

**PRODRUG**

## **INTRODUCTION**

Innovations in drug discovery and development, fueled by rapid advances in technology, have led to novel therapeutics for the prevention and treatment of diseases, greatly improving the quality of patients' lives. These innovations have been driven by increasing investments in research and development by pharmaceutical companies, which to some extent have contributed to the upward-spiraling costs of health care, especially prescription medications. The number of new molecular entities (NMEs) receiving Food and Drug Administration (FDA) approval has declined steadily over the years amid concerns over **safety and efficacy**.

The application of high-throughput screening (HTS) has resulted in bulging drug discovery pipelines full of novel therapeutics with improved receptor binding and efficacy but often without adequate physicochemical or pharmacokinetic properties, resulting in costly failures. Despite these developments, new drug applications and approvals did not increase in the last decade. Consequently, development of line extensions seems to be a logical course of action for pharmaceutical companies in order to protect their revenue pool. Such line extensions can be achieved by designing **novel drug delivery systems** to deliver the existing drugs on the market.

An attractive alternative is a chemical delivery system such as a **pro-drug or soft drug** that changes the drug molecule itself to improve the drug's physicochemical properties and safety/tolerability.

Historically, the term pro-drug or pro-agent was coined by Albert<sup>2</sup> in the late 1950s to denote chemical derivatives that could temporarily alter the

physicochemical properties of drugs in order to increase their therapeutic utility and reduce associated toxicity.

Pro-drugs also have been synonymously referred to as **latentiated drugs, bioreversible derivatives, and congeners**. However, the term pro-drug gained wider acceptance and usually describes compounds that undergo chemical transformation within the body prior to exhibiting pharmacologic activity. Some of the earliest examples of pro-drugs are methenamine and aspirin. In the early stages, pro-drugs were obtained fortuitously rather than intentionally; an example is prontosil, which was discovered in the 1930s and later identified as a pro-drug of the antibiotic sulfanilamide.

A pro--drug strategy can be implemented for existing marketed chemical entities (post hoc design). The pro-drug strategy also can be implemented in early discovery (ad hoc design) during lead optimization to address the physicochemical aspects of the NMEs and to improve the chances of success.

**Pro-drugs are pharmacologically inactive compounds that result from transient chemical modifications of a biologically active species and are designed to convert to biologically active species in vivo by a predictable mechanism.**

**Soft drugs are pharmaceutical agents that are active species in the biological system. However, soft drugs are active isosteric or isoelectric analogues of a lead compound that are metabolized or deactivated in a predictable and controllable fashion after achieving their therapeutic role.** They are usually desired for local activity and administered at or near the site of action. Hence they exhibit pharmacological effect locally and distribute away from the intended site as inactivated metabolites, thus avoiding undesired side effects or

toxicities. Therefore, they can be designed to improve the therapeutic index by simplifying the activity/distribution profile, reducing systemic side effects, eliminating drug interactions by avoiding metabolic routes involving saturable enzyme systems, and preventing long term toxicity owing to accumulation.

Pro-drugs and soft drugs can be used strategically to address different problems. **Pro-drugs and soft drugs are treated by the FDA as new chemical entities, and in most cases they require complete toxicological evaluation prior to submission.** The soft-drug approach is gaining acceptance as a way to build a metabolic pathway to a drug in order to achieve predictable metabolism and address the safety and toxicity issues.

### **RATIONALE FOR PRO-DRUG**

A large number of the new molecular entities with promising therapeutic profiles are dropped from the screening stage because of their inferior physicochemical and biopharmaceutical properties. These undesired properties result in poor absorption, extensive metabolism, and low bioavailability because of physical, biological, or metabolic barriers. If the chemical structure of the drug or lead compound can be modified to overcome these barriers and then revert to the pharmacologically active form, the drug can be delivered efficiently. The rationale for the design of pro-drugs is to achieve favorable physicochemical characteristics (e.g., chemical stability, solubility, taste, or odor), biopharmaceutical properties (e.g., oral absorption, first-pass metabolism, permeability across biological membranes such as the blood-brain barrier, or reduced toxicity), or pharmacodynamics properties (e.g., reduced pain or irritation).

### **Pharmacodynamics objectives**

- Activate cyto-toxic agents in situ.
- Mask reactive species to improve the therapeutic index

### **Pharmaceutical objectives**

- Improve solubility
- Improve odor and taste.
- Improve chemical stability
- Decrease irritation and pain

### **Pharmacokinetic objectives**

- Improved oral absorption
- Decrease pre systemic metabolism
- Improve absorption by non-oral route.
- Improve plasma concentration-time profile
- Provide organ specific delivery of active agent

Multiple benefits associated with pro-drug design include increased bioavailability with ester pro-drugs, increased permeability with hydroxyl amine pro-drugs, enhanced solubility with pro-drug salts, enhanced stability with PEGylated pro-drugs, and enhanced absorption with pro-drugs targeted at intestinal transporters, and improved cancer therapy with gene- and receptor-targeted pro-drugs.

## **ESTER PRO-DRUGS**

Owing to the properties of carbonyl group, **esters generally are more hydrophobic (and consequently more lipophilic) than their parent compounds.**

Using specifics of their chemical structure, properties of ester pro-drugs can be broadly modulated to achieve particular **stability and solubility profiles**, provide **good transcellular absorption, resist hydrolysis during the initial phase of absorption, and transform rapidly and efficiently at the site of action.**

Biotransformation of an ester pro-drug to its active form usually involves enzymatic or non enzymatic hydrolysis; in many cases the initial enzymatic cleavage is followed by non enzymatic rearrangement. Ester pro-drugs can be designed with single or multiple functional groups.

Examples are given in the table below...

General design objective	Goal	Drug	Prodrug
Improvement of physicochemical properties	Improve taste	Chloramphenicol	Chloramphenicol palmitate <sup>22</sup>
	Improve taste	Clindamycin	Clindamycin palmitate <sup>30</sup>
	Decrease pain on injection	Clindamycin	Clindamycin phosphate <sup>30</sup>
	Increase solubility	Palcitaxel	PEG-Palcitaxel <sup>23</sup>
	Increase solubility	Prednisolone	Prednisolone sodium succinate <sup>30</sup>
	Decrease solubility	Erythromycin	Erythromycin <sup>30</sup> Ethyl succinate
Improvement of pharmacokinetic properties	Improve absorption	Adefovir	Adefovir <sup>31</sup>
	Improve absorption	Ro-64-0802	Dipivoxil
	Target to specific transporters	Dopamine	Oseltamivir <sup>31</sup> Levodopa <sup>31</sup>
	Increase duration of action	Doxorubicin	PEG-Doxorubicin <sup>31</sup>
	Increase oral absorption	Ampicillin	Pivampicillin <sup>30</sup>
	Extend duration	Fluphenazine	Fluphenazine decanoate <sup>30</sup>
	Increase site specificity	Dromostanolone	Dromostanolone propionate <sup>30</sup>
	Decrease side effects	Aspirin and <i>N</i> -acetyl- <i>p</i> -aminophenol	Benorylate <sup>30</sup>

- Ester pro-drugs often are designed for **absorption enhancement** by introducing lipophilicity and masking ionization groups of an active compound. For example, **valacyclovir**, the **L-valyl ester pro-drug of acyclovir** used for treatment of herpes, demonstrates an oral bioavailability that is three to five times greater than its parent compound. The pro-drug structure, shown below is responsible for the enhanced carrier-mediated intestinal absorption via the hPEPT1 peptide transporter. Rapid and complete conversion of valacyclovir to

acyclovir results in higher plasma concentrations, allowing for reduced dosing frequency.

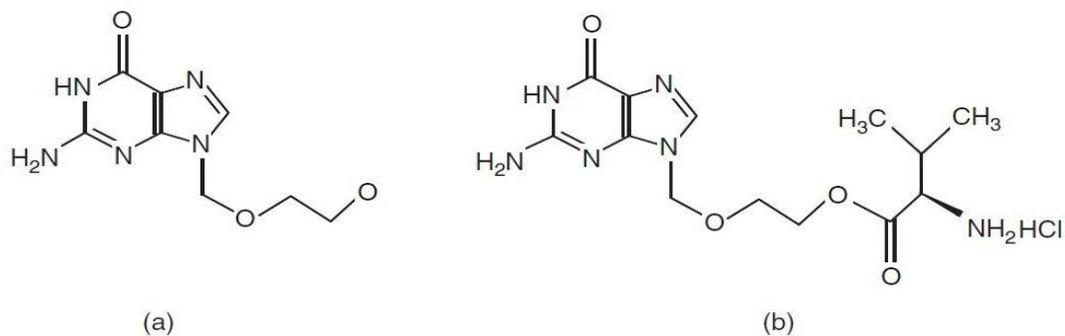


Figure 3.1 Acyclovir (a) and valacyclovir (b).

- Similarly, oral absorption, as well as **transdermal penetration**, of the long-acting angiotensin-converting enzyme (ACE) inhibitor enalaprilat is improved considerably by esterification of one of its carboxyl groups. The improved pharmacokinetic properties are attributed to the significantly higher lipophilicity of the ethyl ester pro-drug **enalapril**.

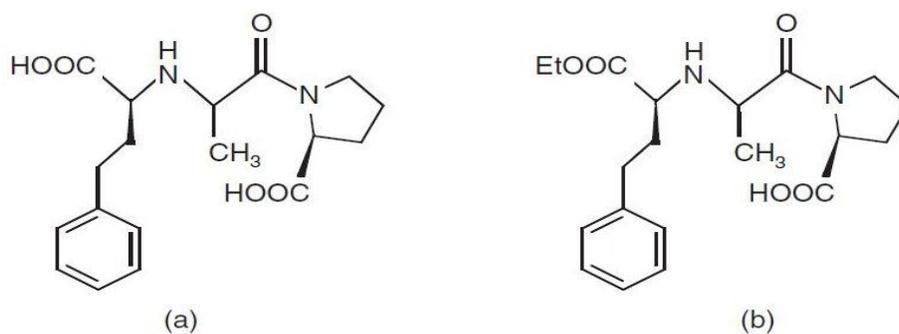


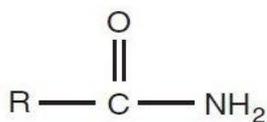
Figure 3.2 Enalaprilat (a) and enalapril (b).

- Ester pro-drugs are also designed to **reduce side effects** by changing the physicochemical properties of active compounds that cause tissue irritation. For example, piroxicam, nonsteroidal anti-inflammatory drugs (NSAID), is well absorbed after oral administration but causes gastrointestinal (GI) bleeding,

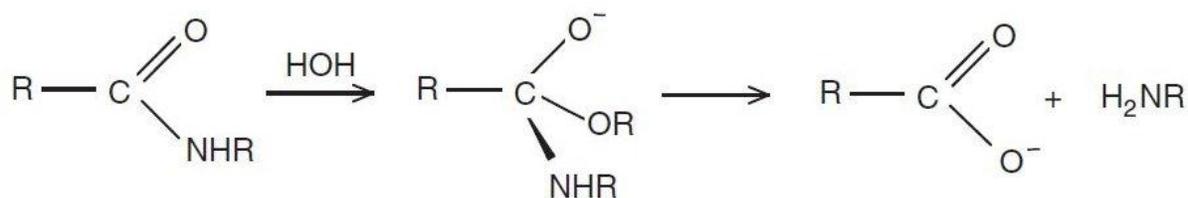
perforation, and ulceration. **Ampiroxicam** a **non-acidic pro-drug**, is an **ester carbonate pro-drug of piroxicam** with comparable therapeutic efficacy to piroxicam and reduced ulcerogenic and GI side effects.

- Another application of ester pro-drugs is related to **stability improvement** of parent compounds by modifying particularly unstable functional groups present in active agents.
- An interesting variation of the ester pro-drug approach is creation of **double pro-drug**, where two functional groups are modified simultaneously to achieve the combined physicochemical properties that would maximize permeability enhancement. A double pro-drug of the direct platelet and thrombin aggregation inhibitor **Melagatran** was developed by converting the carboxylic acid to an ester and hydroxylating the imidine moiety to reduce its basicity. Melagatran originally exhibited a low **oral bioavailability of 5 percent**, which was attributed to the presence of two strongly basic groups and a carboxylic acid group causing the compound to exist as a zwitterion at intestinal pH. The resulting pro-drug, **ximelagatran**, is uncharged at intestinal pH and has 80-fold improved permeability and an **oral bioavailability of 20 percent**.

## AMIDE BASED PRO-DRUGS



Amide



**Figure 3.6** Typical path of enzymatic hydrolysis of esters and amides.

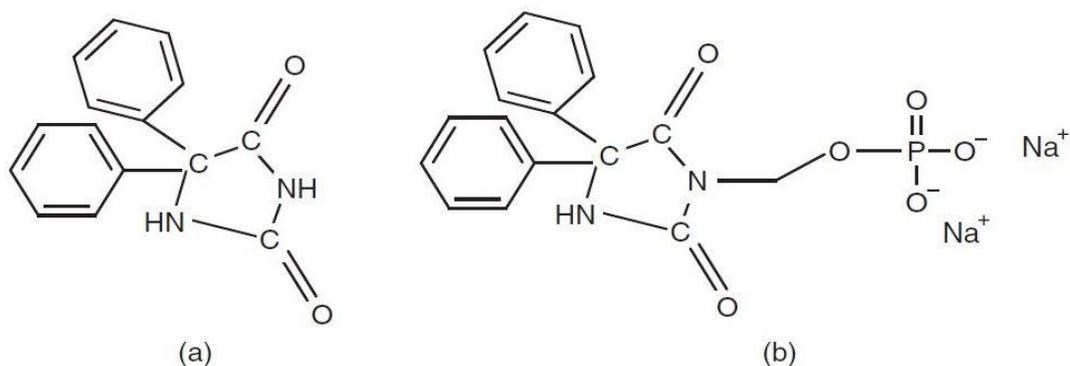
Amide pro-drugs are relatively similar to ester pro-drugs in terms of the chemical nature of the intermolecular linkage. In vivo activation of the amide pro-drug generally involves enzymatic cleavage. Owing to their particular chemical structure, amide pro-drugs can be designed for targeting peptide and nutrient transporters to enhance permeability. In this application, amide pro-drugs are also shown to generally provide superior physicochemical stability compared with more conventional ester derivatives.

**TABLE 3.3 Examples of Amide Prodrugs**

General design objective	Goal	Drug	Prodrug
Improvement of physicochemical properties	Decrease GI irritation	Nicotonic acid	Nicotinamide <sup>30</sup>
	Decrease GI irritation	Valdecoxib	Parecoxib <sup>41</sup>
Improvement of pharmacokinetic properties	Prolong action	Tolmetin sodium	Tolmetin glycine amide <sup>42</sup>
	Prolong action	Doxorubicin	Doxsaliform <sup>43</sup>
	Increase ocular permeability	Amfenac	Nepafenac <sup>44</sup>

### **PRO-DRUGS BASED ON SALT FORMS**

Salt forms are having **higher solubility**. So they are used for the drugs which are having low solubility and by that way to improve bioavailability.



**Figure 3.9** Phenytoin (a) and fosphenytoin (b).

For example, fosphenytoin is designed as a disodium salt ester pro-drug of phenytoin to overcome parenteral delivery problems related to the low aqueous solubility (20 to 25 $\mu$ g/mL) of the parent compound. The **sodium salt of phenytoin** provides good solubility enhancement (50 mg/mL) but lacks stability at pH below 12, resulting in rapid precipitation of phenytoin acid from sodium phenytoin solutions. **Fosphenytoin** provides further improvement of solubility to the level of 142 mg/mL and is stable at pH 7.5 to 8, which essentially results in greater safety, lower irritation, and ease of administration.

**TABLE 3.4** Examples of Salt Prodrugs

General design objective	Goal	Drug	Prodrug
Improvement of physicochemical properties	Increase solubility	Phenytoin	Fosphenytoin <sup>47</sup>
	Increase solubility	Amprenavir	Fosamprenavir calcium <sup>50</sup>
	Improve stability	Ganciclovir	Valganciclovir hydrochloride <sup>51</sup>
	Increase solubility	Mesalamine	Balsalazide disodium <sup>52</sup>
	Increase solubility	Trovafloxacin	Alatrofloxacin <sup>53</sup>

OTHER PRO-DRUGS are designed to achieve the different goals of the pharmaceuticals which are described here...

**TABLE 3.5 Additional Prodrug Types and Applications**

General design objective	Goal	Drug	Prodrug	Linkage
Improvement of physicochemical properties	Increase duration of action	Terbutaline	Bambuterol	Carbamate <sup>54</sup>
Improvement of pharmacokinetic properties	Improve targeting	Gemtuzumab	Gemtuzumab ozogamycin	Hydrazone <sup>31</sup>
	Increase topical penetration	Triamcinolone	Triamcinolone acetonide	Ketal <sup>30</sup>
	Decrease side effects	Chloral hydrate	Dichloral-phenazone	Complex <sup>30</sup> Lactone <sup>55</sup>
Decrease side effects	Lovastatin (mevinolinic) acid	Lovastatin		

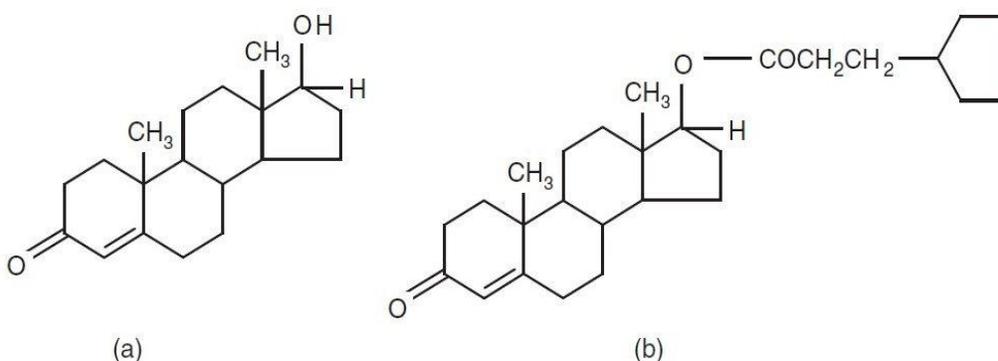
### **PRO-DRUGS FOR PROLONGED THERAPEUTIC ACTION**

For some therapeutic agents, decreased frequency of dosing and constant plasma concentrations can result in considerable enhancement of safety and efficacy of dosage forms by eliminating the **peak-valley effect**. In pro-drugs, two design principles can achieve sustained release:

- (1) The pro-drug is incorporated in a controlled release formulation that governs the rate of delivery (input-controlled systems), and**
- (2) The design of the prodrug-drug complex provides a rate-limiting factor of the drug release effect.**

Employing a controlled release formulation is particularly useful for drugs with poor stability, low aqueous solubility, high polarity, or low melting point. In general, these properties are related to the chemical structure of the drug and specifically to the functional groups with high hydrogen bonding potential such as

carboxylic acids and alcohols. In these cases, prodrugs can be designed to introduce lipophilicity and mask the hydrogen bonding groups of an active compound by adding another moiety. The classic example is in steroid therapy: lipophilic esters of testosterone. In the case of commonly used **testosterone cypionate** the rate of release is determined by the erosion kinetics of the depot formulation, whereas in vivo chemical stability is enhanced by the lipophilic properties of the prodrug.

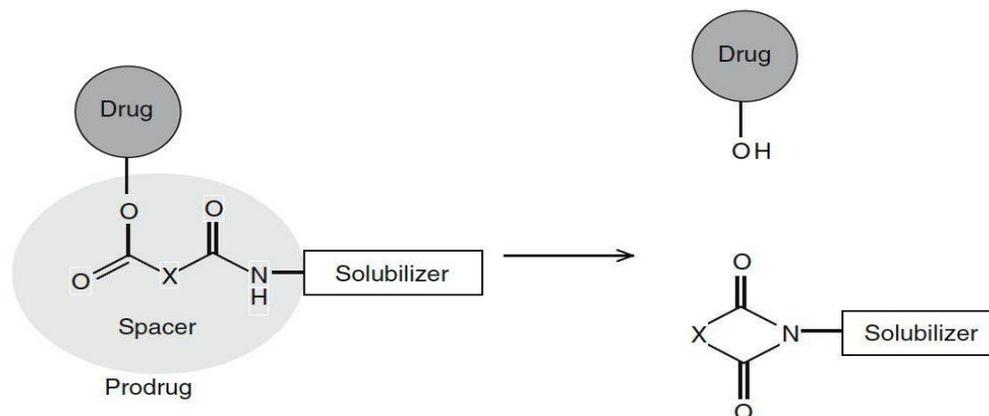


**Figure 3.12** Testosterone (a) and testosterone cypionate (b).

The second approach to prolonged therapeutic action is based on the controlled rate of conversion of the promoiety into the active compound in vivo. This approach requires particularly detailed study of the kinetics of prodrug-drug conversion. A classic example is bioconversion of **azathioprine to 6-mercaptopurine**.

New water-soluble prodrugs of an HIV protease inhibitor were tested recently; these prodrugs contain two linked units, a solubilizing moiety, and a self-cleavable spacer. These prodrugs convert to the parent drug not enzymatically but chemically via intramolecular cyclization through imide formation in

physiological conditions. The release rate of the parent drug is controlled by the chemical structure of both the solubilizing and the spacer moieties.



**Figure 3.14** Intramolecular cyclization of novel water-soluble prodrugs of HIV protease inhibitor in physiologic fluid.<sup>59</sup>

## PRO-DRUGS FOR VARIOUS PATHWAYS OF DRUG DELIVERY SYSTEMS

### 1. PRODRUGS FOR NASAL DRUG DELIVERY

The nasal route offers several advantages, such as high systemic availability and rapid onset of action. The nasal epithelium allows the transport of both charged and uncharged forms of the drug, and it is rich in several metabolizing enzymes such as **aldehyde dehydrogenase, glutathione transferases, epoxide hydrolases, and cytochrome P450–dependent monooxygenases**. These enzymes offer another dimension of flexibility in the design of prodrugs for nasal delivery.

L-Dopa has been systemically delivered using water soluble prodrugs through the nasal route. In rats, nasal administration of butyl ester prodrug afforded higher olfactory bulb and cerebrospinal fluid (CSF) L-dopa concentrations (relative to an equivalent intravenous dose) without significantly affecting plasma dopamine levels. These results indicate preferential delivery to the CNS, which suggests a potential to reduce side effects.

## 2. PRODRUGS FOR OCULAR DRUG DELIVERY

For most ocularly applied drugs, passive diffusion is thought to be the main transport process across the cornea. Major challenges in ocular drug delivery include **the tightness of the cornea<sup>1</sup> epithelium barrier, rapid precorneal drug elimination, and systemic absorption from the conjunctiva.** As a result, less than 10 percent and typically less than 1 percent of the instilled dose reaches the intraocular tissues. Many drugs developed for systemic use lack the physicochemical properties required to overcome the previously mentioned barriers.

Attempts to improve the ocular bioavailability have concentrated on **(1) extending the drug residence time in the conjunctival sac and (2) improving penetration of the drug across the corneal barrier.** Ocular absorption of a drug can be enhanced substantially by increasing its lipophilicity, which can be achieved with prodrug applications.

Key requirements for ocular prodrugs involve good stability and solubility in aqueous solutions to enable formulation, sufficient lipophilic properties to penetrate through the cornea, low irritation profile, and the ability to release the parent drug within the eye at a rate that meets the therapeutic need.

**TABLE 3.6 Prodrugs for Ocular Drug Delivery**

Drug	Prodrug	Advantages	Indication
Epinephrine	Dipivalyl epinephrine	Reduced side effects	Glaucoma <sup>88</sup>
Phenylephrine	Phenylephrine oxazolidine	Improved therapeutic action	Mydriatic <sup>89</sup>
Prostaglandins	Latanoprost, travoprost, bimatoprost, unoprostone	Improved permeability	Glaucoma <sup>90</sup>
Acyclovir	Valacyclovir	Improved bioavailability	HSV keratitis <sup>91</sup>

### 3. PRODRUGS FOR PARENTERAL DRUG DELIVERY

Prodrugs often have been employed in parenteral delivery to improve drug **solubility, disposition, and patient acceptability (e.g., decreased pain on injection)**. Ideally, the parenteral prodrug needs to be converted rapidly to the parent drug in the plasma to obtain a rapid response.

A classic example of using ester prodrugs to improve the parenteral delivery of sparingly water-soluble drugs is **fosphenytoin, a prodrug of phenytoin**. Fosphenytoin is water soluble and intrinsically safe, and it readily bioreverts to phenytoin on parenteral administration through the action of phosphatases. Pharmacokinetic and pharmacodynamics studies in animals and humans have shown that fosphenytoin quantitatively releases phenytoin on parenteral administration and provides better absorption, as well as far greater safety, than phenytoin.

An exciting new field of parenteral drug delivery involves **oil-based depot formulations for protein delivery**. The feasibility of administering such polar drug substances in the form of oil solutions is governed by the attainment of sufficient oil solubility, which can be achieved with prodrugs. Interesting examples of the experimental peptide delivery formulations are 4-imidazolidinone prodrugs of the polar local anesthetic agent **prilocaine**.

### 4. PRODRUGS FOR TRANSDERMAL DRUG DELIVERY

The skin is the major site for noninvasive drug delivery; however, transdermal drug penetration is relatively challenging because of the inherent variability in permeability of the skin. **Percutaneous drug absorption is described by Fick's first law of diffusion**. Therefore, the transdermal controlled delivery

system must alter some of the key mass-transfer parameters, such as **partition coefficient, diffusion coefficient, and drug concentration gradient**, to increase drug absorption. This can be achieved with the **prodrug** approach, in which highly absorbable prodrug molecules are activated within the skin.

The successful delivery of prodrug through the skin requires the following sequential steps:

- (1) Dissolution and diffusion of drug molecules in the vehicle into the skin surface.
- (2) Partitioning of the drug into the stratum corneum (SC).
- (3) Diffusion of the drug into the SC and
- (4) Partitioning of the drug into the epidermis and dermis and uptake into the blood circulation.

Based on these requirements, the desired parameters for transdermal prodrugs include **low molecular mass (preferably less than 600 Da), adequate solubility in oil and water to maximize the membrane concentration gradient (the driving force for diffusion), optimal partition coefficient, and low melting point.**

A good example of a transdermal prodrug is an **alkyl ester prodrug of naltrexone** designed to improve lipophilicity of the parent compound and increase its delivery rate across the skin. The mean naltrexone flux from the prodrug-saturated solutions exceeded the flux of naltrexone base by approximately two- to seven-fold.

## **5. PRODRUGS FOR ORAL DRUG DELIVERY**

Oral delivery is the most preferred route of drug administration; however, it often entails major challenges, namely, limited solubility of the drug and poor

permeation across the GI tract. The major goal of oral drug delivery is to increase the oral bioavailability, which generally is affected by presystemic metabolism (sum of first-pass and intestinal or intestinal membrane metabolisms) and inadequate drug absorption in the GI tract. In both cases, the design of a prodrug must balance the level of stability; premature conversion of prodrug and excessive prodrug linkage both decrease oral bioavailability.

Phosphates or other salts are used often as oral prodrugs to increase the solubility of the parent drugs. Successful examples of this approach include **fosphenytoin and hydrocortisone phosphate**. In both cases, bioconversion to the parent compound involves rapid prodrug dephosphorylation by intestinal membrane-bound **alkaline phosphatase**, yielding high concentrations of the poorly soluble parent drug at the apical membrane. The regenerated lipophilic parent drugs are well absorbed compared with their polar, ionized prodrugs.

Ester prodrugs are employed to enhance membrane permeation and transepithelial transport of hydrophilic drugs by increasing the lipophilicity of the parent compound, resulting in enhanced transmembrane transport by passive diffusion. For example, pivampicillin, a pivaloyloxymethyl ester of ampicillin, is more lipophilic than its parent ampicillin and has demonstrated increased membrane permeation and transepithelial transport in in vivo studies.

## **6. PRODRUGS FOR BUCCAL DRUG DELIVERY**

The buccal delivery route has generated interest lately because it offers a noninvasive route of delivery for proteins and peptides that cannot tolerate the harsh acidic environment of the GI tract. Drug delivery by the buccal mucosa prevents the drug loss of first-pass hepatic metabolism.

Prodrugs in buccal delivery generally improve drug solubility and stability using polymers. Use of buccal devices incorporating prodrugs provides a constant drug release rate, resulting in a reduced total amount of drug and increased patient comfort.

Buccal delivery of opioid analgesics and antagonists can improve bioavailability relative to the oral route. **Esterification of the 3-phenolic hydroxyl group in opioid analgesics such as nalbuphine, naloxone, naltrexone, oxymorphone, butorphanol, and levallorphan improved bioavailability and eliminated the bitter taste.** The prodrugs of morphine, morphine-3-propionate, helps to reduce enzymatic degradation in the oral cavity and enhance permeation across biological barriers.

## **RECENT ADVANCES IN THE PRODRUG THERAPY**

Enzyme-activated prodrug therapy has been used to design specific drug delivery systems for the treatment of cancer. In the initial step, a drug-activating enzyme is targeted and expressed in the tumors. Subsequently, a nontoxic prodrug, which acts as the substrate to the enzyme, is administered systemically, enabling selective activation of the prodrug in the tumor. Several strategies have been identified for targeting the tumor.

### **1. ANTIBODY DIRECTED ENZYME PRODRUG THERAPY (ADEPT)**

In *antibody-directed enzyme prodrug therapy* (ADEPT), a monoclonal antibody to a cancer-specific antigen is conjugated to an enzyme that is normally absent in body fluid or cell membranes (the antibody enables localization of the conjugate in the tumor cells). First, the antibody enzyme conjugate is delivered by infusion.

After the excess conjugate is cleared from the circulation, a nontoxic prodrug is administered, enabling site-specific activation.

For example, Her-2/neu antibody (trastuzumab, Herceptin) recently has received approval for clinical use. ADEPT has been used to target a variety of enzyme systems, such as alkaline phosphatases, aminopeptidases, and carboxypeptidases.

A slight variation of ADEPT called **antibody-generated enzyme nitrile therapy (AGENT)** relies on enzymatic liberation of cyanide from cyanogenous glucosides.

## **2. GENE DIRECTED ENZYME PRODRUG THERAPY (GDEPT) AND VIRAL DIRECTED ENZYME PRODRUG THERAPY (VDEPT)**

Both gene-directed enzyme prodrug therapy (GDEPT) and viral-directed enzyme prodrug therapy (VDEPT) involve physical delivery of genes encoding prodrug activating enzymes to the tumor cells for site-specific. The only notable difference between the two strategies is that **GDEPT uses nonviral vectors for intracellular delivery of genes, whereas VDEPT uses viral vectors for achieving the same purpose.**

The transfected tumor cells express the enzyme protein, which is further converted to active enzyme and selectively catalyzes intracellular activation of inactive prodrug to the active drug (toxic), resulting in cell death.

Another variation of GDEPT is **genetic prodrug activation therapy (GPAT), which involves the use of transcriptional differences between normal and tumor cells to induce the selective expression of drug-metabolizing enzymes to convert nontoxic prodrug into the active toxic moiety.**

Examples of GDEPT include **irinotecan (CPT-11), a prodrug of 7-ethyl-10-hydroxy-camptothecin activated by carboxyl esterase**; 5-fluorocytosine, a prodrug of 5-FU activated by cytosine deaminase; and cyclophosphamide, a prodrug of 4-hydroxycyclophosphamide activated by cytochrome P450, which degrades into acrolein and phosphoramidate mustard.

### 3. MACROMOLECULE DIRECTED ENZYME PRO-DRUG THERAPY

Macromolecule-directed enzyme prodrug therapy (MDEPT) is also referred to as **polymer-directed prodrug therapy (PDEPT)**. It is similar to GDEPT and VDEPT, except that it applies a **macromolecule conjugate of the drug to enable delivery to the tumor**. This method also takes advantage of the enhanced permeation and retention (EPR) of tumors. One of the earliest examples of MDEPT involved **N-(2-hydroxypropyl) Methacrylamide**.

Polymeric prodrugs are currently one of the most investigated topics. This research has resulted in breakthrough therapeutics, and many compounds are under clinical development. Other examples of polymeric prodrug applications include the use of polysaccharides such as **dextran, mannan, and pullulan** to enable active targeting to tumor cells.

**TABLE 3.7 Examples of Polymeric Prodrugs**

Drug-polymer conjugate	Stage of development	Organization
HPMA copolymer-doxorubicin	Phase II	CRC/Pharmacia <sup>118</sup>
HPMA copolymer-doxorubicin-galactosamine	Phase I/II	CRC/Pharmacia <sup>119</sup>
HPMA copolymer-paclitaxel	Phase I	Pharmacia <sup>123</sup>
HPMA copolymer-camptothecin	Phase I	Pharmacia <sup>123</sup>
HPMA copolymer-platinatate	Phase I	Access Pharmaceuticals <sup>123</sup>
Polyglutamate-paclitaxel	Phase II/III	Cell Therapeutics <sup>120</sup>
Polyglutamate-camptothecin	Phase I	Cell Therapeutics <sup>123</sup>
PEG-camptothecin	Phase II	Enzon <sup>124</sup>
PEG-aspartic acid-doxorubicin micelle	Phase I	NCI, Japan <sup>123</sup>
PEG-paclitaxel	Phase I	Pharmacia <sup>124</sup>
Doxorubicin micelle	Phase II/III	Access Pharmaceuticals <sup>124</sup>
HPMA platinatate		

All the systems are described in one figure below...

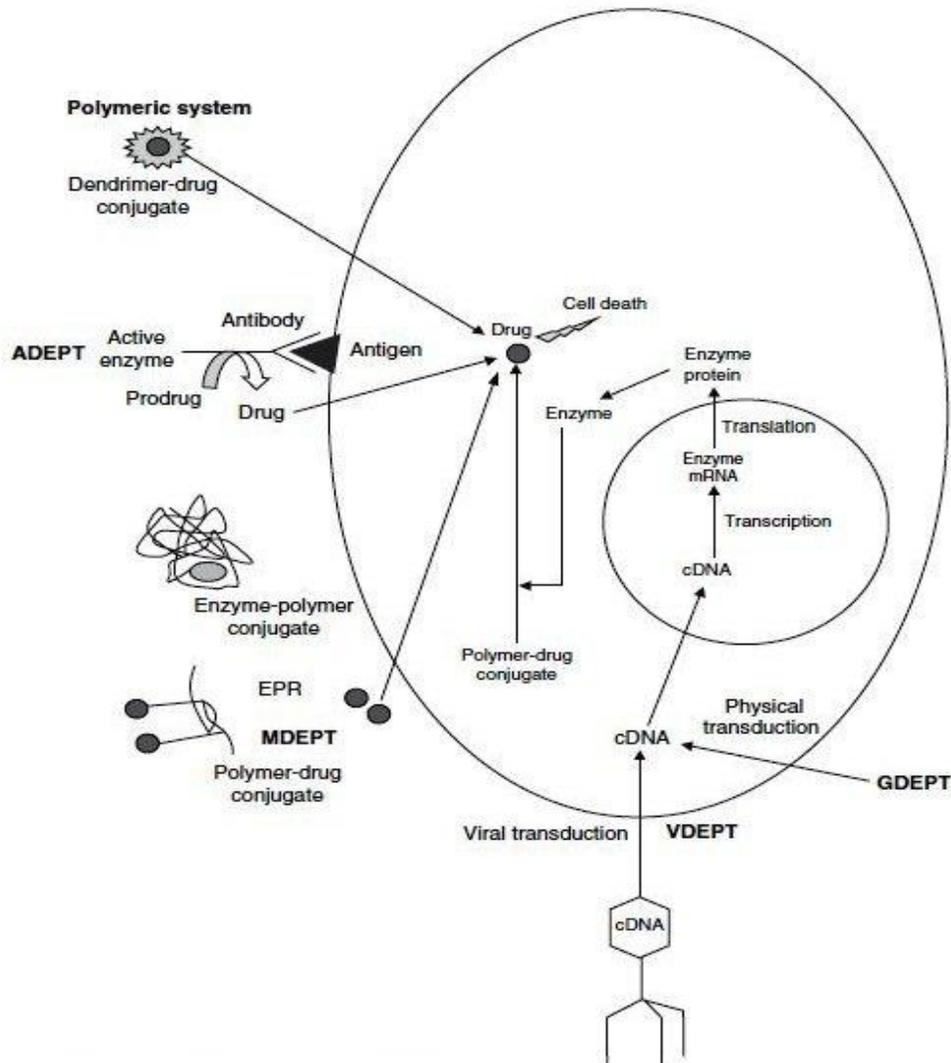


Figure 3.16 Modes of delivery and activation of prodrugs.

#### 4. LECTIN DIRECTED ENZYME ACTIVATED PRODRUG THERAPY

Lectin-directed enzyme-activated prodrug therapy (LEAPT) is a bipartite drug delivery system that first exploits endogenous carbohydrate-to-lectin binding to localize glycosylated enzyme conjugates to specific, predetermined cell types, followed by administration of a prodrug activated by the pre-delivered enzyme at the desired site. For example, the carbohydrate structure of a  $\alpha$ -L-

rhamnopyranosidase enzyme was modified through enzymatic deglycosylation and chemical reglycosylation. Ligand competition experiments revealed enhanced, specific localization by endocytosis and a strongly carbohydrate-dependent, 60-fold increase in selectivity toward target cell hepatocytes that generated a greater than 30-fold increase in protein delivery.

**Tissue-activated drug delivery (TADD)** involves the use of alternating polymers of polyethylene glycol and tri-functional monomers such as lysine. The resulting polymer has a pendant with the PEG forming the chain and lysine providing the reactive carboxylic acid groups at periodic intervals, which can be linked to the drug. The linking group chemistry can be altered to induce activation in specific tissues.

## 5. DENDRIMERS

**Dendrimers are highly branched globular macromolecules.** Several researchers have exploited the multivalency of dendrimers at the periphery for attachment of drug molecules. **A significant advantage of this system is that the drug loading can be tuned by varying the generation of the dendrimer, and the release of drug can be tailored by incorporating degradable linkages between the drug and the dendrimer.**

Conjugates of poly (amidoamine) (PAMAM) dendrimer with cisplatin have been shown to improve aqueous solubility and to reduce systemic toxicity while simultaneously exhibiting selective accumulation in tumors. Propranolol is a poorly soluble drug and is a known substrate of the P-glycoprotein (P-gp) efflux transporter. A prodrug of Propranolol was synthesized by conjugating Propranolol to generation 3 (G3) and lauroyl- G3 PAMAM dendrimer. Both derivatives

demonstrated improved aqueous solubility and bypassed the efflux transporter with improved bioavailability.

### **TYPES OF THE PRODRUG**

#### **1. Carrier-linked prodrugs:**

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

**Carrier-linked prodrugs** can be further subdivided into:

- **Bipartate:** composed of one carrier (group) attached to the drug.
- **Tripartate:** carrier group is attached via linker to drug
- **Mutual prodrugs:** two drugs linked together

#### **2. Bioprecursor**

They metabolized into a new compound that may itself be active *or* further metabolized to an active metabolite (e.g. amine to aldehyde to carboxylic acid).

### **PREVIOUS QUESTIONS**

1. Define “Pro-drug” Discuss pathways of them in therapeutics giving suitable examples.
2. Write potential of the prodrug approach
3. Discuss in detail polymer properties.