A REVIEW ON PRODRUG

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ABSTRACT
A prodrug is a precursor chemical compound of a drug. Instead of administering a drug, a prodrug might be used instead to improve how a medicine is absorbed, distributed, metabolized, and excreted (ADME). A prodrug may be used to improve how selectively the drug interacts with cells or processes that are not its intended target. It is estimated that about 10% of the drugs approved worldwide can be classified as prodrugs. Prodrugs, which have no or poor biological activity, are chemically modified versions of a pharmacologically active agent, which must undergo transformation in vivo to release the active drug. Prodrugs are bio reversible derivatives of drug molecules that undergo an enzymatic and/or chemical transformation in vivo to release the active parent drug, which can then exert the desired pharmacological effect. In both drug discovery and development, prodrugs have become an established tool for improving physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically active agents. It is estimated that about 10% of the drugs approved worldwide can be classified as prodrugs. Prodrugs can also improve drug targeting, and the development of a prodrug of an existing drug with improved properties may represent a life-cycle management opportunity. This reduces adverse or unintended effects of a drug, especially important in treatments like chemotherapy, which can have severe unintended and undesirable side effects. The purpose of this article is to provide a concise overview of this modern prodrug approach.

KEYWORDS: prodrug activation; targeted prodrug approach.

INTRODUCTION
Prodrugs are derivatives of active drug moieties, designed to undergo conversion in the body, thereby releasing the active parent drug. The prodrug approach is taken in order to overcome pharmaceutical, pharmacokinetic, or pharmacodynamic obstacles, such as low oral absorption, inadequate site specificity, poor stability, etc. In recent years, prodrugs have become increasingly popular and successful; to date, ~10% of the global marketed medications are prodrugs, 20% of all small molecular medicines approved between 2000 and 2008 were prodrugs, and when focusing on 2008, it emerges that over 30% of drugs approved in this year were prodrugs. The drug gives pharmacologic response by binding with receptor at the site of action and factor that limits its optimum entering into this site is considered as barrier. The barrier can be overcome by chemically linking promoieties to form prodrug which undergoes biotransformation.
to release the parent drug, so prodrug is a chemically modified inert drug precursor which upon biotransformation converted into the pharmacologically active parent compound\(^4\). During the last two decades, there has been a steady improvement in the physicochemical, biopharmaceutical and/or pharmacokinetic properties of pharmacologically active compounds by the implementation of a prodrug strategy. It is estimated that currently about 10% of worldwide marketed drugs can be classified as prodrugs. Moreover, in 2008, one third of all approved small molecular weight drugs were prodrug. The term prodrug was introduced by Albert who used “prodrug” or “proagent” to refer to a pharmacologically inactive compound that is transformed by the mammalian system into an active substance by either chemical or metabolic means\(^1,2\). Another term drug latentiation, which implies a time lag element or component, was coined by Harper\(^3,4\). Later, the concept of prodrug and latentiated drug for solving various problems was attempted and the definition of drug latentiation was extended to include non-enzymatic regeneration of parent compounds\(^5\). The prodrug approach has emerged as a tool in overcoming various obstacles to drug formulation and targeting such as chemical instability, poor aqueous solubility, inadequate brain penetration, insufficient oral absorption, local irritation and toxicity\(^6\). It is justified by the fact that once the barrier to the use of parent compound has been overcome, these temporary forms can be converted to the free parent compound that can exert its pharmacological activity. A prodrug is thus defined as a biologically inactive derivative of a parent drug molecule that usually requires a chemical or enzymatic transformation within the body to release the active drug, and possess improved delivery properties over the parent molecule\(^7-9\). These attractive features render the prodrugs a well recognized strategy to improve drug targeting, to enhance the physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically potent compounds, and thereby increase the usefulness of a potential drug. The schematic representation of prodrug concept is shown in Fig 1.1.

![Schematic representation of prodrug concept](image-url)
RATIONAL FOR THE USE OF PRODRUGS:

A drug can only exert a desired pharmacological effect if it reaches its site of action. The three major phases involved in the drug receptor interaction or biological bioavailability of drug includes the pharmaceutical phase, the pharmacokinetic phase and pharmacodynamic phase. Many barriers which limit drug’s ability to reach a desired target organ and the subsequent receptor site are considered of pharmacokinetic.

Besides these, barriers of non-pharmacokinetic and pharmacodynamic origin may also prevent a drug from reaching the desired target. It includes pathological limitation such as toxicity, high incidence of side effects and teratogenicity, pharmaceutical limitation such as chemical instability of product or formulation, psychological limitation such as unpleasant taste, pain at injection site and cosmetic damage to the patient and economic barriers. Most of these limitations can be overcome by prodrug approach, but after overcoming the various barriers, the prodrug should rapidly convert into active moiety after reaching the target site. The awareness that the onset, intensity and duration of drug action are greatly affected by the physicochemical properties of drug has promoted the emergence of various theoretical and predictive models for drug design and evaluation. The design of an efficient, stable, safe, acceptable and aesthetic way to target a drug to its site of action while overcoming various physical, chemical and social barriers is certainly an area where the utilization of the prodrug approach holds great potential.

History:

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 to release salicylic acid. Aspirin, 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.\(^9\)

**Definition of Prodrug:**

“Prodrug are pharmacologically inactive compound that is transform by the mammalian system into an active substance by either chemical or metabolic way.”

**IUPAC definition**

Compound that undergoes biotransformation before exhibiting pharmacological effects. Prodrugs can thus be viewed as *drugs* containing specialized nontoxic protective groups used in a transient manner to alter or to eliminate undesirable properties in the parent molecule.\(^{11}\)

Prodrugs are pharmacologically inactive derivatives of active drug that are designed to maximize the amount of active drug that reaches the site of action, through manipulation of physicochemical, biopharmaceutical, pharmacokinetic properties of drug. They are converted into active drug within the body through enzymatic or non-enzymatic reaction. Also called letentiation.

**Classification of Prodrug**

There are two main classes of prodrugs:

**Carrier Linked Prodrug:**

In the carrier-linked prodrugs, the active molecule (thedrug) is temporary linked to a carrier (also known as a promoiety) through a bioreversible covalent linkage. Once in the body, the carrier-linked prodrug undergoes biotransformation, releasing the parent drug and the carrier. Ideally, the carrier should be nonimmunogenic, easy to synthesize at a low cost, stable under the conditions of prodrug administration, and undergo biodegradation to nonactivemetabolites \(^{5,12,13}\). In so-called co-drugs (mutual prodrugs, multipleprodrugs), a prodrug is formed from two pharmacologically active agents coupled together into a single molecule, and act as promoieties of each other.
Examples:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Active form</th>
</tr>
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<tbody>
<tr>
<td>Sulfapyridin</td>
<td>5-aminosalicylic acid</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>L-DOPA</td>
<td>Enthacapone</td>
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<td>Gabapentin</td>
<td>Pregabalin</td>
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<td>Ampicilin</td>
<td>Subactrm</td>
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<tr>
<td>Sulfamethoxazol</td>
<td>Nalidixic acid</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>Cytarabin</td>
</tr>
</tbody>
</table>

The major groups of carrier-linked prodrugs are esters and amides; other groups include phosphates, carbamates, carbonates, oximes, imines and N-Mannich base.

**Bioprecursor**

The bioprecursor prodrug is transformed metabolically or chemically by hydration (e.g., lactonessuch as some statins), oxidation (e.g., dexpantenol, nabumetone) or reduction (e.g., sulindac, platinum(IV) complexes) to the active agent.

Based on the site of conversion into the pharmacologically active agent, the prodrugs can be additionally classified into two groups:

**Properties of Ideal Prodrug**

An ideal prodrug should possess following properties

A). Pharmacological inertness.

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

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

**Objectives of Prodrug design**

Prodrug design is really not different from the general drug discovery process, in which a unique substance is observed to have desirable pharmacological effects, and studies of its properties lead to the design of better drugs.

The main objectives of a prodrug designing are:

- To bring active drugs to their respective active sites.
- To provide the desired pharmacological effects while minimizing adverse metabolic and/or toxicological events.
- To improve the clinical and therapeutic effectiveness of those drugs which suffer from some undesirable properties that otherwise hinder their clinical usefulness.
To avoid the practice of clinically co-administering two drugs in order to enhance pharmacological activity or prevent clinical side effects. Simultaneous administration does not guarantee equivalent absorption or transportation to site of action. So, mutual prodrug concept is useful when two synergistic drugs need to be administered at the same site at the same time. Mutual prodrugs are synthesized toward a pharmacological objective of improving each drug's efficacy, optimizing delivery, and lowering toxicities.

**Prodrug approaches for enhancing administration, permeability, absorption, and distribution of drugs**

**Prodrugs with increased aqueous solubility**

Poor aqueous solubility is considered as a serious problem limiting the therapeutic use of numerous drugs and drug candidates. Among various strategies used to overcome this drawback is the prodrug approach. One frequently employed means of improving the aqueous solubility of a drug is by the use of esters and amides of phosphoric acid, due to the ionic nature of the phosphate group. It should be noted that phosphatederivatives display high chemical stability, often even higher than the parent compound. Under physiological conditions phosphate prodrugs undergo rapid biotransformation by endogenous phosphatases, such as alkaline phosphatase, of the intestine, plasma, and the liver.

**Prodrugs with increased lipid solubility**

In order to improve lipophilicity, and thus passive transport through biological membranes, compounds containing polar or ionizable groups can be converted into ester prodrugs [26, 33, 36, 44, 54]. Examples of ester prodrugs with improved lipophilicity designed for oral administration are listed in Table 2. Prodrugs with increased lipophilicity are also designed for topical administration. For example, esters of ketolac (a non-steroidal anti-inflammatory drug with potent analgesic activity) and fatty acids (stearic, linoleic, oleic) allow the drug to accumulate in the skin with concomitant low skin permeation, leading to increased therapeutic efficiency and reduced side effects of the parent drug [13].

**Prodrugs as substrates for GI membrane transporters**

Gabapentin enacarbil ([(±)-1-((a-isobutanyloxyethoxy) carbonyl] aminomethyl)-1-cyclohexane acetic acid; Horizant®), a prodrug of gabapentin (1-aminomethyl)-cyclohexane acetic acid), is a substrate for monocarboxylic acid transporter-1 (MCT-1) and sodium-dependent multivitamin transporter (SMVT), distributed throughout the intestine. Gabapentin enacarbil is stable at physiological pH and rapidly converted into gabapentin. *In vitro* and *in vivo*
studies have demonstrated that gabapentin enacarbil is endowed with better absorption, bioavailability, and pharmacokinetic properties compared with gabapentin.

**Prodrug approaches CNS for the delivery**

One of the major difficulties in the development of drugs acting at the central nervous system (CNS) is the inability of many therapeutical compounds to cross the blood-brain barrier (BBB). The BBB is formed by endothelial cells of brain microvessels connected by extensive tight junctions. Combined with an absence of fenestrae and an extremely low pinocytotic activity, transport of molecules across the BBBs achieved either through diffusion as a passive process, or with the aid of special carrier systems involving intrinsic transporter proteins localized on the luminal (blood side) and abluminal (brain side) sides of the epithelial cells. The BBB is necessary to provide an optimal chemical environment for brain function.

**Applications**

(a) **PHARMACEUTICAL APPLICATIONS**

1) Improvement of taste
2) Improvement of odor
3) Change of physical form for preparation of solid dosage form Reduction of GI irritation
4) Reduction of pain on injection
5) Enhancement of drug solubility and dissolution rate (hydrophilicity of drug)
6) Enhancement of chemical stability of drug

(b) **PHARMACOKINETIC APPLICATIONS**

1) Enhancement of bioavailability (lipophilicity)
2) Prevention of presystemic metabolism
3) Prolongation of duration of action
4) Reduction of toxicity
5) Site-specific drug delivery (drug targeting)

**Improvement of taste**

One of the reasons for poor patient compliance particularly in case of children, is the bitterness, acidity or causticity of the drug.

Two approaches can be utilized to overcome the bad taste of drug. It is reduction of drug solubility in saliva and to lower the affinity of drug towards taste receptors.

E.G.

Parent drug prodrug
Chloramphenicol Palmitate ester
Prodrug to Increase Patient Acceptance. The antibacterial drug clindamycin is bitter and not well tolerated by children. Clindamycin palmitate is not bitter. Clindomycin (R = H), clindomycin phosphate (R = PO3H2), clindomycin palmitate (R = O{(CH2) 14CH3}) Either not soluble in saliva or does not bind to the bitter taste receptor or both.

Chloramphenicol palmitatechloramphenicol

Improvement of odor

The odor of a compound depends upon its vapor pressure >- A liquid with high vapor pressure will have strong odor.

e.g; Ethyl mercaptan which is a foul smelling liquid, it is useful in the treatment of leprosy, is converted in to its phthalate ester, which has higher b.p. and odorless.

diehyl di thoiso phthalate ethyl mercaptan

Reduction of pain on injection

Intramuscular injection are particularly painful when the drug precipitates or penetrates into the surrounding cells or when the solution is strongly acidic, alkaline or alcoholic, e.g. the low aqueous solubility of clindamycin HCl, the alkaline solution of phenytoin are responsible for pain on injection.

This can be overcome by use of more water soluble prodrugs of such agents. E.g. 2-phosphate ester of clindamycin.
Prodrug to Eliminate Formulation Problems

Formaldehyde is a gas with a pungent odor that is used as a disinfectant. Too toxic for direct use. It is a stable solid that decomposes in aqueous acid. The pH of urine in the bladder is about 4.8, so methenamine is used as a urinary tract antiseptic. Has to be enteric coated to prevent hydrolysis in the stomach.

Prodrug for Improved Absorption Through Skin

corticosteroids - inflammation, allergic, pruritic skin conditions fluocinoloneacetonide (R = H) fluocinonide (R = COCH3). Better absorption into cornea for the treatment of glaucoma. The cornea has significant esterase activity

Prodrug for Increased Water Solubility

Choice of water solubilizing group:-
The ester must be stable enough in water for a shelf life of \( \geq 2 \) years (13 year half-life), but must be hydrolyzed in vivo with a half-life < 10 minutes. Therefore, in vivo/in vitro lability ratio about 106.

To avoid formulation of etoposide with detergent, PEG, and EtOH (used to increase water solubility), it has been converted to the phosphate prodrug

Areas of Improvement for Prodrugs
1. site specificity
2. protection of drug from biodegradation?
3. minimization of side effects
4. Site-specific drug delivery

After its absorption into systemic circulation the drug is distributed to the various parts of the body including the target site as well as the nontarget tissues such a distribution pattern has several

Advantages:
1) Improve patient acceptability of the agent (i.e. reduce pain associated with administration).
2) Alter absorption, alter distribution, alter metabolism or alter elimination.
3) The chemical nature of the prodrug that can be prepared is somewhat limited, however, by the chemical nature of the active.
4) Elimination of unpleasant taste associated with the drug.
5) Decreases toxicity.
6) Increases chemical stability.
7) Decreases metabolic inactivation.
Disadvantages:

Lead to undesirable toxic effects in non-target tissues. A smaller fraction of the drug will reach its target site. If the target site has a long distribution time, the drug may get eliminated without reaching a site. Drug reaches the target cells in sufficient amounts, it may not be able to penetrate into them. Overcome this problems by altering its disposition characteristics. The prodrug converted into its active form only in the target organ or tissue by utilizing either specific enzymes or pH value different from the normal pH for activation.

Example of selective uptake system

» Mesalamine is a useful in treatment of ulcerative colitis. It is not absorbed into the systemic circulation. However following oral administration, the drug is inactivated before reaching the lower intestine, the site of action. Covalent binding of this agent to sulfaphridine yields the prodrug sulfasalazine, an azo compound.

» This prodrug reaches the colon intact where cleavage by the bacterial enzyme azoreductase releases the active mesalamine for local action.

The prodrug approach to better targeting

Prodrugs, the pharmacologically inactive derivatives of active drugs, 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. But new developments are increasingly taking the concept beyond issues of availability to include targeting and enzyme activation. Prodrug design can be very effective in solving many of the stability, solubility, permeability, and targeting problems that plagued drug discovery and development. An inaugural two-day conference on prodrugs, organized by Pharmaceutical Education Associates and chaired by Howard Ando of Pfizer, covered the recent developments in prodrug techniques that are being used to solve delivery and targeting issues in R&D. There are a number of criteria that should be met even before making a prodrug, began Kenneth Sloan of the University of Florida:

1. Is there really a problem that is worth fixing?
2. Is the prodrug really transient, do the components of the prodrug cause extra toxicity, and is the prodrug cheap and simple to make?

Several common promoieties that can be used to make prodrugs of various functional groups, including acyl and ‘soft alkyl’ groups. The chemical stability of prodrugs may be different under enzymatic conditions. For example, the chemical stability of aliphatic carboxylic esters in
buffered aqueous solutions increases with increasing chain length of the aliphatic acid. Enzymatic hydrolysis of esters increases initially with chain length, and then decreases as the chain lengthens beyond 6-7 carbons. Sloan explained several different hydrolysis mechanisms for the conversion of prodrugs to active moieties and the criteria used in the selection of the promoiety: avoid ones that generate toxic metabolites!

**Ester prodrugs:**

Oral absorption is a key component of oral bioavailability. Pfizer’s Kevin Beaumont discussed issues involved in designing ester prodrugs including solubility, efflux and intestinal metabolism. solubility, Gut wall hydrolysis of ester prodrugs could limit oral bioavailability, while non-productive hepatic hydrolysis and biliary excretion could minimize the benefits expected of increased lipophilicity. Prodrugs of simple alkyl esters, cyclic carbonate esters and acyclic double esters often present their own advantages and disadvantages. Simple alkyl esters are not usually substrates of human blood esterases, tending to rely on hepatic hydrolysis, and have been used successfully for many ACE inhibitors. Cyclic carbonate esters and acyclic double esters can be activated by human blood borne esterases and have been used successfully for antibiotics, antivirals, and angiotensin II antagonists. But, there could be issues with their chemical stability and the formation of reactive aldehyde or ketone metabolites.

Esters, the most common type of prodrug, are converted back to the active parent via the ubiquitous esterases present in blood, tissues and organs. One theme throughout the conference was that these esterase enzymes exhibit broad and overlapping substrate specificity towards esters and amides and that their activity varies considerably between species. Aliphatic ester hydrolysis rates typically decrease in the order: rat > rabbit > dog> human. Rodents have some aliphatic esterases that are not present in humans and are believed to contribute to the large inter-species difference in drug disposition. For screening purposes, dogs should be used instead of rodents and whole blood should be used instead of just serum.

**hPepT1-targeted prodrugs**

Everett Perkins of Eli Lilly discussed the use of peptide transporters in increasing membrane permeability. LY-354740 is an agonist for the type-2 metabotropic glutamate receptor (mGluR2), but its high water-solubility and zwitterionic nature result in very low membrane permeability and an oral bioavailability of only ~6% in humans. Simple ester modification of LY 354740 does not result in any viable candidate due to insufficient stability, although derivatization with L-alanine of the primary amine in LY-354740 makes it a good substrate of the intestinal peptide transporter hPepT1. The resulting prodrug LY-544344 is enzymatically
hydrolyzed to release molar equivalents of alanine and LY-354740 in vivo. In vitro, prodrug uptake is concentration-dependent following Michaelis-Menten kinetics and is inhibited by GlySar, a known substrate of hPepT1. LY-544344 is rapidly absorbed and readily converted to the parent drug in rats and dogs, with systemic plasma exposure to the prodrug ≤ 4% of the corresponding values for the parent. The low concentrations of the prodrug in the portal vein of rats and dogs suggest that the primary site of prodrug hydrolysis is within the intestinal epithelium and mesenteric microcirculation. Pharmacokinetics of LY-354740 are generally dose-proportional following oral administration of the prodrug, with exposure to LY-354740 increased up to 16-fold in rats and up to 17-fold in dogs

**Active transporters:**
Targeting active transport pathways can overcome a range of problems that limit drug development including poor intestinal permeability, narrow absorption window, short half-life, high first-pass metabolism, rapid drug efflux, poor absorption due to low solubility, poor CNS penetration, and poor tissue targeting. Kenneth Cundy of XenoPort discussed two efforts to modify drugs into substrates of active transporter systems in the large intestine in order to improve the absorption and distribution

**Characteristics of drugs:**
Gabapentin is an anticonvulsant used for the treatment of epilepsy and post-herpetic neuralgia, but suffers from suboptimal pharmacokinetic properties including saturable absorption, high inter-patient variability, lack of dose proportionality and short half-life. To improve the PK properties of gabapentin, XP-13512 was developed as an oral prodrug. XP-13512 is a substrate of MCT-1, a monocarboxylate transporter (MCT) which is highly expressed in all segments of the colon as well as upper GI, and SMVT, and is a sodium-dependent transport system responsible for transfer and distribution of multiple vitamins from the various absorptive tissues. Oral bioavailability increased from 25% for gabapentin to 85% for XP-13512 in monkeys, and no saturation was observed for increasing prodrug doses. XP-13512 is cleaved to gabapentin by non-specific esterases in the intestines, liver, and blood with low prodrug exposure (<2%) in human clinical trials, while the tablet formulation of the prodrug allows twicedailydosing. XP-13512 is currently in two phase IIa clinical trials for post-herpetic neuralgia and restless leg syndrome. Cundy also discussed briefly XenoPort’s effort to find a novel, patentable single isomer prodrug for baclofen, a GABA Agonist used as a muscle relaxant and antispastic. The company is focusing on XP-19986, which has demonstrated improved PK profiles in animals including a 15-fold increase in colonic
absorption in monkeys. Xenoport plans to file in 2004 an IND application with FDA to start clinical trials.

**Ocular prodrugs:**

The complexity of the human eye presents unique challenges for drug delivery. Ocular bioavailability through topical administration (eye drops) is poor, usually <5%. Therapeutic levels of many drugs may be difficult to achieve in ocular tissues and systemic toxicities are of concern when the oral and intravenous routes of administration are used. Ashim Mitra of University of Missouri-Kansas City presented work on the molecular identification and functional characterization of P-glycoproteins in human and rabbit cornea. P-gps are efflux pumps that pump out the topically applied drugs that enter the cornea, contributing to low ocular bioavailability. An implantable microdialysis probe was used in the same eye of a rabbit to obtain ocular pharmacokinetics of erythromycin in the vitreous and aqueous chambers. The in vivo absorption data showed that P-gp is functional in the cornea and restricts drug absorption into the aqueous. Inhibition with various drugs resulted in increases in AUCs that was concentration-dependent. One strategy was presented to overcome P-gp-mediated efflux through prodrug derivatization utilizing nutrient transporters expressed on the outer leaflet of cellular membranes. Quinidine, a well known substrate of P-gp, was conjugated to valine in the form of an ester. Val-quinidine does not interact with P-gp even at high concentrations. Competition with Gly-Sar and various model amino acid substrates indicates that Val-quinidine is a good substrate for the amino acid and peptide transporters present on the cornea. This led to the identification of various amino acid and peptide transporters on the cornea including a Na+-independent large neutral amino acid transporter LAT1, a neutral and cationic amino acid transporter B₀,⁺, and oligopeptide transport system PepT1. To utilize the peptide transporters present on the cornea, the dipeptide-aciclovir conjugate, Val-Val-ACV, was synthesized and shown to be highly permeable across cornea (2.3-fold that of aciclovir). Though Val-Val-ACV is about 20% less permeable than valaciclovir, it is more stable. The dipeptide prodrug exhibited good affinity for hPepT1 in Caco-2 cells and was cleaved by the enzymes, specifically the dipeptidases, aminopeptidases and cholinesterases, present in the tissues to regenerate the active parent drug, ACV. Val-Val-ACV showed excellent in vitro antiviral activity against HSV1 and very good in vivo activity against HSV1 rabbit epithelial/stromal keratitis.

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