Improved oral drug delivery: solubility limitations overcome by the use of prodrugs

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Abstract

This chapter describes a strategy to improve the oral delivery of poorly water-soluble drugs by chemical derivatization to a water-soluble prodrug. The strategy utilizes esterification of a drug hydroxyl, amine or carboxyl group with a moiety (progroup) designed to introduce an ionizable function or reduce intermolecular interactions responsible for low solubility. The use of spacer groups to introduce derivatizable functions and/or to position ionizable progroups for unhindered hydrolysis is also described. Prodrug strategies coupling drug solubilization with membrane carrier targeting and the use of collapsible and bifunctional prodrugs are outlined. These approaches are illustrated with studies utilizing model compounds to test the strategy as well as examples from various therapeutic classes of drugs in which aqueous solubility limits drug absorption.

Keywords: Soluble prodrug; Oral absorption; Intestinal absorption; Dissolution; Prodrug formulation; Prodrug oral bioavailability

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1. Introduction

Solubility limitations to oral drug delivery are frequently encountered in the development of commercial products. There are a host of formulation and drug design strategies that have evolved to overcome these limitations. The use of surfactants, co-solvents, soluble complexing agents and solid-state manipulation are among the formulation strategies available for nonelectrolytes, while salt formation is routinely employed for ionizable drugs [1]. Feedback from drug delivery groups working with drug discovery has also provided for early drug design modifications when it is apparent that poor aqueous solubility will prove limiting to oral delivery.

Design of soluble prodrugs has been routinely utilized by pharmaceutical industry in the development of parenteral products of poorly soluble drugs. Applications of this prodrug strategy to oral delivery of poorly soluble compounds represents a more recent endeavor. With the strict definition of a prodrug as a bioreversible chemical derivative of an active parent drug, salts and complexes may be regarded as water soluble prodrugs for oral drug delivery [2]. This definition suggests that prodrug reconversion sites may be physicochemical or biochemical in nature. However, targeting of prodrug reconversion sites at the intestinal mucosal membrane or beyond is fundamental to the success of this approach for improving oral absorption of a poorly water-soluble parent drug. Reconversion at the mucosal membrane is illustrated in Fig. 1. The prodrug's high solubility results in a higher driving force (concentration gradient) in the intestinal lumen for absorption than is the case for the parent compound. To take advantage of the parent drug's higher membrane partition coefficient, enzymatic reconversion by a membrane-bound enzyme is targeted to release the permeable parent drug in the vicinity of the mucosal brush border membrane. Reconversion beyond the intestinal mucosal barrier may be utilized when parent drug lipophilicity is not compromised by prodrug derivatization. This may be the case when a soluble prodrug is made to reduce intermolecular hydrogen bonding contributions to poor aqueous solubility in the parent compound.

Similar to the precipitation of a drug sodium salt in the acidic milieu of the stomach, rapid reconversion of any water-soluble prodrug in the gastrointestinal (GI) lumen will serve to regenerate solubility limitations to absorption. In fact, an earlier review on attempts to utilize soluble prodrugs to facilitate absorption predominantly documented cases in which increased solubility did not translate to enhanced bioavailability from oral administration as compared to the parent drug [3]. This suggests that knowledge of the specificity and kinetics of prodrug reconversion, as well as the biological distribution of reconversion sites, is critical for this particular solubilization technique to result in improved absorption.

As pointed out in a previous review, two types of solubilizing prodrug strategy are based on the nature of the physicochemical limitation to oral drug delivery and the properties of the biological reconversion sites [4]. These techniques are drug derivatization with a promoiety designed to decrease the drug's melting point and/or to introduce an ionizable group. Reconversion to the
active drug may be at sites defined by a regionally specialized physicochemical environment and/or a site-specific enzyme target. Since previous reviews in the 1970s and 1980s outlined the fundamental theory underlying these strategies, this chapter will serve as an update on the utilization of prodrug approaches to improve oral drug delivery of poorly soluble drugs with both model drugs and specific clinical classes of examples.

2. Solubilizing progroups

While this chapter will be organized on the basis of drug classes, a summary of the types of progroup utilized to solubilize drugs for improved oral absorption is offered in Table 1. This table is an update of that provided in a previous review [4].

3. Soluble prodrugs for parenteral use

It is often the case that soluble prodrugs of poorly soluble compounds are initially synthesized for parenteral use while formulation of the parent compound is the standard first step for improving oral delivery of such compounds. A recent case in point is the development of ester prodrugs of α-tocopherol. Vitamin E is practically insoluble in water. Acetate and acid succinate esters, which reduce the potential for oxidation, are also poorly water soluble. These same esters also show reduced absorption from oral dosage as compared to the free alcohol form of the vitamin. Soluble aminoalkanecarboxylic esters (Fig. 2) have been recently synthesized to overcome parenteral delivery limitations characteristic of the acetate and succinate esters [5]. Successful targeting of soluble prodrug reconversion for improved gastrointestinal absorption frequently proves to be more difficult than for prodrug reconversion in the liver and/or systemic circulation. In the case of vitamin E, formulation approaches provide for adequate oral delivery. This is often the case for lipid-soluble drugs and this serves to limit the number of examples of water-soluble prodrugs that have

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**Table 1** Examples of solubilizing progroups for poorly-soluble drug D-X

<table>
<thead>
<tr>
<th>Progroup Type</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemisuccinate esters</td>
<td><img src="image1" alt="Structure" /></td>
</tr>
<tr>
<td>Phosphate esters</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>Phosphoryloxymethyloxycarbonyls</td>
<td><img src="image3" alt="Structure" /></td>
</tr>
<tr>
<td>Dimethylaminosuccinates</td>
<td><img src="image4" alt="Structure" /></td>
</tr>
<tr>
<td>Amino acid esters</td>
<td><img src="image5" alt="Structure" /></td>
</tr>
</tbody>
</table>

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**Table 2** Examples of solubilizing progroups for poorly-soluble drug X-NH

<table>
<thead>
<tr>
<th>Progroup Type</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline esters</td>
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</tr>
<tr>
<td>β-Dimethylaminoacetates</td>
<td><img src="image7" alt="Structure" /></td>
</tr>
<tr>
<td>Amino acid esters</td>
<td><img src="image8" alt="Structure" /></td>
</tr>
<tr>
<td>N-Alkoxycarbonyl derivatives</td>
<td><img src="image9" alt="Structure" /></td>
</tr>
</tbody>
</table>

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**Table 3** Examples of solubilizing progroups for poorly-soluble drug X-COOH

<table>
<thead>
<tr>
<th>Progroup Type</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ester prodrugs</td>
<td><img src="image10" alt="Structure" /></td>
</tr>
<tr>
<td>Phosphoryloxymethyloxycarbonyls</td>
<td><img src="image11" alt="Structure" /></td>
</tr>
<tr>
<td>Amino acid esters</td>
<td><img src="image12" alt="Structure" /></td>
</tr>
<tr>
<td>N-Alkoxycarbonyl derivatives</td>
<td><img src="image13" alt="Structure" /></td>
</tr>
</tbody>
</table>
been developed for oral use. However, soluble prodrugs for parenteral use often provide good tools for initial investigations on strategies to improve oral delivery of poorly soluble compounds.

4. Model compounds

4.1. Illustrative study

An illustrative study from our own work goes back to the mid-1980s in which the potential advantage of using an amino acid steroid ester as a soluble prodrug to improve intestinal absorption was tested [6]. In this research, the 21-lysine ester of hydrocortisone was synthesized for the purpose of comparing its oral absorption with the parent drug and two commercially available water-soluble hydrocortisone derivatives used as injectable products. Lyophilized hydrocortisone 21-succinate is routinely reconstituted immediately before intravenous administration because of limited stability in aqueous solution while the stable hydrocortisone 21-phosphate is manufactured as a solution for intrabursal use. The parent drug and the three prodrugs were studied in rat intestinal perfusions to compare membrane permeabilities and by oral administration to dogs to compare rate and extent of absorption as assessed from drug plasma level measurements.

Jejunal permeability of the lysinate prodrug was comparable to that of the parent drug. This was apparently due to rapid hydrolysis of the lysinate ester over the time course of the perfusion experiment. The sodium succinate ester yielded very low permeability since the polarity of this prodrug provided low permeation and the half-life for nonenzymatic hydrolysis was substantially longer than the perfusion residence time. The low permeability for the succinate suggested limited esterase activity in this experimental preparation. Jejunal perfusion of the phosphate prodrug resulted in higher membrane permeability than for the parent compound (Table 2). This was a surprising result, as prodrug hydrolysis to the parent compound by membrane-bound alkaline phosphatase would have been anticipated to give the same permeability as hydrocortisone. Interestingly, ileal perfusions did not show as much hydrolysis of the phosphate ester as in jejunal perfusions and membrane permeability was significantly lower than that observed in the jejunum.

![Chemical structure of aminoalkane carboxylic acid esters of the lipophilic d-α-tocopherol and their aqueous solubilities at 25°C.](image)

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**Table 2**

<table>
<thead>
<tr>
<th>Drug</th>
<th>( P_{\text{eff}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1.5 ± 0.15</td>
</tr>
<tr>
<td>Hydrocortisone succinate</td>
<td>0.9 ± 0.23</td>
</tr>
<tr>
<td>Hydrocortisone phosphate</td>
<td>13.4 ± 1.86</td>
</tr>
<tr>
<td>Hydrocortisone lysinate</td>
<td>1.8 ± 0.41</td>
</tr>
</tbody>
</table>

\( P_{\text{eff}} \) = dimensionless effective permeability.
In dog experiments, oral administration of the parent drug resulted in a greater extent of absorption than for any of the prodrugs (Table 3). Hydrocortisone levels from the lysinate prodrug, while lower than from the parent compound showed a similar plasma level versus time profile. Plasma levels from the succinate prodrug were significantly lower than from the phosphate and lysinate, consistent with poor permeability and incomplete intestinal hydrolysis. The phosphate prodrug yielded an earlier $t_{\text{max}}$ and higher $C_{\text{max}}$ than from the parent drug. This was consistent with the high membrane permeabilities observed in rat jejunum. However, the plasma levels dropped sharply as a function of time while hydrocortisone plasma levels reached a maximum at later times from oral administration of the parent compound. The sharp drop-off in hydrocortisone plasma levels from phosphate prodrug administration can be accounted for by diminished levels of alkaline phosphatase activity in the lower intestine and poor permeability of the dianionic phosphate prodrug. This was consistent with the lower membrane permeabilities observed for hydrocortisone phosphate in rat ileal perfusions. The longer $t_{\text{max}}$ for the parent compound was consistent with continued dissolution and subsequent absorption of hydrocortisone in the lower intestine (Fig. 3, Table 3). These data suggest that improving the oral absorption of a poorly soluble drug through a soluble prodrug approach is limited by prodrug stability as well as distribution and activity of enzymatic reconversion sites.

4.2. Carrier-targeted prodrugites

The work on amino acid esters of hydrocortisone as a model drug was generated by earlier work with other model compounds. The l-lysine esters of estrone and p-nitroanilide were tested in a rat perfusion system as model amino acid prodrugs to improve oral absorption [7]. The end result of this work indicated that the membrane permeability of the water-soluble prodrugs was not compromised as compared to the parent compounds which possessed good membrane partition properties but poor aqueous solubility. This was consistent with membrane-bound aminopeptidase hydrolysis of the progroup to release the parent compound in the neighborhood of the absorbing membrane. In line with the topic of this chapter, total flux of parent drug across the jejunal membrane was limited by aqueous solubility while the prodrug provided flux values up to three orders of magnitude greater than the parent compound consistent with the increased prodrug solubility (Fig. 4).

![Fig. 3. Hydrocortisone plasma concentrations (mean±SE, n = 4) following the administration of 50-mg equivalent oral doses of hydrocortisone and its 21-phosphate, succinate and lysinate esters in beagle dogs. (○) Hydrocortisone; (□) succinate; (■) phosphate; (□) lysinate.](image)

Table 3

<table>
<thead>
<tr>
<th>Drug</th>
<th>$t_{\text{max}}$ (min)</th>
<th>AUC ($\mu$g min ml$^{-1}$)$^a$</th>
<th>Relative $F$$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>78±12.0</td>
<td>88±12.3</td>
<td>-</td>
</tr>
<tr>
<td>Hydrocortisone succinate</td>
<td>48±7.2</td>
<td>20±5.7</td>
<td>0.23±0.07</td>
</tr>
<tr>
<td>Hydrocortisone phosphate</td>
<td>33±3.0</td>
<td>57±6.4</td>
<td>0.66±0.07</td>
</tr>
<tr>
<td>Hydrocortisone lysinate</td>
<td>45±4.8</td>
<td>63±14.5</td>
<td>0.72±0.17</td>
</tr>
</tbody>
</table>

$^a$AUC = area under the plasma concentration vs. time curve.

$^b$F = fraction absorbed.
While these soluble model prodrugs were targeted for intestinal enzyme reconversion prior to membrane permeation, amino acid and peptide prodrugs may provide strategies for improved solubility coupled with targeting for carrier-mediated uptake.

More recently, glucose and galactose conjugates of model compounds p-nitrophenol and \( \beta \)-naphthol were used to demonstrate targeting of compounds for intestinal monosaccharide carriers [8]. The work reported with these conjugates suggested that this approach was useful for both poorly permeable and poorly water-soluble compounds. C3 bile acid esters of model compounds have also been studied in intestinal absorption models [9]. Benzoyl- and tosyl-cholic acid esters were tested in isolated in situ jejunal and ileal segments in the rat to examine the permeability of these conjugates which were targeted to intestinal bile-acid carriers. While these glycoside and bile acid model conjugate studies were actually carried out to target specific intestinal transporters as oral delivery strategies, similar derivatization could be employed with poorly soluble drugs to couple carrier transport with improved solubility. Monosaccharides and bile acids offer a diversity in structure for this purpose similar to the amino acids.

### 4.3. Collapsible prodrugs

Phosphoryloxymethyl carbamates and carbonates of poorly water-soluble model compounds have been synthesized as water-soluble prodrugs of amines and sterically hindered secondary and tertiary alcohols [10]. Benzocaine, 2-indanol and \( \beta \)-(3,4-dimethoxyphenyl)ethylamine were employed as model compounds. This work was carried out to expand the potential of phosphate prodrugs for drug delivery, since bioconversion of these prodrugs was slow compared to that of phosphononoester prodrugs of primary alcohols and unhindered phenols. An oxymethyloxy carbonyl moiety is utilized as a spacer group between the hydroxyl or amine group and the phosphate functionality to decrease the steric hindrance toward hydrolysis. Inherent in this approach is that subsequent to phosphatase-mediated hydrolysis, spontaneous decomposition of the spacer group (collapse) must occur. Selection of carbamate and carbonate components in the spacer group provides the required hydrolytic lability (carbonate being more labile than carbamate). An application of this approach will be discussed in the section on anticancer drugs.

### 5. Examples from therapeutic classes

#### 5.1. Antibacterial drugs

Benzimidazole carbamates like mebendazole and albendazole are routinely employed as gastrointestinal anthelminthic agents. Low aqueous solubility makes these compounds less suitable for the treatment of systemic infections like alveolar and cystic echinococcosis which are caused by infection with the larval stage of cestodes. The synthesis of N-alkoxycarbonyl prodrugs (Fig. 5) has been shown to increase the aqueous solubility of mebendazole by two orders of magnitude [11]. These derivatives serve to decrease the melting point of these compounds while maintaining log octanol/water apparent partition coefficients close to 3 (Table 4). This particular example illustrates the potential for prodrugs to improve oral bioavailability by increasing the aqueous concentration gradient driving force without compromising drug lipophilicity for absorption. Since the prodrug permeation properties are equivalent to those of the parent drug, cleavage of the promoiety may be
targeted beyond the intestinal mucosal membrane.

Interestingly, some cephalosporin prodrugs have been made to improve oral absorption by overcoming solubility limitations. This is somewhat surprising since most cephalosporins are characterized by a dipeptide-like structure containing a free carboxyl group which is ionized at intestinal pH, as well as often containing a relatively basic amino group. The resultant polarity predisposes this class of drugs to poor membrane permeation unless there is high specificity for the intestinal peptide carrier. An approach to increase molecular lipophilicity would be the anticipated prodrug strategy to increase absorption if carrier permeability is low. An ester prodrug approach is often employed with β-lactam antibiotics in which a basic amino group is esterified to increase lipophilicity and resultant membrane permeation while maintaining sufficient aqueous solubility for dissolution. Esters of ampicillin provide examples of this approach [12]. In cases where β-lactams lack a basic amino side chain and the carboxyl group is esterified, oral activity is low. This has been attributed to poor aqueous solubility and ‘bifunctional’ prodrugs have been synthesized to overcome the solubility limitation. An example is the compound, KY-109 (Fig. 6), in which a side chain hydroxyl group in the monofunctional prodrug, KY-106, has been esterified with L-alanine to increase aqueous solubility [13]. The oral absorption of this bifunctional prodrug was shown to be significantly better in rats than both the parent compound and the monofunctional prodrug.

### 5.2. Antiviral drugs

As is the case with many antibacterial drugs, antiviral drugs are usually very polar molecules with good aqueous solubility. However, similar to the β-lactam antibiotics, there have been cases where a prodrug approach to increase antiviral drug solubility was used to improve oral absorption. While 200 mg oral doses of acyclovir have been adequate to treat herpes simplex virus types 1 and 2, the higher oral doses required to treat both the varicella zoster and human cytomegalovirus have not proved as successful. This is thought to be a function of the limited oral bioavailability of the drug which is partially a membrane permeability problem. At higher doses, limited acyclovir solubility may also be responsible for inadequate drug plasma levels from oral administration. While acyclovir dissolution should be complete within typical GI residence times at low doses, this may not be the case at higher doses. Amino acid ester prodrugs have been synthesized both to improve intestinal membrane permeability and increase aqueous...
solubility [14]. Although increased permeability by targeting a membrane carrier was responsible for enhanced bioavailability, the potential for improved delivery at higher oral doses was provided by greater prodrug solubility. The success of the L-valyl ester of acyclovir in this regard has been further documented [15,16]. This prodrug approach contrasts with those used for other antivirals like penciclovir [17], PMEA [18] and D4T [19] for which prodrug esters with increased lipophilicity have been synthesized to strictly increase passive membrane permeation.

5.3. Anticancer drugs

The poorly water-soluble agents etoposide and taxol have shown some evidence for improved oral bioavailability in preliminary studies utilizing phosphate ester prodrugs. This was in contrast to the approach taken to improve the oral bioavailability of the water-soluble anticancer drug, fluorouracil, in which synthesis of a more lipophilic prodrug decreased susceptibility to first-pass metabolism [20]. A more general chapter on prodrugs of anticancer and antiviral drugs by Sinhababu and Thakker is also provided in this issue (pp. 115-130). This section will focus on prodrug applications to improve oral delivery.

Etoposide (Fig. 7) is a glycoside of podophyllotoxin, with a wide spectrum of clinical activity, and relatively few side effects. It is used for treatment of small cell lung cancer and testicular carcinoma. However, it is plagued by a number of problems, notably, precipitation upon dilution of the parenteral product, a bulky gelatin capsule for oral dosing, and some toxicity due to the vehicle [21]. Etoposide absorption from a powder suspension has been shown to be extremely erratic with low and varying oral bioavailability, absorption ranging from 25 to 75% [22], and almost negligible availability from an in situ rat model [23]. This could be due to multiple factors, including low aqueous solubility, slow dissolution rate and instability in acidic pH [24]. A phosphate ester, etopofos (Fig. 7), has undergone several preclinical studies with mixed results. In plasma, there was rapid conversion of the phosphate prodrug to etoposide, both in vitro and in vivo, with reports of 70% of the intravenously administered dose of etopofos converted to parent form within 5 min in mice [25]. Given orally to rats, there was a 10-fold increase in $C_{\text{max}}$ over etoposide, and total area under the plasma level versus time curve (AUC) twice that of the parent. While these results in animals point toward success for this oral prodrug approach, a recent clinical study indicates a questionable prodrug advantage.

In contrast to animal model studies, some studies in cancer patients given oral etoposide (200 mg/day) for 5–8 days have shown a promis-
Fig. 7. Chemical structures of etoposide (II) and its phosphate ester prodrug (I).

ion response rate (79%) and survival time (9.5 months), similar to those achieved by an intensive intravenous program [26]. While there is linear etoposide absorption with increasing dose, at doses >200 mg/day, the bioavailability has been found to drop. At low doses (50 mg/day), bioavailability is nearly 100%. However, such low doses are impractical for treatment. In light of these successes, it has been suggested that oral delivery substitute for I.V. administration. With the enhanced solubility of etoposofos, a recent clinical study sought to compare the oral bioavailability of the parent drug, etoposide, with that of the phosphate prodrug, etoposofos [27]. While there was some evidence of increased plasma levels of etoposide form oral administration of etoposofos at higher doses, the results were not as dramatically successful as in the animal studies.

Another anti-tumor drug which has exploited the solubility enhancing effects of phosphate linkages is the diterpene product, taxol. Taxol has been shown to be highly cytotoxic and to possess potent antileukemic and tumor inhibitory properties. It is approved for use in treatment of ovarian cancer, and demonstrates remarkable efficacy against breast, lung cancer, and melanoma. Like its counterpart, etoposide, it also suffers from poor solubility (0.25 μg/ml). As a result, current formulations of taxol rely on the addition of solubilizing agents, such as Cremophore EL (polyethoxylated castor oil) which has been suggested as the source of some of the adverse effects associated with taxol treatment [28]. In response to the low solubility, several phosphate ester prodrugs of taxol were synthesized which gave much improved solubility (>10 mg/ml). However, these prodrug esters were stable in both rat plasma and solutions of purified bovine intestinal alkaline phosphatase suggesting hindered attack by alkaline phosphatase [29]. Follow-up prodrugs were made as phosphonooxyphenyl propionate esters of taxol which served to push the phosphate moiety away from the taxol nucleus thus providing for less hindered enzyme access [30] (Fig. 8). Subsequent to alkaline phosphatase cleavage of the phosphate group, rapid lactonization serves to regenerate taxol. This is an example of a collapsible prodrug approach outlined in a previous section. These esters were shown to be stable in deionized water over a 24 h period, and were readily cleaved in vitro, in the presence of purified alkaline phosphatase (bovine intestinal mucosa) at physiological pH. Reports indicated >90% conversion to taxol in 25 min at 37°C. However, in vivo, the prodrug displayed extremely poor conversion to parent drug when incubated with
Fig. 8. Phosphoryl oxymethoxy carbonyl esters of taxol are collapsible prodrugs. Subsequent to enzymatic phosphate cleavage, lactonization of the spacer group provides a chemical mechanism to rapidly regenerate the parent taxol.

rat, or dog plasma; no trace of taxol was reported even after 24 h incubation. In plasma, the addition of albumin slowed the generation of taxol [31] which suggested that one reason for the lack of prodrug reconversion could be that the protein bound prodrug was effectively inaccessible to the alkaline phosphatase active site. In light of these results, the potential for parenteral administration of these soluble prodrugs appears limited. Oral delivery, however, could prove to be effective, as the prodrug satisfies two very important criteria for an oral prodrug: high solubility and good reconversion by a membrane bound enzyme alkaline phosphatase. The prospects for stability in the GI lumen with prodrug reconversion by mucosal alkaline phosphatase needs to be examined.

5.4. Antiepileptic drugs

In another chapter, Dr. Stella (pp. 115–120) has presented fosphenytoin, a phosphate prodrug, as a case study. In this chapter we will focus on those studies investigating this prodrug’s potential for improving oral delivery.

Fosphenytoin (Cerebyx®) is the sodium, monophosphate ester derivative of phenytoin (5,5-diphenylhydantoin, Dilantin®). The addition of the phosphate ester functionality resulted in a prodrug stable in aqueous solution [32] with over a 7000-fold increase in aqueous solubility from 0.02 mg/ml to 142 mg/ml [33]. In addition, phenytoin, with a pKₐ of 8.1, a log oil/water intrinsic partition coefficient of 2.4 and a dimensionless membrane permeability ≥ 4 [34], provides the desired membrane transport characteristics for the parent drug. Biological reconversion of fosphenytoin proceeds by enzyme-catalyzed generation of the unstable 3-(hydroxymethyl)-5,5-diphenylhydantoin intermediate (Fig. 9, II) that, in turn, spontaneously forms phenytoin. This spontaneous decomposition of the hydroxymethyl spacer group to release free drug provides another example of a collapsible prodrug (Fig. 9).

Early studies demonstrated that, while reconversion was slow and species-dependent in plasma and whole blood, there was rapid hydrolysis in rat intestinal homogenates [34]. Further mechanistic studies using preparations from rat small intestine and colon demonstrated highly selective hydrolysis of fosphenytoin at the small intestinal brush border membrane [35]. Further mechanistic studies using preparations from at the small intestinal brush border membrane (BBM) [35]. Inhibition studies with 4-nitrophenylphosphate and inorganic phosphate confirmed the involvement of alkaline phosphatase in fospheny-
toin hydrolysis. Site-specific reconversion potentially confers advantages in controlling the oral delivery of phenytoin via a water-soluble prodrug. Pharmacokinetic studies in dogs demonstrated a 3.5-fold increase in oral bioavailability of phenytoin when administered as the disodium phosphate versus sodium phenytoin, from 14% to over 50% [36].

Parallel studies with the dimethylglycyl prodrug of phenytoin confirmed a comparable increase in aqueous solubility, but more rapid hydrolysis in plasma from rat, dog and human than that observed for fosphenytoin [33]. Oral bioavailability of the amino acyl ester was higher (65%) but more variable than either parent or fosphenytoin in dogs [36].

5.5. Antihypertensive drugs

Prazosin is an α1-antagonist used in the treatment of hypertension. Recent work has been reported on the development of N-amino acid derivatives of the primary aromatic amine function to improve the aqueous solubility of the parent drug [37]. Alanyl, prolyl and lysyl derivatives of prazosin were synthesized with the expectation that the amide bonds would provide greater prodrug stability than amino acid ester derivatives while maintaining enzymatic susceptibility toward reconversion. However, intramolecular nucleophilic attack of the amino acid α-amino group yielded an intramolecular rearrangement. Carbamylation of the α-amino group resulted in greater chemical stability toward this rearrangement but with an unacceptable degree of hydrolytic lability for delivery applications by a prodrug approach.

Renin inhibitors (RI) were medically anticipated as the more pharmacologically specific successors to angiotensin-converting enzyme (ACE) inhibitor therapy; however, overcoming oral bioavailabilities in the single-digit and lower range proved a formidable task. As a compound class, RIs were of relatively high molecular mass (> 600 Da), lipophilic (log P ≥ 3) and poorly water-soluble. Low and variable absorption ensuing from low aqueous solubility was further complicated by instability to gastrointestinal enzymes for earlier compounds, as well as extensive hepatic extraction. Although several RI candidates have entered clinical trials, none has reached the marketplace.

In an effort to address absorption issues, a targeted prodrug strategy was undertaken with a tripeptidic RI template (Fig. 10, structure I) [38]. Two series of analogs had hydroxyl groups incorporated into P2 and P4 subsites on the RI backbone to serve as handles for amino acid esters [39–41] (Fig. 10, structures IIa–e and IIIa,b). As shown in Table 5, introduction of the hydroxyl group alone increased the aqueous solubility by 5–10-fold. Esterification with various amino acids raised the solubility as much as 28-fold in the P2 series, with L-Lys having the greatest solubilizing power and L-Asp, the least. In the P2 series, the acidic amino acids, L-Glu and L-Asp, were doubly selective over L-Lys, L-Gln and L-Ala for intestinal BBM hydrolysis versus reconversion in the intestinal lumen. L-Asp esterification at the N-terminus P4 position resulted in a reconversion-site selectivity that rose to greater than 12-fold. This finding supported the critical role of prodrug design in successful drug delivery. Intestinal permeabilities
Fig. 10. Based on a renin inhibitor template (structure I), ester prodrugs (IIa-e) of P-2 hydroxyl derivatives and (IIIa, b) of P-4 hydroxyl derivatives have been synthesized to increase aqueous solubility.

were comparable within the P2 series, while prodrug permeability was higher than parent permeability in the P4 series, indicating that rate of reconversion was not rate-limiting to flux across the membrane. Although these results were encouraging with respect to increasing the intestinal absorption of renin inhibitors [42], improvements in total bioavailability were not realized due to extensive hepatic extraction.

5.6. Antiasthmatic drugs

A number of effective antiallergic-antiasthmatic drugs have been limited to topical aerosol use because of poor gastrointestinal absorption. There are three examples in the recent literature for which water-soluble prodrugs have provided improved oral bioavailability. In the case of disodium cromoglycate (DSCG), poor gastrointestinal absorption is attributed to its low lipophilicity dictated by strongly acidic twin carboxyl groups. Poor absorption based on low lipophilicity is a more typical problem limiting oral drug delivery in this drug class and a more standard prodrug approach was initially attempted to resolve the problem. Esterification of the carboxyl groups with lipophilic progroups substantially increased log octanol/water partition coefficients [43]. However, water solubility was severely compromised and bioavailability of DSCG was not significantly improved by this derivatization (Table 6). Amino acid esterification of an available hydroxyl group to the lipophilic prodrugs provided a prodrug of a prodrug (double prodrug) which substantially increased oral bioavailability (Table 7). In these studies, the amino acid components of the prodrugs were shown to be rapidly hydrolyzed by the pancreatic enzyme, α-chymotrypsin, a process which should occur in the intestinal lumen. However, low levels of this enzyme in the fasted state may dictate prodrug hydrolysis of the amino acid moiety by brush-border bound aminopeptidase releasing the lipophilic prodrug close to the absorbing membrane. The improved bioavailability from the amino acid prodrug in the face of lumenal reconversion was demonstrated in rabbits but not in rats following gastric administration [44]. The species difference was attributed to greater biliary excretion and a greater first-pass clearance in rats as compared to rabbits.

The lipoxygenase inhibitor, BI-L-266, a 2,6-disubstituted 4-(2-arylethenyl)phenol, as is the case for other leukotriene antagonists and biosynthesis inhibitors, has shown promise in the treatment of asthma, allergic rhinitis and inflammatory bowel disease. However, its use is restricted to aerosol administration as little activity has been observed from administration by the
Table 5
Summary of solubility, stability and membrane permeability parameters for amino acid prodrugs of renin inhibitors

<table>
<thead>
<tr>
<th>Compound</th>
<th>Aqueous solubility (mM) at pH 6.5</th>
<th>BBM* half-life (min)</th>
<th>Selectivityb</th>
<th>Permeabilityc</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.01</td>
<td>Stabled</td>
<td>na</td>
<td>1.7±0.2</td>
</tr>
<tr>
<td>II-Parent</td>
<td>0.60</td>
<td>Stable</td>
<td>na</td>
<td>2.0±0.4</td>
</tr>
<tr>
<td>II-l-Ala</td>
<td>9.03</td>
<td>54.1</td>
<td>0.93</td>
<td>1.45±0.3</td>
</tr>
<tr>
<td>II-l-Gln</td>
<td>4.33</td>
<td>72.6</td>
<td>0.96</td>
<td>nd</td>
</tr>
<tr>
<td>II-l-Lys</td>
<td>16.67</td>
<td>36.9</td>
<td>0.99</td>
<td>nd</td>
</tr>
<tr>
<td>II-l-Glu</td>
<td>4.72</td>
<td>235</td>
<td>1.7</td>
<td>nd</td>
</tr>
<tr>
<td>II-l-Asp</td>
<td>2.49</td>
<td>291</td>
<td>2.0</td>
<td>2.2±0.6</td>
</tr>
<tr>
<td>III-Parent</td>
<td>0.12</td>
<td>Stable</td>
<td>na</td>
<td>4.2±1.7</td>
</tr>
<tr>
<td>III-l-Asp</td>
<td>1.60</td>
<td>171</td>
<td>12</td>
<td>10.3±0.8</td>
</tr>
</tbody>
</table>

*Intestinal brush border membranes.

**Defined as (half-life in intestinal perfusate)/(half-life in BBM).

*Dimensionless permeabilities were calculated using the method of Amidon et al. [42].

*Less than 10% degradation over 4 h.

na, not applicable; nd, not determined.

Table 6
Physicochemical properties and oral bioavailability of lipophilic prodrugs of disodium cromoglycate (DSCG)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Aqueous solubilityd (mg/ml)</th>
<th>Log P&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Bioavailability&lt;sup&gt;f&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSCG</td>
<td>195.3</td>
<td>&lt; -3.0</td>
<td>5.1 ± 2.4</td>
</tr>
<tr>
<td>1</td>
<td>&lt;0.001</td>
<td>n.d.</td>
<td>7.2 ± 2.1</td>
</tr>
<tr>
<td>2</td>
<td>0.012</td>
<td>2.7</td>
<td>12.0 ± 3.0</td>
</tr>
<tr>
<td>3</td>
<td>n.d</td>
<td>1.8</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>4</td>
<td>0.0052</td>
<td>2.7</td>
<td>7.2 ± 0.8</td>
</tr>
</tbody>
</table>

*In water.

<sup>e</sup><sup>P</sup>= apparent partition coefficient between octanol and phosphate buffer (0.1 M, pH 7.0) at 25°C.

*In rabbits (mean±SE, n=3).

n.d., not determined.

Table 7
Aqueous solubility and oral bioavailability of hydrophilic prodrugs of DSCG prodrug 4

<table>
<thead>
<tr>
<th>Compound</th>
<th>Aqueous solubilityd (mg/ml)</th>
<th>Bioavailability&lt;sup&gt;f&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.0052</td>
<td>7 ± 0.8</td>
</tr>
<tr>
<td>5</td>
<td>7.2</td>
<td>35 ± 1.5</td>
</tr>
<tr>
<td>6</td>
<td>8.3</td>
<td>29 ± 1.5</td>
</tr>
<tr>
<td>7</td>
<td>5.5</td>
<td>29 ± 4.3</td>
</tr>
<tr>
<td>8</td>
<td>12.8</td>
<td>33 ± 8.2</td>
</tr>
<tr>
<td>9</td>
<td>12.5</td>
<td>17 ± 4.4</td>
</tr>
<tr>
<td>10</td>
<td>35.5</td>
<td>43 ± 4.8</td>
</tr>
</tbody>
</table>

*In water.

<sup>f</sup>In rabbits (mean±SE, n=3).

oral route. The synthesis of the succinate ester, BI-L-357, has resulted in a prodrug which showed oral activity [45]. Again, the poor oral absorption of the parent compound is attributed to poor aqueous solubility. Not only does derivatization of the phenol moiety to a succinate ester provide for increased water solubility but also appeared to block first-pass glucuronidation. Furthermore, a duration of action of greater than 4 h was observed.

Merck’s MK 0287 is a platelet-activating factor antagonist that has been evaluated in clinical studies for the treatment of asthma. This compound is poorly water-soluble, making formulation for intravenous administration difficult and limiting the potential for oral delivery. A phosphate ester prodrug of a primary alcohol derivative of MK 0287 was recently synthesized. This prodrug has been shown to release the parent compound via hydrolysis by phosphatases in whole blood. The phosphate ester was shown to be equally effective whether administered intravenously or intraduodenally in guinea pigs...
and was equipotent with the parent drug when given by the oral route to rats [46]. However, the higher solubility of the prodrug might provide for higher drug blood levels at doses above the aqueous solubility of the parent drug.

5.7. Antiinflammatory drugs

Oral prodrugs of nonsteroidal antiinflammatory drugs have been synthesized primarily to overcome gastric irritation by masking the carboxylic acid moiety responsible for local irritation and inhibition of prostaglandin cytoprotection factors [47,48]. A number of antiinflammatory steroids are available as phosphate esters for administration by injection. These include phosphate prodrugs of hydrocortisone [6], prednisolone [46], dexamethasone [46], triamcinolone [49] and betamethasone. A study comparing the clinical pharmacokinetics of two betamethasone tablet formulations with betamethasone phosphate solution following oral administration was carried out a number of years ago [50]. Similar to our early results with oral hydrocortisone phosphate administration in dogs (see model compounds), the phosphate prodrug did not show an increase in oral bioavailability above that observed from oral administration of the parent steroid. While aqueous solubility of these steroids is moderately low, the oral dose administered was sufficiently low in both studies to ensure complete dissolution of the parent compound within the typical residence time of the small intestine. The results of these studies are in contrast to older clinical work documenting improved absorption in pediatric patients from oral administration of triamcinolone phosphate and prednisolone phosphate compared to the parent compound [51].

6. Conclusions

A previous review on this topic [3] cited a limited number of examples in which drug solubility had been increased by chemical derivatization to a prodrug. However, in each case, plasma levels from oral prodrug administration did not show an improvement over those generated by oral administration of the parent drug. This update cites many more examples of this prodrug approach, but with the exception of a few animal studies, the success of the strategy has been limited. The greatest successes have been observed in those cases in which prodrug derivatization increases drug solubility by reducing intermolecular hydrogen bonding or prodrug targeting to a carrier is coupled to a solubility increase.

The fact that relatively few successful oral prodrugs have been developed is the result of a couple of factors. Often, the wrong drug candidate has been selected to demonstrate and advantage for this approach. In those cases where the dose of a poorly water-soluble drug is low enough that complete dissolution is likely within typical GI residence times, drug absorption may be variable but essentially complete. In these situations, a soluble prodrug is unlikely to provide any advantage. If an estimate of the drug dissolution time can be shown to be substantially longer than typical GI residence times, then a soluble prodrug approach is a reasonable alternative strategy to formulation approaches for improving oral drug delivery. This situation may occur when a high oral dose of a poorly water-soluble drug is required to obtain a desired therapeutic effect. The second reason for limited success in this area is that the need to balance the properties of prodrug chemical stability and enzymatic lability in concert with prodrug solubility and parent drug or prodrug intestinal permeability provides a formidable challenge. It is advisable that these factors be carefully weighed during the drug discovery process to optimize the potential for improving oral delivery through a soluble prodrug approach.

7. Notation

GI, gastrointestinal
RI, renin inhibitors
ACE, angiotensin-converting enzyme
DSCG, disodium cromoglycate
AUC, area under the curve
BBM, brush-border membrane
References


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