Pro-drug Developments

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**ABSTRACT**

Prodrugs are chemically modiﬁed derivatives introduced in therapy due to their advantageous physico-chemical properties (greater stability,

improved solubility, increased permeability), used in inactive form. Biological effect is exerted by the active derivatives formed in organism

through chemical transformation (biotransformation).

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To come out pharmacokinetic & pharmacodynamic limitations of active drugs there is an effective strategy to overcome that is design and developments of prodrugs. A large numbers of prodrugs are already available in market and well established in recent years. Also in recent years there is particular enhance in the use of prodrugs as an advancement of parent drugs for treatment of different types diseases. Prodrugs are modified derivatives of active moiety entered in therapy because of their superior physicochemical properties like eminent stability, better solubility, improved permeability, used in inactive form. Active derivatives formed in organism by chemical transformation (biotransformation) exerts their biological effect. A prodrug strategy includes changes in active moiety and making different derivatives that provides much advantages over parent moiety like enhancing membrane permeability, overcome pharmacokinetic barriers like poor solubility, absorption, rapid excretion and pharmacodynamic barriers such as toxicity, side effects and poor efficacy. site specification, transporter targeting, improving aqueous solubility and so many. Recently, out of pharmaceutical products 10% are available as prodrugs. 50% of prodrugs changed to the active form by hydrolysis mechanism and majorly by hydrolysis of ester. Now we can identify prodrugs produced by chemical derivatisation, targeted delivery systems and bioprecursors.

**INTRODUCTION**

One of the eective methods of modern research in the

eld of medicine is the development of prodrugs that have

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UPDATE

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Prodrug Strategy in Drug Development

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Prodrugs are chemically modiﬁed derivatives introduced in therapy due to their advantageous physico-chemical properties (greater stability,

improved solubility, increased permeability), used in inactive form. Biological effect is exerted by the active derivatives formed in organism

through chemical transformation (biotransformation). Currently, 10% of pharmaceutical products are used as prodrugs, nearly half of them

being converted to active form by hydrolysis, mainly by ester hydrolysis. The use of prodrugs aims to improve the bioavailability of compounds

in order to resolve some unfavorable characteristics and to reduce ﬁrst-pass metabolism. Other objectives are to increase drug absorption,

to extend duration of action or to achieve a better tissue/organ selective transport in case of non-oral drug delivery forms. Prodrugs can be

characterized by chemical structure, activation mechanism or through the presence of certain functional groups suitable for their preparation.

Currently we distinguish in therapy traditional prodrugs prepared by chemical derivatisation, bioprecursors and targeted delivery systems. The

present article is a review regarding the introduction and applications of prodrug design in various areas of drug development.

Keywords: prodrugs, classiﬁcation of prodrugs, drug development, optimization of bioavailability

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Introduction

Development of prodrugs is one of efficacious methods of latest research work in the field of medical science that gained more significance in present treatment. A prodrug is a pharmacologically inactive substance that becomes active invivo after metabolism or biotransformation and exerts its effects. Prodrug converted to active substance by biotransformation. Biotransformation is a metabolic process occurs in liver through various enzymes or chemical transformation. Biotransformation mechanism may includes oxidation, reduction, hydrolysis etc. The prodrug concept was introduced in late 19th century and aim was to improve undesirable properties of drugs but at the end of 1950s the actual term “prodrug” was introduced by Adrien Albert for the first time for drugs that are inactive but become an active derivative by biotransformation. In 1959 Harper completed the concept who initiate the term drug latentiation means drugs that was especially designed to need bioactivation.

 IUPAC definition of prodrug states that: Prodrug is a compound that go through biotransformation before revealing pharmacological effects. In fig 1. there is some prodrugs. Medicines that have specific protective groups, can be defined also as prodrugs in sequence to prevent unnecesary properties of the parent molecules. Prodrugs are simply derivatives of chemical that are only one or two enzymatic steps away or chemicals away from parent drug (active). But, some prodrugs have not a transporter or promoiety, but outcome from molecular modification of the prodrug itself, which creates a new active compound. The prodrug concept is different from active drugs that are active of their own, but on biotransformation they form many active metabolites and the therapeutic effect occurs similar as a same outcome of metabolites and original drugs and. This type of drugs are called as “limited” prodrugs like diazepam, carbamazepin). In few cases a prodrug is made up of two pharmacological active moieties that are coupled together with in a molecule and work as promoiety for each. These are known as codrugs. (Eg, sulfasalazine, sultamicillin, benorilate, levodopa-entacapone).

**Purpose behind Prodrug design:**

Main purpose of prodrug designing is to amend physicochemical properties like enhancing chemical, metabolic stability, to get organized delivery. Below are other purposes for drug design:

1. Overcome Pharmacokinetic Limitations of drug like absorption, poor solubility, rapid excretion
2. Overcome Pharmacodynamic Limitations like poor bioavailibilty, poor efficacy, side effects,

Purpose regarding improving bioavailability that is due to poor water solubility, low lipophilicity, bitter or unacceptable smell or taste, pain any irritation, chemical instability, poor penetration through biological membrane, slow absorption by parentral route, increased first pass metabolism, lack of specificity in tissues.



Fig. 1 Some Prodrugs

**Prodrug Advantages :**

Prodrugs with optimised pharmacokinetic and pharmacodynamic properties have following advantages:

1. Increased absorption from GIT

2. Avoids pain or irritation at injection site

3. Tissue/organ specific drug administration

4. Enhance passage through Blood Brain Barrier

5. Decrease side effects and toxicity profile.

6. Masks unpleasant tastes and odors.

7. More potent, safer and more convenient in administration.

**Prodrug Classification :**

Prodrugs are classified according to their chemical structure, mechanism of action and modified functional groups.

1. By chemical Structure
2. Conventional prodrugs : obtained from chemical derivatization, and objective is to optimize transport properties;

called as carrier-linked prodrugs. Some functional groups are added to improve absorption.

1. Bio precursors :these are precursor of a biochemical compound which after chemical reactions exerts their physiological role. Eg. Lovastatin, some vitamins B1,B6 on phosphorylation and oxidation (Vit D) acts as prodrugs.
2. Drug Delivery Systems : conjugates are formed here like polymers of drug conjugates. Drug is bind to a macromolecule that commends its transportation. In case of antibody conjugates, target delivery is carry out by antibodies.
3. By activation Mechanism
4. Enzymatic Activation : Drugs that faces enzyme activation can be planned; but problems can arise because of genetic polymorphism, biological variability between drug interaction potential, species.
5. Non- enzymatic Activation : drugs that faces non-enzymatic activation is unforced, but unsufficient chemical stability can leads to issues in conservation before use.

Activation mechanism of classification is built on the reactions that results in active form, like hydrolysis (imide, ether ester, amide, etc.); reduction, oxidation; and other reactions.

1. By Cellular sites of coversion
2. Intracellular or type I : bioactivation location is therapeutic action site eg. Statins, Antiviral phosphorylated nucleoside.
3. Extracellular or type II: where no bioactivation occurs in digestive fluids or the systemic circulation. Eg. fosamprenavir, valganciclovir, and virus-directed enzyme, antibody-, gene prodrugs.

 This new classification might help in getting drug product’s safety, efficacy and pharmacokinetics,.

**Bioavailability** **Optimization**

In most cases prodrug synthesis purpose is increasing bioavailability. Drug physicochemical parameters like solubility, good permeability, adequate lipophilicity, are important aspects in drug development that are strongly effected by acid-base properties of the molecules.

**Prodrugs with improved lipophilicity**

Presence of carboxyl functional group in many medications serve as necessary functional group for their pharmacological property. But, its existance also causes higher polarity in case of oral administration, as in small intestine at pH 5-7, much ionization occurs, which stops the transit of molecules from membranes through passive diffusion. Carboxyl groups esterification with aliphatic alcohol of short or long chain are majorly used methods.

Ethyl ester prodrugs are ACE inhibitors (enalapril, benazepril, trandolapril, quinapril) Fig 2. Ethyl esters as a result increases lipophilicity, and thus enhance absorption. Methyl esters occurs more rarely, as on hydrolysis methyl alcohols (toxic) are released. Hence this method of prodrugs designing is rarely used in case of low dose medicines, only and in esters case with very short duration of action. Various ester prodrugs are made for levodopa, but only methyl esters are available in therapy (Levomet) (Fig 3).



Fig. 2. Ester prodrug Examples



Fig 3. Esterification of Levomet

Some compounds are available where the methyl esters are not available as prodrug, and the ester functional group is necessary for pharmacological effect, whereas free acid have no therapeutic effect. Chemical or metabolic hydrolysis of methyl esters generally ocurs rapidly , that is why methyl esters shows short duration of action For e.g beta-blocker esmolol and cocaine with ultra-short effect.

Local corticosteroids (anti-inflammatory) has prodrugs clobetasol propionate, clobetasol butyrate, flumeta- sone pivalate), in these C21- OH or C17-OH group is changed to ester. Another example is Terbutaline,( a selective α2-agonist bronchodilator) dispensed in high dose orally; whereas its prodrug is bambuterol (di methylcarbamic acid ester of phenolic hydroxyl group) has increased lipophilicity and low hydrolysis rate converted by cholinesterase enzyme, given in 20 mg once daily because it is sufficient dose and has prolonged effect.

Classical antipsychotics group having depot acting preparations formed by esterification with fatty acids. Eg. prodrugs haloperidol decanoate, fluphenazine enanthate, and zuclopenthixol decanoate oily solutions has decreased the dose and now administered once or twice in a month. These ultra lipophilic esters deposited in fat stores later released slowly slowly and converted into the active form. Effect seen up to even 14-28 days, hence patient adherence is improved.

**Improved aqueous solubility Prodrugs**

Aqueous solubility can be enhanced by adding polar structures, hence enable oral or parentral administration. Polar groups may be non ionisable which easily degrades in the body. Eg NSAIDS- Sulfoxide derivatives. See Fig. 4



Fig. 4. Prodrugs with improved aqueous solubility

# Targeted drug delivery

Site-specific drug delivery is an efficacy criteria in some therapies, when site specific drugs are given to act on specific sites. This Prodrug synthesis is a considerable challenge in research industry. On behalf of research results we would like to highlight two ways of prodrug utilization that are tumor targeting and antigen targeting.

**Prodrugs in cancer therapy**

# Cancer chemotherapy will enhance the effectiveness if the active substances enters directly to targeted tumor cell without harming body cells. Hence target sites delivery with help of prodrugs is now a prime concern in drug research.

# Tumors can be made specific by using enzymes, transporters or development of prodrug-antibody which is selectively recognized by tumor cells. It is advantageous to administer drug orally.

# Eg. capectitabine , a 5-fluorouracil (5-FU) prodrug, it requires 3 enzymes cascade for the biotransformation to the active drug. Carboxyl esterase present in liver the first degradation takes place here, and lipophilic character (pentyl alcohol) is removed. Cytidine Deaminase present both in liver and tumor cells deaminate by selectively releasing 5-FU in the tumor cells by thymidine phosphorylase, this shows very high activity in tumor cells rather than in normal cells. Absorbtion of prodrug occurs fastly and completely almost from GIT and supplies high quantity of 5-FU in targeted tumor cells. Capecitabine administered orally in treatment of metastatic colon cancer and in treatment of other cancers in combination therapy (figure 5).



Fig. 5. Capecitabine metabolic conversion

# Conclusions

# A lot of prodrugs has been designed already to overcome delivery, formulation and toxicity barriers, however development of a prodrug might be very challenging. This prodrug strategy is a simple and easy method to improve the unpredictable properties of new drugs or drugs present in market already. Prodrug approach is constructive method to improve bioavailability of medicines.

Prodrug synthesis improves pharmacokinetic properties and new compounds can be obtained for oral or parenteral administration.

Obtaining target drug delivery in modern therapy is a great challenge in modern era, especially in cancer therapy, because research on the use of prodrugs at a large scale is conducted now a days.

In early stages of prodrug development chemical and pharmacological characterization must be taken carefully, because toxic active intermediaries can be find.

A limitation in prodrug development is that its synthesis is expensive and time taken.

Prodrug approach is one of the most promising approaches in drug development to improve therapeutic efficacy or to lessen the adverse effects of pharmacologically active ingredients by different mechanisms, like, stability, increased solubility, improved permeability and bioavailability, tissue-targeted delivery, and prolonged biological half-life time,.

Besides the extraordinary progress in field of prodrug design, there are more studies clearly needed, specially at early stages of the drug discovery to achieve the modern modern pharmacotherapy.

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