CHAPTER 1
INTRODUCTION

Numbers of drugs possess some undesirable and poor organoleptic, physicochemical and biological properties. Their therapeutic efficacy can be improved by minimizing or eliminating the undesirable properties while retaining the desirable ones. This can be achieved through biological, physical or chemical means. The biological approach is to alter the route of administration, which may or may not be acceptable to the patient. The physical approach involves modification of the design of the dosage form such as controlled delivery of drugs, while the chemical approach emphasizes on the enhancement of selectivity to minimize toxicity.

Various chemical means of optimizing the drug therapeutics are as follows:

1. Design and development of new drugs with desirable features: This approach, however, requires screening of thousands of molecules for biological activity of which only one may become a clinically useful drug.
2. Design of hard and soft drugs: These are basically analogs of existing drugs with desirable characteristics.
3. Design of Prodrug.

In the latter two approaches, the aim of the design is to develop moieties having predictable biotransformation or excretion in contrast to conventional new drug development methods.

A hard drug is a chemical entity resistant to biotransformation and therefore, has a long biological half-life. Such drug will be eliminated by the body through excretion in unchanged form only. Design of hard drugs involves metabolic stabilization of the existing drug molecule by replacing functional groups susceptible to biotransformation with the stable ones. Apart from enhanced duration of action and less loss of active moiety, a hard drug also avoids generation of potentially harmful metabolites, decrease tendency for drug-drug interaction and limits inter-subject variations e.g. Chlorpropamide is a hard drug designed by replacement of 4-methyl by chlorine atom in the Tolbutamide structure to increase the biological half-life from 6 hr to 33 hr.
Too long half life of hard drug results in potential risk of drug accumulation leading to subsequent fluctuations in plasma drug concentration level on long term therapy. In hard drugs, metabolic stabilization is involved whereas, the concept of metabolic switching or metabolic promotion is used in ‘Soft Drug’ and ‘Prodrug’ design, which involves introduction of a functional group of predictable metabolic reactivity in a pharmacophore moiety.

A Soft Drug is a biologically active compound that is biotransformed in vivo in a rapid and predictable manner into nontoxic moieties. Such an agent has therefore a very short duration of action e.g. Insulin and adrenaline- natural endogenous agent. Design of synthetic soft drugs involves introduction of a group or a bond susceptible to rapid metabolic action. e.g. replacement of a part of the alkyl side chain of the drug with an ester group that can be readily hydrolyzed in vivo. An important advantage of soft drugs is formation of relatively inert metabolites.

A Prodrug is a chemically modified inert drug precursor which upon biotransformation liberates the pharmacologically active parent compound. Thus in contrast to soft drugs, prodrugs are inactive per se and biotransformed in a predictable manner into active metabolites.

1.1 PRODRUG APPROACH

The term ‘Prodrug’ or ‘Proagent’ was first introduced by Albert (1958) to describe any compound that undergoes biotransformation prior to exhibition of its pharmacological effect. The term ‘Prodrug’ signifies a pharmacologically inactive chemical derivative that could be used to alter the physicochemical properties of drugs in a temporary manner to increase their usefulness and/or to decrease associated toxicity. Prodrug is also called as ‘Proagent’, ‘Bioreversible derivative’ or ‘Latentiated drug’, but prodrug is the most commonly accepted term. The prodrug design approach is also referred to as “Drug Latentiation”. The chemical modification of a biologically active compound forms a new compound that, upon in vivo enzymatic attack will liberate the parent compound.

Prodrug can be defined as pharmacologically inert chemical derivatives that can be enzymatically or non-enzymatically converted in vivo to the active drug molecule to exert a therapeutic effect. Ideally, Prodrug should be converted to the original drug followed by the
subsequent rapid elimination of the released derivatizing group as soon as the goal is achieved.

1.2 CLASSIFICATION OF PRODRUGS

Depending upon the constitution, lipophilicity, method of bioactivation and the catalyst involved in bioactivation, prodrugs are classified as:

a) Carrier linked prodrug
   1. Double prodrug
   2. Macromolecular prodrug
   3. Site specific prodrug
   4. Mutual Prodrug
b) Bioprecursor prodrug

a) Carrier linked prodrugs (Simple Prodrug)

![Figure 1: Carrier type Prodrug: formulation and drug release](image)

As shown in Fig.1, carrier linked prodrug consists of the active drug covalently linked to an inert carrier or transport moiety, 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. The Prodrug and carrier released after in vivo enzymatical or non-enzymatical attack must be nontoxic. The unique feature of this approach is that the physicochemical properties can be tailored by means of changing the structure of the promoiety.
Chapter-1: Introduction

Figure 2: Dipivfrin 9 - the prodrug of Epinephrine.

Carrier linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties. The subsequent enzymatic or non-enzymatic mechanism releases the active drug moiety. Hence, the carrier linked prodrugs have a major drawback that they are linked through covalent linkage with specialized nontoxic protective groups or carriers or promoieties in a transient manner to alter or eliminate undesirable properties in the parent molecule.

Depending upon the nature of carrier, the carrier linked prodrug may further be classified into:

1) Double prodrug

Prodrug approach is highly practiced to improve the drug delivery and drug targeting. Target specific cleavage mechanism is followed in a prodrug design to encourage the site specific drug delivery. But it will not serve the purpose if it is not possible to reach the target. Also, stability problems are observed in the prodrugs involving chemical release of active drug. These problems can be improved through double prodrug approach in which enzymatic release mechanism is essential prior to the spontaneous release of the parent compound.

Double prodrug also termed as ‘Pro-prodrug’ or ‘Cascade-Latentiated prodrug’ (Fig. 4) is a prodrug further derivatized in such a fashion such that only enzymatic conversion to prodrug is possible before the later can cleave to release the active drug.
2) Macromolecular prodrug

Macromolecules like polysaccharides dextrans, cyclodextrins, proteins, peptides and polymers may be used as carriers to form the macromolecular prodrugs \(^\text{12}\) e.g. Naproxen-2-glyceride.

3) Site specific prodrug

Site specific drug delivery can be achieved by two distinct ways i.e., site directed drug delivery and site specific bioactivation. Site directed drug delivery is based on efforts for increased or selective transport of the parent drug to the site of action. On contrary, in site specific bioactivation derivative of prodrug goes everywhere, but undergoes bioactivation only on the target site.

In this approach, prodrug is designed using a carrier which acts as a transporter of the active drug to a specified targeted site \(^\text{13}\) e.g. Progabide- Diethyl stilbesterol.
4) Mutual Prodrug

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 (Fig. 5).

![Figure 5: Representation of Mutual Prodrug](image)

**Figure 5: Representation of Mutual Prodrug**

![Figure 6: Benorylate a mutual prodrug of Aspirin & Paracetamol](image)

**Figure 6: Benorylate a mutual prodrug of Aspirin & Paracetamol**

This agent is not hydrolyzed in the gastric juice and is more slowly absorbed than either Acetyl salicylic acid or Paracetamol. However, after absorption, it gets hydrolyzed quantitatively to the parent drugs. The major advantage of Benorylate as a prodrug of acetylsalicylic acid is that, it can be used to treat chronic inflammation at a decreased dosage and reduced risk of irritation to the gastric mucosa. Furthermore, it is believed that Paracetamol inhibits the erosion action of Acetyl salicylic acid by stimulating the stomach prostaglandin synthetase.

The carrier selected may have the same biological action as that of the parent drug to give synergistic action or some additional biological action that is lacking in the parent drug, thus ensuring some additional benefits. The carrier can 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 effect of the parent drugs as well.

b) Bioprecursors or metabolic precursors

They are inert molecules obtained by chemical modification of the active drug but do not contain a carrier. Such a moiety has almost the same lipophilicity as the parent drug and is bioactivated generally by redox biotransformation only enzymatically.

Bioprecursor don’t have a temporary linkage between the active compound and carrier group but results from a molecular modification of the active compound itself. This modification generates new compound which acts as substrate for the metabolizing enzyme, a metabolite being the expected active agent.

\[ R=H \text{ Phenylbutazone} \]
\[ R=\text{CH Oxyphenbutazone} \]

Figure 7: Phenyl butazone a bioprecursor of oxyphenbutazone.
1.3 PREREQUISITES OF IDEAL PRODRUG

An ideal prodrug should possess following properties \(^{16}\):

1) Pharmacological inertness.

2) Rapid transformation, chemically or enzymatically, into the active form at the target site.

3) Non-toxic metabolic fragments followed by their rapid elimination.

1.4 APPLICATIONS OF PRODRUG APPROACH

Prodrug approach has been extensively studied amongst the drug design scientist for a wide range of applications. As illustrated with few examples in Table 1, it has been successfully applied to encompassing variety of drugs various goals achieved not only for correction of pharmacokinetic behavior but also pharmaceutical, organoleptic, physical and chemical properties of parent drug compound which enhance the stability and patient compliance improving the efficacy of therapy.
### Table 1: Applications of Prodrug Approach

<table>
<thead>
<tr>
<th>Application</th>
<th>Parent Drug</th>
<th>Prodrug</th>
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<tbody>
<tr>
<td><strong>Taste Masking</strong></td>
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<tr>
<td>Chloramphenicol</td>
<td>Palmitate ester</td>
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<td>Clindamycin</td>
<td>Palmitate ester</td>
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<td>Sulfisoxazole</td>
<td>Acetyl ester</td>
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<td>Triamcinolone</td>
<td>Diacetate ester</td>
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<td><strong>Odor Masking</strong></td>
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<td>Ethyl mercaptan</td>
<td>diethyl isophthalate</td>
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<td><strong>Change of physical form</strong></td>
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<tr>
<td>Ethyl mercaptan</td>
<td>1,3-diester</td>
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<tr>
<td><strong>Reduction of pain on injection</strong></td>
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<td>Clindamycin HCl</td>
<td>2′-phosphate ester</td>
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<td><strong>Solubility Enhancement</strong></td>
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<td>Chloramphenicol</td>
<td>Sodium succinate ester</td>
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<td>Diazepam</td>
<td>L-lysine ester</td>
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<td>Tetracycline</td>
<td>Tetra lysine</td>
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<td>Metronidazole</td>
<td>Amino acid ester</td>
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<tr>
<td>Sulphanilamide</td>
<td>Glucosyl sulphanilamide</td>
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<tr>
<td><strong>Reduction of G.I. irritation</strong></td>
<td></td>
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<tr>
<td>Salicylic acid</td>
<td>Salsalate, Aspirin</td>
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<tr>
<td>Diethyl stilbestrol</td>
<td>Fosfestrol</td>
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<td>Kanamycin</td>
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<tr>
<td>Phenylbutazone</td>
<td>N-methyl piperazine salt</td>
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<td>Nicotinic acid</td>
<td>Nicotinic acid hydrazide</td>
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<tr>
<td><strong>Chemical stability of drug</strong></td>
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<td>Azacytidine</td>
<td>Bisulfite prodrug</td>
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<td><strong>Bioavailability Enhancement</strong></td>
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<tr>
<td>Erythromycin</td>
<td>Ester of Erythromycin</td>
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<td>Ampicillin</td>
<td>Bacampicillin,</td>
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<td>Ampicillin</td>
<td>Talamipicillin</td>
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<tr>
<td>Ampicillin</td>
<td>Pivampicillin,</td>
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<td><strong>Prevention of First-pass</strong></td>
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<td>Propranolol</td>
<td>Isovaleryl Propranolol</td>
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<td>Propranolol</td>
<td>Butyryl Propranolol</td>
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<td><strong>Prolongation of action</strong></td>
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<td>Testosterone</td>
<td>Testosterone cypionate</td>
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<td>Testosterone</td>
<td>Testosterone propionate</td>
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<tr>
<td>Estradiol</td>
<td>Estradiol propionate</td>
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<td><strong>Reduction of toxicity</strong></td>
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<tr>
<td>Timolol</td>
<td>Alkyl ester of Timolol</td>
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<tr>
<td><strong>Site specific drug delivery</strong></td>
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<tr>
<td>Salicylic acid</td>
<td>5-Amino salicylic acid</td>
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1.4.1 Pharmaceutical application

The undesirable organoleptic properties and physicochemical problems associated with drug formulation can be resolved.

\[ \text{Figure 8: Prodrug used in taste masking problems} \]

\[ \text{Figure 9: Esterification of Ethyl mercaptan for Odor Masking} \]

\[ \text{c) Change of physical form of the drug} \]
Chapter-1: Introduction

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 a liquid drug into solid prodrug involves formation of symmetrical molecules having a higher tendency to crystallize e.g. P-Acetamidobenzoic acid ester.

\[
\text{Cl}_3\text{CCH}_2\text{OH} \rightarrow \text{Cl}_4\text{CH}_2\text{COOC} \rightarrow \text{NHCOCH}_3
\]

Trichloroethanol  P-Acetamidobenzoic acid ester

Figure 10: Esterification of Trichloroethanol

**d) Reduction of G.I. irritation**

Several drugs cause irritation and damage to the gastric mucosa through direct contact, increased stimulation of acid secretion or through interference with protective mucosal layer \(^{20}\). The NSAIDs, salicylates lower the gastric pH and induce or aggravate ulceration. This can be overcome by use of prodrug approach e.g. Salsalate.

**e) Reduction of pain on injection**

Intramuscular injections are painful when the drug precipitates or penetrates into surrounding cells or when the solution is strongly acidic, alkaline, alcoholic or poor solubility of drugs \(^{21}\) e.g. intramuscular injection of antibiotic like Clindamycin and anticonvulsant drug like Phenytoin are responsible for pain on injection. This can be overcome by making phosphate ester prodrugs respectively and maintaining the formulation at pH 12.
Hydrophilicity or water solubility is desired where dissolution is the rate limiting step in the absorption of poorly aqueous soluble agents or when parental or ophthalmic formulation of such agents is desired. Many drugs in the pipeline in recent drug development are hydrophobic in nature (BCS Class-II) and possess poor bioavailability. Prodrug approach can be applied for rectification of the solubility problem. Drugs with hydroxyl functional group can be converted into their hydrophilic forms by use of half esters such as hemisuccinate, hemiglutarates or hemipthalates. The other half of these acidic carriers can form sodium, potassium or amine salts and render the moiety more water soluble. Phenolic drugs and some alcohols, as in the case of steroidal drugs such as Cortisol, Prednisolone, Betamethsone and Dexamethasone, the sodium succinate salts, have poor chemical stability and hence phosphate esters are preferred. Glycosidic prodrugs of some agents and L-lysine ester of benzodiazepines are also water soluble. Such hydrophilic promoieties, when used for
parental use are advantageous over their propylene glycol solution which is toxic or painful. The prodrug approach is also made useful for better gastrointestinal absorption. It was observed that Sulindac, a prodrug of Sulindac sulfide being more water soluble with sufficient lipophilicity, makes this drug suitable for oral administration.

Figure 13: Prodrugs with altered solubility

g) Enhancement of chemical stability

A drug may destabilize during its shelf life stability. The commonest conventional approach is to lyophilize the solution into a powder, which can be reconstituted before use. The prodrug design of such agents is a good alternative to improve stability e.g. Antineoplastic drug- Azacytidine (Fig.1.14). The aqueous solution of azacytidine is readily hydrolyzed but the bisulfite prodrug shows stability to such degradation at acidic pH and is also more water soluble than the parent drug. The prodrug gets converted to active drug at the physiological pH.

Figure 14: Stable Prodrug of Azacytidine
**1.4.2 Pharmacokinetic Application**

Pharmacokinetic properties of drugs are important for its pharmacodynamic efficacy. Therefore drawbacks in pharmacokinetic parameters which affect the bioavailability and mean residence time of drug in body can be modulated by Prodrug approach. Following are the goals achieved by prodrug approach.

**a) Enhancement of bioavailability (Lipophilicity)**

Passive diffusion is the commonest pathway for transportation of drug from site of administration to systemic circulation through a lipoidal membrane. Hence, optimum lipophilicity is important prerequisite for better absorption. Some drugs due to poor lipophilicity (BCS Class-III) remain poorly absorbed from most of the administration routes. Thus improvement in the lipophilic character serves as a tool for betterment of bioavailability. Two reasons can be attributed to the enhanced oral bioavailability of lipophilic compound.

i. The lipophilic form of a drug has enhanced membrane /water partition coefficient as compared to the hydrophilic form thus favoring passive diffusion e.g. Pivampicillin, Bacampicillin and Talamipicillin prodrugs of Ampicillin are more lipophilic, better absorbed and rapidly hydrolyzed to the parent drug in blood.

![Figure 15: Prodrugs used in enhanced oral absorption.](image)

ii. The lipophilic prodrugs have poor solubility in gastric fluids and thus greater stability and absorption e.g. ester of Erythromycin. The dipalmitoyl glycerol ester of the NSAID Naproxen produces less gastric irritation and higher plasma concentration.
The bioavailability of topically administered drugs also depends upon lipid solubility. Skin penetrability of polar drugs can be improved by esterification to form lipid soluble compound. One of the best approaches in enhancement of topical availability of drug with carboxyl function is their esterification with one of the hydroxyl group of propylene glycol or glycerol. The latter are common penetration enhancer components of topical formulation e.g. Glycerol ester of Naproxen.

b) Prevention of Pre-systemic Metabolism

Phenolic moiety, oxidative N- and O- dealkylation, ester cleavage and peptide degradation are responsible for the pre-systemic metabolism of various drugs. In fact, two types of drugs fall into this category. The first are drugs rapidly degraded by the acid condition of the stomach and the drugs of second category degrade due to enzymes present in the gastrointestinal mucosa and liver. Enzymatic degradation is perhaps of greater significance than chemical degradation. Following oral administration, a drug must pass through two metabolizing organs i.e., liver and gastrointestinal mucosa, before reaching the general circulation.(Fig.16)

**Figure 16: Schematic representation of pre-systemic metabolism of drugs**

Rapid metabolism of drugs in these organs is termed as first pass effect. The first pass metabolism of a drug can be prevented if the functional group susceptible to metabolism is protected temporarily by derivatization. Alternatively manipulation of the drug to alter its physicochemical properties may also alter the drug- enzyme complex formation.
(a) Corticosteroid prodrug

Triamcinolone → 16α-17α-acetonide of triamcinolone

(b) Morphine prodrug

R' = R'' = H Morphine
R = R' = COCH₃ Heroin

(c) Prodrugs of terbutaline and N-butylarternol

R = H Terbutaline
R = COCH(CH₃)₂ Buterol

Figure 17: Prodrugs used in prevention of pre-systemic metabolism

c) Prolongation of duration of action

Frequent dosing is required for drugs having short biological half lives. This can be overcome by use of controlled release devices as well as prodrug approach which can be employed for delayed and controlled drug release in systemic circulation. As depicted in Fig. 18, the two rate controlling steps in the enhancement of drug action are as follows:

Figure 18: Rate limiting steps in the release of a drug from prodrugs
a) The rate of release of prodrug from the site of application or administration into the systemic circulation.

b) The rate of conversion of prodrug into active drug in the blood.

The easier approach is controlling the release rate of prodrug.

e.g. Intra-muscular depot injections of lipophilic ester prodrugs of steroids (Testosterone cypionate and propionate, Estradiol propionate) and antipsychotics (Fluphenazine enanthate and deaconate) since Testosterone and Estradiol are natural soft drugs; their lipophilic prodrugs are sometimes called as ‘Pro-soft drug’.

![Diagram of Testosterone prodrug]

![Diagram of Fluphenazine prodrugs]

Figure 19: Prodrugs used for longer duration of action

Though the second approach of controlled conversion of prodrug to active drug was difficult, it was successfully utilized to deliver Pilocarpine to eyes in the treatment of glaucoma. The diesters of drug when applied as ophthalmic solution showed better intraocular penetration due to improved lipophilicity and slow conversion of the ester prodrug to active Pilocarpine resulted into prolonged the therapeutic effect. The rate of conversion however, is greatly dependent upon the ester group. Bitoterol, a diptolate ester prodrug of N-t-butyl noradrenalin has a longer duration of bronchodilator activity than the parent drug. Moreover the drug preferentially distributes in the pulmonary tissues and therefore, does not show adverse cardiovascular effects.
Different types of prodrugs used as site specific drug delivery system include bioprecursor prodrug, macromolecular prodrug, drug-antibody conjugate, enzymatically activated reduction reaction prodrug, enzymatically activated hydrolysis reaction prodrug, oxidation activated prodrug, reduction activated prodrug, hydrolysis activated prodrug, gene directed enzyme prodrug therapy (GDEPT) and antibody directed enzyme prodrug therapy (ADEPT).

These approaches are based on the activation of specially designed prodrug by specific antibody enzyme conjugates targeted to tumor associated antigens or by enzymes expressed by exogenous genes in the tumor cells. Recent advances in molecular biology provide direct availability of enzymes and carrier proteins, including their molecular and functional characteristics. The targeted prodrug approaches, which can be combined with gene therapy and controlled expression of enzymes and carrier proteins, are promising strategy for precise and efficient drug delivery. Enzymes activated prodrug approach was designed as purine nucleoside prodrug used for the treatment of viral infection like Hepatitis and AIDS. Recently Viramidin a prodrug of Ribavarin is being investigated for human use for the treatment of chronic Hepatitis C. Recently antibody directed enzymes prodrug therapy (ADEPT) has been used for anticancer molecules to target tumor cells. 

\[d)\] **Reduction of Toxicity**

One of the desired properties in drug design and targeting is to have therapeutic activity without toxicity. It seems very difficult unless site specific delivery of drug is achieved. Various non steroidal anti inflammatory drugs like salicylic acid and indomethacin severely damage the GI mucosa due to presence of free carboxylic group. Few other therapeutic agents such as sulindac sulfide, 5-ethyl phenylhydrazine and phenytoin, and antibiotic such as adriamycin suffer with the problem of toxicity due to inadequate aqueous solubility, improper distribution and high tissue distribution respectively.
Figure 20: Prodrugs with diminished local or systemic toxicity

e) Site specific drug delivery

After its absorption into the systemic circulation, the drug is distributed to the various parts of the body including the target site as well as the non-target tissue. Such distribution pattern has several disadvantages like undesirable toxic effects in the non-targeted tissue (especially if its therapeutic index is low), decreased concentration at target site, drug accumulation in lipoidal tissues and development of tolerance due to excess exposure of drug to receptors.\textsuperscript{33-35}

These problems can be overcome by targeting the drug specifically to its site of action by altering its disposition characteristics. There are several approaches for drug targeting including prodrug design. The prodrug is converted into its active form only in the target organ/tissue by utilizing either specific enzymes or a pH value different from the normal pH for activation e.g. 5- amino salicylic acid.
1.5 APPROACHES FOR FORMATION OF PRODRUGS

Various types of functional groups are present in different therapeutic agents. These functional groups react with other functional groups of non-toxic promoiety to form prodrugs. Various prodrugs for compounds containing different functional groups are given below.

1) Ester

Groups like -COOH, -OH can easily undergo esterification reaction. Bioavailability of drug can be improved by ester formation. Enzyme esterase which is present widely in vivo can easily break up the linkage at target organ so that targeted delivery is achieved e.g. Thioester of Erythromycin, palmitate ester of Clindamycin.

2) Amides

The utility of the N-(acyloxy alkoxy carbonyl) derivative is limited due to the resistance to undergo enzymatic cleave in vivo. However, certain activated amides are chemically labile and also certain amides formed with amino acids may undergo enzymatic cleavage. For example the γ-glutamyl derivatives of dopamine, L-Dopa and sulfamethoxazole are rapidly hydrolyzed by γ-glutamyl trans peptidase in vivo. Similarly N-glycyl derivative, midorin and N-1-isoleucine derivative of dopamine are the enzymatically labile amide prodrugs.

![Figure 21: N-glycyl derivative of dopamine](image)

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20
3) Prodrugs of amides, imides and urides \(^9, 38\)

a) **N-hydroxymethylation** \(^{39}\)

The N-hydroxyl methyl derivatives of amides or imide type compounds are more water soluble than the parent compounds. By replacing a proton bind to nitrogen atom by a hydroxyl methyl group, intra or intermolecular hydrogen bonding in such molecules may be increased resulting in a decrease in melting point and increase in water solubility.

![Figure 22: The mechanism for the decomposition of N-hydroxyl methyl derivatives](image)

b) **N-acyloxymethylation** \(^{40}\)

Plasma enzyme catalyzed hydrolysis of the N-acyl derivatives makes N-acylation of amide or imide fruitful in some cases such as N-acetyl-5-fluorouracil and N-ethoxy carbonyl-2-fluorouracil. Improved physicochemical properties and easy bioconversion of N-acyl derivative of 5-fluorouracil enhances the oral and rectal absorption of the parent drug.

By this approach solubility can be improved as they undergo hydrogen bonding in solid phase.
c) N-Mannich Bases and Acyloxy Derivatives

N-Mannich bases can function as a prodrug candidate for compounds such as amides, imides and urea derivatives. The reaction mechanism of decomposition of Mannich bases is shown in (Fig 1.24) Similarly, N-α-acyloxy alkylation of various amides, imides and N-heterocyclic amines also were adopted as a common approach to obtain prodrugs. Though the derivatives showed good stability in aqueous solution in vitro, they are in general rapidly cleaved in vivo by virtue of enzyme mediated hydrolysis. (Fig. 25).

Figure 23: N-acetyl prodrugs of 5-fluorouracil

Figure 24: Reaction mechanism of decomposition of Mannich bases
c) Enamine formation 42

This type of prodrug is formed with aim to protect the molecule and stabilize the molecule against dimerization reaction e.g. Prodrug of Cycloserine with acetyl acetone.

4) Ring formation derivative 43, 44

Thiamine quaternary ammonium compounds like Hydantoin, Barbituric acid etc can undergo ring opening and show in vivo pharmacological properties.

5) Glycol amide esters 45

These are bioavailable products of carboxylic group e.g. Benzoic acid esters.

6) Carbamates 46

They exhibit restricted distribution in the body. Carbamates do not have any specific enzyme for hydrolysis. However, enzymes such as esterase can hydrolyze carbamates e.g. co-carboxy methyl phenyl ester of Amphetamine.

Other approaches used in the formation of prodrug are phosphamides 47, glycosides, ethers, acetals and keta.lds.
1.6 NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used primarily to treat inflammation, mild to moderate pain and fever. The diverse uses of NSAIDs comprise the treatment of headache, arthritis, gout, inflammatory arthropathies, dysmenorrhea, sports injuries, migraine, post-operative pain, tissue injury, sciatica and rheumatism. NSAIDs structurally consist of an acidic moiety which is represented by a carboxylic acid group, an enolic group, a hydroxamic acid group and a sulfonamide or tetrazole ring. The centre of acidity is attached to a planar aromatic or hetero aromatic ring of NSAIDs. The anti inflammatory activity depends on the acidic centre attached to the planar aromatic or hetero aromatic ring. The lipophilicity of NSAIDs is due to the formation of alkyl chain or additional aromatic ring attached to the planar moiety.

**Figure 26: General structure of NSAIDs**

1.6.1 Mechanism of Action

NSAIDs act by inhibiting the biosynthesis of prostaglandin (PG), which is the basic cause behind fever, pain and inflammatory conditions. The biosynthesis of PG involves the release of arachidonic acid (AA) from damaged cell membranes by the action of phospholipase. AA is metabolized by cyclooxygenase (COX) into prostanoids and by lipoxygenase into leukotrienes respectively. (Fig. 27).
COX exists in two isoforms, COX-1 and COX-2. COX-1 is present in tissues of central nervous system, platelet, kidney and gastric mucosa. COX-1 plays an important role in platelet aggregation, thromboxane production and also found responsible for the synthesis of PGs involved in the formation of the mucous protective barrier against gastric acid. COX-2 is mostly an inducible isoform present in brain and kidney and is associated with elevated concentration of PGs during inflammation, pain and fever. The NSAIDs inhibit both COX-1 and COX-2 and thus reduces pain and inflammation. The NSAIDs inhibit both COX-1 and COX-2 and thus reduces pain and inflammation

1.6.2 Beneficial Actions Due To Inhibition of PG Synthesis

(i) Analgesia:

NSAIDS are mild analgesics. NSAIDs do not affect the tenderness induced by direct application of PGs, but block pain induced by them. Other mechanisms for pain relief at the peripheral or central neurons are also being put forth for NSAIDs.

(ii) Antipyretic:

NSAIDs reduce body temperature in fever but do not cause hypothermia in normal individuals. Fever during infection is produced through generation of pyrogen, interleukins and interferons which induce PG production in hypothalamus. NSAIDs block the production of action of pyrogens but not that of PGE2 induced in to hypothalamus.

(iii) Anti inflammatory:
The most important mechanism of anti-inflammatory action of NSAIDs is inhibition of PG synthesis at the site of injury. The anti-inflammatory potency of different compounds corresponds with their potency to inhibit COX. Inflammation is a result of concentrated participation of large number of vasoactive, chemotactic and proliferative factors where there are many targets for anti-inflammatory action.

1.6.3 Adverse Effects of NSAIDs

(i) Gastrointestinal Toxicity:

GI events are the most frequently recognized adverse effects of NSAIDs. They are nausea, dyspepsia, vomiting, diarrhea and gastric ulceration/bleeding. The more an NSAID blocks COX-1, the greater is its tendency to cause ulcers and promote bleeding. Deficiency of PGs reduces mucus and HCO$^3$ secretion, tends to enhance the acid secretion. Thus NSAIDs are ulcerogenic.

(ii) Renal effect:

Renal effect of NSAIDs is not marked in normal individuals but significant in those with congestive heart failure and hypovolemia. The ability to inhibit biosynthesis of prostaglandins helps them to prevent the formation of thromboxane A$_2$, a potent aggregating agent leads to increasing bleeding time. The most common side effects are nausea, vomiting, diarrhoea, constipation, decreased appetite, rashes, dizziness, head ache and drowsiness. NSAIDs may also cause fluid retention leading to oedema.

(iii) Hepatic toxicity:

NSAIDs result in increased transaminase enzyme and hepatic failure.

(iv) CNS toxicity:

It includes headache, mental confusion, behavioral disturbances and seizure precipitation.

(v) Hematological toxicity:
The various hematological toxicity problems associated with NSAIDs are bleeding, thrombocytopenia and agranulocytosis.

**(vi) Miscellaneous Effects:**

The other effects include asthma, exacerbation, skin rashes, pruritis, nausea, vomiting and epigastric distress.

**1.7 CONCLUSION**

Prodrug is one of the classical and highly studied topics by researchers in pharmaceutical developments in the past. Still, it remains the subject of interest due to the fact that the drugs in the developmental pipeline do possess some pharmaceutical or pharmacokinetic drawbacks. Hence, this approach has been used to overwhelm various undesirable drug properties and to optimize the therapeutic outcomes of the drug. Molecular biology has provided direct availability of enzymes and carrier proteins, including their molecular and functional characteristics which can be very helpful to study the prodrug characteristics and properties of the metabolites. Thus prodrug design is becoming more expanded in the development of efficacious and more site-selective drug delivery systems thus making prodrug as a promising strategy for precise and efficient drug delivery and the enhancement of therapeutic outcomes.