CORRELATION APPROACH OF PRO-DRUG AND CO-DRUG IN BIOTRANSFORMATION

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“Prodrug is a pharmacologically inactive substance that is the modified form of a pharmacologically active drug to which it is converted (as by enzymatic action) in the body”

ABSTRACT
Prodrug is a substance which after administration is metabolized into a pharmacologically active drug. Actually Prodrug has least medicinal value in in-vitro/in-vivo but after biotransformation by metabolism in in-vivo it releases the active medicament. A drug is a substance which is a chemical entity, has definite structural skeleton, obtained by natural or synthetic or semisynthetic source, which can fit on bioreceptor platform having controlling capacity to control over the biochemical malfunction. Every drug is xenobiotic because it is coming from outer source (xeno) and active in biological unit (biotic). Prodrug is the precursor of drug which is made by derivatization of the same to enhance the bioavailability by pharmacokinetics, lipid solubility by partition coefficient and increase the physicochemical & biochemical parameters by pharmacodynamics. Prodrug is a precursor (forerunner) of a drug. A prodrug must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent. For example, sulfasalazine is a prodrug. It is not active in its ingested form. It has to be broken down by bacteria in the colon into two products: 5-aminosalicylic acid (5ASA) and sulfapyridine; before becoming active as a drug. It is a compound that, on administration, must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent; a precursor of a drug. It is called as biotransformation which produce active drug for pharmacological response from prodrug which is inactive.

KEYWORDS: Pro-drug, Co-drug, Biotransformation, ADME, Xenobiotic, Receptor, Pharmacodynamics, Pharmacokinetics, DEPT, ADEPT, GDEPT, VDEPT, PDEPT, CDEPT.

INTRODUCTION
A prodrug is a medication or compound that, after administration, is metabolized (i.e., converted within the body) into a pharmacologically active drug. Inactive prodrugs are pharmacologically inactive medications that are metabolized into an active form within the body. Instead of administering a drug directly, a corresponding prodrug might be used instead to improve how a medicine is absorbed, distributed, metabolized and excreted (ADME). Prodrugs are often designed to improve bioavailability when a drug itself is poorly absorbed from the GIT. A prodrug may be used to improve how selectively the drug interacts with cells or processes that are not its intended target. This reduces adverse or unintended effects of a drug, especially important in treatments like chemotherapy, which can have severe unintended and undesirable side effects.⁷¹

Figure-1: Prodrug approach
Many herbal extracts historically used in medicine contain glycosides (sugar derivatives) of the active agent, which are hydrolyzed in the intestines to release the active and more bioavailable aglycone. For example, salicin is a β-D-glucopyranoside that is cleaved by esterases enzymes to release salicylic acid. Salicin is an alcoholic β-glucoside. Salicin is produced in (and named after) willow (Salix) bark and acts as an anti-inflammatory agent in the human body. Salicin is also commonly found in the bark of Populus species, and the leaves of willows and poplars. It is also found in castoreum, which was used as an analgesic, anti-inflammatory and antipyretic. The activity of castoreum has been credited to the accumulation of salicin from willow trees in the beaver's diet, which is transformed to salicylic acid and has an action very similar to aspirin. Salicin was the historical origin of aspirin and is chemically related to it. When consumed, the acetalic ether bridge is broken down. The two parts of the molecule, glucose and salicyl alcohol, then are metabolized separately. By oxidizing the alcohol function the aromatic part finally is metabolized to salicylic acid. Salicin tastes bitter like quinine. Aspirin is acetylsalicylic acid, first made by Felix Hoffmann at Bayer in 1897, is a synthetic prodrug of salicylic acid. However, in other cases, such as codeine and morphine, the administered drug is enzymatically activated to form sugar derivatives (morphine-glucuronides) that are more active than the parent compound. The first synthetic antimicrobial drug, arsphenamine, discovered in 1909 by Sahachiro Hata in the laboratory of Paul Ehrlich, is not toxic to bacteria until it has been converted to an active form by the body. Likewise, prontosil, the first sulfa drug (discovered by Gerhard Domagk in 1932), must be cleaved in the body to release the active molecule, sulfanilamide. Since that time, many other examples have been identified.

Terfenadine, the first non-sedating antihistamine, had to be withdrawn from the market because of the small risk of a serious side effect. However, terfenadine was discovered to be the prodrug of the active molecule, fexofenadine, which does not carry the same risks as the parent compound. Therefore, fexofenadine could be placed on the market as a safe replacement for the original drug. Loratadine, another non-sedating antihistamine, is the prodrug of desloratadine, which is largely responsible for the antihistaminergic effects of the parent compound. However, in this case the parent compound does not have the side effects associated with terfenadine and so both loratadine and its active metabolite, desloratadine, are currently marketed.

**Classification**

Prodrugs can be classified into two major types, based on how the body converts the prodrug into the final active drug form:
Type-I prodrugs are bioactivated inside the cells (intracellularly). Examples of these are anti-viral nucleoside analogs that must be phosphorylated and the lipid-lowering statins.

Type-II prodrugs are bioactivated outside cells (extracellularly), especially in digestive fluids or in the body's circulatory system, particularly in the blood. Examples of Type-II prodrugs are salicin and certain antibody-, gene- or virus-directed enzyme prodrugs used in chemotherapy or immunotherapy.

Both major types can be further categorized into subtypes, based on factors such as (Type-I) whether the intracellular bioactivation location is also the site of therapeutic action, or (Type-II) whether or not bioactivation occurs in the gastrointestinal fluids or in the circulation system. Type-IA prodrugs include many antimicrobial and chemotherapy agents (e.g., 5-fluouracil). Type-IB agents rely on metabolic enzymes, especially in hepatic cells, to bioactivate the prodrugs intracellularly to active drugs. Type-II prodrugs are bioactivated extracellularly, either in the milieu of GI fluids (Type-IIA), within the systemic circulation and/or other extracellular fluid compartments (Type-IIB), or near therapeutic target tissues/cells (Type-IIC), relying on common enzymes such as esterases and phosphatases or target directed enzymes. Importantly, prodrugs can belong to multiple subtypes (i.e., Mixed-Type).[4]

![Pro Drug to Active Drug](image)

**Figure-3: Prodrug converts into active drug after biotransformation**

A Mixed-Type prodrug is one that is bioactivated at multiple sites, either in parallel or sequential steps. For example, a prodrug, which is bioactivated concurrently in both target cells and metabolic tissues, could be designated as a “Type-IA/IB” prodrug (e.g., HMG Co-A reductase inhibitors and some chemotherapy agents; note the symbol “//” applied here). When a prodrug is bioactivated sequentially, for example initially in GI fluids then systemically within the target cells, it is designated as a “Type-IIA-IA” prodrug (e.g., tenofovir disoproxil; note the symbol “//” applied here). Many antibody- virus- and gene-directed enzyme prodrug therapies (ADEPTs, VDEPTs, GDEPTs) and proposed nanoparticle- or nanocarrier-linked drugs can understandably be Sequential Mixed-Type prodrugs. To differentiate these two Subtypes, the symbol dash “-” is used to designate and to indicate sequential steps of bioactivation and is meant to distinguish from the symbol slash “/” used for the Parallel Mixed-Type prodrugs.[5]

Aspirin is hydrolyzed to salicylic acid, 6-Monoacetylmorphine (6-MAM) is a heroin metabolite which converts into active morphine in in-vivo, ALD-52 and MLD-41 will both convert into the active psychedelic LSD-25, BL-1020 (perphenazine 4-aminobutanoate trimesylate) is converted into perphenazine and GABA into the brain, Carisoprodol is metabolized into meprobamate, Chloramphenicol succinate ester is used as an intravenous prodrug of chloramphenicol, because pure chloramphenicol does not dissolve in water, Codeine is converted into morphine by cytochrome P450 enzyme CYP2D6, Cyclophosphamide is a prodrug activated by liver cytochrome P450 (CYP) enzymes to form the metabolite 4-hydroxy cyclophosphamide, Dipivefrine, given topically as an anti-glaucoma drug, is bioactivated to epinephrine, Enalapril is bioactivated by esterase to the active enalaprilat, Fenofibrate is an isopropyl ester of fenofibrin acid, Fesoterodine is an antimuscarinic that is bioactivated to 5-hydroxymethyl tolterodine, the principle active metabolite of tolterodine, Fosamprenavir is hydrolyzed to the active amprenavir, Fospropofol is metabolized by alkaline phosphatases to an active metabolite, propofol, Heroin is deacetylated by esterase to the active morphine, Latanoprost is an isopropyl ester, that is hydrolyzed by esterases in the cornea to the biologically active acid, Leflunomide is rapidly metabolized to the active teriflunomide in the gut wall and liver, Levodopa is bioactivated by DOPA decarboxylase to the active dopamine, Lisdexamfetamine is L-lysyl amide
that is metabolized in the small intestine to dextroamphetamine at a controlled (slow) rate for the treatment of attention-deficit hyperactivity disorder. Molsidomine is metabolized into linsidomine which decomposes into the active compound nitric oxide. Mycophenolate mofetil is an ester of mycophenolic acid used in transplant medicine, Olmesartan medoxomil is hydrolyzed to olmesartan during absorption from the gastrointestinal tract, Paliperidone is an atypical antipsychotic for schizophrenia. It is the active metabolite of risperidone, Prednisone, a synthetic corticosteroid drug, is bioactivated by the liver into the active drug prednisolone, which is also a steroid. Primidone is metabolized by cytochrome P450 enzymes into phenobarbital, which is major and phenylethylmalonamide, which is minor, Psilocybin is dephosphorylated to the active psilocin, Tenofovir disoproxil fumarate is an anti-HIV drug (NtRTI class) that is bioactivated to tenofovir (PMPA), Valaciclovir is bioactivated by esterase to the active acyclovir, Ximelagatran is dealkylated and dehydroxylated to the active melagatran.⁶

<table>
<thead>
<tr>
<th>Classification of prodrugs</th>
<th>Type</th>
<th>Bioactivation site</th>
<th>Subtype</th>
<th>Tissue location of bioactivation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type-I Intracellular</td>
<td></td>
<td></td>
<td>Type-IA</td>
<td>Therapeutic target tissues/cells</td>
<td>Aciclovir, fluorouracil, cyclophosphamide, diethylstilbesterol, L-DOPA, mercaptopurine, mitomycin, zidovudine</td>
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<tr>
<td>Type-IB</td>
<td></td>
<td></td>
<td>Metabolic tissues (liver, GI mucosal cell, lung etc.)</td>
<td>Carbamazepine, captopril, carisoprodol, heroin, molsidomine, leflunomide, paliperidone, phenacetin, primidone, psilocybin, sulindac, fursultiamine, codeine</td>
<td></td>
</tr>
<tr>
<td>Type-II Extracellular</td>
<td></td>
<td></td>
<td>Type-IIA</td>
<td>GI fluids</td>
<td>Loperamide oxide, oxphenisatin, sulfasalazine</td>
</tr>
<tr>
<td>Type-IIB</td>
<td></td>
<td></td>
<td>Systemic circulation and other extracellular fluid compartments</td>
<td>Acetylsalicylate, bacampicillin, bambuterol, chloramphenicol succinate, dipivefrin, fosphenytoin, lisdexamfetamine, pralidoxime</td>
<td></td>
</tr>
<tr>
<td>Type-IIC</td>
<td></td>
<td></td>
<td>Therapeutic target tissues/cells</td>
<td>DEPTs, ADEPTs, GDEPTs, VDEPTs, PDEPTs, CDEPTs</td>
<td></td>
</tr>
</tbody>
</table>

Examples

- 6-Monoacetylmorphine to Heroin (ester cleavage)
- ALD-52 and MLD-41 to LSD-25 (amide cleavage)
- BL-1020 to Perphenazine and GABA (ester cleavage)
Carisoprodol to Neprobamate (carbamate cleavage) Chloramphenicol succinate to Chloramphenicol (ester cleavage)

Codeine to Morphine (ether cleavage) Cyclophosphamide to 4-hydroxy cyclophosphamide (methylene oxidation)

Dipivefrine to Epinephrine (ester cleavage) Enalaprilat to Enalapril (ester cleavage)

Fenofibrate to Fenofibric acid (ester cleavage) Fesoterodine to 5-hydroxymethyl tolterodine (ester cleavage)

Fosamprenavir to Amprenavir (phosphate cleavage) Fospropofol to Propofol (phosphate cleavage)

Heroin to Morphine (ester cleavage) Latanoprost to the biologically active acid (ester cleavage)
Leflunomide to Teriflunomide (O/N ring cleavage)  Levodopa to Dopamine (decarboxylation)

Lisdexamfetamine to Dextroamphetamine (amide cleavage)  Molsidomine to Linsidomine (carbamate cleavage)

Mycophenolate to Mycophenolic acid (ester cleavage)  Olmesartan medoxomil to Olmesartan

Paliperidone to Risperidone (hydroxyl reduction)  Prednisone to Prednisolone (keto reduction)

Primidone to Phenobarbital (keto reduction)  Psilocybin to Psilocin (phosphate cleavage)

Tenofovir disoproxil fumarate to Tenofovir (PMPA) (phosphate cleavage)
A **codrug** or “mutual prodrug” consists of two synergistic drugs chemically linked together, in order to improve the drug delivery properties of one or both drugs. The constituent drugs are indicated for the same disease, but may exert different therapeutic effects via disparate mechanisms of action.

Some examples of codrugs include:

Sulphasalazine, which is a combination of Sulfapyridine and 5-Amino-salicylic acid

Benorylate, which is an esterified product of Paracetamol and Acetyl salicylic acid.

Sultamicillin, which is an ester of Ampicillin and Sulbactam

An effective codrug should be pharmacologically inactive in its own right, but should release the constituent drugs upon biochemical breakage of the chemical linkage at the target tissue where their therapeutic effects are needed. As such, the chemical linkage (usually a covalent bond) should be subjectable to biodegradation, such as hydrolysis, by an enzymatic or non-enzymatic mechanism. The differential distribution
of enzymes capable of catalyzing the breakage of the chemical linkage in different tissues may be exploited to achieve tissue-specific metabolism of the codrug to release the constituent drugs.

OVERVIEW
Almost all drugs possess some undesirable physiochemical and biological properties. Drug candidates are often discontinued due to issues of poor pharmacokinetic properties or high toxicities. Their therapeutic efficacy can be improved by 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 patient. The Physical approach is to modify the design of dosage form such as controlled drug delivery of drug. The best approach in enhancing drug selectivity while minimizing toxicity, is the chemical approach for design of prodrugs. The term prodrug, introduced in 1958 by Adrien Albert, relates to "Biologically inert derivatives of drug molecules that undergo an enzymatic and/or chemical conversion in-vivo to release the pharmacologically active parent drug." A prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent compound.

The first compound fulfilling the classical criteria of a prodrug was acetanilide, introduced into the medical practice by Cahn and Hepp in 1867 as an antipyretic agent. Acetanilide is hydroxylated to biologically active acetyaminophen. Another historical prodrug is Aspirin (acetylsalicylic acid), synthesized in 1897 by Felix Hoffman (Bayer, Germany) and introduced into medicine by Dreser in 1899. The prodrug concept was intentionally used for the first time by the Parke-Davis company for modification of chloramphenicol structure in order to improve the antibiotic’s bitter taste and poor solubility in water. Two prodrug forms of chloramphenicol were synthesized: chloramphenicol succinate with a good water solubility and chloramphenicol palmitate used in the form of suspension in children.

There are three basic, overlapping objectives in prodrug research:

1. **Pharmaceutical Objectives:** To improve solubility, chemical stability and organoleptic properties. To decrease irritation and/or pain after local administration. To reduce problems related with the pharmacological technology of the active agent. To improve absorption (oral and by non-oral routes). To decrease presystemic metabolism to improve time profile. To increase organ/tissue-selective delivery of the active agent.
2. **Pharmacokinetic Objectives:** To improve absorption (oral and by non-oral routes). To decrease presystemic metabolism to improve time profile. To increase organ/tissue-selective delivery of the active agent.
3. **Pharmacodynamic Objectives:** To decrease toxicity and improve therapeutic index. To design single chemical entities combining two drugs (co-drugs strategy).

**Prodrug concept:** 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 prodrugs. Most of the 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 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 the utilization of the prodrug approach holds great potential.\[8\]

**Carrier linked prodrug:** 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. Active Drug→Inert Carrier→Inert carrier+Drug

**Formation→Chemical/Enzymatic cleavage in-vivo Covalent Bond.**

**Bipartite prodrug:** It is composed of one carrier (group) attached to the drugs. 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. Tolmetin-glycine prodrug.

**Tripartite prodrug:** The carrier group is attached via linker/spacer to drug.

**Mutual Prodrugs:** 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. A mutual prodrug is a bipartite or tripartite prodrug in which the carrier is a synergistic drug with the drug to which it is linked. Benorylate is a mutual prodrug of aspirin and paracetamol. Sultamicillin, which on hydrolysis by an esterase produces ampicillin & sulbactum. Aspirin+Paracetamol produce Benorylate, Sulbactum+Ampicillin produce Sultamicillin.

**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. e.g.: phenylbutazone. Phenylbutazone gets metabolized to oxypHENbutazone that is responsible for the antiinflammatory activity of the parent drug. Polymere Prodrugs: 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. e.g.: p–phenylene dianime mustard is covalently attached to polyamino polymer backbone polyglutamic acid.\[9\]
Diethyl stilbestrol to Fosfestrol

Phenylbutazone to Oxyphenbutazone

Oleandrin to Oleandrin acetate

Fosphenytoin to Phenytoin

Sulindac sulfide to Sulindac

Testosterone to Testosterone phosphate ester

Hetacillin to Ampicillin

Ibuterol to Terbutaline

**Figure-6:** Active Drug→Inert Carrier→Inert carrier+Drug Chemical→Prodrug Formation→Chemical/Enzymatic cleavage in-vivo Covalent Bond Cleavage

**Novel Classification:** Type-I Prodrugs and Type-II Prodrugs. Type-I prodrugs are bioactivated inside the cells (intracellularly). Examples of these are anti-viral nucleoside analogs that must be phosphorylated and the lipid-lowering statins. Type-II prodrugs are bioactivated outside cells (extracellularly), especially in digestive fluids or in the body's circulation system.\(^{[10]}\)

**Bioactivation site:** Subtype Tissue location of bioactivation. Examples: Type-I Intracellular Type-IA Therapeutic target tissues/cells: Aciclovir, fluorouracil, cyclophosphamide, diethylstilbestrol diphasphate, L-DOPA, mercaptopurine, mitomycin, zidovudine. Type-IB Metabolic tissues (liver, GI mucosal cell, lung etc.): Carbamazepine, captopril, carisoprodol, heroin, molsidomine, lefunomide, paliperidone, phenacetin, primidone, psilocybin, sulindac, fursultiamine, codeine.

Type-II Extracellular Type-IIA GI fluids: Loperamide oxide, oxyphenisatin, sulfasalazine. Type-IIIB Systemic circulation and other extracellular fluid compartments: Acetylsalicylate, bacampicillin, bambuterol, chloramphencol succinate, dipivefrin, fosphenytoin, lisdex, amfetamine, pralidoxime. Type-IIIC Therapeutic target tissues/cells: DEPTs, ADEPTs, GDEPTs, PDEPTs, CDEPTs.

**Applications of Prodrugs:** Pharmaceutical applications in masking of taste or odour. Undesirable taste arises due to adequate solubility and interaction of drug with taste receptors. It can be solved by lowering the solubility of drug or prodrug in saliva. e.g.; chloramphenicol palmitate is the sparingly soluble prodrug of chloramphenicol, which is practically tasteless due to its low aqueous solubility, as well as it is hydrolyzed to...
active chloramphenicol by the action of pancreatic lipase. e.g.: Ethyl mercaptan has a boiling point of 25°C and a strong disagreeable odour but diethyl dithio isophthalate, prodrug of ethyl mercaptan has a higher boiling point and is relatively odourless. Reduction of gastric irritation. e.g.: Aspirin is a prodrug of salicylic acid is designed to reduce gastric irritation. Drug+Prodrug=Diethyl stilbestrol~Fosfestrold, Phenylbutazone~Oxyphenbutazone, Oleandrin~oleandrin acetate. [11]

Reduction in Pain at Site of Injection: Pain caused by intramuscular injection is mainly due to the weakly acidic nature or poor aqueous solubility of drugs. e.g.: IM injection of antibiotics like clindamycin and anticonvulsant like phenytoin was found to be painful due to poor solubility. So, prodrugs are produced like 2’phosphate ester of clindamycin and hydantoic ester prodrug of phenytoin (fosphenytoin) an aqueous soluble form of phenytoin respectively. Fosphenytoin~Phenytoin.

Enhancement of drug solubility and dissolution rate: The prodrug approach can be used to increase or decrease the solubility of a drug, depending on its ultimate use. e.g.: 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. The prodrug approach is also made useful for better gastrointestinal absorption. e.g.: sulindac, a prodrug of sulindac sulfide being more water soluble with sufficient lipophilicity, makes this drug suitable for oral administration. Testosterone→testosterone phosphate ester, Tetraacycline→tetraysine, Diazepam→diazepam L-lysine ester. [12]

Enhancement of chemical stability: Chemical stability is an utmost necessary parameter for every therapeutics agent. 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. e.g.: Inhibiting the auto aminolysis, which occur due to capability of NH2 group of side chain to attach β-lactam ring of other molecule, in ampicillin molecule in concentrated solution it generates polymeric species of ampicillin. 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.

Pharmacokinetic Applications: Improvement of Bioavailability, Enhancement of Oral Bioavailability, 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.

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. Penta acetyl prodrug of gitoxin has four to five times more aqueous solubility. To increase aqueous solubility esterification with amino acids is done. Examples of such prodrugs are valaciclovir and valganciclovir, which are valine esters of the antiviral drugs acyclovir and ganciclovir, respectively.


Prevention of Presystemic metabolism: Following oral administration, a drug must pass through two metabolizing organs i.e., liver and gastrointestinal mucosa, before reaching the general circulation. Phenolic moiety, oxidative N– and O– dealkylation, ester cleavage and peptide degradation are responsible for the pre-systemic metabolism of various drugs. 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.

Prodrugs may protect a drug from presystemic metabolism. Naltrexone (treatment of opioid addiction) and is readily absorbed from GIT and hence undergoes presystemic metabolism. Ester prodrugs such as O-nitrobenzoate and acetylsaliclylate increased bioavailability 45 and 28 fold respectively. Drug/Prodrug: Propranolol+Propranolol hemisuccinate, Dopamine+L-DOPA, Morphine+Heroin. [14-16]

Prolongation of duration of action: Drugs with short half life require frequent dosing with conventional dosage forms to maintain adequate plasma concentration of the particular drug. In plasma level time profile and consequently patient compliance is often poor. Prolongation of duration of action of a drug can be accomplished by the prodrug. Prodrug can be formed by two approaches: Control the release of the drug from complex, Control the conversion of prodrug into the parent drug. Drug/Prodrug: Testosterone+Testosterone
propionate, Estradiol+ Estradiol propionate, Fluphenazine+ Fluphenazine deaconate.

Reduction of Local and Systemic Toxicity of Drugs: An important objective of drug design is to develop a moiety with high activity and low toxicity. Gastric irritation and ulcerogenicity associated with aspirin use due to presence of free carboxylic group. Esterification of aspirin (R=alkyl) and other nonsteroidal anti-inflammatory agents (NSAIDs) greatly suppresses gastric ulcerogenic activity. Another example is the biopreursor Sulindac, as it is a sulphoxide, it doesn’t cause any gastric irritation and also better absorbed. The prodrug Ibuterol is isobutyrate ester of Terbutaline (a selective β-agonist useful) in glaucoma. This prodrug, is 100 times more potent, has longer duration of action and is free from both local and systemic toxicity.17,18

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. These problems can be overcome by targeting the drug specifically to its site of action by 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. Tumour cells contain a higher concentration of phosphatases and amidases than normal cells. Consequently a prodrug of cytotoxic agent could be directed to tumour cells if either of these enzymes was important to prodrug activation process. Diethylstilbestrol diphosphate (fosfestrol) was designed for site-specific delivery of diethylstilbestrol to prostatic carcinoma tissue.

Site specific Drug Delivery in Chemotherapy: Directed Enzyme Prodrug Therapy (DEPT): Many chemotherapy drugs for cancer lack tumour specificity and the doses required to reach therapeutic levels in the tumour are often toxic to other tissues. DEPT uses enzymes artificially introduced into the body to convert Prodrugs, which have no or poor biological activity, to the active form in the desired location within the body. DEPT strategies are an experimental method of reducing the systemic toxicity of a drug, by achieving high levels of the active drug only at the desired site. Directed enzyme prodrug therapy (DEPT) uses enzymes artificially introduced into the body to convert Prodrugs, which have no or poor biological activity, to the active form in the desired location within the body. Many chemotherapy drugs for cancer lack tumour specificity and the doses required to reach therapeutic levels in the tumour are often toxic to other tissues. DEPT strategies are an experimental method of reducing the systemic toxicity of a drug, by achieving high levels of the active drug only at the desired site. This article describes the variations of DEPT technology.19-21

Antibody-directed enzyme prodrug therapy (ADEPT): ADEPT is a strategy to overcome the problems of lack of tumor selectivity. An antibody designed/developed against a tumor antigen is linked to an enzyme and injected to the blood, resulting in selective binding of the enzyme in the tumor. When the discrimination between tumor and normal tissue enzyme levels is sufficient, a prodrug is administrated into the blood circulation, which is converted to an active cytotoxic drug by the enzyme, only within the tumor. Selectivity is achieved by the tumor specificity of the antibody and by delaying prodrug administration until there is a large differential between tumor and normal tissue enzyme levels. Schematic presentation of antibody-directed enzyme prodrug therapy (ADEPT). mAb-enzyme conjugate is given first, which binds to antigens expressed on tumor surfaces. Prodrug is given next, which is converted to active drug by the pre-targeted enzyme.22-24

Gene-directed enzyme prodrug therapy (GDEPT): GDEPT is a suicide gene therapy in which the enzyme required for prodrug conversion is produced within the target cell, using a gene delivered to it by gene therapy. When an adequate differential exists between the targeted cell and endogenous tissue, non-toxic prodrug is administered and is subsequently converted into its toxic form within the target cell. Systems that use viral vectors to deliver the gene are known as VDEPT. GDEPT Enzyme Prodrug~Drug: Cytochrome p450 Cyclophosphamide, ifosfamide Phosphamide mustard, acrolein Cytosine deaminase, 5-Fluorocytosine 5-Fluorouridine, 5-Fluorouracil Nitroreductase, 5-(Aziridin-1-yl)-2,4- dinitrobenzamide, 5-(Aziridin-1-yl)-4- hydroxylamino-2- nitrobenzamide. GDEPT, is a two-step process. In the first step, the gene for a foreign enzyme is delivered to tumor cells. In the second step, a non-toxic agent is administered systemically and converted by the enzyme to its cytotoxic metabolite. Gene for foreign enzyme is transected to tumor cells, which express the enzyme to activate the systemically administered prodrug.

Virus-directed enzyme prodrug therapy (VDEPT): VDEPT is the term given to the use of a virus to deliver the gene for GDEPT. VDEPT can potentially be used to enhance the therapeutic potential of oncolytic viruses.

Polymer-directed enzyme prodrug therapy (PDEPT): PDEPT uses polymer-drug conjugates, drugs contained within a polymer ‘shell’ such as HPMA and designed to be released only by a specific enzyme.25-27
Clostridia-directed enzyme prodrug therapy (CDEPT): CDEPT is the use of Clostridia to convert prodrugs into active drug agents. CDEPT exploits the hypoxic environment of solid tumors to target drugs to tumors using anaerobic bacteria resident in the tumour to convert the pro-drug to the active form. Intravenously injected clostridial spores exhibit a specificity for tumours, colonising the hypoxic areas of the tumours. Solid tumours, in contrast to normal tissues, grow rapidly. As a result, the cancerous tissues may suffer from inadequate blood and oxygen supply. Therefore, clostridia can grow in tumor and destroy it specifically. In CDEPT, a prodrug-converting enzyme expressed by a clostridial expression plasmid converts a prodrug into an active drug form within the tumor. While the prodrug is the inactive form and can be administrated in the blood, the products of the prodrug cleavage are highly cytotoxic and show their effect only in the vicinity of tumor cells.\[28,29\]

**Antibody Prodrug-Drug Tumor target:**
L6=Mitomycin-C phosphate+Mitomycin-C. Lung adenocarcinoma= BW413 Etoposide phosphate+Etoposide. Colon carcinoma: L6=Doxorubicin phosphate+Doxorubicin. Lung adenocarcinoma:

Polymer-directed enzyme prodrug therapy (PDEPT): PDEPT uses polymer-drug conjugates, drugs contained within a polymer 'shelf' such as pHPMAs and designed to be released only by a specific enzyme.

Prodrug design is a part of the general drug discovery process, in which a unique combination of therapeutically active substances is observed to have desirable pharmacological effects. In human therapy prodrug designing has given successful results in overcoming undesirable properties like absorption, nonspecificity, and poor bioavailability and GI toxicity. Thus, prodrug approach offers a wide range of options in drug design and delivery for improving the clinical and therapeutic effectiveness of drug.\[30–35\]

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