PRODRUG: A BRIEF CONCEPT

Abstract

Prodrugs are the pharmacologically inactive forms of the active substances of a drug. The active substance undergoes chemical and / or enzymatic biological transformation to release the relevant active drug. The resulting conversion product (the parent drug) then provides the pharmacological response required. Since synthesizing new compounds is time-consuming and expensive, developing derivatives of existing drugs is certainly an exciting and promising field of research. High attrition in drug development is largely due to pharmacokinetic and pharmaceutical issues. Prodrug design addresses these issues effectively. Poorly permeable drugs are lipophilic, which can be improved by connecting the drug with a lipophilic drug linker. This allows the drug to be delivered orally, ocularly or locally. In addition, prodrugs can bind to polar or ionizing groups to enhance water solubility. Site selectivity is achieved by targeting specific enzymes or receptors.

Keywords: Prodrug, Pharmacokinetic, Lipophilic drug.

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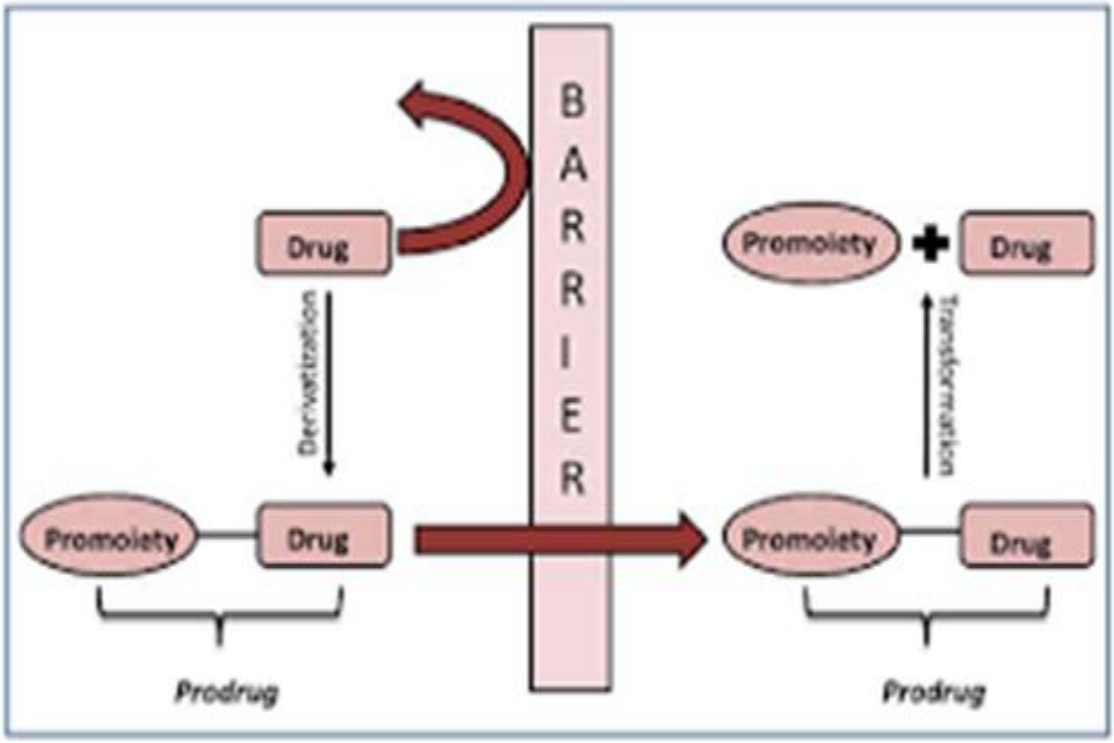
I. INTRODUCTION TO PRODRUG

In 1958, the terms "Prodrug" and "Pro-agent" were first used. A prodrug is a chemical molecule that lacks pharmacological activity but is metabolized by the body to create an active drug. It functions essentially as a precursor molecule intended to be changed into its active form upon delivery. Prodrugs are frequently created to enhance a drug's characteristics, such as solubility, bioavailability, stability, or targeting. Prodrugs can be made synthetically or semi-synthetically, either intentionally or unintentionally, during the drug-making process. They can be found in nature as various phytochemicals/botanical components and endogenous molecules.



Ideal requirements of a Prodrug

- It should not have any intrinsic pharmacological action.
- It should undergo rapid metabolism chemically or enzymatically into active form where desired.
- The metabolic fragments apart from the active drug should be non-toxic.

II. CLASSIFICATION OF PRODRUGS

1. **Based on type of Carrier Moiety:** Prodrugs are classified into two broad categories:

- Carrier-linked prodrugs and
- Bioprecusors

There are a variety of ways to categorize prodrugs. This may include the following:

- **Based on Therapeutic Categories:** For example, anticancer prodrugs, antiviral prodrugs, antibacterial prodrugs, Nonsteroidal anti-inflammatory prodrugs, Cardiovascular prodrugs, etc

- **Based on The Categories of Chemical Linkages or Moiety/Carriers:** That Attach to the Active Drug: for example, esteric prodrugs, glycosidic prodrugs, bipartite prodrugs, tripartite prodrugs, and antibody, gene, virus-directed enzyme prodrugs.

- **Based on Functional Categories:** Using Strategic Approaches to Deficiencies Inherent to The Active Drug: for example, prodrugs for improving site specificity, prodrugs to bypass high first-pass metabolism, prodrugs for improving absorption, and prodrugs for reducing adverse effects.

2. **New Classification:** Based on cellular site of bioactivation Cyclization-activated prodrugs Oligopeptides are promising carriers for cyclization-activated prodrugs, as they are generally nontoxic, non-immunogenic, specifically targeted at epithelial transporters such as hPEPT1 or hPEPT2 and provide chemical diversity through their side chains so that drug release rates can be finely tuned. Further, their di- or tri-functionality offers a wide span of chemical routes for both prodrug synthesis and intramolecular activation. Oligopeptides can be attached to a drug through their amino groups, hence offering the C-terminal carboxyl group as nucleophile to promote intramolecular activation.

3. **NO Releasing Prodrugs (NO-Prodrugs):** The general structural features of NO–NSAIDs (nitric oxide releasing) enable a large number of variations within the linking spacer and the NO-donating moiety. Owing to the ease of formation of these nitrate esters, several derivatives could be prepared for a given spacer. Two NO-releasing aspirins are 3-(nitroxymethyl) phenyl 2-acetoxybenzoate (NCX-4016) and 4-nitroxybutyl 2- acetoxybenzoate (NCX-4215).

4. **Goals of Prodrug Design**

- Formulation and pharmacokinetic aspects Pharmaceutical goal involves overcoming the following:

  - Unpleasant taste
  - Pain on injection
  - Poor solubility
  - Slow dissolution
  - Poor bioavailability
  - Short duration
  - High first pass metabolism
  - Toxicity or side effects
  - Non specificity

- Conversion site- The main goal of all Prodrug is that they should be quantitatively converted to drug after the specific problem has been outweighed. After completion of task the complete conversion of Prodrug to drug should happen immediately

- Bioavailability- Prodrug absorption should be fast and complete and its conversion in blood is instantaneous if the goal is to increase the bioavailability.
- Prolonged duration

- Stability

III. ADVANTAGES OF PRO-DRUG

1. Improved Pharmacokinetics: Prodrugs can be designed to alter the pharmacokinetic properties of a drug, such as its absorption, distribution, metabolism, and excretion (ADME). This can lead to better bioavailability and a longer duration of action.
2. Enhanced Targeting: Prodrugs can be designed to selectively target certain tissues or cells. This can reduce off-target effects and enhance the therapeutic index of the drug by delivering the active compound specifically to the intended site of action.
3. Increased Stability: Some drugs are chemically unstable or prone to degradation. Prodrugs can be formulated to be more stable, allowing for better shelf life and storage conditions.
4. Reduced Toxicity and Side Effects: By altering the chemical structure of a drug through prodrug design, it's possible to reduce the inherent toxicity or side effects of the active compound. This can make the drug safer for patients.
5. Improved Solubility: Some drugs have poor solubility, which can limit their absorption and effectiveness. Prodrugs can be designed to improve solubility, leading to better bioavailability and therapeutic outcomes.
6. Masking Bitter Taste or Odor: Certain drugs have unpleasant taste or odor, making them difficult for patients to take. Prodrugs can be formulated to mask these undesirable attributes, improving patient compliance.
7. Patent Extension: Pharmaceutical companies can develop prodrug versions of existing drugs to extend patent protection. This allows them to continue profiting from the drug's sales even after the original patent expires.
8. Overcoming Metabolic Barriers: Some drugs are rapidly metabolized or eliminated by the body before they can exert their therapeutic effects. Prodrugs can be designed to bypass these metabolic barriers and deliver the active drug to its target.
9. Alternative Administration Routes: Prodrugs can enable the use of alternative administration routes that might not be feasible with the active drug itself. For example, a prodrug could be designed for oral administration of a compound that would otherwise be ineffective or unstable when taken orally.
10. Tailored Drug Release: Prodrugs can be engineered to release the active drug in a controlled manner, allowing for sustained therapeutic effects over time.

IV. IMPROVEMENT OF BIOAVAILABILITY

Drugs are chemically modified to make them more soluble, stable, and lipophilic. Oral drug bioavailability is really important for drug development because low oral absorption can cause variability between and within patients. One way to make drugs more bioavailable is to use prodrugs. Lipophilic drugs need to be dissolved in the gastrointestinal fluid, and polar drugs need to be transported through the gastrointestinal mucosa. Prodrugs are used to make lipophilic drugs more or less bioavailable.

V. PRODRUGS TO INCREASE LIPOPHILICITY

Prodrugs are designed to be lipophilic so that they can be administered orally, ocularly, or topically. The primary reason for designing a prodrug is to improve oral bioavailability and intestinal absorption which are improved by masking a drug's polar moiety. For example, a highly potent inhibitor of active site thrombin, is a very polar molecule (logP = -2.4, n-octanol / buffer pH = 7.4) and therefore has no oral bioavailability.The first oral alternative for warfarin was dapagliflozin . The prodrug of dapigliflozine is dapagliflanzine. When dapigliflanzine is administered orally, the prodrug of dipigatran is converted into the active drug dapigatran esterase 6.5%.

VI. OPHTHALMIC DRUG DELIVERY

Prodrugs that are lipophilic are used to make it easier for people to take them into their eyes. For example, Latanoprost is a type of prodrug that is made up of isomers of the parent drug. Travoprost is another type of prodrug. These esters have a higher lipophilic content, which makes it easier for them to get into the cornea.

VII. TOPICAL DRUG DELIVERY

Lipophilic Prodrugs are used to make certain drugs more likely to be absorbed through the skin. For instance, ester Prodrugs with a higher lipophilic content can get stuck in the skin, making them more effective and less likely to cause any side effects.

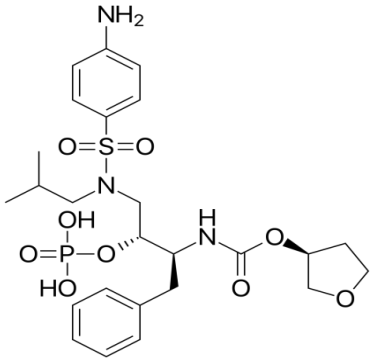
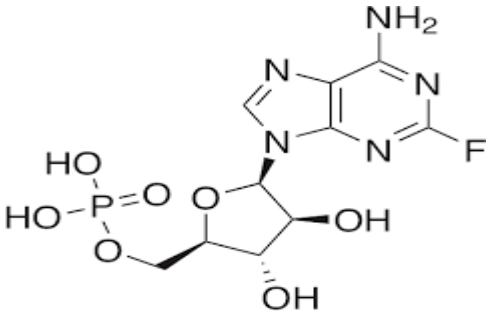
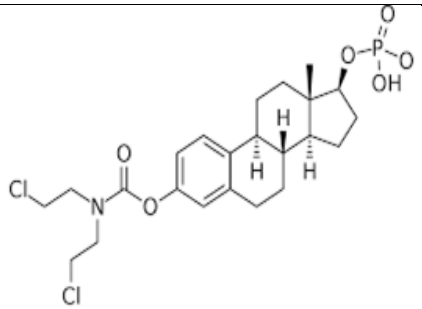
Corticosteroids that are topically administered are commonly used as anti inflammatory and immune- suppressive agents for skin conditions. However, topical corticosteroids can be systemically absorbed and cause adverse reactions.

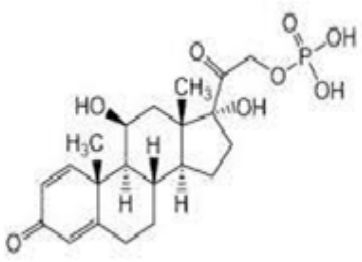
For instance, the prodrug fluocinolones (fluocinolone acetate ester) have high membrane retention in the epidermis and low permeation, which is preferred for topical corticosteroid administration. Due to the high lipophilic activity of the prodrug, it is more potent than its parent drug fluocinoline acetate, which is less lipophilic.

VIII. PRODRUGS TO INCREASE POLARITY

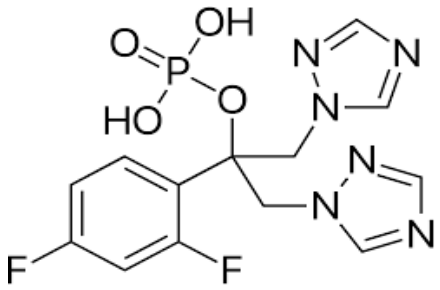
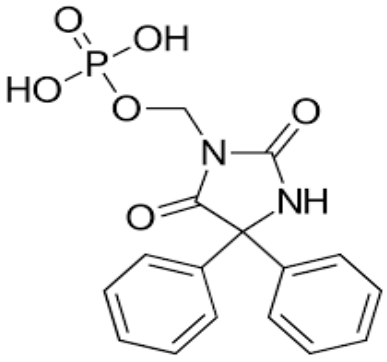
Prodrugs are designed to increase aqueous solubility by esterification with amino acids or phosphate group.

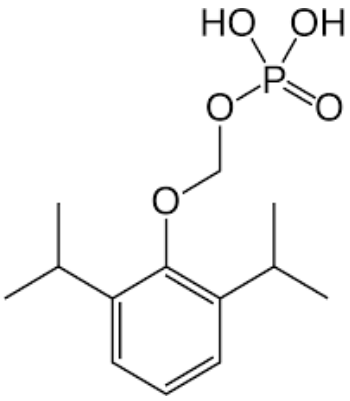
1. Phosphate Prodrug for Oral Delivery

Pro drug name ; Functional group	Structure	Action
Fosamprenavir (Telzir); phosphate ester of amprenavi		Bioconverted by alkaline Phosphatases to amprenavir, a HIV protease inhibitor. Antiviral, HIV infections
Fludarabine phosphate (Fludara); phosphate ester of fludarabine		Bioconverted by alkaline phosphatases to fludarabine. Fludarabine undergoes transformation to 2-fluoro-9-b-D- arabino furanosyladenine, which after uptake into cells isconverted to active 2-fluoro-9-b-D-arabino-furanosyladenine 5'-triphosphate. Antiviral
Estramustine phosphate (Emcyt); phosphate ester of estramustine		Bioconverted by alkaline phosphatases to estramustine, which is further transformed into estromustine. Antimitotic.

Prednisolone phosphate; phosphate ester of prednisolone (Inflamase, Orapred ODT)		Bioconverted by alkaline phosphatases to prednisolone. Anti-inflammatory, antiallergic

2. Phosphate Prodrug for Parenteral Administration

Pro drug name ; Functional group	**Structure**	**Action**
Fosfluconazole (Procif); Phosphate ester of fluconazole		Bioconverted by alkaline phosphatases to fluconazole. Antifungal.
Fosphenytoin (Pro-dilatin, Pro-epanutin, Cerebryx); phosphate ester of phenytoin		Rapidly bioconverted by alkaline phosphatases to phenytoin. Anticonvulsant**.**

Propofol phosphate; phosphate ester of propofol		Rapidly bioconverted by alkaline phosphatases to propofol. Anaesthetic.

IX. PRODRUGS FOR SITE SELECTIVE DRUG DELIVERY

Prodrugs are drugs that are specifically designed to target an organ or tissue. Prodrugs are commonly used in chemotherapy. Prodrugs that are specifically targeted to a specific enzyme or membrane transport are used to enhance absorption and reduce toxicity.

1. **Tumor Targeted Drug Delivery:** Cancer chemotherapy prodrugs are toxic, nonselective, which limits their use in cancer therapy. Their selectivity is dependent on the number of rapidly dividing cells, which are more susceptible to toxic effects. As a result, they are toxic to rapidly proliferating normal tissues such as hair follicle, gut epithelium, bone marrow, red blood cell, etc. To improve toxicity and efficacy, chemotherapy prodrugs have been designed to target cancer cells; this targeting occurs when drugs bind to ligands with high affinity to particular antigens/receptors/transporters that are extensively expressed in tumor cells. One of these targeting methods is enzyme-activated prodrug therapy, where the non-toxic prodrug converts into the active drug in tumor tissue. The enzyme must be specifically expressed/over expressed in tumor. Examples of tumor-associated enzymes that are used to activate prodrugs in malignant cells include plasmin (plasmin), prostate specific antigen (PSA), matrix metallicoproteae (Matrix Metalloproteae), cathepsin (Cathepsin B), D, H, and L. MAb (Monoclonal Antibody) have high affinity and are therefore the first ligands.

2. **Drug-Antibody Conjugate:** Tumor specific mAbs bind to receptors on tumor cells and the cytotoxic drug is selectively delivered to the tumor. For example, mylotarge consists of anti-CD33 mAbs conjugated to the cytotoxic ozogamicin, which was approved by the FDA for treatment of AML, acute myeloid Leukemia.

3. **Antibody Enzyme Conjugates:** Antibody-directed enzyme prodrug therapy (ADEPT) In this method, the tumor-specific antibody is delivered directly into the tumor cells. Subsequently, the prodrug is delivered systemically and transformed into the active toxic drug within the tumor.

4. **Gene-directed enzyme prodrug therapy (GDEPT):** In this method, the first step is the delivery of a gene that encodes the activating enzyme to the tumor cells. In the second step, the inactive prodrug is administered to the tumor cells and the tumor enzyme converts it into the toxic drug. The most commonly used gene delivery vectors are viral vectors.

X. SUMMARY AND CONCLUSION

Bioreversible derivatives (or prodrugs) are substances that have been developed over the last 50 years to modify the physicochemical properties, pharmacokinetics and biopharmacology of drugs. Prodrugs are the pharmacologically inactive forms of the active substances of a drug. The active substance undergoes chemical and / or enzymatic biological transformation to release the relevant active drug. The resulting conversion product (the parent drug) then provides the pharmacological response required. Since synthesizing new compounds is time-consuming and expensive, developing derivatives of existing drugs is certainly an exciting and promising field of research. High attrition in drug development is largely due to pharmacokinetic and pharmaceutical issues. Prodrug design addresses these issues effectively. Poorly permeable drugs are lipophilic, which can be improved by connecting the drug with a lipophilic drug linker. This allows the drug to be delivered orally, ocularly or locally. In addition, prodrugs can bind to polar or ionizing groups to enhance water solubility. Site selectivity is achieved by targeting specific enzymes or receptors. For example, an enzyme over expresses in tumor cells can be targeted to improve site selectivity.

Prodrugs are designed to be drug conjugates or antibody enzymes conjugates. Targets are membranes transporters. Prodrugs are used to enhance absorption. For example, prodrugs for the treatment of Valacyclovirus are used. Other prodrugs have been used to prolong the action of drugs. Buprenorphine Decanoate Prodrugs and Fluphenazine Decanoate Ester Prodrugs. Other drugs are used to reduce pain at injection sites by making them water soluble. Bitter taste masking and odor improvement are important applications to improve patient compliance. The taste masking process involves blocking chemical groups involved in the interaction of the drug with the bitter taste receptors.

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