



Prodrug: A Novel Approach of Drug Delivery

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ABSTRACT

For the targeting of drugs in the body various approaches are used for example nanotechnology, microcapsules, micro emulsions etc. But most of these approaches suffering from a lot of problems such as stability problem and entrapment efficiency etc. These problems can be easily overcome by using Prodrug approach. Prodrugs are often designed to improve oral bioavailability in cases where the intended drug is poorly absorbed through the gastrointestinal tract.

Keywords: Proagent, target drug delivery, carrier linkage, chemical modification.

INTRODUCTION

A prodrug is a medication that is initially administered to the body in an inactive (or less than fully active) form, and then becomes converted to its active form through the normal metabolic processes of the body. Prodrugs can be used to improve how the intended drug is absorbed, distributed, metabolized and excreted (ADME).¹ Almost all the drugs possess undesirable physicochemical and biological properties such as poor bioavailability, incomplete absorption, adverse effects, first pass metabolism etc.^{2,3} The therapeutic efficacy of these drugs can be easily improved by eliminating the above discussed problems and these problems can be removed by using physical, chemical or biological means.⁴

The physical means include introduction of controlled release formulation such as sustained release, prolong release formulation etc.

The biological means to change the route of administration which do not have the surety to be accepted by the patients.

The third and the last approach is the chemical means which include introduction of prodrug which is best among physical and biological means.⁵

Prodrug approach

The term 'Prodrug' or 'Proagent' was first introduced by Albert (1958)⁶ to describe any Compound that undergoes biotransformation prior to exhibition of its pharmacological effect.

The term 'Prodrug' signifies a pharmacologically inactive chemical derivative that could be used to alter the physicochemical properties of drugs in a temporary manner to decrease associated toxicity and increase their therapeutic efficacy. The chemical modification of a biologically active compound forms a new compound that, upon in vivo enzymatic attack will liberate the

parent compound. The prodrug design approach is also referred to as "Drug Latentiation".⁷

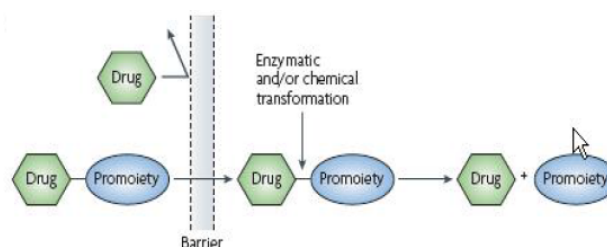


Figure 1: Fate of Prodrug approach

Classification of Prodrug:⁸

1. Carrier linkage prodrug

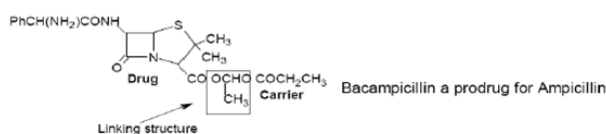
In this a chemical group is attached with the parent drug molecule which can be easily removed from the drug. The chemical group mainly used is ester or amide. The carrier-linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties and then subsequent enzymatic or nonenzymatic mechanism to release the active drug moiety. The covalent bond is used for the cross linkage. It can be classified in three categories.

a) Bipartate Prodrug

This prodrug consists of the active drug covalently linked to an inert carrier or transport moiety, generally ester or amide. Such prodrugs have greatly modified lipophilicity due to the attached carrier. The active drug is released by hydrolytic cleavage either chemically or enzymatically. The Prodrug and carrier released after in vivo enzymatical or non-enzymatical attack must be nontoxic.

b) Tripartate Prodrug

In this the drug moiety is not directly attached to the carrier moiety. First the drug moiety is attached with the linker and then this linker is attached with carrier.

**Figure 2:** Mechanism of Tripartate Prodrug**Figure 3:** Example of Tripartate Prodrug

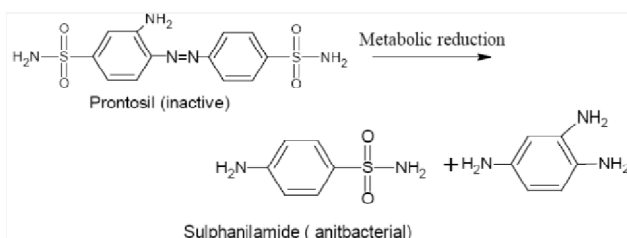
c) Mutual prodrug

In this the carrier used is another biologically active drug instead of some inert molecule. A mutual prodrug consists of two pharmacologically active agents which are coupled together in such a way to act 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.

2) Bioprecursor Prodrug

This approach does not include any carrier molecule. In this an inactive drug undergoing chemical modification to convert into a compound which itself is active drug or further metabolized into active form which have a desired therapeutic efficacy. The chemical reaction occurs in this process include oxidation or reduction.

For e.g: Prontosil is an inactive compound which undergo metabolic reduction to produce sulphanimide which is an active compound having antibacterial activity.

**Figure 4:** Example of Bioprecursor Prodrug

Advantages of prodrug:

1. It reduces adverse effects of drug.
2. Drug can be targeted to the desired sites.
3. Synergistic effects can be obtained without side effects.
4. Give additional biological action as that of parent drug.

Limitations associated with prodrug approach:

1. Formation of toxic metabolites:

The main limitation of prodrug is the formation of toxic unexpected metabolites which are produced from the total drug conjugates. Another problem is the release of pharmacokinetic modifier which may cause enzyme induction or alter drug excretion.

2. The active doses of two mutual prodrugs of the same parent drugs may appear to be same in rats but may be quite different in clinical investigations.⁹

3. The prodrug might consume a vital cell constituent such as glutathione during its activation stage which causes depletion of prodrug.¹⁰

APPLICATIONS OF PRODRUG APPROACH

Prodrug approach has been extensively studied for a wide range of applications. It has been widely used now a day for its property of correction of pharmacokinetic as well as pharmaceutical, organoleptic, physical and chemical properties of parent drug compound which enhance the stability and patient compliance. The applications of prodrug are as follows.

1. Brain Targeting

The hydrophilic drugs cannot be administered as such in the brain and thus the therapeutic efficacy cannot be achieved. The hydrophilic drugs can be converted into their lipophilic forms achieve the goal but this leads to the systemic toxicity due to the penetration of drugs into the other tissues. For this reason dihydropyridine pyridinium type redox system was developed for brain specific sustained delivery of drug. The drug containing amine group is made lipophilic by coupling to dihydropyridine promoiety that facilitate penetration of prodrug through the blood brain barrier. In the CNS dihydropyridine group converted to polar pyridinium salt, thus becomes poorly permeable to blood brain barrier and thus remain at the site and cleavage provides sustained release for action.¹¹

2. Colon Targeting

For e.g. sulphasalazine which is formed by coupling of diazotized sulphanilamide pyridine with 5-amino salicylic acid (ASA). On oral administration intact sulphasalazine reaches the colon. The azo reductase associated with colonic microflora convert sulphasalazine to its constituents entities, the active species 5ASA available for absorption in colon, while precolonic absorption responsible for side effects is reduced¹¹.

3. To enhance aqueous solubility

Prodrug can be used to increase the aqueous solubility of poorly aqueous soluble drugs. Prednisolone is a poorly aqueous soluble drug which should be converted into water soluble form for their delivery into the body. So this can be done by preparation of prodrug i.e prednisolone phosphate which is activated in vivo by the phosphatase.¹²⁻¹⁴

4. Odour masking

The odour of a compound is due to its vapour pressure. Low boiling point liquids will have a strong odour e.g. Ethyl mercapta having a Foul smell liquid of boiling point 35°C useful in the treatment of leprosy. Its foul smell is removed by converted it into its phthalate ester, diethyl isophthalate, which has higher boiling point and odorless.^{15, 16} The prodrug is administered by rubbing on

the skin, after absorption, the ester is metabolized to parent drug by thioesterase.

5. Reduction of gastrointestinal irritation

Many drugs react with the acid secretion in stomach and causes gastric irritation for e.g NSAIDS. In case of NSAIDS this problem can be overcome by preparation of prodrug salsalates.

6. Drug targeting

When the drug is administered after its absorption it will distribute to different tissues including target as well as non targeting tissues. The distribution to non target tissues causes toxicity and reduction of drug concentration in the target tissues due to which optimum therapeutic action can not be achieved. So for obtaining desired therapeutic action drug targeting is necessary and this can be easily achieved by prodrug approach.

7. Reduction of stability problem

Most of the drugs may be rapidly metabolized and rendered inactive before it reaches the site of action. The structure may be modified to block the metabolism until the drug is at the desired site. Some prodrugs protect the drug from first-pass effect.

For e.g: Propranolol, (R=R₁=H) is a widely used antihypertensive drug, but its oral bioavailability is very low because of first pass metabolism. The hemisuccinate ester of propranolol (R=H R¹=, COCH₂COOH) was prepared to block glucuronide formation. Hence oral administration of propranolol hemisuccinate elevates plasma levels of propranolol for about 8 times.¹²⁻¹⁴

8. Increase in patient compliance

Many drugs have unpleasant taste, odour and some may causes GIT irritation and when given in form of injection causes pain. These problems cause poor patient compliance.

Table 1: Examples of Prodrug and their active metabolites¹⁷

Prodrug	Active Drug
Protosil	Sulfanilamide
Levodopa	Dopamine
Talampicillin	Ampicillin
Cyclophosphamide	Phosphoramidate mustard
Diazepam	Oxazepam
Azathioprine	Mercaptopurine
Cortisone	Hydrocortisone
Dipivefrin	Adrenaline
Prednisone	Prednisolone
Enalapril	Enalaprilat

Some detailed examples of prodrugs¹⁶

Pivampicillin, talampicillin and bacampicillin are all prodrugs of ampicillin. These prodrugs are produced by

esterification of the polar carboxylate group to form lipophilic, enzymatically labile esters.

Enalapril is the ethyl ester prodrug of the active diacid, enalaprilat. Enalaprilat is poorly absorbed from the gastrointestinal tract (less than 10%), but absorption of the prodrug enalapril is greatly improved (about 60%).

Dopamine cannot be distributed into the central nervous system (CNS) as it cannot cross the blood-brain barrier. But dopamine is essential for the treatment of Parkinson's disease. Thus its prodrug levodopa is used for the treatment of Parkinson's disease. Levodopa can easily cross the blood-brain barrier via an amino acid carrier and is then converted (decarboxylated) into dopamine by dopa decarboxylase in the CNS.

CONCLUSION

Recently many drugs have been formulated by using prodrug approach. Synthesizing a new compound is a very time consuming and also a costly one, but by using prodrug approach derivatives of compound can be easily prepared which is less time consuming and economical also. By using this approach the toxic effects associated with other approaches can be minimized. This approach not only improves the pharmacokinetic properties but also target the drugs on the specific site.

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