# PRODRUG

**Abstract**

A **Prodrug** is a specialized substance designed to contain the parent drug while remaining either inactive or only partially active. These molecules are intentionally engineered to undergo biotransformation within the body, either through chemical or enzymatic cleavage, in order to release the active compound at levels suitable for therapeutic effects. The prodrug approach holds great promise as a strategic modification in drug development, capable of addressing various pharmaceutical, pharmacokinetic, and pharmacodynamic challenges. The primary goal of prodrug development is to overcome barriers such as inadequate chemical stability, poor solubility, undesirable taste or odor, irritation or discomfort, insufficient oral absorption, limited blood-brain barrier permeability, substantial pre-systemic metabolism, and toxicity issues.

Furthermore, the addition of a pro-moiety to the active moiety offers an innovative solution for circumventing the obstacles that hinder the full utilization of the active compound's potential. This chapter seeks to offer a comprehensive exploration of prodrugs, including their historical context, objectives, associated benefits, and therapeutic applications. It also advocates for the integration of prodrug technology into modern healthcare systems to enhance the effectiveness and safety of pharmaceutical treatments.

In summary, prodrugs are a valuable tool in the realm of pharmaceutical science, serving as a means to optimize drug performance and overcome various limitations. This chapter endeavors to shed light on their multifaceted role and promote their integration within contemporary healthcare practices

**Keywords:** Prodrug, development, historical context, objectives, associated benefits, and therapeutic applications.

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## I. INTRODUCTION

A **Prodrug** is a substance that contains the parent drug but is either inactive or just partially active; these molecules must undergo biotransformation in vivo, either chemical or enzymatic cleavage, to allow for the distribution of the active molecule at therapeutic concentrations. The prodrug strategy shows promise as a molecular modification that may be used to alter the pharmacokinetics, pharmacodynamics, and toxicity of a drug.

In simple words, Prodrugs are chemically modified forms of an active drug moiety that are intended to be converted in the body and thereby eliminate the drug's negative effects. The chemical modifications of the pharmaceuticals are intended to be activated in order to generate the active parent drug after an enzymatic or chemical reaction once they have been delivered into the body. This activation process takes place after the parent drug has been produced.

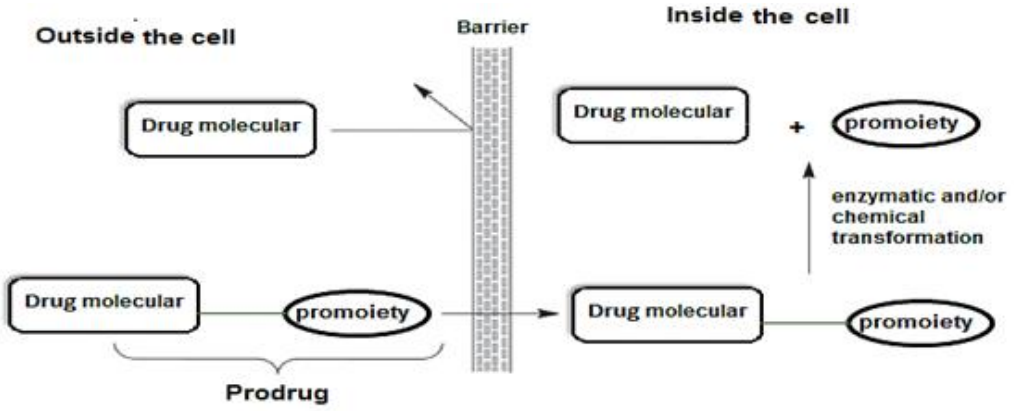


**Figure 1:** Concept of Prodrug

The majority of these strategies were focused to finding novel chemical entities that give the most significant contact with the required receptors or enzymes and have the ability to have minimal interactions with other molecules that are not sought. This method, on the other hand, is challenging expensive, and time-consuming since it requires testing thousands of compounds for biological activity, of which only a single candidate may make it to the medication market. One of the most appealing and potentially effective methods is known as the prodrug strategy. In this way, the active drug molecule is covered over by a promoiety in order to modify its undesirable qualities.

Albert was the first to use the word "prodrug" to describe a pharmacologically inactive component that undergoes biotransformation into an active form inside the body. The method of designing a prodrug is also known as the "Drug Latentiation" technique.

## II. HISTORY OF PRODRUG

The word "prodrug" was first used in Albert's book "selective toxicity," published in 1958. Any substance that undergoes biotransformation in living organisms is included in this category. Others, like Harper, supported for the idea, but they referred to it as "drug

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latentiation," which contains the prodrug that is meant to undergo biotransformation in the body. A few years later, Albert observed he had coined a misleading word and expressed regret, saying that "pre-drug" better described or appropriate term.

The first prodrug was not intended to be a prodrug when it was created; rather, its nature was decided at a later time. Earlier examples of substances that fulfilled into the conventional definition of prodrug were molecules called acetanilide and phenacetin. These compounds didn't show their actions until after they were metabolised in the body.

The antipyretic drug acetanilide was first used in 1886. Paracetamol is the end product of its metabolism (aromatic hydroxylation). O-dealkylation of phenacetin yields paracetamol, a pain reliever (shown in figure 2).

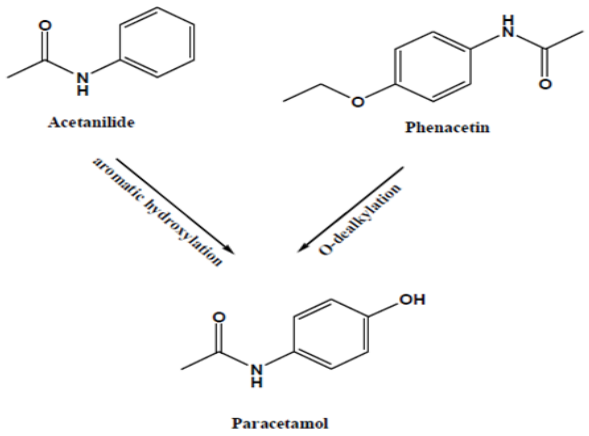


**Figure 2:** Metabolism of acetanilide and phenacetin yields paracetamol

In the last decade of the nineteenth century, a chemist working at the Bayar Company named Felix Hoffman synthesised the antipyretic agent known as aspirin (acetylsalicylic acid), which was first used in clinical practice in the year 1899. Aspirin can be considered as a less corrosive prodrug form of salicylic acid, and it was designed to minimise the gastric irritation and ulcerogenicity that are associated with salicylic acid (Shown in figure 3).

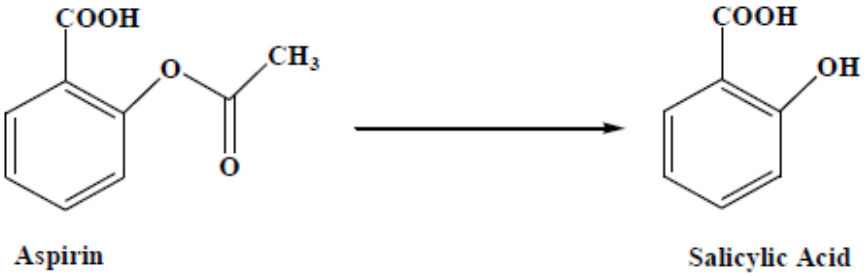


**Figure 3:** Chemical structure of aspirin and its prodrug salicylic acid

It is still up for debate whether aspirin is a prodrug or not. The discovery of prodrugs like methenamine and the first sulfa prodrug, prontosil, are more examples of accidental prodrugs and the role that serendipity had in their creation.

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Inactive prodrug methenamine, which leads the antimicrobial formaldehyde, was discovered by Schering. In the treatment of a urinary tract infection, it is carried to the urinary bladder, where it gets acidified and serves as a medium for the production of formaldehyde (Figure 4).

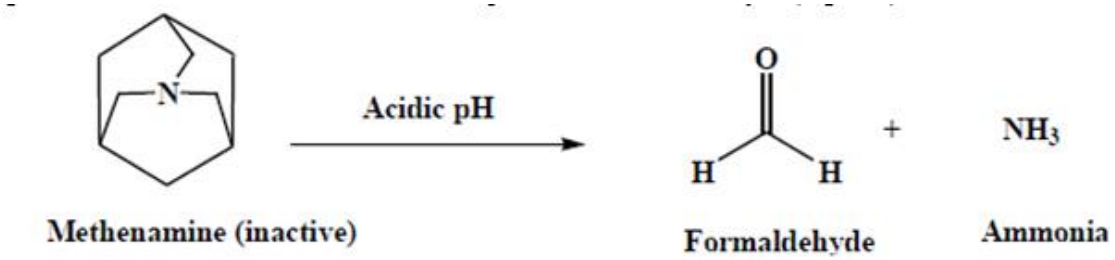


**Figure 4:** Activation of methenamine (prodrug) through acidic pH

Prontosil was proven to be effective only in vivo, and not in vitro, against bacterial infections.

Sulfanilamide, the first known sulfonamide, was the product of its breakdown in the body through the enzyme azo reductase (Figure 5).

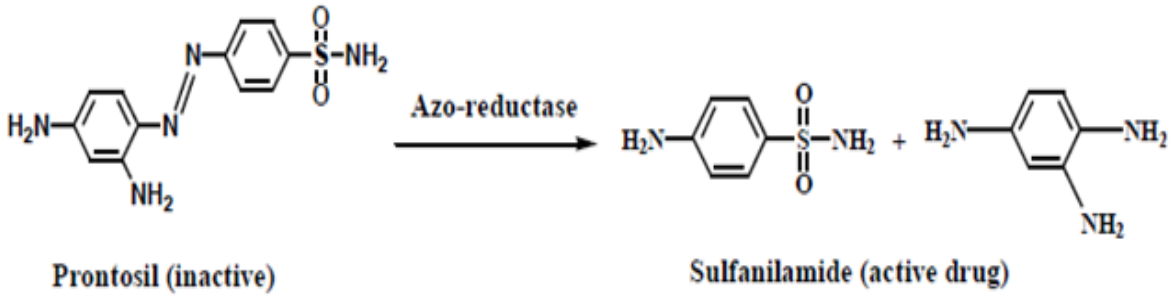


**Figure 5:** Activation of protonsil (prodrug) through azo reductase

In the middle of the twentieth century, the prodrug idea was first applied on purpose when the Parke-Davis Company altered the structure of chloramphenicol to reduce its bitter taste and increase its solubility in water. This led to the synthesis of two chloramphenicol prodrugs: the highly water-soluble chloramphenicol sodium succinate, which is used for intravenous, intramuscular, and ocular administration, and chloramphenicol palmitate, which is administered orally or in suspension form to children (Figure 6).

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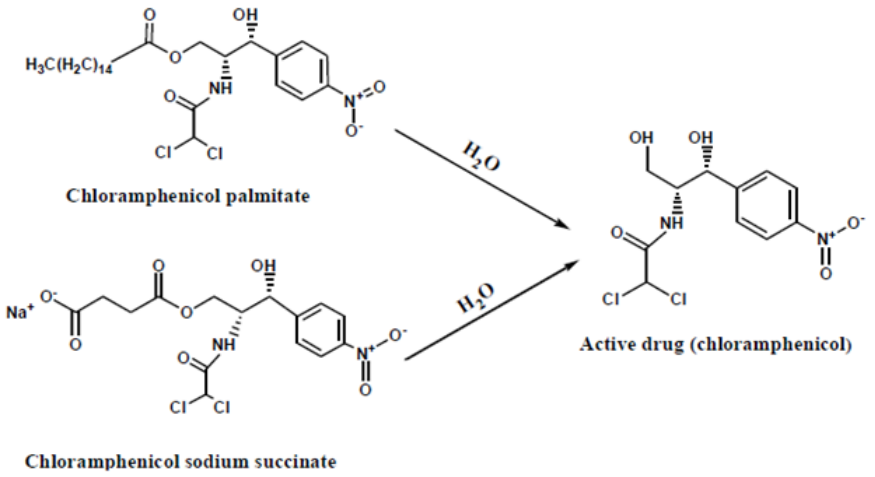
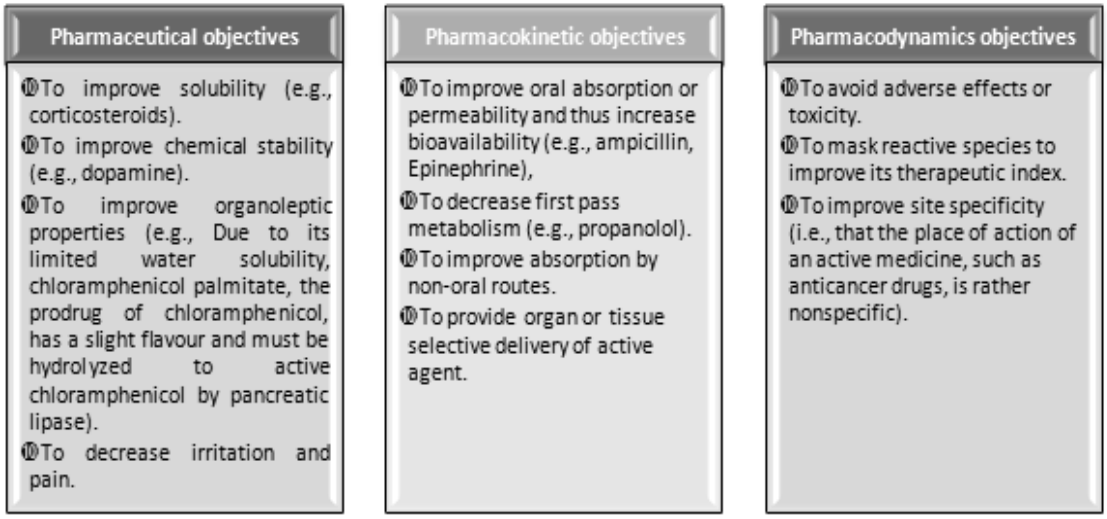



**Figure 6:** Conversion of chloramphenicol prodrugs to active drug chloramphenicol

## III. OBJECTIVE OF PRODRUG

Podrugs are created with the intention of overcoming pharmaceutical, pharmacokinetic, or pharmacodynamic barriers. These barriers include insufficient chemical stability, poor solubility, unacceptable taste or odour, irritation or pain, insufficient oral absorption, inadequate blood-brain barrier permeability, marked pre-systemic metabolism, and toxicity. In addition, the addition of a pro-moiety to the active moiety offers a means of overcoming the challenges that prevent the full potential of the active principle from being used.

The objective of prodrug divided in to three categories listed below-

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## IV. METHODS OF PRODRUG CATEGORIZATION

Prodrugs are divided into two categories on the basis of their chemical structure, lipophilicity, bioactivation strategy, and catalyst.

- Carrier – linked Prodrug
- Bio precursor Prodrug

1. **Carrier – linked Prodrug-** It contains an enzymatically removable component (such as an ester) that masks the active pharmaceutical ingredients. The connecting bond must be labile for effective activation in vivo, and the removed group ideally is pharmacologically inactive and harmless. A carrier linked prodrug is a modified form of an active drug created by attaching a carrier group to the drug.

Depending on the nature of the carrier used, it may be categorised as:

- **Bipartate Prodrug (Double prodrugs or cascade-latentiated prodrug)-** The active pharmaceutical ingredient in this prodrug is covalently joined to an inert carrier or transport molecule, commonly an ester or an amide. Due to the connected carrier, these prodrugs' lipophilicity has been significantly altered. Chemically or enzymatically mediated hydrolytic cleavage releases the active medication. After an in vivo enzymatic or non-enzymatic assault, the prodrug and carrier must be released, and they must not be toxic. Bipartate prodrug, which consists of a single carrier (promoiety) that is directly connected to the medication,

- **Tripartate Prodrug-** In this case, the carrier moiety and drug moiety are not joined directly. The linker is first connected to the drug moiety, and then the carrier is joined to this linker.

- **Macromolecular Prodrugs-** The macromolecules utilised as carriers include polysaccharides, dextrans, cyclodextrins, proteins, peptides, and polymers.

- **Site- specific Prodrugs:** In this type of Prodrug, When a carrier transports the active medication to a certain targeted site.

- **Mutual Prodrug:** when another physiologically active medication is employed as the carrier rather than an inert molecule. A mutual prodrug is made up of two pharmacologically active substances that are joined such that one serves as a promoiety for the other and the viceversa. The chosen carrier may have a biological action that is similar to that of the parent medicine and so may have a synergistic effect, or the carrier may have a biological action that is different from that of the parent drug and thus provides an extra advantage. The parent medication may be targeted to a particular location, organ, or group of cells with the aid of the carrier drug, which might also enhance the parent drug's site specificity. Some parent medication negative effects may also be controlled with the help of the carrier drug.

The mutual prodrugs method provides an effective technique for enhancing the clinical and therapeutic efficacy of a medication that is suffering from certain unwanted qualities that are preventing it from being beneficial in clinical applications. Benorylate is a

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popular example of this strategy. Benorylate contains aspirin that has been covalently bonded to paracetamol by an ester linkage. Benorylate promises to reduce gastrointestinal irritation while also providing a synergistic analgesic effect (Shown in figure 6).

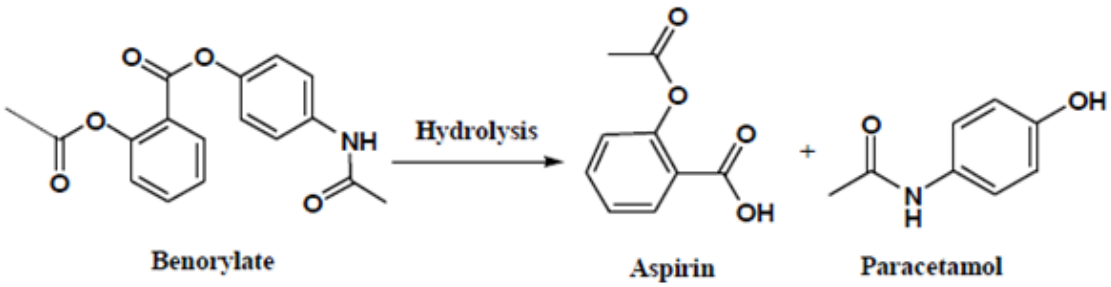


**Figure 6:** Example of Mutual Prodrug

2. **Bioprecursor Prodrug-** There are no carrier molecules used in this method. In this case, an inactive medication is being chemically altered to become a molecule that is already an active medicine or is being further metabolised into an active form that exhibits the necessary therapeutic efficacy. This process involves chemical reactions like oxidation or reduction (amine to aldehyde to carboxylic acid).

Classification **on the basis of their cellular site of bioactivation**

On the basis of the site at which they undergo conversion into the pharmacologically active substance, they may be divided into two groups:

- Type I
- Type II

- **Type I-** Metabolised intracellularly at the cellular targets of their therapeutic effects; examples include acyclovir, cyclophosphamide, 5-fluorouracil, L-DOPA, and zidovudine. The other medications, such as carbamazepine, captopril, molsidomine, and primidone, are metabolised and converted into their parent compounds by metabolic organs, especially the liver.

- **Type II-** Prodrugs that are metabolised extracellularly. This includes, firstly, prodrugs that are metabolised in the milieu of the gastrointestinal fluid, such as loperamide oxide and sulfasalazine; second, prodrugs that are metabolised within the circulatory system and/or other extracellular fluid compartments, such as aspirin, bambuterol, and fosphenytoin; and finally prodrug that is metabolised near or inside therapeutic target/cells (ADEPT, GDEPT).

- Both types are further classified into subtypes (Type IA, IB and Type IIA, IIB, and IIC), and these subtypes are dependent on whether or not the intracellular converting region is the site of therapeutic action, as well as whether or not the conversion happens in the gastrointestinal (GI) fluids or systemic circulation (Table 1).

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**Table 1: Classification of Prodrug on the basis of their cellular site of bioactivation**

| Prodrug Types | Conversion Site | Subtype | Tissue Location of Conversion | Examples |
|---|---|---|---|---|
| **Type I** | Intracellular | A | Therapeutic Target Tissues/Cells | **Type IA:**<br>• Acyclovir<br>• 5-Flurouracil<br>• Cyclophosphamide<br>• Diethlstilbestrol diphosphate<br>• L-Dopa<br>• 6-Mercaptopurine<br>• Mitomycine C<br>• Zidovudine |
| | | B | Metabolic Tissues (liver, GI mucosal cell, lung, etc.) | **Type IB:**<br>• Cabamazepine<br>• Captopril<br>• Carisoprodol<br>• Heroin<br>• Molsidomine<br>• Paliperidone<br>• Phenacetin<br>• Primidone<br>• Psilocybin<br>• Suldinac<br>• Tetrahydrofurfuryl disulfide |
| **Type II** | Extracellular | A | GI Fluids | **Type IIA:**<br>• Lisdexamfetamine<br>• Loperamide oxide<br>• Oxyphenisatin<br>• Sulfasalazine |
| | | B | Systemic Circulation and Other Extracellular Fluid Compartments | **Type IIB:**<br>• Acetylsalicylate<br>• Bacampicillin<br>• Bambuterol<br>• Chloramphenicol succinate<br>• Dihydropyridine pralixoxime<br>• Dipivefrin<br>• Fosphenytoin |

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| | | | | |
|---|---|---|---|---|
| | | C | Therapeutic Target Tissues/Cells | **Type IIC:**<br>• ADEPs<br>• GDEPs<br>• VDEPs |

## V. BENEFITS OF PRODRUG

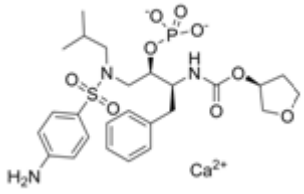
Various pharmacokinetic considerations require the creation of prodrugs:

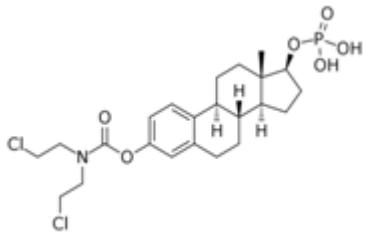
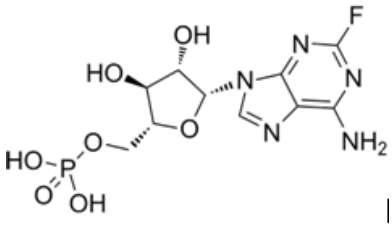
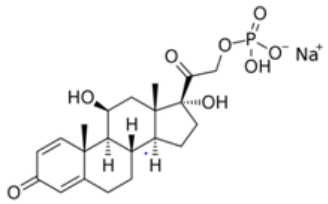
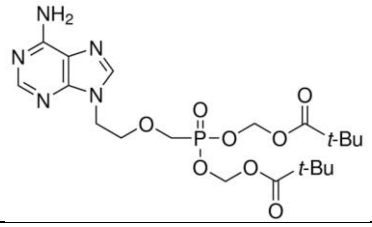
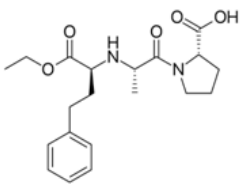
- To improve the rate of or increase medication absorption.
- The onset or duration of a drug's effects may be improved by adjusting the drug's absorption, distribution, or elimination.
- To prevent unwanted systemic effects by selectively activating a medication in the targeted target tissue.
- To avoid excessive presystemic metabolism, which results in inadequate and variable systemic bioavailability.
- To facilitate entry into the target site, such as the brain by bypassing the blood-brain barrier.
- Reduction of pain on injection.
- Improve patient acceptance.

## VI. EXAMPLE OF PRODRUG WITH THEIR THERAPEUTIC USE

Oseltamivir (Antiviral, Anti-influenza), Capecitabine (Anti-cancer), Famciclovir ((Herpes virus), Valacyclovir (Herpes virus infection), Prasugrel (Treat acute coronary syndrome), Gabapentin enacarbil (Restless legs syndrome, Neurologic disorder), Tenofovir alafenamide (HIV/AIDS & chronic hepatitis B), etc. Some other examples of prodrug listed below-

**Table 2**

| **Prodrug** | **Structure of Prodrug** | **Theraputic Use** |
|---|---|---|
| **Fosamprenavir (Telzir®)** |  | Anti-viral, HIV infections |

| | | |
|---|---|---|
| **Estramustine Phosphate (Emcyt and Estracyt)** |  | Antimitotic, Antineoplastic agent |
| **Fludarabine Phosphate (Fludara®)** |  | Anti-viral, Antineoplastic agent |
| **Prednisolone Phosphate (Inflamase®, Orapred ODT®)** |  | Anti-inflammatory, Anti-allergic |
| **Adefovir dipivoxil (Viread®)** |  | Anti-HIV, Hepatitis B |
| **Enalapril (Innovace®, Vasotec®, Renitc®)** |  | hypertension, Ischemic heart disease |
| **Remdesivir (Veklury)** | | Anti-viral, Treat Corona virus disease-2019 |

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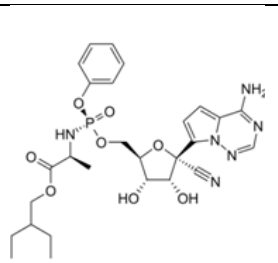
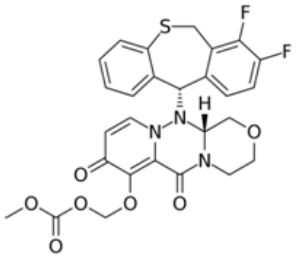
|---|---|---|
| |  | |
| **Baloxavir marboxil (Xofluza ®)** |  | Influenza, Anti-viral |

## VII. APPLICATION OF PRODRUG

The prodrug strategy has a wide variety of potential applications, including the following:

### 1. Theraputic/Pharmacological Application

- **Anti-cancer-** Agent for chemotherapy treatment A two-stage process was used to connect paclitaxel to poly (hydroxyl ethyl aspartamide) using a succinic spacer arm. The first step was the synthesis of 2′-O-succinyl-paclitaxel, and the second step was the synthesis of PHEA-2′-O-succinyl-paclitaxel. An investigation that was carried out using a cell line derived from murine myeloid shown that the polymeric prodrug preserves a portion of paclitaxel's pharmacological action. When compared to both the free medication and the uncovered polymer, the conjugation was eliminated from the circulation at a considerably more rapid rate.

- **Anti-Tubercular-** Potent antitubercular medicines such as ethambutol (EB), isoniazid (INH), and p-amino salicylic acid (PAS) may cause a variety of adverse effects owing to the development of toxic metabolites in the body. Synthesis and characterization of the mutual prodrugs of EB with PAS (PE), PAS with PAS (PP), and INH with PAS (PI) were carried out. Hydrolysis tests conducted in vitro in SGF and SIF demonstrate that these mutual prodrug conjugates do not hydrolyze significantly and are absorbed in their unhydrolyzed state. In investigations conducted on living subjects, the blood concentrations of EB, PAS, and INH were shown to be higher when they were administered together than when they were given separately; isoniazid concentrations were also found to be higher, with the exception of PP. The mutual prodrugs PI and PE minimise the issue of rapid metabolism, as well as toxicity and local irritation, and they also greatly lower the required therapeutic dosages.

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- **Reduced GI Problem-** sulphasalazine is produced by the reaction of diazotized sulphanilamide pyridine with 5-amino salicylic acid, which results in the formation of the compound. When taken by mouth, the colon is still in control of unaltered sulphasalazine. The azo reductase that is linked with colonic microflora converts sulphasalazin to its component entities, making the active species 5ASA accessible for absorption in the colon while simultaneously reducing the precolonic absorption that is responsible for adverse effects.

- **In CNS (Cross BBB)-** L-dopa is the only prodrug that is used in therapeutic applications with the purpose of primarily penetrating the brain through LAT1-mediated transport. Due to the hydrophilic nature of the neurotransmitter dopamine, it is unable to penetrate the blood–brain barrier (BBB). Dopamine can only be taken up by the brain via the LAT1 transporter if it is first converted into its -amino acid, which is called Ldopa. L-amino acid decarboxylase, which is found in the tissue of the brain as well as the peripheral circulation, is responsible for the conversion of L-Dopa to dopamine. Although nearly 95% of L-dopa is converted to dopamine in the peripheral tissues, the amount of remaining L-dopa has been therapeutically sufficient to employ this method in clinic practise for more than 30 years.

- **Hypo-cholestremic**- Simvastatin (SV), a lactone prodrug that lowers cholesterol, goes through reversible metabolism and is known as a cholesterol-lowering prodrug or hypro-cholestremic agent. It is a powerful inhibitor of HMG-CoA reductase when it is in the form of the hydroxy acid (SVA).

- **ADHD Treatment-** One of the most prevalent forms of neurobehavioral disorders that may afflict children is known as attention deficit hyperactivity disorder, or ADHD. Using prodrug technology, the one and only produced prodrug stimulant, lisdexamfetamine dimesylate (LDX), offers a promising therapy option for attention deficit hyperactivity disorder (ADHD). When compared to d-amphetamine, the overdose potential risk profile of LDX is much improved.

Prodrugs possess not only gave pharmacological applications. they are also used to get overcome Pharmacokinetic and Pharmaceutical applications to improve a drug's biological bioavailability and many other. Which is mentioned below-

## 2. Pharmaceutical Applications

- **Taste Masking-** Masking the bitter taste of oral medications is particularly critical for patient compliance in paediatric and geriatric populations, demonstrating the importance of taste in the formulation of dosage forms.

  Drugs cause a bitter taste by stimulating the tongue's taste buds. Physical barriers, chemical or solubility alteration, and solid dispersion are only some of the methods explored for dealing with this problem.

  The prodrug strategy involves chemically modifying the drug to remove the interaction with taste receptors. The bitter flavour of the pain reliever and fever reducer paracetamol is thought to be caused by the drug's phenolic hydroxyl group

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hydrogen bonding with bitter taste receptors. As a result, the interaction may be inhibited and the bitter taste of paracetamol might be masked by blocking the hydroxyl group with a suitable linker (Figure-7). Paracetamol's bitter taste was removed from several prodrugs synthesised by Karaman's group

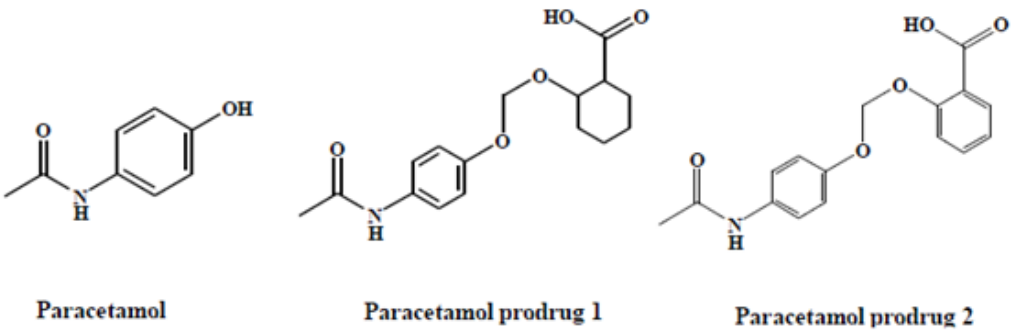


**Figure 7:** Structure of Paracetamol and Prodrug Paracetamol

- **Odour Masking-** Drugs having a high vapour pressure or low boiling point provide an aesthetic challenge due to their unpleasant odour. Ethyl mercaptan, a tuberculostatic drug used to treat leprosy, has an unpleasant odour since its boiling point is just 25 degrees Celsius. Diethyl dithiolisophthalate, a prodrug of ethyl mercaptan, was produced and shown to be extremely active and odourless, its ethyl thiol esters were the most appealing derivative prodrugs (Figure-8).

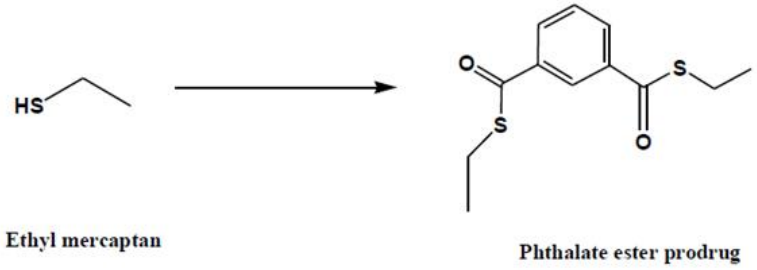


**Figure 8:** Structure of ethyl mercaptan and its phthalate ester prodrug

- **Increase Polarity/Improve solubility-** Prodrugs use esterification with amino acids or phosphate groups to promote water solubility.

For example, the antiviral fosamprenavir, which is a protease inhibitor, may be changed into amprenavir by the action of the enzyme alkaline phosphatase in the gut epithelium. Because the phosphate moiety of fosamprenavir (Figure-9) is coupled to a free hydroxyl group, it is about ten times more water soluble than amprinavir. Producing this antiviral prodrug results in improved patient compliance since, instead of having to give the drug eight times per day, the dose regimen only has to be followed twice daily.

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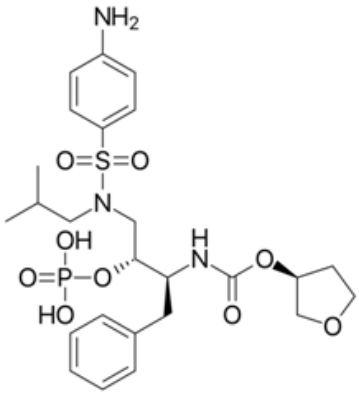

**Figure 9:** Structure of Prodrug fosamprenavir

- **Reduction of Pain at injection site-** The precipitation of the medication at the injection site induces cell lysis and tissue damage, which results in pain at the injection site. There is a possibility that this issue is connected to the formulation requirements for the vehicle pH or vehicle composition, respectively. For instance, phenytoin injection, which is authorised for the treatment of status epilepticus but has low aqueous solubility, requires that the pH of the vehicle for injection be adjusted to 12. This results in soft tissue damage and discomfort at the site of delivery, which is caused by phenytoin precipitation.

In 1996, the Food and Drug Administration gave its approval to fosphenytoin, which is a phosphate ester prodrug of phenytoin (Figure-10). This prodrug has a good aqueous solubility, no noticeable discomfort was experienced while using it, and it has a bioavailability 100% when administered intramuscularly.

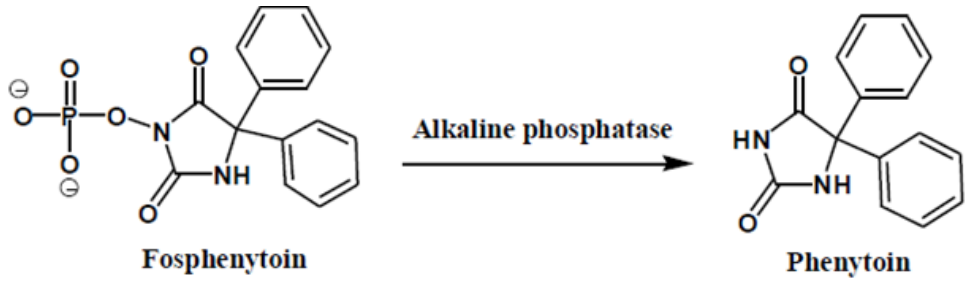


Figure-10: Activation of fosphenytoin to phenytoin

**Figure 10:** Activation of fosphenytoin to phenytoin

- **Increase/Improve Chemical Stability-** During the course of a drug's shelf life, its stability might deteriorate. The lyophilization of the solution into a powder that may be reconstituted before it is put to use is the typical method that is used the most often. The creation of such an agent as a prodrug is an excellent approach that may increase stability.

Antineoplastic medication, azacytidine. The aqueous solution of azacytidine can be hydrolyzed with easily; however, the bisulfite prodrug demonstrates stability in the presence of such degradation at acidic pH. In addition, the bisulfite prodrug is

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more water soluble than the parent drug. The physiological pH is necessary for the conversion of the prodrug to the active drug.

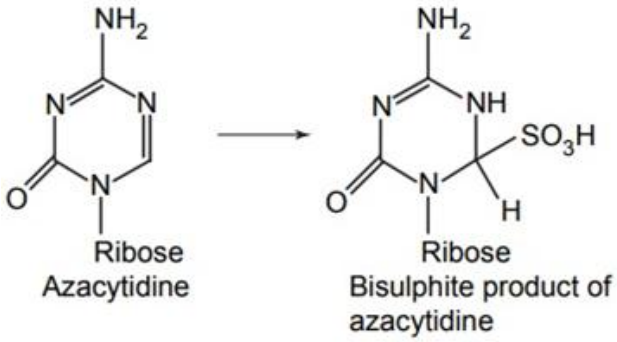


**Figure 11:** Structure of stable bisulphte prodrug of azacytidine

## 3. Pharmacokinetic Applications

- **Improve Bioavailability**- Physicochemical qualities, such as solubility, stability, and lipophilicity, may be improved by the application of chemical modification of pharmaceuticals. Oral medication bioavailability is essential for the development of novel therapeutics since poor oral absorption may lead to variability in both between and within patients. Prodrugs are one of the ways that have been developed to improve the oral bioavailability of a substance.

When taken orally, the bioavailability of lipophilic medications is determined by their capacity to dissolve in the fluids of the gastrointestinal tract, while the bioavailability of polar pharmaceuticals is determined by their ability to be transported through the mucosal lining of the gastrointestinal tract. As a result, prodrugs are developed with the intention of either increasing or decreasing the lipophilicity of the medication.

Prodrugs are used to improve the lipophilicity of drugs in order to make them suitable for oral administration, ophthalmic administration, or topical administration as drug delivery methods. The primary objective in the development of prodrugs is to improve oral bioavailability and intestinal absorption, both of which may be achieved by hiding the polar moiety of the active ingredient in the medication. For example, dabigatran, a powerful inhibitor of the active site of thrombin, is an extremely polar molecule with a logP of 2.4 (n-octanol/buffer pH 7.4); as a result, the oral bioavailability of dabigatran is almost nonexistent. Dabigatran was initially modified to produce dabigatran etexilate (Figure-12), which went on to become the first oral alternative to warfarin. Esterases are responsible for the transformation of dabigatran etexilate into the active form of the medication dabigatran after oral intake. 6.5% of the drug dabigatran etexilate is available for absorption via the mouth .

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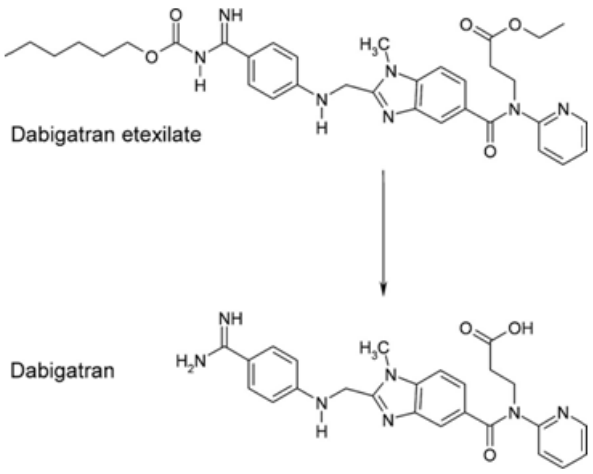


**Figure 12:** Structures of dabigatran prodrug and its active drug

- **Improve/Increase Duration of action-** When a medicine has a short half-life, it must be dosed more often in order to maintain the same concentration in the blood. This may lead to poor patient compliance as well as fluctuations in the drug's concentration. The creation of prodrugs that have a long time of action is one method that may be used to overcome these challenges**.**

Treatment with an antipsychotic medication that has a long acting duration is essential for symptom management and the prevention of repeated episodes.These long-acting medicines not only enhance patient compliance but also improve the treatment's overall effectiveness. As an example, fluphenazine decanoate, which is an ester prodrug of fluphenazine (Figure-13), is used as a long-acting intramuscular depot injection for the treatment of schizophrenia; this prodrug is delivered once every 2 weeks.

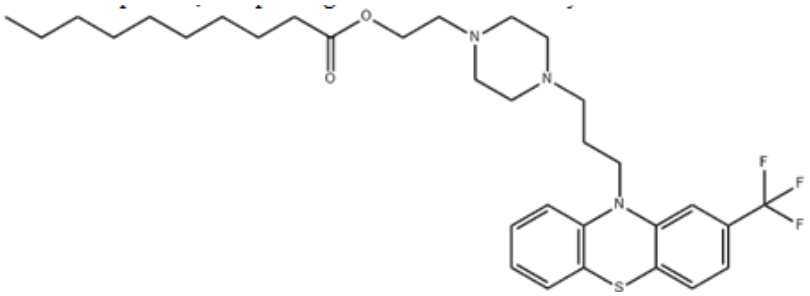

**Figure-13: Structure of Fluphenazine Decanoate Prodrug**

- **Reduced Toxicity-** It is ideal for therapeutically useful medications to have no or very little toxicity; hence, prodrugs may be used to reduce the harmful effects of a wide variety of drugs. For instance, the anthracycline antibiotic doxorubicin is widely used as an anticancer medicine; but, because of the cardiotoxicity it reasons, its use is restricted. As a result, there was an essential desire to develop a drug targeting system that could raise the amount of doxorubicin that was available in tumour tissue while simultaneously lowering the amount that accumulated in cardiac tissue. A galactoside

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prodrug has been produced (Figure-13), which is connected to doxorubicin through a carbamate spacer. since of the hydrophilic nature of the galactoside molecule, this prodrug cannot be distributed to any other tissues since it can only be activated by the enzyme -galactosidase, which is extensively expressed in tumour tissue. Due to the low concentration that it has in heart tissue, this prodrug is more efficacious and less harmful than its parent drug.

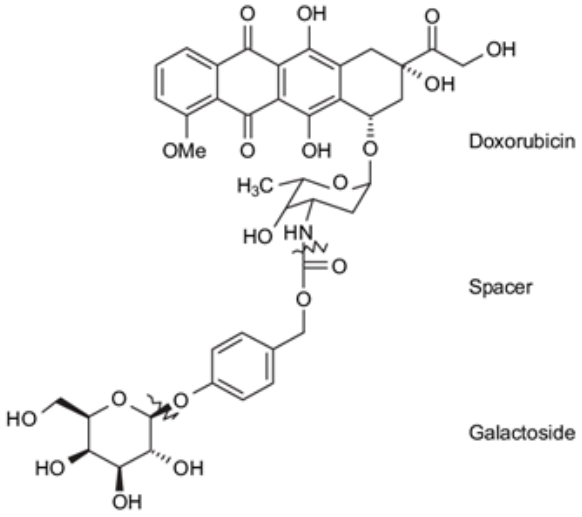


**Figure 14: Structure of Doxorubicin Galactoside Prodrug**

- **Preventing Rapid Metabolism and Excretion-** Certain sites or groups in the molecule are susceptible to presystemic metabolism, resulting in limited oral bioavailability of pharmaceuticals; prodrugs may be utilised to inhibit these sites and improve oral bioavailability.

However, nalbuphine's limited oral bioavailability of 17% is a result of presystemic metabolism at the 3-hydroxyl position, making it a poor choice for treating moderate to severe pain. An ester prodrug of nalbuphine (Figure-14), nalbuphine acetylsalicylate, has a 5-fold higher oral bioavailability in dogs than nalbuphine.

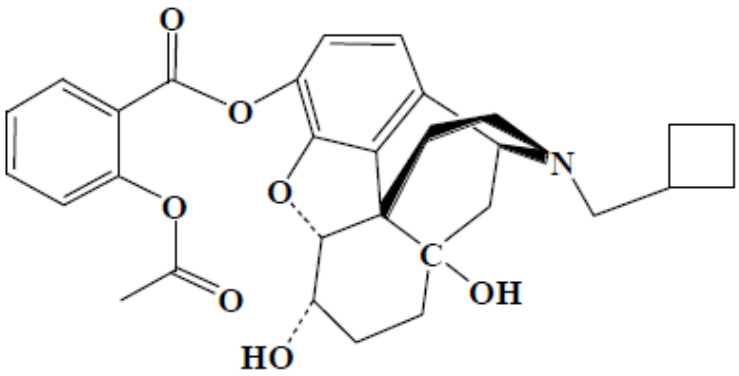

**Figure 14:** Structure of Nalbuphine Ester Prodrug

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- **Site Selective Drug Delivery-** Prodrugs are used in the process of chemotherapy because of their ability to direct drugs to a certain organ or tissue of the body. Targeted prodrugs are used to improve absorption while simultaneously reducing toxicity; they are designed to bind specifically to an enzyme or membrane transporter.

- **Tumor Targeted Drug Delivery-** Chemotherapeutic agents for cancer are known to be toxic and nonselective, which restricts their use in cancer treatment. Their selectivity is determined by the quickly dividing cells, which are the ones that are more vulnerable to the damaging effects. As a result, normal tissues that are quickly reproducing, such as hair follicles, gut epithelia, bone marrow, and red blood cells, are susceptible to damage from them. Therefore, in order to improve both toxicity and effectiveness, chemotherapeutic prodrugs have been developed to specifically target tumour cells. This targeting is accomplished by attaching drugs to ligands that have a high affinity for certain antigens, receptors, or transporters that are highly expressed in tumour cells.

  Enzyme-activated prodrug treatment is one of the targeted strategies. In this kind of therapy, the nontoxic prodrug is transformed into the active drug in the tissue of the tumour. It is necessary for the enzyme to be overexpressed or selectively expressed in the tumour. Some examples of tumor-associated enzymes that are used for prodrug activation in cancerous cells include plasmin, prostate specific antigen, matrix metalloproteaes, and cathepsin B, D, H, and L.
  Monoclonal antibodies (mAbs) have such a high affinity for their targets, they were the first ligands to be used in tumour targeting. MAbs may be developed as drug-antibody conjugates or antibody enzyme conjugates.

## 4. Limitations of Prodrug

Prodrug design has been very useful in reducing a lot of drawbacks of medications, but it has also introduced a number of new challenges, particularly in the evaluation of the drugs' pharmacological, pharmacokinetic, toxicological, and clinical characteristics.

- **At Pharmacological level-** Due to the need of bioactivation for the purpose to transform these compounds into their active species, early in vitro screening procedures, such as binding studies, reuptake of neurotransmitter, and enzyme inhibition measurement, cannot be performed on these substances.
- **At Pharmacokinetic level-** The mutual prodrug may not be the best substrate for the enzymes that activate it. Numerous misconceptions may result from pharmacokinetic research. When comparing mutual prodrugs and parent molecules, one must take into consideration the variations in their individual time courses of action. AUC should be compared since it provides a better standard by which to compare results because the maximal activity may manifest later for mutual prodrugs than for parent substances.
- **At Toxicological level-** Certain toxicity mechanisms of prodrug that are not created by the parent pharmaceuticals include the formation of a toxic metabolite, the consumption of an essential element during the prodrug activation process, and the release of a pharmacokinetic modifier that may induce an enzyme or modify drug excretion.

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- **At Clinical level-** Animal experimentation's ability to predict behaviour in humans is also debatable. The active dosages of two related prodrugs from the same parent medication may seem the same in rats, but they might vary significantly in clinical studies.

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