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# RESEARCH ARTICLE

## THE PRODRUG APPROACH IS A CHALLENGE OF TARGETED DRUG DELIVERY SYSTEM AND DRUG DESIGN

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## ABSTRACT

Biologically inert derivatives of drug molecules that undergo an enzymatic and chemical conversion in-vivo to release the pharmacologically active parent drug. The prodrug design is the best approach and enhancing drug selectivity while minimising toxicity. Prodrug as a novel approach for lipophilicity, solubility, permeability and drug targeting that affect drug delivery system. The design and development of prodrugs is the most common and the effective strategy to overcome pharmacokinetic and pharmacodynamic drawbacks of active drugs . It is estimated that about 10% of drugs approved world wide can be classified as prodrug. This article include introduction rationale approach, strategy drug design of prodrug, functional groups utilised for drug design, classification of prodrug, requirements of prodrug design for targeted drug delivery system and recent advancement of prodrug and conclusion.



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# INTRODUCTION

The prodrug concept was first proposed by Albert in 1958. Albert & his co-worker described prodrug as pharmacological inactive chemical derivatives that could be used to alter the physicochemical properties of drug in a temporary manner to increase their usefulness & to decrease associated toxicity .They have also been called 'Latentiated drugs', Bioreversible derivatives' & 'Congeners'[1]. Prodrugs are simple chemical derivatives that one or two chemical or enzymatic steps away from the active parent drug. Some of prodrugs lack an obvious carrier or promoiety, but result from a molecular modification of the active drug itself in vivo. E.g- Metabolic oxidation or reduction that generates a new and active compound. Such type of prodrugs areb usually referred to as BIOPRECURSOR prodrugs."Another cases, a prodrug may consist of two pharmacologically active drugs that are coupled together in a single molecule. So that each drug acts as a promoiety for the other. Such kind of derivatives are called CODRUG"[2].In contrast to prodrugs, soft drugs are active drugs as such but are designed to transform into an inactive form in vivo after achieving their therapeutic effect. Promoiety a functional group used to modify the structure pharmacologically active agents to increase physicochemical, biopharmaceutical or pharmacokinetic properties. The drug promoeity is the prodrug that is typically pharmacologically inactive. The drug & promoiety are covalently linked via, bioreversible groups that are chemically or enzymaticallkylabile. The prodrugmust release active drug & cross linked promoiety before during after absorption within specific target tissue depending upon the purpose of prodrug strategy.Now a days,a prodrug methodology is considered the most favourable site specific drg delivery strategy that is applied to liver a drug substance to target site or target tissue.[3]

**[Schematic Representation Of Modify the Structure of Using Promoiety as Functional Group]**

## RATIONALE OF PRODRUG DESIGN

- Enhancing permeability & absorption.
- Protecting from rapid metabolism.
- Changing distribution profile.
- Improving formulation & administration.
- Overcoming toxicity problem.
- Major phases involved in the drug receptor interaction.
- Stability.
- Favourable organoleptic properties.[4]

**BASIC OF PRODRUG IN DRUG DESIGN:** The design of an apperopriate prodrug structure should be considered in the early stages of preclinical development, because prodrug may alter the tissue distribution, efficacy, and even toxicity of the parent drug. The main factor that should be carefully considered when designing a prodrug structures are as follows:

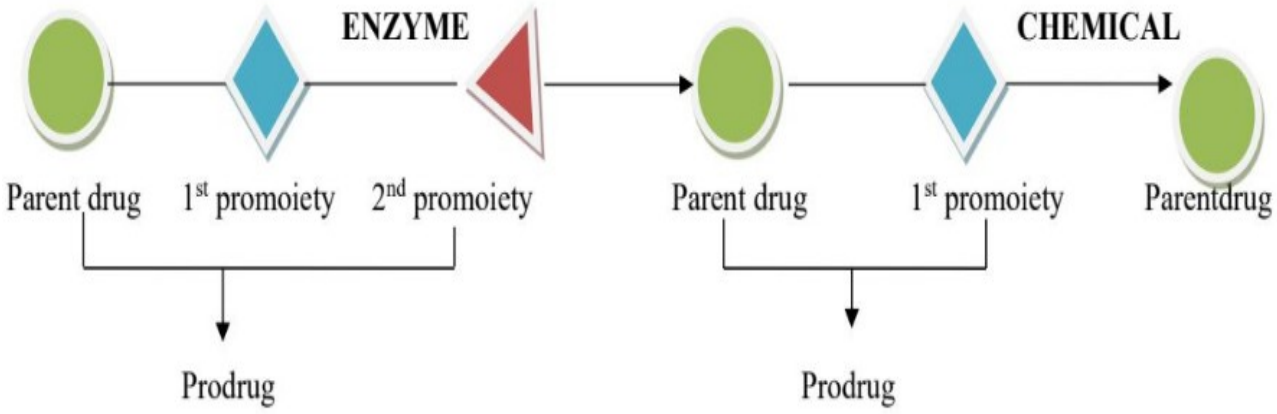



**Fig. 1. Schematic Representation Of Modify the Structure of Using Promoiety as Functional Group**

- Which functional groups of the parent drug are amenable to chemical derivatisation?
- Chemical modification made to the parent drug must be reversible and allow the prodrug to be converted back into the parent drug by in vivo chemical or enzymatic reaction.
- The choice of promoiety and relative safety should be considered with respect to the disease state, dose and the duration of therapy, because the promoietyshouid be safe and rapidly excreated from the body.
- The absorption, distribution, metabolism and excretion properties of parent drug and prodrug require a comprensive understanding.
- Possible degradation by-products can affect both chemical and physical stability that lead to the formation of new degradation products.[5]

## STRATEGY FOR DRUG DESIGN OF PRODRUG

### Carrier

- Carrier is an inert molecule or the promoeityattached to the active site drug moiety through a metabolically laqbile linkage.
- The carrier imparts some desirable to the drug such as increased lipid or water solubility.

### Specifiers

- Carrier that helps in directly the active moiety to the target site is called as specifier.

E.g,-Antibody Directed Enzyme Produce Therapy.
Gene Directed Enzyme Prodrug Therapy.
Polymer Directed Enzyme Prodrug Therapy.[6]

### Linker

• A releasable linker or spacer is placed between the carrier or specifier & active drug moiety.
•Incorporation of linker appropriate linkage between promoiety& active drug.

### Sample Spacer

- This fig-2 represent sample spacer briefly in given below;
- Firstly cleavage then activation will occure after that specifier, released drug & linker will be activated separately.
- Prodrug involve chemical modifications & syntheses of new structures as well as the establishment of systems that deliver activedrug.[7]

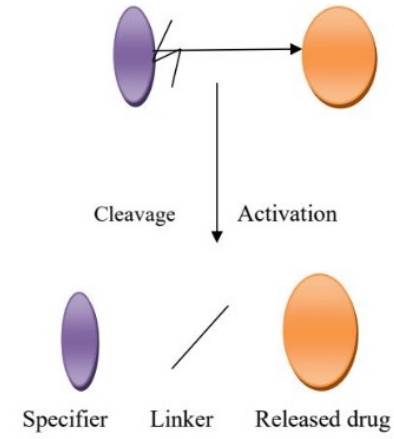



**Fig. 2. Schematic Representation Of Sample Spacer**

## FUNCTIONAL GROUPS UTILISED IN PRODRUG DESIGN

### Ester

- COOH,-OH groups can easily undergo esterification
- Esterase enzymeeasily break up the linkage at targate organ so that targated delivery is achieved.
- E.g-Drug-COORDrug-COOH+ROH.
- PRODRUGACTIVEDRUG.

### Amide

- Certain activated amides are chemicaly labile & also certain amides formed with aminoacids may under enzymatic cleavage.
- Lipophilicity of various compounds like acid chlorides and acids can be altered in many groups of compounds by amide formation.

Thiols amides functional groups is a successful approach to improve in vivo stability of pharmaceutical agents and targated drug delivery due to presence of enzyme amidase.[8]

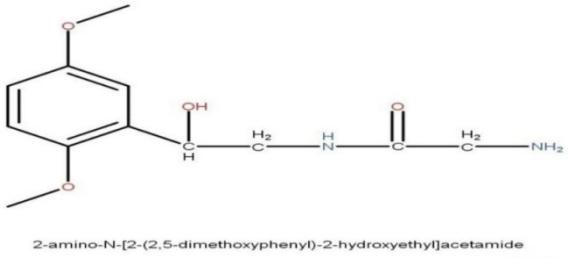



**Fig-3. Structure of N-glycoside derivative**

**Imides and Urides**

- Intramolecular and intermolecular hydrogen bonding in such molecules may be increased resulting in a decrease in water solubility.
- Imide and uride type compounds are more water soluble than the parent compound.[9]

**Oximide Derivatives**

- Oximes are hydrolysed by the versatile microsomal cytochrome {CYP450} enzyme.
- Oximes are strongly basic than amidines and guanodoximes can be used to enhance the membrane permeability and absorption of a parent drug.
- Oximes derivatives providing to modify molecules that lack hydroxyl,amine or carboxyl functionalities.

**Glycol amide Ester**

- These are bioreversible products of carboxylic group.[10]

**Carbates and Carbonates**

- It do not have any specific enzyme for hydrolysis.They exhibit restricted distribution in the body.
- Carbonates are derivatives of carboxylic acids and alcohols, and carbamates are carboxylic acid and amine derivatives.

The bioconversion of many carbonate and carbamate prodrug requires esterase for the formation of the parent drug.[11]

**PRODRUG LINKAGE AND ENZYME INVOLVED IN HYDROLYSIS OF LINKAGE:[12]**

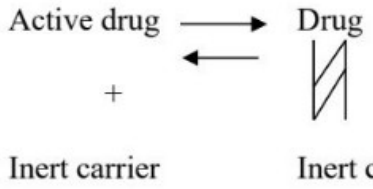
| PRODRUG LINKAGE | HYDROLYSIS LINKAGE |
|---|---|
| ESTER | ESTERASE |
| SHORT CHAIN AND MEDIUM CHAIN | CHOLINE ESTERASE |
| ALIPHATIC | LIPASE,CHOLESTEROL,ESTER HYDROLASE |
| LONG CHAIN ALIPHATIC COMPONDS | PANCREATIC LIPASE, CARBOXY PEPTIDASE. |
| PHOSPHATE ORGANIC | ACID PHOSPHAATAE,ALKALINE PHOSPHATASE |
| SULPHATE ORGANIC | STEROID SULFATASE |

**CLASSIFICATION**

- Carrier Linked Prodrug.
- Bioprecursor.
- Polymeric Drug.

**CARRIER LINKED PRODRUG**

- Bipartite.
- Tripartite.
- Mutual Drug.




**CARRIER LINKED PRODRUG:** Carrierr linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties. A drug is linked with carrier through covalent linkage during chemical prodrug formation. Prodrug subsequently undergoes chemical or enzymatic cleavage in vivo to release active drug &inner carrier.

**Drawback:** Which are covalent linkage to change or get rid of their undesirable physicochemical properties

**Bipartite-**It consist of both glycine & tolmetin, that means one carrier attached to the drug.[13]

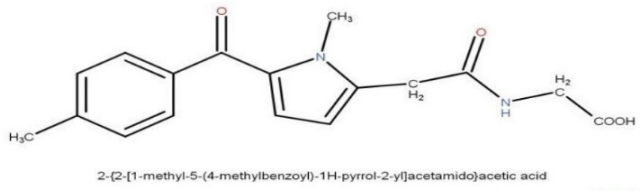
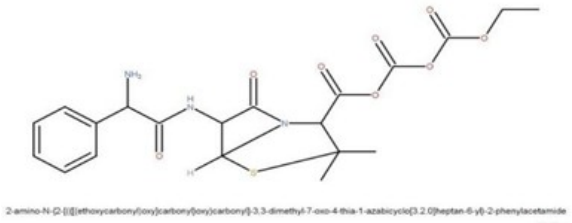


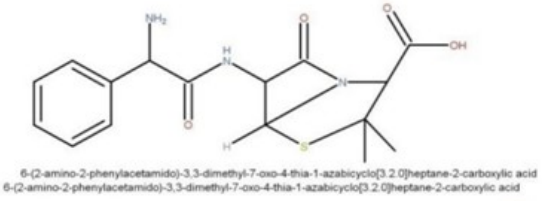

**Fig-5. Structure Of Bipartite**

**Tripartite-**Bacampacillin to convert ampicillin in the presence of esterase enzymethat means carri group is attached via linker to the drug.

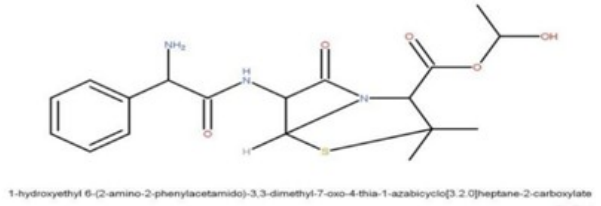



**[BACAMPACILLIN]**

**ESTERASE**



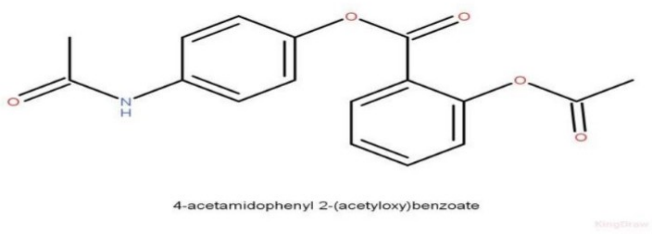

**+$CO_2$ [AMPICILLIN]**




**+$CH_3CH_2OH$+$CO_2$**

**Mutual drug**: This type of drug carrier having synergistic property with the drug to which it is linked. It carry both bipartite & tripartite prodrug. It consist of two of two agents act as promoiety for the other agent & vice versa. Benorylate is a mutual prodrug.

e.g, mutual prodrug aspirin & paracetamol.[14]



4-acetamidophenyl 2-(acetyloxy)benzoate

[BENORYLATE]

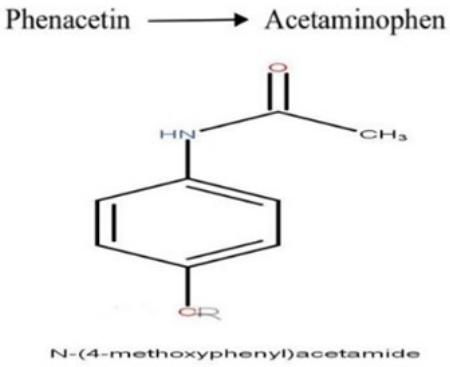
**Fig. 7. Structure Of Benorylate**

## BIOPRECURSOR

A Bioprecursor is a prodrug that does not imply the linkage to a carrier group but results from a molecular modification of the active principle itself. Bioprecursor prodrug rely on oxidative or reductive activation reactions unlike thev hydrolytic activation of carrier –linked prodrug.

It produces in vivo chemical modification of their inactive form.

E.g- o-Dealkylation




**[Structure O-Dealkylation derivatives]**

Phenacetin ($R=CH_2CH_3$)
Aetaminophen (R=H)

**POLYMERIC DRUG:** It can be defined as latent pharmaceutical agents which must undergo chemical or parent E.g- p-phenylene diamine mustard is covalently attached to poly amino polymer backbone of polyglutamic acid.[15]

**CLASSIFICATGION BASED ON THE SITE OF CONVERSION:** Prodrugs have been classified according to several criteria; for example, based on the therapeutic categories, based on categories of chemical linkages between the parent drug and the promoiety and based on the mechanism of action of a prodrug. A recently proposed more systematic approach categories prodrugs on the basis of their two cellular sites of conversion: intracellular and extracellular.[16]

**TYPE 1A DRUG**

Metabolised at cellular targets of their therapeutic action.

E.g,-DOPA, Acyclovir.

**TYPE 1B DRUG**

It converts into parent drugs by metabolic tissues, namely by the liver.

E.g,-Captopril, Carbamazepin, Primidone

***TYPE 2A*: GI Fluid**

E.g-Loperamide.

***TYPE 2B:*** Systemic circulation &extrcellular fluid compartments.

E.g-Chloramphenicol, Pralidoxime.

***TYPE 3C*:**Therapeutic target tissues or cell.

E.g- ADEPTs, GDEPs, VDEPs.[17]

## REQUIREMENTS FOR PRODRUG DRSIOGN FOR TARGATED DRUG DELIVERY SYSYEM

- The tissue associated biomolecule must be present in significantly elevated levels in that particular tissue compared to normal tissue.
- Prodrug level must be high enough to genetrate therapeutic levels of free drug in the target tissue.
- Prodrug activation at other sites must be Targated sites.
- Prodrug must br good substrate or p0sses high binding affinity for tissue associate molecule.
- It must not be rapidly eliminated from the body not enters cells randomly.
- Targated prodrug s have also been explored in onvcology in order to minimize side effects and improve the tolerability of chemotherapy.[18]

## METHODS OF EVALUATION

PH, SOLUBILITY&LIPOPHILICITY ARE THE KEY FACTORS IN DETERMINING IN VIVO BEHAVIOUR OF DRUGS.

**Partition Coefficient**: It measure the lipophilicity of a drug & an indication of its ability to cross the cell membrane. Ratio between-ionised drug distributed between the organic & aqueous layer at equilibrium. E.g-Diclofenac prodrugs for enhancing transdermal drug delivery system. Key role is that to ensure & maintain absorption in adequate portion within selective biological environment.

**Bioconversion Rate Determination:** Conversion rates of the prodrug ancitabine to cytrabine measured by invivo & invitro. These observed pH-dependent in vitro rate constants were consistent with those for controls using Tris buffers.Hydrtsolysis of ancitabine to cytrabine is chemically ,not enzymatically, mediated.

**Solubility Determination:** The solubilities of the diclofenac prodrug in deionised water .pXH2.5 adjust with of6N(HCl) were determined by adding excessive amount of prodrug & equilibrium.then at room temperature under stirring condition.Then go for centrifugation after to founf supernatant liquid go for HPLC ANALYSIS.[19]

**RECENT ADVANCEMENT OF PRODRUG**

- Prodrugs In Novel Drug Delivery System-
- This is one type of carrier system that used to deliver drug into its active sites in its intact form.

E.g-Liposomes using phospholipid ,nanosomes using triglyceride core to protect the drug & to increase solubility, permeability.

**GENE DIRECTED ENZYME PRODRUG THERAPY**

- It included gene expressing the foeign enzyme is delivered.
- Activation of prodrug to respective tumorcell,enzyme,this gene is used to deliver enzyme associate.
- E.g,-ganciclovir is an antiviral drug to phophorylate to gorm ganciclovir tripphosphate which disrupt DNA synthesis &cell death.[20]

**VIRUS DIRECTED ENZYMES ORODRUG THERAPY**

- This field used as viral vectors for the efficient delivery to suicide gene of tumor cell which convert a non-toxic prodrug to cytotoxic agent
- It involve both VDEPT &GDEPT encoding prodrug enzymes to the tumor cells for site-specific activation.

**ANTIBODY DIRECTED ENZYME PRODRFUG THERAPY**

- An antitumor-antibody is conjugated to an enzyme localised in the tumor cell & not present extracellular fluid &carrier cell membrane.
- Allowing conjugate to clear from blood after that is activated by the enzyme delivered to the tumor cell.
- E.g,-Amygdalin is a prodrug is activated by enzyme beta – glycosidase associated by monoclonal antibody.[21]

**VARIOUS APPROACHES OF THE PRODRUG**

**Tumor targeting-**Hypoxic cells are resistance to radiotherapy.Higly toxic with narroe therapy. Irregular blood flow to tumor cells lead to reduce supply of glucose and other nutrient.Thus, decrease their rate of cell division ,makingits difficult for chemotherapeutic agents to target.

e.g-N-Oxide bioreductivetriapazamine is used in treatment of lung cancer with cisplatin.

e.g,-Folate required all eukaryotic cells for carbon metabolism and nucleotide synthesis.

**Occular delivery**-It include tightness of corneal epithelium pre-corneal drug elimination. *Key requirements are ocular prodrug have good stability and solubility in aqueous solutions to enable formulation, penetrate cornea due to lipophilicity character, and release the parent drug within eye at a rate that needs the therapeutic need.*[22]

*TWO STEP Measure* taken in improving the bioavailabilities are:

*A-Firstly extending the prodrug residence time in the conjuctival sac.*

*B-Secondly improving penetration of drug across corneal barrier.*

**Buccal delivery**: It is non-invasive route of delivery for protein and peptides that cannot tolerate the acidic environment of the GI tract.So that prodrug generally improve drug solubility, stability, constant drug release rate,increased patient comfort.

e.g,-Oxymorphol, butorphanol.

**BLOOD –BRAIN BARRIER**: It helps protect the CNS by allowing certain types of molecules to pass.
e.g,-Dihydro trigolline drug can be linked to dopamine and targeted to brain.

e.g,-Dihydropyridine-pyridinium salt redox system also across the blood brain barrier.[23]

**BENEFITS OF PRODRUG**

- ***Achieve optimal permeability***-Chemical modification can increase its solubility.The polar molecules on the prodrug alters the parent drugs chemical properties to increase water and lipid solubility and transported in to the targeted site at appropriate concentration.
- ***Reduce toxic effects of an active drug on the other parts of the body***-The prodrug targets delivery of a potentially toxic active drug to the site where it is transformed and retained in the site-specific tissue.
- ***Enhancement patient compliance***-The structure of the active drug can be altered by the prodrug to lessen and relieves these complications and thereby increase patient compliance
- ***Offer protection from rapid metabolism and elimination***-A drug can be metabolised and rendered inactive before reaches the targeted sites.But in case prodrug can stabilize the active drug and prevent the drug metabolism interact with enzyme.

The modified prodrug blocks metabolism until the drug is at the desired sites.

***Improve the selective targeting of drugs to specific organ sites, tissues and enzymes***-Systematic site specific drug delivery system is very complex than local site-specific drug delivery system because the drug pass through the circulatory system and multiple barrier ultimately reach the specific site.
The prodrug uses a functional group ofr chemical linkage that acts to transport the active drug tob the specific site.[24]

# CONCLUSION

Prodrug were design to improve pharmacokinetic and drug delivery system. The prodrug is converted into active form only in the target tissue by utilizing either specific enzymes or pH value different from the normal pH for activation. Recent advancement of prodrug design to develop targeting the drug delivery of parent drugs to specific sites within the body.

Prodrug approach of functional groups that ensure development of future drug substances. The [prodrug strategy is a versatile and powerful method that can be applied to a wide variety of pharmaceuticals whose pharmacologic limitations compromise their clinical use.

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