CHAPTER 1
INTRODUCTION

1.1 PRODRUGS

The term prodrug was introduced by Albert who used “prodrug” or “proagent” to refer to a pharmacologically inactive compound that is transformed by the mammalian system into an active substance by either chemical or metabolic means \(^1, 2\). Another term drug latentiation, which implies a time lag element or component, was coined by Harper \(^3, 4\). Later, the concept of prodrug and latentiated drug for solving various problems was attempted and the definition of drug latentiation was extended to include non–enzymatic regeneration of parent compounds \(^5\).

The prodrug approach has emerged as a tool in overcoming various obstacles to drug formulation and targeting such as chemical instability, poor aqueous solubility, inadequate brain penetration, insufficient oral absorption, local irritation and toxicity \(^6\). It is justified by the fact that once the barrier to the use of parent compound has been overcome, these temporary forms can be converted to the free parent compound that can exert its pharmacological activity.

A prodrug is thus defined as a biologically inactive derivative of a parent drug molecule that usually requires a chemical or enzymatic transformation within the body to release the active drug, and possess improved delivery properties over the parent molecule \(^7-9\). These attractive features render the prodrugs a well recognized strategy to
improve drug targeting, to enhance the physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically potent compounds, and thereby increase the usefulness of a potential drug. The schematic representation of prodrug concept is shown in Fig 1.1.

**Fig 1.1 Schematic representation of prodrug concept**

**1.2 RATIONAL FOR THE USE OF PRODRUGS**

A drug can only exert a desired pharmacological effect if it reaches its site of action. The three major phases involved in the drug receptor interaction or biological bioavailability of drug includes the pharmaceutical phase, the pharmacokinetic phase and pharmacodynamic phase.\(^{10}\)

Many barriers which limit drug’s ability to reach a desired target organ and the subsequent receptor site are considered of pharmacokinetic origin as shown in Fig 1.2.
Besides these, barriers of non-pharmacokinetic and pharmacodynamic origin may also prevent a drug from reaching the desired target. It includes pathological limitation such as toxicity, high incidence of side effects and teratogenicity, pharmaceutical limitation such as chemical instability of product or formulation, psychological limitation such as unpleasant taste, pain at injection site and cosmetic damage to the patient and economic barriers.

Most of these limitations can be overcome by prodrug approach, but after overcoming the various barriers, the prodrug should rapidly convert into active moiety after reaching the target site. The awareness that the onset, intensity and duration of drug action are greatly affected by the physicochemical properties of drug has promoted the emergence of various theoretical and predictive models for drug design and evaluation 11, 12. The design of an efficient, stable, safe, acceptable and aesthetic way to target a drug to its site of action while overcoming
various physical, chemical and social barriers is certainly an area where the utilization of the prodrug approach holds great potential.

1.3 PHARMACEUTICAL PHASE

The pharmaceutical phase can be considered as the phase of development which involves the identification of a new chemical entity with measured or proposed therapeutic potential and its incorporation into a drug delivery system. The delivery system may be one of the traditional forms such as tablet, capsules, injection and creams/ointment as well as the new drug delivery modes like liposomes, implants etc. Two barriers identified in the development phase of commercially usable drug products are:

(i) Aesthetic properties such as odour, taste (in case of pediatric use or when intended for oral administration), pain upon injection, gastrointestinal (GI) irritability of the new molecule.

(ii) Drug formulation problems. viz., stability profile, undesirable physicochemical properties like solubility, polarity, partition coefficient and $P_{Ka}$ values due to which precludes its incorporation into a specific drug delivery system.

1.4 USE OF PRODRUGS TO OVERCOME PHARMACEUTICAL BARRIERS

The utility of prodrugs to overcome the various aesthetic and drug formulation problems are discussed in the following section.
1.4.1 Masking Taste or Odour

The undesirable taste arises due to adequate solubility and interaction of drug with taste receptors, which can be solved by lowering the solubility of drug or prodrug in saliva. Chloramphenicol, an extremely bitter drug has been derivatized to chloramphenicol-palmitate, a sparingly soluble ester. It possesses low aqueous solubility which makes it tasteless and later undergoes in vivo hydrolysis to active chloramphenicol by the action of pancreatic lipase.

Odour is another aesthetic concern for some drugs, that are often volatile liquid or solids with significant vapour pressure that makes them difficult to formulate. A classic example is the volatile mercaptans used as tuberculostatic agents for the treatment of leprosy. The ethyl mercaptan has a boiling point of 25°C and a strong disagreeable odour. On the other hand, diethyl dithio isophthalate, a prodrug of ethyl mercaptan has a higher boiling point and is relatively odourless. Structures of prodrugs are shown in Fig 1.3.

(a) Chloramphenicol prodrug

(b) Mercaptane prodrug

Fig 1.3 Prodrug used in taste masking and odour problems
1.4.2 Minimizing Pain at Site of Injection

Pain caused by intramuscular injection is mainly due to the weakly acidic nature or poor aqueous solubility of drugs. For example, intramuscular injection of antibiotic like clindamycin and anticonvulsant drug like phenytoin was found painful due to poor aqueous solubility and could be overcome by making phosphate ester prodrugs respectively and maintaining the formulations at pH 12. The structures are shown in Fig 1.4.

(a) Clindamycin–2 dihydrogen phosphate- prodrug of clindamycin

(b) Phenytoin and its prodrug

Fig 1.4 Prodrugs causes reduction of pain at injection site
1.4.3 Alteration of Drug Solubility

The prodrug approach can be used to increase or decrease the solubility of a drug, depending on its ultimate use. For example, chloramphenicol succinate and chloramphenicol palmitate, ester prodrugs of chloramphenicol, have enhanced and reduced aqueous solubility respectively. On the basis of altered solubility, chloramphenicol sodium succinate prodrug is found suitable for parenteral administration \(^{19}\). 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 \(^{20, 21}\). Structures are shown in Fig 1.5.

![Structures of Sulindac and Sulindac sulfide with oxidation-reduction reactions](image)

**Fig 1.5 Prodrugs with altered solubility**

1.4.4 Enhancement of Chemical Stability

Chemical stability is an utmost necessary parameter for every therapeutic agent to elicit its pharmacological activity for a longer duration. A shelf life of at least 2 years is desirable except for vaccines, cytotoxic agents and other life saving drugs. Although chemical unstability can be solved to a greater extent by appropriate
formulations, its failure necessitates the use of prodrug approach. The prodrug approach is based on the modification of the functional group responsible for the instability or by changing the physical properties of the drug resulting in the reduction of contact between the drug and the media in which it is unstable.

This approach was successfully used to inhibit the auto aminolysis, which occur due to capability of NH$_2$ group of side chain to attach β-lactam ring of other molecule, in ampicillin molecule in concentrated solution it generates polymeric species of ampicillin$^{22, 23}$. By making hetacillin, a prodrug of ampicillin formed by the reaction of acetone and ampicillin ‘ties up’ the amine group and thus inhibits auto aminolysis$^{24}$. Structures are shown in Fig 1.6.

![Prodrug with enhanced chemical stability](image)

**Fig 1.6** Prodrug with enhanced chemical stability

### 1.5 PHARMACOKINETIC PHASE

The pharmacokinetic phase can be considered as the phase involving absorption, distribution, metabolism and excretion of the drug. The pharmacokinetic studies provide valuable information
regarding the \textit{in vivo} properties of a drug’s limitation such as poor absorption, too rapid elimination and pre systemic metabolism. If these properties can be related back to the physicochemical and dosage form properties of the system, then corrections will require prodrug interventions. The principal barriers identified in the pharmacokinetic phase are:

(i) Incomplete absorption of the drug from the delivery system or across biological barriers such as the gastrointestinal mucosal cells and the blood brain barrier.

(ii) Incomplete systemic delivery of an agent due to pre-systemic metabolism in the gastrointestinal lumen mucosal cells and liver.

(iii) Toxicity problems associated with local irritation or distribution into tissue other than the desired target organ.

(iv) Poor site specificity of the drug.

1.6 \textbf{USE OF PRODRUGS TO OVERCOME PHARMACOKINETIC BARRIERS}

Prodrug approach can be successfully used to overcome the various pharmacokinetic barriers, thereby improving the therapeutic value of parent drug.

1.6.1 \textbf{To Overcome Absorption Problems}

Poor absorption of drug may be due to physicochemical properties of drug itself. Bioavailability after oral dosing of various water insoluble agents is often dissolution rate limited, whereas the absorption of highly polar agents is often limited by their transport across the gastrointestinal cell membrane. Since most drugs are
absorbed by passive diffusion, a degree of lipophilicity is necessary for efficient absorption through the gastrointestinal barrier \(^{25}\). For highly polar compounds, the administration of less polar and more lipophilic prodrug promotes gastrointestinal absorption. Also, many drugs are poorly absorbed into the central nervous system, eye or through the skin due to their highly polar nature and prodrug approach helps in overcoming these barriers.

### 1.6.2 Enhancement of Oral Absorption

Various therapeutic agents such as water soluble vitamins, structural analogues of natural purine and pyrimidine nucleoside, dopamine, antibiotics like ampicillin and carbenicillin, phenytoin and cardiac glycoside such as gitoxin suffers with poor gastrointestinal absorption. The prime cause of the poor absorption of these agents is their highly polar nature, poor lipophilicity and/or metabolism during the absorption process. On contrary gitoxin, a cardiac glycoside has very poor oral bioavailability due to limited aqueous solubility \(^{26}\).

This problem could be manipulated successfully by using the prodrug approach. The absorption of water soluble vitamin was enhanced by derivatization of thiolate ion to form lipid soluble prodrugs. Dopamine was made useful by making its precursor L-Dopa. Though L-Dopa is highly polar, it is actively transported through specific L–amino acid active transport mechanism and regenerates dopamine by decarboxylation.

It is observed that acyloxymethyl ester of ampicillin such as bacampicillin, telampicillin and pivampicillin have bioavailability
characteristics superior to ampicillin \(^{27, 28}\). Similarly \(\alpha\)-carboxy ester such as carbecillin (\(\alpha\)-carboxyphenyl ester) and geocillin (carbenicillin indanyl sodium) were found suitable to overcome the problems associated with carbenicillin \(^{29, 30}\). Another study showed that pentaacetyl prodrug of gitoxin has four to five times more aqueous solubility\(^{31}\). Prodrugs used in enhanced oral absorption are shown in Fig 1.7.

(a) Thiamine prodrugs

(b) Prodrugs of azauridine

(c) Dopamine prodrug
(d) Ampicillin prodrugs

\[ \text{H}_2\text{N-} \quad \text{O} \quad \text{CH}_3 \quad \text{N} \quad \text{O} \quad \text{C} \quad \text{H}_3 \quad \text{OR} \quad \text{O} \quad \text{C} \quad \text{H}_3 \]

R = H Ampicillin
R = CH(\text{CH}_3)\text{OCOOCH}_2\text{CH}_3 Bacampicillin
R = CH\text{CO}(=\text{O})\text{C}(\text{CH}_3)_3 Pivampicillin
R = \text{H}

Talampicillin

(e) Carbenicillin prodrugs

\[ \text{H}_2\text{N-} \quad \text{O} \quad \text{C} \quad \text{H}_3 \quad \text{NH} \quad \text{C} \quad \text{O} \quad \text{O} \quad \text{C} \quad \text{H}_3 \]

\[ \text{H}_2\text{N-} \quad \text{O} \quad \text{C} \quad \text{H}_3 \quad \text{OR} \quad \text{O} \quad \text{C} \quad \text{H}_3 \]

R = \text{Carfecillin}
R = \text{Geocillin}

(f) Phenytoin prodrug

\[ \text{H}_2\text{N-} \quad \text{O} \quad \text{C} \quad \text{H}_3 \quad \text{NH} \quad \text{C} \quad \text{O} \quad \text{O} \quad \text{C} \quad \text{H}_3 \]

Fig 1.7 Prodrugs used in enhanced oral absorption

1.6.2.1 Enhancement of Ophthalmic Absorption

The usefulness of epinephrine as adrenergic agent in the treatment of glaucoma is limited due to its highly polar nature. Dipivalyl derivative of epinephrine formed by the acylation of phenolic
hydroxyl groups showed enhanced therapeutic effectiveness. Lipid solubility of dipivalyl derivatives is far superior to its parent compound, which facilitates its transport through a lipoidal barrier during corneal absorption (Fig 1.8).

Fig 1.8 Prodrugs used in enhancement of opthalmic absorption

1.6.2.2 Enhancement of Percutaneous Absorption

Mefenide and corticosteroid are used in the treatment of inflammatory, burn therapy, allergic and pruritic conditions, but have limited application due to poor percutaneous absorption. It was observed that mefenide hydrochloride and mefenide acetate salt showed better response than parent drug \(^3^2\). But due to much stronger basic nature of acetate ion, the equilibrium is forced towards the formation of parent drug rapidly in comparison to hydrochloride salt (Fig 1.9). The problem of poor percutaneous absorption of corticosteroid was overcome by making various ester prodrugs \(^3^3\).

Fig 1.9 Prodrugs for enhanced percutaneous absorption
1.6.3 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 1.10).

**Fig 1.10 Schematic representation of pre-systemic metabolism of drugs**

Rapid metabolism of drugs in these organs is termed as first pass effect \(^{34}\). 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.
The prodrug approach was successfully used to overcome the problem of considerable metabolism of steroidal drugs, propranolol, dopamine, morphine and catecholamines by making acetylated derivates of various steroids, 17α, 21–acetonides of various corticosteroids, hemisuccinate ester of propranolol, L–Dopa prodrug in case of dopamine, diacetyl prodrug of morphine and ibuterol and bitoterol prodrugs of terbutaline and N–(t butyl arternol) respectively. All the prodrugs besides enhancing absorption and bioavailability protect the therapeutic agent from metabolism also 35, 36 (Fig. 1.11).

(a) Corticosteroid prodrug

(b) Morphine prodrug

(c) Prodrugs of terbutaline and N–butylarternol

Fig 1.11 Prodrugs used in prevention of pre-systemic metabolism
1.6.4 Longer Duration of Action

Drugs with short half life require frequent dosing with conventional dosage forms to maintain adequate plasma concentration of the particular drug. Frequent dosing for drugs rapidly cleared from the body results in sharp peak and valley effect. In plasma level time profile and consequently patient compliance is often poor. The peak and valley effect can be minimized by drug delivery at a controlled and predictable rate, such as zero order delivery.

Prolongation of duration of action of a drug can be accomplished by the prodrug approach and can take two forms. First the input of drug into the body can be controlled by a prodrug/drug delivery formulation complex, which by design releases drug at a controlled rate at the absorption site, followed by conversion to drug prior to or just after absorption. Second a prodrug can be designed wherein the conversion to the parent drug becomes the release rate limiting factor in the systemic milieu.

The present approach is most useful in case of neuroleptic drugs to avoid large fluctuation in plasma levels. This could be successfully achieved by administering hepatanoate and decanoate esters of fluphenazine in sterile sesame oil. Similarly, the problem of testosterone and propranolol is overcome by administering 17-propionate ester, 17-phenylacetylate and 17-cypionate ester of testosterone in oil vehicle and by controlled conversion rate of hemisuccinate prodrug of propranolol. The prodrugs are shown in Fig 1.12.
(a) Testosterone prodrug

![Testosterone prodrug diagram]

(a) Fluphenazine prodrugs

![Fluphenazine prodrugs diagram]

**Fig 1.12 Prodrugs used for longer duration of action**

### 1.6.5 To Diminish Local and Systemic Toxicity of Drugs

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, 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.\(^{41}\) (Fig 1.13).
(a) Adriamycin prodrug

(b) Indomethacin prodrug

(c) Prodrug of 5, 5-ethyl phenyl hydantoin

**Fig 1.13 Prodrugs with diminished local or systemic toxicity**

**1.7 CLASSIFICATION OF PRODRUGS**

Prodrugs are categorized into four classes. They are given as follows

(i) Carrier Linked Prodrugs

(ii) Tripartite Prodrugs

(iii) Mutual Prodrugs

(iv) Polymeric Prodrugs

**1.7.1 Carrier Linked Prodrugs**

Various adverse physicochemical properties of drug can be tailored and side effects can be minimized by attaching a non toxic carrier group or promoiety to form a new compound i.e., prodrug, from
which the parent drug is regenerated \textit{in vivo}. Common example is dipivalyl ester of epinephrine, which enhances the corneal absorption and inhibits the rapid metabolic destruction of epinephrine. In addition prodrug produces less cardiovascular side effects \textsuperscript{42}.

\textbf{1.7.2 Tripartite Prodrugs}

Structures of most prodrugs are bipartite in nature in which parent drug is attached directly to promoiety. However in some cases bipartite prodrug may be unstable due to inherent nature of the drug-promoiety bond. This can be overcome by designing a tripartite prodrug, utilizing a spacer or connector group between the drug and promoiety. The spacer or connector group must be designed in such a way that the initial activation is followed by spontaneous cleavage of remaining drug spacer bond under physiological condition to release parent drug e.g. a model tripartite prodrug \textit{P–N–(tert-butyloxy carbonyl) lysyl amido) benzoyloxy carbonyl–P–nitro aniline} has been designed in which \textit{N–tert butyloxy carbomyl lysine} group is promoiety, \textit{P–amido benzoyloxy carbonyl} group is spacer group and \textit{P–nitro aniline} is the drug.

\textbf{1.7.3 Mutual Prodrugs}

Mutual prodrugs are defined as two pharmacologically active agents joined together so that each acts as a promoiety for the other and vice versa \textsuperscript{43}. Benorylate is a common example of this category which is a prodrug of acetyl salicylic acid and paracetamol. Major advantage associated with this prodrug is in treatment of chronic inflammation at decreased dose and reduced risk of irritation (Fig 1.14).
**Fig 1.14 Mutual prodrug of acetyl salicylic acid and paracetamol**

**1.7.4 Polymeric Prodrugs**

In this type, which is also known as macromolecular prodrug, the drug is dispersed or incorporated into the polymer (both naturally occurring and synthetically prepared) system without formation of covalent bond between drug and polymer. Example is p-phenylene diamine mustard is covalently attached to polyamino polymer backbone polyglutamic acid.

**1.7.4.1 Bioprecursors**

The bioprecursor does not contain a temporary linkage between the active drug and carrier moiety, but designed from a molecular modification of an active principle itself. Numerous drugs are currently known which exert pharmacological effects after their conversion into active metabolite. One such example is that of phenylbutazone. Phenylbutazone gets metabolized to oxyphenbutazone that is responsible for the anti inflammatory activity of the parent drug.
1.8 BIO REVERSIBLE DERIVATIVES FOR VARIOUS FUNCTIONAL GROUPS

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.

1.8.1 Esters

Ester derivatives are suitable prodrug for therapeutic agents containing carboxyl and hydroxyl functional groups. Chemical reactivity of esters is readily predictable on the basis of the steric and electronic properties of the substitutes in both the acyl and alcohol molecules and on the other hand hydrophilic properties and charge of ester may play a major role in enzyme hydrolysis \(^{46}\).

1.8.2 Prodrug for Amides, Imides and Other Acidic Compounds

1.8.2.1 N-Mannich Bases and Acyloxy Derivatives

N-Mannich bases can function as a prodrug candidate for compounds such as amides, imides and urea derivatives \(^{47}\). The reaction mechanism of decomposition of Mannich bases is shown in Fig 1.15. Similarly, N-\(\alpha\)-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 \textit{in vitro}, they are in general rapidly cleaved \textit{in vivo} by virtue of enzyme mediated hydrolysis \(^{48}\) (Fig 1.16).
Fig 1.15 Reaction mechanism of decomposition of Mannich bases

Fig 1.16 The regeneration of NH group from N-α-acyloxy alkyl derivatives

1.8.2.2 N-Acyl Derivatives

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. 49 (Fig 1.17).
1.8.2.3 N–Hydroxy Methyl Derivatives

The N–hydroxy 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.\(^5\) (Fig 1.18).

**Fig 1.18 The mechanism for the decomposition of N-hydroxy methyl derivatives**

1.8.3 Prodrugs for Amines

Prodrugs of amines are generally designed by making their amide, N–(acyloxy alkoxy carbonyl) derivatives and oxazolidine derivatives.
1.8.3.1 N–(Acyloxy alkoxy carbonyl) Derivatives and Amide Derivatives

The utility of the N–(acyloxy alkoxy carbonyl) derivative is limited due to the resistance to undergo enzymatic cleavage 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 transpeptidase in vivo. Similarly, N–glycyl derivative, midorin and N–1–isoleucine derivative of dopamine are the enzymatically labile amide prodrugs (Fig 1.19).

![Midorin Structure]

Fig 1.19 N-glycyl derivative of dopamine

1.8.3.2 Oxazolidines

Oxazolidines are cyclic condensation products of β-amino alcohols and aldehydes or ketone, and they undergo a facile and complete, hydrolysis in aqueous solution. Alteration in carbonyl moiety controls the rate of formation of given β-amino alcohol. Oxazolidines are weaker bases ($P^{Ka}$ 6–7) than parent β-amino alcohols and found as more lipophilic than the parent compound at physiological pH. For example, the oxazolidine prodrug of phenylephrine prepared from pivaldehyde has penetrated the cornea much more easily than the parent drug as a result of increased lipophilicity (Fig 1.20).
1.8.4 Prodrugs with Carbonyl Groups

Weakly basic character of carbonyl containing drugs may be advantageous as the transformation of such drugs into oxazolidine, introduces a readily ionizable moiety, which allows the preparation of derivatives with increased aqueous solubilities at acidic pH.

1.8.4.1 Thiazolidines

Thiazolidine has been applied as prodrug derivative for various steroids containing a 3-carbonyl group to improve their topical anti-inflammatory activity. Thiazolidine derivatives of hydrocortisone and hydrocortisone 21-acetate prepared with cysteine esters to related β-aminothiols, have been shown to be readily converted to the parent corticosteroids at conditions similar to those prevailing in the skin, thus meeting the requirement for a prodrug (Fig 1.21).
1.8.4.2 Enol Esters

Enol form, of keto–enol equilibrium under proper conditions can be trapped by alkylation or acylation. Such enol esters and ethers may readily undergo hydrolysis with liberation of free enol, which then reverts to the keto form almost instantaneously. In the presence of plasma or liver enzymes, the enol esters are readily hydrolyzed. For example the chemical stability of enol ester of acetophen is similar to that of phenol ester with maximum stability at pH 3.3. On contrary it is rapidly hydrolysable in plasma and liver enzymes (Fig 1.22).
1.9 THE DOUBLE PRODRUG CONCEPT

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.

Prodrugs such as acyclovir, a useful antiherpetic agent, antitumor drug 6-acetyl papavarine, a prodrug of coralyne and ocular prodrug pilocarpine suffer with the problem of poor bioavailability and poor aqueous solubility, inadequate stability in aqueous solution and low ocular bioavailability and rapid elimination from the site of action, respectively. These shortcomings could be overcome by making 6-deoxy acyloxy prodrug of acyclovir, enol ester of 6-acetyl papavarine and by esterifying the pilocarpine acid ester. Structures of acyclovir, pilocarpine and coralyne prodrugs are shown in Fig 1.23.
(a) Acyclovir prodrug

6-deoxyacyclovir

6-deoxy-6-aminocongener of acyclovir

Xanthine oxidase

Adenosine deaminase

Acyclovir

(b) Coralyne prodrug

Enol ester of 6'-acetyl papaverine

6'-acetyl papaverine

Coralyne
(c) Pilocarpine prodrug

![Chemical structure of Pilocarpine prodrug]

Alkyl and aryl ester of pilocarpic acid

Fig 1.23 Prodrugs based on double prodrug concept

1.10 SITE SPECIFIC DRUG DELIVERY

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.\(^5^2\).

1.10.1 Site Directed Drug Delivery

Site directed drug delivery can further be divided into localized drug delivery and systemic site specific delivery.

1.10.1.1 Localized Drug Delivery

The therapeutic success achieved in this case arise mainly from increased absorption or transport of the prodrug across the biological membrane to which it is applied e.g. improved site specific delivery of the prodrugs of antiglaucoma agents epinephrine, timolol and
phenylephrine were observed with an improved corneal permeability characteristics. This in turn, leads to decreased concentrations of the parent drug at sites such as the systemic circulation where it is unwanted. A reduction of the dose necessary for eliciting the biological effects was obtained with a markable reduction in side effect 52.

1.10.1.2 Systemic Site Specific Delivery

In this approach the drug intended to deliver to the brain is coupled to a quaternary carrier, QC (e.g. N–methyl nicotinic acid) and the obtained (D–QC) is reduced chemically to the neutral, lipophilic dihydro form (D–DHC). Its lipophilic nature permits the distribution of the drug throughout the body including the brain. Later on lipophilic form enzymatically oxidizes back to the original quaternary salt (D–QC). Due to hydrophilic character of (D–QC) it readily eliminates from the body except from the brain. Slow enzymatic cleavage of (D-QC) will then result in a steady release of the parent drug in the brain 36 (Fig 1.24).

1.10.2. Site Specific Bioactivation

1.10.2.1 Kidney

Kidney is an organ highly active in the uptake and metabolism of \( \gamma \)-glutamyl derivatives of amino acids and other compounds containing an amino function. Based on this finding, \( \gamma \)-glutamyl derivatives and L–Dopa have been developed as kidney specific prodrugs 53 (Fig 1.25).
Fig 1.24 Schematic representation of systemic site specific drug delivery

Fig 1.25 Mechanism of kidney specific prodrug
1.10.2.2 Colon

Anaerobic colonic bacteria produce *azoreductase*, an enzyme which releases the parent drugs from azo linked prodrugs. For e.g. sulphasalazine and osaiazine, azo linked prodrugs of 5-aminosalicylic acid, are used in the treatment of ulcerative colitis owing to site specific bioactivation and insignificant absorption in small intestine (Fig 1.26).

![Mechanism of colon specific drug](image)

**Fig 1.26 Mechanism of colon specific drug**

1.10.2.3 Stomach

An excellent example of prodrug with site specific drug delivery is omeprazole. They possess a high degree of site specific bioactivation. Omeprazole has been proved as an effective inhibitor of gastric acid secretion. The process involves the transformation of omeprazole within the acid compartment of the parietal cells into cyclic sulphaenaid, an active inhibitor. This reacts with the thiols group in the enzyme with the formation of a disulfides complex, thus inactivating the H⁺, K⁺, ATPase, which are mainly responsible for gastric acid secretion (Fig 1.27).
**Fig 1.27 Schematic representation of inactivating the $H^+$, $K^+$, ATPase**

**1.11 NSAIDS**

Non steroidal 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, dysmenorrhoea, sports injuries, migraine, post-operative pain, tissue injury, sciatica and rheumatism\(^5\)\(^6\).

NSAIDs structurally consist of an acidic moiety which is represented by a carboxylic acid group, an enolic group, a hydroxamic acid group and a sulphonamide or tetrazole ring (Fig 1.28). 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.
Fig 1.28 General structure of NSAIDs

1.11.1 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.\(^{57}\) (Fig 1.29).

Fig 1.29 Biosynthetic pathway of prostaglandins

COX exists in two isoforms, COX-1 and COX-2. The 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 \(^{58}\).

### 1.11.2 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 \(^{59}\).

(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 PGE\(_2\) induced in to hypothalamus.

(iii) **Anti inflammatory:** The most important mechanism of anti inflammatory action of NSAIDs is considered to be 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 the result of concentrated participation of large number of vasoactive, chemotactic and proliferative factors where there are many targets for anti inflammatory action.
1.11.3 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 trans aminase enzyme and hepatic failure.

(iv) CNS toxicity: It includes head ache, mental confusion, behavioral disturbances and seizure precipitation.

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

(vi) Other Effects: The other effects include asthma, exacerbation, skin rashes, pruritis, nausea, vomiting and epigastric distress.