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## Review Article

### PRODRUG DESIGN FOR OPTIMIZED DRUG DELIVERY SYSTEMS

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#### Abstract

The term prodrug refers to a pharmacologically inactive compound that is converted to an active drug by a metabolic bio transformation. Prodrug design may be useful in circumventing problems associated such as Solubility, absorption and distribution, site specificity, Instability, prolonged release, Toxicity. Prodrug design comprises an area of drug research devoted to optimization of drug delivery. These are designed to maximize the amount of active drug that reaches its site of action, through manipulation of the physicochemical, biopharmaceutical or pharmacokinetic properties of the drug. Almost all drugs possess some undesirable 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 prodrug approach, a chemical approach using reversible derivatives, can be useful in the optimization of the clinical application of a drug. Hence prodrug approach gained attention as a technique for improving drug therapy.

**Keywords:** Prodrug, carrier-Linked prodrugs, mutual prodrug, bio pre cursors agents, site specificity, DEPT, ADEPT, GDEPT PDEPT.

## INTRODUCTION

Prodrugs are compounds which may be inactive in themselves, but which can be converted by chemical or enzymatic means to an active drug. They have been useful in tackling problems such as acid sensitivity, poor membrane permeability, drug toxicity, and short duration of action. Or it can be defined in another word as the term prodrug refers to a pharmacologically inactive compound that is converted to an active drug by a metabolic bio transformation which may occur prior, during and after absorption or at specific target sites within the body. Almost all drugs possess some undesirable 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<sup>1,2</sup>.

- The biological approach is to alter the route of administration which may or may not be acceptable to patient.
- The physical approach is to modify the design of dosage form such as controlled drug delivery of drug.
- The third and best approach in enhancing drug selectivity while minimizing toxicity is the chemical approach for design of prodrugs.

It is also useful from a pharmaco-chemistry perspective to examine prodrugs using chemical arguments. Thus, medicinal chemists find it useful to distinguish between four major classes of prodrugs, namely:

- Carrier-linked prodrugs, where the active agent (the drug) is linked to a carrier (also known as a pro moiety), and

whose activation occurs by hydrolysis (esters, amides, imines, etc.), oxidation, or reduction (e.g., prontosil )

- Bio precursors which do not contain a pro moiety yet are activated by metabolism like hydration, oxidation, or reduction;
- Drug-polymer conjugates, where the carrier is a macromolecule such as a polyethyleneglycol; and
- Drug-antibody conjugates and enzyme-directed prodrug therapies, where the carrier is an antibody raised against tumour cells.

#### Non prodrugs

**Hard drug:** Hard drugs are compounds that pharmacologically active but in form that is not susceptible to metabolic or chemical transformation. In this way the production of any toxic metabolite is avoided and there is increased efficiency of action since the drug is not inactivated by metabolism it may be less readily eliminated. An example of this approach is chlopropamide (not really a true hard drug since it is metabolized, though slowly), an analogue of tolbutamide with p- methyl replaced with chloro group.

**Soft drug:** Soft drugs are active compounds that after exerting their desired pharmacological effect are designed to undergo metabolic inactivation to give a nontoxic product. Such drug has very short duration of action. Several natural endogenous agent such as insulin and adrenaline, are soft drug. Design of synthetic soft drugs involves introduction of a group or a bond susceptibility to rapid metabolic action; for example, replacement of part of the alkyl side chain of drug with an ester group that can be readily hydrolyzed *in vivo*. An

important advantage of soft drug is formation of relatively inert metabolite<sup>3,6,7</sup>.

### Objectives of prodrug design

The prodrug concept has found a number of useful applications in drug research and development, and discussed in this section. However, it should be clear from the onset that such a view is too schematic, prodrug objectives being intertwined. Thus, an improved solubility can greatly facilitate oral absorption, while improving the chemical stability of an active agent can allow tissue-selective delivery and even lead to its in situ activation<sup>5,7,8</sup>.

### Pharmaceutical objectives

- Improved solubility
- Improved chemical stability
- Improved taste, odour
- Decreased irritation and pain

### Pharmacokinetic objectives

- Improved oral absorption
- Decreased pre systemic metabolism
- Improved absorption by non-oral routes
- Improved prolong duration of action

### Pharmacodynamic objectives

- Masking of a reactive agent to improve its therapeutic index
- In situ activation of a cytotoxic agent

### Pharmaceutical Objectives

Pharmaceutical scientists are often faced with serious formulation problems resulting from poor solubility, insufficient chemical stability, or poor organoleptic properties. While pharmaceutical technology can solve such problems in favourable cases (e.g., by improving the solubility of cyclosporine), success is not guaranteed and may be time consuming to achieve. Rather than to wait for an uncertain and delayed pharmaceutical solution to a problem of solubility or stability, project leaders may prefer to take advantage of a prodrug strategy, and hope an early solution. Examples illustrate different chemical strategies to achieve better water solubility. Thus, buparvaquone is an effective anti leishmania drug belonging to the class of hydroxynaphthoquinones, but its oral and topical availability suffers from poor water solubility. Two prodrugs were therefore prepared and examined for their solubility, rates of hydrolysis, and permeation properties. An example of

chemical interest is that of isotaxel, a prodrug of the potent antitumor agent paclitaxel. Paclitaxel has a very poor water solubility (about 0.25 mg/L), which necessitates co-injection of a detergent. Taking advantage of the well-known mechanism of intermolecular nucleophilictransacylation, Hayashi *et al.* prepared an analogue of paclitaxel with the benzoic group located on the  $\alpha$ -hydroxy group rather than on the amino group (estimated pKa about 8). As a result, what is an amido function in paclitaxel becomes a basic amino group in isotaxel, and solubility is greatly improved by protonation.

### Pharmacokinetic Objectives

Pharmacokinetic objectives are currently the most important ones in prodrug research. Foremost among there is a need to improve oral bioavailability by improving the oral absorption of the drug, and/or by decreasing its pre systemic metabolism. Other objectives are to improve absorption by parenteral (nonenteral, e.g., dermal, ocular) routes, to lengthen the duration of action of the drug by slow metabolic release, and, finally, to achieve the organ/tissue-selective delivery of an active agent. Some of these objectives are exemplified below with clinically successful prodrugs. An illustration is found within the neuraminidase inhibitors of therapeutic value against type A and B influenza in humans. Here, target-oriented rational design has led to highly hydrophilic agents that are not absorbed orally. One of the two drugs in current clinical use is zanamivir, a highly hydrophilic drug administered in aerosol form. The other active agent is Ro-64-0802, which also shows very high *in vitro* inhibitory efficacy toward the enzyme but low oral bioavailability due to its high polarity. To circumvent this problem, the active agent was derivatized to its ethyl ester prodrug, known as oseltamivir. Following intestinal absorption, oseltamivir undergoes rapid enzymatic hydrolysis, and produces high and sustained plasma levels of the active agent. As demonstrated by this example, the prodrug concept may thus be a valuable alternative to disentangle pharmacokinetic and pharmacodynamic optimization. A conceptually different and particularly elegant approach to slow metabolic release has been achieved with bambuterol, a prodrug of the  $\beta_2$ -adrenoreceptor agonist terbutaline. Compared with terbutaline 5 mg taken three times daily, bambuterol 20 mg taken once daily provides smooth and sustained plasma levels of terbutaline, and a greater symptomatic relief of asthma with a lower incidence of side effects.

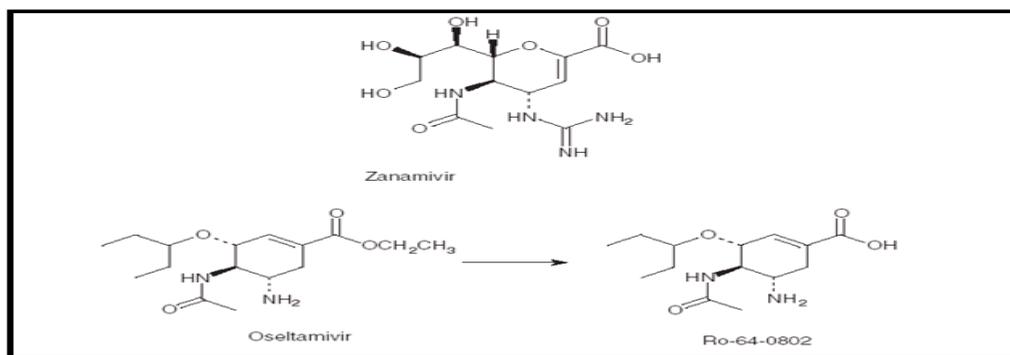


Figure 1: Zanamivir and the Prodrug oseltamivir, whose Active Agent Is Ro-64-0802

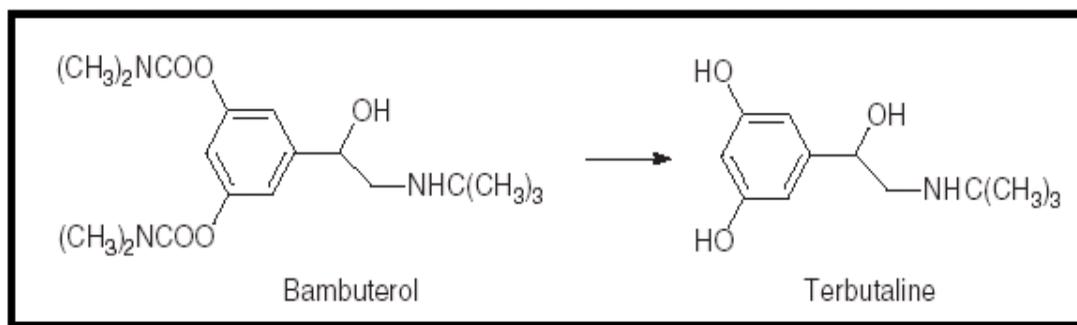


Figure 2: Structure of the useful prodrug bambuterol and its active metabolite terbutaline

### Pharmacodynamic Objectives

Pharmacodynamic objectives can be understood as being synonymous with decreasing systemic toxicity. Two major cases are illustrated here, namely the masking of a reactive agent to improve its therapeutic index, and the *in situ* activation of a cytotoxic agent. The masking of a reactive agent to improve its therapeutic index is aptly exemplified by the successful anti aggregating agent clopidogrel. This compound, whose molecular mechanism of action was poorly understood for years, is now known to be a prodrug. However, it is of interest among prodrugs in that its major metabolic route in humans (about 85 % of a dose) is indeed one of hydrolysis, but this reaction leads to the inactive acid. In contrast, clopidogrel is activated by cytochrome P450 3A in a two-step sequence. First, the cytochrome P450-catalyzed reaction oxidizes clopidogrel to 2-oxoclopidogrel. This is followed by a spontaneous and rapid hydrolysis of the cyclic thioester to a highly reactive thiol metabolite, which irreversibly antagonizes platelet ADP receptors via a covalent S-S bridge. Interestingly, the same activation mechanism appears to account for the potent and irreversible inhibition of human cytochrome P450 2B6 by clopidogrel, again demonstrating the high reactivity of the thiol metabolite.

### Classification of prodrugs

#### According to chemical nature

##### Carrier-Linked Prodrugs

- Bipartate
- Tripartate
- Mutual prodrug

##### Bio precursors and Bio reductive Agents

- Bio precursors activated by phosphorylation
- Bio precursors activated by metabolic oxidation
- Bio precursors activated by metabolic reduction (bio reductive agents)<sup>6-8</sup>

#### According to functional groups

- Prodrugs of acids and alcohol
- Prodrugs of amines and amides
- Prodrugs of carbonyl

#### According to chemical nature

##### Carrier-linked prodrugs

The carrier strategy remains the most common in prodrug design, although reductive bio precursors are attracting an ever increasing interest. Here, we illustrate and discuss a number of common and innovative pro moieties classified according to the functional group in the active drug to which they are linked.

- Contain a group that can be easily removed enzymatically (such as ester) to reveal the true drugs.
- Ideally the group removed is pharmacologically inactive and nontoxic while the connecting bond must be labile for efficient activation *in vivo*.

Prodrugs are the ones where the active drug is covalently linked to an inert carrier transport moiety. They are generally esters or amides. Such prodrugs have greatly modified lipophilicity due to the attached carrier and the active drug is released by hydrolytic cleavage, either chemically or enzymatically.

It can be subdivided into-

- **Bipartate**- Composed of one carrier (group) attached to the drugs. e.g. golmetin-glycine prodrug
- **Tripartate**- Carrier group is attached via linker to drug. e.g. Bacampicillin, a prodrug for ampicillin
- **Mutual prodrugs**- Two drugs linked together.

A slight variation on the carrier-linked prodrug is seen with mutual prodrug in which the carrier also has activity. The anti neoplastic agent Estramustine, which is used in the treatment of prostatic cancer, provides an example of such an approach. Estramustine is composed phosphorylated steroid (17 $\beta$ -estradiol linked to a normustard [HN (CH<sub>2</sub>CH<sub>2</sub>Cl)<sub>2</sub>] through a carbamate linkage. The steroid portion of the molecule helps to concentrate drug in the prostate, where hydrolysis occurs to give the Normustard and exerts a cytotoxic effect on the 17 $\beta$ -estradiol also has an anti androgenic effect on the prostate and there by slows the growth of the cancer cells. Since both the steroid and the mustard possess activity, estramustine is termed as mutual prodrug. Note that phosphorylation of the estradiol can be used to increase the water solubility which also constitute a prodrug modification both types of esters (carbamate and phosphates) are hydrolyzed by chemical or enzymatic means.

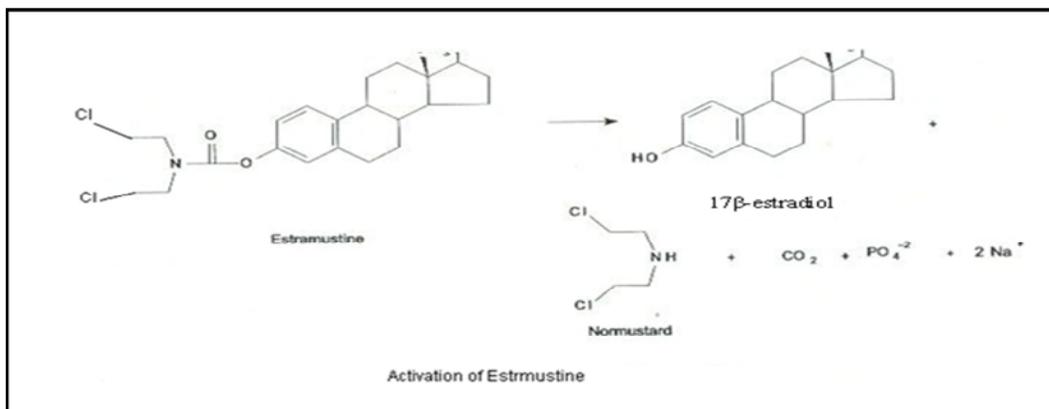


Figure 3: Mutual prodrug in estramustine

### Bio precursors and bio reductive agents

As defined above, bio precursors are prodrugs containing a functional group whose bio transformation generates the active agent without release of any pro moiety. As for carrier-linked prodrugs, the bio activation of bio precursors can involve a reaction of oxidation, reduction, or hydrolysis/hydration. But while hydrolysis is by far the most frequent mechanism of activation of the carrier-linked prodrugs, a majority of known bio precursors are activated by reduction.

### Bio precursors activated by metabolic oxidation

The abundance of oxidizing enzymes in the body has made this type of bio activation a popular route. Isoenzyme of cytochrome p-450 can oxidize a wide variety of functionality, generally to produce more polar compounds that can be exerted directly or undergo phase 2 conjugation reaction and subsequently undergo elimination. A good example of prodrug that requires oxidative activation is the NSAID nabumetone. NSAIDs produce stomach irritation, which in

patients with pre existing condition or patients taking large amounts of NSAIDs for extended periods may be severe. This irritation is associated in part with the presence of an acidic functionality in this agent. The carboxylic acid functionality commonly found in this agent is un-ionized in the highly acidic environment of stomach. As a result, these agents are more lipophilic in nature and may pass into cell of gastric mucosa. The intracellular pH of these cells is more basic than that of stomach lumen, and the NSAID becomes ionized. This result in backflow of H<sup>+</sup> from the lumen into these cells, with concomitant cellular damage. This type of damage could be prevented if the carboxylic acid function could be eliminated from these agents; this functional group is required for activity.

### Bio precursors activated by metabolic reduction

Sulfasalazine is used in the treatment of inflammatory bowel disease (ulcerative colitis). Anaerobic bacteria in the lower bowel metabolically reduce sulfasalazine to the therapeutic agent 5-aminosalicylic acid.

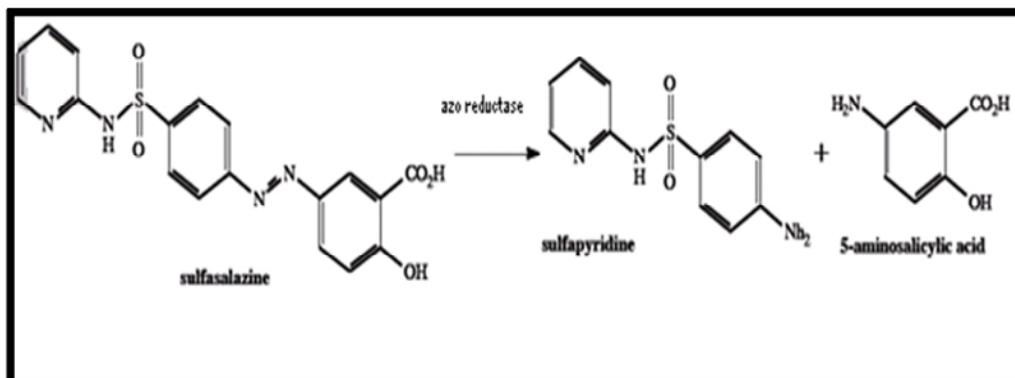


Figure 4: Metabolic reduction of Sulfasalazine

### Prodrugs applications

#### Prodrugs reduce drug toxicity and side-effect

Cyclophosphamide is a successful anticancer drug which is not toxic itself, but which is converted in several steps to the toxic phosphoramide mustard. This is a strong alkylating agent which will alkylate a cell's DNA and thus kill the cell.

Since there is a high level of phosphoramidase enzyme in some tumors cells, it was hoped that the drug could be directed selectively against these cells. Some selectivity has indeed been observed and it is hoped that complete selectivity can eventually be achieved.

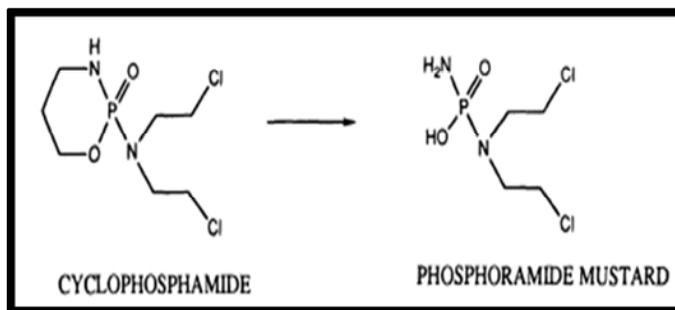


Figure 5: Prodrugs reducing drug toxicity Cyclophosphamide and phosphoramidate mustard

Prodrugs can be used to mask the side-effects and toxicity of drugs. For example, salicylic acid is a good painkiller, but causes gastric bleeding due to the free phenolic group. This is

overcome by masking the phenol as an ester (aspirin). The ester is later hydrolyzed by esterase to free the active drug<sup>9,11</sup>.

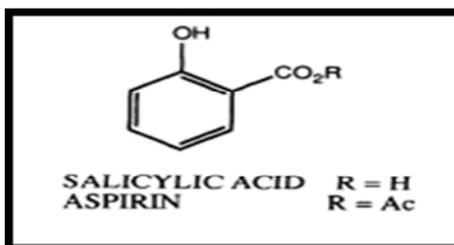


Figure 6: Prodrugs reducing drug side effects, salicylic acid and aspirine

**Prodrugs to improve membrane permeability (improvement of bioavailability)**

Problem of membrane permeability is to design a prodrug which can take advantage of a carrier protein in the cell membrane, such as the one responsible for carrying amino acids into a cell. The best known example of such a prodrug is levodopa. Levodopa is a prodrug for the neurotransmitter dopamine and as such has been used in the treatment of

Parkinson's disease, a condition due primarily to a deficiency of the neurotransmitter dopamine. Dopamine itself cannot be used since it is too polar to cross the blood-brain barrier. Levodopa is even more polar and seems an unlikely prodrug. However, it is an amino acid and as such can make use of the special 'arrangements' made in order to move amino acids across the blood-brain barrier.

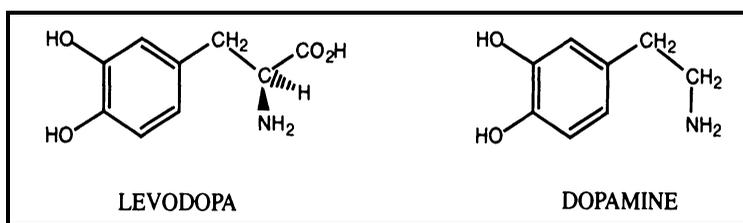


Figure 7: Prodrugs which improve of bioavailability

**For site specificity**

Selective uptake system: Dopamine, a neurotransmitter, produce Vasodilatation of renal tissue by binding to specific receptor in kidney and this can be used to treat renal hypertension. However, the therapeutic index of dopamine is

small as it precipitates high blood pressure by interaction with adrenergic receptor. This can be overcome by taking advantage of fact those gultamyl derivatives of amino acid and peptides selectively accumulate in kidney.

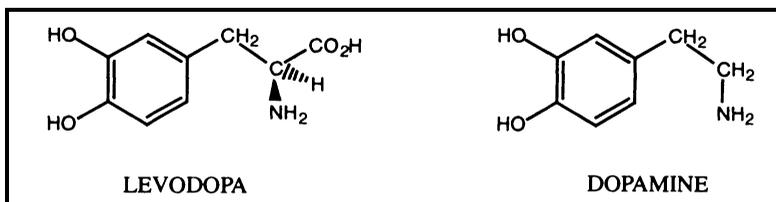


Figure 8: Prodrug used for site specificity action

Such a derivative of dopamine, on reaching the kidney it is acted upon successively by two enzymes that are present in high concentration in renal tissue, glutamyltranspeptidase and L-aromatic amino acid decarboxylase to release the active drug dopamine locally. This increase in dopamine levels produces a marked increase in renal blood flow. Same principle can be used to deliver sulfonamides selectively to kidneys, the prodrug used are N-acyl-glutamyl sulfonamides.

For urinary tract infection: Hexamine is a stable inactive compound at pH greater than 5. However, in mere acidic pH, the compound disintegrates spontaneously to form formaldehyde, which has antibacterial properties. This is useful for treatment of urinary tract infections. The normal pH of blood is slightly alkaline and so the drug circulates in the body as unchanged. However, once it is excreted into urinary tract, it encounters urine, which is acidic as a result of bacterial infection.

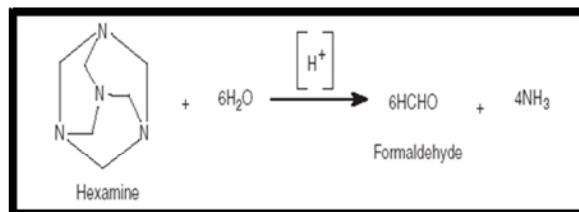


Figure 9: Prodrug used for inhibition of urinary tract infection

### Prodrug prevent first pass metabolism

Prodrugs may protect a drug from 1st-pass metabolism. Naltrexone (treatment for opioid addiction) is non addicting and is readily absorbed from the G.I. tract and as a result

undergoes extensive first-pass metabolism. Ester prodrugs such as the anthranilate (o-nitrobenzoate) and the acetylsalicylate increased bioavailability 45- and 28-fold, respectively.

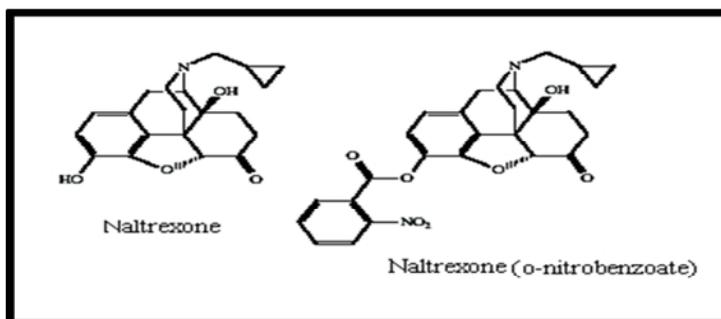


Figure 10: Prodrug preventing first pass metabolism

### Recent advances in prodrugs:

#### Principle of Directed Enzyme-Prodrug Therapies (DEPT):

- Prodrugs or bio precursors targeted toward specific tissues and/ or enzymes, and whose activation occur selectively around or in the target tissues. Note that prodrugs containing a polymer promoiety also show great promise. We briefly examine prodrug strategies targeting specific enzymes (directed enzyme-prodrug therapies, DEPT). Such strategies fall into a few categories, and by far their most important applications are in antitumor treatment. The first case is the targeting of endogenous enzymes over-expressed by the target tissues. A second case is seen when exogenous enzymes are imported to the target tissues by antibodies (ADEPT). A third case is seen when exogenous enzymes are produced from genes transferred to the tumor cells (GDEPT)<sup>6-13</sup>.
- Antibody-directed enzyme prodrug therapy

- Gene-directed enzyme prodrug therapy
- Polymer-directed enzyme prodrug therapy

#### Antibody-directed enzyme prodrug therapy (ADEPT)

In the straight forward form of antigen-targeted therapy, a drug is coupled to an antibody raised against tumor cells. Activation occurs by cleavage of the drug-antibody conjugate after its localization on target cells. ADEPT is different and more complex. Here, an exogenous enzyme is coupled to a monoclonal antibody (mAb) targeted to tumor cells. This enzyme-mAb conjugate is administered, and allowed sufficient time to localize on tumor cells and clear from the circulation. In a second step, a prodrug is administered, which, being a selective substrate of the exogenous enzyme, will be selectively activated at the tumor site. A schematic representation of this strategy, with the enzyme-mAb conjugate binding selectively to tumor cells and activating the prodrug near their surface.

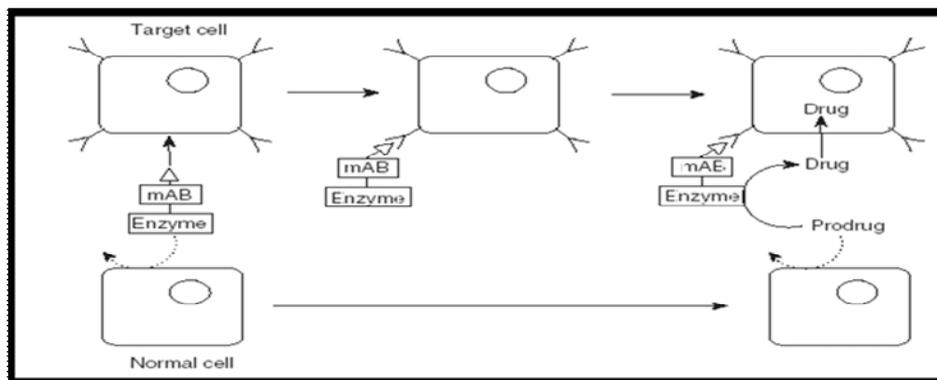


Figure 11: Schematic representation of a selective delivery obtained by ADEPT

### Gene-directed enzyme prodrug therapy (GDEPT)

In GDEPT, the gene encoding an exogenous enzyme is transferred to tumor cells, where it is to be expressed. Two gene vectors are available, namely viral vectors (virus-directed enzyme prodrug therapy) and non-viral vectors composed of chemical gene delivery agents. In a second step, a prodrug is administered that is selectively activated by the exogenous enzyme expressed by the tumor cells. As an example, this strategy was also used to activate methotrexate-Phe and other methotrexate-a-peptides in the vicinity of tumor cells. Carboxypeptidase A is normally synthesized as a zymogen that is inactive without proteolytic removal of its

propeptide end by trypsin. To adapt this system to GDEPT, a mutant form of the enzyme Carboxypeptidase AST3 was engineered. This mutant did not require trypsin-dependent zymogen cleavage but was activated by ubiquitously expressed intracellular propeptidases. All evidence indicated that mature Carboxypeptidase AST3 was structurally and functionally similar to the trypsin-activated, wild-type enzyme. Furthermore, tumors cells expressing Carboxypeptidase AST3 were sensitized to the MTX prodrugs in a dose- and time-dependent manner.

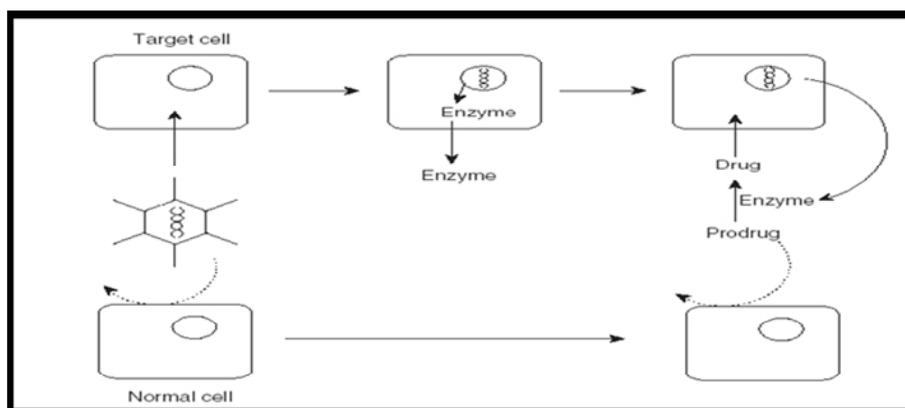


Figure 12: Schematic representation of a selective delivery obtained by GDEPT

### Polymer directed enzyme prodrug therapy (PDEPT)

PDEPT proposes initial administration of the polymeric prodrug to promote tumour targeting before administration of the activating polymer-enzyme conjugate. Polymer-enzyme conjugates such as polyethylene glycol (PEG)-L-asparaginase (Oncaspar®) have already been developed to the market. PEGylation of proteins reduces their immunogenicity and prolongs circulation time. Although a new departure in cancer chemotherapy, several polymer-drug conjugates are already in early clinical trial. These include the N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer anticancer conjugates PK1, PK2 and PNU and a PEG camptothecin conjugate. Reduced toxicity and activity in chemotherapy refractory patients has been described. In phase I HPMA copolymer-doxorubicin (dox) (PK1) displayed a maximum tolerated dose of 320 mg/m<sup>2</sup> and also showed anti tumour activity. Moreover the clinical pharmacokinetics (PK1 t<sub>1/2α</sub> = 1.8 h with no dose dependency of clearance) were very similar to those reported

in animals. Combination of polymer-drug and polymer-enzyme conjugates can capitalise on the ability of both to target solid tumour tissue passively by a mechanism termed the enhanced permeability and retention (EPR) effect. This occurs due to the poorly organised tumour vasculature resulting in enhanced permeability towards circulating molecules. The lack of lymphatic drainage in tumour tissue leads to increased 'retention'. The aim of this study was to establish the feasibility of the PDEPT concept using PK1 and HPMA copolymer-cathepsin B as a model combination. PK1 has proven ability to target solid tumours by the EPR effect with concomitant renal elimination resulting in low blood levels within 1-5 h in animals and man. HPMA copolymer-cathepsin B was selected for PK1 activation as the PK1 Gly-Phe-Leu-Gly polymer-dox linker was designed to permit intra lysosomal dox liberation due to action of the lysosomal cysteine proteases. First it was necessary to prepare an HPMA copolymer-cathepsin B conjugate that would retain sufficient enzyme activity after conjugation. Activity was

monitored *in vitro* using a low molecular weight substrate N-Benzoyl-Phe-Val-Arg-p-nitroanilide hydrochloride (Bz-Phe-Val-Arg-NAp) and the polymeric substrate PK1. The bio distribution of 125I-labelled HPMA copolymer-cathepsin B and 125I-labelled cathepsin B was assessed in mice bearing subcutaneous (s.c.) B16F10 tumours and this model was also used to measure the kinetics of doxorubicin release after intravenous (i.v.) administration of PK1 alone (drug liberation by endogenous lysosomal enzymes) or PK1 followed, after 5 h, by HPMA copolymercathepsin B. Preliminary studies were conducted to establish the antitumour activity of PDEPT combination using the B16F10 model and a human non-small-cell lung carcinoma xenograft (COR-L23).

## CONCLUSION

In conclusion it can be found that, the prodrug approach has been used to overcome various undesirable drug properties and to optimize the clinical drug application. Classical prodrug design often represents a nonspecific chemical approach to mask undesirable drug properties such as Solubility, absorption and distribution, site specificity, Instability, prolonged release, Toxicity limited bioavailability. While targeted prodrug design represents a new strategy for directed and efficient drug delivery. Particularly, targeting the prodrugs to a specific enzyme or a specific membrane transporter, or both, has potential as a selective drug delivery system in cancer chemotherapy or as an efficient oral drug delivery system. The targeted prodrug approach, which can be combined with gene delivery and controlled expression of enzymes and carrier proteins, is a promising strategy for precise and efficient drug delivery and the enhancement of therapeutic efficacy. Site-selective targeting with prodrugs can be further enhanced by the simultaneous use of gene delivery to express the requisite enzymes or transporters. It is clear from the foregoing that design of drug cannot be based just on chemical synthesis. Recent advances in molecular biology provide direct availability of enzymes and carrier proteins, including their

molecular and functional characteristics. Thus prodrug design is becoming more elaborate in the development of efficient and selective drug delivery systems. Hence, prodrug design can no longer be considered as just a chemical modification to solve problems associated with drugs.

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