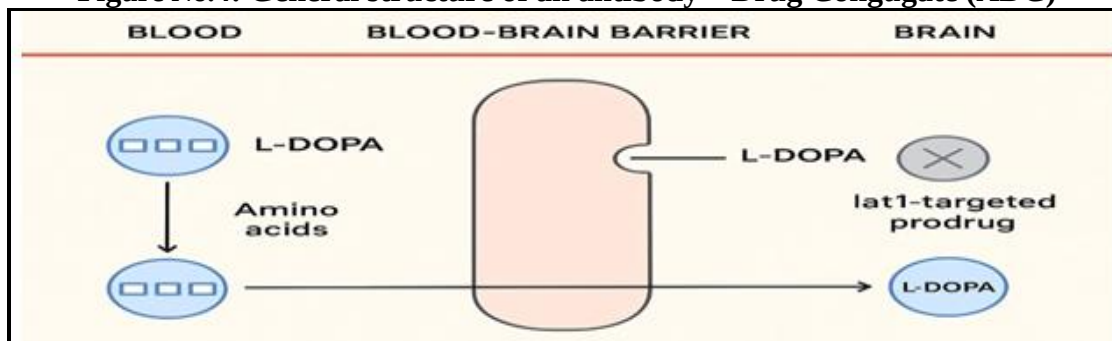


Figure No.5: L- DOPA and prodrug strategies interact with the BBB

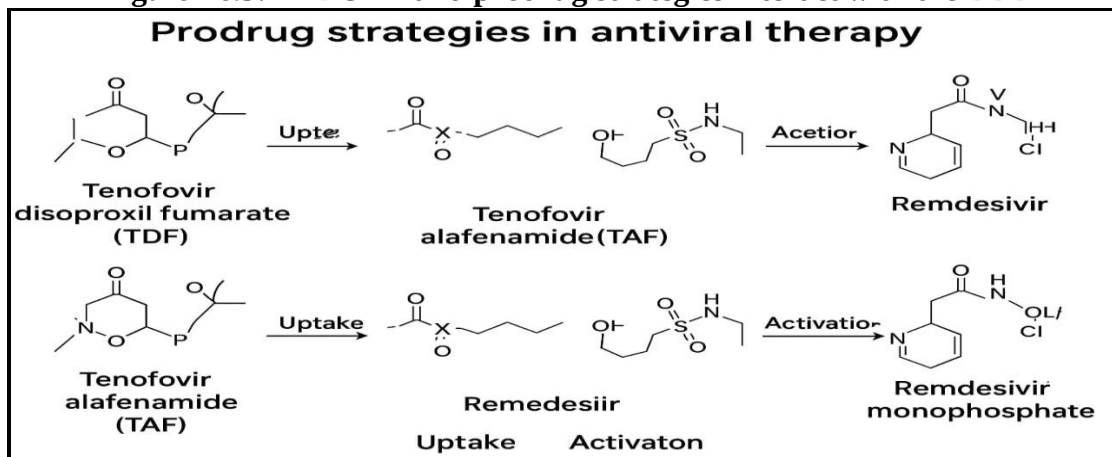


Figure No.6: TDF (Vs) TAF demonstrate safety optimization while remdesivir shows rapid intracellular activation for antiviral potency

CONCLUSION

Prodrugs represent an innovative and versatile strategy in modern drug design, aimed at overcoming limitations such as poor solubility, low bioavailability, toxicity and lack of target selectivity. Targeted prodrugs represent a promising advancement in modern therapeutics by combining the benefits of site-specific drug delivery with controlled activation. By utilizing chemical linkers, enzyme-sensitive moieties, or receptor-mediated mechanisms, these prodrugs minimize off-target toxicity and enhance therapeutic efficacy. In clinical practice, they have shown particular success in areas such as oncology, infectious diseases and inflammatory disorders, where selective drug release at diseased sites is critical. Although challenges remain-such as inter patient variability, complex regulatory requirements, and optimization of activation pathways-ongoing research and technological innovations are steadily overcoming these barriers. With the integration of nanotechnology and AI-driven design strategies, targeted prodrugs are poised to become integral components of personalized medicine, offering safer and more effective treatments in the future.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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