

## Prodrugs

An inactive precursor of a drug, converted into its active form in the body by normal metabolic processes. Prodrugs are used when drugs have unattractive physicochemical properties

Prodrugs are bioreversible derivatives of drug molecules that undergo an enzymatic and/or chemical transformation in vivo to release the active parent drug, which can then exert the desired pharmacological effect. In both drug discovery and development, prodrugs have become an established tool for improving physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically active agents. About 5-7% of drugs approved worldwide can be classified as prodrugs, and the implementation of a prodrug approach in the early stages of drug discovery is a growing trend. To illustrate the applicability of the prodrug strategy, this article describes the most common functional groups that are amenable to prodrug design, and highlights examples of prodrugs that are either launched or are undergoing human trials.

### Undesirable Properties

- Physical Properties
  - Poor aqueous solubility
  - Low lipophilicity
  - Chemical instability
- Pharmacokinetic Properties
  - Poor distribution across biological membranes
  - Good substrate for first-pass metabolism
  - Rapid absorption/excretion when long-term effect desired

- Not site-specific

Prodrugs can be classified into two major types, based on how the body converts the prodrug into the final active drug form.

Type I prodrugs are bioactivated intracellularly.

Examples of these are anti-viral nucleoside analogs and lipid-lowering statins.

Type II prodrugs are bioactivated extracellularly, especially in digestive fluids or in the body's circulation system.

Examples of these are antibody-, gene- or virus-directed enzyme prodrugs [ADEP/GDEP/VDEP] used in chemotherapy or immunotherapy.

Some examples of Prodrug are

- Carisoprodol is metabolized into meprobamate. Until 2012, carisoprodol was not a controlled substance in the United States, but meprobamate was classified as a potentially addictive controlled substance that can produce dangerous and painful withdrawal symptoms upon discontinuation of the drug.
- Enalapril is bioactivated by esterase to the active enalaprilat.
- Valaciclovir is bioactivated by esterase to the active aciclovir.
- Fosamprenavir is hydrolysed to the active amprenavir.
- Levodopa is bioactivated by DOPA decarboxylase to the active dopamine.

- Chloramphenicol succinate ester is used as an intravenous prodrug of chloramphenicol, because pure chloramphenicol does not dissolve in water.
- Psilocybin is dephosphorylated to the active psilocin.
- Heroin is deacetylated by esterase to the active morphine.
- Molsidomine is metabolized into SIN-1 which decomposes into the active compound nitric oxide.
- Paliperidone is an atypical antipsychotic for schizophrenia. It is the active metabolite of risperidone.
- Prednisone, a synthetic cortico-steroid drug, is bioactivated by the liver into the active drug prednisolone, which is also a steroid.
- Primidone is metabolized by cytochrome P450 enzymes into phenobarbital, which is major, and phenylethylmalonamide, which is minor.
- Dipivefrine, given topically as an anti-glaucoma drug, is bioactivated to epinephrine.
- Lisdexamfetamine is metabolized in the small intestine to produce dextroamphetamine at a controlled (slow) rate for the treatment of attention-deficit hyperactivity disorder
- Diethylpropion is a diet pill that does not become active as a monoamine releaser or reuptake inhibitor until it has been *N*-dealkylated to ethylpropion.
- Fesoterodine is an antimuscarinic that is bioactivated to 5-hydroxymethyl tolterodine, the principle active metabolite of tolterodine.
- Tenofovir disoproxil fumarate is an anti-HIV drug (NtRTI class) that is bioactivated to tenofovir (PMPA).

## Steps in Prodrug Design

- Identification of drug delivery problem
- Identification of desired physicochemical properties
- Selection of transport moiety which will give prodrug desired transport properties be readily cleaved in the desired biological compartment

Depending upon the nature of carrier used, the carrier-linked prodrug may further be classified into:

1. Double prodrugs, pro-prodrugs or cascade-latentiated prodrugs, where a prodrug is further derivatized in a fashion such that only enzymatic conversion to prodrug is possible before the latter can cleave to release the active drug.

2. Macromolecular prodrugs, where macromolecules like polysaccharides, dextrans, cyclodextrins, proteins, peptides, and polymers are used as carriers.

3. Site-specific prodrugs where a carrier acts as a transporter of the active drug to a specific targeted site.

4. Mutual prodrug, where the carrier used is another biologically active drug instead of some inert molecule. A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and *vice versa*. The carrier selected may have the same biological action as that of the parent drug and thus might

give synergistic action, or the carrier may have some additional biological action that is lacking in the parent drug, thus ensuring some additional benefit. The carrier may also be a drug that might help to target the parent drug to a specific site or organ or cells or may improve site specificity of a drug. The carrier drug may be used to overcome some side effects of the parent drugs as well.

### **Criteria for Prodrug**

A well-designed carrier-linked prodrug should satisfy certain criteria. The linkage between the drug and the carrier should usually be a covalent bond. As a rule, the prodrug itself should be inactive or less active than the parent drug. The linkage should be bioreversible. The prodrug and the carrier released after *in vivo* enzymatic or non-enzymatic attack should be nontoxic. The generation of active form must take place with rapid kinetics to ensure effective drug levels at the site of action.

The bioavailability of carrier-linked prodrug is modulated by using a transient moiety. The lipophilicity is generally the subject of profound alteration of parent molecule. Bioactivation process is exclusively hydrolytic and sometimes a redox system.

An ideal carrier should be without intrinsic toxicity. It should be non-immunogenic and non-antigenic and should not accumulate in the body. It should possess a suitable number of functional groups for drug attachment and adequate loading capacity. It should be stable to chemical manipulation and autoclaving. It should be easy to characterize and should mask the liganded drug's activity until release of active agent at the desired site of action. In mutual prodrug approach, the carrier should have some biological activity of its own.

## **Applications of prodrug**

### **Prodrug to Improve Patient acceptability**

One of the reason for poor patient compliance, particularly in case of children is bitterness, acidity or causticity of the drug. Two approaches can be utilized to overcome the bad taste of drug. The first is reduction of drug solubility in saliva and the other is to lower the affinity of drug towards taste receptor. Chloramphenicol has a bitter taste, so it is not well accepted by children. The palmitate ester of it is less soluble in saliva, so it masks the bitter taste.

Several drugs (NSAIDS, Nicotinic acid, Kanamycin, Diethylstilboestrol) cause irritation and damage to gastric mucosa. Examples of prodrug designed to overcome such problems of gastric distress are given below (Aspirin & INH).

### **Prodrug to improve Stability**

Many drugs are unstable and may either breakdown on prolonged storage or are degraded rapidly on administration. Several drugs may decompose in GIT when used orally. Although enteric coatings may be used, it is also possible to utilize prodrug design to overcome this problem. An antineoplastic drug Azacytidine hydrolyses readily in acidic pH, but the bisulfite prodrug of it is more stable.

### **Prodrug to improve absorption**

Ampicillin a wide spectrum antibiotic is readily absorbed orally as the inactive prodrug, Pivampicillin, Bacampicillin and Talampicillin which are then converted by enzymatic hydrolysis to Ampicillin.

### **Prodrug for slow and prolonged release (sustained drug action)**

A common strategy in the design of slow-release prodrug is to make long-chain aliphatic esters, because these esters hydrolyze slowly and to inject them intramuscularly. Fluphenazine has shorter duration of action (6-8h), but prodrug Fluphenazine deconate have duration of activity about month.

### **Prodrug to Improve Membrane Transport**

Dopamine used for the treatment of Parkinson's disease can be improved by administering its prodrug 3, 4-dihydroxy phenyl alanine (Levodopa).

### **Prodrug for Prolonged duration of action**

Nordazepam, a sedative drug loses activity quickly due to metabolism and excretion. A prodrug Diazepam improves the retention characteristics, due to the presence of N-methyl group.