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EXPERT REVIEW

Impact of Excipient Interactions on Drug Bioavailability from Solid Dosage Forms

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ABSTRACT Excipients are generally pharmacologically inert, but can interact with drugs in the dosage form and the physiological factors at the site of absorption to affect the bioavailability of a drug product. A general mechanistic understanding of the basis of these interactions is essential to design robust drug products. This paper focuses on drug-excipient interactions in solid dosage forms that impact drug bioavailability, the drug substance and drug product properties affected by excipients, and the impact of excipients on physiologic processes. The extent to which drug bioavailability is affected by these interactions would vary on a case-by-case basis depending upon factors such as the potency and dose of the drug, therapeutic window, site of absorption, rate limiting factor in drug absorption (e.g., permeability or solubility limited), or whether drug metabolism, efflux, complexation, or degradation at the site of absorption play a role in determining its bioavailability. Nonetheless, a mechanistic understanding of drug-excipient interactions and their impact on drug release and absorption can help develop formulations that exhibit optimum drug bioavailability.

KEY WORDS adsorption · bioavailability · complexation · excipients · interactions · solid dispersion · tablets

ABBREVIATIONS

API	active pharmaceutical ingredient
CCS	croscarmellose sodium
CMC	carboxymethyl cellulose
GIT	gastro-intestinal tract
HPMC	hydroxypropyl methylcellulose
ITC	isothermal titration calorimetry
IVIVC	*in vitro-in vivo* correlation
PEG	polyethylene glycol
P-gp	P-glycoprotein
PVP	polyvinyl pyrrolidone or povidone
RT-PCR	reverse transcription–polymerase chain reaction
SDS	sodium dodecyl sulfate
SEDDS	self-emulsifying drug delivery systems
SMEDDS	self-microemulsifying drug delivery systems
SSG	sodium starch glycollate
TPGS	d-α-tocopheryl-polyethylene glycol-1000 succinate

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INTRODUCTION

The therapeutic effectiveness of a drug depends upon the ability of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacologic response. This property of a dosage form is generally considered as pharmacological availability. The measurement of drug concentration at the site of action, however, is usually impractical. Therefore, drug concentrations are typically measured in the systemic blood circulation, which delivers therapeutically active drug to its site of action. Drug bioavailability refers to the rate and extent at which the active drug reaches the systemic circulation (1–3). For most drugs, their pharmacological availability can be directly related to bioavailability.

For most of the drugs administered as oral solid dosage forms, except in case of controlled release formulations, disintegration and deaggregation occur rapidly. In these cases, the rate limiting processes in the absorption of dosage forms are (a) dissolution rate and (b) rate of drug permeation through the biological membrane. Dissolution is the rate

determining step for hydrophobic, poorly water soluble drugs. In case of hydrophilic drugs with high aqueous solubility, dissolution is rapid and the rate determining step in the absorption is often the rate of permeation through the biological membrane. Drug instability during absorption can affect its bioavailability. Two major stability problems resulting in poor bioavailability of an orally administered drug are degradation of the drug into inactive form, and interaction with one or more components of the dosage form or those present in the GIT to form a complex that is poorly soluble or is unabsorbable.

Most recent drugs have poor aqueous solubility, which can adversely impact their rate of release and absorption from solid dosage forms since a drug must be presented to the absorption site in a dissolved state for it to be absorbed. Hence, the dynamic process of drug dissolution is related to drug absorption, with dosage form design playing a crucial role in ensuring sufficient and acceptable bioavailability.

Dosage forms are typically formulated with excipients to modulate API stability, bioavailability, manufacturability, and uniformity of dosage units. Excipients can frequently affect the processes of dosage form disintegration, drug dissolution, stability, or interaction of drug with the physiological factors by modifying biorelevant drug product or drug substance characteristics (4). In this paper, we discuss some of the mechanistic basis of impact of excipients on the bioavailability of drugs from solid dosage forms.

FACTORS AFFECTING BIOAVAILABILITY

Bioavailability of a drug from its dosage form depends upon pharmaceutical factors related to physicochemical properties of the drug and characteristics of the dosage form, pathophysiology of the disease, and route of administration.

Physicochemical Properties of the Drug Substance

Drug substance in a solid dosage form must dissolve at the site of absorption for it to be absorbed. Thus, the rate of drug absorption can be limited by either the rate of drug dissolution in the aqueous media at the site of absorption (dissolution-limited drug absorption) or the solubility of the drug in that media (solubility-limited drug absorption). The total amount of absorbed drug increases with increasing dose in the case of dissolution-limited drug absorption, but not in the case of solubility-limited drug absorption. These mechanistically different limitations to drug absorption also lead to differences in approaches that may be adopted to optimize drug bioavailability.

Particle Size and Surface Area

Physicochemical properties of the drug that affect the rate and extent of drug dissolution include solubility, surface area, polymorphism, and salt form. Particle size and surface area of a solid drug are inversely related to each other. Smaller the drug particle size, greater is its surface area to volume ratio. Since the surface area increases with decreasing particle size, micronization generally leads to higher dissolution rates. For example, micronization of poorly water soluble drugs griesofulvin, chloramphenicol, and tetracycline resulted in higher dissolution rates when compared with their non-micronized forms (5,6). Micronization has been used for dissolution rate enhancement of griesofulvin (6), aspirin (7), and several other drugs. Dissolution rate of hydrophobic drugs can be further enhanced by the concomittant use of surfactants (e.g., Tween-80) and hydrophilic polymers [e.g., polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG)] as wetting agents to decrease the interfacial tension and displace adsorbed air on the surface of solid particles.

Micronization sometimes leads to the unexpected observation of decrease in surface area and dissolution rate. This is often due to the aggregation of micronized particles due to high surface energy and/or electrostatic charge during the micronization process. In such cases, use of excipients during or after micronization is helpful in reducing aggregation. Thus, deposition of micronized drug on excipient surface can also lead to increase in surface area and dissolution. For example, microparticles of nevirapine, a poorly water soluble drug, were prepared by supercritical antisolvent method and deposited on the surface of excipients such as lactose and microcrystalline cellulose. The nevirapine/excipients mixture showed faster dissolution rate compared to drug microparticles alone or when physically mixed with the excipients (8). This could be due to the minimization of aggregation in micronized drug particles.

Polymorphism, Salt Form, and Prodrug

Polymorphism refers to the existence of drugs in more than one crystalline form, which often exhibit differences in melting point, solubility, dissolution rate, stability, and/or bioavailability. For example, the three polymorphs of chloramphenicol palmitate exhibited differences in solubility and dissolution rates (9), and bioavailability (10). Polymorphic conversion in the dosage form can lead to changes in drug dissolution and absorption. Viscosity-inducing hydrophilic macromolecules such as povidone, carboxymethyl cellulose (CMC), pectin, and gelatin, when incorporated in intimate mixture with the drug in the dosage form, can minimize the rate of inter-conversion of one polymorphic form into another. Selection of the right polymorphic form

that is adequately stable and bioavailable is important to the development of a robust drug product.

Passive transport of drugs across the biological membrane is governed by the proportion of the unionized form present, which is governed by the drug's dissociation constant (pKa) and pH at the site of absorption, and lipid solubility of the unionized drug. Prodrug strategies that alter the pKa and lipophilicity of drug molecules can impact their absorption. Also, conversion of drugs to their salt forms can also improve their solubility and dissolution rate, thus impacting bioavailability.

Biorelevant Drug Product Properties

Biorelevant drug product properties that are impacted by excipients include disintegration of the solid dosage form, drug dissolution, microenvironmental pH, and retention at the site of absorption. An understanding of the mechanistic basis of such drug product properties is important to the design of an optimum dosage form. For example, tablet disintegration is affected by not only the type and concentration of the disintegrant, but also the porosity of tablets (11). Tablets with higher porosity allow rapid internalization of the aqueous medium into the dosage form during dissolution. The effect of tablet porosity may be observed in the role of processing variables (such as the rate and extent of shear during wet granulation), binder quantity, and tablet strength (during compression) on drug release and bioavailability.

Physiological Factors

GI physiological characteristics often interact with drug substance or dosage form characteristics to impact drug absorption. In addition, inter-individual variability in the physiological characteristics can lead to variability in a drug's pharmacokinetic parameters. An understanding of the interaction of physiological variables with drug and dosage form can allow drug product design strategies that may minimize or mitigate variability in drug absorption.

GI Motility

Peristaltic motion of the stomach and the intestines carry their contained mass forward to the progressing segments of the GI tract. Normal motility of the GI tract is characterized in terms of transit time through different 'compartments' of the GI tract, which are utilized in modeling drug absorption. The transit time is defined as the time taken for a dosage form or its components to pass through a compartment. For example, the following parameters are utilized in the GastroPlus software (Simulations Plus, Inc., Lancaster, CA) for simulation of human drug absorption after oral administration.

Stomach. Gastric emptying time in the fasted transit time is generally less than half an hour, while high fat breakfast can increase the gastric emptying time to several hours.

Small Intestines. Transit time through different intestinal segments is estimated based on the volume of fluid in each segment. The average small intestinal transit time is considered about 3.3 h.

Caecum. Transit time for human caecum is 4.5 h.

Colon. Human colon transit time is generally considered to be 13.5 h.

The rate of transfer of drug product from one segment of the GI tract to the next can influence the time period available for drug dissolution or absorption available in one particular component. Of all the stages of GI transit, gastric emptying provides greatest influence on the rate of oral drug absorption since an orally administered dosage form encounters the stomach first. In addition to the emptying of stomach contents, the gastric muscles exert mechanical pressure on the dosage form. GI transit times can influence oral drug bioavailability through a multitude of mechanisms, such as the following.

Gastric Emptying. Basic drugs that are administered as solid particles or tablets that must first dissolve in the acidic gastric environment before being transported as drug solutions to the upper intestinal tract, where most of the drug absorption takes place. In some cases, rapid gastric emptying can lead to incomplete drug dissolution in the stomach, leading to transfer of partially undissolved drug particles in the duodenum. This can not only lead to incomplete drug dissolution and absorption, but the undissolved drug particles can serve as nucleation sites for precipitation of dissolved drug in the duodenum – which can further reduce the extent of drug absorption and also introduce inter-individual variability. This phenomenon is the main reason for variability in drug absorption in monkey models for many drugs that exhibit pH-based solubility leading to supersaturation in the duodenum.

Intestinal Transit Rate. General increase in intestinal motility can increase the rate of drug transport from one intestinal segment to the next. This can impact the total duration of time a drug has for absorption from the proximal segments of the intestine (such as duodenum), which have higher surface area than latter segments (such as ileum and colon). Thus, the effect of GI motility on the extent of drug absorption would depend on the rate of drug absorption or effective permeability of the compound across the GI membrane for drugs absorbed by passive diffusion. The impact can be higher for drugs with a specific and short window of absorption.

GI motility can be affected by several factors, including pharmacological effect of the drug itself.

Food and pH Effect

Food intake can affect drug absorption either by directly interacting with the dosage form or by affecting GI physiological parameters relevant to drug absorption. For example, GI fluid volumes are different in the fed and the fasted state, as illustrated in Table I (12).

Food also influences gastric pH. Thus, while the normal gastric pH is 1 – 3 in the fasted state, the fed state gastric pH in humans can be 4.3 – 5.4 (13). The effect of gastric pH on oral drug absorption can be most predominant for weakly basic compounds that have high solubility at acidic pH in the stomach and low solubility at the basic pH in the intestines. The rate and extent of oral bioavailability of these drugs in humans is dependent on their rapid dissolution from an oral solid dosage form in the acidic stomach. Change in gastric pH, due to coadministration of food or other reasons such as the use of antihistaminic drugs, can lead to altered oral drug bioavailability.

In addition to the quantity and type of food (e.g., liquid ingestion *versus* solid food), fat content in the food can affect GI motility, concentration of bile in upper intestines, and drug release characteristics from the dosage form. Fat and high calorie meals delay gastric emptying. The presence of surfactants in the intestinal milieu (e.g., from the bile) can lead to solubilization of drug at the site of absorption (small intestine), leading to supersaturation of drug. This prevents precipitation of a weakly basic compound that dissolved in the low gastric pH and was subsequently transported to the high intestinal pH environment, in which it has low solubility. In cases where the supersaturation phenomenon contributes to oral drug bioavailability, alterations in bile secretion or other physiological changes in the intestinal fluids can alter oral drug bioavailability.

Window of Absorption

Passive absorption of orally administered drugs is assumed to follow uniform rate of permeation across the GI tract. The rate of absorption for these drugs, therefore, is a function of the relative area of a GI segment and the residence time of the drug in that segment of the GI tract. Some drugs, however, display significantly high absorption in some specific region of the GI tract, while the absorption rate may be very low in other segments. The high absorption regions for these drugs are termed as 'window of absorption'. The phenomenon of window of absorption of a drug can also be related to differential drug solubility and stability in various regions of the GI tract.

Table I Gastro-Intestinal Fluid Volumes in the Fasted and Fed State

Compartment	Fasted state volume (mL, mean ± SD)	Fed state volume (mL, mean ± SD)
Stomach	45 ± 18	686 ± 93
Small intestine	105 ± 72	54 ± 41
Large intestine	13 ± 12	11 ± 26

Ascertaining the window of absorption of a drug *in vitro* can be carried out by measuring drug permeability across different sections of the GI tract mounted in an Ussing chamber. *In vivo* assessment or confirmation of a window of absorption is generally deductive based on the plasma concentration time profile of a drug after administration to different regions of the GI tact. Such studies may be carried out using, for example, a radio-frequency-based remote controlled delivery capsule coupled with real-time visualization of capsule location in the GI tract using gamma scintigraphy. In addition, direct administration of a drug to different intestinal segments using animals that are ported for direct drug administration to such regions of the GI tract can help elucidate relative absorption rates of the drug from different segments. Significant change in the exposure of the drug after administration to different regions is indicative of a window of absorption.

Drugs that show a window of absorption in the proximal regions of the small intestine, such as the duodenum, can potentially limit the oral bioavailability of drugs and also present an obstacle to the development of controlled release formulations. Drugs that show higher permeability in the upper intestinal regions include ciprofloxacin, levodopa, furosemid, captopril, acyclovir, and gabapentin. Oral drug absorption from these drugs is sensitive to physiological parameters, such as GI motility, and this sensitivity is reflected in the inter- and intra-subject variability in their oral drug absorption. In addition, such drugs are also amenable to dosage form strategies that target to maximize and prolong drug concentration in the upper GI tract – such as gastroretentive dosage forms or bioadhesive microspheres. For example, a prolonged release gastroretentive dosage form of ciprofloxacin prolonged the exposure of the drug in humans (14).

Variability in Metabolizing Enzymes and Efflux Transporters

Several drugs are substrates of drug metabolizing enzymes in the GI tract, such as the cytochrome P450 (CYP) enzymes in the intestinal mucosa, and efflux transporters, such as the P-glycoprotein (P-gp) family of transporters. CYP enzymes are membrane bound heme containing proteins that are responsible for the metabolism of endogenous compounds such as steroids and fatty acids, and are often the metabolizing enzymes of drugs and xenobiotics. Isoform 3A4 of the cytochrome P450 metabolizing enzyme has been recognized as

dominant in the gut wall metabolism of drugs. P-gp is the active transporter that secretes drugs back in the GI tract and is located on the mucosal surface of GI epithelial cells. P-gp expression in normal tissues, such as canalicular side of hepatocytes, apical surface of renal proximal tubules, and endothelial cells of the blood–brain barrier, serve to minimize physiological exposure to potentially toxic xenobiotics.

Oral absorption of drugs that are substrates of efflux transporters and metabolizing enzymes is understandably affected by the inter-individual expression level and intra-individual distribution of these proteins in the GI tract. The distribution of P-gp transporter and CYP3A4 metabolizing enzymes differs across regions of the GI tract, which can contribute to variability in oral drug absorption. P-gp transport has been linked to the low and variable oral bioavailability of several compounds such as propranolol and felodipine (15). Drugs such as itraconazole and cyclosporin are substrates for both CYP3A4 and P-gp. In addition, drugs whose absorption is affected by transporters and metabolizing enzymes can also be sensitive to certain food effects. For example, grapefruit juice is an inhibitor of CYP3A4 (16), and can thus affect the oral absorption of drugs that are CYP3A4 substrates.

PHYSICOCHEMICAL INTERACTIONS IN DOSAGE FORMS

Dosage form factors that can impact the bioavailability of drugs include the interaction of excipients with drug substances and the physiological factors at the site of absorption. Excipients can also affect drug bioavailability through physicochemical interactions in the dosage form that, in turn, affect drug absorption. These interactions could be drug–excipient or excipient–excipient interactions.

Drug-Excipient Interactions

Excipients can initiate, propagate or participate in physical or chemical interaction with drugs that can affect the therapeutic efficacy of the drugs. Excipients may have functional groups that can react with the drugs. Drug excipients interactions can be a result of physical (polymorphism, crystallization), chemical (oxidation, hydrolysis) or biopharmaceutical interactions. In this paper, we will discuss some of the common mechanisms of physicochemical interactions and how they affect drug bioavailability.

Complex formation of a drug with an excipient can be used to alter the physicochemical and biopharmaceutical properties of a drug since the complexed drug becomes the predominant molecular entity in the dosage form with its distinct physicochemical properties such as solubility, stability, and diffusion coefficient. Most complexes dissociate at the site of absorption or *in vivo* leading to free drug being absorbed and present in the plasma. Cyclodextrin has been used as a complexing agent to increase the solubility and bioavailability of several drugs including griesofulvin (17), ursodeoxycholic acid (18), cinnarizine (19), acyclovir (20), artemesinin (21), glibenclamide (22), ibuprofen (23), and nifedepine (24).

Adsorption of drugs on the surface of certain excipients can lead to increase in the surface area of drugs, thus increasing the rate drug release (25,26). For example, indomethacin showed an improved dissolution rate when it was formulated with adsorbents kaolin or microcrystalline cellulose (26).

Intimate co-processing of drugs with excipients, such as by spray drying, co-precipitation, co-grinding, or the formation of solid dispersions or co-grinding, can lead to improvement in drug solubility and/or dissolution rate. Solid dispersions are generally dispersions of active ingredients in molecular, amorphous and/or microcrystalline forms in an inert hydrophilic carrier (27). Formulation of hydrophobic drugs in solid dispersions is most commonly used for enhancing their dissolution. The use of polymers for amorphous solid dispersions has been reviewed recently (28). D-glucosamine hydrochloride was used as a potential hydrophilic carrier for poorly water soluble drugs like carbamazepine to enhance their dissolution and bioavailability (29). Similarly, meloxicam, which has poor solubility and wettability, showed an increase in dissolution rate when formulated as a binary mixture with PEG 6000 (30).

Excipient-Excipient Interactions

Although drug-excipient interactions occur more commonly compared to excipient-excipient interactions (31), the latter are frequently used to enhance or decrease dissolution rate of a drug from a dosage form. Excipient-excipient interactions can be utilized in the use of more than one excipient to form a 'base' for a dosage form, which can be used in developing sustained release formulations. For example, sustained-release theophylline tablets were prepared in a crosslinked matrix base formed by interaction between the excipients sodium alginate and calcium gluconate which regulates the release of theophylline from the formulated tablets (32). In another study, matrix was prepared by cross-linking of cationic chitosan in acidic media with sodium sulfate during the preparation of granules by wet granulation (33).

Thus, interactions in solid dosage forms between its components (such as drug-excipient and excipient-excipient interactions) and of its components with the physiological processes can affect the bioavailability of drugs. A basic mechanistic understanding of such phenomena is important to avoid their undesired consequences, while also promoting utilization of some of these facets in dosage form

design for intended drug delivery needs. The following sections will discuss some of the pathways by which excipients impact drug bioavailability.

EFFECT OF EXCIPIENTS ON PHYSIOLOGICAL PROCESSES

Excipient interaction with physiological processes such as pH of gastrointestinal fluids in the immediate vicinity of the dosage form, GI transit time, effective membrane permeability, drug degradation in the GI fluids, and drug metabolism and efflux during absorption can alter the rate and extent of drug absorption.

pH of GI Fluids

The pH of GI fluids can significantly influence drug absorption by its effect on both drug substance and drug product related factors. Most of the drugs are either weak acids or weak bases, with pH-dependent solubility (34). Immediate release formulations are designed to release the drug in the gastric environment. Dissolution of most weak acid or weak base drugs that show pH-dependent solubility depends on the pH of the gastric fluid. A pH that favors ionization of the drug can enhance its dissolution.

Drug absorption from the stomach is generally higher for weak acids, compared to weak bases, since weakly acidic compounds would have greater proportion of unionized species at acidic pH. Similarly, drug absorption from the intestines is generally higher for weak bases, compared to weak acids, since weakly basic compounds have greater proportion of unionized species at basic pH. Overall extent of drug absorption for a passively absorbed compound that does not have a window of absorption, however, is generally governed by the extent of absorption through the small intestines due to their higher surface area and transit time.

For most passively absorbed compounds that show pH-dependent solubility and whose predominant site of absorption is the small intestine (due to its large surface area), overall drug absorption can be increased by solubilization in the acidic pH of the stomach. Increase in pH when the drug transitions from the stomach to the small intestine results in higher amount of dissolved drug, than the equilibrium solubility of the drug at intestinal pH. This phenomenon is known as supersaturation and can lead to improved drug absorption from the intestine. On the other hand, drug absorption may be limited for compounds that do not sustain supersaturation in the intestinal environment and precipitate rapidly.

In terms of formulation-related influence of gastrointestinal pH on drug absorption, the disintegration of some dosage forms is pH sensitive. For example, enteric coated formulations are designed to disintegrate only in the basic intestinal pH. Some colonic delivery formulations are further designed for disintegration above a certain pH (35). In these cases, inter- or intra-subject variation in the pH of GI fluids due to non-dosage form related factors can lead to variability in drug absorption.

In some cases, interaction of excipients in the dosage form with the gastric fluids can aid in disintegration. For example, when erythromycin acistrate, a prodrug of antibiotic erythromycin, was formulated in hard gelatin capsules, addition of sodium bicarbonate to the formulation enhanced its bioavailability (36). Similarly, use of sodium bicarbonate in a hard gelatin capsule formulation of ibuprofen formulations led to fast drug absorption, compared to a formulation containing aluminum hydroxide (37). Sodium bicarbonate containing formulation of ibuprofen capsules also resulted in more rapid absorption compared to the formulations containing lactose or dicalcium phosphate (38). These effects of highly basic salts were attributed to enhanced *in vivo* capsule disintegration and dissolution, possibly due the release of carbon dioxide on the reaction of sodium bicarbonate with hydrochloric acid in the stomach, which results in enhanced tablet disintegration due to internal pressure – a phenomenon known as the effervescent effect. In addition, solubility due to the ionization of the drug remain important criteria in drug dissolution. Erythromycin acistrate is a highly hydrophobic ester prodrug of a macrolide antibiotic (39,40) that is expected to show pH-independent solubility. Ibuprofen is a weak acid with a pKa of 4.5–4.6 and high solubility at basic pH (41). Thus, while effervescent effect might be the predominant factor that explains the observations for erythromycin acistrate, both pH-induced solubility enhancement due to greater ionization and effervescent effect may be involved in improving the bioavailability of ibuprofen formulations.

Microenvironmental pH of Dosage Form

Excipients can also act as microenvironmental pH regulators in solid dosage forms that aid in modulating drug release. Modification of the microenvironmental pH of solid dosage forms is required in cases where drug solubility is pH dependent and the drug has a tendency for crystallization or precipitation during dissolution (42). For example, weakly basic drugs that are formulated as salt forms and show pH dependent solubility, precipitation or crystallization of the free base during dissolution may lead to slow and incomplete drug release. This phenomenon can result in lower drug bioavailability at elevated gastric pH as a result of antacid or food consumption, a phenomenon known as gastric pH interaction (43–46).

For drugs that show gastric pH-dependent drug absorption, acidification of the microenvironment and rapid

disintegration of the dosage form can help achieve complete drug release. For example, Badawy *et al.* utilized tartaric acid to provide acidic microenvironment and overcome gastric pH interaction of a factor Xa inhibitor drug, BMS-561389 (47).

This drug was a hydrochloride salt of a weak base with very low intrinsic solubility and two basic pKa values (2.2 and 7.4). It exhibited pH-dependent solubility, with higher solubility at lower pH. While this drug seemed to be well absorbed under normal gastric pH condition, significant reduction in plasma AUC and Cmax were observed when the immediate release tablets were coadministered with H2 receptor antagonists in dogs. The authors hypothesized that the reduced oral bioavailability under these circumstances was due to the precipitation of the free base, which exhibited slow rate of dissolution (Fig. 1). The authors were able to overcome this gastric pH-interaction of the compound by addition of 16.7 % tartaric acid in the formulation, which was verified in a dog model (47).

Similar modulation of microenvironmental pH of a weakly basic drug can be used in the design of controlled drug delivery systems to achieve pH-independent drug release. For example, Ploen *et al.* were able to achieve pH-independent release of propiverine, a weakly basic drug, from its extended release pellet formulation, when they utilized citric acid cores instead of microcrystalline cellulose cores on which the drug layer was coated (48). The authors observed sustained release of both the drug and the pH modifier throughout the dissolution period of 17 h, suggesting a role of the microenvironmental pH modifier in maintaining low pH inside the pellets, leading to controlled, pH-independent drug release.

GI Transit Time

Excipients can affect GI motility, which may adversely impact oral drug absorption (49). For example, an effervescent tablet formulation of the H2 receptor antagonist ranitidine using sodium acid pyrophosphate as the acid showed lower absorption compared to its tablet formulation (50), which could be related to the effect of sodium acid pyrophosphate on decreasing small intestinal transit time (49). The lower residence time of the drug at its site of absorption could lead to reduced drug absorption.

Decrease in small intestinal transit time effect has also been reported with nonabsorbable sugar alcohol monosaccharides mannitol (49,51) and xylitol (52), and the disaccharide lactulose (53–55). Interestingly, while lactulose decreased small intestinal transit time, it did not significantly alter the gastric emptying rate or the whole gut transit time (55). These effects of sugars could be related to their poorly or non-absorbable nature, raising the possibility that such effects may be possible with other such sugars, e.g., sorbitol (56). The effect of unabsorbed sugars and sodium acid pyrophosphate in decreasing the intestinal transit time could be related to their osmotic effect. High osmotic pressure in the intestinal lumen can lead to increased bulk (which stimulates peristalsis) and retention of water (which can lead to diarrhea in some cases) (57–61).

Presence of lipids, whether from food or dosage form, can enhance gastro-intestinal motility, which may depend on their presence at specific site(s) in the GI tract (62–64). Consequently, use of lipid excipients can contribute to variability in oral drug absorption, especially if one or more components of the dosage form undergo digestion in the GIT (65). Dosage forms that extensively utilize lipids include self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery systems (SMEDDS), micelles, liposomes, solid-lipid dispersions, and nanoparticles (66,67). For example, Porter *et al.* compared oral bioavailability of danazol from two SMEDDS systems based on long (C18) and medium (C8-10) chain lipids in beagle

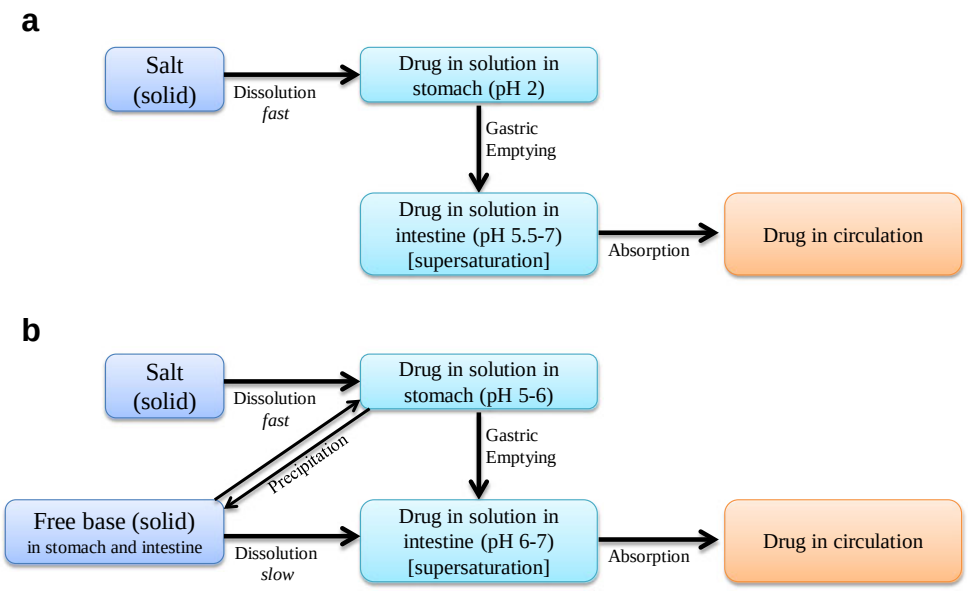

Fig. 1 Mechanistic pathways involved in oral drug absorption of a weakly basic compound that shows gastric pH interaction (47). (**a**) Drug absorption under normal, acidic gastric pH conditions. (**b**) Drug absorption under elevated gastric pH conditions. At elevated gastric pH, drug precipitation in its free base form can lead to slowdown of drug dissolution.

dogs (68). The authors observed a significant increase in bioavailability of the drug from long chain lipid-based SMEDDS but not from medium chain lipid based SMEDDS. These results correlated well with the *in vitro* digestion studies with pancreatin that showed greater precipitation of medium chain lipid-based SMEDDS (Fig. 2). These results led the authors to hypothesize that digestion of the microemulsion preconcentrate formulations can lead to reduced oral bioavailability *in vivo*.

The effect of excipients on GI motility is dependent on the concentration of excipients and a possible overlap of multiple mechanistic pathways of excipient influence on drug absorption. For example, when Schulze *et al.* investigated oral bioavailability of ranitidine in formulations with different concentrations of PEG 400, low concentrations of PEG 400 enhanced the absorption of ranitidine possibly via modulation of intestinal permeability, while high concentrations had a detrimental effect on ranitidine absorption presumably via a reduction in the small intestinal transit time (69). Concentration dependence of the effect of excipients on GI motility has been observed for mannitol (70) and PEG 400 (69). Thus, the GI motility effect of excipients can be avoided or minimized by lowering its concentration in the formulation. Nevertheless, the effect of these excipients on drug absorption or permeability across the GI mucosa may not be completely ruled out or predictable even at low doses given the complex nature of these phenomena.

Whether change in GI transit time would affect drug bioavailability would vary on a case-by-case basis depending upon factors such as site of absorption, rate limiting factor in drug absorption (e.g., permeability or solubility limited), and whether drug metabolism, efflux, complexation, or degradation at the site of absorption plays a role in determining its bioavailability. Often factors such as saturable kinetics of efflux or drug metabolizing enzymes and phenomena such as limited window of absorption can lead to non-linearity of dose-bioavailability and dose–response curves. Thus, excipients that affect GI transit time may affect the oral bioavailability of some, but not all, drugs. Thus, cimetidine showed reduced bioavailability in a formulation that contained mannitol, when compared to another formulation with sucrose (51). Also, in line with the known effect of PEGs on increasing GI motility (71), coadministration of ranitidine with PEG 400 resulted in reduced rate and extent of drug absorption (72).

The relative impact of selected excipients on GI transit time and drug bioavailability was investigated by Schulze *et al.* in beagle dogs using gamma scintigraphy imaging and plasma drug concentration measurement (73). The authors studied the effect of 1 g PEG 400, 2 g propylene glycol, 1 g d-α-tocopheryl-polyethylene glycol-1000 succinate (TPGS), and 1 g labrasol on GI transit and absorption of a 200 mg dose of ampicillin or a 100 mg dose of antipyrine in a capsule formulation. The range of mean small intestinal transit times (154–195 min) and absolute oral bioavailability (32–42 % for ampicillin and 73–85 % for antipyrine) (Fig. 3) did not indicate significant difference from control in the doses administered.

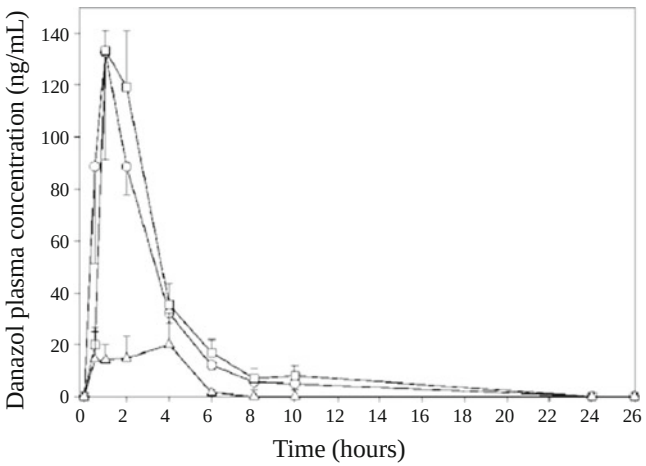

Fig. 2 Mean plasma concentration-time profiles of danazol (mean ± standard error, $n=4$) following oral administration of medium chain lipid-based SMEDDS (triangles), long chain lipid-based SMEDDS (circles), or triglyceride solution of the drug (squares) demonstrating the importance of *in vivo* digestion of a bioavailability enhancing carrier. Higher bioavailability from long chain lipid-based SMEDDS, similar to that from triglyceride solution, than medium chain lipid-based SMEDDS, correlated well with their greater stability to pancreatic digestion in an *in vitro* assay (68).

Modulation of Drug Degradation and Membrane Permeation

Stabilization of drug degradation in the gastro-intestinal tract can improve oral drug bioavailability if drug degradation is a significant factor in drug absorption. Whether a drug delivery approach that prevents degradation during absorption would impact bioavailability also depends on the nature of the drug, its dose, window of absorption, and related factors that affect whether degradation is a significant factor affecting drug bioavailability.

Complexation of a drug substance can alter its stability against degradation during absorption, thus impacting its oral bioavailability. For example, chlorpromazine hydrochloride, an antipsychotic drug, is a relatively high solubility compound that undergoes metabolic transformation and degradation in the gastrointestinal tract. When delivered as a 1:1 complex with β-cyclodextrin, the drug had improved stability, higher partition coefficient, and greater bioavailability (74).

Prodrugs that involve conjugation of lipoamino acids or sugar residues to small molecule or peptide drugs can improve their oral bioavailability by increasing membrane permeability and/or reducing drug degradation in the GI fluids. For

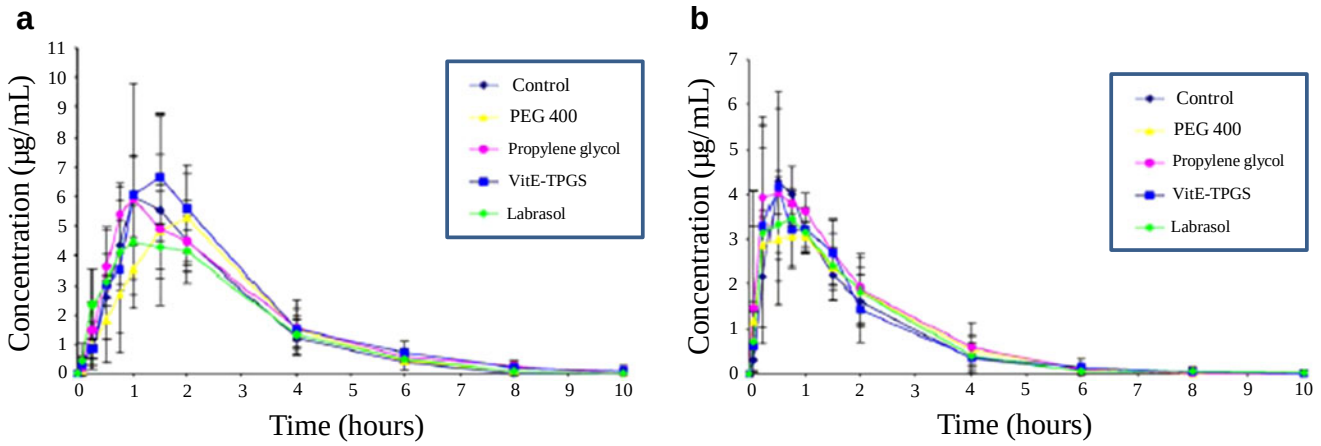

Fig. 3 Oral plasma concentration-time profile of ampicillin (**a**) and antipyrine (**b**) capsule formulations in the presence of excipients known to increase GI transit (73). The data indicates lack of *in vivo* relevance of presence of excipients for these drugs in the concentrations used in the study.

example, conjugation of lipoamino acids to naproxen through a diethylamine spacer increased the lipophilicity and interaction of prodrugs with dimyristoylphosphatidylcholine phospholipids, forming either multilamellar vesicles or monolayers, as biomembrane models (75). Greater membrane interaction of lipophilic prodrugs is often associated with advantages such as higher intracellular accumulation and greater activity. Thus, lipophilic derivatives of the anticancer drug paclitaxel were prepared by its conjugation to lipoamino acid using a succinic acid group as a spacer. When evaluated for *in vitro* anticancer activity in a human thyroid anaplastic cancer cell line, the paclitaxel prodrugs showed higher cytotoxic activitiy and intracellular accumulation than the parent compound (76). Lipoamino acid conjugate of the thymic hormone thymopoietin resulted in both increased *in vitro* stability to hydrolysis as well as membrane penetration (77).

Inhibition of Drug Metabolism and Efflux

Cytochrome p-450 (CYP) Enzymes

There have been increasing reports in literature suggesting the possible role of excipients in inhibiting drug metabolizing cytochrome p-450 (CYP) enzymes (78–81). Ren *et al.* found that surfactants and polymers are the most common class of pharmaceutical excipients that inhibited intestinal and liver CYP 3A4 by more than 50 % *in vitro* (82). These effects were concentration dependent (Fig. 4). Further *in vivo* evaluation of 5 of these excipients in rats in single and multi-dose studies through investigation of pharmacokinetics of midazolam and its primary metabolite 1′-hydroxymidazolam indicated increase in midazolam area under the curve and decreased clearance to bioavailability ratio as well as decreased AUC ratio of metabolite/midazolam (82).

P-glycoprotein (P-gp) Efflux Transporters

Excipients can also alter the activity of membrane spanning proteins such as transporters, which can affect drug absorption, metabolism, elimination, and transport (83,84). The P-glycoprotein (P-gp) multi-specific efflux transporter is known to play a major role in influencing bioavailability of anticancer drugs, and several other drugs (85,86). Some excipients can alter P-gp transporter activity, leading to altered drug absorption, distribution, and elimination (87). For example, excipients such as Tween® 20/80, Span® 20, Poloxamer®,

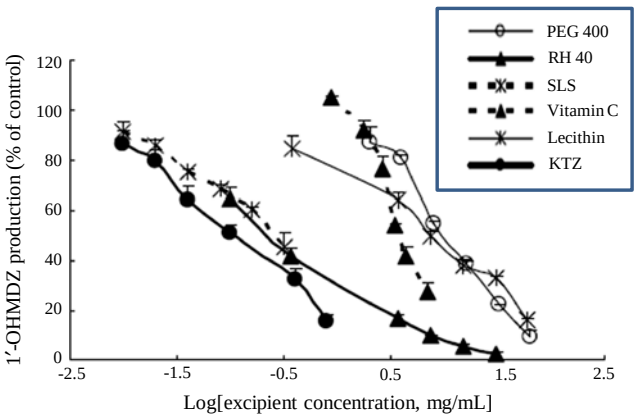

Fig. 4 Concentration dependent inhibition of the activity of CYP 3A4 for selected excipients *in vitro* (82). The CYP 3A4 activity was assessed indirectly by the production of 1′-hydroxymidazolam, (1′-OHMDZ) a metabolite of midazolam. Recombinant CYP3A4 microsomes were incubated with midazolam in the presence of mentioned excipients in different concentrations. Abbreviations: PEG400, polyethylene glycol 400; RH40, polyoxyl 40 hydrogenated castor oil; SLS, sodium lauryl sulfate; KTZ, ketoconazole.

and Pluronic® have been used as P-gp inhibitors in developing anti-cancer formulations (86).

Excipients-induced inhibition of P-gp in the intestine can lead to enhanced drug absorption. These effects were seen with surfactants, solubilizers, and lipids, which are commonly used in improving the solubility and dissolution rate of poorly soluble drugs. For example, Pluronic P-85 increased the permeability of a broad spectrum of drugs in caco-2 cell monolayers and also in the Ussing chamber (88). Pluronic P-85 also increased the permeability of several drugs across the blood brain barrier by inhibiting P-gp transporter in bovine brain microvessel endothelial cells (89). Lipid excipients are commonly used to enhance the bioavailability of poorly soluble drugs (66). Excipients such as peceol and gelucire decreased the P-gp mediated efflux of rhodamine 123 in caco-2 cells (90).

PEG 400, a commonly used solubilizer, showed a concentration dependent effect on the bidirectional transport of ranitidine across Caco-2 cell monolayers (Fig. 5). At low doses, PEG 400 not only improved the absorptive transport but also significantly reduced the efflux-mediated secretory transport, in a concentration dependent manner (91). The authors indicated that the interaction of PEG 400 with P-gp could be the mechanistic basis of their earlier observations on ranitidine absorption enhancement *in vivo* (92) (Fig. 5). Interestingly, the authors reported that PEG 400 enhances absorption of ranitidine in male subjects, not females. The reason for this observation was not known. Similarly, Shen *et al.* reported inhibition of secretory transport of P-gp substrates prednisolone, methylprednisolone, and quinidine by PEG 20,000 across the isolated rat intestinal membranes using an *in vitro* diffusion chamber (93). In this study, PEG 20,000 did not affect the transport of luciver yellow, a non-P-gp substrate.

The mechanistic basis of inhibition of metabolizing enzyme or efflux transporter activity, however, is unknown. It could involve surface level interaction, modification of membrane properties, or changes in expression. For example, Tompkins *et al.* studied mRNA and protein expression of CYP3A4 in immortalized human liver cells, primary human hepatocytes, and intestinal cells using real-time reverse transcription – polymerase chain reaction (RT-PCR) and immunoblot analyses. The authors studied 19 commonly used pharmaceutical excipients from different functional classes. They observed that while no excipient activated CYP3A4, three excipients – polysorbate 80, pregelatinized starch, and hydroxyprpyl methylcellulose (HPMC) – reduced mRNA and protein expression (81). Inhibition of P-gp protein expression in Caco-2 cells was also reported for lipid excipients Peceol® (90), Gelucire® 44/14 (90), and monoglycerides (94).

Biological Activity of Excipients

Excipients may exhibit biological activities other than metabolic or efflux inhibition such as antidiabetic effect (95) or modulation of nerve impulses *in vivo* (96,97). For example, Apte suggested that excipients such as L-Arginine, magnesium, guar gum, inositol, niacin, and alpha-lipoic acid can exert certain anti-diabetic effects and may be useful in formulating anti-diabetic dosage forms (95). The authors hypothesized that a combination of these excipients, if formulated together, can be used to mitigate diabtetes or insulin resistance indepdent of an active pharmaceutical ingredient. The mechanistic basis for these excipients exerting the antidiabetic effect can be diverse. For example, L-Arginine is an excipient used in tissue plasminogen factor formulation, Activase®. It enhances the levels of cyclic guanosine monophosphate (cGMP), a second messenger of nitric oxide, in diabetic subjects – resulting in decreased insulin resistance by normalizing the vasodilatory respsone (98) and by increasing glucose transport (99). On the other hand, magnesium chloride solution, commonly used as an oral electrolyte supplement, improves insulin sensitivity and metabolic control in type 2 diabetic patients by increasing serum magnesium levels (100). This can restore hypomagnesemia-induced defective tyrosisne kinase activity of insulin receptors (101).

Benzon *et al.* studied the effect of PEG on mammalian nerve impulses (96) based on reports that PEG causes neurodysfunction was used as a vehicle for depot steroid preparations injected into the epidural or intrathecal space, such as the formulations of methylprednisolone acetate and triamcinolone diacetate used to relieve low back pain. The authors observed that PEG, in concentration up to 40 %, does not cause neurolysis. However, higher (20–30 %) concentrations cause mild to moderate depression of the compound action potential amplitudes and marked slowing of the conduction velocities in nerves. Exposure of the nerve to 40 % PEG for 1 h resulted in a complete block of nerve transmission. The effects of PEG was the same in the sheathed and desheathed nerves and were independent of pH. The mechanistic basis of such effects, however, may be common with their effect on drug absorption, such as possible effects of PEG on membrane fluidity (102).

MODIFICATION OF BIORELEVANT DRUG SUBSTANCE PROPERTIES BY EXCIPIENTS

Drug-excipient interactions are frequently utilized and/or known for affecting drug release or dissolution. However, changes in drug dissolution may or may not have an impact on drug bioavailability. For example, increase in drug dissolution by complexation with cyclodextrin corresponded with increased oral bioavailability of griseofulvin (17) and spironolactone (103); but not of naproxen (104) and tolbutamide (105). Also, reduction in dissolution by complexation of halofantrine with magnesium carbonate (106) and of tetracycline with magnesium aluminum silicate (veegum)

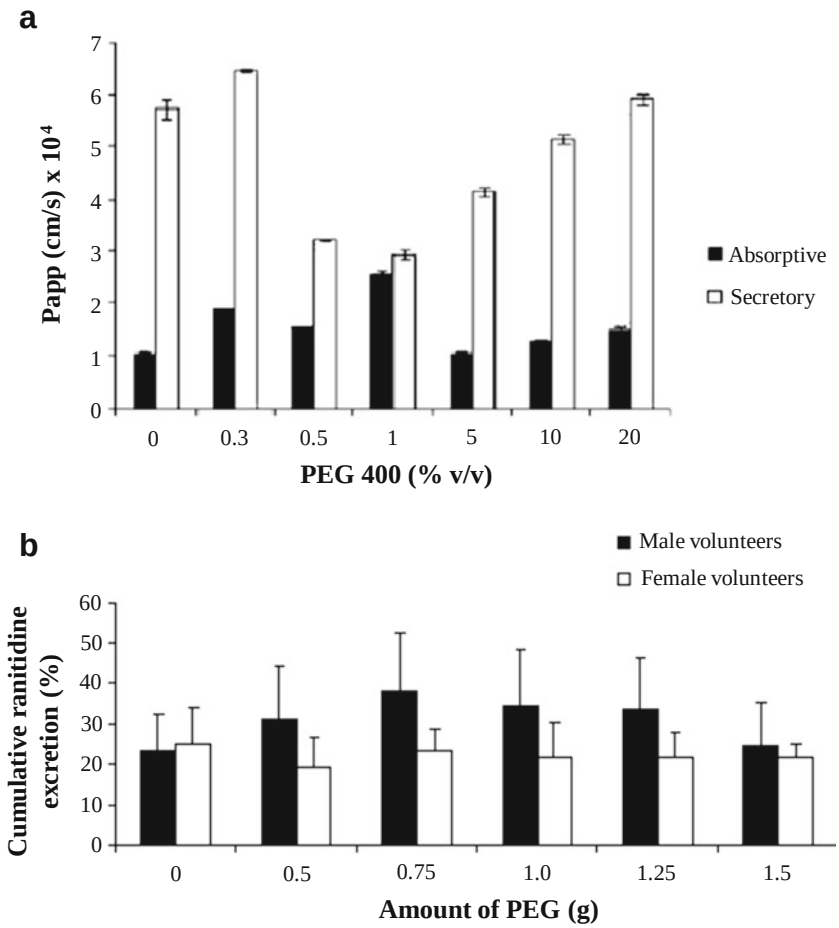

Fig. 5 Effect of PEG 400 on bidirectional transport of ranitidine in Caco-2 cell monolayers (**a**) (91) and on the amount of ranitidine excreted in urine in healthy male and female volunteers over a 24 h period after administration of an oral solution of ranitidine in water containing different amounts of PEG 400 (**b**) (92). Thus, while PEG 400 affected the secretory pathway of ranitidine in a concentration dependent manner, its impact on oral bioavailability was only slightly evident in male subjects.

(107) corresponded with their reduced oral bioavailability; but not for the complexation of phenylpropanolamine with croscarmellose sodium (CCS) (108). These observations of whether drug-excipient complexation influences *in vitro* drug release and *in vivo* absorption depends on a multitude of factors, including the relative extent and strength of complexation. Since only the free form of the drug can pass through biological membranes, drug absorption is dependent upon the equilibrium between the free and drug complex (109,110). These aspects are discussed in more detail in below section on nonspecific drug excipient binding using an unrelated example (111).

The correlation of dissolution with drug absorption depends on the biorelevance and discriminatory nature of the dissolution method (112), the extent of difference in the rate of drug release caused by the excipient, and whether the interaction observed in an *in vitro* dissolution test is relevant *in vivo* in the GI fluids. Establishing *in vitro in vivo* correlation (IVIVC) of drug release with drug absorption is highly valuable in drug product development, and has been reviewed elsewhere (113–117). In this paper, we discuss mechanistic basis of some of these interactions, that also form the basis of assessing their biorelevance.

Specific Drug-Excipient Binding

Complex formation has long been utilized to alter the physicochemical and biopharmaceutical properties of a drug, such as modification of solubility, dissolution rate, and absorption. In addition to changes in solubility and dissolution rate, a complexed drug can also have altered stability, molecular size, and diffusion coefficient. Complexes are usually pharmacologically inert and generally dissociate readily in the GIT or in the systemic circulation.

Cyclodextrin is a complexing agent that has been used to increase the bioavailability, solubility of poorly water soluble or unstable drugs (118–120). They are cyclic oligomers of glucose that have a lipophilic interior and hydrophilic exterior , which should enable the formation of inclusion complexes with hydrophobic drugs (121). Not all drug-cyclodextrin complexes, however, are inclusion complexes. Cyclodextrins have been widely used in pharmaceutical research and development and there are currently more than 30 marketed cyclodextrin pharmaceutical products (122,123). Cyclodextrins have shown to enhance the bioavailability of several drugs including griesofulvin (17), ursodeoxycholic acid(18), cinnarizine (19), acyclovir (20), artemesinin (21), glibenclamide (22), ibuprofen (23), nifedepine (24), and theophylline (124).

The dissolution of ibuprofen and ketoprofen was increased when they were formulated with N-methylglucamine. This was considered to be a result of formation of complex of ibuprofen with N-methylglucamine. However, the possibility of formation of water soluble salts resulting in enhanced dissolution could not be ruled out (125).

Complexation of drugs can also decrease the rate of drug absorption and bioavailability of certain drugs due to formation of poorly soluble or poorly absorbable complexes. The poor bioavailability of these complexes can be attributed to their failure to dissociate at the site of absorption and large molecular size of complex that cannot diffuse through the cell membrane. For example, complexation of tetracycline with divalent cations like calcium can decrease its bioavailability (1). Phenobarbital formed an insoluble complex with PEG 4000 leading to its decreased absorption (126). Drug release rate may not always be indicative of oral absorption. For example, in one study prednisolone formulations with certain excipients showed increased *in vitro* dissolution, but the molecular weights of complex was too large to pass through the dialysis membranes, indicating low free drug available for absorption (127).

Formation of insoluble complexes was postulated to be the mechanism behind phenytoin toxicity that was observed in 1960s with a change in formulation. The patients being treated with phenytoin started showing various symptoms including double vision, vomiting, psychiatric disturbances, and high plasma phenytoin levels (128–130). The patients were given formulation of phenytoin containing lactose as excipient compared to initial formulations which contained calcium sulfate as an excipient. The formulations, containing lactose resulted in high blood levels of phenytoin. Calcium sulfate formulation of phenytoin interacts with phenytoin to form an insoluble complex having less membrane permeability through the GIT (128,130). Thus, a formulation of phenytoin sodium that contains calcium sulfate is expected to have lower drug absorption compared to the lactose formulation.

Insoluble or poorly soluble complexes of drugs can sometimes be micellar in nature. When surfactants polysorbate 80 and sodium lauryl sulfate was added to chlorpromazine formulations, a decrease in permeability was observed when tested *in vitro*. Complex formation between lauryl sulfate anions and chlorpromazine cations resulted in decreased permeability through a dimethyl polysiloxane membrane (131). This decrease in permeability of chlorpromazine in the presence of polysorbate 80 was attributed to the formation of insoluble micellar complexes.

Nonspecific Drug-Excipient Binding

Drug-excipient binding interactions are frequently observed during the development of immediate release oral solid dosage forms. These interactions frequently are ionic interactions that are facilitated by acid–base pairing of drug and the excipient in the dosage form. Ionic drug-excipient binding interactions are known to affect recovery of drug during analytical testing and drug release in dissolution tests. Whether drug-excipient binding interactions affect oral drug bioavailability is not well understood. It is commonly believed that a binding interaction that is not disrupted by physiological salt concentration in the dissolution medium can impact a drug's oral bioavailability. For example, the interaction between anionic weakly acidic excipient croscarmellose sodium and the cationic weakly basic drug phenylpropanolamine HCl resulted in a 40 % decrease in drug release *in vitro*, compared to formulation containing starch as excipient in distilled water (108). The interaction between croscarmellose sodium and the phenylpropanolamine HCl did not lead to a difference in oral drug absorption (108). The author hypothesized that the reason for non-biorelevance of the interaction was that the interaction was based on a nonspecific ion exchange mechanism.

Nonspecific ionic drug-excipient binding interactions are most commonly encountered in the use of ion exchange resins, such as sulfonated and/or carboxylated polystyrene backbone for binding basic drugs, for controlled/sustained drug delivery (132). For example, complexation of dextromethorphan (133) and phenylpropanolamine (134) with ion exchange resins reduces drug release that corresponds with altered oral bioavailability. Whether a release-modifying drug-excipient interaction results in altered oral bioavailability of a drug is conventionally determined on a case-by-case basis (111).

Drugs frequently interact with superdisintegrants such as croscarmellose sodium (CCS), crospovidone and sodium starch glycolate (SSG), which are commonly used in solid formulations to decrease disintegration time. Fransen *et al.* (135) investigated interactions between superdisintegrants and drugs of different physicochemical characteristics, and whether these interactions can affect their bioavailability following *in vivo* absorption, e.g., mucosal administration. The binding of sodium salicylate, naproxen, methyl hydroxybenzoate (methylparaben), ethyl hydroxybenzoate (ethylparaben), propyl hydroxybenzoate (propylparaben), atenolol, alprenolol, diphenhydramine, verapamil, amitriptyline and cetylpyridinium chloride monohydrate to the superdisintegrants and one unsubstituted comparator (starch) was studied spectrophotometrically. Authors observed ion exchange interactions between the anionic hydrogels formed by SSG and CCS, whereas the neutral crospovidone exhibited lipophilic interactions with the non-ionic substances. The authors postulated that amphiphilic drugs could interact with superdisintegrants to a greater extent than simply by ion exchange due to greater entropic gain caused by the aggregation of surfactant (drug) inside the polyelectrolyte (135).

There were almost no ionic interactions at physiological conditions compared to high ionic interactions at low salt concentrations. These studies indicated that drug interactions that may alter drug release *in vitro*, under certain conditions, may not happen under physiological conditions *in vivo*, and, hence, may not alter the bioavailability of a drug. Therefore, the *in vitro* experimental conditions used in studying drug-excipient interactions are important in the assessment of whether an interaction is likely to affect a drug's bioavailability.

The mechanistic basis of interaction of drugs with polyelectrolyte surfactants might include entropic gain by aggregation of a surface active drug, in addition to ionic interactions. Interactions between surface active (surfactant) drugs and polyelectrolyte excipients are greatly enhanced by aggregation of surfactant inside the polyelectrolyte rather than ion exchange interactions. In this scenario, the critical aggregation concentration, which is the concentration of surfactant needed for aggregation is normally lower than critical micellar concentration, drug substances having amphiphilic character could interact with superdisintegrants rather than by simple ion exchange interactions. This type of interaction cannot be eradicated by simply increasing the ionic strength leading to decreased drug release (135).

Reversibility of interaction at physiologically relevant salt concentration is currently the only criteria used to assess biorelevance of an ionic interaction in the dosage form. Nevertheless, amphiphilic drugs could interact with superdisintegrants to a greater extent than simply by ion exchange due to greater entropic gain caused by the aggregation of surfactant inside the polyelectrolyte (135). These interactions may not be overcome by ionic concentration in the dissolution medium. To seek guidance on the biorelevance of such interactions and to identify an objective test method that can be utilized to assess the relative strength of different drug-excipient binding interactions, we studied the interaction of a model basic amine drug with croscarmellose sodium (111). The interaction was probed with *in vitro* techniques such as Langmuir binding isotherm and isothermal titration calorimetry to assess the extent and strength of an interaction. The effect of this interaction on oral drug absorption was predicted by mathematical modeling of the interaction in the GI tract (Fig. 6), and compared to the results of an *in vivo* study in monkeys. The results of *in vivo* study confirmed modeling predictions and isothermal titration calorimetry (ITC) assessment that the drug-excipient interaction was weak and not likely to be biorelevant. Further, general guidance on whether a drug-excipient binding interaction is likely to be biorelevant was derived based on drug dose, pharmacokinetic parameters, and the strength of an interaction (Fig. 7). These simulations indicated that reversible and pH dependent weak drug-excipient binding interactions are unlikely to affect bioavailability of high dose drugs (111). These studies further indicated that ITC, Langmuir adsorption modeling, and pharmacokinetic simulation could be better tools to assess the biorelevance of drug-excipient binding interactions than ion displacement studies.

Drug Adsorption on Excipient Surface

Adsorption of drugs on excipient surface can alter the rate and extent of drug release in solution phase, thereby affecting its activity or bioavailability. Thus, hydrophilic silica aerogels enhanced the dissolution of poorly soluble drugs ketoprofen and griseofulvin by adsorption from their solution in supercritical carbon dioxide (136). Dissolution rate of a poorly water soluble drug fenofibrate was increased by its adsorption to silica (137), which was done by dissolving the drug in supercritical carbon dioxide and then depressurizing the solution onto silica.

Adsorption of drugs on excipients that promote wetting can enhance drug release. Drugs like griseofulvin, indomethacin, prednisone showed an increased dissolution rate when formulated with colloidal magnesium aluminum trisilicate (138). This was attributed to the binding of these drugs to colloidal magnesium aluminum silicate by weak van der waals forces. Also, the hydrophilic and swelling properties of colloidal magnesium aluminum silicate enhanced wetting of the drugs resulting in faster release of the drug.

Adsorptive capacity and surface area of the excipient determine the extent of drug adsorption. Thus, when the adsorption of diazepam was investigated on magnesium tricilicate, MgO, $Al(OH)_3$, $CaCO_3$, $MgCO_3$, $(BiO)_2CO_3$, bismuth subsalicylate, talc, $CaHPO_4$, magneisum stearate, kaolin, and charcoal, magnesium trisilicate and charcoal exhibited the highest adsorptive capacity for the drug – which could be related to surface area of the excipient. The presence of a specific interaction between diazepam and surface sites of the adsorbing materials was suggested (139).

While adsorption can lead to increase in the rate of drug release due to increase in the surface area of the drug exposed to the solution phase, it can also lead to reduced drug release in cases of strong drug binding to an insoluble excipient. For example, the antimicrobial activity of cetylpyridinium chloride decreased when it was formulated with magnesium stearate as tablet-based lozenges (140). This decrease in activity was attributed to ionic interaction facilitated adsorption of cetylpyridinium chloride cations on magnesium stearate anions. There was also a decrease in absorption of dicumarol upon coadministration with excipients colloidal magnesium aluminum silicate, aluminum hydroxide, starch, and talc (141). Adsorption of dicumarol to these excipients was postulated to be the reason for reduced oral drug bioavailability. Similar results were obtained for the oral absorption of chlordiazepoxide, an anxiolytic agent, due to its adsorption to talc (142). The

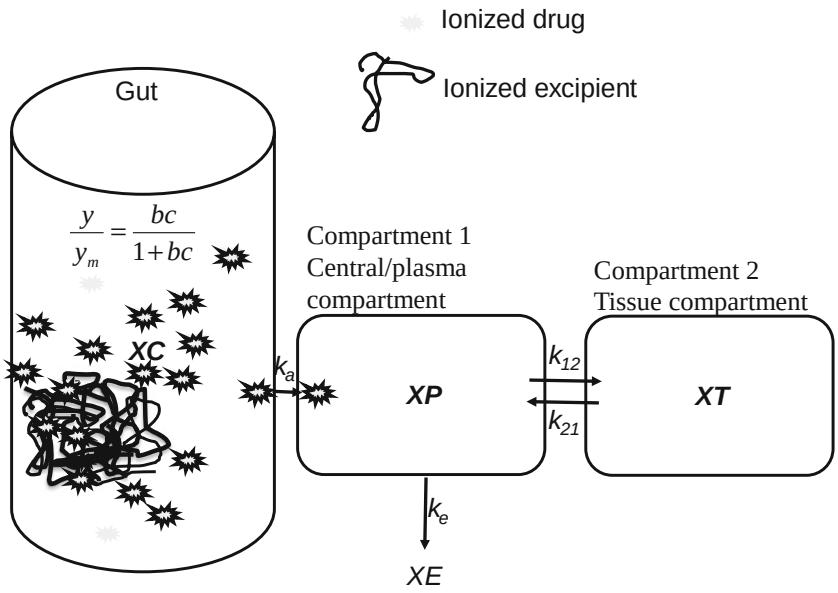

Fig. 6 Schematic of a model for assessing the effect of drug-excipient binding interaction on oral absorption and plasma pharmacokinetics (111). This figure shows the presence of both the drug and the polymeric excipient in the gut compartment with the Langmuir binding isotherm equation and the transport of drug between the gut, the central/plasma compartment (compartment 1), the tissue compartment (compartment 2), and the elimination pathways. The equations shown in these compartments are for a typical two compartmental pharmacokinetic model.

amount of talc used in the formulation was much higher than commonly used. This property of excipients such as activated charcoal is important to their use as antidote for overdose of drugs.

The physicochemical forces responsible for drug adsorption on the excipient surface determine the strength of binding. For example, ketotifen fumarate, an orally active prophylactic agent used for the management of bronchial

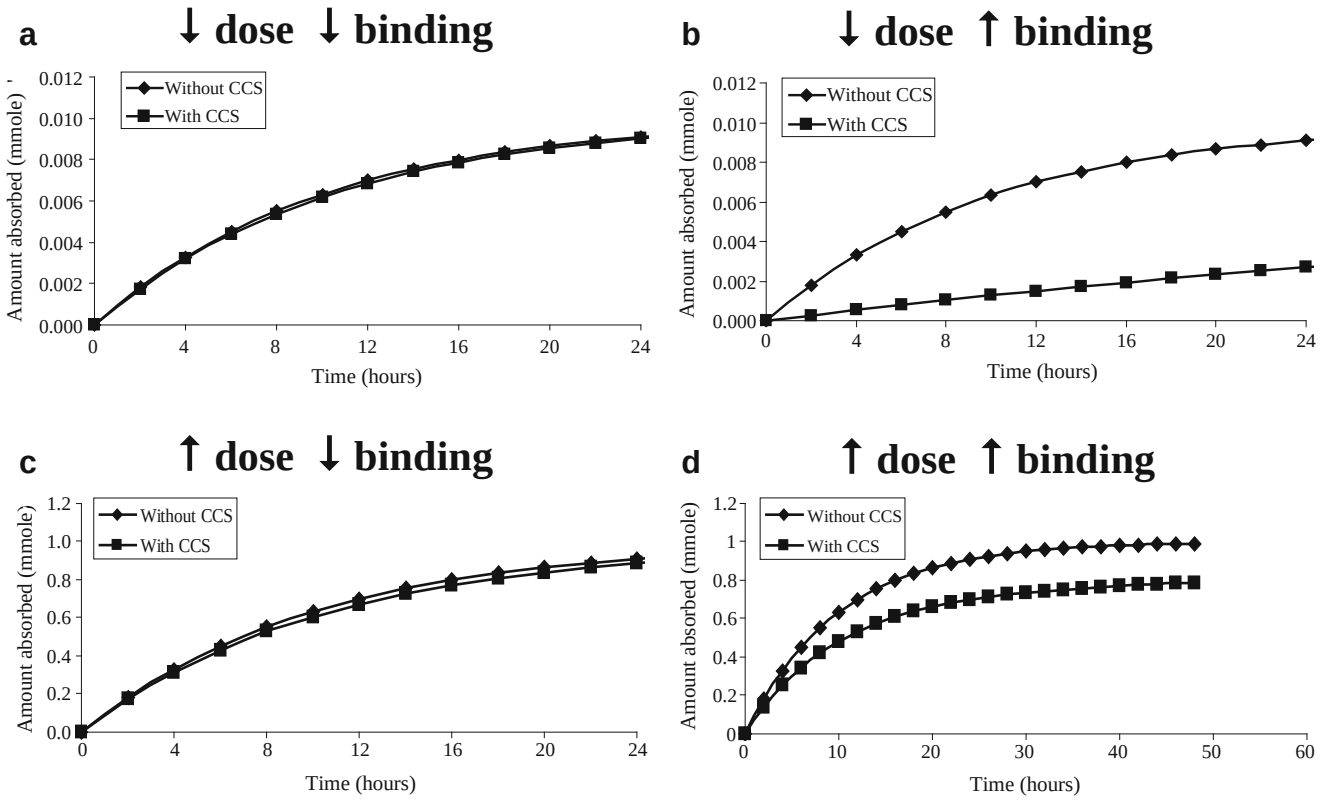

Fig. 7 Modeling the effect of drug-CCS binding on oral drug absorption (111). Simulated amount of drug absorbed as a function of time for a (**a**) low dose drug with low CCS binding affinity and capacity (using parameters BA=5 mg/tablet, CCS=5 mg/tablet, y_m=0.5 mmole BA/mmole CCS, b=1 mM^{-1}, and k_a=0.1 h^{-1}), (**b**) low dose drug with high CCS binding affinity and capacity (using parameters BA=5 mg/tablet, CCS=5 mg/tablet, y_m=2.0 mmole BA/mmole CCS, b=50 mM^{-1}, and k_a=0.1 h^{-1}), (**c**) high dose drug with low CCS binding affinity and capacity (using parameters BA=500 mg/tablet, CCS=30 mg/tablet, y_m=0.5 mmole BA/mmole CCS, b=1 mM^{-1}, and k_a=0.1 h^{-1}), and (**d**) high dose drug with high CCS binding affinity and capacity (using parameters BA=500 mg/tablet, CCS=30 mg/tablet, y_m=2.0 mmole BA/mmole CCS, b=50 mM^{-1}, and k_a=0.1 h^{-1}).

asthma and allergic disorders, adsorbs onto microcrystalline cellulose, croscarmellose sodium and pregelatinized starch (143). The affinity of binding was in the order croscarmellose sodium, followed by microcrystalline cellulose, and then pregelatinized starch. Data fit to the Freundlich adsorption isotherm indicated that adsorption was a continuous function of the initial drug concentration. Drug adsorption to croscarmellose sodium was pH dependent with negative/exothermic heat of adsorption ($\triangle H$) (143). These suggest that the involvement of ionic interactions increases the strength of interaction.

The correlation of adsorption affecting drug release and passive membrane permeation as the mechanistic route of reduced oral bioavailability was assessed using diffusion of chlorpromazine through a dimethyl polysiloxane membrane as an experimental model. Chlorpromazine adsorption to the surface of talc and kaolin resulted a decrease in membrane permeability of chlorpromazine (131).

The impact of adsorption of drugs to excipients on oral drug bioavailability becomes most significant in the case of low solubility drugs that are passively absorbed upon oral administration, in addition to the solubility of the excipient and the strength of adsorption.

MODIFICATION OF BIORELEVANT DRUG PRODUCT PROPERTIES BY EXCIPIENTS

Excipients are primarily utilized in dosage form development to impart desirable characteristics to the dosage forms. These characteristics include large scale manufacturability, stability, and bioavailability. While almost all excipients may interact with each other, the drug substance, and the biological systems in different functional ways to affect each of these characteristics, certain excipients and their manner of use (processing) predominantly influence the bioavailability of drug by affecting important dosage form characteristics.

Disintegration

Excipients, such as croscarmellose sodium, crospovidone, sodium starch glycollate, and starch are routinely utilized to induce rapid dosage form disintegration in the presence of aqueous fluids, thereby enhancing the rate and extent of drug dissolution. This can enhance the bioavailability of drugs where disintegration and dissolution are the rate limiting steps for absorption. Thus, tablet formulations of the antihelmintic agent praziquantel that had higher disintegration time showed reduced oral bioavailability (144). Also, the dissolution of anti-diabetic drug tolbutamide was enhanced when it was spray dried in combination with a disintegrant, partly pregelatinized corn starch (145). The authors hypothesized that the drug was released more rapidly from the spray died particles due to rapid disintegration caused by swelling of partly pregelatinized corn starch. In addition, the presence of the drug in smaller crystalline form after spray drying could play a role in increased rate of drug dissolution from this system.

In addition, drug release properties are substantially affected by excipient dissolution characteristics in intimate drug-excipient mixtures. For example, the poorly water soluble drug gliclazide showed varying dissolution rates with water soluble excipients lactose, mannitol, sorbitol, maltitol, and sodium chloride. While drug dissolution rate increased in the presence of all water soluble excipients, the order of dissolution rate was mannitol > lactose > maltitol > sorbitol > sodium chloride (146). Interestingly, reducing the carrier particle size decreased the dissolution rate of the drug.

For pH-dependent delayed release dosage forms, such as enteric coated tablets, disintegration of the solid dosage form must be preceded by dissolution of the film. In addition to the effect of pH on film dissolution, interaction of film components with other excipients in the dosage form or components of food or the gastric fluid can lead to changes in disintegration characteristics. For example, Cilurzo *et al.* observed reduced disintegration of poly(methacrylic acid-methyl methacrylate) polymer coating on acetaminophen tablets in the presence of divalent cations, Ca^{2+}, Mn^{2+} and Zn^{2+} (147). This phenomenon was attributed to high affinity complexation between the studied metal ions and the drug. The authors concluded that ingestion of such metal ions at high concentrations can affect drug release from such dosage forms.

Co-processing

Co-processing refers to different techniques that may be utilized to modify surface properties of APIs by preparing their intimate mixtures with one or more excipients. These techniques do not lead to the chemical modification of the API. Methods commonly used for co-processing include spray drying and co-precipitation. These techniques include spray dried amorphous solid dispersions of two components. For example, Babcock *et al.* reported solid amorphous dispersion of 50 % torcetrapib in 50 % HPMCAS with unique degrees of substitution of hydroxypropoxy, methoxy, acetyl, and succinoyl groups to improve drug solubility, dissolution rate, and physical stability. This composition resulted in enhanced *in vivo* drug release in dogs and higher relative bioavailability, compared to the amorphous drug.

Co-processing is commonly utilized to modify excipient properties (148). For example, Prosolv Easytab® is a co-processed dry binder constituting microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate and sodium stearyl fumarate that improves the compaction and disintegration properties of tablets (149), co-processing of α-lactose

monohydrate with corn starch improved its flow and compressibility (150), and co-processing of microcrystalline cellulose with silicon dioxide (151,152) improves compactibility, strength, and disintegration time of tablets. The use of excipients with modified properties, such as higher strength and lower disintegration time at low tablet hardness, can help optimize drug bioavailability of certain drugs.

Modification of biorelevant surface properties by co-processing can alter drug bioavailability. For example, co-grinding of nifidepine with hydrophilic carriers (partially hydrolyzed gelatin, PVP, sodium dodecyl sulfate (SDS), hydroxypropyl methylcellulose (HPMC), PEG, urea or Pluronic F108 enhanced its dissolution rate (153). The increase in dissolution rate was not only due to particle size reduction but also from the ability of some carriers such as PVP and HPMC to prevent reaggregation of particles. Also, PVP, HPMC, and PHG formed a powder with amorphous drug and they also improved the wettability of the ground products.

In addition to improved wettability and surface area, co-processing with bioadhesive excipients can lead to longer residence time of the drug at the absorptive surface resulting in improved bioavailability. The selection of co-processing technique can significantly influence the outcome in terms of drug bioavailability. For example, co-processing of a mucoadhesive combination of a maize starch and a cross-linked acrylic acid-based polymer (Carbopol® 974P) on metoprolol tartrate enhanced its nasal drug delivery in rabbits when physical mixture of a combination of drug and mucoadhesive polymers was freeze dried compared to freeze drying of a co-spray dried powder (154). The enhanced bioavailability effect of using a physical mixture for freeze drying was attributed to deprotonation of poly(acrylic acid) during neutralisation of the dispersion prior to freeze-drying, leading to repulsion of the ionised carboxyl groups and a lower interaction between poly(acrylic acid) and starch. Thus, freeze drying resulted in a less compact matrix upon hydration of the polymer and allowed faster diffusive transport of metoprolol tartrate from the matrix. The use of a spray dried dispersion for freeze drying, on the other hand, might prevent molecular mobility to achieve the same degree of porosity.

Preparation of solid dispersions of drugs is commonly utilized to improve drug dissolution rate by changing the form and/or particle size of the drug, while also physically stabilizing such a high energy form in a matrix in the solid state. Solid dispersions have been prepared by melt fusion, hot melt extrusion, spray drying, freeze drying, and supercritical fluid precipitation using hydrophilic carriers such as PVP and HPMC (155–157). Solid dispersions have been extensively used to prepare amorphous drugs that lead to improved dissolution rate and bioavailability (158–161).

In addition, PEG's have been commonly used in the preparation of microcrystalline solid dispersions. PEG can disaggregrate in a physical mixture, thereby reducing the electrostatic binding and aggregation of drug particles, resulting in enhanced dissolution (162). Several solid dispersions have been formulated with different molecular weights of PEGs and drugs like nifedepine (163), norfloxacin (164), piroxicam (165), oxodipine (162), griseofulvin (162), and ibuprofen (166). Most drugs tend to form crystals with PEG when formulated as solid dispersions. The mechanism of increase in dissolution in these cases is either an increase in the surface area of the drugs or decrease in the electrostatic interaction and aggregation between drug particles (162,165).

There are also instances where formation of a solid dispersion did not improve the extent of drug absorption. For example, when indomethacin was formulated with hydroxyl-propyl cellulose as an amorphous solid dispersion, there was a 30-fold increase in dissolution rate compared to drug alone (157). The solid dispersion showed faster rate of oral drug absorption, but the extent of absorption of drug from the solid dispersion was similar to that of drug alone. This behavior is likely due to high permeability (167) and low solubility (168) of the compound, indomethacin being a BCS class II drug, thus showing dissolution rate limited absorption. Thus, while improving drug dissolution rate by formulation of an amorphous solid dispersion provided advantage of rapid absorption, the extent of drug absorption is complete irrespective of the drug release rate from the formulation.

Solid dispersions can also be formulated as ternary systems. Ternary systems include another excipient in addition to the hydrophilic carrier, such as a surfactant or a pH modifier (e.g. citric acid, malic acid, fumaric acid, succinic acid, tartaric acid) (169,170), which can further enhance drug release by reducing contact angle between the drug and the solvent of the disperse system. Different surface active agents that have been used in formulation of solid dispersions include Tween-20, polysorbate-80, phosphatidylcholine, and sodium lauryl sulfate (156,162,163,166,171–175). Subsequent *in vivo* studies of some of these formulation showed enhanced bioavailability (175).

CONCLUSIONS

Excipients are an integral part of any formulation and even though they are considered to be inert, their interaction with the active ingredient will affect its bioavailability either favorably or adversely. In this paper, we reviewed some of the known mechanisms of the impact of excipients on drug bioavailability. The extent to which drug bioavailability is affected by these interactions would vary on a case-by-case basis depending upon factors such as the potency and dose of the drug, therapeutic window, site of absorption, rate limiting

factor in drug absorption (e.g., permeability or solubility limited), whether drug metabolism, efflux, complexation, or degradation at the site of absorption plays a role in determining its bioavailability. Nonetheless, a mechanistic understanding of drug-excipient interactions and their impact on drug release and absorption can help develop solid dosage forms that exhibit optimum drug bioavailability.

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