**PRODRUG DEVELOPMENT**

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**HISTORY:**

Prodrug concept has been used to improve undesirable drug properties since the late 19th century, Adrien Albert first used the term "Prodrug" at the end of the 1950s to describe drugs that are inactive on their own but transform into an active derivative through biotransformation in 1958. In 1959, Harper finished the idea and coined the term "drug latentiation" to describe medicines that were created to need bioactivation[1]. Acetanilide was originally used as a Prodrug in 1867 by Cahn and Hepp, who also brought it to medicine. The biologically active molecule acetaminophen, which has both antipyretic and analgesic properties, is created in the body when acetanilide is subjected to hydroxylation.

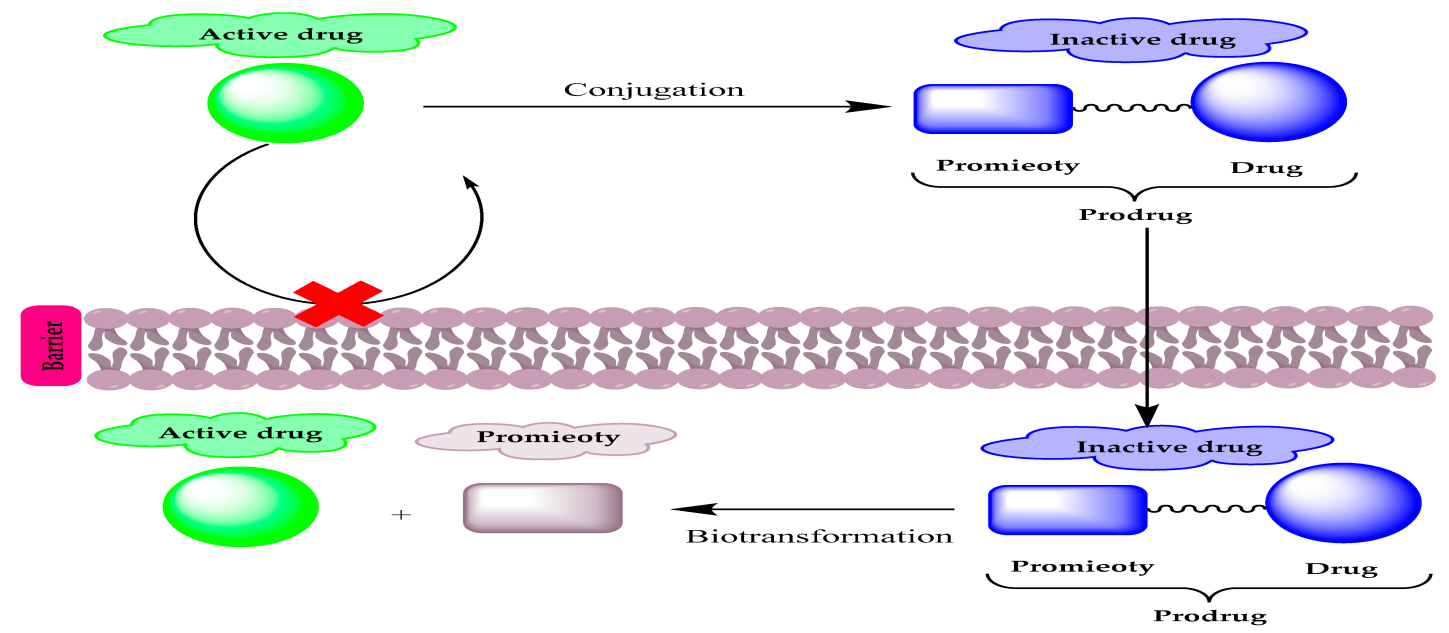
**DEFINITION:**

The IUPAC defines a Prodrug as a molecule that goes through biotransformation before revealing pharmacological effects, which is still the definition that applies today.

A Prodrug is a pharmacologically inert drug or substance that, after consumption, it metabolized (i.e., transformed within the body) into an active drug.

**INTRODUCTION:**

Prodrug that, through chemical or enzymatic cleavage, undergoes some in vivo biotransformation, enabling the delivery of the active molecule at effective levels and having the capacity to turn into the active parent drug inside the human body. When a medication is poorly absorbed from the digestive tract, Prodrugs are frequently created to increase bioavailability. When a medicine interacts with cells that are not its intended target, a Prodrug can help the drug engage with them more selectively [2,3,4]. The Prodrug technique is used to optimize recently discovered chemical entities as well as to enhance the qualities of medications that have already been put on the market. Utilizing the pro drug approach, which aims to get around physicochemical, biological, and organoleptic barriers of some of the currently marketed drugs suffering from low bioavailability and patient noncompliance, is one way to improve the Pharmacokinetics profile (Absorption, Distribution, Metabolism, and Excretion (ADME) for a drug.



**Fig. 1. Schematic representation of Prodrug Concept[5]**

In order to achieve optimal oral bioavailability and subsequent therapeutic effect, the Prodrug approach is used to overcome Biopharmaceutic, Pharmacokinetic, or Pharmacodynamic challenges, such as poor chemical stability, solubility restrictions, lack of site-specificity, extensive drug metabolism, passing through biological barriers, utilizing endogenous metabolic pathways, toxicity, or compliance challenges (unacceptable taste/odor).

In the last ten years, the Food and Drug Administration (FDA) of the United States has approved about 30 Prodrugs (12% of all novel small-molecule entities). Prodrugs are thought to make up about 10% of all commercially marketed medications worldwide.

The Prodrug strategy was once thought of as a last option in the development of drugs. However, today it is also taken into consideration at the very beginning phases of drug research and development. While creating a Prodrug does include working with a novel chemical entity, the expense is lower than that of creating a novel drug medicine development is accelerated by the better performance (in comparison to the parent medicine), which could ultimately result in time, money, and effort savings.

**BENEFITS OF PRODRUGS [6]:**

Here are several justifications for employing the Prodrug method in drug development:

* Improved solubility in water.
* Enhanced distribution and absorption.
* Site particularity.
* Increased drug stability.
* Long-term release.
* Decreasing toxicity.
* Inadequate patient acceptance.

**THE OBJECTIVES OF CREATING PRODRUGS [7]:**

Prodrug design specifically aims to maximize chemical or metabolic stability, optimize undesirable physicochemical features, and achieve desired delivery.

***Increasing bioavailability when a drug candidate lacks the attributes of a medicine because they have undesirable physical characteristics, such as:***

* Poor solubility in water.
* Reduced lipophilicity.
* Chemical shakiness.
* Unpleasant odors or tastes.
* Soreness and discomfort localized.

***Enhancing bioavailability when the drug candidate is not a medicine because of its pharmacokinetics:***

* Minimal bioavailability.
* The inability of biological membranes to be penetrated.
* Higher first-pass metabolism.
* Parenteral route lagging absorption.
* Quick absorption/elimination as opposed to prolonged effects.
* Lacking in specificity in some tissues.

***The benefits of Prodrugs with improved pharmacokinetic characteristics include:***

* Enhancing gastrointestinal absorption following oral delivery.
* The acquisition of parenteral preparations.
* Disguising offensive flavors and scents.
* Preventing pain or irritation at the injection site.
* Preventing quick shutdown of the administration site.
* Facilitating crossing of the blood-brain barrier.
* Medication delivery to specific tissues or organs.
* Decreasing the use of multiple drugs.
* Toxicity profile and side effects have improved.

Prodrugs have the potential to be safer, more convenient, and more effective than traditional medications.

**Prodrugs Classification [8]:**

***I. Based on structural association of molecules***

Prodrugs can be divided into two major categories

**A. Carrier-linked Prodrugs**

**B**. **Bioprecursors**

**A. Carrier-linked Prodrugs:** Further classified into four types

**(i) Bipartite Prodrugs -** In which the carrier is directly attached to the parent drug.



Examples: Prednisolone sodium phosphate, latanoprost, dipivefrin, etoposide phosphate.

**(ii) Tripartite Prodrugs** - In which a spacer joins the carrier to the parent drug.

Chemical groups like ester, amide, carbamate, carbonate, ether, imine, and phosphate are frequently used to link carriers to one another.

Examples: Pivampicillin, Bicampicillin.

**(iii) Mutual Prodrugs** - In the co-drug strategy, two Pharmacologically active chemicals are mixed and one serves as a promoter for the other in which it has two linked active molecules, Through their combined effects, these Prodrugs are more effective.



Examples: Estramustine, Sultamucilin.

**(iv) Macromolecular Prodrugs**–It is a different kind of carrier-linked prodrug that utilizes polymeric backbones as a carrier. To create prodrugs that will cleave inside a cell and in targeted drug-delivery devices, Improved medication solubility, stability, release, and pharmacokinetics are all benefits of this strategy.

Examples: Ribavarin.

**B. Bioprecursors:**

Bioprecursors are inactive substances without a carrier that are quickly transformed into active drugs through metabolic reactions, which are typically redox reactions.

The activation mechanism, which releases the active parent drug from the Prodrug in an efficient and well-characterized manner to fulfill the therapeutic objective, is one of the key factors to take into account when designing Prodrugs, as was before discussed. Prodrug activation may be based on chemical processes (such as oxido-reduction) or may occur by enzyme-mediated hydrolysis, including oxidoreductases (such as cytochrome P450), hydrolytic enzymes (such as carboxylesterases, phosphatases, esterase), transferases, and lyases.

Examples: Prontosil, Sulindac.

***II. Based on how the Prodrug is transformed by the body into the final active drug form***

Prodrugs can be divided into two major categories.[9]

Type I Prodrugs undergo Intracellular bioactivation; these include lipid-lowering statins and phosphorylation-required antiviral nucleoside analogs.

Type II Prodrugs undergo Extracellular bioactivation which occurs most frequently in digestive fluids or the body's circulatory system, more frequently in the blood. Prodrugs used in chemotherapy or immunotherapy.

|  |
| --- |
| **CLASSIFICATION OF PRO DRUGS** |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type** | **Bio Activation Site** | **Sub Type** | **Tissue location of Bio location** | **Examples** |
| Type I | Intracellular | Type IA | Therapeutic target tissues/cells | [Aciclovir](https://en.wikipedia.org/wiki/Aciclovir), [fluorouracil](https://en.wikipedia.org/wiki/Fluorouracil), cyclophosphamide[diethylstilbestroldiphosphate](https://en.wikipedia.org/wiki/Diethylstilbestrol_diphosphate), [LDOPA](https://en.wikipedia.org/wiki/L-DOPA),  [mercaptopurine](https://en.wikipedia.org/wiki/Mercaptopurine),  [mitomycin](https://en.wikipedia.org/wiki/Mitomycin), [zidovudine](https://en.wikipedia.org/wiki/Zidovudine) |
| Type IB | Metabolic tissues (liver, GI mucosal cell, lung etc.) | [Carbamazepine](https://en.wikipedia.org/wiki/Carbamazepine), [captopril](https://en.wikipedia.org/wiki/Captopril), [carisoprodol](https://en.wikipedia.org/wiki/Carisoprodol), [heroin](https://en.wikipedia.org/wiki/Heroin), [molsidomine](https://en.wikipedia.org/wiki/Molsidomine), [leflunomide](https://en.wikipedia.org/wiki/Leflunomide), [paliperidone](https://en.wikipedia.org/wiki/Paliperidone), [phenacetin](https://en.wikipedia.org/wiki/Phenacetin), [primidone](https://en.wikipedia.org/wiki/Primidone), [psilocybin](https://en.wikipedia.org/wiki/Psilocybin), [sulindac](https://en.wikipedia.org/wiki/Sulindac), [fursultiamine](https://en.wikipedia.org/wiki/Fursultiamine) |
| Type II | Extracellular | Type IIA | GI fluids | Loperamideoxide, [oxyphenisatin](https://en.wikipedia.org/wiki/Oxyphenisatin), [sulfasalazine](https://en.wikipedia.org/wiki/Sulfasalazine) |
| Type IIB | Systemic circulation and other extracellular fluid compartments | [Acetylsalicylate](https://en.wikipedia.org/wiki/Acetylsalicylate), [bacampicillin](https://en.wikipedia.org/wiki/Bacampicillin), [bambuterol](https://en.wikipedia.org/wiki/Bambuterol), [chloramphenicolsuccinate](https://en.wikipedia.org/wiki/Chloramphenicol_succinate), [dipivefrin](https://en.wikipedia.org/wiki/Dipivefrin), [fosphenytoin](https://en.wikipedia.org/wiki/Fosphenytoin), [lisdexamfetamine](https://en.wikipedia.org/wiki/Lisdexamfetamine), [pralidoxime](https://en.wikipedia.org/wiki/Pralidoxime) |
| Type IIC | Therapeutic target tissues/cells | [ADEPTs](https://en.wikipedia.org/wiki/ADEPT_(medicine)), [GDEPTs](https://en.wikipedia.org/wiki/GDEPT), [VDEPTs](https://en.wikipedia.org/wiki/VDEPT) |

**THERAPEUTIC APPLICATIONSOF PRODRUGS[10,11,12,13]:**

**Therapeutic applications of prodrugs:**

1. **Undesirable taste of many drugs can be altered by converting into prodrug.**

* Undesirable taste is due to its solubility and interaction with taste receptors so it can be reduced by decreasing the polarity of the drug by attaching non polar functional groups.
* Chloramphenicol is an antibiotic which is very bitter in taste due to its aqueous solubility. The bitter taste of this drug is reduced by converting into Chloramphenicol palmitate which is a sparingly soluble prodrug of chloramphenicol. After administration by the action of pancreatic lipase which hydrolyses and releases chloramphenicol and exerts its pharmacological action.



1. **Reduces pain at the site of Injection**

* Some drugs upon IM administration produces pain at the site of injection this due to its weak acidic nature or less solubility which gets deposited in the tissues and causes necrosis results in pain so it can be reduced by enhancing the solubility by attaching polar function groups.



* Clindamycin is an antibacterial agent used orally in the treatment of gram-positive and anaerobic infections. When it administered IM produces pain at site of injection, which is overcome by converting into prodrug clindamycin 2-phosphate. After injection it is rapidly converted into clindamycin in presence of phosphatase. Clindamycin 2-phosphate, unlike clindamycin, is highly water soluble and does not produce pain upon injection.
* Phenytoin is an anticonvulsant drug which upon IM administration produces pain at the site of injection, which can be reduced by converting it into Fosphenytoin.



* Timolol is a medication used to treat and manage open-angle glaucoma and ocular hypertension. It is in the beta-blocker class of drug. Timolol is less lipophilic in nature the log P value is very less, the lipophilicity of timolol is enhance by converting into butyryltimolol.



1. **Site directed drug delivery:**

* Various drugs due to their instability they bypass various pharmacokinetic and pharmaceutical barriers after administration. Gabapentin is having less absorption, bioavailability and pharmacokinetic properties these problems overcome by prodrug Gabapentin enacarbil which is used to treat moderate-to-severe primary Restless Legs Syndrome (RLS).



1. **Enhancement of drug solubility and dissolution rate:**

* Prodrug approach can be used to increase or decrease the solubility of a drug depending on its ultimate use. Sulindac sulfide is the active form of sulindac which is generally used as anti-inflammatory agent, which is being more water soluble with sufficient lipophilicity, makes this drug suitable for oral administration.



* Chloramphenicol succinate and chloramphenicol palmitate are ester type of prodrugs of chloramphenicol, have enhanced and reduced aqueous solubility respectively then chloramphenicol succinate prodrug found suitable for parentral administration.



1. **Reduction of gastric irritation:**

* Aspirin, Ibuprofen and Diclofenac are NSAIDS which possess carboxylic group in its structure, because of free carboxylic group the produces gastric irritation, then by applying the concept of prodrugs the free carboxylic group converted into ester, amide or salt without altering the pharmacological action.
* Diclofenac is generally available as Diclofenac sodium and aspirin itself is a prodrug of salicylic acid.



1. **Enhancement of Chemical Stability:**

* Chemical stability is very important for therapeutic activity of drug, the concept of prodrug is used to enhance the stability of drug by modification of the functional group responsible for instability or by changing the physical properties of the drug.
* Hetacillin is a prodrg of ampicillin which is formed by reaction between ampicillin with acetone by which the free amino group of ampicillin cyclized with acetone and produces Hetacillin . This change increases the stability of ampicillin by inhibiting auto aminolysis.



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