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Mini Review

Amorphous Solid Dispersions or Prodrugs: Complementary Strategies to Increase Drug Absorption

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ABSTRACT

Maximizing oral bioavailability of drug candidates represents a challenge in the pharmaceutical industry. In recent years, there has been an increase in the use of amorphous solid dispersions (ASDs) to address this issue, where a growing number of solid dispersion formulations have been introduced to the market. However, an increase in solubility or dissolution rate through ASD does not always result in sufficient improvement of oral absorption because solubility limitations may still exist at high doses. Chemical modification in the form of a prodrug may offer an alternative approach for these cases. Although prodrugs have been primarily used to improve membrane permeability, examples are available in which prodrugs have been used to increase drug solubility beyond what can be achieved via formulation approaches. In this mini review, the role of ASDs and prodrugs as 2 complementary approaches in improving oral bioavailability of drug candidates is discussed. We discuss the fundamental principles of absorption and bioavailability, and review available literature on both solid dispersions and prodrugs, providing a summary of their use and examples of successful applications, and cover some of the biopharmaceutics evaluation aspects for these approaches.

Introduction—the Pursuit for High Oral Bioavailability

The oral route of administration of a drug is typically preferred due to the convenience of self-administration, ease of handling of the dosage form by the patient, and lower cost of the final drug product. In a drug discovery setting, oral bioavailability (F) is perhaps the most commonly used pharmacokinetic measure of drug candidate suitability for oral administration. The oral bioavailability of a drug is defined as the fraction of an oral dose of the drug that reaches the systemic circulation.[1] High oral bioavailability is important to ensure sufficient therapeutic levels after ingestion of an oral dosage form within acceptable dose ranges, thus avoiding potential side-effects with higher doses, and to reduce both between subject and within subject plasma concentration variability. It is often used to optimize structure-activity relationships of the molecule and has led to development of drug-likeness criteria that are commonly used in early drug discovery.[2,3]

Numerous publications have discussed efforts toward improving oral bioavailability both in academic and industrial settings. One illustrative case is that of saquinavir, a potent protease inhibitor with a minimum effective concentration of 100 ng/mL that requires a high pill burden of 600 mg dosed 3 times daily. Saquinavir's low human bioavailability (4%) from the original hard gelatin capsule formulation was attributed to a combination of extensive presystemic metabolism (cytochrome P450 3A4 mediated) and incomplete absorption, resulting in high plasma variability and lack of response in many patients.[4] To improve oral bioavailability and systemic levels of saquinavir, Hoffman-La Roche introduced Fortovase®, a reformulated soft gel capsule formulation containing vitamin E TPGS and ritonavir (a cytochrome P450 3A4 inhibitor) that delivered a 3-fold improvement in oral bioavailability. Low bioavailability can also result in high intersubject variability, a subject of the work by Hellriegel et al.,[5] where an inverse relationship was demonstrated between absolute oral bioavailability and intersubject variability, implying high variability for drugs with low oral bioavailability. For example, high pharmacokinetic variability (75% coefficient of variation) and low bioavailability (8%) limits oral therapeutic use of docetaxel, but coadministration with cyclosporine improved oral bioavailability to

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circa 90% and also reduced variability in systemic concentration.[6] And finally, the erratic oral bioavailability of methotrexate (28%-94%) in the management of rheumatoid arthritis led to the development of a therapeutically preferred but less convenient subcutaneous parenteral formulation.[7]

As mentioned previously, the drivers to achieve high oral bioavailability are self-evident and well documented. Assuming a drug is stable in the gastrointestinal fluids, oral bioavailability is dependent on both fraction absorbed (F_a), that is, the percent of drug that crosses from the lumen in the intestinal wall and first-pass metabolism in the intestinal wall or the liver. However, the first-pass metabolism may be altered by chemical modification or coadministration of inhibitors, such as the case of saquinavir or ritonavir highlighted previously. For formulation and biopharmaceutics scientists, the focus is typically on maximizing intestinal absorption (F_a). F_a is strongly governed by both pharmaceutical factors (drug solubility, dissolution rate, release rate from the formulation, intestinal permeation, and stability in gastrointestinal [GI] tract) as well as physiological factors (transporters, GI motility, fluid volume, and disease state). This interplay between compound physicochemical properties, drug product properties, and intestinal physiology eventually dictates the success in oral delivery of a new chemical entity. Only 30%-35% of the top 200 immediate release orally administered drugs in the United States, United Kingdom, Spain, and Japan markets are classified as Biopharmaceutics Classification System (BCS) I (highly soluble and/or highly permeable) compounds, meaning it is likely that there are no physicochemical and/or formulation limitations to their absorption. In addition, poor aqueous solubility is rapidly becoming the leading hurdle for formulation scientists working on oral delivery of drug compounds.[8] It has been suggested that up to 90% of new chemical entities would be categorized as BCS class II or IV compounds.[9] Therefore, there is a clear need for adoption of strategies that would overcome these absorption limitations.

Salt formation, active pharmaceutical ingredient (API) particle size reduction (traditionally to micronized and more recently nanosized range), use of lipid vehicles and cosolvents in the form of liquid-filled capsules, complexation (e.g., cyclodextrins), and more recently amorphous solid dispersions (ASDs) are used as formulation solutions to improve the solubilization of compounds in the gastrointestinal tract and thus subsequently improve their oral bioavailability. Prodrugs have also been similarly used to improve both the permeability and the solubility of orally administered compounds. In this mini review, we focus on discussing what can be considered as divergent but complementary approaches to the oral absorption and/or bioavailability challenge: the use of prodrugs or ASDs. Among the different formulation technologies, we focus on ASDs on account of the recent increase in their uptake as a formulation solution, as evidenced by the appearance of several ASD products in the market in the last decade (Table 1). We contrast this formulation approach to that of the chemical modification approach via prodrug strategy, with approved products also listed in Table 1.

Oral Absorption and Oral Bioavailability—in the Context of Formulation Development

Although it is common to use the term bioavailability to describe formulation performance of orally administered drugs, it is important to distinguish between absorption and bioavailability when it comes down to understanding the formulation limits. This distinction is important especially in the discovery space when drug discovery teams are looking to optimize the compound structure-activity and related physicochemical properties.

After ingestion of an immediate-release solid oral dosage form, disintegration or dispersion of the drug product and dissolution of the API must occur before absorption can take place. It is commonly accepted that the intrinsic dissolution rate of an API is proportional to its solubility.[10-13] The BCS allows for categorization of compounds to reflect whether solubility is a limiting factor to their absorption. For low solubility BCS II and IV drugs, oral formulation technologies such as ASDs discussed within this review are designed to maximize the availability of the API in the dissolved state in the lumen. Alternatively, chemical modifications of the drugs in the form of their prodrugs also can be used for the same end purpose of increased solubility, although examples of such application are less common and prodrug application has been mostly focused on improving intestinal permeability of ionizable and/or highly polar compounds. Whether this increase in solubility results in an increased absorption or bioavailability depends not only on the formulation but also on physicochemical properties and the metabolic profile of the specific compound. It is important for

Table 1
Select Orally Administered Amorphous Solid Dispersions and Prodrugs Approved in the Last Decade

Drug or Prodrug (Proprietary Name)	Company (Year of Approval)	Bioavailability Enhancement Technology
Ritonavir/lopinavir (Kaletra®)	Abbott (2005)	ASD
Lisdexamfetamine dimesylate (Vynase®)	New River (2007)	Prodrug
Etravirine (Intelence®)	Janssen (2008)	ASD
Fesoterodine fumarate (Toviaz®)	Pfizer (2008)	Prodrug
Prasugrel (Effient®)	Eli Lilly (2009)	Prodrug
Everolimus (Zortress®)	Novartis (2010)	ASD
Ritonavir (Norvir®)	Abbott (2010)	ASD
Itraconazole (Onmel®)	Stiefel (2010)	ASD
Dabigatran etexilate (Pradaxa®)	Boehringer Ingelheim (2010)	Prodrug
Vemurafenib (Zelboraf®)	Roche (2011)	ASD
Telaprevir (Incivek®)	Vertex (2011)	ASD
Gabapentin enacarbil (Horizant®)	Xenoport (2011)	Prodrug
Azilsartan medoxomil (Edarbi®)	Takeda (2011)	Prodrug
Ivacaftor (Kalydeco®)	Vertex (2012)	ASD
Posaconazole (Noxafil®)	Merck (2013)	ASD
Tacrolimus (Astagraf XL®)	Astellas (2013)	ASD
Dimethyl fumarate (Tecfidera®)	Biogen IDEC (2013)	Prodrug
Sofusbuvir (Sovaldi®)	Gilead (2013)	Prodrug
Tedizolid phosphate (Sivextro®)	Cubist (2014)	Prodrug
Suvorexant (Belsomra®)	Merck (2014)	ASD
Ombitasvir/paritaprevir/ritonavir/ dasabuvir (Veikira Pak™)	Abbvie (2014)	ASD
Ledipasvir/sofosbuvir (Harvoni®)	Gilead (2014)	ASD/Prodrug
Isavuconazolium sulfate (Cresemba®)	Astellas (2015)	Prodrug

drug discovery and development scientists to keep in mind that a highly solubilizing formulation may still not lead to sufficient bioavailability if the limitation to bioavailability is not only the availability of drug presented in the lumen. Two subsequent steps, the permeation of the compound into the enterocytes and first-pass metabolism in the intestine and the liver will dictate the final oral bioavailability of the compound.

Although the benefits of high oral bioavailability are well documented, it should also be acknowledged that compounds with low bioavailability may still be developed as successful commercial products as long as sufficient plasma levels are achieved at acceptable dose ranges. For example, bisphosphonates such as alendronate have extremely low bioavailability due to ionization-limiting intestinal permeability; alendronate bioavailability has been reported at 0.76% across a 5-80 mg dose.[14] In some cases, the exact mechanism for the low bioavailability may not be clear, as in the case of aliskiren, where the low oral bioavailability of 2.6% may be limited by efflux transporters.[15] Drugs where the liver is the site of action (e.g., statins) or those with high clearance also may show low bioavailability despite being formulated to achieve high absorption. For example, the oral bioavailability of atorvastatin is estimated at circa 14% although oral absorption is considered likely complete.[16] Therefore, the use of oral bioavailability (F) as the measuring point of formulation success is not sufficient, and an estimation of F_a is a more appropriate way to understand the performance of a dosage form. We acknowledge that in certain cases, the extent of first-pass metabolism is related to the rate and extent of absorption if metabolic processes are saturable. In that case, formulation, absorption, and first-pass metabolism connections may be more complex. However, a detailed discussion around this is beyond the scope of this mini review. With the advancement in preclinical *in vitro* and computation tools including physiologically based pharmacokinetic modeling,[17,18] discovery scientists are in a better position nowadays to decouple the contribution of different factors to the overall pharmacokinetic profile of a compound, and can better identify whether or not the root cause of low bioavailability can be solved using formulation approaches.

Increasing Bioavailability Via ASDs

ASDs rely on the higher apparent solubility of the amorphous form of an API relative to its crystalline phase [19-21] to increase the dissolution rate in the gastrointestinal tract, which in turn will lead to increased rate and extent of absorption. Successful use of ASD as a bioavailability-increasing formulation approach has been demonstrated for both BCS II compounds such as posaconazole,[22] itraconazole,[23] and fenofibrate,[24] as well as BCS IV compounds such as ritonavir,[25] vemurafenib,[26] and furosemide.[27] Although the potential benefits of the amorphous form of an API in improving intestinal absorption have been discussed for several decades, only in the last decade a significant number of ASD-based pharmaceutical products have appeared in the market (Table 1). The delay between proof-of-principle of this approach to the introduction of commercial products may be caused, in part, by perceived or observed risks around stability and manufacturability.[28] However, the continuous increase in the number of BCS II and IV compounds in the development pipelines across pharmaceutical companies, coupled with improved biopharmaceutical understanding, characterization techniques, and formulation or manufacturing processes on ASD, has led to their increased use.[28-30]

The primary concern around use of ASD has been around the stability of the amorphous phase, both chemically and physically. Because the amorphous form of the API is at a higher energy state and possesses greater molecular mobility compared with its crystalline counterparts,[31] the amorphous form is typically but not always more chemically reactive, leading to faster degradation kinetics,[32] for example, as shown for beta-lactam antibiotics[33] and cefoxitin sodium.[34] Even when sufficient chemical stability is achieved, recrystallization in the solid form[35,36] has also been a concern. The conversion of the amorphous form of an API to its corresponding crystalline forms is governed by thermodynamic[37,38] as well as kinetic factors.[31,39-42] Different strategies have been evaluated to reduce this risk. The most common strategy is mixing a polymer at the molecular level, forming what is referred to as an amorphous solid solution. Because of larger molecular size, polymers have slower coordinated molecular motions, which are reflected in higher glass transition temperatures (T_gs). When such polymers are intimately mixed with the API, the T_gs of the mixed systems will be increased in proportion to the fraction of polymer, indicating reduced coordinated molecular motions. This was exhibited, for example, with felodipine-polyvinylpyrrolidone (PVP),[43] sucrose-PVP, and sucrose-polyvinylpyrrolidone-co-vinyl acetate systems.[44] The reduction in coordinated molecular motions effect is enhanced in the presence of molecular coupling between the polymer and the API.[45,46] In addition to the coordinated global molecular motions (also referred to as α-relaxation motions), molecules also experience local molecular motions (referred to as β-relaxation motions). Recent advances show that β-relaxation motions are better indicators of the physical stability of amorphous APIs, especially below their T_gs.[40,47,48] Other factors such as miscibility and pairwise interactions also have to be considered in designing mixed API-polymer systems.[48-50]

Assuming stability concerns can be addressed, the next important consideration is the selection of a formulation composition that would result in the desired bioavailability. Although the high amorphous solubility of the API is favorable for faster and more complete absorption, it is important that the formulation composition facilitates this by ensuring rapid release of the API. Because BCS II and IV compounds that would be formulated as ASD have hydrophobic characteristics, the inclusion of a surfactant such as sodium lauryl sulfate or vitamin E d-α-tocopheryl polyethylene glycol 1000 succinate can enhance the API release rate during dissolution.[30,51] The selection of the polymer system can also impact the API release rate by achieving the appropriate balance between disintegration of the dosage form versus dissolution of the API. The use of polymers with pH-dependent solubility such as hypromellose acetate succinate (HPMCAS) may be advantageous to avoid premature gel layer formation, which can effectively slow down the rate of API release by inhibiting rapid disintegration.[52] However, the final release kinetics of the API are not solely dictated by the pH-dependency of the polymer, and the gelling effect should not be confused with a true delay in API release, such as in the case of enteric-coated delayed-release formulations; most HPMCAS formulations on the market retain immediate-release product characteristics. The initial dispersion (or disintegration) of the tablet can also be the rate-limiting step in the absorption process, if dissolution of the primary ASD particles is relatively fast. This disintegration time may depend not only on the polymer selected but also on tablet properties such as tablet tensile strength, as demonstrated for the ASD of suvorexant.[53]

On dissolution, preventing rapid API crystallization could be considered as the next critical step in achieving bioavailability enhancement.[54,55] Crystallization can occur from the supersaturated solution or through solid-solid conversion.[56,57] The selection of the appropriate surfactant and polymer systems for the specific API can greatly aid in slowing down the crystallization rate. Konno et al.[58] reported that HPMCAS was more effective than poly(vinyl pyrrolidone) at maintaining the supersaturation of felodipine during dissolution, while Trasi et al.[59] found that poly(vinyl pyrrolidone) and hypromellose were effective inhibitors of the

desupersaturation of acetaminophen. In another study, Chen et al. showed that the use of sodium dodecyl sulfate and Polysorbate 80 promoted the crystallization of celecoxib from ASD suspensions, whereas sodium taurocholate and Triton X-100 inhibited its crystallization.[60] For systems with low tendency of crystallization such as telaprevir, the formation of a wet glassy colloidal state on dispersion into aqueous media has also been reported.[61] Recent advances suggest that in addition to the maintenance of supersaturation, the formation of nanoparticulate species can be critical to the bioavailability enhancement performance of amorphous-based formulations, for example, as shown for ritonavir and ABT-102.[62-65] However, it should be acknowledged that direct translation of *in vitro* observations to *in vivo*, especially as related to precipitation, is challenging, and the significance of *in vitro* observations may not be always clear.

ASDs represent a very active area of research. Since 2012, more than 600 articles concerning ASDs can be found through Scopus and Web of Science™ research websites. In Table 2, we have summarized some of the newest directions of research around ASDs, both on building the fundamental understanding of their bioperformance as well as expanding their utility in delivery of BCS II and IV molecules.

It is clear that a continuous understanding of behavior and performance of ASDs has allowed for a shift in the approach for designing these systems from empirical trials of API with different polymers to achieve high amorphous solubility and high T_g, to more elaborate formulation development paradigms encompassing the selection of the right polymer(s), surfactant(s), or other functional excipients. This increased understanding can be leveraged to design formulations or polymers specifically aimed at intended solid state properties and dissolution rate characteristics to achieve desirable pharmacokinetic profiles.

Prodrugs for Increasing Permeability and Solubility

Unlike the ASD strategy presented in the preceding section which focuses on a formulation approach to increase oral bioavailability for BCS II and IV compounds, the prodrug strategy is considered a “chemistry” approach because a transient covalent modification is made on the drug molecule to directly influence its pharmaceutical and/or pharmacokinetic properties. Prodrugs, whether pursued prospectively as a new chemical entity or progressed retrospectively as in an effort to improve an existing product (e.g., life-cycle management), have resulted in marketed products which has validated their design and the concept.[88-90]

Prodrugs, parallel to formulation approaches, have been explored where oral absorption and bioavailability of drug candidates was suboptimal. In an role beyond the solubility and dissolution rate improvement via ASDs, prodrugs have been designed to increase both solubility as well as permeability of highly polar and ionizable water-soluble drugs, where intestinal membrane permeation may limit oral absorption. The prodrug is designed to mask the charge or increase the lipophilicity of the molecule, leading to more favorable passive membrane permeation, or to provide chemical modifications that would facilitate uptake by intestinal transporters. In the former cases, covalently-linked lipophilic carboxylate and/or phosphonate ester functional groups are used to increase passive diffusion. Once the parent drug is absorbed, the prodrug is rapidly cleaved by an enzyme to release the parent drug. Thus, instead of BCS II and IV compounds, this prodrug application typically focuses on BCS III molecules, as exemplified by adefovir, enalaprilat, and gabapentin. In some cases, the prodrug may result in a change of BCS classification, as is the case for gabapentin (BCS III) where esterification resulted in a BCS II prodrug (gabapentin enacarbil). Another example of this approach

Table 2
Select Examples of Directions for Active Research in ASD Formulations and Fundamental Understanding of Their Bioperformance

Research Area	Motivation	Select Examples and References
Formulations with sustained-release (SR) profiles for BCS II/IV compounds	BCS II and IV compounds, at higher doses, represent a challenge for delivery as SR formulations due to low solubility and small volume of liquid in the lower GI that could lead to low bioavailability	Examples of sustained-release ASDs include polyelectrolyte-drug complex of enalapril maleate and Eudragit® E100,[66] tanshinone in glyceryl monostearate-PEO system,[67] controlled-release diclofenac sodium in Compritol® 888 ATO (glyceryl behenate),[68] Eudragit® E100, or Eudragit® S100,[69] self-emulsifying solid dispersion of isradipine with poloxamer 407 which was formulated into hypromellose controlled-release tablet,[70] and penta-ethyl ester prodrug of diethylenetriamine pentaacetic acid with blends of polyvinylpyrrolidone (PVP), Eudragit® RL PO and α-tocopherol.[71]
New polymers or new polymer combinations	Improve stability or further tailor release kinetics and/or better maintain supersaturation with the goal to improve absorption or bioavailability	Combinations of HPMC-PVP and HPMC-PVPVA led to better physical stability, solubility and bioavailability of a BCS II drug with very low T_g,[72] while phase separated Eudragit® EPO and PVPVA systems exhibited better release and stability of felodipine.[73] Simvastatin microparticles containing solid dispersions in Eudragit® E 100 and poly(3-hydroxybutyrate) exhibited very fast dissolution.[74] The chemistry space of HPMCAS is probed by varying the ratios of acetyl and succinoyl substitution groups,[63] while completely novel cellulose-derived polymers such as cellulose acetate adipate propionate,[75] carboxymethyl cellulose acetate butyrate,[76] and ω-carboxyesters derivatives[77] have been synthesized to provide better maintenance of super-saturation, increased absorption, or improved physicochemical stability.
Formulations with lipidic excipients	Looking for a synergistic effect from lipidic excipients to increase solubility and/or permeability	Sodium caprate was included as absorption enhancer for berberine,[78] while Gelucire® 50/15 was added to increase the solubility of ursolic acid.[79]
Addition of other agents	Achieve stability or bioperformance benefits by means other than polymer/surfactant changes	Incorporation of citric acid provided microenvironmental pH modification,[80] while alkalizer was added to enhance the dissolution rate in rebamipide/sodium alginate/sodium carbonate system.[81] The formation of aminoclay complex with telmisartan led to improved AUC and C_{max},[82] while the potentials of bile salts to prevent API crystallization and enhance absorption have also been studied.[60,83] The use of inorganic salts as kosmotropic agents to disrupt gel strength and promote dissolution has been investigated,[84] while API complexation with weak acids led to increased solubility.[85]
Studying mechanism of absorption	Understand critical parameters to absorption to improve formulation design, establishment of *in vitro–in vivo* relationships and *in vitro–in vivo* correlations	The impact of super-saturation to membrane transport[86] and increasing solubility without reducing permeability[87] are areas of active research. Further discussion on bioperformance aspects takes place in the “Biopharmaceutics Assessment of Formulation” section of this manuscript.

PVPVA, polyvinylpyrrolidone-co-vinyl acetate.

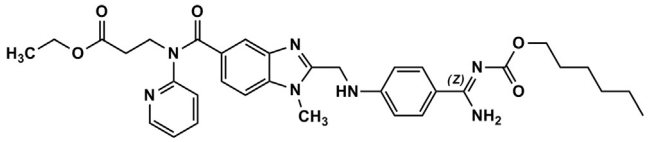

Figure 1. Chemical structure of dabigatran etexilate.

is the case of orally administered anticoagulant dabigatran. The presence of zwitterionic charge and polarity (log P −2.4) from the amidinium and carboxylate groups resulted in negligible oral bioavailability for dabigatran.[91] In designing dabigatran etexilate, a double prodrug, the amidinium group was masked as a carbamate whereas the carboxylate was derivatized to an ester (see Fig. 1). By doing so, the absolute bioavailability of dabigatran after oral administration of its prodrug dabigatran etexilate was improved significantly to approximately 7%, and dabigatran etexilate is considered a BCS II compound.

In the case of membrane transporter targeted prodrugs, a promoiety can be incorporated into polar and/or charged drugs to target specific intestinal membrane carrier-mediated uptake transporters. For example, the intestinal membrane permeation of valganciclovir was mediated by dipeptide and tripeptide transporters (hPEPT1) that are distributed widely across the small intestine. As a result, a 3-10 fold improvement in intestinal permeation rate was observed in the case of valganciclovir, the L-valine ester prodrug of ganciclovir. Although ganciclovir has low and variable oral bioavailability (7%), its prodrug offers an oral bioavailability of circa 60% in fed humans due to improved intestinal permeation. Both ganciclovir and valganciclovir are classified as BCS III compounds.

Modulation of permeability via orally administered prodrugs has led to many successful marketed products. Huttunen et al.[92] estimated that up to 10% of all marketed medicines can be classified as prodrugs. Table 3 lists examples of such prodrugs, with a brief rationale or pharmacokinetic advantage in pursuing the prodrug methodology. The examples are intended to highlight different chemical modifications and the impact on bioavailability; covering all the prodrug aspects is not possible as part of this mini review, and the readers are referred to extensively available literature. In reviewing the data in Table 3 for each of the prodrugs, it quickly became apparent that the degree of bioavailability improvement varies widely between compounds. For example, the bioavailability of dabigatran even after the prodrug modification is only 3%-7%, whereas 60% absorption is obtained for enalapril compared to 3% for enalaprilat. Thus absolute bioavailability alone is not the sole determinant of success for a prodrug strategy. As long as the prodrug modification allows for obtaining sufficient plasma concentration levels, they represent a possible approach to enabling oral administration of a difficult to deliver parent drug. It is also apparent that the final BCS classification spans all 4 BCS classes, again confirming that there is no one-size-fits-all rule in setting the criteria for a successful prodrug strategy on BCS III compounds.

Prodrugs have been successfully used to improve both solubility and permeability of the parent compounds. Generally speaking, it would appear that a formulation approach is preferred to the chemical modification to address solubility limitations. Nevertheless, some examples are available which demonstrate the application of a prodrug strategy to parent drugs that show either a dissolution rate or solubility-limited absorption. Incorporation of a di-ionized phosphate promoiety is one of the classic examples in prodrug chemistry to improve the solubility of orally administered poorly water-soluble drugs. Some other examples are listed in Table 4, such as etoposide, amprenavir, and so forth. One contemporary prodrug example targeting increased solubility is isavuconazonium sulfate, a water-soluble triazolium salt of the azole antifungal isavuconazole, which was approved in March 2015 for the treatment of invasive aspergillosis and mucormycosis in adults (see Fig. 2). The high lipophilicity is a characteristic of the azole antifungals and is required for therapeutic efficacy, which in turn reduces aqueous solubility. Isavuconazonium sulfate is designed as a substrate of butylcholinesterases, which on hydrolysis of the glycine ester, initiates a rapid intramolecular cyclization-elimination reaction that concurrently releases isavuconazole and 2 inactive cleavage by-products (see Fig. 3).[133] The prodrug is formulated for both oral (as capsules) and intravenous (lyophilized sterile powder in vial) administration. The prodrug chemistry offers dosing flexibility (intravenous or oral) as well as an injectable cyclodextrin-free intravenous formulation, thereby removing concerns of nephrotoxicity due to the use of cyclodextrins as solubilizing agents, as is the case with voriconazole.[134] Of interest to note is the fact that isavuconazonium sulfate is the first commercially successful prodrug obtained by derivatizing a triazole functional group on the parent drug and reinforces the importance of critically selecting a suitable functional group for derivatization.

From the typical solubility improvement seen with prodrugs in the relatively limited cases applied, it is fair to conclude that the solubility enhancement is generally higher compared with what can be achieved by formulation approaches. However, it should be acknowledged that chemical modification is not always readily feasible and does result in a new chemical entity that may require additional studies and qualifications. The premise for prodrug chemistry, perhaps obvious, is that the drug has a functional group that can be suitably derivatized with the promoiety. The choice of promoiety as well as the site of derivatization is important with respect to achieving adequate product shelf-life (chemical stability), as well as rapid *in vivo* bioconversion to liberate parent drug.

Whereas examples in Tables 3 and 4 highlight only one prodrug for oral bioavailability enhancement of each parent drug, it is acknowledged that developing prodrugs is an iterative, resource-intensive process requiring a multidisciplinary team of scientists to design the appropriate prodrug. Once conceptualized, *in vitro* and *in vivo* assessment of the prodrug candidates is essential so as to ensure the limitations of the parent drug have been addressed and intended results are achieved. Selection of a promoiety is also critical for bioavailability enhancement via prodrug, which include aspects such as ease of synthesis and site of linking to parent drug, metabolism site, and by-products of the promoiety, choice of counterion (if applicable), and chemical stability to afford desired shelf-life of the formulation.

Biopharmaceutics Assessment of Oral Absorption—Comparison Between the 2 Formulation Techniques and Preclinical Evaluation

Both bioavailability enhancement approaches highlighted previously have clear benefits in increasing the oral bioavailability of a poorly soluble API. In the case of ASD systems, it has been suggested that this approach may be more favorable relative to other approaches such as lipid or cosolvent formulations or complexation agents, as the ASD approach promotes true higher concentration of “free drug” in the lumen. Because only “free drug” (i.e., drug in true solution in aqueous environment of the gastrointestinal tract) can permeate through the enterocyte membrane, a formulation approach that promotes true supersaturation may be more advantageous; this has been demonstrated through *in vitro* and *in silico* models.[87,135] However, it should be acknowledged that the *in vivo* absorption process is more complex and more dynamic than what can be captured *in vitro*, which may result in different behaviors from what is suggested by *in vitro* measurements.

Table 3
Select Orally Administered Prodrugs for Permeation Enhancement of Therapeutically Active Drugs

Prodrug	*In Vivo* Bioconversion to Parent Drug/Active Metabolite	Rationale and/or Benefit From a Prodrug
Adefovir dipivoxil	Adefovir	The oral bioavailability of adefovir is ≤10% primarily due to high polarity. Esterification of the phosphonic acid moiety in adefovir dipivoxil improves adefovir bioavailability to 59% in humans.[20,93,94] Both parent and prodrug are BCS class III compounds.
Azilsartan medoxomil	Azilsartan	A bioisostere replacement of the acidic tetrazole and esterification of the polar carboxylic group was done to improve oral bioavailability. Simple alkyl esters were precluded because they showed slow bioconversion in rat plasma and liver homogenate, resulting in selection of the double ester promoiety, a learning leveraged from prodrugs of β-lactam antibiotics.[95] The prodrug is hydrolyzed to azilsartan by esterases in the gastrointestinal tract and/or during absorption with a peak plasma concentration occurring within 1.5-3.0 h, an absolute oral bioavailability of 60% in humans, and no effect of food on bioavailability.[96,97] Azilsartan medoxomil is a BCS IV compound.
Bacampicillin	Ampicillin	The zwitterionic charge on ampicillin at absorption-relevant pH limits its intestinal permeation and absorption. By esterification, the polarity of the prodrug is reduced, resulting in improved oral bioavailability (86%) in comparison to dosing ampicillin (62%) *per se*.[98] Although ampicillin would be categorized as a BCS III compound, bacampicillin appears to be a BCS II compound.
Cefditoren pivoxil	Cefditoren	Esterification of the polar carboxyl group increases lipophilicity, leading to improved intestinal permeation of cefditoren pivoxil. The absolute bioavailability of cefditoren is 16% and 2.5% when cefditoren pivoxil is taken with low-fat and high-fat meals, respectively.[99,100] Cefditoren pivoxil is categorized as a Biopharmaceutics Drug Disposition Classification System IV compound.
Dabigatran etexilate	Dabigatran	Dabigatran etexilate was designed to mask the zwitterionic charge and polarity (log P −2.4) on dabigatran, which resulted in negligible oral bioavailability. To increase lipophilicity, the 2 polar groups, amidinium, and carboxylate, were derivatized by carbamic acid and carboxylic acid ester, respectively. As a result, after oral administration of the prodrug, rapid and complete deesterification resulted in the formation of dabigatran, with ≤7% absolute oral bioavailability.[91,101] Dabigatran etexilate is considered a BCS II compound.
Dimethyl fumarate	Monomethyl fumarate	After oral administration of the prodrug, rapid presystemic esterase-catalyzed conversion to the active metabolite monomethyl fumarate occurs with a median T_{max} of 2-2.5 h.[102] The delayed-release capsule formulation has no clinically relevant food effect; although it increases T_{max} from 2 h to 5.5 h and reduces flushing by 25%. Dimethyl fumarate is a BCS class I compound.
Enalapril	Enalaprilat	By masking an ionized group on enalaprilat, the extent of absorption of enalapril increases to 60% (vs. 3% for enalaprilat), resulting in a human oral bioavailability of 36%-44% for enalaprilat independent of food.[103,104] Both enalapril and enalaprilat are classified as BCS III compounds.
Fesoterodine fumarate	5-hydroxymethyl tolterodine (5-HMT)	Nonspecific esterases rapidly and completely hydrolyze the isobutyric ester on the phenolic hydroxyl of fesoterodine to its active metabolite, a muscarinic receptor antagonist. The absolute oral bioavailability of 5-HMT is <52%, C_{max} is reached in 5 h post dosing of the extended release tablet and is unaffected by the presence of food.[105,106] Fesoterodine fumarate is a BCS class I compound.
Gabapentin enacarbil	Gabapentin	Gabapentin, a structural analog of the neurotransmitter gamma-aminobutyric acid (GABA), has unfavorable human pharmacokinetics (high variability, saturation of uptake transporter at absorption site, and short half-life) leading to less than desired therapeutic benefits.[107,108] The prodrug was designed to be stable in the gastrointestinal pHs and overcome erratic uptake by being actively transported by high-capacity nutrient transporters (monocarboxylate transporter Type 1 [MCT-1] and the sodium-dependent multivitamin transporter [SMVT]).[109] The prodrug is rapidly deesterified to the active gabapentin primarily in the enterocytes, with a 2-fold higher bioavailability (75%) in fed state than in fasted fed state (36.6%).[110] Although gabapentin is generally considered a BCS III compound, gabapentin enacarbil is classified as a BCS II compound.
Mycophenolate mofetil	Mycophenolic acid	Mycophenolic acid has variable and low oral bioavailability (<40%). In contrast, the absolute bioavailability of mycophenolic acid in humans is 94% after oral administration of its prodrug.[111,112] Mycophenolate mofetil is a BCS II compound.
Prasugrel	Pras-AM (R-138727)	Prasugrel is a third-generation thienopyridine prodrug designed to have faster onset of action, increased potency, and less variability with regard to platelet inhibitory activity.[113] In humans, human carboxylesterase (hCE-2) hydrolyzes prasugrel to a thiolactone intermediate, which then undergoes oxidation to the active metabolite Pras-AM via intestinal and hepatic cytochrome P450 enzymes.[114] The bioavailability of prasugrel is circa 79% with plasma peak concentration of Pras-AM occurring within 30 mins after dosing.[115] Prasugrel HCl is a BCS class II compound.
Tenofovir alafenamide fumarate (TAF)	Tenofovir diphosphate	As a nucleotide reverse transcriptase inhibitor, TAF was specifically synthesized to offer improved plasma stability and reduced renal toxicity. In plasma, TAF is more stable than tenofovir disproxil fumarate (TDF) and permeates virally infected cells intact. Intracellularly, TAF is converted to its active metabolite, tenofovir diphosphate, by carboxylesterase 1 (CES1) within hepatitis-B virus infected hepatocytes and by cathepsin A within HIV-infected lymphoid cells.[116] The high intracellular concentration of the active metabolite due to high plasma stability results in TAF's lower dose (25 mg), lower toxicity, and comparable efficacy in comparison to TDF (300 mg) in the treatment of both HIV-1[117] as well as chronic hepatitis B infection.[118]
Valganciclovir	Ganciclovir	The low human oral bioavailability of ganciclovir (7%) is due to high polarity (Log P = −1.65) and moderate solubility (6 mg/mL, 37°C). The highly soluble (70 mg/mL) L-valyl monoester prodrug is a substrate for PEPT1 intestinal peptide uptake transporter and rapidly converts to ganciclovir with human absolute oral bioavailability of circa 60% in fed state.[119-121] Both parent drug and prodrug are BCS III compounds.
Ximelagatran	Melagatran	Ximelagatran offers improved fraction absorbed due to the masking of charges, a human oral bioavailability of 20%, which is 3-6 times higher than melagatran administration *per se*, reduced intersubject variability, and no food effect.[122,123]
Zofenopril	Zofenoprilat	Once absorbed, zofenopril is rapidly (human T_{max} 0.4 h) and completely deesterified to its sulfhydryl containing active metabolite zofenoprilat. In humans, the 10-mg dose of zofenopril has an average bioavailability of 70%.[124]

Table 4
Select Orally Administered Prodrugs for Solubility Enhancement of Therapeutically Active Drugs

Prodrug	*In Vivo* Bioconversion to Parent Drug/Active Metabolite	Rationale and/or Benefit From a Prodrug
Etoposide phosphate	Etoposide	Nonlinear and erratic oral absorption of etoposide, presumably due to low aqueous solubility, results in highly variable bioavailability of 40%-76%. The water-soluble phosphate prodrug is rapidly absorbed with 19% higher bioavailability and less variability compared with oral etoposide.[125,126]
Fludarabine phosphate	Fludarabine	The phosphate prodrug offers improved solubility (10 mg/mL in water), dose-independent and predictable bioavailability, low intrasubject variability, and no food effect.[127,128]
Fosamprenavir	Amprenavir	Low aqueous solubility of amprenavir (0.04 mg/mL) required high ratio of solubilizing excipients to favor intestinal absorption (16 of the 150 mg softgel capsule per day). To improve this solubility-limited absorption, the monocalcium phosphate ester prodrug was designed (54 mg/mL solubility, pH 3.3) which dramatically dropped patient pill burden (4 of the 700 mg tablet per day). Oral dosing of fosamprenavir results in rapid blood levels of amprenavir (0.25 h) with a C_{max} of 1.5-2.5 h post dosing, with no effect of food on bioavailability.[129]
Isavuconazonium sulfate	Isavuconazole	On oral administration of the water-soluble prodrug, plasma esterases (predominantly butylcholinesterases) hydrolyze the prodrug to generate the active azole antifungal. Human T_{max} is achieved within 2-3 h; absolute oral bioavailability is 98%, and can be administered independent of food.[130]
Tedizolid phosphate	Tedizolid	Phosphorylation of the 5-position hydroxymethyl adduct in the prodrug leads to an improved aqueous solubility (>50 mg/mL), rapid bioconversion, and a human bioavailability of ≥90%.[131,132]

Even for compounds where ASD works well, it should be an expectation that the amorphous formulation will hit an absorption limit dictated by the apparent aqueous solubility of the amorphous form of the compound. The difference between apparent amorphous and crystalline solubility is compound dependent; while the range varies widely, in our experience the difference in apparent solubility is typically about 10 fold. Such an increase in apparent solubility, although definitely beneficial, may be insufficient to drive high absorption for a very low solubility or high-dose compound. One can conceptualize this absorption limit by applying the concept of BCS on the basis of the apparent amorphous solubility: if even with apparent amorphous solubility the compound is classified as a BCS II/IV, absorption limitations will persist. ASDs have also been reported to result in extensive speciation on dissolution that results in generation of different nanosized and micron-sized structures.[63] These different species influence the apparent dissolution rate and apparent solubility of the compound and have different capacities in providing drug available for absorption. Understanding the *in vitro* behavior of solid dispersion is an area of active research.

Prodrugs, on the other hand, can lead to great increases in absorption by increasing aqueous solubility beyond what ASD can offer, for example, as illustrated by fosamprenavir (54 mg/mL, pH 3) and its parent drug amprenavir (0.04 mg/mL).[136] Prodrugs may also be able to address oral absorption issues from a permeability perspective, something that formulation techniques such as ASDs may not be able to accomplish. However, the chemical structure and the availability of functional groups on the parent drug to design its prodrug can be the limiting factors in its application. In our experience, unless the prodrug option is considered early on and a drug candidate is designed with the prodrug in mind, it is not a straightforward proposition to go back and progress an existing compound as its prodrug.

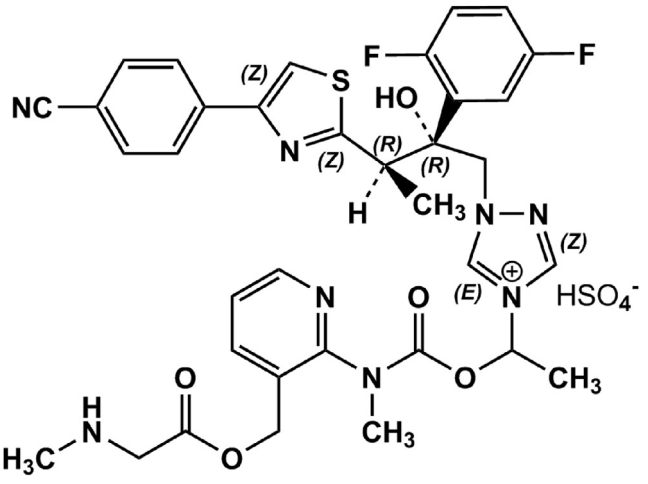

Figure 2. Chemical structure of isavuconazonium sulfate.

Evaluating the ability of either approach to increase absorption and/or bioavailability in a preclinical setting is critical to their successful application. Preclinical formulation evaluation in a pharmaceutical industry setting typically encompasses both *in vitro* assays and *in vivo* testing in animal models. It is common that the screening is performed in a staged fashion: first formulations are screened in dissolution assays before dosing the most promising ones to preclinical models.[137] In recent years there have been significant advances in the field of dissolution including the development and adoption of biorelevant media that has led to a significant expansion of the role of dissolution as a formulation screening tool past the traditional use as a quality-control release assay.[17] Traditional dissolution testing in biorelevant media is considered generally adequate for prediction of *in vivo* performance of conventional dosage forms based on crystalline API. Several publications have shown the ability of dissolution to provide discriminatory data on comparing factors such as particle size and to use these data as input in PBPK type of models to forecast clinical pharmacokinetics.[18,138] However, traditional dissolution tests may not be sufficient to fully reflect the behavior of solubilizing formulation. For ASDs, the ability of the system to capture the supersaturation generated is a critical aspect of the *in vitro* evaluation. As a result, methodologies that measure the ability of the formulation to maintain higher solubility[139,140] have been proposed as an initial estimation of the supersaturation propensity *in vivo*. However, these methodologies focus on assessing the availability of the compound in the lumen and not necessarily the availability of compound available for absorption. To that extent, more recent systems that simulate simultaneous dissolution and absorption have been proposed, either in the form of biphasic dissolution or with use of systems where dissolution is combined with an artificial membrane or a cell monolayer.[141-144] These systems may provide higher likelihood for meaningful assessment of formulation performance of supersaturating systems. But more research is still required to fully assess the improvement in predictability and to also allow for application of these tools in routine formulation screening. Finally, more complex systems that also try to simulate both the transit and absorption of the compound in the GI tract have been developed.[145] These systems, along with the dissolution

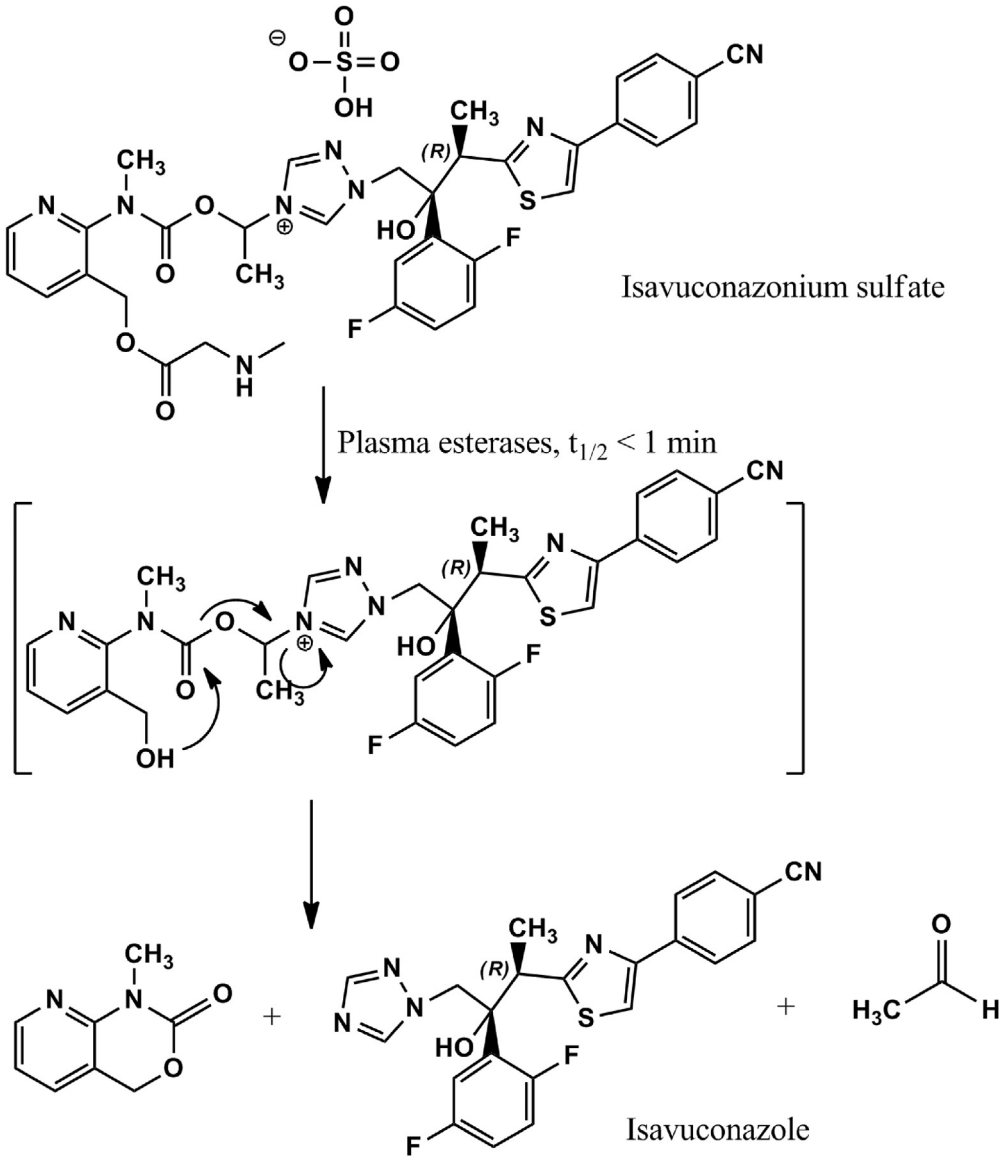

Figure 3. Suggested bioconversion pathway of the prodrug isavuconazonium sulfate.[134]

and/or cell monolayer systems, may also be of interest in understanding behavior of prodrugs and the potential solubility and/or permeability interplay as discussed in the literature.[146,147] Although advances in the field of biorelevant dissolution in regard to understanding the behavior of solubilization-enabling formulations have been significant, the predictability of the tools across compounds is still questionable. This has led to cross-industry efforts to try to further validate these tools and understand their applications and/or limitations such as the Oral Biopharmaceutics Tools Innovative Medicines Initiative.[148]

However, the ultimate test to judge the success of formulations is *in vivo* testing. The application of animal models is common in the pharmaceutical development paradigm. The use of animal models in most cases is driven by compound-specific properties (including understanding of pharmacokinetics and safety) and/or practical considerations (e.g., it is not possible to test clinical formulations such as tablets in rodents)[137] and must be done on a case-by-case basis. In the case of prodrugs, an additional consideration may be the selection of a species where prodrug conversion may be more similar to human. This was highlighted in a recent study by Borde et al.,[149] where the authors suggested that dog intestinal fluid may be a reasonable surrogate for human intestinal fluid in terms of understanding the stability of 3 prodrugs, although quantitative differences were still apparent. Thus, an *a priori* knowledge of such information especially in a quantitative fashion may not be possible. At the end, for both prodrugs and ASDs, the ultimate decision is influenced by clinical relative bioavailability studies.

Concluding Remarks

Oral administration of drugs in humans will remain a preferable dosing option due to convenience and compliance. Progress made over the years with the development of *in silico*, *in vitro* tools, and *in vivo* data has enabled a better understanding of molecular properties that affect bioavailability and to identify the rate-limiting steps in the oral absorption cascade. This in turn has led to a more rational selection of drug candidate compounds around their pharmaceutical properties, including the use of prodrugs as a means to improve primarily compound permeability, and to a

lesser extent solubility, and implementation of a variety of formulation technologies such as ASDs that improve the *in vivo* solubilization and dissolution rate of the drug candidate compound. The concepts of ASDs and prodrugs are not new, but at least for the former there is a clear increase in use in the last decade, as also judged by the application in marketed products. The 2 approaches have been discussed in this review as divergent but complementary approaches to achieve the bioavailability goals for BCS II, III, and IV drug candidates. Future developments in the field of ASDs may involve the use of novel excipients and polymers or combinations of polymers and/or other excipients that coupled with the continuous advancement in mechanistic understanding of absorption can drive the use of the technology toward further modulation of pharmacokinetic profiles and not just an increase in bioavailability. With prodrugs, the focus is on improved synthetic methodologies for promoiety incorporation, chemistry of the selected promoiety and its counterion *per se*, and designing prodrugs that are substrates for specific disease tissue or organ enzymes in humans to cause localized bioconversion or drug release. Regardless of the selected approach for a new drug candidate, the complexity of the absorption process and the underlying challenges with the biopharmaceutics evaluation mandate a collaboration between chemists, formulators, and biopharmaceutics scientists to lead to a successful implementation of the chosen strategy in the different pharmaceutical discovery and subsequently development phases.

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