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A Review On Prodrug

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ABSTRACT:

Prodrugs represent a class of drug derivatives that can be metabolized enzymatically and/or chemically within the body, resulting in the release of the active parent drug. This subsequent release allows the drug to exert its intended pharmacological effect. The utilization of prodrugs offers several advantages when compared to traditional drug administration methods. By modifying the physicochemical, biopharmaceutical, or pharmacokinetic properties of drugs, prodrugs can enhance the efficiency of drug delivery to specific targets. This article provides a comprehensive overview of prodrugs, including their classification, impact on solubility, chemical stability, bioavailability, prolonged duration of action, and targeted site-specific challenges. Additionally, examples of prodrugs are presented to illustrate their role in facilitating more effective treatments for various diseases.

Keywords: - Prodrug, Pharmacokinetic, Pharmacodynamic, Solubility, Drug Design

Introduction:

The concept of "prodrug" or "pro-agent" was initially introduced by Albert in 1958. Prodrugs are compounds that are initially inactive but undergo chemical or enzymatic metabolism in the body to produce the active parent drug. A prodrug is defined as a compound that undergoes biotransformation before exhibiting its therapeutic effect(1). Essentially, prodrugs are reversible derivatives of drug molecules that undergo enzymatic and/or chemical transformations in vivo to release the active parent drug, which then exerts the desired pharmacological effect. In these cases, an active moiety is attached to an inactive moiety, which is subsequently broken down in the body through the action of enzymes. It is crucial that the inactive moiety is non-toxic and preferably eliminated from the body quickly(2). Therefore, a prodrug can be seen as a drug that contains a specialized non-toxic protective group, used temporarily to modify or eliminate undesirable properties in the parent drug. The design of prodrugs is necessary to overcome various formulation, pharmacokinetic, or pharmacodynamic limitations. One of the prominent drawbacks that prodrugs aim to address is….

I. Gastric irritation resulting in an unpleasant taste or odor,
II. A broad spectrum of negative effects,
III. Reduced duration of effectiveness,
IV. Lack of stability,
V. Lack of specificity in targeting sites,
VI. Inadequate absorption or distribution,
VII. Limited solubility in water,
VIII. Certain compounds exhibit higher activity but are unable to reach their intended site of action, such as GABA (3).

Prodrug is a drug that does not have a pharmacological active ingredient. It is converted to an active drug through a metabolic biotransformation.

Soft Drugs, on the other hand, are active compounds that are readily converted to non-toxic products through metabolic inactivation. Examples include insulin. Hard Drugs are compounds that have a high lipid or watersoluble half-life and are not metabolized. Because they are not metabolized, they have a high efficiency but are less easily eliminated due to lack of metabolic activity. Examples include cocaine and heroin.

Antedrugs: are compounds that are designed to work locally and when released into the body, must be metabolized or chemically transformed to an inactive compound (e.g., a steroid drug used topically for treating an allergic condition).

What is a prodrug?

A prodrug is an inactive precursor to an active drug. Its primary purpose is to bioconvert (activate) the parent drug after administration.

Prodrugs have proven to be successful for a long time. One of the first prodrugs to reach the colon is sulfasalazine. Bacteria metabolize sulfasalazine to produce two active metabolites: sulapyridine (5-AAsa) and sulfasalazine (SAA). Salsaalazine was first approved in the United States in 1950 and is still the first line treatment for autoimmune conditions like Crohn's disease and Ulcerative Colitis (UCI).

Prodrug approaches have proven to be very successful in the last few years. It is estimated that 10% to 20% of all drugs on the market today belong to prodrugs Small molecule weight drugs approved from 2000 to 2008 accounted for 20% of all small molecule weight drugs and from 2008 to 2017 the drug market share was 12%.

History Of Prodrug:

Acetanilide, the first compound to meet the classical criteria of a prodrug, was brought into medical practice by Cahn and Hepp in 1867 as an antipyretic agent. Through hydroxylation, acetanilide is converted into the biologically active acetaminophen. Another notable prodrug in history is Aspirin (acetylsalicylic acid), which was synthesized by Felix Hoffman of Bayer, Germany in 1897 and introduced into medicine by Dreser in 1899. The Parke-Davis company was the first to intentionally employ the prodrug concept, using it to modify the structure of chloramphenicol. This modification aimed to enhance the antibiotic's bitter taste and poor solubility in water. As a result, two prodrug forms of chloramphenicol were synthesized: chloramphenicol sodium succinate, which exhibited good water solubility, and chloramphenicol palmitate, which was utilized as a suspension for children.

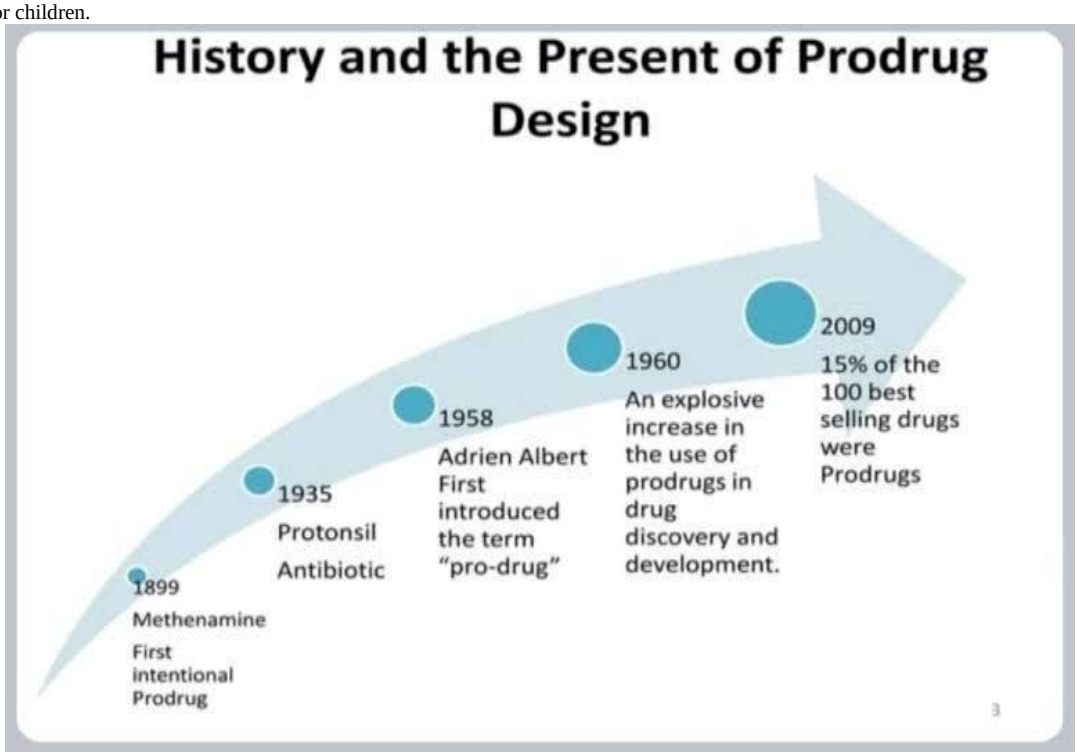


Fig 1 .History of Prodrugs

Prodrug Concept:

Prodrugs, in essence, are modified versions of active drug components that are specifically designed to undergo a transformation within the body, thereby addressing any undesirable properties associated with the drug. These modifications are strategically made so that the prodrug can be activated through either an enzymatic or chemical reaction once it is administered into the body. The primary objective of prodrug design is to conceal any unfavorable drug properties, such as limited solubility in water or lipid membranes, lack of target selectivity, chemical instability, unpleasant taste, irritation or pain upon local administration, pre-systemic metabolism, and toxicity. The overarching goal of utilizing prodrugs is to optimize the absorption, distribution, metabolism, excretion, and minimize any unwanted toxicity (commonly referred to as ADMET properties) of the parent drugs. Traditionally, the term "prodrug," coined by Adrien Albert in 1958, pertains to biologically inactive derivatives of drug molecules that undergo enzymatic and/or chemical conversion within the body to release the pharmacologically active parent drug.The active drug undergoes conversion from its inactive form to its active form either before, during, or after absorption of the prodrug. Some medications are only released once they have reached their intended targets. The purpose of a prodrug is to enhance the bioavailability and therapeutic efficacy of the parent drug. While the term prodrug is commonly used today, these compounds have also been referred to as reversible or bioreversible derivatives, or biolabile drug-carrier conjugates. Testa (74) outlines three main objectives in prodrug research:

1. Pharmaceutical: to enhance solubility, chemical stability, and organoleptic properties; to reduce irritation and/or pain following local administration; to address issues related to the pharmaceutical technology of the active ingredient.
2. Pharmacokinetic: to improve absorption (both orally and through non-oral routes), to decrease presystemic metabolism, to optimize the time profile, and to enhance the selective delivery of the active ingredient to specific organs or tissues.
3. Pharmacodynamic: to minimize toxicity and enhance the therapeutic index, to develop single chemical entities that combine two drugs (co-drugs strategy). It is important to highlight that advancements in prodrug design over the past decade have primarily focused on strategies to enhance oral bioavailability and achieve targeted delivery to the brain and tumors.

Clasification of prodrug :

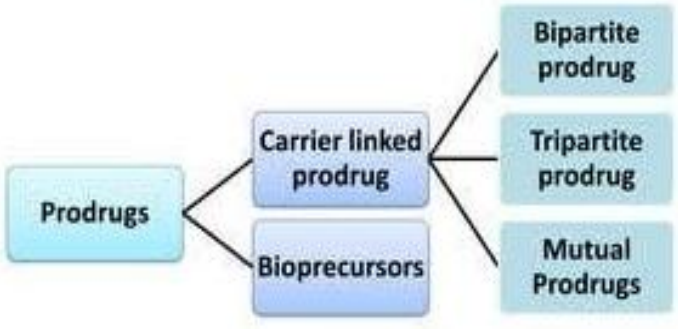
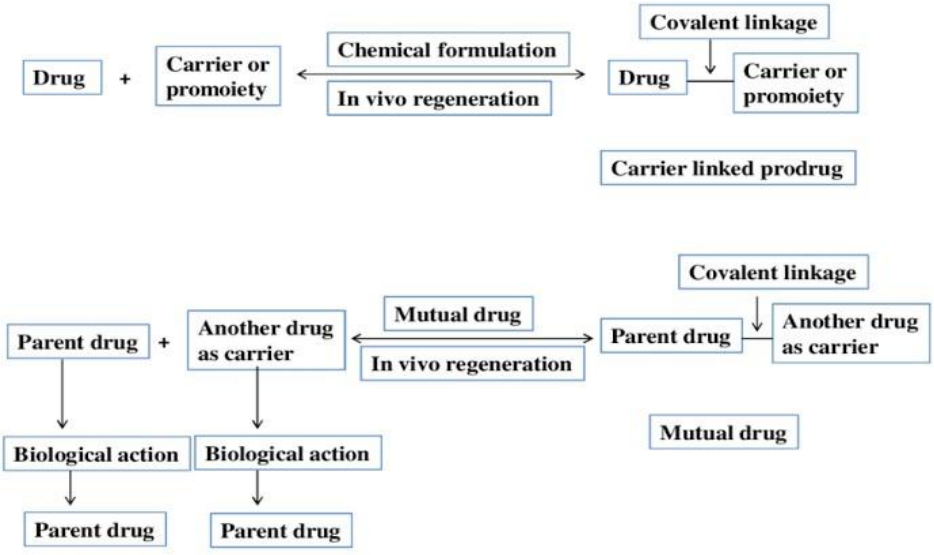


Fig 2 - Classification Of Prodrug

Carrier linked prodrugs are a type of prodrug where the active drug is covalently linked to a carrier group, also known as a pro-moiety. This linkage allows for easy cleavage of the pro-moiety from the active drug, either through enzymatic or non-enzymatic processes, resulting in the release of the parent drug. The addition of the carrier group helps to modify the physicochemical properties of the drug, making it more suitable for its intended use. It is important that the carrier used is non-immunologic, cost-effective, stable during administration, and capable of undergoing biodegradation to form inactive metabolites. Common types of carrier linked prodrugs include esters, amides, phosphates, carbamates, oximes, imines, and N-Mannich bases.



Depending on the type of carrier (pro-moiety) used, carrier-linked prodrugs can be further classified into the following categories:

1. **Double prodrugs:**

In this category, a prodrug is modified in such a way that only enzymatic conversion to the prodrug is possible before it can break down and release the active drug. These are also known as pro-prodrugs or cascade-latentiated prodrugs, where the prodrug is further modified in a manner that allows only enzymatic conversion to the prodrug before it can cleave and release the active drug.

2. **Site-specific prodrugs:**

In this category, a carrier acts as a transporter of the active drug to a specific targeted site in the organ or receptor. These site-specific prodrugs utilize a carrier to transport the active drug to a specific targeted site.

3. **Macromolecular prodrugs:**

This category involves the use of macromolecules such as polysaccharides, dextrans, cyclodextrins, proteins, peptides, and polymers as carriers or pro moieties. Macromolecular prodrugs utilize these larger molecules as carriers or pro moieties for the active drug.

A mutual prodrug is a type of prodrug that involves two pharmacologically active agents that are chemically linked together. In this case, each agent acts as a pro moiety for the other, meaning that they are mutually dependent on each other for their pharmacological activity. Unlike traditional prodrugs, which use inert molecules as carriers, a mutual prodrug utilizes another biologically active drug as the carrier.

The selection of the carrier drug is crucial in a mutual prodrug. It can either have the same biological action as the parent drug, resulting in a synergistic effect when both agents are released in the body, or it can possess additional biological actions that are lacking in the parent drug, providing additional therapeutic benefits. Additionally, the carrier drug can be chosen to target the parent drug to a specific site, organ, or cells, enhancing the drug's site specificity. It may also help overcome some of the side effects associated with the parent drugs.

Overall, a mutual prodrug offers a unique approach to drug delivery by combining two pharmacologically active agents and utilizing a biologically active carrier. This strategy can potentially enhance the therapeutic effects of the drugs and improve their overall efficacy.

Bioprecursor prodrug:

A bioprecursor prodrug refers to a type of prodrug that does not rely on the attachment to a carrier or pro moiety, but rather undergoes a molecular modification of the active drug itself. The activation of a bioprecursor prodrug is dependent on metabolism, which introduces an active functional group. This activation can occur through various processes such as oxidation, reduction, nucleotide activation, phosphorylation activation, and decarboxylation. Bioprecursor prodrugs can be categorized based on the method of activation, either through phase 1 or phase 2 metabolism.
An example of a bioprecursor prodrug is Acetaminophen, which is derived from the
O-demethylation of phenacetin. Acetaminophen exhibits superior analgesic activity compared to phenacetin.

Prodrug Barrier

Classification of prodrug Barriers -

1)Pharmaceutical barriers
Insufficient chemical stability
Poor solubility Offensive taste and odour
2)Pharmacokinetic barriers
Low oral absorption
Marked presystemic metabolism
Short duration of action
3)Pharmacodynamic barriers
Toxicity

Barriers to Drug Development

In figure 1, the term 'barrier' is utilized in a broad sense. While it is simple to imagine a genuine biological barrier, like the blood-brain barrier, in the context of drug delivery to the central nervous system (CNS), there are numerous other barriers that may not always be acknowledged by end users of a drug product. These barriers must be addressed before a new chemical entity can effectively become a therapeutic drug. Aliens and Simonis (1974) outlined the drug development process as consisting of three phases: the pharmaceutical, pharmacokinetic, and pharmacodynamic phases. The pharmacodynamic phase, which focuses on the interaction between the drug and its receptor, is typically not where prodrugs are thought to act. However, Bey (1978) proposed that suicide substrates or Kc a t inhibitors (compounds containing latent reactive groups that are specifically activated by target enzymes) could be classified as prodrugs.
2.1 Pharmaceutical Phase
The pharmaceutical phase can be defined as the stage of development that occurs between the identification of a new chemical entity with proven or potential therapeutic effects and its integration into a drug delivery system. This delivery system may take the form of traditional methods such as tablets, capsules, injections, creams/ointments, etc., or innovative drug delivery mechanisms like transdermal patches or implanted devices. Two obstacles in this phase that hinder the progression of a commercially viable drug product are:
The phase of pharmacokinetics involves the examination of how a drug is absorbed, distributed, metabolized, and excreted in the body. These investigations offer crucial insights into the drug's in vivo characteristics, such as issues with absorption, rapid elimination, and metabolism before reaching the systemic circulation. By linking these characteristics back to the physicochemical and dosage form attributes of the drug, adjustments can be made. In some cases, these adjustments may necessitate the use of prodrugs.
The main obstacles identified in the pharmacokinetic phase include:

1. Inadequate absorption of the drug from the delivery system or through biological barriers like the gastrointestinal mucosal cells and the blood-brain barrier.
2. Either too fast or too slow transport of the drug within the body, requiring optimization of the drug's onset of action.
3. Incomplete systemic delivery of a drug due to metabolism before reaching the systemic circulation in the gastrointestinal tract, mucosal cells, and liver.
4. Toxicity issues arising from local irritation or distribution to unintended tissues.
5. Lack of specificity in targeting the desired organ.

There are numerous clinical cases and references in the literature that discuss the use of prodrugs to address the aforementioned challenges. Many of these instances have been documented in comprehensive reviews (refer to table I). This article presents some clinically relevant or potentially relevant examples of prodrug use, along with the associated issues. For a more detailed examination of the topic, readers are encouraged to consult the reviews listed in table I.

Use of Prodrugs to Overcome Pharmaceutical Barriers

The development of a novel chemical compound that is believed to have therapeutic benefits necessitates the formulation of the drug into a delivery form that is chemically stable, devoid of taste and odor issues (especially if it is intended for pediatric use or parenteral administration), and causes

minimal irritation upon administration. In the case of intravenous usage, the drug should possess sufficient water solubility and remain in solution for an adequate duration to allow for the complete administration of the prescribed dose.

3.1 To address taste or odor problems, chloramphenicol, which is known for its extremely bitter taste, is often unsuitable for use in pediatric formulations. However, chloramphenicol palmitate, a sparingly soluble ester of chloramphenicol, is practically tasteless due to its low solubility in water (Glazko et al., 1952). It is important to note that reducing the aqueous solubility of a drug or prodrug to mask taste issues may lead to a more significant problem, such as incomplete dissolution of the prodrug in the gastrointestinal tract, resulting in incomplete absorption. Nevertheless, the commercially available form of chloramphenicol palmitate efficiently undergoes hydrolysis by pancreatic lipase, converting it into active chloramphenicol (Andersgaard et al., 1974). Interestingly, other tasteless polymorphs of chloramphenicol palmitate do not yield satisfactory plasma concentrations of chloramphenicol due to their poor solubility and the absence of lipase-catalyzed solid-to-solution transition. Table II provides additional examples of prodrugs used to mask taste. Odor is another aesthetic concern for certain drugs, particularly those that are volatile liquids or solids with significant vapor pressure, making their formulation challenging. An illustrative example of this is the use of volatile mercaptans as tuberculostatic agents and for leprosy treatment. E.

3.2 Alleviation of Discomfort or Inflammation at Injection Sites

Discomfort or inflammation at the site of injection can arise from drug precipitation, cell lysis caused by hypo- or hyperosmotic solutions, the characteristics of the drug, or the corrosive effects of the drug on nerve endings. Certain issues may be associated with the composition of the vehicle or the pH of the vehicle required for formulation purposes.

WHY TO USE PRODRUG?

1. Various pharmacokinetic justifications exist for the development of prodrugs. These include enhancing the drug's absorption to achieve more complete or predictable outcomes, minimizing incomplete and variable systemic bioavailability by preventing extensive presystemic metabolism, enhancing access to the site of action such as crossing the blood-brain barrier, selectively activating a drug in the target tissue to avoid unwanted systemic effects, optimizing the drug's onset or duration of action by improving absorption, distribution, or elimination characteristics, improving patient acceptability by reducing pain upon injection, not being site-specific, serving as a good substrate for first-pass metabolism, and addressing issues related to poor aqueous solubility.

Objectives of prodrug

There are three primary objectives in prodrug research, which are interrelated and complement each other. The first set of objectives, known as pharmaceutical objectives, aims to enhance the properties of the prodrug. This includes improving its solubility, chemical stability, and organoleptic properties. Additionally, it seeks to minimize irritation and pain that may occur after local administration of the prodrug. Furthermore, it aims to address any challenges associated with the pharmaceutical technology of the active agent.

The second set of objectives, referred to as pharmacokinetic objectives, focuses on optimizing the absorption of the prodrug. This applies to both oral and non-oral routes of administration. It also aims to reduce presystemic metabolism, thereby improving the time profile of the prodrug. Moreover, it aims to enhance the selective delivery of the active agent to specific organs or tissues.

Lastly, the third set of objectives, known as pharmacodynamic objectives, aims to enhance the therapeutic profile of the prodrug. This involves reducing its toxicity and improving the therapeutic index, which is the ratio between the desired therapeutic effect and the adverse effects. Additionally, it involves the design of single chemical entities that combine two drugs, known as the co-drugs strategy.

Overall, these objectives in prodrug research encompass various aspects of pharmaceutical, pharmacokinetic, and pharmacodynamic considerations, with the ultimate goal of developing safer and more effective therapeutic agents.

Limitations of prodrug

The total prodrug can give rise to an unexpected metabolite that may have toxic effects. Additionally, the cleavage of the prodrug can generate an inert carrier that has the potential to transform into a toxic metabolite. During the activation phase, the prodrug may deplete an essential cellular component. The prodrug approach often overcomes various challenges, including chemical instability, low water solubility, rapid metabolism before reaching the systemic circulation, poor absorption, and toxicity. The toxicity can be attributed to the inert carrier formed by the cleavage of the promoiety and drug conjugates, which subsequently converts into a toxic metabolite.

Properties of prodrugs

Pharmaceutical inertness refers to the property of a prodrug that undergoes rapid transformation, either chemically or enzymatically, into its active form at the desired location within the body. This process is accompanied by the generation of non-toxic metabolite fragments, which are promptly eliminated from the system. It is crucial for the prodrug to exhibit lower toxicity compared to the active drug. Additionally, the prodrug should either be inactive or exhibit significantly reduced activity compared to the parent drug. The rate at which the drug is formed from the prodrug should be sufficiently fast to maintain the desired drug concentration within the therapeutic window. Furthermore, the metabolites produced by the carrier should possess minimal toxicity or exhibit a low degree of toxicity. Lastly, the prodrug should demonstrate site-specificity, targeting the intended site of action.

Advantages and Disadvantages of prodrugs

Advantages

1. It mitigates the negative impacts of the medication.
2. Medication can be directed towards specific target areas.
3. Achieving combined effects without any accompanying adverse reactions.
4. Providing additional biological functions similar to the original drug.
5. Enhancing water solubility through the use of sodium succinate esters like chloramphenicol succinate in intravenous injections.
6. Enhancing lipid solubility: a- Prolonging the drug's effects by utilizing lipid-soluble esters. b- Improving oral absorption by using esters for highly polar drugs or N-methylation.
7. c- Enhancing the absorption of steroids topically by esterification or acetonidation of the OH group.
8. 7) Reducing water solubility to enhance taste, as seen in chloramphenicol palmitate. 8) Minimizing gastrointestinal irritation (side effects) like in aspirin.
9. Targeting specific sites like in methyldopa.
10. Extending half-life and chemical stability, as demonstrated in cefamandole acetate, a stable prodrug compared to the unstable solid dosage form of the parent cefamandole. Hetacillin is another prodrug for ampicillin.

Disadvantages

1. Generation of harmful byproducts.
2. The effective dosages of two related prodrugs derived from a common precursor may exhibit similar pharmacokinetic profiles but could demonstrate distinct variations in clinical studies. 3) The prodrug may utilize an essential cellular component like glutathione during its conversion process, leading to the depletion of the prodrug.

Applications of prodrug

Prodrugs are commonly utilized to surmount pharmacokinetic and pharmaceutical obstacles, thereby enhancing the bioavailability of the drug. Following the overcoming of these barriers, the prodrug must undergo conversion into its active form at the specific site of action. The various applications of prodrugs include enhancing the taste and odor of the drug, increasing its bioavailability, enabling site-specific drug delivery, prolonging the duration of action, minimizing toxicity, protecting from pre-systemic metabolism, improving the chemical stability of the drug, reducing pain at the injection site, providing protection from rapid metabolism and excretion, reducing toxicity, and enhancing the lipid solubility of the drug. The applications of prodrugs are exemplified in the context of anticancer agents, such as chemotherapeutic agents like paclitaxel, which have been conjugated with polymeric carriers to enhance their pharmacological activity and improve their pharmacokinetic profile.

The concept of reviving anti-cancer prodrugs through antibody directed enzymes is based on two approaches: ADEPT (Antibody-Directed Enzyme Prodrug Therapy) and GDEPT

(Gene-Directed Enzyme Prodrug Therapy). ADEPT involves the activation of specially designed prodrugs by antibody enzyme conjugates that are targeted to tumor-associated antigens. On the other hand, GDEPT relies on the use of enzymes expressed by exogenous genes in tumor cells to activate the prodrugs.

1. To illustrate the effectiveness of this concept, monoclonal antibodies against tumor-associated antigens can be considered. For instance, a fusion protein consisting of a human single chain Fv antibody called C28, which targets the epithelial cell adhesion molecule, and the human enzyme b-glucuronidase, has been developed. This fusion protein has proven to be valuable in delivering enzymes selectively to the tumor site for the activation of a non-toxic prodrug. By converting a non-toxic prodrug of doxorubicin, known as N-[4-doxorubicin Ncarbonyl(oxymethyl)phenyl]-O-b-glucuronyl carbamate, into doxorubicin, the fusion protein induces cytotoxicity.
2. In addition to antibody-directed therapies, gene-directed therapies have also been explored. One example is the use of a 5-fluorouracil-cephalosporin prodrug in the treatment of colorectal and other cancers. This prodrug was evaluated in the presence of Enterobacter cloacae P99 βL (ECl βL), revealing specific kinetic parameters such as a Km value of 95.4 μM and a Vmax value of 3.21 μMol min−1 mg−1. These findings highlight the potential of antibody directed enzymes and gene-directed therapies in the development of targeted anti-cancer treatments.
3. Various strategies have been developed to target the colon in GIT problems, including the use of prodrug formulations, pH-sensitive systems, time-dependent release mechanisms, microbial degradation, and osmotic pressure. These approaches aim to formulate different dosage forms such as tablets, capsules, multiparticulates, microspheres, and liposomes for colon targeting. In the treatment of inflammatory bowel disease (IBD), prodrugs that are specifically designed to target colonic release or are degraded by colonic bacteria can be beneficial. For instance, a mutual azo prodrug of 5-ASA was synthesized by combining L-tryptophan with salicylic acid to deliver the drug specifically to the inflamed colonic tissue in IBD. In vitro studies demonstrated that 87.18% of 5-aminosalicylic acid was released in rat fecal matter, with a half-life of 140.28 minutes following first-order kinetics. This synthesized azo conjugate exhibited a comparable mitigating effect to sulfasalazine on colitis in rats, but without the ulcerogenicity associated with 5-aminosalicylic acid. Another example is omeprazole, which is a prodrug of a sulfonamide that exerts its anti-ulcer effects by modifying cysteine residues on the luminal side of the proton pump in the stomach. However, this prodrug only exhibits its anti-secretory effect in the acidic environment of the stomach's oxyntic mucosa. Additionally, an amide prodrug called FLU-GLY was synthesized by coupling flurbiprofen with L-glycine. This prodrug demonstrated

reduced toxicity and ulcerogenic activity compared to the parent drug. Targeted drug delivery to the colon can be advantageous in terms of reducing the administered dose and minimizing undesirable side effects.

4. Immunomodulators are a class of drugs that have the ability to modify the immune response in the body. Leflunomide is a novel immunomodulatory agent that exhibits strong anti-inflammatory properties. It is particularly effective in treating autoimmune diseases, preventing graft rejection, and as a therapeutic option for tumor therapy. Leflunomide is an isoxazole derivative that acts as a prodrug, meaning it is converted into its active metabolite, A 77 1726 (M1). This active metabolite works by blocking the activity of dihydroorotate dehydrogenase, which is a key enzyme involved in the synthesis of pyrimidine, an essential component of DNA and RNA. By inhibiting this enzyme, leflunomide helps to regulate the immune response and reduce inflammation.
5. In the field of anti-tubercular agents, there are several potent drugs available, such as Ethambutol (EB), isoniazid (INH), and p-amino salicylic acid (PAS). However, these drugs can have various side effects due to the formation of toxic metabolites. To address this issue, mutual prodrugs of these agents have been synthesized and characterized. For example, prodrugs of EB with PAS (PE), PAS with PAS (PP), and INH with PAS (PI) have been developed. These mutual prodrug conjugates have been found to be stable and are absorbed without significant hydrolysis. In vivo studies have shown that these prodrugs result in higher serum concentrations of the respective drugs compared to when they are administered alone. This approach not only helps to eliminate the problem of fast metabolism, toxicity, and local irritation but also allows for a reduction in therapeutic doses.
6. In the context of antiviral activity, researchers have reported the diastereoselective synthesis of aryloxy phosphoramidate prodrugs of 30-deoxy-20, 30-didehydrothymidine monophosphate (d4TMP). A chiral auxiliary, (S)-4-isopropylthiazolidine-2-thione-1, was used to introduce the desired stereochemistry at the phosphorus atom. The final step of the synthesis involved the introduction of the nucleoside analogue d4T to a stereochemically pure phosphordiamidate, resulting in the formation of almost diastereomerically pure phosphoramidate prodrugs. These prodrugs have shown promising antiviral activity.

Conclusion

In this review, we have provided a concise overview of the historical background of prodrug research and the rationale behind their design. The utilization of the prodrug strategy holds great potential in the development of more potent primary drugs while minimizing any potential side effects or toxicity. With the continuous discovery of new enzymes, microbes, and receptors within the human body, there is a vast array of targets that can be explored, leading to the emergence of a new era of target-specific medications with desired pharmacological profiles. This advancement will undoubtedly contribute to the enhancement of clinical drug application. Additionally, we have elucidated the concept of prodrugs, their classification, and the functional groups involved, as well as the bioconversion processes of certain prodrugs. Presently, the prodrug approach has gained widespread recognition and is extensively employed to overcome unfavorable pharmacokinetic properties and optimize therapeutic efficacy, all while preserving the inherent benefits of the drug molecule.

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