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Prodrug strategies to overcome poor water solubility ☆

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Abstract

Drug design in recent years has attempted to explore new chemical spaces resulting in more complex, larger molecular weight molecules, often with limited water solubility. To deliver molecules with these properties, pharmaceutical scientists have explored many different techniques. An older but time-tested strategy is the design of bioreversible, more water-soluble derivatives of the problematic molecule, or prodrugs. This review explores the use of prodrugs to effect improved oral and parenteral delivery of poorly water-soluble problematic drugs, using both marketed as well as investigational prodrugs as examples. Prodrug interventions should be considered early in the drug discovery paradigm rather than as a technique of last resort. Their importance is supported by the increasing percentage of approved new drug entities that are, in fact, prodrugs.

Keywords: Prodrug; Solubility; Novel strategy; Phosphates; Ionizable and non-ionizable promoeities; Bioreversible; Parenteral; Oral delivery

Contents

1. Introduction — why prodrugs?

The use of a prodrug strategy as a chemical/biochemical approach to overcome various barriers which can hinder drug delivery, including solubility, is the subject of two new books and some recent reviews [1–4]. The focus of this paper is the use of prodrugs to overcome poor water solubility, not only of already marketed drugs with solubility limitations, but more important, how the prodrug strategy should become an integral part of the drug design paradigm.

Why prodrugs now, when the concept has been around for many years? One main reason is the recent slump in the number of drugs approved by worldwide regulatory agencies. This, in

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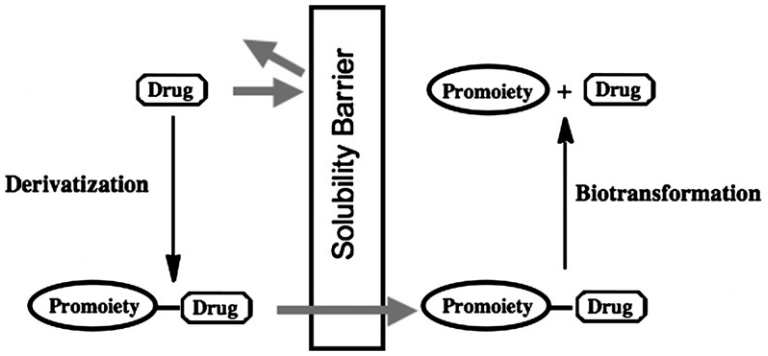


Scheme 1. An illustration of the prodrug concept.

turn, can be attributed to changes in drug candidate identification methodologies implemented years earlier, the conservative nature of the pharmaceutical industry, and ever tougher regulatory and safety standards. Because of new high throughput receptor based screens/assays (HTS) initiated in the late 1980s and the use of combinatorial chemistry approaches to drug design, many drug candidates during this era had pharmacokinetic/pharmacodynamic and physical/chemical properties that limited their chance of being developed into pharmaceutical products. In a recent series of edited books [5,6] these issues were discussed in great detail. During the mid- to late-1990s, the introduction of HTS for pharmaceutical properties, such as solubility, stability and metabolic stability and cellular permeability led to better identified molecules that were more likely to be "developable". Data mining exercises such as those published by Lipinski and co-workers [7–9] supported the need to design drugs with delivery in mind.

While one can be critical of our drug design colleagues for some of the current failures, those currently responsible for new drug design strategies have embraced the need for studies that identify early, drug candidates with greater chance for success because of good physicochemical and ADME properties. On the other hand, it can be argued that because we ignored some of this for a period, we did begin to explore chemical space that we may not have gone to if we only looked for molecules with desirable delivery properties.

Solubility has been identified as a critical parameter and one amenable to manipulation via a prodrug strategy [1–4,10–13]. The previous chapters in this ADDR issue have identified structural elements that contribute to poor water solubility mainly where it affects the oral delivery of drug molecules, and some of the formulation approaches that can be used to overcome solubility limitations. These formulation strategies can often perform very well for low-dose potent molecules and for molecules whose solubility is just below that needed for delivery. Does that mean that we should not explore molecules with more severe solubility limitations as drug candidates? At some limit, the answer is yes. That limit may be when the free or unbound drug concentration in plasma is below that which could be achieved due to solubility limitations i.e., the highest concentration of free, unbound drug in plasma must be its solubility, and more realistically, some fraction of that value. However, provided one is not too close to this limitation, one can manipulate drug solubility for delivery purposes through the use of a prodrug strategy.

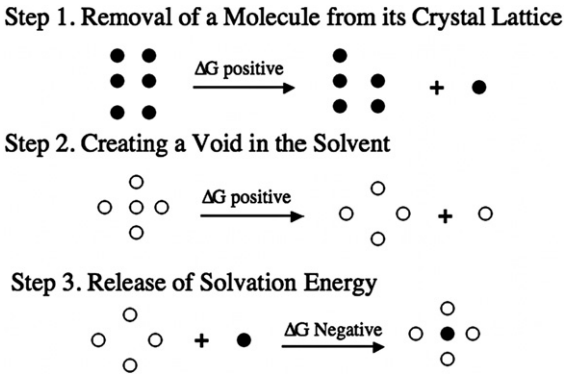
The benefits of the prodrug strategy are most often illustrated by Scheme 1 below. For the purposes of this paper, the barrier to drug delivery is solubility.

2. Structure/solubility relationships and solubility manipulation through prodrugs

In the course of consulting to the pharmaceutical industry for over 30 years (V.S.), the proposal of molecules with limited water solubility as drug candidates has been observed repeatedly. Some of these molecules performed poorly, as expected, while others performed better than expected based on their solubility characteristics. Over the years, some general trends have become clear:

First, and obvious, the larger the dose the bigger is the delivery challenge. This applies even to drugs displaying moderately low, as opposed to extremely low solubility [14].
Second, drugs with high melting points and crystallinity that display poor water and lipid solubility (lipid solubility here meaning solubility in relatively non-polar organic solvents, not in hot DMSO) have a higher probability of being the "bad actors". These are the so-called "brick dust" molecules.
Third, drugs with low melting points that display poor water solubility but high lipid solubility often perform better, orally, than expected. The reason for this is now obvious, the content of the gastrointestinal tract is conducive to dissolving such molecules because they have properties not unlike many fatty food components that are dispersed and dissolved by the presence of bile acids and lecithin mixed micelles in the GIT [15–17]. These drug molecules are often referred to as "grease ball" molecules.
Fourth, solubility is often assumed to be the etiology of poor oral performance when in fact, in many cases, poor water solubility masks poor permeability characteristics e.g. because the drug is an efflux candidate, or lacks oral bioavailability due to presystemic metabolism.

A way to illustrate points two and three above is to refer to the Scheme 2, a variation of one suggested earlier by Hildebrand and Scott [18].



Scheme 2. An illustration of the three steps needed for drug solubility [18,74].

As illustrated in Scheme 2, high crystal packing energy requires a lot of free energy to free a molecule from its crystal (*step 1*) and that has to be compensated for by the release of solvation energy in *step 3*. *Step 2* illustrates that the bigger the molecule, the larger the cavity required in the solvent and thus, for a solvent like water, the more hydrogen bonds need to be broken. For molecules that do not have high crystal packing energy, such as low melting solids and oils, water solubility limitations are usually due to poor interactions with the solvent, water.

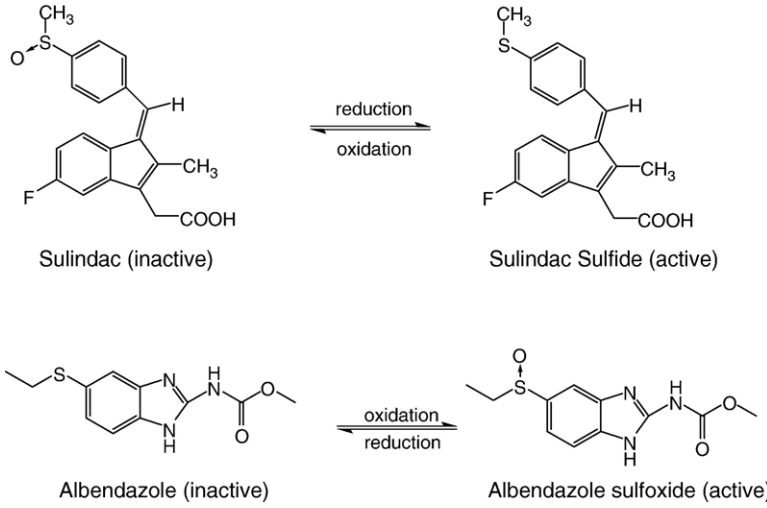
3. Oral drug delivery of poorly water-soluble compounds

How does this discussion relate to prodrug design to effect better delivery of poorly water-soluble molecules? First, we need to make the assumption, often not validated in the early phases of a drug discovery effort, that solubility is the major culprit affecting poor performance. Next, we believe that it is helpful to identify the etiology of the poor solubility. Is the molecule one that displays high crystallinity, a "brick dust" molecule, or is it a low melting or "grease ball" molecule? Obviously, a continuum exists, with most molecules not fitting either extreme. If the molecule has the characteristics of a "grease ball" molecule and usual formulation approaches do not work, solubility enhancement through the use of a polar promoiety may prove useful, as shown in the following examples. If one has a "brick dust" molecule a polar promoiety may work, as might strategies that disrupt the intermolecular interactions that led to the high crystallinity (see Section 3.2).

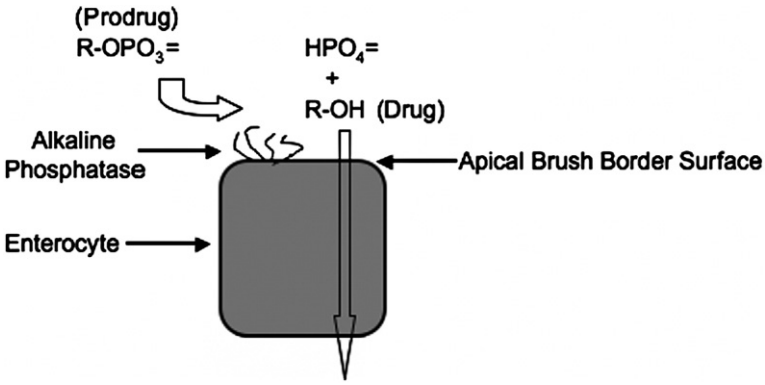
3.1. Enhanced water solubility for enhanced oral drug delivery via the addition of polar functionalities

Conventional wisdom dictates that placing a polar functional group in the structure of a molecule with limited aqueous solubility should enhance solubility. In the case of a prodrug, that functionality would have to be removed/modified, either chemically or enzymatically, to regenerate the parent drug. There are surprisingly few examples of commercially approved prodrugs that were designed to enhance water solubility for improved oral delivery; parenteral delivery examples will be considered in Section 4.

Placing a non-ionizable functionality in the structure may meet the solubility enhancing goal if improved solvation compensates for any increase in intermolecular interactions occur in the crystal. An excellent example of a non-ionizable group used to effect better oral delivery is the drug sulindac as a more water-soluble delivery form of its sulfide metabolite, which is an effective NSAID [19]. The sulfoxide group is more polar, and therefore has better interaction with the solvent than the reduced sulfide. This example is illustrated in Scheme 3. Sulindac is also said to be less locally irritating because it is a poorer inhibitor of prostaglandin synthetase activity [19]. The reversible metabolic reduction/oxidation seen with sulindac is an interesting prodrug example whose characteristics are not shared by many other examples. Note, however, that the drug albendazole (Scheme 3) is also reversibly metabolized to its sulfoxide. Here the albendazole sulfoxide is not only the more active component but is much more water-soluble [20]. That is, the innovators in this case chose the wrong molecule to develop; the active drug had better properties than its precursor. In their



Scheme 3. Oxidation/reduction equilibrium between sulfoxides and sulfides [19,98,99].



Scheme 4. Scheme showing the conversion of a phosphate ester prodrug ($R–OPO_3^=$) to its parent drug (R–OH) by the brush-border enzyme, alkaline phosphatase, and the subsequent passive absorption of R–OH [21].

defense, this is an older drug and at the time it was developed it was not known that the sulfoxide was the more active component.

Many prodrugs designed to increase water solubility involve the addition of an ionizable promoiety to the parent molecule. Because charged molecules have greater difficulty crossing biological membranes, one must balance increased water solubility with the potential for decreased permeability. For example, one might argue that a phosphate ester of a drug with an alcohol functionality in its structure would produce a poorly, membrane permeable prodrug. However, phosphate esters have been shown to be very effective at improving the delivery of poorly water-soluble parent drug molecules after oral delivery. The reason for the success of phosphate esters is illustrated in Scheme 4.

For R–OH, a highly permeable drug, bioavailability after oral dosing is limited by slow dissolution. The prodrug, $R–OPO_3^=$ is much more soluble, rapidly dissolves in the content of the GIT but is cleaved to R–OH by the presence of the enzyme, alkaline phosphatase, seen in abundance on the brush border surface of the cells lining the small intestine, the enterocytes. R–OH, being permeable, readily crosses the enterocyte membranes and enters the systemic circulation. The process can be viewed as a semi-coupled metabolism/transport event. Others have noted limitations to this approach: first, the phosphate prodrug must be a good substrate for alkaline phosphatase; second, R–OH must be permeable once cleaved; and third, too rapid a cleavage of a very insoluble R–OH can result in precipitation of R–OH, and thus poor re-dissolution [21]. Table 1 lists some examples of phosphate ester prodrugs of sparingly water-soluble drugs that have been used to effect better oral delivery.

For illustrative purposes, two examples are worthy of further discussion. The first is fosamprenavir, a phosphate prodrug of the HIV protease inhibitor, amprenavir. Amprenavir was originally formulated in a 150 mg capsule containing TPGS, PEG 400 and propylene glycol, requiring patients to take 8 capsules to achieve a dose of 1600 mg twice a day, clearly at a competitive disadvantage to other lower dose and more conveniently administered antiAIDS drugs. Amprenavir has a secondary alcohol group in its structure that was synthetically phosphorylated to produce fosamprenavir. Although phosphate esters had previously been used to effect improved oral delivery and had been extensively discussed in the literature[21–23], the commercial success of fosamprenavir has made an impact. Fosamprenavir is in the form of a calcium salt, chosen because of its superior pharmaceutical properties compared to the di-sodium salt, and is approximately 10 times more soluble than amprenavir. Because of this superior solubility, even more so at low pH values where the calcium salt dissociates, fosamprenavir can be formulated as a 700 mg tablet (equivalent to 600 mg of amprenavir) thus reducing the dosing to 2 tablets twice a day. The oral availability of amprenavir from fosamprenavir is essentially equivalent to amprenavir from the original capsules. Many advantages ensue, the first being the more convenient dosing to the patients, the second being the competitive advantage of the product in the market and the third being the longer patent clock provided by the fosamprenavir patent [24–27].

The second example is fosphenytoin, a prodrug of phenytoin. Although fosphenytoin is not marketed for oral use, it results in very good oral delivery of phenytoin, an erratically absorbed, poorly water-soluble drug [21,28,29]. Phenytoin is a hydantoin drug with only the two N–H groups at the 1- and 3-positions in the hydantoin ring structure readily available for derivatization. Phenytoin does not have a ready "handle" on to which a phosphate group can be attached. Varia et al. [30–33], recognized that phenytoin reacts with formaldehyde under basic pH conditions to form 3-hydroxymethylphenytoin. In the absence of excess formaldehyde, 3-hydroxymethylphenytoin, at physiological pH and temperature, readily releases the formaldehyde with a half-life in the order of a few seconds. Thus the hydroxyl group on 3-hydroxymethylphenytoin provides a synthetic "handle" that can be phosphorylated to produce fosphenytoin [29,30]. This example demonstrates the use of as "spacer" or "linker" group in prodrug chemistry, whereby a specific function group can be attached not to the molecule itself but via the spacer group. Phenytoin oral availability from fosphenytoin is excellent [34]. The parenteral use of fosphenytoin will be mentioned in Section 4. Some of the examples presented in this paper will provide further illustrations of the use of a spacer group.

Table 1
Examples (with references) of phosphate prodrugs showing enhanced oral delivery

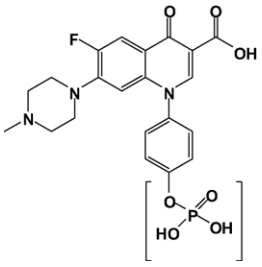
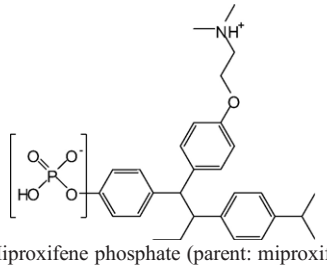
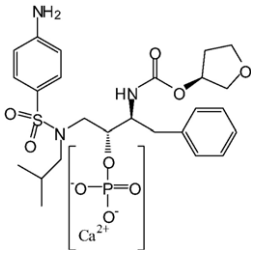
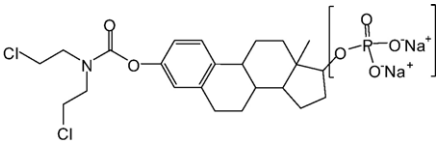
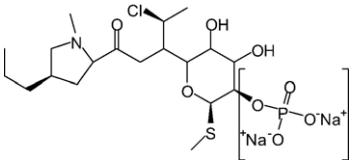
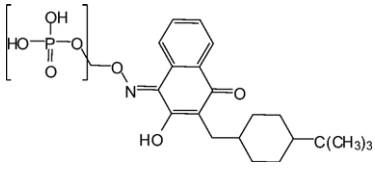
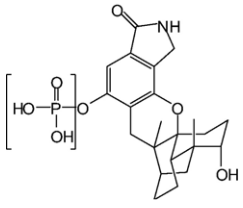
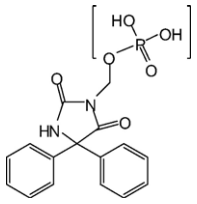
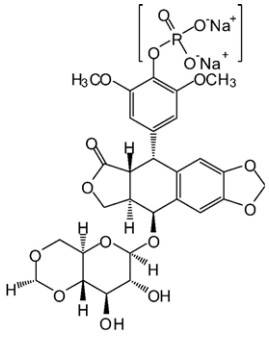
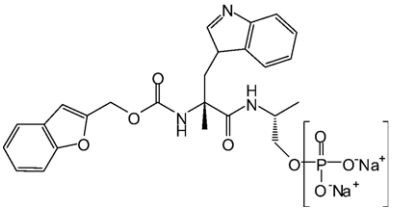
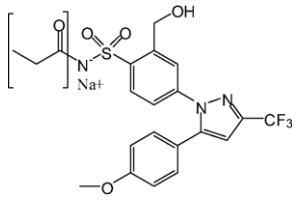
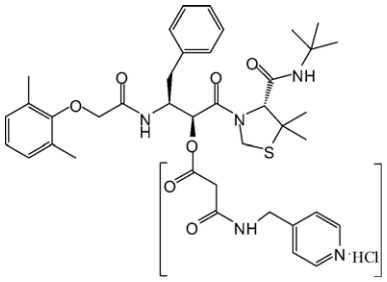
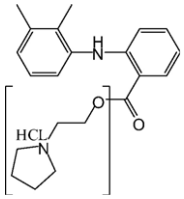
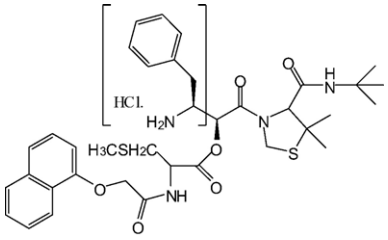
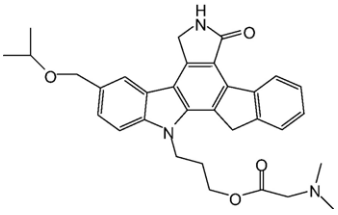
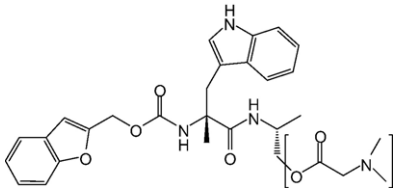
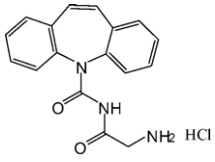
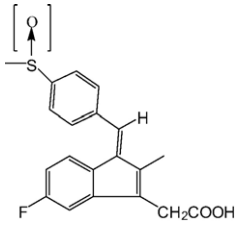
Prodrug	Ref	Prodrug	Ref
 PA2808 (parent: PA2789).	[75]	 Miproxifene phosphate (parent: miproxifene)	[21]
 Fosamprenavir (parent: amprenavir)	[26,76–79]	 Estramustine phosphate (parent: estramustine)	[80,81]
 Clindamycin phosphate (parent: clindamycin)	[82,83]	 (Parent: bupuravaquone)	[84]
 Stachyflin phosphate (parent: stachyflin)	[85]	 Fosphenytoin (parent: phenytoin)	[29,86]
 Etoposide disodium phosphate (parent: etoposide)	[87–89]	 Cam 5223 (parent: CAM 4451)	[90]

Table 2
Examples (with references) of non-phosphate prodrugs on poorly water-soluble parent drugs intended for enhanced oral delivery

Prodrug	Ref	Prodrug	Ref
 (Parent: celecoxib)	[91,92]	 (Parent: KNI-727)	[93–95]
 (Parent: mefenamic acid)	[96]	 (Parent: KNI-272)	[94,95]
 CEP 7055 (parent: CEP 5214)	[97,98]	 CAM 4562 (parent: CAM 4451)	[90]
 *N*-gly-carbamazapine (parent: carbamazapine)	[57]	 Sulindac sulfoxide(Clinoril®)	[19,99,100]

Phosphate groups are not the only way to increase water solubility. Table 2 contains examples of water-soluble prodrugs designed to effect better oral availability. Most prevalent are prodrugs that employ an amine group capable of being protonated to form a more water-soluble salt. Unlike the phosphate group, amine group containing prodrugs are often capable of being absorbed intact from the GIT because the neutral free-base form of the drug is present in sufficient quantities to allow permeation across biomembranes.

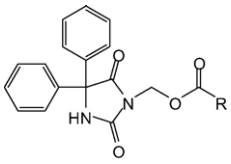
The table illustrates the diversity of pro-groups that have been utilized, including some instances where the prodrug requires significant rearrangement to regenerate the parent drug.

3.2. Decreased crystal packing and enhanced oral availability, the role of the GI tract contents

A strategy not often considered to effect better oral delivery of poorly soluble drugs is one that attempts to convert a "brick dust" molecule to a "grease ball" molecule. The rationale for this approach is as follows. The Noyes–Whitney model, mathematically defined by Eq. (1) describes the dissolution rate (DR) of a drug under sink conditions,

$$\mathrm{DR} = \frac{D^{*}A^{*}\mathrm{Cs}}{h} \tag{1}$$

Table 3
Physical properties of phenytoin and some 3-acyloxymethyl phenytoin prodrugs [37]



	Mp (°C)	pH 6.4 buffer solubility[a] ($M\times10^5$)	Cylcohexane solubility ($M\times10^3$)	SIBLM[b] solubility ($M\times10^4$)	DR pH 6.8 buffer $\times10^{-11}$ mol/cm^2/s	DR SIBLM $\times10^{-11}$ mol/cm^2/s
Phenytoin	296	8.0	0.16	5.5	10.1	28.7
$R=-CH_3$	158–9	3.4	0.19	2.7	5.1	13.5
$R=-C_2H_5$	172–4	1.24	0.24	1.3	1.4	5.9
$R=-C_3H_7$	134–5	0.85	1.08	1.4	1.1	6.0
$R=-C_4H_9$	89–92	4.3	14.7	4.3	1.9	28.4
$R=-C_5H_{11}$	107–8	0.13	4.5	1.9	0.2	9.8
$R=-C_6H_{13}$	87–8	0.05	9.9	2.1	0.07	10.0
$R=-C_7H_{15}$	67.5–8	0.03	150	5.4	0.04	55.9
$R=-C_8H_{17}$	78.5–80	ND[c]	48	3.4	ND[c]	33.8
$R=-C_9H_{119}$	56–7	ND[c]	701	6.1	ND[c]	30.7

[a] Isotonic pH 6.4 phosphate buffer.
[b] SIBLM is described by Stella et al. [37].
[c] ND, the properties could not be determined because the concentrations were below the limit of quantification.

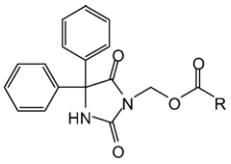
where D is the diffusion coefficient, A is the surface area available to the dissolution media, h is the unstirred film thickness and Cs is the equilibrium solubility in the dissolution media. Although this equation has some limitations, it illustrates that DR should be proportional to solubility, Cs, but solubility in what? Although the aqueous solubility should help define the DR in water, the GIT fluids in animal species commonly used in preclinical work do not consist of just water, and also not of simple buffer solutions typically used for solubility determinations, e.g. pH 6.4 isotonic aqueous, phosphate buffer. Because of the presence of mixed micelles of bile salts and lecithin as well as food digestion products, the GIT presents an environment conducive to dissolving the poorly soluble, lipophilic compounds which can be solubilized by this complex milieu [14–17,35–38].

A systematic study of this concept was presented in a series of papers that used phenytoin as a model compound [35–38]. The N–H at the 3-position of phenytoin is known to hydrogen bond with the carbonyl of a second phenytoin molecule. Thus, removing or blocking the N–H group at the 3-position dramatically changes the properties of the molecule. The melting points of a series of 3-acyloxymethyl prodrugs of phenytoin is shown in Table 3 along with their solubility in water, cyclohexane and in a bile salt/lecithin mixture used to simulate the GIT contents (referred to here by the acronym SIBLM, for simulated bile salt, lecithin mixture). Also included in Table 3 are the dissolution rates for a few of the derivatives in pH 6.4, phosphate buffer and SIBLM. Note the melting behavior of the pentanoyl- (C_4H_8CO-) and octanoyl- ($C_7H_{15}CO$-) derivatives, which have melting points lower than their higher and lower homologs, and the relationship between melting point and the solubility of the various prodrugs in the hydrocarbon solvent, cyclohexane. Similar behavior was seen in various triglyceride and fatty acid esters suitable for soft gelatin capsule formulations [38].

Clearly if one were to only consider water solubility and DR in water, phenytoin itself would be the superior candidate. When one considers the DR in the SIBLM however, the choice becomes less clear, with the DR of the octanoate prodrug superior to that of phenytoin in this medium [36,37]. The oral, absolute bioavailability of phenytoin from phenytoin, the pentanoate and the octanoate was assessed in fed and fasted dogs. The results are given in Table 4. The bioavailability of phenytoin is enhanced in the fed state, consistent with an increase in DR in the presence of the enhanced levels of bile salts and lecithin triggered by food [36,37]. The bioavailability of phenytoin from the two prodrugs is superior in both the fed and fasted state despite their lower aqueous solubility. In the fed state, phenytoin bioavailability from the pentanoate and the octanoate is close to complete, even though the octanoate had limited aqueous solubility and no measurable DR in water.

The observations made with the phenytoin prodrugs is also consistent with the studies of Shaw et al. [39] who showed superior oral activity seen with a *N*-acyl prodrug of a urea

Table 4
Absolute phenytoin bioavailability of oral suspensions, in fasted and fed beagle dogs, from phenytoin and the pentanoate ($R=-C_4H_9$) and octanoate ($R=-C_7H_{15}$) esters of 3-hydroxymethyl phenytoin, lipid soluble, all low melting point prodrugs of phenytoin [35]



	Fasted absolute % bioavailability (±%SD)	Fed absolute % bioavailability (±%SD)
Phenytoin	21.0 (6.9)	37.8 (9.3)
$R=-C_4H_9$	44.2 (16.2)	84.2 (16.5)
$R=-C_7H_{15}$	40.7 (19.8)	77.5 (22.1)

Table 5
Examples (with references) of water-soluble prodrugs for parenteral delivery of poorly water-soluble parent molecules

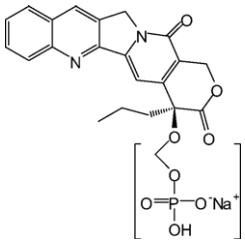
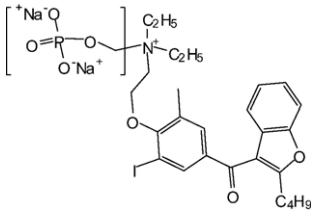
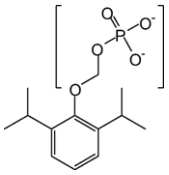
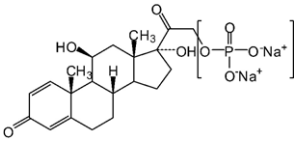
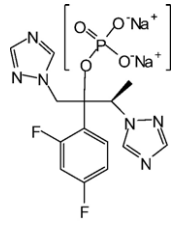
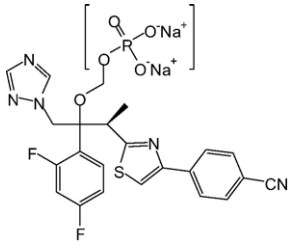
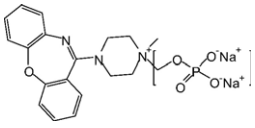
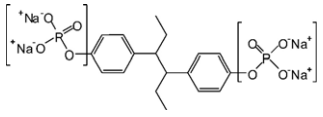
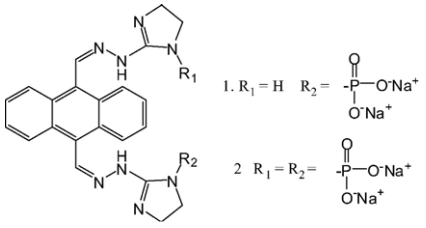
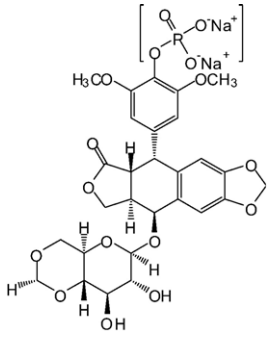
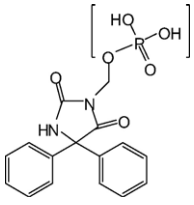
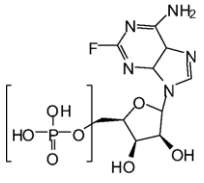
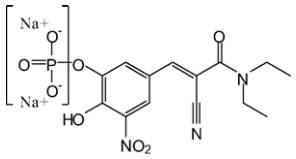
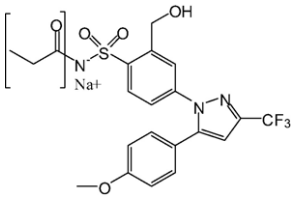
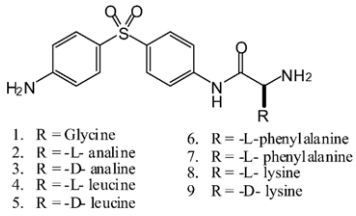
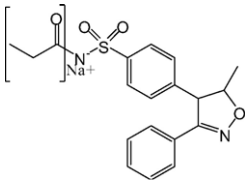
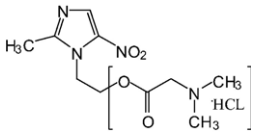
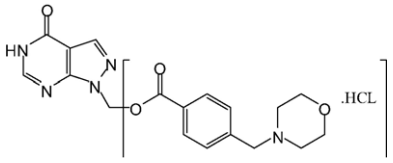
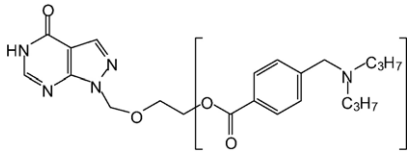
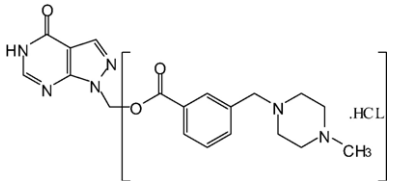
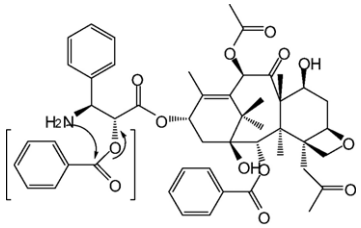
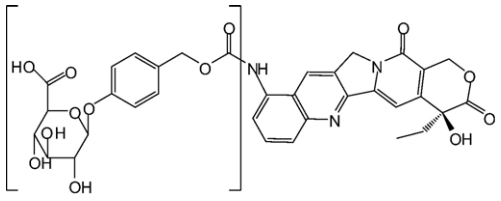
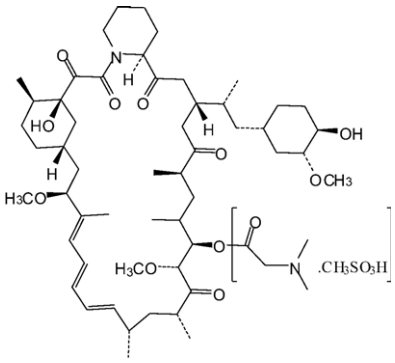
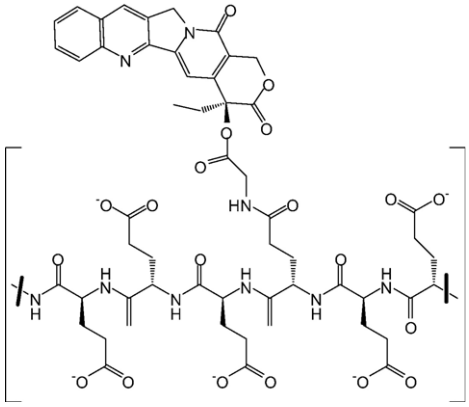
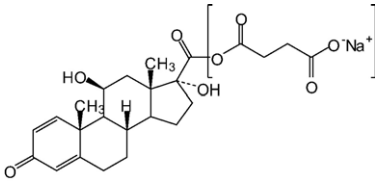
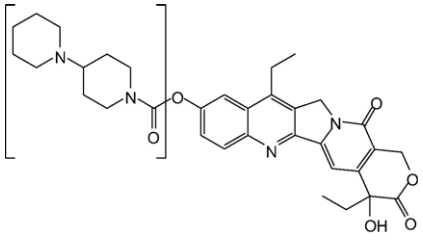
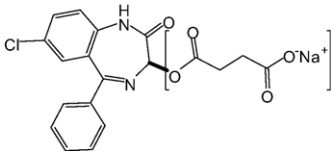
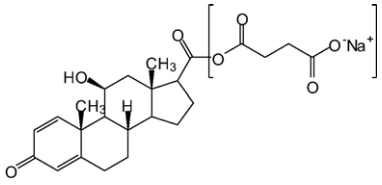
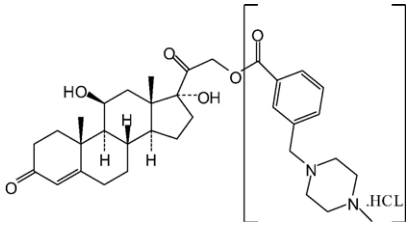
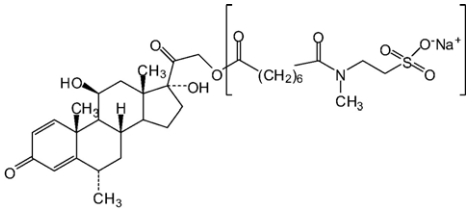
Prodrug	Ref	Prodrug	Ref
 20-Phosphoryloxymethyl camptothecin (parent: camptothecin)	[47,71]	 Aminodarone disodium phosphate (parent: aminodarone)	[101]
 Aquavan (parent: propofol)	[43,102,103]	 Prednisolone sodium phosphate (parent: prednisolone)	[51,104]
 Fosfluconazole (parent: fluconazole (Difluca®))	[105,106]	 (Parent: ravuconazole)	[107,108]
 (Parent: loxapine)	[109,110]	 (Parent: diethylstilbesterol)	[111,112]
 (Parent: bisantrene)	[113,114]	 Etoposide disodium phosphate (parent: etoposide)	[87–89]
 Fosphenytoin (parent: phenytoin)	[29,86]	 Fludarabine phosphate (Fludara®) (parent: vidarabine)	[115,116]

Table 5 (*continued*)

Prodrug	Ref	Prodrug	Ref
 Comtan® (Entacapone phosphate) (parent: entacapone)	[21,117]	 (Parent: celecoxib)	[91,92]
 1. R = Glycine 2. R = -L- analine 3. R = -D- analine 4. R = -L- leucine 5. R = -D- leucine 6. R = -L-phenylalanine 7. R = -L- phenylalanine 8. R = -L- lysine 9 R = -D- lysine (Parent: dapsone)	[118,119]	 Parecoxib sodium (parent: valdecoxib)	[3,120–123]
 Metronidazole *N*,*N*-dimethylglycinate (parent: metronidazole)	[124]	 (Parent: allopurinol)	[125]
 Aminomethylbenzoate ester of acyclovir (parent: acyclovir)	[126]	 (Parent: allopurinol)	[125]
 Isotaxel (parent: paclitaxel)	[127]	 (Parent: 9–aminocamptothecin)	[128,129]

(continued on next page)

Table 5 (*continued*)

Prodrug	Ref	Prodrug	Ref
 (Parent: rapamycin)	[130,131]	 Poly-(L-glutamic acid)-gly-camptothecin (parent: 20 (S)-camptothecin)	[129,132,133]
 Prednisolone sodium succinate (parent: prednisolone)	[51,104]	 Irinotecan (parent: camptothecin)	[133]
 Oxazepam sodium succinate (parent: oxazapam)	[134–136]	 Hydroxydione sodium succinate (parent: hydroxydione)	[137,138]
 (Parent: hydrocortisone)	[139]	 Promedrol® (parent: methylprednisolone)	[63,140]

molecule. The parent molecule had a melting point of >320 °C while an *N*-benzoyl derivative had a significantly lower melting point, lower water solubility but superior activity after oral dosing to dogs [39].

4. Parenteral drug delivery

Because this paper relates to aqueous solubility issues, parenteral formulations of prodrugs intended for prolonged

drug release, including pegylated drugs, are not discussed here. The reader is directed to more extensive reviews on this subject [40–42]. The examples presented here will focus on water-soluble prodrugs intended for rapid drug release after IV, SC or IM administration. Although sparingly water-soluble drugs can be formulated with suitable excipients for parenteral use, most formulation techniques present their own challenges with respect to safety and chemical and physical stability. Also, when large increases in solubility are needed, prodrugs often present the best chance of success. Some of the best and most successful marketed prodrugs are those intended for parenteral use. Table 5 provides a cross-section of marketed and investigational parenteral prodrugs.

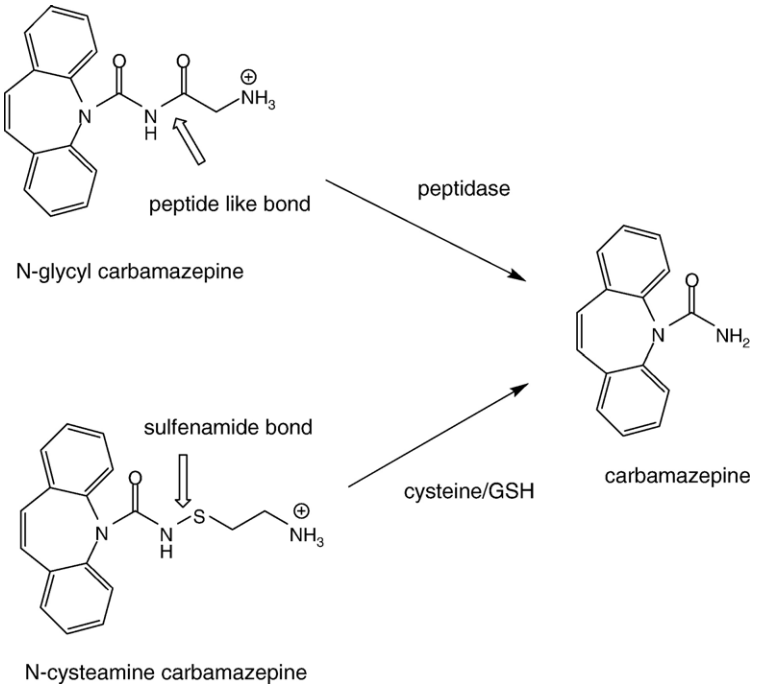
4.1. Enhanced water solubility via the addition of polar functionalities

The majority of parenteral prodrugs listed in Table 5 involve prodrug modifications whereby a polar, most often an ionizable promoiety, is utilized to increase water solubility. Many recent examples have focused on the use of the phosphate group either directly linked to the parent drug, where possible, or through a linker group such as formaldehyde [29,43–47]. Unlike some other promoieties, many phosphate esters show good chemical stability while undergoing rapid and often quantitative cleavage *in vivo* via alkaline phosphatases [22,29–32,47–49]. Hemi-succinate esters on the other hand, are chemically metastable and weak substrates for esterase cleavage. This has resulted in incomplete conversion to the parent drug [50–55]. Three of the earliest parenteral prodrugs are chloramphenicol, prednisolone and methylprednisolone hemisuccinates [50–55].

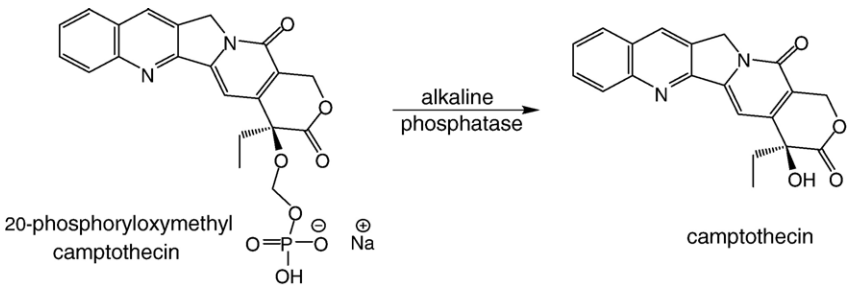
An interesting phosphate prodrug undergoing clinical trials is aquavan, a water-soluble, pain free prodrug of the anesthetic drug, propofol (see Table 5). Propofol is used in general anesthesia and in ICU use for maintaining patients in an induced coma. Because of its fast onset and offset rate, and minimal after-effects, it would be an ideal anesthetic if it did not cause significant brachial pain and acutely lower blood pressure. Furthermore it is formulated in an o/w emulsion, which can lead to hyperlipidemia when used long-term to maintain ICU patients in a coma. Stella et al. [56] synthesized and evaluated a water-soluble, phosphoryloxymethyl ether prodrug of propofol, aquavan, which was subsequently clinically evaluated [43–46]. It is currently in the final stages of Phase III clinical trials for light sedation with further trials planned. In clinical studies, aquavan shows no brachial pain as the arm veins only "see" the prodrug and not the pain-causing propofol. Additionally, the drop in blood pressure is less severe. And because the prodrug can be formulated in a purely aqueous vehicle, hyperlipidemia is not a problem.

Direct phosphorylation of propofol did produce a water-soluble form of propofol but studies in animals showed slower conversion to propofol, presumably because of the steric hindrance by the *ortho*-di-isopropyl groups, than the formaldehyde linked molecule. The directly phosphorylated molecule also showed an unfavorable EEG behavior in experimental animals [unpublished results].

Carbamazepine is an antiseizure drug for which there is no parenteral form. Recently, Hemenway [57] evaluated two water-soluble prodrugs of carbamazepine (see Scheme 5). The first is the *N*-glycyl derivative. It was argued that even though the *N*-glycyl derivative is an acyl urea, the glycine-carbamazepine bond resembles a peptide bond and so may be subject to cleavage by peptidases. *N*-glycylcarbamazepine was found to be a peptidase substrate and to be rapidly and quantitatively cleaved to carbamazepine in rats after i.v. administration in rats



Scheme 5. Two water-soluble prodrugs of carbamazapine [57].



Scheme 6. A water-soluble prodrug of camptothecin [71].

[13,50,57]. On oral dosing, *N*-glycylcarbamazepine resulted in superior oral bioavailability of carbamazepine compared to the parent drug. A limitation seen with the glycine derivative as a parenteral prodrug was its marginal chemical stability, requiring the drug to be formulated as a freeze-dried product for reconstitution.

A second carbamazepine prodrug that was more chemically stable was the *N*-cysteamine derivative [13,50,57,58] (Scheme 5). Guarino et al. [59], earlier showed that sulfenamide derivatives of ureas and amides are quite chemically stable but readily revert to the parent urea or amide in the presence of cysteine, glutathione and other sulfhydryl molecules. After i.v. administration to rats, *N*-cysteamine carbamazepine resulted in rapid and quantitative conversion to carbamazepine. The use of sulfenamides as prodrugs of acidic N–H molecules was recently reviewed by Guarino and Stella [60,61].

4.2. Formulation challenges

Parenteral formulations present some unique challenges compared to oral formulations. The two most obvious are the need for sterility and that the formulation for i.v. use must be free of significant particulates. Sterility can be achieved through either sterile filtration or terminal heat sterilization. Because prodrugs, by design, are intended to be metastable by being cleaved by a chemical or enzyme mediated pathway to the parent drug, most prodrug solutions cannot be heat sterilized; they are too chemically unstable at room temperature to be formulated as ready-to-use solutions, even when *in vivo* performance requires enzymatic versus chemical cleavage. As a result, many parenteral prodrugs are formulated as freeze-dried products for reconstitution.

A second significant challenge, also related to chemical stability, is the precipitation limit to the shelf-life of many prodrug solutions. Since most products must maintain a content specification of ±10% of labeled amount, the shelf-life of many drugs is usually determined by the time to degrade 10% of the drug content. This is not always the case for many water-soluble prodrugs of poorly water-soluble parent drugs. The chemical degradation of a prodrug often results in formation of the sparingly soluble parent drug as the primary degradation product. When the parent drug is formed in excess of its solubility in the formulation, it can precipitate, taking the product out of specification due to the present of particulates/precipitates. Consider the following example. Fosphenytoin is formulated as a 50 mg/mL, mole equivalent solution of sodium phenytoin. At pH 7.4 in the presence of fosphenytoin, phenytoin has a solubility of about 45 μg/mL in the absence of a phenytoin solubility enhancer [62]. Therefore, the shelf-life of fosphenytoin at pH 7.4 is dictated by the time for fosphenytoin to degrade from 50 mg/mL to 49.955 mg/mL, or the time for only approximately 0.1% of the fosphenytoin to degrade to phenytoin. Even this calculation assumes that the fosphenytoin API contains 0% phenytoin as an impurity at time zero. For this reason fosphenytoin was initially formulated at pH>8.5 because phenytoin is not the principal degradation product in this pH range and the products formed are water-soluble. However, because of the greater intrinsic instability at pH>8.5 compared to pH 7.4, the formulation requires refrigeration, limiting its use to areas with ready access to refrigeration. Narisawa and Stella [62] solved this problem by formulating fosphenytoin at pH 7.4–8 at room temperature in the presence of 60 mM sulfobutylether-β-cyclodextrin, which is capable of selectively solubilizing the formed phenytoin in the presence of high fosphenytoin concentrations. Thus a sophisticated formulation approach combined with a prodrug was able to provide a unique solution to the solubility/stability issues.

Some water-soluble prodrugs can solubilize their sparingly water-soluble degradation products because the prodrugs tend to be amphiphilic and capable of forming micelles [63–65]. Thus, the shelf-life may be longer than the value that would be expected by considering just the solubility of the parent drug. Consider the investigational prodrug, 20-phosphoryloxymethyl camptothecin (Scheme 6) [47]. This prodrug is formulated at pH 4 for reasons related to the facile E-ring opening at higher pH values [47]. Table 6 shows the increase in solubility of camptothecin in the presence of increasing concentration of 20-phosphoryloxymethyl camptothecin at pH 4. In this case, the

Table 6
Solubility of camptothecin at 25 °C in 20 mM aqueous citrate buffer, pH 4.0, in the presence of increasing concentrations of its 20-phosphoryloxymethyl ether prodrug (see Scheme 6 for structures) [71]

20-phosphoryloxymethyl camptothecin concentration, mg/mL (camptothecin equivalents)	Camptothecin solubility, mg/mL
0 (0)	2–3
1.3 (1)	45
3.3 (2.5)	95
6.6 (5)	175
13.1 (10)	290

prodrug does not appear to form micelles, but rather a complex with the camptothecin "sandwiched" between two molecules of the prodrug [unpublished results]. Although the shelf-life of 20-phosphoryloxymethyl camptothecin is still determined by the conversion to and possible precipitation of camptothecin, the shelf-life is much longer than that predicted by assuming no interaction between the camptothecin and its prodrug.

4.3. Bortezomib (Velcade®), a novel example

An example of a recent "surprising" prodrug is the boronic acid, proteasome inhibitor, bortezomib, marketed as Velcade, which is used to treat lymphomas. Although the chemical structure of bortezomib is usually drawn as illustrated in Scheme 7, in the solid state as the pure API, it actually exists as the very insoluble boroxine, a cyclic boronic acid anhydride. When placed in water, the boroxine dissociates to form an equilibrium between itself and the monomeric bortezomib resulting in an apparent water solubility of about 0.5–1 mg/mL, still not sufficient for formulation purposes. As part of work performed in collaboration with the innovator and the National Cancer Institute, bortezomib was found to be oxidatively unstable [66], requiring the development of a freeze-dried formulation. A stable formulation was found by first by dissolving bortezomib in warm *t*-butyl alcohol, then adding water (to 50–60% water) and mannitol (1%, bulking agent), followed by freeze-drying. On reconstitution, bortezomib was found to rapidly dissolve and was significantly more soluble due to the *in situ* formation of boronic acid esters by reaction with diol groups of mannitol during the freeze-drying process [67]. The mannitol esters play two roles, first the esters themselves may be more soluble, and second, in forming the esters during the freeze-drying step, it prevents or competes with formation of the less soluble and slowly dissolving boroxine. The kinetics of formation and dissociation of the diol esters has (to our knowledge) not been published for bortezomib but studies in our laboratory with other boronic acids have suggested that the half-lives are in the order of seconds. The FDA allowed the innovator significant leeway in defining bortezomib as the active agent while the final formulation contains the diol ester prodrugs. On *in vivo* administration, it was successfully argued that the mannitol esters rapidly and quantitatively dissociate [68].

5. What have you done for me lately?

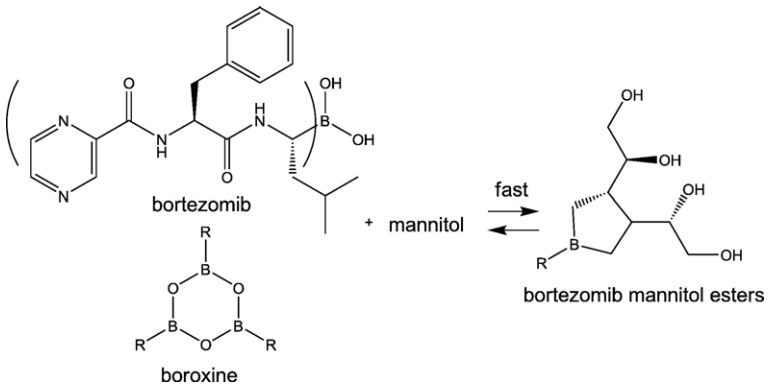
Many still question the use of a prodrug strategy as a problem solving technique. Some of these concerns are valid, namely, the additional time and cost when a prodrug approach is needed to solve a specific formulation or delivery problem. It can be argued that if the prodrug strategy became an integral part of the drug design paradigm, little additional time and expense is needed. The prodrug becomes the NCE — that happens to have an active metabolite.

According to Hedge and Schmidt [69], of the 24 NCEs approved in 2005, 19 were small molecules, while five were polypeptides or macromolecules (biotech products). Of the 19 small molecules, two were clearly identified as prodrugs (10.5%). There was one pegylated antiviral approved that was probably a prodrug (raising the percentage to 15.8%). There were two other small molecule antivirals that owed their activity to being phosphorylated and are therefore technically prodrugs but not always valued as such. If one includes all five molecules, 26.3% of all drugs approved in 2005 were prodrugs, with 15.8% clearly by design. Similar evaluations over longer time periods show that a significant number of drugs marketed over the last 15 years were prodrugs [70]. Ettmayer et al. [3] confirmed this trend, stating that 6.9% of all marketed drugs in Germany are prodrugs.

As stated earlier, there many successful examples of parenteral, water-soluble prodrugs of poorly water-soluble drugs. In fact, other than prodrugs to overcome permeability barriers, they are by far some of the best prodrug examples. Surprisingly, there are few marketed prodrugs designed to improve the oral delivery of sparingly water-soluble drugs. This is, however, an active area of interest and one that is likely to lead to many new products in the future.

6. Why the occasional failures?

The reticence of some to explore a prodrug solution to a problem can usually be traced to previous failures or by management wanting a fast solution that will not delay compound development. Previous failures can usually be traced to a poor choice of drug candidate to begin with, poor choice of prodrug strategy, misidentification of the etiology of the



Scheme 7.

delivery barrier, unrealistic expectations, generation of a new problem in solving the initial problem, or misleading results in animal models with respect to improved availability.

When a drug displays poor water solubility, it is almost always assumed that poor performance after oral dosing was related to the solubility limitation. This is often reinforced when a solution form of the drug in a co-solvent mixture or a SEDDS formulation outperforms a suspension of the drug. However, the problem may lie elsewhere. Other barriers, such as poor permeability or first pass metabolism may well be at play. Especially in the last five years, there has been growing awareness about the role of efflux pump transporters such as *P*-glycoprotein (Pgp) in curtailing transport of molecules across biomembranes, even for those molecules with apparently ideal log P properties.

An additional difficulty is getting reliable pharmacokinetic parameters for a poorly soluble drug from i.v. studies. How do you administer a poorly soluble drug i.v. without the use of exotic vehicles? Therefore, it becomes difficult and sometimes impossible to determine, with accuracy, the absolute bioavailability of a drug after oral dosing and questionable whether one can identify the barrier(s) to delivery. For similar reasons, identifying whether a drug is a Pgp substrate (permeability studies that require the drug to be present in reasonable concentrations on the apical side of a cell mono-layer) or is rapidly cleared (requiring accurate and precise pharmacokinetic measurements) can also be a challenge.

Therefore, when one does not "know" the cause, one often "assumes," and poor solubility is nearly always assumed to be the cause of the poor performance. However, poor permeability and presystemic metabolism can be hidden by poor water solubility. We studied the parenteral and oral availability of the anticancer drug camptothecin from its 20-phosphonooxymethyl prodrug [12,47,71]. After i.v. administration, the prodrug quantitatively released camptothecin [71]. It was argued that the poor oral availability of camptothecin was due to its low water solubility of about 3 μg/mL and ensuing slow dissolution rate. The oral bioavailability of camptothecin in rats from an oral suspension was found to be 2%, while its availability from a complex co-solvent vehicle was 4%, or double that from the suspension. The oral availability of camptothecin from its water-soluble phosphate prodrug was also only 4%. At the time, we did not realize that camptothecin was a very good Pgp substrate. Thus, the poor oral availability of camptothecin was not only due to poor water solubility, but also its poor permeability. Presystemic metabolism of camptothecin may also have been contributing to the poor oral availability in the rat model.

The second relates to the comment that in solving one problem a second can be created. As seen earlier, to increase water solubility one often attempts to incorporate a water-solubilizing moiety in the prodrug structure. A favorite of chemists is an amino group (1°–3°). In forming the prodrug, the molecular weight is also increased. The combination of an amine group and increased molecular weight increases the potential for the prodrug to be a Pgp substrate [72,73]. So, while solubility and dissolution may be increased, the new molecule, the prodrug, may be less permeable and thus poorly absorbed.

The third relates to choice of animal models. One could spend a lot of time on this point and one would be not the much wiser for it. The recently published new book by Testa and Mayer [2] contains many excellent discussions of the bioreversible, enzymes based mechanisms for prodrugs and differences seen between animal species. Clearly a prodrug strategy that relies on only a single animal model for initial screening of prodrugs can lead to both false positives as well as negatives, but this is not unique to prodrugs, analog assessment suffers from the same limitations. With respect to oral availability assessments, there are several differences among species which may affect drug dissolution and absorption. For example, bile flow is continuous in the rat whereas in all other species, increased bile flow is often triggered by feeding. In the dog, the bile acid and lecithin content of the small intestinal fluids after meals is much higher than in many other animal species. With respect to enzyme activity, it should be noted that glucuronidation is poor in dogs. By contrast, esterase activity in rodents appears to be generally quite high. Understanding the limitations of the animal species chosen helps to recognize the potential dangers associated with interpreting the results in terms of human application and refines the choice of prodrug candidates in a second animal model. Ultimately however, one still needs to make an educated "guess". If that "guess" is off, and the prodrug strategy does not meet with success in a clinical trial, there will be less willingness to invest in prodrug strategies going forward. However, it seems appropriate to mention at this juncture that this same reticence is rarely applied to analog development, i.e., just because one does not synthesize a new blockbuster drug on the first try, one does not conclude that the analog approach is not a good way to discover a new drug!

7. Conclusion

Prodrugs continue to be an exciting area of research. The heightened interest of late comes from the fact that more and more drug candidates present significant delivery challenges, with poor water solubility being an increasingly frequent problem. The relatively high percentage of recently approved drugs that are, in fact, prodrugs supports claims for the heightened recent interest in prodrugs. We hope this paper will encourage creative prodrug research to help solve some of the unmet drug delivery challenges, especially those related to limited solubility.

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Glossary

ADDR: advanced drug delivery reviews
ADME: absorption, distribution, metabolism and elimination
AIDs: autoimmune deficiency syndrome
BCS: biopharmaceutics classification system
DMSO: dimethylsulfoxide
DR: dissolution rate
GIT: gastrointestinal tract
HIV: human immunodeficiency virus
HTS: high throughput screening
ICU: intensive care unit
i.m.: intramuscular
i.v.: intravenous
NCE: new chemical entityNCE
PEG 400: polyethylene glycol 400
Pgp: *P*-glycoprotein
s.c.: subcutaneous
SEDDS: self-emulsifying drug delivery system
SIBLM: simulated intestinal bile salt and lecithin mixture
TPGS: *d*-α-tocopheryl polyethelene glycol 1000 succinate