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TOPIC. PRODRUGS AND ITS APPLICATION

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ABSTRACT
In this study there are many applications of prodrugs.the basic aim of prodrugs design is to mark undesirable drug properties,such as low solubility in water or lipid membranes,low target selectinity, chemical instability, undesirable taste,irritation or pain after local administration, presyspemic matebolism and toxicity. prodrugs improved oral absorption, aqueous solubility, improved lipophilicity, parental administration etc.

Prodrugs

Prodrug is an inactive substance that is converted to a drug within the body by the action of enzyme or other chemicals. Prodrug must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent. For ex- sulphasalazine is aprodrug.it is not active in its ingested form. It has to be broken down by bacteria in the colon into two products- 5-amino salicyclic acid(5asa) and sulphapyridine before becoming active active as a drug.

APPLICATIONS OF PRODRUGS

Improved oral absorption

The oral bioavailability of a potential drug may be limited by its aqueous solubility, low permeability, rapid and extensive hepatic metabolism and biliary excretion. Some prodrug strategies overcome poor absorption by enhancing permeability, which is achieved by masking polar or charged moieties of a poorly permeable parent drug. These prodrugs are often carboxylic acid esters (Shi *et al.* 2012; Harnden *et al.*1989; Nakamura *et al.*2006)or phosphonic acid esters (Eisenberg *et al.*2001; Hwang *et al.*1989) of orally permeable but aqueous soluble parent drugs. Valaciclovir is an interesting example of a prodrug with 3-5 times better bioavailability than acyclovir. It is the L-valyl ester of the parent drug, and is rapidly converted to acyclovir after oral administration.

Improved aqueous solubility.

Prodrugs offer an alternative tool to overcome the solubility limitations of poorly soluble drugs when first-pass metabolism is low to moderate and not the main cause of systemic drug availability. Many of the water soluble prodrugs for enhanced oral drug delivery include the addition of an ionizable progroup to the parent compound (such as a phosphate group). However, enhanced water solubility, and thus, better oral bioavailability may also be achieved by decreasing the crystal packing or by affecting the melting point of the parent drug (Li *et al.*2008).

A good example of a water-soluble oral prodrug is the non-steroidal anti-inflammatory indene derivative, sulindac. This is a bioprecursor prodrug that does not contain a promoiety, but instead, its inactive sulphoxide form is reduced to the active sulphide form after oral absorption (Duggan *et al.* 1981; Hare *et al.*1977; Duggan *et al.*1978) Sulindac sulphoxide, the prodrug, is about 100-times more water-soluble than the pharmacologically active sulphide. Phosphate esters can increase the oral bioavailability of many poorly water-soluble drugs.

Improved lipophilicity

Prodrugs are most frequently applied to mask polar and ionizable groups within a drug molecule with the aim of improving oral drug delivery. Increasing drug lipophilicity promotes membrane permeation and oral absorption. Some of the best examples of prodrugs in this category include ACE inhibitors and ampicillin prodrugs. Most nucleoside antivirals are polar and thus poorly absorbed after oral administration. In the case of tenofovir and adefovir, high hydrophilicity of the phosphonic acid moieties have been postulated to account for their poor oral bioavailability (<5%) but tenofovir disoproxil has been well tolerated, with an oral bioavailability of approximately 39%, and is now approved for the treatment of HIV (Gallant *et al.* 2003)similarly, the lipophilic adefovir dipivoxil was developed and approved as a bispivalate ester prodrug for the treatment of hepatitis B after an initial trial for the treatment of HIV. (Dando *et al.*2003).

Carrier-mediated absorption.
Prodrugs targeted towards specific membrane transporters are designed to have structural features that would allow them to be taken up by one of the endogenous transporters present at the intestinal epithelium. Peptide transporters appear to be attractive targets for prodrug design, as they are widely distributed throughout the small intestine and show sufficiently high transport capacity and broad substrate specificity (Yang *et al.*1999; Yang *et al.* 2001)Good examples of prodrugs that exploit carrier-mediated transport are Valaciclovir and Valganciclovir They are l-valyl esters (for example, amino-acid valine as the promoiety) of acyclovir and ganciclovir, which both have limited and variable oral bioavailability owing to their high polarity. These amino-acid prodrugs increased the intestinal permeation of their parent drugs by 3–10- fold, and their membrane transport was not passive but mediated predominantly by the di- and tripeptide transporter (hPEPT1) (Sugawara *et al.*.2008)expressed in the intestinal epithelial cells (Tsuda *et al.*2006). Following their membrane transport, both prodrugs are readily bioconverted back to their parent drugs by intracellular hydrolysis (Sugawara *et al.*2008; Han *et al.*2000).

Improved parenteral administration
There are numerous successful prodrugs with improved aqueous solubility properties for parenteral administration. The most commonly used prodrug-based approach to increase water solubility is to introduce an ionizable polar promoiety to the parent drug. As the increase in solubility imparted by the dianionic phosphate group is often of several orders of magnitude, several phosphoric acid esters have been developed as potential water-soluble prodrugs for parenteral administration and, less commonly, for oral administration. Fosphenytoin is a phosphate ester prodrug of poorly water-soluble phenytoin for the acute treatment of seizures, and can be used for both intravenous and intramuscular administration **(**Boucher *et al.* 1996).

Improved topical administration
The topical administration of drugs encompasses all external membranes, but here we consider only ocular and dermal prodrug applications.

Ophthalmic drug delivery
The corneal barrier limits the permeation of topically administered ophthalmic drugs into the intraocular tissues. As a result, only a small percentage of the applied dose is absorbed, most (50–99%) of which escapes into the systemic circulation. Dipivefrin, a dipivalic acid diester prodrug of adrenaline, penetrates the human cornea 17-times more rapidly than adrenaline (Mandell *et al.* 1978)owing to its 600-fold increase in lipophilicity (at pH 7.2) compared with that of adrenaline (Wei *et al.* 1978). In addition, systemic side effects are greatly reduced. The prostaglandin analogues represent a new class of active ocular hypotensive agents for the treatment of glaucoma. They are lipophilic isopropyl ester (latanoprost, travoprost, unoprostone) or ethanolamine amide (bimatoprost) prodrugs that are rapidly hydrolysed inside ocular tissue to biologically active prostaglandins (Hellberg *et al.*2003; Susann *et al.* 2002). In their carboxylic acid forms, these agents are poorly permeable and cause irritation, whereas the lipophilic prodrugs achieve improved ocular absorption and safety.

Dermal drug delivery
The unfavorable physicochemical properties of many drug molecules lead to poor permeation across the skin(sinha *et al.* 2001). Numerous studies have demonstrated that both water and lipid solubilities, and a balance of the two, are important in the optimization of drug permeation. (Sloan *et al.*2006)These optimal features can often be achieved by prodrugs. In the case of tazarotene, its active carboxylic acid form is esterified to a more lipophilic ethyl ester, which still maintains adequate water solubility. Tazarotene was effectively and reliably absorbed percutaneously, exerted less skin irritation and was rapidly converted to tazarotenic acid The less lipophilic tazarotenic acid subsequently released, showed no accumulation in fat and other tissues in part due to the reduced systemic half-life of this parent drug achieved by the introduction of a metabolically labile sulphur group that undergoes rapid oxidative deactivation and thus prevents accumulation in tissues. Thus, tazarotene is not only a carboxylic acid prodrug with enhanced skin permeability, but it is also a soft drug with enhanced systemic metabolism. Both can be important features for drugs aimed at topical treatment.

Site-selective drug delivery
An ultimate goal in drug delivery is that it is site selective, and this may be the most exciting possibility that prodrugs offer. Site selectivity may be achieved in four different ways: by passive drug enrichment in the organ; through transporter-mediated delivery; by selective metabolic activation through enzymes; and by antigen targeting. Examples of the most frequently studied applications are listed in sub-sections below. It is to be noted, however, that possible prodrug applications are not restricted to those listed.

Central nervous system (CNS) drug delivery
Clinically, the CNS is one of the most challenging organs to target, mainly due to the blood–brain barrier (BBB)(Abbott *et al.* 2010). A traditional approach to increase CNS drug concentration has been to increase the lipophilicity of the parent drug. For this approach to be successful the prodrug must have easy access to the brain tissue, bioconversion back to the parent drug should be highly site-selective, and the parent drug should exhibit prolonged retention within the brain tissue (Anderson *et al.*1996). Once the lipophilicity of the drug is increased by the development of a prodrug, it has improved access to the CNS. However, increased lipophilicity alone does not ensure a higher concentration of the parent drug in

the target tissue. Bioconversion in the target tissue needs to be rapid and selective enough to compete with elimination, and also to ensure that any premature bioconversion of the prodrug is kept to a minimum.

Tumour targeting

The aim in cancer therapy is to target an inactive prodrug selectively to tumour cells, where the active drug may then be released without causing toxicity to normal, healthy tissue .Owing to the high proliferation rates of tumour cells, in addition to bioreductive activity, the levels of certain enzymes are often elevated in these cells and have been exploited in targeted prodrug-tumour delivery (Afshar *et al.* 2009;Altaner *et al.* 2008). A need for reduced normal tissue exposure of the cytotoxic drug, 5-fluorouracil (5-FU), has led to the development of a prodrug that is activated by tumour-selective enzymes (Quinney *et al.*2005 Walko *et al.*2005) Capecitabine is an orally administered carbamate prodrug of 5-FU that requires a cascade of three enzymes for the bioconversion to the active drug (Miwa *et al* 1998). Intact capecitabine is absorbed from the intestine and undergoes bioconversion in tumours, thus, avoiding any systemic toxicity(Miwa *et al.*1998;Venturini *et al.*2002) The bioavailability of 5-FU after oral administration of capecitabine is almost 100% and the Tmax of 5-FU is reached within 1.5–2 hours *(*Walko et al 2005).

Liver-targeted delivery.

Of all organs, the liver may hold the greatest potential for organ-specific targeted drug delivery, because, as the metabolizing organ, it possesses a wide variety of liver-specific metabolizing enzymes (Van *et al.*2003) that are capable of prodrug activation. Pradefovir mesylate is a cyclic 1,3-propanyl ester prodrug of a nucleoside monophosphate (NMP), adefovir that is under development for the treatment of hepatitis B (Erion *et al.* 2006;Erion *et al.*2004) Pradefovir undergoes a CYP450-catalysed oxidation reaction predominantly in hepatocytes in the liver . (Erion *et al.*2004) In Phase II clinical trials in patients with hepatitis B, pradefovir has demonstrated good efficacy with low systemic adefovir levels, which is indirect evidence for liver targeting (Erion *et al.* 2006).

Prolonged duration of drug action

Although various pharmaceutical formulations are frequently used to prolong the duration of drug action, a few examples that use prodrugs exist. Highly lipophilic prodrugs of several steroids (for example, testosterone nandrolone) and neuroleptics (for example, fluphenazine, flupenthixol, haloperidol) are slowly released in the circulation from the site of intramuscular injection and result in a prolonged duration of action. Once released from the injection site, prodrugs are usually rapidly bioconverted, with no attenuation of their therapeutic action in most cases. As an example, the onset of action of fluphenazine is generally between 24–72 hours after injection of its lipophilic decanoate ester prodrug, which continues for 1–8 weeks with an average duration of 3–4 weeks.[105] In the case of the bronchodilator and β2-agonist terbutaline, sustained drug action is provided with its bisdimethylcarbamate prodrug, bambuterol protection of a phenolic moiety, which is susceptible for rapid and extensive pre-systemic metabolism, also avoids first-pass intestinal and hepatic metabolism. After oral administration, bambuterol is slowly bioconverted to terbutaline, predominantly outside the lungs via a cascade of hydrolysis and oxidation reactions (Svensson *et al.* 1988; Tunek *et al.* 1988). As a result of prolonged action, a once-daily bambuterol treatment provides relief of asthma symptoms with a lower incidence of side effects than terbutaline, which is taken three times a day **(**Persson *et al.*1995.).

Safety assessment of prodrugs

In general, while the fundamental process of safety assessment for a prodrug is no different to that of any other drug molecule, the extra facets provided by prodrugs is likely to require additional consideration and, therefore, effort and cost. However, considering the high cost of drug development and the low rate of drug success, carefully designed prodrugs will warrant the increased costs of additional complexity. The safety assessment of prodrugs was recently comprehensively reviewed, (Grossman *et al.*2007) and is briefly discussed below. When considering prodrugs, a prerequisite is the lack of toxicity of the promoieties. The choice of promoiety should be considered with respect to the disease state, dose and the duration of therapy. A risk assessment is often worthwhile if a questionable structure provides properties superior to that of other structures. Two frequently discussed examples are formaldehyde- and pivalate-releasing promoieties. There are several marketed prodrugs (for example, fosphenytoin, tenofovir disoproxil fumarate, propofol phosphate), in which formaldehyde is being released in the body during the bioactivation process. A good example of pivaloyl derivatives that form the pivalate-group (trimethylacetic acid) and that may interrupt carnitine homeostasis in humans is adefovir dipivoxil. Despite common concerns, normal formaldehyde input from the diet and the environment exceeds the exposure from formaldehyde- releasing prodrugs (Rautio J,*et al.*2008) and simultaneous carnitine supplementation may be administered with a pivalate generating prodrug (Brass *et al.* 2002)

Amino acid prodrug

Amino acid prodrugs are known to be very useful for improving the aqueous solubility of sparingly water soluble drugs. Therefore, we synthesized eleven novel combretastatin A-4 amino acid derivatives and evaluated their anti-tumor activities in vitro and in vivo. Among them, compound 15 exhibited high efficacy in tumor-bearing mice, and pharmacokinetic analysis in rats indicated that compound 15 was an effective prodrug as well. Besides, compound 15 significantly inhibited tubulin polymerization in vitro and in vivo by binding to the colchicine binding site. In addition, compound 15

induced cell cycle arrest in the G2/M phase and triggered apoptosis in a caspase-dependent manner. In conclusion, our study showed that compound 15 could have significant anti-tumor activity as a novel microtubule polymerization disrupting agent with improved aqueous solubility (Yu *et al. 2015*, Li *et al.* 2008)Prodrug approaches with amino acid modification have been widely employed to improve intestinal absorption of poorly permeant drugs (Sofia *et al.*2011) The antiviral drug valacyclovir is an example of a successful amino acid ester prodrug strategy [34].(Harnden *et al.* 1989.) The improved oral bioavailabiliy of valacyclovir has been attributed to the enhanced transport by intestinal oligopeptide transporters [14, 24, 35]. (Rautio et al. 2008 ; Shi *et al.* 2012, Harnden *et al.*1989) Dipeptide and tripeptide compounds, along with mono amino acid derivatives, have been investigated for their suitability as substrates for the oligopeptide transporter [16-18, 21, 28, 36-39].(Testa *et al.*2004; Huttunen *et al.*2011; Albert *et al.*1958;Graf *et al.2012;* Bobeck *et al.*2010) Mono amino acid ester prodrugs of antiviral and anticancer drugs such as gemcitabine, acyclovir, and 2-bromo-5,6-dichloro- 1-(β-D-ribofuranosyl) benzimidazole (BDCRB) have been synthesized and evaluated for their suitability as transporter substrates in our previous reports.[15,24,40-43] (Heimbach *et al.*2007; Testa *et al.*2009) Amino acid and dipeptide prodrugs have been developed to examine their potential in enhancing aqueous solubility and permeability as well as to bypass P-glycoprotein (P-gp) mediated cellular efflux of prednisolone. These compounds also exhibited higher stability under acidic conditions relative to basic medium. Prodrugs have been synthesized and identified with LC/MS/MS and NMR. Prodrugs displayed significantly higher aqueous solubility relative to prednisolone[14]-(Rautio *et al.2008;* Kumpulainen *et al.*2006) Erythromycin uptake remained unaltered in the presence of valine-valine-prednisolone (VVP) indicating lower affinity toward P-gp. Moreover, VVP generated significantly higher transepithelial permeability across MDCK-MDR1 cells compared to prednisolone. Moreover, prednisolone was regenerated from VVP due to enzymatic hydrolysis in SIRC cell homogenate and its results obtained from these studies clearly suggest that peptide transporter targeted prodrugs is a viable strategy to improve aqueous solubility and overcome P-gp mediated cellular efflux of prednisolone.[112] (Sheng *et al.*2015).

Amino acid prodrugs for oral delivery should have high chemical stability in the gastrointestinal environment, but rapidly and quantitatively convert to parent drug prior to the systemic circulation. Chemical stability and bioactivation of amino acid prodrugs depends on the functional link between the amino acid and parent (e.g., ester or amide), site of linkage, structure of parent and promoiety (steric and electronic effects) and stereochemistry (Stella *et al.* 2006;Stella *et al.*2007) Esters and amides are hydrolyzed by the same general mechanism and by the same hydrolases. (Stella *et al.*2004). However, as a general rule, the amide bond is more resistant than the ester bond to chemical and enzymatic hydrolysis. During the development of prodrugs, it is important to understand the structure–activation relationship between prodrugs and hydrolytic enzymes. The mechanisms involved in the chemical hydrolysis of amino acid prodrugs are well understood; however, the field of enzymatic activation has been largely neglected, and very rarely attempts are made to identify if a specific or a group of hydrolases are involved in prodrug activation.

The research on amino acid prodrugs has been and will continue to be an integral part of prodrug design and development. In the future, we expect to see continual research in use of amino acid prodrugs to improve solubility for oral and parentral delivery, improve permeability via passive or active transport mechanisms, controlled drug release, site-specific delivery by targeting specific transporters or enzymes overexpressed in tissues and tumors, and mechanistic understanding of absorption and activation by hydrolases. In conclusion, amino acid prodrugs have a proven track of improving oral delivery of the drugs that have poor solubility and permeability, and more recently providing controlled drug release. The amino acid prodrugs have a proven commercial and regulatory track record, which is beneficial in bringing such drugs to the patient and this track record should be enhanced to the benefit of the patient by future developments in prodrug technology.

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