INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Review Article

PRODRUG DESIGN: AN OVERVIEW

Supriya Shirke*, Sheetal Shewale and Manik Satpute

Department of Pharmaceutics, Satara College of Pharmacy Satara, Maharashtra, India.

ABSTRACT

The poor drug properties such as solubility, permeability, stability, toxicity, drug targeting are serious challenges for the successful development and commercialization of drug molecules and this is major reason only one out of ten clinically studied drug molecule reach to the market. Prodrug design is fruitful approach for drug targeting by changing the physiochemical, biopharmaceutical or pharmacokinetic properties.Prodrugs, are therapeutic active chemical agent, which must undergo transformation *in vivo* to release the active drug. About 10-14% drug approved worldwide can be classified as prodrugs. The present article takes a review of introduction, basic functional groups that are amenable to prodrugdesign, major applications of the prodrug strategy.

Keywords: Prodrug, Pharmacokinetic, solubility, stability.

INTRODUCTION

The potency, safety and financial investment of chemical entities are important issues for development of new drug molecules. The therapeutic efficacy can be improved by overcoming the undesirable properties while retaining the desirable ones[1,2]. This can be achieved through biological, physical or chemical ways.The biological approach is to alter the route of administration which may or may not be acceptable to patient. The physical approach is to modify the design of dosage form such as controlled drug delivery of drug. The third and the best approach in enhancing drug selectivity while minimizing toxicity, is the chemical approach for design of prodrugs.

Prodrugs may offer a way to overcome the poor druglike properties and provide the opportunity to convert a nondevelopablemolecule into a potentcandidate for clinical use[3]. The term prodrug was first introduced by albert -1958 to describing, any compound that undergoes biotransformation prior to exhibiting its pharmacological effects. Harper referred to this process as drug latentiatin that is chemical modification of a biologically active compound to form a new compound that, upon in vivo enzymatic attack will liberate the parent compound[4] (Fig. 1) Prodrugs have become an established concept and a powerful tool in optimizing the pharmacologically potent structures and overcoming physicochemical, pharmaceutical and biopharmaceutical barriers to a drug's usefulness.

➢ **Barrier related to physicochemical properties of drug**

1. Poor aqueous solubility – which being prevent the drug from administrated in the form injectables.
2. Low lipophilicity- which limits the design lipid bond formulation.
3. Chemical instability- which prevent the drug to incorporate into adequate forms.

➢ **Barrier in the pharmacokinetic phase**

1. Incomplete absorption across biological membrane such as GIT mucosa & BBB.
2. Low & variable bioavailability due to extensive First pass effect.
3. Too rapid absorption or excretion when longer duration of the action is desired.
4. Lack of site specificity.

The properties of the prodrug enable it to cross the limiting barrier and it is designed ideally to be cleaved efficiently by enzymatic or non-enzymatic processes. This is followed by rapid elimination of the released pro-moiety.

Objectives of prodrug design[5]

The main objectives of a prodrug designing are

- To bring active drugs to their respective active sites.
- To provide the desired pharmacological effects while minimizing adverse metabolic and/or toxicological events.
- To improve the clinical and therapeutic effectiveness of those drugs which suffer from some undesirable properties that otherwise hinder their clinical usefulness.
- To avoid the practice of clinically co-administering two drugs in order to enhance pharmacological activity or prevent clinical side effects. Simultaneous administration does not guarantee equivalent absorption or transportation to site of action. So, mutual prodrug concept is useful when two synergistic drugs need to be administered at the same site at the same time. Mutual prodrugs are synthesized toward a pharmacological objective improving each drug's efficacy, optimizing delivery, and lowering toxicity.

Classification of prodrugs[6,7]

Depending upon constitution of the constitution lipophilicity method of bioactivationand catalyst involved; they are classified in two groups.

A. carrier – linked prodrugs
B. Bio precursor prodrug

1. Carrier linked prodrug

- They are one where the active drug is covalently linked to an inert carrier. They are 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.
- E.g. Ditrimethylethanoate groups of dipivaloyladrenaline hydrolyse to original-OH groups on adrenalin in presence of esterase enzyme.

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 depending upon the nature of carrirer used the Classification: carrier- linked prodrug may further be classified into

2. Double prodrugs pro-prodrugs or cascade-latentiated prodrug

where a prodrug is futherderivatized in a fashion such that only enzymatic conversion to prodrug is possible before the latter can cleave to release the active drug.

3. Macromolecular prodrugs

where macromolecules like polysaccharides, dextrans, cyclodextrins, proteins, peptides and polymers are used as carriers.

4. Site- specific prodrugs

where a carrier acts as a transporter of the active drug to a specific targeted site.

5. Mutual prodrug

where the carrier used is another biologically active drug instead of some inert molecule. A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts 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. The carrier may also be a drug that might help to target the parent drug to a specific site or organ or cells or may improve site specificity of a drug. The carrier drug may be used to overcome some side effects of the parents drugs as well.

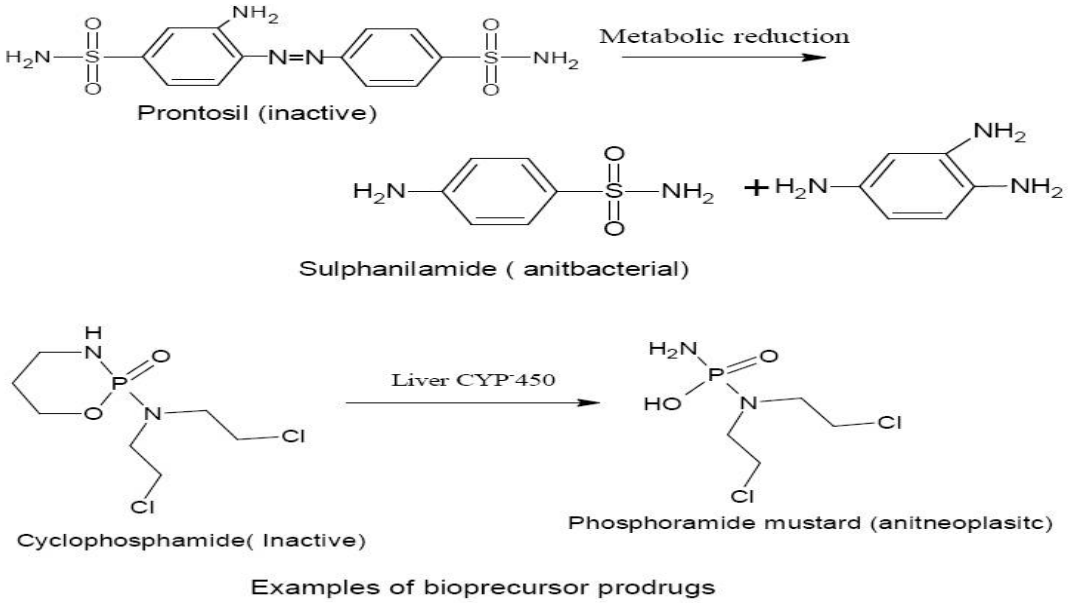
Advantages

- Increased absorption
- Injection site pain relief
- Elimination of unpleasant taste
- Decreased toxicity
- Decreased metabolic inactivation
- Increased chemical stability

2. Bioprecursor/Metabolic precursor

This prodrug does not contain carriers but ready up on metabolism to induce the necessary functionally active species.

Bioprecursor prodrugs rely on oxidative or reductive activation reactions unlike the hydrolytic activation of carrier-linked prodrugs. They metabolized into a new compound that may itself be active or further metabolized to an active metabolite (e.g. amine to aldehyde to carboxylic acid).



Examples of bioprecursor prodrugs

Significance of prodrug design

Therapeutically significant drug may have Limited Utilization in clinical practice because of poor organoleptic properties, poor bioavailability, short duration of action, nonspecificity, incomplete absorption, poor aqueous solubility, high first- pass metabolism or other adverse effects. There is a great emphasis on research to discover methods aimed at improving their therapeutic efficacy by minimizing or eliminating this undesirable properties.

Sometimes, an adequate pharmaceutical formulation can overcome these drawbacks, but often the galenic formulation is inoperant and a chemical modification of active molecule is necessary to correct its pharmacokinetics to convert an interesting active molecule into a clinically acceptable drug, insufficiencies.

This chemical formulation process, is often called Prodrug design, mutual prodrug is a type of carrier- linked prodrug, where the carrier used is another biologically active drug instead of some inert molecule. A mutual prodrug consists of twopharmacologically active agents coupled together so that each acts as a promoiety for the other agent and vice versa.

Mutual prodrug design is really no different from the general 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.

It is a very fruitful area of research, and its introduction in human therapy has given successful results in improving the clinical and therapeutic effectiveness of drugs suffering from some undesirable properties that otherwise hinder their clinical usefulness.

Functional groups amenable to prodrug design[8,9]

Ideally, the design of an appropriate prodrug structure should be considered at the early stages of preclinical development, bearing in mind that prodrugs might alter the tissue distribution, efficacy and the toxicity of the parent drug. Several important factors should be carefully examined when designing a prodrug structure, including

- **Parent drug**

Which functional groups are amenable to chemical prodrugderivatization.

- **Promoiety**

This should ideally be safe and rapidly excreted from the body. The choice of promoiety should be considered with respect to the disease state, dose and the duration of therapy.

- **Parent and prodrug**

The absorption, distribution, metabolism, excretion (ADME) and pharmacokinetic properties need to be comprehensively understood.

Some of the most common functional groups that are amenable to prodrug design include carboxylic, hydroxyl, amine, phosphate/phosphonate and carbonyl groups. Prodrugs typically produced via the modification of these groups include esters, carbonates, carbamates, amides, phosphates and oximes.

However, other uncommon functional groups have also been investigated as potentially useful structures in prodrug design. For example, thiols react in a similar manner to alcohols and can be derivatized to thioethers and thioesters. Amines may be derivatized into imines and N‑Mannichbases (Fig.2).

1. Esters as prodrugs of carboxyl, hydroxyl and thiol functionalities

Esters are the most common prodrugs used, and it is estimated that approximately 49% of all marketed prodrugs are activated by enzymatic hydrolysis. Ester prodrugs are most often used to enhance the lipophilicity, and thus the passive membrane permeability, of water soluble drugs by masking charged groups such as carboxylic acids and phosphates. The synthesis of an ester prodrug is often straightforward. Once in the body, the ester bond is readily hydrolysed by ubiquitous esterases found in the blood, liver and other organs and tissues, including carboxyl esterases, acetylcholinesterases, butyrylcholinesterases, paraoxonases and arylesterases.

2. Carbonates and carbamates as prodrugs of carboxyl, hydroxyl or amine functionalities

Carbonates and carbamates differ from esters by the presence of an oxygen or nitrogen on both sides of the carbonyl carbon. They are often enzymatically more stable than the corresponding esters but are more susceptible to hydrolysis than amides. Carbonates are derivatives of carboxylic acids and alcohols, and carbamates are carboxylic acid and amine derivatives. The bioconversion of many carbonate and carbamateprodrugs requires esterases for the formation of the parent drug.

3. Amides as prodrugs of carboxylic acids and amines

Amides are derivatives of amine and carboxyl functionalities of a molecule. In prodrug design, amides have been used only to a limited extent owing to their relatively high enzymatic stability *in vivo*. An amide bond is usually hydrolyzed by ubiquitous carboxylesterases, peptidases or proteases. Amides are often designed for enhanced oral absorption by synthesizing substrates of specific intestinal uptake transporters.

4. Oximes as derivatives of ketones, amidines and guanidines

Oximes (for example, ketoximes, amidoximes and guanidoximes) are derivatives of ketones, amidines and guanidines, thus providing an opportunity to modify molecules that lack hydroxyl, amine or carboxyl functionalities. Oximes are hydrolyzed by the versatile microsomal cytochrome P450 (CYP450) enzymes, better known as xenobiotic metabolizing enzymes. Oximes, especially strongly basic amidines and guanidoximes, can be used to enhance the membrane permeability and absorption of a parent drug.

PRODRUG INCORPORATED DELIVERY SYSTEM[10,11]

The colloidal drug delivery system works as a controlled and sustained delivery by releasing the encapsulated drug while in circulation or after the recognition by cell, so it is necessary that the delivery system must contain miximum quantity of drug for optimum efficacy. The encapsulation depends upon the physicochemical properties which can suitably modified by linking with promoiety and altering as prodrug

Liposome

Liposomes are consisted of lipid (mainly phospholipids) bilayer in which between lipid bilayer intervening water molecules are present. The drug is incorporated into either aqueous compartment or in the lipid bilayer as the drug has its physicochemical property. The less hydrophobic drug exhibit low entrapment efficiency and making them more hydrophobic by derivative of fatty acids, improves the entrapment efficiency of delivery system e.g. the tramcinolone 21 palmitate (prodrug) showed 85% entrapment efficiency as compared to triamcinolone acetonite which has 5% entrapment efficiency.

Liporotein

Lipoprotein are endogenous transporter of lipids in the circulation, they are nonimmunogenic escapes recognition by reticuloendothelial system. Their structural component are Neo HDL particles consisting of nonpolar triglyceride core surrounded by phospholipids monolayer in which specific apoprotein are imbedded. Since apoprotein are necessary for the recognition of L.D.L. so drug should be into the lipid moiety but most of the drug has not sufficient lipophilic so there is need to prepare lipophilic prodrug.

Emulsion

The oil in water emulsion are used as sustained drug delivery, by passing targeted to macrophages and active targeting by ligand attachment, so in this case the lipophlicity of the drug is necessary to make as oil in water

emulsion as sustained delivery system e.g. Esterified phenolic 4 hydroxy derivative of etoposide is used as lipophilic prodrug which is soluble in lipid emulsion in which cholesteryl ester oil used as oil component.

Soild Lipid Nanoparticle

Solid lipid nanoparticle consisted of high melting point triglyceride aas the solid core a phospholipids coating. Its advantage over the other system is use of natural lipid and incorporation of drug in triglyceride core which may be applicable for prolonged release. For prolonged release it is desirable to incorporate the drug into triglyceride phase of emulsion e.g. Azidothymidinepalmitate ester prodrug incorporation increases as compared to Azidothymiding cleavage provides sustained release for action. The same process in periphery due to high hydrophilicity rapidly excreted and toxicity eliminates.

APPLICATION OF PRODRUG[12-14]

A. Pharmaceutical Application

- Improvement of taste.
- Improvement of odour.
- Change of physical form for preparation of solid dosage forms.
- Reduction of pain on injection.
- Enhancement of drug solubility and dissolution rate.

B. Pharmacokinetic application

- Enhancement of bioavailability (lipophilicity),
- Prevention of presystemic metabolism,
- Prolongation of duration of action,
- Reduction of toxicity,
- Site-specific drug delivery

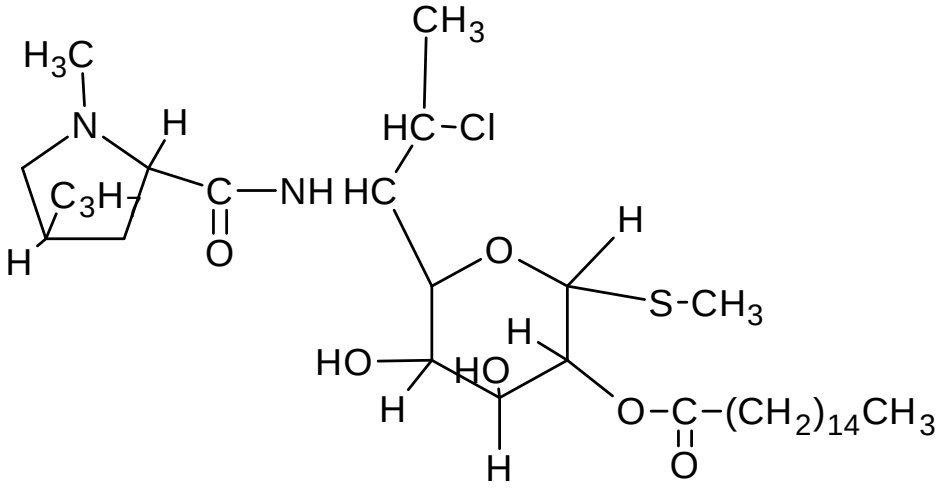
Pharmaceutical Applications

1) Improvement of taste

One of the reasons for poor patient compliance, particularly in case of children, is the bitterness, acidity or causticity of the drug. Two approaches can be utilized to overcome the bad taste of drug.

1. **Reduction of the drug solubility in saliva.**
2. **To lower the affinity of drug towards taste receptor**
    - Thus making the bitterness or causticity impercseptible.
    - Prodrug with improved taste

Parent Drug	Prodrug with improved taste
1.chloramphenicol	Palmitate ester
2.Clindomycin	Palmitate ester
3.Sulfoxazole	Acetyl ester
4.triamcinolone	Diacetate ester

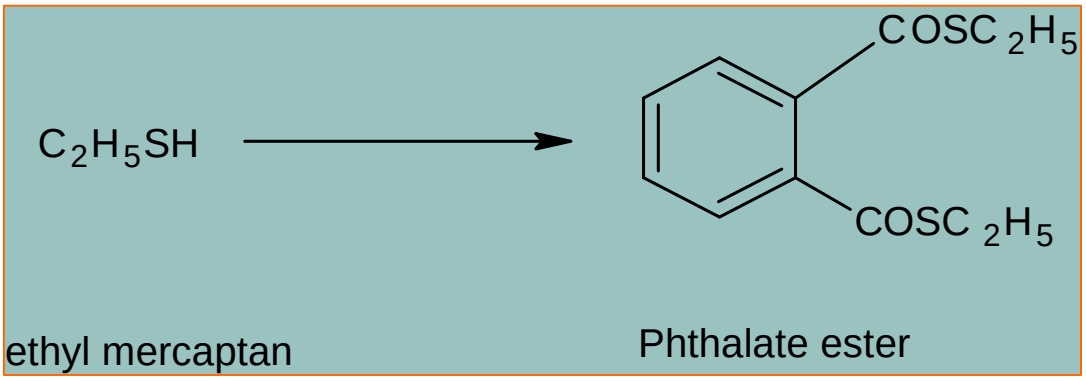


Clindomycin (Bitter taste) →Clindomycin-2-palmitate (Bland taste)

2) Improvement of odour

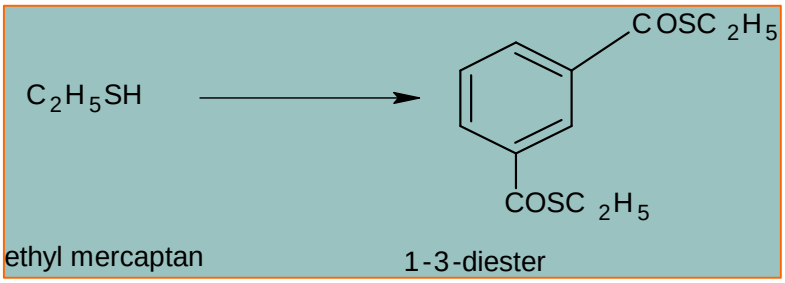
The odor of the compound depends upon the pressure of vapour's liquid with high vapour pressure (& low B.P.) will have string odour.

- E.g. ethylmercapto is one such drug which is foul smelling liquid at B.P. 35c the drug useful in treatment of leprosy is converted into its phthalate ester.
- Diethyldithio-isopthalate which has high B.P. &odorless. The prodrug is administered by rubbing on skin after absorption the esters are metabolized to parent drug by thioesterase.



3) Change of physical form of drug

- Some drugs which are in liquid form are unsuitable for formulation as a tablet especially if their dose is high. The method of converting such liquid drug in solid prodrug involves formation of symmetrical molecule having higher tendency to crystallize.
- Example: - ester of ethyl mercapto & trichloro –ethanol



4) Reduction in GIT irritation

Several drug cause irritation & damage to the gastric mucosa through directcontact increased stimulation of acid secretion or through interference with protective mucosal layer. The NSAID's especially salicylates have such a tendency. They lower gastric PH & induce ulceration.

Examples of prodrug design to overcome such problems of gastric distress are given below.

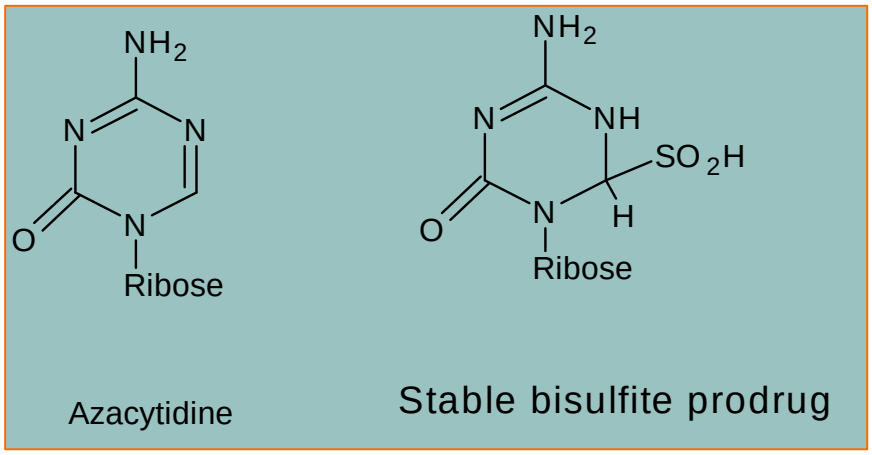
Parent drug	Prodrug that cause little / no gastric distress
1.salicylic acid	Aspirin
2.Kanamycin	Kanamycin pamoate

5) Reduction of pain on injection

- Intramuscular injections are particularly painful when the drugs precipitate in to the surrounding cell or when the solution is strongly acidic, alkaline or alcoholic.
- For example: the low aqueous solubility of clindomycin hydrochloride & alkaline solution of the phenytoin are responsible for the pain on injection. This can be overcome by use of more water soluble prodrug of such agent like the 2-phosphate ester of clindomycin.

6) Enhancement of chemical stability

- A drug may stabilize either during its selflife or in the GIT when used orally. Selflife stability is particularly important in case of the drug for I.V. use. The convential approach is to lyophilize such solution in to powder which can be reconstituted before use. The prodrug design of such agent is also a good alternative to improve stability.
- An example of anti-neoplastic drug azacytidine. The aqueous solution of this drug is readily hydrolyzed but the bisulfiteprodrug is stable to such as degradation at acidic PH & is more water soluble than the parent drug.
- The prodrug converts to the active drug at the physiological PH of 7.4.



Pharmacokinetic application

1) Enhancement of bio-availability (lipophilicity)

- lipophilicity is an important prerequisite.
- A big advantage of increased bioavailability through increased lipophilicity is the reduction in new dosage.
- For example: bacampicillin is as effective as ampicillin in just one-third of the dose of latter.

2) Prevention of presystemic metabolism

- Several corticosteroids undergo extensive first-pass hepatic metabolism which can be prevent by use of their esters or either prodrugs.
- For example: triamcin
- Frequent dosing is required for drug having short biological half-lives. This can be overcome by use of both controlled release &prodrug approaches.
- The two rate controlling steps in enhancement of duration of action of drug are:-

1. The rate of release of prodrug from the site of application or administration in to the systemic circulation.
2. The rate of conversion of prodrug in to active drug in the blood.

3) Reduction of toxicity

- An important objective of a drug design is to develop one which high active & low toxicity.
- Example of drug for systemic use with local side effect such as gastric distress with NSAID's which can beovercome by prodrug design have already been discussed.
- Another example is bioprecursorsulindac. As a sulfoxide it does not cause any gastric distress & is absorbed better in blood, it is converted.

4) Site-specific drug delivery

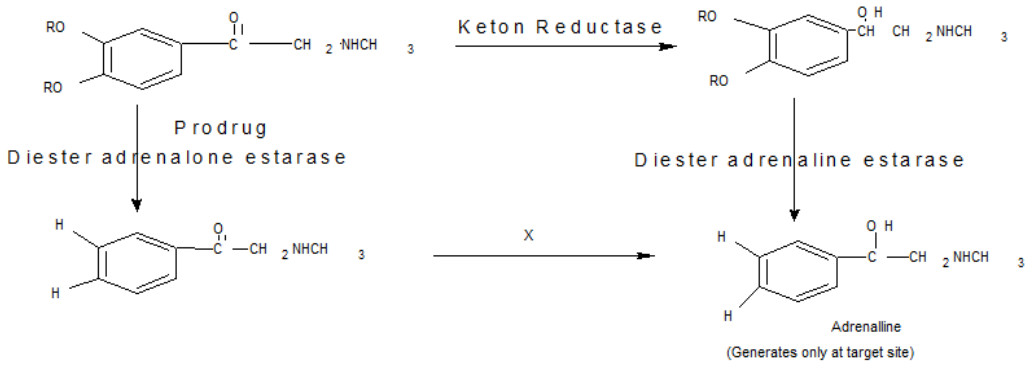
- After its absorption in to the systemic circulation the drug is distributed to the various part of body including target site as well as non-targeted tissue.
- A distribution pattern has various several.

Disadvantages

a. The drug may lead undesirable toxic effect on non-targeting tissue.

b. A smaller fraction of the drug will reach its site because of dilution.
c. If target site has long distribution time, drug may be eliminated without reaching such site.

- These problems can be overcome by targeting the drug to its site of action by altering its deposition characteristics. There are several approaches to drug targeting & prodrug design is one of them.



Methods of evaluation of prodrugs[15,16]

The pharmacokinetics (ADME) of drug is greatly influenced by physicochemical properties such as solubility, lipophilicity, pH, surface area, molecular weight of molecule. Out of this pH, solubility and Lipophilicity are the key factors in determining in vivo behavior of drugs.

Solubility Measurement

The solubility measurement is carried out by placing an excess amount of mutual prodrug in separate vials containing different solvents like 10 ml deionized water, n-hexane, phosphate buffer of different pH etc and then stirring at 37°C for 24 hours. The solutions are centrifuged for 5 min at 9000 rev/min and the supernatant is filtered with cellulose acetate membrane filters. The mutual prodrug concentration in each filtrate is determined by suitable analytical technique like HPAE-PAD/UV spectroscopy/HPLC after the appropriate dilution.

Determination of Partition Coefficients

The partition coefficient between water or buffer and n-octanol or cyclohexane is the most widely used measure of chemical compound lipophilicity. Lipophilicity is a major structural factor governing both pharmacokinetics and pharmacodynamics of drugs. The partition coefficient of a chemical compound provides a and ammonium ions.Because the pH of urine in the bladder is mildly acidic, methenamine is used as a urinary tract antiseptic. To prevent hydrolysis of this prodrug in the acidic environment of the stomach the tablets are enteric coated. thermodynamic measure of its hydrophilicity-lipophilicity balance.

The octanol-water partition coefficient (log P value) of a drug substance is an indicator of compound lipophilicity and solubility.

The log P of a compound is constant for a given specific pair of aqueous and organic solvents. However, the calculated log P value for a compound in water vs. a simple organic compound like octanol or hexane can provide a guideline for predicting its solubility characteristics in other aqueous and organic solvents. The octanol-water partition coefficient (log P value) of a drug substance is an indicator of compound lipophilicity and solubility. The log P value determination is a useful parameter in Drug Discovery and Development and is used to predict transport properties across cell membranes, establish quantitative structure-activity relationships (QSARs), and as an indicator of protein binding characteristics.

In vitro pH Hydrolysis study

Hydrolysis studies are carried out in aqueous buffer so as to study whether the prodrughydrolyzes in an aqueous medium and to what extent or not, suggesting the fate of mutual prodrug in the system. The kinetics of hydrolysis is monitored by the increase of free drug concentration with time and the order of the reaction and half-life (*t*1/2) are calculated. The rate of hydrolysis is calculated using the equation:

$Kh = (2.303/t) \log (a/a–x)$

Where, Kh represents the hydrolysis constant, „
t is the time in min,

a is the initial conjugate concentration,
x is the amount of Mutual prodrughydrolyzed and „
(a–x) is the amount of the remaining prodrug.
The graph between % cumulative amounts of drug release after hydrolysis versus time is also plotted to study the *in vitro* hydrolysis of mutual prodrug.
rate of hydrolysis is calculated using the equation: Kh = (2.303/t) log (a/a–x)
Where, Kh represents the hydrolysis constant, „t" is the time in min, „a" is the initial conjugate concentration, „x" is the amount of Mutual prodrughydrolyzed and „(a–x)" is the amount of the remaining prodrug. The graph between % cumulative amounts of drug release after hydrolysis versus time is also plotted to study the in vitro hydrolysis of mutual prodrug.

CONCLUSION

The prodrug strategy is one of the most promising approachesto enhance the therapeutic efficacy and/orreduce the adverse effects of the pharmacologicallyactive agents *via* different mechanisms, including increasedsolubility, stability, improved permeabilityand bioavailability, prolonged biological half-lifetime, and tissue-targeted delivery. Hence, not surprisingly,
prodrugs are becoming an integral part of the drug discovery paradigm. Their importance is supported by the increasing percentage of approved new drug entities that are, in fact, prodrugs. 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.

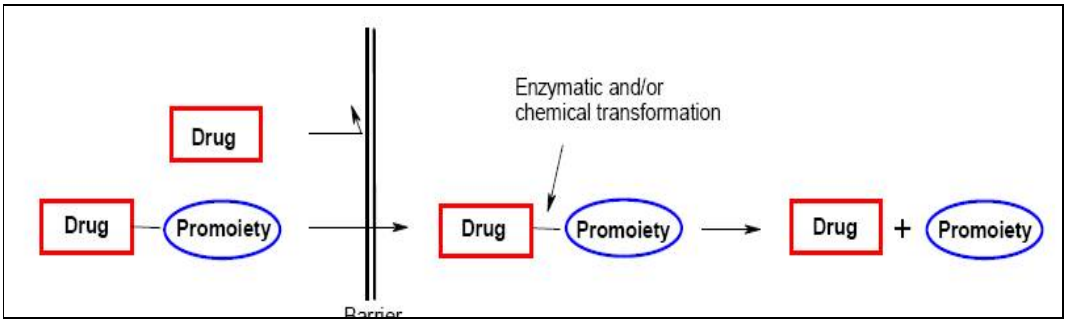


Fig. 1: Schematic illustration of the Prodrug Concept

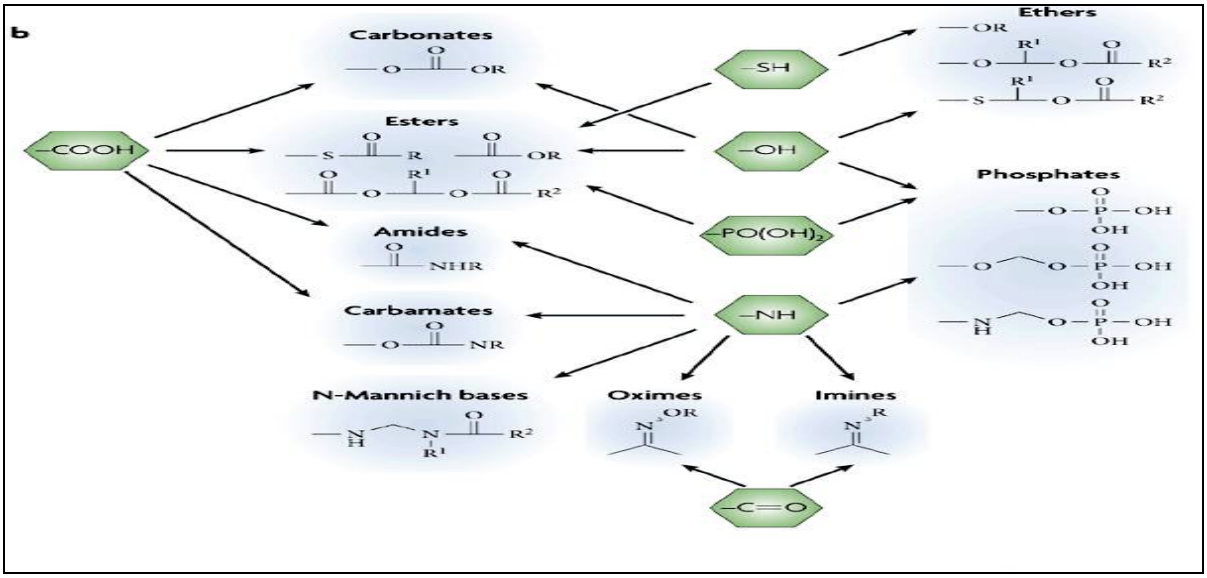


Fig. 2: Functional groups amenable to prodrug design

REFERENCES

1. http://www.wikipedia.com/PharmaceuticalProdrug- by Mitul Shah /Pharmaceutical htm.
2. Smith and Williams. Introduction to the Principles of Drug Design and Action, 4th Ed, Taylor and Francis Group, USA: 216-230.
3. Brahmankar DM and Jaiswal SB. Biopharmaceutics and Pharmacokinetics- A Treatise, Vallabh Prakashan, Delhi. 1995;162-168.
4. Albert A. Nature. 1958;182(B):421.
5. Gennaro R and Alfanso W. Remington: The science and practice of pharmacy, Lippincott Williams & Wilkins. 2003;20(1):913-914.
6. Williams DA. Foye Principles of Medicinal Chemistry, 5thEd., Lippincott Williams and Wilkins Publishers, Philadelphia, PA.2002.
7. Krogsgaard P. Textbook of Drug Design and Discovery, Tayler and Francis Publication, New York, USA. 2004;410-458.
8. Bundgaard H. Design of Prodrug Elsevier Amersterdam, Chapter 1, New York-Oxford. 1985;3-9.
9. Patil SJ and Shirote PJ. Prodrug approach: an effective solution to overcome side-effects. Int J Med Pharm Sci. 2011;1(7):1-13.
10. Ohlanet. Mutual prodrugs- a swot analysis. IJPSR. 2011;2(4):719-729.
11. Longqin HU. Prodrug: Effective solutions for solubility, permeability and challenges Drugs. 2004;7(8).
12. Hanna K. Novel Prodrug Structures for Improved Drug Delivery, Dept. Pharmaceutical Chemistry, Kuopio University, Finland. 2007;67.
13. Singh H and Kapoor VK. Medicinal and Pharmaceutical Chemistry,2nd Ed, Vallabh Prakashan, Delhi. 2005;264-280.
14. Vermanet. Prodrug As A Chemical Delivery System: A Review. Asian J Research Chem. 2009;2(2):100.
15. Shargel AB and Andrew BC. Applied Biopharmaceutics and Pharmacokinetics, 4th Ed., McGraw-Hill Medical Publishing Division, US. 47-66, 129-154.
16. Harper NJ and Binns TB. Absorption and Distribution of Drugs. Mdr, India. 1964;103.