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REVIEW ARTICLE

Enhancing Drug Design Through Prodrugs

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Abstract: Prodrugs represent a class of drug molecules engineered to undergo reversible chemical or enzymatic transformations in vivo, releasing the active parent drug. This strategic modification facilitates enhanced pharmacological effects while mitigating drawbacks associated with conventional drug administration. Ideal prodrugs exhibit pharmacological inactivity prior to conversion, swift and specific conversion to the active drug compound, and incorporation of non-toxic moieties. Effective prodrug design addresses challenges such as stability, toxicity, solubility, permeability, and drug targeting, which significantly impact drug discovery and development. By altering physicochemical, biopharmaceutical, or pharmacokinetic properties, prodrug design achieves precise drug delivery. Approximately 10-14% of globally approved drugs fall under the prodrug classification. This article comprehensively explores objectives, classifications, activation mechanisms, conceptual frameworks, prerequisites for clinically viable prodrugs, as well as their diverse applications across drug discovery and development endeavors.

Keywords: Prodrug development; Drug optimization; Enzymatic biotransformation; Pharmacokinetic properties; Computational prodrug design.

1. Introduction

The concept of prodrugs, also known as "pro-agents," was first introduced by Albert in 1958. Prodrugs represent chemically modified inactive forms of active drugs that, upon administration, undergo enzymatic or chemical reactions within the body to yield the active therapeutic compound. Certain therapeutic agents exhibit undesirable characteristics, leading to suboptimal distribution and adverse effects. To address these limitations, modifications in physicochemical, biological, and organoleptic properties are implemented to enhance therapeutic efficacy, minimize toxicity, and improve patient adherence. Harper further elucidated this concept in 1959, referring to drugs designed specifically to necessitate bioactivation as "Drug Latentiation." The primary objective of prodrug development lies in optimizing the pharmacokinetic properties of drug compounds, particularly considering their impact on absorption, distribution, metabolism, and excretion, which can significantly influence the drug development process. A crucial requirement for prodrugs is their conversion into active forms through controlled or predictable chemical or enzymatic biotransformation prior to exerting therapeutic effects. The term "prodrug" signifies the presence of a chemical bond between the active ingredient of a drug and a "promoiety" (Figure 1). This strategic approach aims to surmount barriers through chemical modifications rather than solely relying on formulation techniques. Various prodrug strategies are employed, with one of the most common being functionalization with cleavable groups, rendering the prodrug susceptible to enzymatic activation by various enzymes.

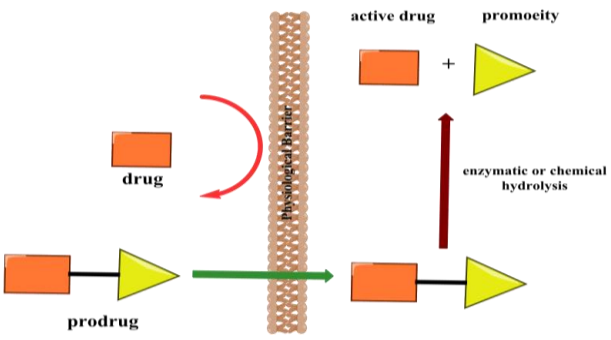

Figure 1. Schematic representation of the prodrug

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Prodrugs serve multiple purposes, including extending the duration of drug action by acting as chemical sustained-release forms. Prodrug design often incorporates computational methodologies such as molecular mechanics (MM) and molecular orbital (MO) calculations, correlating experimental and calculated values to optimize intramolecular processes. Recent advancements in prodrug development include the introduction of pretomanid in 2019, a nitroreductase enzyme (Ddn) activated prodrug used for tuberculosis treatment (Figure 2). In 2020, ebanga, a monoclonal antibody-type drug for Zaire ebolavirus infection, was developed. Additionally, tozinameran, designed in 2020, aims to induce immunity against SARS-CoV-2 [3, 4]

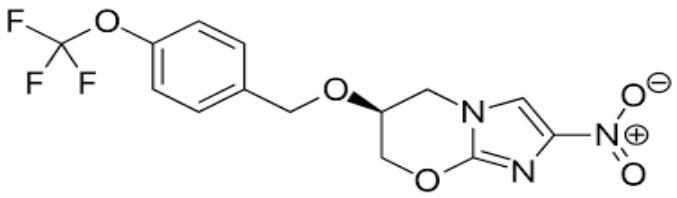

Figure 2. Chemical structure of Pretomanid

2. Need for Prodrugs

2.1. Pharmaceutical objectives

Prodrug design aims to achieve various pharmaceutical objectives, including:

2.1.1. Enhancing Solubility

For instance, the prodrug of corticosteroids like Prednisolone is formulated to improve solubility, thereby enhancing drug dissolution and absorption.

2.1.2. Improving Chemical Stability

Prodrugs, such as Azacytidine, are developed to enhance chemical stability, ensuring prolonged shelf-life and efficacy of the active drug, especially in the case of antineoplastic agents.

2.1.3. Enhancing Organoleptic Properties

Prodrugs may be designed to address undesirable organoleptic characteristics, such as odor. For example, ethyl mercaptan, a prodrug of etisul, is employed to improve the odor of drugs used in leprosy treatment.

2.1.4. Minimizing Irritation and Pain

Prodrugs like clindamycin palmitate are formulated to reduce irritation and pain upon administration, enhancing patient comfort and compliance.

2.1.5. Incorporation into Innovative Pharmaceutical Forms

Prodrug design may involve the development of novel pharmaceutical formulations to optimize drug delivery and efficacy.

2.2. Pharmacokinetic objectives

Prodrug design targets pharmacokinetic objectives to improve drug absorption, distribution, metabolism, and excretion:

2.2.1. Enhancing Oral Permeability and Bioavailability

Prodrugs such as carbecillin and geocillin are engineered to enhance oral permeability, facilitating improved drug absorption and bioavailability.

2.2.2. Diminishing First-Pass Metabolism

Certain prodrugs, like Propanolol, are designed to bypass or reduce first-pass metabolism in the liver, thereby increasing the concentration of the active drug in systemic circulation.

2.2.3. Improving Absorption via Nonoral Routes

Prodrugs may be developed to enhance drug absorption through nonoral routes of administration, broadening therapeutic options and improving patient convenience.

2.2.4. Extending Duration of Action

Prodrug formulations, such as fluphenazine ester prodrugs, aim to prolong the duration of drug action, reducing dosing frequency and enhancing patient compliance.

2.2.5. Reducing Presystemic Metabolism

Prodrugs like the acetonide of triamcinolone are designed to minimize presystemic metabolism, ensuring a higher proportion of the active drug reaches systemic circulation intact.

2.3. Pharmacodynamic objectives

Prodrug design also targets pharmacodynamic objectives to enhance therapeutic efficacy and safety:

2.3.1. Minimizing Toxicity and Improving Therapeutic Index

Prodrugs are engineered to reduce adverse effects and enhance the therapeutic index, optimizing the balance between efficacy and safety.

2.3.2. In Situ Activation of Cytotoxic Agents

Prodrugs like tirapazamine are designed for in situ activation, ensuring selective activation of cytotoxic agents within target tissues, minimizing systemic toxicity.

2.3.3. Designing Co-Drugs

The strategy of designing single chemical entities combining two drugs (co-drugs) allows for synergistic therapeutic effects while minimizing adverse interactions.

2.3.4. Improving Site Specificity

Prodrugs may be tailored to enhance site-specific drug delivery, minimizing off-target effects and maximizing therapeutic efficacy.[9]

3. Classification of prodrugs

Prodrug classification is based on various factors such as constitution, lipophilicity, method of bioactivation, and catalyst. Prodrugs can be categorized into the following types

3.1. Carrier linked prodrugs

Carrier-linked prodrugs involve the covalent bonding of an active drug molecule with a carrier moiety. The bond between the active drug and carrier is designed to be cleaved by enzymatic or chemical reactions within the body, facilitating the release of the active drug. Carrier molecules typically consist of lipophilic compounds such as fatty acids or polymers like PEG (polyethylene glycol). Examples include [10].

3.1.1. Bipartite prodrugs

In bipartite prodrugs, a single drug molecule is attached to a single carrier moiety. This bond can be cleaved by chemical or enzymatic hydrolysis, releasing the active drug. Examples include prednisolone sodium phosphate and tolmetin glycine prodrug.

Prednisolone Sodium Phosphate: This prodrug has significantly enhanced water solubility compared to prednisolone, achieved by attaching a phosphate promoiety to the free hydroxyl group of prednisolone.

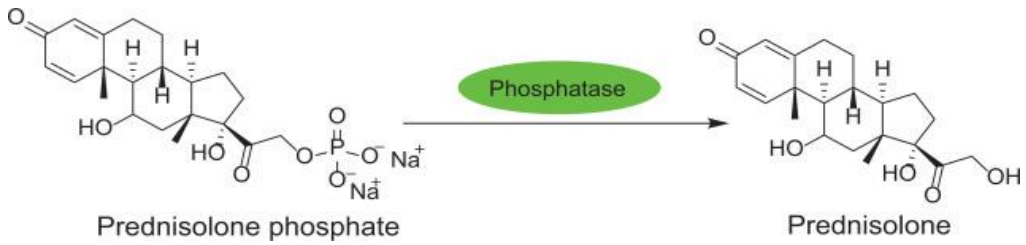

Figure 3. Prednisolone phosphate is converted to prednisolone by phosphatase

Tolmetin Glycine Prodrug: Upon enzymatic hydrolysis, this prodrug releases tolmetin, the active drug, along with the glycine carrier.

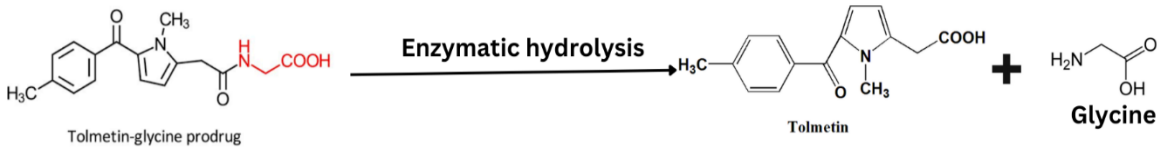

Figure 4. Bioactivation of the bipartite prodrug tolmetin-glycine to the active drug tolmetin by enzymatic hydrolysis

3.1.2. Tripartite prodrugs

Tripartite prodrugs involve the attachment of the carrier to a linker, which is then linked to the drug moiety. This configuration allows for more complex drug-carrier interactions. An example is becampicillin, a prodrug of ampicillin.

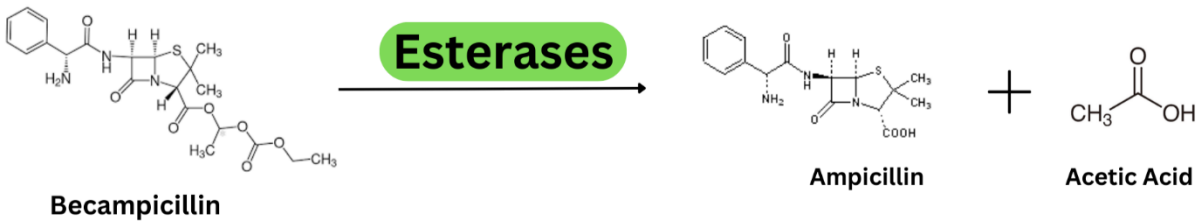

Figure 5. Becampicillin is an esterase that produces ampicillin

3.1.3. Macromolecular prodrugs

Macromolecular prodrugs are high-molar-mass conjugates containing multiple drug copies. These prodrugs often utilize carriers such as polysaccharides, dextrans, proteins, or polymers to optimize pharmacokinetics. An example is Naproxen-2-glyceride.

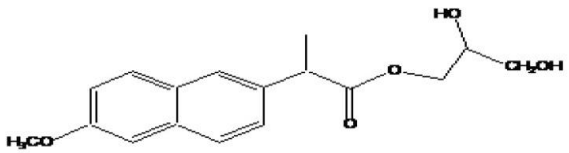

Figure 6. The chemical structure of Naproxen-2-glyceride

3.1.4. Site specific prodrugs

Site-specific prodrugs target the active drug to a specific site, enhancing drug delivery efficiency. Sulfasalazine is an example where an azo link connects 5-aminosalicylic acid and sulfapyridine, releasing 5-aminosalicylic acid in the colon.

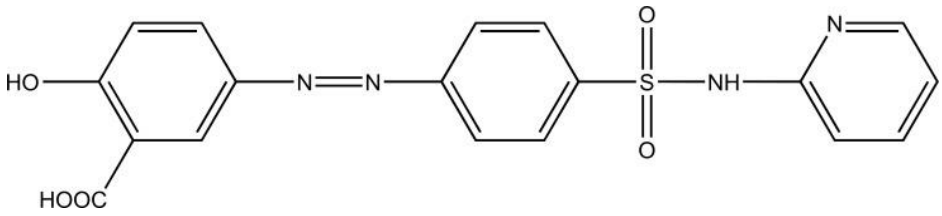

Figure 7. Chemical structure of sulfasalazine

3.1.5. Mutual prodrugs

Mutual prodrugs involve two pharmacologically active substances linked together, with each acting as a promoiety for the other. This strategy can enhance drug efficacy or improve site specificity. Examples include benorylate and sulfasalazine.

3.2. Bioprecursor/ metabolic prodrugs

Bioprecursor prodrugs undergo metabolic transformation in vivo to generate the active drug. These prodrugs are designed to mimic the metabolic pathway of endogenous compounds, utilizing phase I metabolizing enzymes. Modification of the active drug molecule facilitates conversion into the desired active form. Examples include oxidation or reduction reactions transforming an amine into an aldehyde and then into a carboxylic acid. The activation mechanisms and examples of bioprecursor prodrugs are listed out in Table 1

Table 1. Activation pathway and examples of metabolic prodrugs

Activation Pathway	Example	Drug
Proton activation	Omeprazole	Proton pump inhibitor
Elimination activation	Leflunamide	Anti-inflammatory
Oxidative activation		
- N and O Dealkylation	Triazolam	Benzodiazepine
- Oxidative Deamination	Cyclophosphamide	Antineoplastic
- N-Oxidation	Pralidoxime	Antidote for organophosphate poisoning
- S-Oxidation	Brefeldin A	Antimicrobial
Reductive activation		
- Azo reduction	Prontosil	Antibacterial
- Sulfoxide reduction	Sulindac	Nonsteroidal anti-inflammatory
- Disulfide reduction	Primaquine	Antimalarial
- Bioreductive alkylation	Mitomycin C	Antineoplastic
Nucleotide activation	Abacavir	Antiretroviral
Phosphorylation activation	2-deoxy-D-glucose	Glucose metabolism inhibitor
Decarboxylation activation	Levodopa	Dopaminergic agent

4. Classification of prodrugs

4.1.1. Classification based on potential action of prodrugs

Table 2 provides the classification of prodrugs based on their potential action

Table 2. Classification of prodrugs based on their action

Classification Criteria	Example	Prodrug Type
1. Therapeutic Categories		
- Anticancer prodrugs	Capecitabine	5'deoxy-5-fluorocytidine
- Antiviral prodrugs	Lamivudine, Pencyclovir	Lamivudine: Nucleoside reverse transcriptase inhibitor; Pencyclovir: Antiviral agent
- Antibacterial prodrugs	Ceftaroline fosamil	Ceftaroline: Broad-spectrum cephalosporin antibiotic
- NSAID prodrugs	Salsalate, Nabumetone	Salsalate: Nonsteroidal anti-inflammatory drug (NSAID); Nabumetone: Prodrug of active metabolite, NSAID
- Cardiovascular prodrugs	Ximelagatran, Dabigatran Etexilate	Ximelagatran: Prodrug of melagatran, Thrombin inhibitor; Dabigatran Etexilate: Prodrug of dabigatran, Direct thrombin inhibitor

2. Chemical Linkages or Moieties		
- Ester prodrugs	Trandolapril, Oseltamivir	Trandolapril: Angiotensin-converting enzyme (ACE) inhibitor; Oseltamivir: Antiviral, Influenza neuraminidase inhibitor
- Glycosidic prodrugs	Doxorubicin prodrug	Doxorubicin: Anthracycline antibiotic, Antineoplastic; Prodrug designed to reduce cardiotoxicity
- Bipartite prodrugs	Latanoprost, Dipivefrin	Latanoprost: Prostaglandin analog, Glaucoma treatment; Dipivefrin: Prodrug of epinephrine, Ophthalmic agent
- Tripartite prodrugs	Pivampicillin	Pivampicillin: Antibiotic, Prodrug of ampicillin
- Antibody-directed enzyme prodrugs	Daunorubicin glucuronide prodrug	Daunorubicin glucuronide: Prodrug activated by tumor-specific enzymes, Cancer chemotherapy
3. Intentional and Fortuitous Prodrugs		
- Fortuitous prodrugs	Aspirin, Prontosil	Aspirin: Antiplatelet, Analgesic, Antipyretic; Prontosil: Antibacterial, First sulfonamide antibiotic

4.1.2. Classification based on cellular site of bioactivation

Prodrugs play a crucial role in mitigating undesirable pharmacodynamic or pharmacokinetic properties associated with active drugs. These modifications aim to enhance bioavailability or minimize adverse effects, thereby optimizing therapeutic outcomes. A novel classification approach has emerged, focusing on the cellular site of bioactivation, delineating prodrugs into distinct categories.

Prodrugs are primarily classified into two types based on their cellular sites of bioactivation, namely Type I and Type II. Type I prodrugs undergo bioactivation intracellularly, while Type II prodrugs are bioactivated extracellularly, typically in digestive fluids or the systemic circulation. Notably, Type I prodrugs encompass anti-viral nucleoside analogs and lipid-lowering statins, exemplified by drugs like etoposide phosphate, valganciclovir, and fosamprenavir, along with antibody-, gene-, or virus-directed enzyme prodrugs utilized in chemotherapy or immunotherapy. Table 3 provides the classification of prodrugs based on cellular site of activation

Table 3. Classification of prodrugs based on cellular site of activation

Prodrug Types	Site of Conversion	Subtypes	Tissue location of Conversion	Examples
Type I	Intracellular	Type IA	The therapeutic target tissue Cells	L-DOPA, Cyclophosphamide, 5-fluorouracil, Acyclovir.
		Type IB	Metabolic tissues (Liver, Gastrointestinal Tract, lungs, etc.)	Primidone, Carisoprodol, Sulindac, Heroin.
Type II	Extracellular	Type IIA	Gastrointestinal fluids	Loperamide oxide, Sulfasalazine.
		Type IIB	Systemic circulation and Other extracellular fluids Compartments	Bambuterol, Fosphenytoin, Dipivefrin, Pralidoxime.
		Type IIC	Therapeutic target tissues And cells	ADEPTs, GDEPTs, VDEPTs.

5. Applications

The utilization of the prodrug approach spans across various therapeutic domains, demonstrating its versatility and efficacy in addressing specific medical needs.

5.1. Treatment of ADHD

Attention deficit hyperactivity disorder (ADHD) poses significant challenges in pediatric care. Prodrug methodologies have paved the way for novel stimulant treatments, such as lisdexamfetamine dimesylate (LDX). Upon ingestion, LDX is rapidly absorbed in the gastrointestinal tract and subsequently metabolized into d-amphetamine, offering a promising therapeutic avenue for ADHD management.

5.2. Cholesterol-Lowering Prodrugs

Prodrugs play a pivotal role in modulating cholesterol levels, exemplified by simvastatin (SV). SV, in its lactone prodrug form, undergoes reversible metabolism to yield the active hydroxy acid form (SVA), a potent inhibitor of HMG-CoA reductase. This mechanism underscores the efficacy of prodrugs in combating dyslipidemia and reducing cardiovascular risk.

5.3. Thrombolytic Agents

Thrombolytic therapy, essential for managing thromboembolic events, necessitates precise control to minimize bleeding complications. The prodrug strategy, involving heparin/protamine-based formulations, facilitates the controlled delivery of plasminogen activators like tissue-type plasminogen activator (tPA). Through antibody-targeted, triggered, electrically modified prodrug-type strategies (ATTEMPTS), inactive tPA is selectively delivered to the target site, ensuring localized thrombolysis with minimized systemic effects.

5.4. Treatment of Hypotension

L-Threo-3,4-dihydroxyphenylserine (LDOPS or droxidopa), a norepinephrine prodrug, offers therapeutic relief for orthostatic hypotension. Its chemical structure facilitates conversion into norepinephrine, augmenting sympathetic tone and mitigating hypotensive symptoms, thus enhancing patient quality of life.

5.5. Carboxylesterase [CE]/Irinotecan System

The CE/Irinotecan system represents an innovative approach for combating colorectal cancer, gliomas, and other malignancies. This enzyme-prodrug system capitalizes on carboxylesterase-mediated activation of irinotecan, enhancing its cytotoxic effects selectively within tumor cells while minimizing systemic toxicity.

5.6. Horseradish Peroxidase (HRP)/Indole-3-Acetic Acid (IAA) System

Recombinant variants of HRP isoenzymes, coupled with indole-3-acetic acid, offer promising therapeutic avenues for breast and bladder cancer. The HRP/IAA system demonstrates considerable efficacy in targeted tumor therapy, leveraging enzymatic activation mechanisms to elicit tumor-specific cytotoxicity while sparing healthy tissues

6. Conclusion

It is estimated that approximately 10% of all drugs available on the market are prodrugs. The prodrug approach stands out as a promising method to enhance the therapeutic effectiveness and mitigate potential side effects of pharmacologically active agents. This enhancement is achieved through a diverse array of mechanisms, including improved permeability, solubility, stability, bioavailability, and targeted delivery to specific tissues. Prodrug design necessitates early consideration during drug development, as modifications to the pharmacokinetic properties of drug molecules may inadvertently introduce undesirable characteristics. The activation of prodrugs is influenced by various factors, including genetic polymorphisms, age-related changes in metabolism, and potential drug interactions. As such, prodrugs are poised to play a significant role in modern pharmacotherapy, offering tailored solutions to optimize therapeutic outcomes

References

[1] Smith, A. B., Jones, C. D., & Johnson, E. F. (2019). Prodrug Strategies for Improving the Oral Absorption of Drugs. Journal of Medicinal Chemistry, 62(1), 144-158.

[2] Tummala SR, Amgoth KP. Development of GC-MS/MS Method for Simultaneous Estimation of Four Nitrosoamine Genotoxic Impurities in Valsartan. Turkish Journal of Pharmaceutical Sciences. 2022 Aug;19(4):455

[3] Wang, Y., Li, J., Chen, T., Gan, S., Zhang, L., & Zhang, L. (2020). Recent Advances in Prodrug Design for Anticancer Chemotherapy. Current Pharmaceutical Design, 26(20), 2420-2442.

[4] Stella, V. J., & Nti-Addae, K. W. (2007). Prodrug strategies to overcome poor water solubility. Advanced Drug Delivery Reviews, 59(7), 677-694.

[5] Dahan, A., Markovic, M., Epstein, S., & Barenholz, Y. (2016). Prodrugs for Improved Drug Delivery: The Role of Transporters in Drug Release. Advances in Drug Delivery Reviews, 101, 240-250.

[6] Boddu, S. H. S., Jwala, J., Wang, S., & Hu, Y. (2018). Prodrug Approaches to Enhance the Intestinal Permeability of Drugs. Current Topics in Medicinal Chemistry, 18(26), 2242-2254.

[7] Shah, B., Kakumanu, V. K., & Bansal, A. K. (2006). Analytical Techniques for Quantification of Prodrugs. Journal of Pharmaceutical Sciences, 95(6), 1177-1195.

[8] Kumar SP, Kanthal LK, Durga S, Satyavati K. Phytochemical Evaluation and Screening of Cardiotonic, Antibacterial and Anthelmintic Activities of Sida cordifolia L. Int J Pharm Sci Nanotechnol. 2014 Aug 31;7(3):2567-73.

[9] Rautio, J., Kumpulainen, H., Heimbach, T., Oliyai, R., Oh, D., Järvinen, T., & Savolainen, J. (2008). Prodrugs: design and clinical applications. Nature Reviews Drug Discovery, 7(3), 255-270.

[10] Sarella PN, Dadishetti JP, Asogwa PO, Kakarparthy R. Pharmacological and Non-pharmacological Management of Bipolar Disorder with Comorbid Huntington's Disease: A Case Report. Journal of Clinical and Pharmaceutical Research. 2023 Apr 30:5-8.

[11] Di, L., & Kerns, E. H. (2015). Drug-like Properties: Concepts, Structure Design and Methods from ADME to Toxicity Optimization (Second Edition). Academic Press.

[12] Sallustio, B. C., Stolk, P., & Boddy, A. V. (2014). In silico prediction of the permeability of prodrugs by a decision tree. European Journal of Pharmaceutical Sciences, 51, 1-7.

[13] Sinko, P. J. (2013). Martin's Physical Pharmacy and Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences. Lippincott Williams & Wilkins.

[14] Stella, V. J., & Charman, W. N. (2000). Prodrugs: Do they have advantages in clinical practice? Drugs, 39(5), 760-773.

[15] Sneader, W. (2005). Drug discovery: a history. John Wiley & Sons.

[16] Huttunen, K. M., & Rautio, J. (2019). Prodrugs—An efficient way to breach delivery and targeting barriers. Current Topics in Medicinal Chemistry, 19(25), 2272-2286.

[17] Thummala UK, Vallabhareddy PS, Sarella PN. Enhancing Oral Absorption of Orlistat through Gastroretentive Mucoadhesive Pellets: Formulation and Evaluation. Journal of Clinical and Pharmaceutical Research. 2023 Apr 30:9-17.

[18] Williams, D. A., & Lemke, T. L. (2002). Foye's principles of medicinal chemistry. Lippincott Williams & Wilkins.

[19] Mendes, L. F., & Pan, J. (2020). Synthetic approaches for the design of prodrugs. Chemical Society Reviews, 49(21), 7234-7267.

[20] Arji SR, Eranki SS, Kadimi A, Sarella PN, Mangam VT. Development and validation of an HPLC method for the simultaneous estimation of salbutamol, theophylline and ambroxol in tablet dosage form. International Journal of Science and Research Archive. 2023;10(2):634-45.

[21] Savjani, K. T., Gajjar, A. K., & Savjani, J. K. (2012). Drug solubility: importance and enhancement techniques. ISRN Pharmaceutics, 2012.

[22] Pouliot, M., & Jean, M. (2019). Targeted delivery of prodrugs as a strategy to overcome the limited bioavailability: An old concept revisited. Current Topics in Medicinal Chemistry, 19(25), 2306-2330.

[23] Boddy, A. V., & Yule, S. M. (1999). Metabolism and pharmacokinetics of oxazaphosphorines. Clinical Pharmacokinetics, 36(4), 291-304.

[24] Sarella PN, Thammana PK. Potential applications of Folate-conjugated Chitosan Nanoparticles for Targeted delivery of Anticancer drugs.

[25] Stella, V. J., & Rajewski, R. A. (1997). Cyclodextrins: their future in drug formulation and delivery. Pharmaceutical Research, 14(5), 556-567.

[26] Amidon, G. L., Lennernas, H., Shah, V. P., & Crison, J. R. (1995). A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical Research, 12(3), 413-420

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