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Prodrugs : An approach to improve the effectiveness and properties of the drug

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Abstract : A clinically used drug may have limitations in practice because of undesirable side effects, poor solubility, poor bioavailability, short duration of action, first-pass effect, poor absorption & adverse effects. To overcome such undesirable properties, one of the approaches to convert the existing molecule to a more efficient molecule is prodrug design. Prodrug can be synthesized to impart desirable properties in it. Prodrugs are inert in nature but after administration they get activated through metabolic reactions invivo. The activated form then shows the pharmacological activity. Properties of a drug can be improved by selecting proper carrier moiety during its design.The design of mutual prodrug is very fruitful in the area of research & has given successful results in increasing the clinical & therapeutic effectiveness of the drugs.In present article such prodrugs prepared of drugs from various classes are discussed.

Key Words : drugs, undesirable properties. side effects, prodrug design,mutual prodrugs

Introduction : Every pharmaceutical drug exhibits undesirable effects in addition to desirable. These drugs are known for biological as well physicochemical properties. Drugs known to exhibit desirable as well as undesirable physicochemical and pharmacological properties. Medicinal chemists are taking great efforts to optimize these drugs either for improving pharmacological properties or physicochemical properties or both. Efforts are aimed either to eliminate undesirable properties or to reduce them. This is one way of improving therapeutic efficacy of drugs. Further a chemical moiety exhibiting required counterpart to fit with its therapeutic receptor may not be able to reach to the receptor because of undesirable physicochemical properties may be like poor solubility, chemical instability etc [1].

A Pharmacologically important drug may have inadequate deployment in clinical

practice because of the different inadequacy such as chloramphenicol because of poor solubility and bitter taste, ampicillin because of poor bioavailability, pilocarpine as consequence of short duration of action, epinephrine because of incomplete absorption, corticosteroids because of poor aqueous solubility, propranolol because of first pass effect. Some of the problems can be solved using a formulation development approach but in some cases, chemical modification in the molecule is necessary to correct the pharmacokinetic

parameters. A solid approach is required to convert such types of molecules into clinically acceptable drug candidates. One such approach is the prodrug approach [2].

The prodrug term was coined by Albert for the description of the compounds which undergo bio-transformation before they produce its clinical response [3]. Another scientist namely Harper called this process as latentiation of a drug, that is, chemical modification of a pharmacologically active compound to form a novel chemical entity which will liberate parent compound in-vivo after enzymatic cleavage. These prodrugs later were grouped into two classes that are carrier linked prodrugs and bio-precursor. The carrier linked prodrug possesses linking of the carrier group to the biological active molecule to form altered physicochemical properties followed by cleavage by means of enzymatic or non enzymatic means to regain active moiety. Carrier which links is also known as promoiety, become linked covalently to active molecule, essentially promoiety must be non toxic which will alter the physicochemical properties of the parent biologically active molecule.

Prodrugs are also considered as drug which known to contain dedicated safe shielding groups used in a short-lived manner for the alteration or elimination of disagreeable characteristics present in the parent drug molecule.Normally, biotransformation (metabolic transformation) is required for the conversion of prodrugs into the parent drug. This biotransformation is catalyzed by specific enzymes, generally hydrolyses. This biotransformation is so designed to occur in the target organ to avoid the undesirable side effects which would occur at target receptors [3].

Objectives of prodrug approach In drug discovery and development processes, the prodrug approach is known to exhibits large number of significance as it allows different, biological and / or physicochemical objectives need to be fulfilled. These include solubility, cellular permeation, stability against enzymes, chemical stability, oral bioavailability, penetration through blood brain barrier penetration or toxicity [4-8].

Few other objectives of prodrug research are as follows;

Pharmaceutical Objectives (PH) :

- ❖ To improve water solubility of drug
- ❖ To make drug chemically stable
- ❖ To improve organoleptic properties of the drug
- ❖ To decrease local irritation and pain sensation of the drug

Pharmacokinetic objectives (PK):

- ❖ To improve absorption of the drug
- ❖ To modulate metabolic fate of the drug
- ❖ To improve time profile of drug
- ❖ To make selective tissue or cell delivery of drug

Pharmacodynamic objectives (PD)

- ❖ To decrease the toxicity of the drug

❖ Activation to reactive agent

Key objectives of prodrug approach are 1) Improving water solubility,

2) Improving membrane permeability,

3) Improving absorption

4) Targeted release

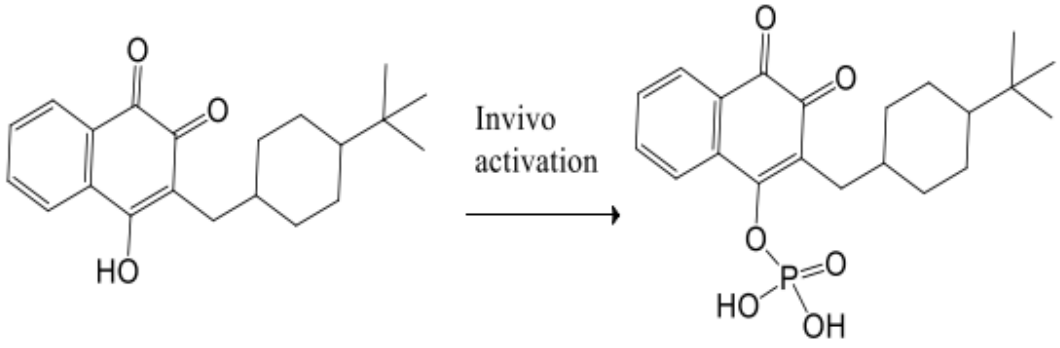
5) Reducing undesired effect and optimizing metabolism.

Improving water solubility

For improving water solubility general approach involve incorporation of some ionizable groups such as hemisuccinate, phosphate or amino ester etc. Number of prodrugs are reported to be prepared for poorly water-soluble drug by incorporating phosphate directly or via linker for intravenous administration or oral administration of drugs [9].

Thus, phosphate or phosphate-derived prodrugs, either directly attached to a molecule or incorporated via linkers, have been used to successfully enhance the water solubility of a range of compounds administered by either intravenous or oral routes. Buparvaquone is a is known to be less active in vivo as compared to in vitro activity against infection of Leishmania donovani. Factor which account for this is high lipophilicity and poor water solubility as a result bioavailability of drug become lower. So Mäntylä et al., [3] attempted synthesis of phosphate prodrugs of this drug Buparvaquone by incorporating phosphate moiety on the hydroxyl group.

Resultant phosphate prodrug has been known for improved water solubility

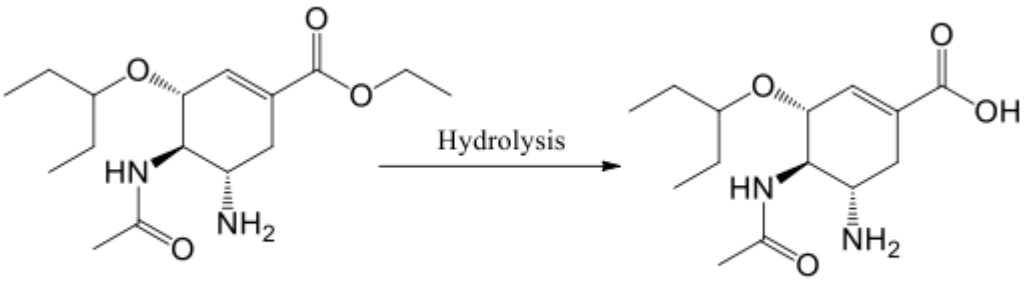


Buparvaquone

Phosphate prodrug

Improving absorption and membrane permeability In order to cross cell membrane drug must be sufficiently lipophilic in nature. Polar functional present in drug becomes obstacle in crossing cell membrane absorption and are sometimes important for receptor binding . common example of such type of group is carboxylic acid. So carboxylic acid can be modified in to form ester which will help in crossing the membrane and become hydrolyzed as well to form parent carboxyl group. Numerous prodrugs having ester group have been synthesized for masking phosphate, phenolic, carboxylate and alcoholic groups [11].

For example compound RO-64-0802,is highly active against type A and B influenza in humans in vitro. But has known for poor bioavailability. Its ester derivative is known as Oseltamivir. This is called as now prodrug and it is well absorbed after taken orally and with enhanced bioavailability as compared to the parent drug

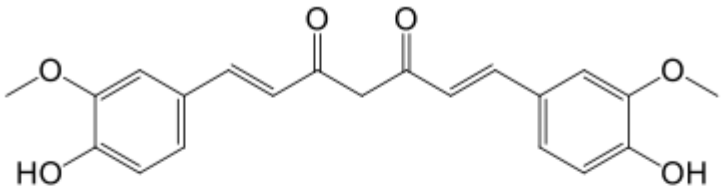


Oseltamavir
Prodrug

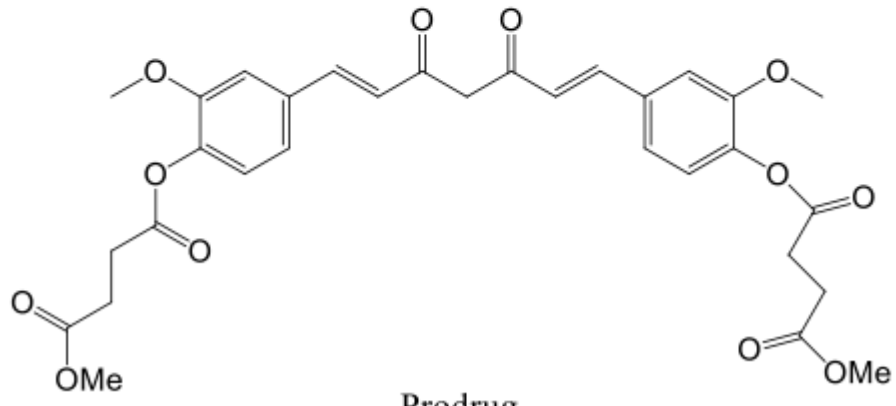
RO-64-0802

For reduction of side effects and metabolism Due to the presence of labile functional groups, many drugs undergo metabolism very fast and extensively. In some cases they may form toxic metabolites quickly and in some cases its potency becomes decreased.

For example curcumin is an important ingredient obtained from turmeric extract which is widely useful as an antimicrobial, antioxidant and anti-inflammatory agent. Further it lacks any reported toxicity. The main hurdle in use of curcumin is fast metabolism, low bioavailability and unstability in biological environment Rojsitthisak et al., attempted successful synthesis of its prodrug by modifying succinyl ester moieties and resultant compound showed anti colon cancer activity.



Curcumin



Prodrug

Classification of Prodrugs: There are different types of promoieties and depending up on nature of carrier or promoities linked properties of the drug molecule changes.. Wermuth, after surveying the literature, has classified the prodrugs as carrier-linked prodrugs & Bioprecursors.

A. Carrier linked prodrugs

According to the International Union of Pure And Applied Chemistry [IUPAC], a carrier-linked prodrug "is a prodrug that contains a momentary linking of a given active substance with a transient group named as carrier group which produces optimized pharmacokinetic or physicochemical characteristics and this carrier can be cleaved easily in vivo.

As per linkage between drug and transport substance, at least one chemical functional group of the drug molecule is engaged with the carrier molecule. The functional which is preferred is the amino or hydroxyl group for forming covalent bond. Functional group such as carbonyl group or carboxyl group can also be employed Carrier-linked prodrug activation may occur by enzymatic or non-enzymatic cleavage of the temporary bond between the carrier and the drug molecule, or by a sequential combination of both, i.e., an enzymatic step followed by a nonenzymatic cleavage.

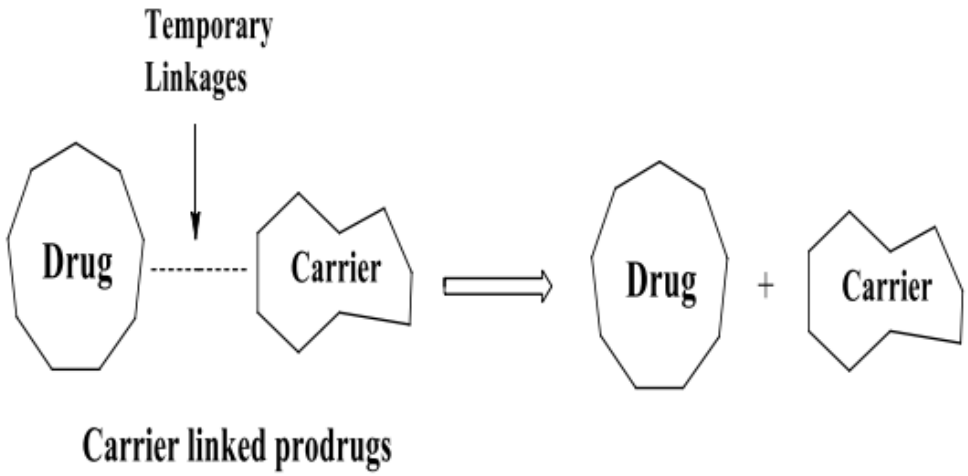


Fig.: Carrier linked prodrugs

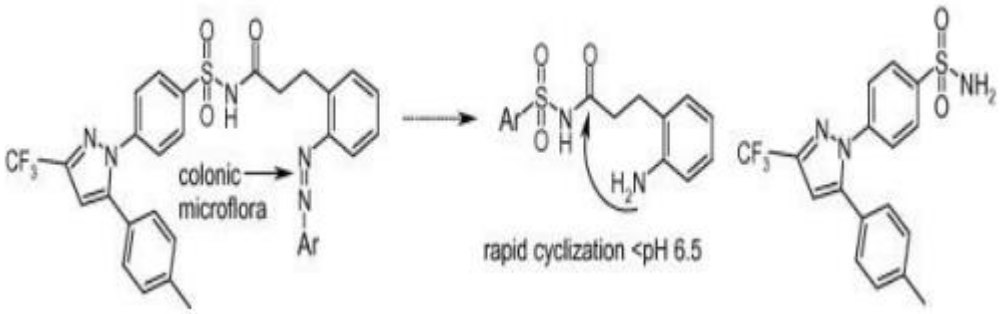
Ideally carrier linked prodrugs shall satisfy following characteristics

- ❖ Prodrug must be less active or inactive than the parent drug molecule.
- ❖ Both carrier molecule as well as prodrug must be inactive and non toxic
- ❖ The linkage between drug and carrier moiety shall be cleavable in vivo
- ❖ The generation of active form of drug molecule from its prodrug must follow rapid kinetics
- ❖ It ensures effective drug levels at the site of action

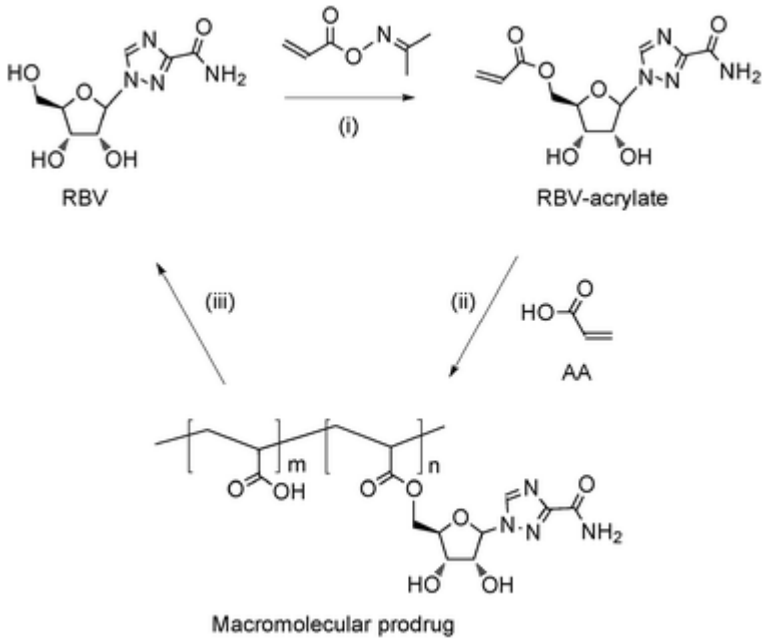
Carrier linked prodrugs consist of a carrier moiety attached to the drug through a metabolically labile linkage. This carrier moiety imparts some physicochemical properties to the resulting molecule based on its structure & properties. Carrier linked prodrugs are further classified into 3 types.

a) Double prodrug - Here prodrug is further converted to another molecule that can be easily converted to prodrug. When prodrug is further modified chemically, in manner that only enzymatic conversion to prodrug will occur before prodrug release active molecule. Double prodrug is also called as cascade-latentiated prodrugs or proprodrug.

Juan F.M. et.al., reported design , synthesis and targeted delivery of celecoxib an COX-II inhibitor drug. The double prodrug approach involves first activation by azoreductases followed by by cyclization triggering release of drug [12]



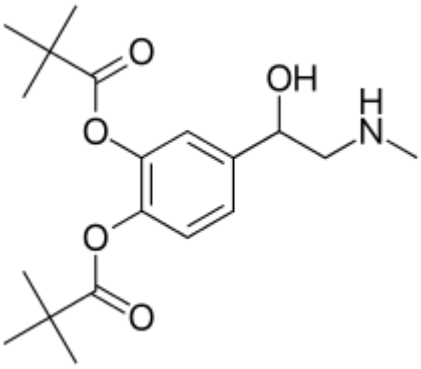
b) Macromolecular prodrug- In this case macromolecular such as polymers, dextrans, polysaccharides, proteins, cyclodextrins, and peptides are used as carrier or pro moieties. For example Ribavirin acrylate which combats side effects and toxicity of ribavirin without loss of activity.



c) Site-specific prodrugs - In this type promoiety acts as a carrier to a specific site.

Drug is actively transported to the site of action and there it is released. After release the drug is rapidly acting on its receptors due to which site specific action is achieved.

For example Dipivefrine, a prodrug of epinephrine, is useful to reduce intraocular pressure due to its high lipophilicity. Dipivefrine penetrates the cornea and is then hydrolysed to epinephrine by esterase enzymes. It is used in the form of 0.1 % eye drops in treatment of open angle glaucoma.



Dipivefrine

B. Mutual prodrugs - Here carrier moiety is not inert but is having some useful activity that is supportive to the activity of drug molecule.In the case of mutual prodrugs, carrier molecule is also a drug. Here two drugs are made to link with one another covalently. Among the two, drug which is a carrier is expected to optimize physicochemical properties of the other drug.

So in the case of mutual prodrugs, two medicinally important drugs are made to link covalently with each other. Carrier drug may exhibit similar biological action as that of parent drug or parent drug and carrier drug may have different pharmacological action. When both carrier and parent drug exhibits similar biological action, they might be produce synergistic response. Whereas, if carrier drug and parent do differ in their pharmacological action, we expect additional medicinal benefit in such case [13].

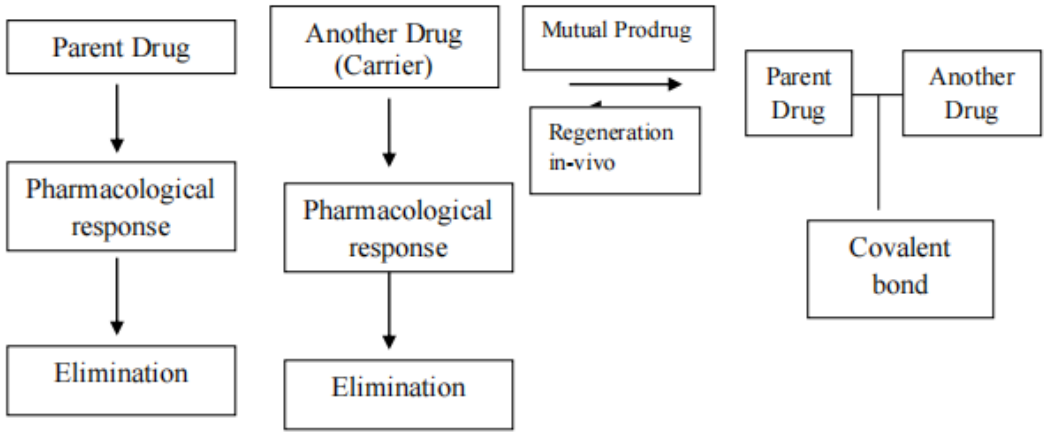


Fig.: Schematic representation of mutual prodrugs

Carrier drug may also help in making parent drug target to its respective target or cells or may help in improving site specificity of drug. Sometimes carrier drug may be used to overcome undesired effects of the parent drug [10]

Significance of mutual prodrugs

Purpose of mutual prodrug is similar to the general drug discovery process, in which a unique of its kind compound is designed to possess desirable pharmacological effects. The key objectives of mutual prodrug are as follows;

❖ To optimize therapeutic usefulness of those agents which exhibits undesirable

characteristics which limits their medicinal usefulness

❖ To make target specific delivery of drugs

❖ To minimize metabolism related issues

❖ To minimize toxicity of the drugs

❖ Mutual prodrug approach is useful when two synergistic drugs need to be administered at the same site simultaneously.

Mutual Prodrug synthesis includes some important factors such as therapeutic combinations of candidate drugs and probable linkage between drugs that may form the basis of selection criteria for mutual prodrug synthesis. The significant parameters which are to be considered before the synthesis of mutual prodrug are summarized below:[4]

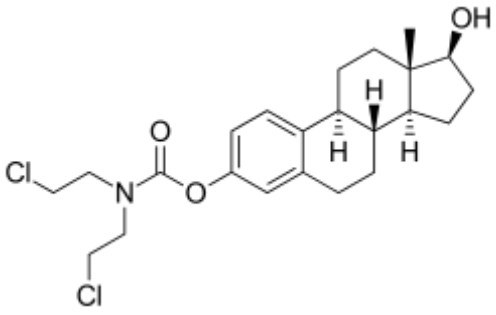
i) The candidate drugs selected for mutual prodrug synthesis can be from one therapeutic category or different therapeutic categories. Similarly, the constituent drugs of a mutual prodrug can act on the same biological target with a similar mechanism of action or act on different biological targets with different mechanisms of action.

ii) The candidates for making mutual prodrugs can be the pairs of drugs that are currently used in combination therapy (including those combination studies at the investigational stage) in various therapeutic areas provided each of those drugs

possesses the requisite functional group(s). There are several therapeutic areas where such combination therapy is applied routinely and successfully.

iii) The linkage between the first and second components should be cleavable. For example, the linkage may be hydrolyzable and/or maybe enzymatically cleavable. Preferably, the linkage should be cleavable under physiological conditions, such as those present in a mammalian body, particularly a human body.[2]

For example Estramustine which is a prodrug of estradiol with normustine. It is used to treat prostate cancer. It breaks down to estradiol and anticancer agent normustine in vivo and both of them are useful in controlling cell growth in prostate cancer. Estrogen level increases and controls cell growth in the prostate and normustine acts as alkylating agent to kill the cancer cells.



Estramustine

Table 1 : Mutual prodrugs example of few therapeutic classes

Sr no.	Therapeutic Area	Mutual prodrug	Objective
01	Antituburcular Drugs	Mutual prodrugs of	To eliminate the problem

		isoniazid, *p*-amino salicylic acid and ethambutol	of fast metabolism toxicity and local irritation and reduction of therapeutic doses.
02	Anti Viral Agents	Mutual prodrugs of 2', 3'-dideoxyinosine with 3- octadecyloxy propane-1, 2-diol.	To show different synergistic effect mechanisms and to release the parent drugs at desired site of action
03	Cardiovascular agents	Mutual prodrugs of Amlodipine and Atorvastatin.	For the treatment of arthrosclerosis, angina pectoris, combined hypertension and hyperlipidaemia and the management of cardiac risk.
04	Antipsychotics	Mutual prodrug ester of GABA and perphenazine.	To minimize the extrapyramidal effects
05	Antiinflammatory Drugs (NSAIDS)	Indomethacin–flavonoid Mutual prodrug	For Reduction of Gastrointestinal side effects and ulcerogenicity of NSAIDs
06	Anticancer	5-Fluorouracil / Cytarabine Mutual Prodrugs.	To show synergistic effect therefore help in reduction of dose dose as well as toxicity
07	Anticancer	Mutual prodrugs All *trans*-Retinoic Acid and histone Deacetylase Inhibitors	To show differential antiproliferative potencies in both MDA-MB-231 and PC-3 cell lines

08	Pulmonary Inflammation and Bronchoconstriction	Mutual Prodrugs of Anti-Inflammatory Signal Transduction Modulators (AISTM's)	For producing synergistic effects with different mechanism of action in the treatment of Pulmonary inflammation
09	Non–steroidal Antiinflammatory Drugs (NSAIDS)	Naproxen propyphenazone mutual prodrugs	For Reduction of Gastro intestinal side effects and ulcerogenicity of NSAIDs
10	Non–steroidal Antiinflammatory Drugs (NSAIDS)	Glucosamine conjugate prodrug of NSAIDs.	To show additional antiarthritc activity

Bio-precursor prodrugs These are known to produce effect after in vivo chemical derivatization or modification the inactive form. Bioprecursor prodrugs bank on either reductive or oxidative activation chemical reactions un-like hydrolytic activation which occurs in the carrier-linked prodrugs. For example Acyclovir, Flurouracil, Cyclophosphamide

C. Depending on how the human body makes biotransformation prodrugs can be of two kinds known as Type I prodrugs and Type II prodrugs [14].

Type I prodrugs:

Prodrugs which become bioactivated intracellularly that is inside the cells are called as type I prodrugs. Examples of Type I prodrugs is lipid lowering drugs statins and antiviral agents which are nucleoside analogues which must be phosphorylated

Type II prodrugs

Prodrugs which become bioactivated extracellularly that is outside the cells are called as type II prodrugs. Type II kinds of prodrugs do become bioactivated generally in fluids of the digestive system or circulatory systems, mainly blood.

Examples of Type II prodrugs include few antibodies and salicine.

Both of these types can be further subdivided depending on the fact that the intracellular location of bioactivation is also the receptor for therapeutic activation or the whether or not biotransorformation or bioactivation do produce in gastrointestinal fluids or in blood [15].

Table 2 Examples of prodrugs

Bioactivation site	**Subtype**	**Location of bioactivation**	**Examples**

		(tissues)	
Type I	Type IA	Therapeutic target tissues/cells	Acyclovir,Flurouracil, Cyclophosphamide
Type I	Type IB	Metabolic tissues (liver, GI mucosal cell, lung etc.)	Codiene, Captopril, Phenacetin
Type II	Type IIA	GI fluids	Sulphasalazine, Loperamide oxide
Type II	Type IIB	Systemic circulation and other extracellular fluid compartments	Chloramphenicol Succinate, Bacampicillin

Recent prodrugs

Roughly ten percent of all the marketed pharmaceutical drugs across the globe can be considered as prodrugs. Since 2007, as a minimum thirty prodrugs have been agreed by the FDA. About 07 prodrugs in the year 2015 were approved and in the year 2017 about 06 prodrugs were approved. Recently approved prodrugs are known to include aripiprazole lauroxil, dabigatran etexilate , benzhydrocodone, , sofosbuvir, tedizolid, selexipag, phosphate, isavuconazonium and gabapentin enacarbil [14-16].

Sr. Name of prodrug	**Year of approval**
1. Benzhydrocodone	2018
2. Latanoprostene bunod	2017
3. Selexipag	2015
4. Aripiprazole lauroxil	2015
5. Sofosbuvir	2015
6. Gabapentin	2011
7. Dabigatran etexilate	2010

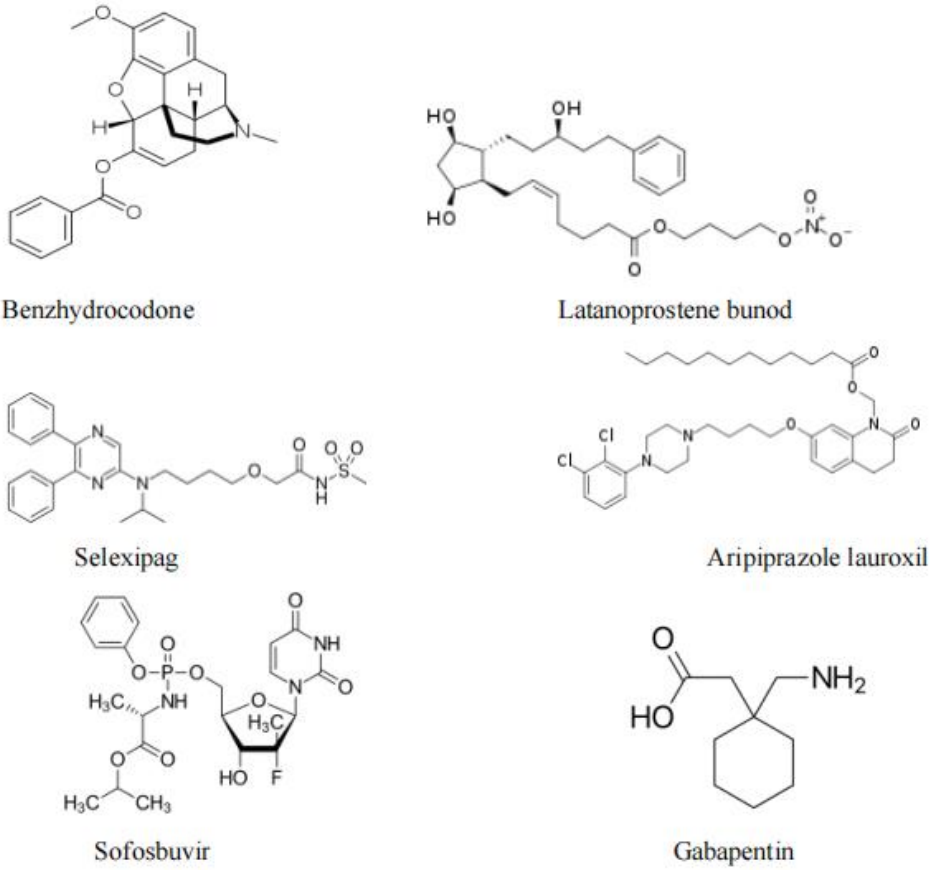


Fig. : Structures of few recently approved prodrugs

Mechanism of activation of prodrugs

The prodrug is transformed into the respective components, that is active drugs inside the body by enzymatic and/or non-enzymatic reactions [16].

***In vivo* metabolic activations of prodrugs**

A) Reductive Activation

- ❖ Nitro Reduction
- ❖ Bioreductive Alkylation
- ❖ Sulfoxide Reduction
- ❖ Azo- Reduction
- ❖ Disulfide Reduction

B) Oxidative Activation

- ❖ N-Oxidation
- ❖ *N*- and *O*-Dealkylation
- ❖ Epoxidation
- ❖ Oxidative Deamination

C) Decarboxylation activation

D) Hydrolysis of linkage between carrier and parent drug is also one of the mechanisms for prodrug activation.

2) Intramolecular activation:

Active Drug as the cyclic product of intramolecular activation is one of the important approach proposed to explain the activation of some prodrugs. This approach found application in explaining the release the parent drugs from carbamate mutual prodrugs in aqueous buffer (pH 6-11) and plasma (pH 7.4) through intramolecular reactions due to a hydroxyl nucleophile.

Limitations and drawbacks :

At the pharmacological level, prodrugs cannot be submitted to preliminary in vitro screening tests like binding studies, reuptake of neurotransmitter and enzyme inhibition measurement because bioactivation to their active species is necessary.[17] At the toxicological level,even though prodrugs are derived from well-known active principles, they have to be regarded as new entities. In a review by Gorrod, he has cited certain toxicity mechanisms like formation of toxic metabolite of total prodrug which is not produced by the parent drug, consumption of vital constituent during prodrug activation process, generation of a toxic derivative from a supposedly inert transport moiety, release of a pharmacokinetic modifier which may cause enzyme induction or alter drug excretion. The pharmacokinetic studies may lead to numerous misinterpretations. When a prodrug and parent molecule are being compared, onemust take into account the differences in their respective time courses of action. The maximum activity may appear later for prodrug than for parent compound, so area under the curve should be compared as it presents a better criterion for comparison. At the clinical stage, the predictive value of animal experiments is also questionable. The active doses of two prodrugs of the same parent drug may appear to be the same in rats but may be quite different in clinical investigations.[17]

Conclusion :

The introduction of prodrug in human therapy has given successful results in overcoming undesirable properties like absorption, nonspecificity, poor bioavailability and GIT toxicity. Prodrug design is really important in drug discovery process, in which a unique substance is observed to have desirable pharmacological effects, and studies of its properties lead to the design of better drugs. The review of prodrugs suggests that the gain in therapeutic benefit from such an approach may either be modest or marked. For well-accepted and useful drugs with minor undesirable properties, which can be improved through prodrug design. On the other hand, for the active compounds that suffer from severe limitations, like lack of site specificity, poor bioavailability or lack of particular activity, prodrug design leads to a marked therapeutic gain. Thus, the prodrug approach offers a very important area of research and an efficient tool for improving the clinical and therapeutic effectiveness of a drug that is suffering from some undesirable properties hindering its clinical usefulness otherwise.

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