A review on prodrugs

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Abstract
A Prodrug is a combination of active drug with an inactive or inert material which will undergo biotransformation in vivo to yield the active drug to produce pharmacological action. The prodrug has certain characters which it should undergo or obey to be an ideal prodrug. The wide range of application of prodrug shows the importance of prodrug in modern medicine. Some types of prodrugs like photosensitive prodrug therapy, ADAPT and ADEPT are now a developing concept which sooner will emerge as major part in one of the newer trends of medicine. Few limitations of the prodrugs are seen which should be minimised and their use should be increased.

Keywords: Prodrug, Inert material, Photosensitive Prodrug therapy, ADEPT, ADAPT, Newer trend.

INTRODUCTION
Prodrug [1] was first used by Albert [2] in late 1950’s to indicate pharmacologically inactive compounds that could be used to modify the physical and chemical properties of a drug to increase its use and/or to decrease associated toxicity [3].

Prodrugs are chemically modified inactive drug precursor bonded covalently. It has a weak link between drug and inert chemical which may be broken to provide drug. The link may be broken by enzymatic or non enzymatic process in the body to provide therapeutic effect.

There are various terms used to denote Prodrugs they are proagent [4], congeners, latentiated and reversible or bioreversible derivatives. The design approach is referred as drug latentiation or simply latentiation process. The Prodrug consists of active drug and promoiety. The promoiety is not essential for exerting pharmacological action but is carefully selected to pass on a desirable property to the drug, resulting is the compound with desired pharmacological property. The promoiety should be safe and excreted from the body as soon as possible.

Prodrug can exist naturally, such as many phytochemicals, botanical constituents and endogenous material [10] or they may be synthetic or semisynthetic derivative produced intentionally as a part of a rational drug design or unintentionally during drug development [5].

Release of active drug is controlled process can occur before, during or after drug absorption or at the specific site of action within the body depending on the purpose for which the Prodrug was designed [6-7]. Release of free drug is accomplished either by enzymatically or chemically [8].

Prodrug can be changed into pharmacologically active species. Mostly one or more metabolites have a pharmacologic profile similar to parent drug others have a different profile and some are responsible for ADR. The duration and intensity of the reaction to a drug related to the time course of all active substances in the body, the pharmacokinetic of active metabolites as well as that of the compound administered is therefore of therapeutic concern.

Ideal requirements of a prodrug
• It should not have any intrinsic pharmacological action.
• It should undergo rapid metabolism chemically or enzymatically into active form where desired.
• The metabolic fragments apart from the active drug should be non toxic [9].

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Types of prodrug

1. Carrier linked prodrug
The carrier linked Prodrugs are further classified into following types

Bipartite Prodrug
It is formed by linkage between carrier and drug molecule.

Tripartite Prodrug
In this there will be linkage between carrier, linker and drug(double Prodrug).

Mutual Prodrug
In this there will be 2 synergistic drug are attached to each other where 1 acts as carrier for other.

Ideal requirements of a carrier
- It should be biologically inactive non toxic and non immunogenic.
- Reduce the activity of drug
- Must minimize the toxicity of host drug
- Should carry and release the drug at specific required site of action.
- Should allow release of drug chemically or enzymatically.

2. Bioprecursor
The bioprecursor produce new compound by molecular alterations of active principle. These Prodrug contain embryo of active species within their structure and metabolism of which gives an active drug. The main difference is that it does not contain any carrier [10-12].

3. Photoactivatedprodrug
A photo activated Prodrug is a compound are activated by irradiation with specific wavelength of visible light or long wavelength uv (uv-A). Generally, UV radiation excites the energy of drug to interact by a number of mechanisms with cellular substrate. Using this therapy for the treatment is referred as photodynamic therapy (PDT). It needs special lasers, lamps, optical fibres to focussing the radiation on particular organs or tissues in the body [13].

Activation of a photosensitive drug & its possible modes of action

<table>
<thead>
<tr>
<th>Drug (ground energy state)</th>
<th>Decay with fluorescence</th>
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<tbody>
<tr>
<td>Drug (singlet excited energy state)</td>
<td>hv</td>
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<tr>
<td>Drug (triplet excited energy state)</td>
<td>The activated drug interacts with oxygen to cause photo oxidation the substrate by superoxide and hydroxyl free radicals</td>
</tr>
<tr>
<td>formation of singlet oxygen which react with substrate</td>
<td>reaction of the activated drug with substrate</td>
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Example
Dr. P.Marks used photofrin a photosensitive drug, it deposits in tumour tissue to treat advanced brain tumours. Photofrin is an optical fibre with laser attached was inserted into the patient's brain through the nose and drug was activated. It results in destruction of tumour tissues.

Limitation
It should be used with care since it causes photosensitation patient cannot tolerate sunlight
and other bright light. In addition skin disfigurement, blistering other unwanted side effects can also occur.

4. Antibody directed enzyme prodrug therapy (a dept)
Antibody directed enzyme Prodrug therapy used in an attempt to develop drugs specifically target cancer cells. This method is based such that Prodrugs are enzyme activated. It uses antibody enzyme conjugate to deliver the enzyme to the target. Once concentration of enzyme reached tumour site administered Prodrug reaches tumour and it is transferred by enzyme carried by the antibody to the active drug.

Example
The drug anticancer agent-ETOPOSIDE is a semisynthetic derivative of podophyllotoxin which is isolated from Podophyllum peltatum.
In ADEPT, photofrin is phosphorylated and used as Prodrug and is converted into etoposide by the enzyme alkaline phosphatase. Through diffusion process, Etoposide phosphate destroys tumour. Through similar approaches of ADEPT, GDEPT-Gene Directed Enzyme Prodrug Therapy and ADAPT- Antibody Directed Abzyme Prodrug Therapy are in initial stages.

5. Hard prodrug
A hard Prodrug is a biologically active compound with a high lipid solubility or high water solubility having along biologic half life eg: cocaine and heroin [14].

6. Soft prodrug
A soft Prodrug is a biologically active compound that is biotransformed in vivo in a rapid and predictable manner into non toxic moieties. Eg: insulin and adrenaline [14].

Goals of prodrug design
A. Formulation and pharmacokinetic aspects
Pharmaceutical goal involves overcoming the following
- unpleasant taste
- pain on injection
- poor solubility
- slow dissolution
Pharmacokinetic goal involves overcoming following
- Poor bioavailability
- Short duration
- High first pass metabolism
- Toxicity or side effects
- Non specificity.

B. Conversion site
The main goal of all Prodrug is that they should be quantitatively converted to drug after the specific problem has been outweighed. After completion of task the complete conversion of Prodrug to drug should happen immediately.

C. Bioavailability
Prodrug absorption should be fast and complete and its conversion in blood is instantaneous if the goal is to increase the bioavailability.

D. Prolonged duration
E. Stability
The duration of drug in plasma is determined by 2 steps
- The rate of input of Prodrug from site of administration to blood.
- The subsequent conversion of Prodrug to drug in blood.

The stability of Prodrug is required in two different area, they are
At Gastrointestinal tract
The conversion of Prodrug in intestine is a useful way for bypassing the problems other than stomach instability ie applicable to
- Poor soluble drugs
- Drug with bad odour and taste
- Those upset stomach

At storage
Prodrug increases shelf life of product. Prodrug must be stable on storage by resisting conversion on storage but convert in vivo condition. This requires a special mechanism known as Trigger [11]. A trigger may be based on availability of enzymes in the body or on the hydrogen ion concentration difference between product and body fluid [12].

Applications of prodrug
Prodrug has wide range of application the following are some of most important applications are,
A. Increase in solubility
Some drugs show poor solubility, in order to increase their solubility Prodrugs may be used. Example methylprednisolone is converted to methyl prednisolone sodium succinate.

**B. Increase in bioavailability**
Increase in lipophilicity causes increase in passive transport therefore by imparting lipophilic carrier to drug its bioavailability can be increased.
Example Acyclovir is converted to 6 deoxy acyclovir which is 5-6 times more bioavailable and 18 times more water soluble than parent compound.

**C. Reduction of toxicity**
When the drug has toxicity it can be reduced using the Prodrug formation.
Example: Methotrexate an antitumour drug acts equally on both healthy and tumour cell but its poly(L-lysine) derivative is toxic only to tumour cells.

**D. Prolonged action**
When the plasma half life is decreased there will be high clearance from the body hence frequent dosing is essential but by Prodrug, the action may be prolonged to few month or more.
Example: Fluphenazine when converted to decanoate derivative of fluphenazine it shows action for 1 month.

**E. Target drug delivery**
Site specific drug release causes maximum drug absorption avoiding toxicity associated with availability of drug in non target area as well as early biotransformation of drug. The second approach used to increase target drug delivery are
- Alteration in hydrophilic or lipophilic properties of drug/coupling the drug with special site specific carrier molecule to direct drug to target site.
- Site specific activation of Prodrug molecule to release the drug.

**F. Improvement in patient compliance**
Generally patient will not take drugs which are unpalatable in taste and odour so solubility in saliva and in turn contact with taste buds can be minimised by the esterification of drugs with long chain fatty acids
Example: Clindamycin palmitate less bitter than clindamycin.

**Limitations of prodrug**
One main disadvantage is toxicity due to formation of unexpected metabolite from the total Prodrug may be toxic. The inert carrier generated following cleavage of Prodrug may also transform into a toxic metabolite. Drug activation stage, the Prodrug might consume a vital cell constituent such as glutathione leading to its depletion.

**CONCLUSION**
Prodrug can be a tool for overcoming the various problems of drugs. Newer types of Prodrugs like ADEPT, ADAPT and Photosensitive Prodrug should be developed and should used. The Prodrug plays major role in rationalized use of drugs by increasing patient compliance, reducing toxicity and increasing stability.

**ACKNOWLEDGEMENT**
Nil

**CONFLICT OF INTEREST**
Not interest.

**REFERENCE**
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