PRO-DRUG DEVELOPMENTS

Abstract

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 due to their advantageous physico-chemical properties (greater stability, improved solubility, increased permeability,) used in inactive form. Biological effect occurs by the active derivatives formed in organism through chemical transformation (biotransformation). 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, bioprecursors and targeted delivery systems

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I. INTRODUCTION

Development of prodrugs is one of efficacious methods of latest research work in the field of medical science that gained more importance in present therapy. 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 introduced the term drug latentiation means drugs that were specifically designed to require bioactivation.

IUPAC definition which states that: A prodrug is a compound that undergoes 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 carrier or promoiety but result 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 more active metabolites and the biological effect occurs similar as a same result of metabolites and original drugs and. This type of drugs are called as "limited" prodrugs (e.g. 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).

1. **Purpose behind prodrug design:** Main purpose of prodrug design is to amend physicochemical properties to enhance chemical or metabolic stability, to achieve organized delivery. Below are other purposes for drug design:
   - Overcome Pharmacokinetic Limitations of drug like absorption, poor solubility, rapid excretion
   - Overcome Pharmacodynamic Limitations like poor bioavailibilty, poor efficacy, side effects,

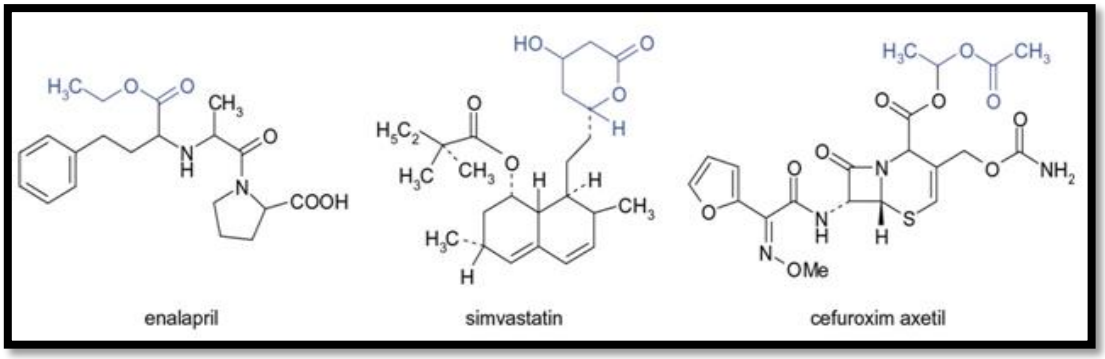

Figure 1: Some Prodrugs

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.

2. **Prodrug advantages :** Prodrugs with optimised pharmacokinetic and pharmacodynamic properties have following advantages:
   - Increased absorption from GIT
   - Avoids pain or irritation at injection site
   - Tissue/organ specific drug administration
   - Enhance passage through Blood Brain Barrier
   - Decrease side effects and toxicity profile.
   - Masks unpleasant tastes and odors.
   - More potent, safer and more convenient in administration.

3. **Prodrug classification:** Prodrugs are classified according to their chemical structure, mechanism of action and modified functional groups.
   - **By chemical Structure**
     - 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.
     - 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.
     - Drug Delivery Systems: conjugates are formed here like polymers of drug conjugates. Drug is bind to a macromolecule that commends its transport. In case of antibody conjugates, target delivery is performed by antibody.

   - **By activation mechanism**
     - **Enzymatic activation:** Drugs that faces enzymatic activation can be planned; but problems may arise due to genetic polymorphism, biological variability between drug interaction potential, species.
     - **Non- enzymatic activation**: drugs that faces non-enzymatic activation- it is unforced, but unsufficient chemical stability can leads to problems in conservation before use.
     - Activation mechanism of classification is based on the reactions that results in active form, like hydrolysis (imide, ether ester, amide, etc.); reduction, oxidation; and other reactions.

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

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

4. **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 which are strongly affected by acid-base properties of the molecules.

5. **Prodrugs with improved lipophilicity:** Presence of carboxyl functional group in many medications exists as must function for their pharmacological activity. But, its presence also causes too high polarity in case of oral administration, as in the small intestine at pH 5-7, much ionization occurs, which stops the passage of molecules through membranes by passive diffusion. Carboxyl groups esterification with short or long aliphatic alcohol majorly used method.

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

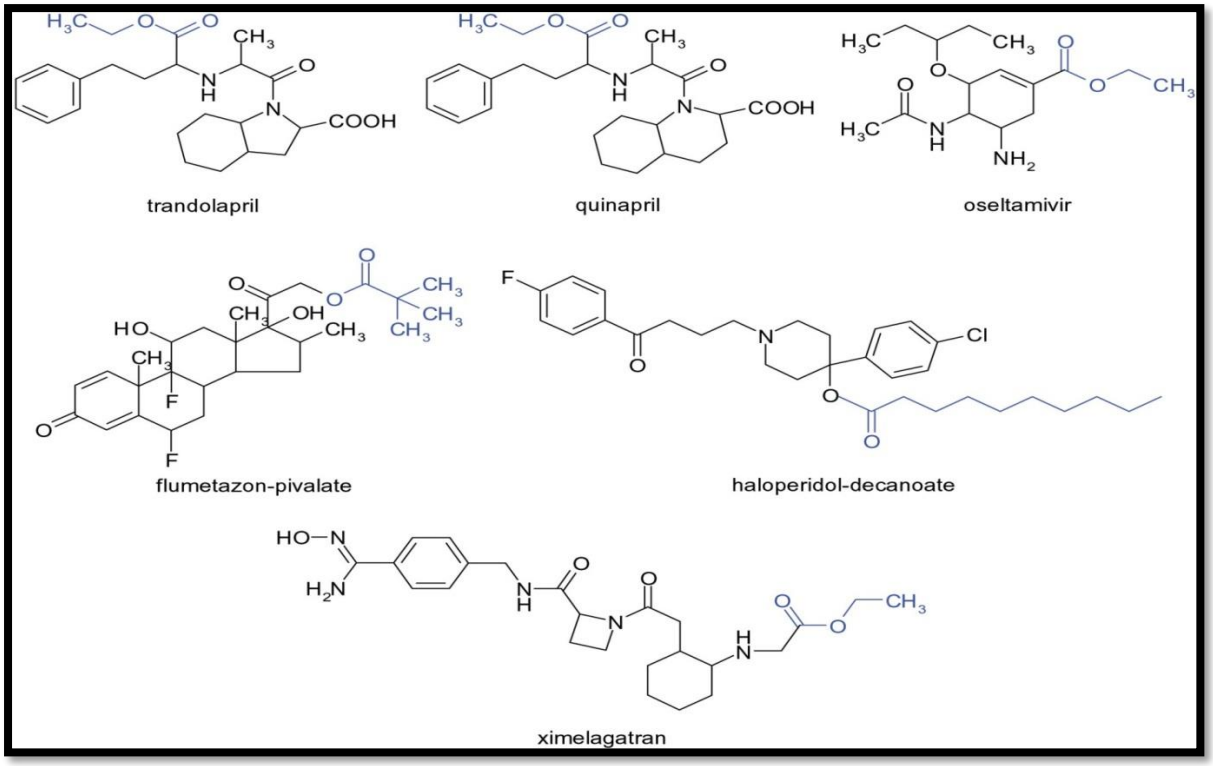

Figure 2: Ester Prodrug Examples

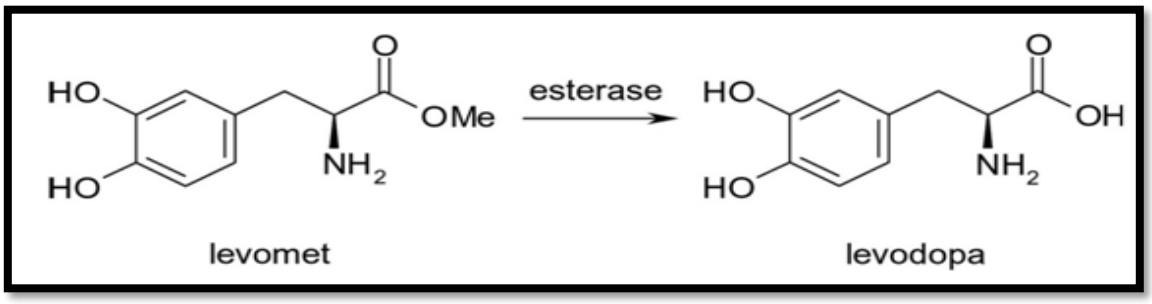

Figure 3: Esterification of Levomet

Some compounds are available where the methyl ester is not a prodrug, and the ester functional group is necessary for pharmacological effect. whereas free acid is without any therapeutic effect. Chemical or metabolic hydrolysis of methyl esters generally ocurs very fast, that is the reason methyl esters have short duration of action For e.g. cocaine or the beta-blocker esmolol with ultra-short effect.

Local anti-inflammatory corticosteroids series has prodrugs clobetasol propionate, clobetasol butyrate, flumeta- sone pivalate), in these C21- OH or C17- OH group is converted to ester. Another example is Terbutaline, a selective 2-agonist bronchodilator given in high doses orally; while its prodrug form is bambuterol (di- methyl-carbamic 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.

6. **Improved aqueous solubility prodrugs:** Aqueous solubility can be increased by adding polar structures, thus enable oral or parentral administration. Polar groups may be non ionisable which easily degrades in the body. Eg NSAIDS- Sulfoxide derivatives. See Fig. 4

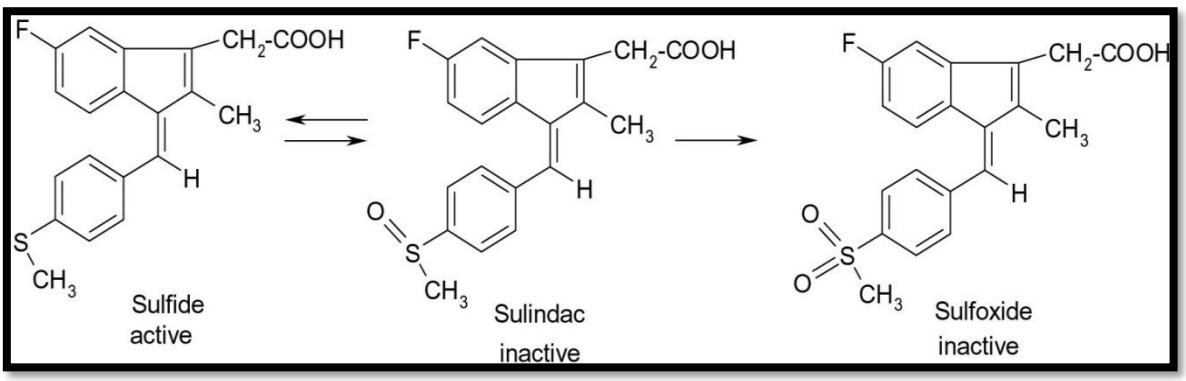

Figure 4: Prodrugs with Improved Aqueous Solubility

Targeted drug delivery: Site-specific drug delivery is efficacy criterion in some therapies, when site specific drugs are given to act on specific sites. This Prodrug synthesis is a great challenge in research industry. Based on research results we would like to emphasize two directions of utilization of prodrugs: tumor targeting and antigen targeting.

Prodrugs in cancer therapy: Cancer chemotherapy would increase the effectiveness if the active substance reach directly to the targeted tumor cell without damaging body cells. Hence target sites delivery with prodrugs is now a priority 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. capecitabine, Prodrug of 5-fluorouracil (5-FU), it requires 3 enzymes cascade for the bioconversion to the active drug. Carboxyl esterase present in liver the first degradation takes place here, and pentyl alcohol of lipophilic character, is eliminated. Cytidine Deaminase present both in liver and tumor cells deaminate by selective release of 5-FU in the tumor cells under the action of thymidine phosphorylase, which shows much higher activity in tumor cells than in normal cells. Absorbtion of prodrug occurs rapidly and almost completely from GIT and provides high concentration of 5-FU in targeted tumor cell. Capecitabine is used orally in treatment of metastatic colon cancer and in combination therapy inother types of cancer (figure 5).

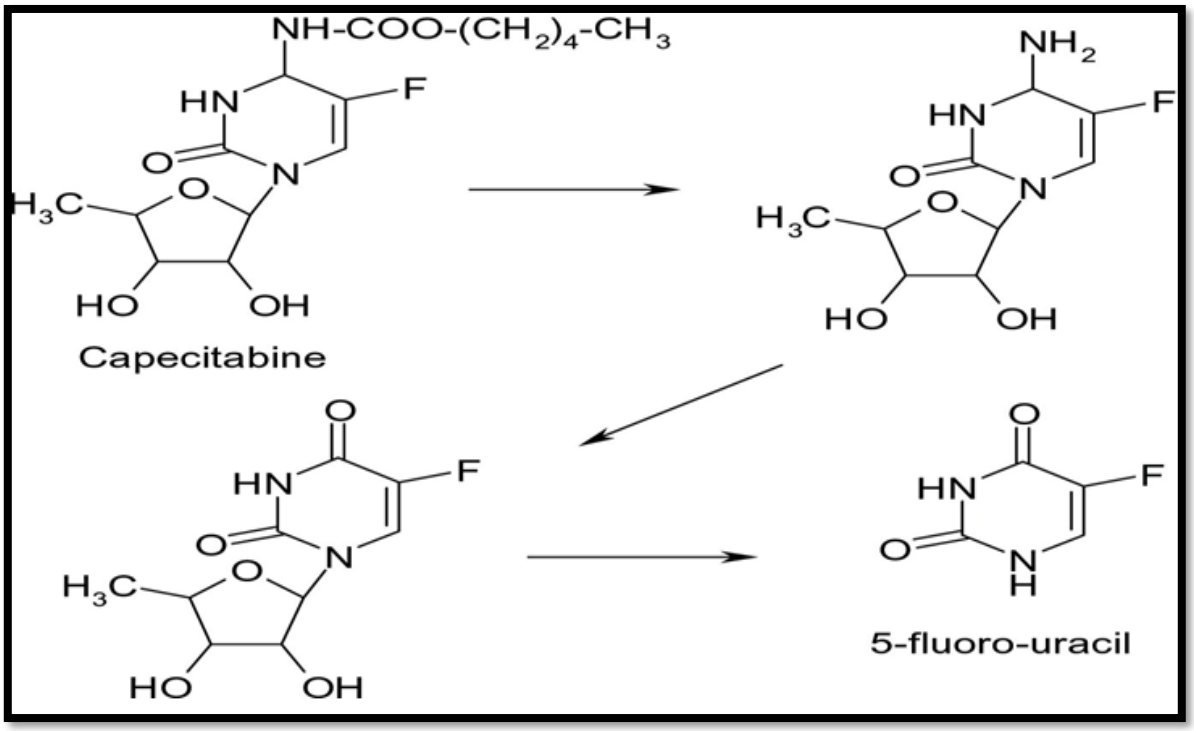

Figure 5: Capecitabine Metabolic Conversion

II. CONCLUSIONS

A lot of prodrugs have 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 way to improve the erratic properties of new drugs or drugs already present in market. Prodrug approach is an effective 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 extensive research on the use of prodrugs is conducted now a days.

In early stages of prodrug development full careful chemical and pharmacological charac- terization must be taken, because toxic active intermediaries may find.

A limitation in prodrug development is that it requires long and expensive syntheses. Prodrug approach is one of the most promising approaches in drug development to enhance the therapeutic efficacy or to reduce the adverse effects of the pharmacologically active agents via different mechanisms, including, stability, increased solubility, improved permeability and bioavailability, prolonged biological half-life time, and tissue-targeted delivery.

Despite the remarkable progress made in the field of prodrug design, more studies are clearly needed, especially at early stages of the drug discovery, for prodrugs to achieve the desired state of art and take their place in modern pharmacotherapy.

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