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Lipid-associated oral delivery: Mechanisms and analysis of oral absorption enhancement

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ABSTRACT

The majority of newly discovered oral drugs are poorly water soluble, and co-administration with lipids has proven effective in significantly enhancing bioavailability of some compounds with low aqueous solubility. Yet, lipid-based delivery technologies have not been widely employed in commercial oral products. Lipids can impact drug transport and fate in the gastrointestinal (GI) tract through multiple mechanisms including enhancement of solubility and dissolution kinetics, enhancement of permeation through the intestinal mucosa, and triggering drug precipitation upon lipid emulsion depletion (*e.g.*, by digestion). The effect of lipids on drug absorption is currently not quantitatively predictable, in part due to the multiple complex dynamic processes that can be impacted by lipids. Quantitative mechanistic analysis of the processes significant to lipid system function and overall impact on drug absorption can aid in the understanding of drug-lipid interactions in the GI tract and exploitation of such interactions to achieve optimal lipid-based drug delivery. In this review, we discuss the impact of co-delivered lipids and lipid digestion on drug dissolution, partitioning, and absorption in the context of the experimental tools and associated kinetic expressions used to study and model these processes. The potential benefit of a systems-based consideration of the concurrent multiple dynamic processes occurring upon co-dosing lipids and drugs to predict the impact of lipids on drug absorption and enable rational design of lipid-based delivery systems is presented.

1. Overview

Lipid-based systems have garnered a large amount of excitement based on their ability to markedly increase overall absorption of poorly water soluble drugs, potentially resulting in several-fold increases in bioavailability [1–3]. However, there are few examples of commercial lipid-based formulations (LBFs) [4]. This is due, in part, to lack of mechanistic, quantitative guidance regarding when lipid-based systems will enhance bioavailability and how to best formulate drugs to achieve the desired impact. Lipid-based delivery systems can also potentially result in no enhancement, or even a reduction in bioavailability [5–7]. There have been many excellent reviews on lipid-based delivery systems [8–11]. We focus specifically in this review on the quantitative analysis and modeling of the mechanistic aspects of lipid-based formulation function. The key questions that we seek to answer include: 1. What experimental techniques can be applied to understand mechanisms of LBF function, and what key insights have these techniques revealed? and 2. How can modeling be used to relate mechanistic analyses *in vitro* to *in vivo* function and predict the overall impact on bioavailability? Moreover, much of the noted methodology and associated literature is also applicable to food-based lipids, which can also significantly impact oral bioavailability, and in fact share common mechanisms of function with lipid-based drug carriers.

2. The importance and under-utilization of LBFs

As more than 50% of commercially available oral drugs are poorly water soluble (PWS), effective solubilization technologies can make a significant impact on oral drug delivery, potentially reducing the required dose and enabling oral delivery of compounds that may otherwise require injection. While the solubility of some PWS compounds may not be increased by lipids, LBFs have shown efficacy in enhancing the bioavailability of several poorly water-soluble drug compounds as well as nutritive supplements [12–20]. Despite this, commercial LBF-formulated drugs constitute only 2–4% of the pharmaceutical market, according to a survey conducted in the United Kingdom, United States, and Japan [21]. The relatively low number of marketed LBFs, despite the potentially large benefits they offer in oral drug delivery, is due to several factors. For example, manufacturing processes for LBFs can employ complex and costly instruments and procedures [21]. Not all compounds are suitable for LBF formulation due to low solubility or stability

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issues in the formulation components. Additionally, LBFs can result in drug precipitation upon dilution in gastric fluids, thus failing in their intended function of maintaining drug in solution and consequently resulting in poor bioavailability [22,23]. Moreover, there is an incomplete mechanistic understanding of and ability to predict LBF function in the gastrointestinal (GI) tract. Predictability of the effect of lipids on overall drug absorption is often elusive due to the multiple concurrent dynamic processes impacted by orally ingested lipids. This last challenge is the focus of this review.

Ingestion of LBFs triggers a cascade of processes that change the physical and chemical nature of the gastrointestinal milieu and directly affect the behavior of oral compounds in the GI tract. The digestion of lipids is significant to LBF function due to impact on both oil emulsion droplets and other colloidal species (most notably bile micelles) into which digestion products partition. Interaction of lipid digestion products with micelles was first observed by Patton and Carey in 1979 [24]. Size and structure of colloids are important to study as they directly affect oral drug partitioning and capacity to serve as a vehicle for drug transport along the GI tract [2]. The insertion of lipid digestion products, such as fatty acids (FA) and monoglycerides (MG) into bile-originating colloids (*e.g.*, micelles, vesicles) causes them to swell, changing the effective volume, chemical nature, and solubilization capacity of the colloidal phase during digestion. The altered colloidal phase can impact drug release kinetics from LBFs into the colloid-rich aqueous intestinal lumen. The increased drug concentration in the aqueous lumen serves as a driving force for drug absorption, often resulting in enhanced bioavailability. Recent studies have shown that fast depletion of the lipid (triglyceride) phase relative to drug release from formulation can result in precipitation [25], potentially making re-solubilization the rate-limiting step in overall absorption. A mechanistic representation of these concurrent processes that may affect overall drug absorption are shown in Fig. 1.

Lipids are not only used in drug delivery, but are also a major component of food consumed daily. Thus, understanding the mechanisms that govern lipid-drug interactions in the GI tract would also aid in predicting the food effect on drug absorption, and could allow rational development of food-drug dosing schemes that enhance drug bioavailability. Several marketed drugs known to have a positive food effect on absorption and bioavailability, including oral chemotherapeutics, are taken under fasting conditions despite potential food benefits of reducing dosing and local GI side effects [26]. One reason patients are instructed to take drugs in the fasted state is concern over varying efficacy and potential safety issues associated with the high variability in dietary intake and its impact on pharmacokinetic (PK) profiles. Telaprevir, a Hepatitis C oral drug, was prescribed in conjunction with a meal containing 20 g of fat [27]. However, production of telaprevir was discontinued due to failing demand in relation to competition from other hepatitis C treatments. Enhanced mechanistic understanding and ability to predict drug-lipid and drug-food interactions could enable more effective oral delivery of drug compounds as well as nutritive supplements.

Similar to LBFs, co-administration with lipid-rich food can allow enhanced solubilization capacity of the aqueous intestinal milieu. The colloidal structures present and evolving during lipolysis directly affect dissolution kinetics, as dissolved drug can partition into them. Fig. 2 shows the cascade of processes affecting the absorption of a solid drug in the presence of food-associated lipids. It is important to note that the presence of food also impacts other physiological factors of importance to pharmacokinetics such as gastric emptying, blood flow, and pH [28].

There are several other proposed processes, not explicitly shown in Figs. 1 and 2, by which lipids affect oral drug absorption. For example, a study by Yeap et al. indicated that release of lipids from bile micelles at the unstirred water layer adjacent to the intestinal epithelium, and their absorption by enterocytes, can result in drug supersaturation and an associated high driving force for drug absorption [29]. Other studies have indicated that lipid emulsifiers such as bile salts and excipients can inhibit drug efflux transporters, increasing effective drug intestinal permeability and overall drug absorption [3,30]. Another proposed mechanism by which lipids can mediate drug absorption is *via* engulfment of the nano-sized colloids by enterocytes through endocytosis, resulting in an increase in drug absorption relative to dosing of drug alone [31]. These examples attest to the complexity of understanding oral drug behavior in the GI tract upon co-dosing with lipids.

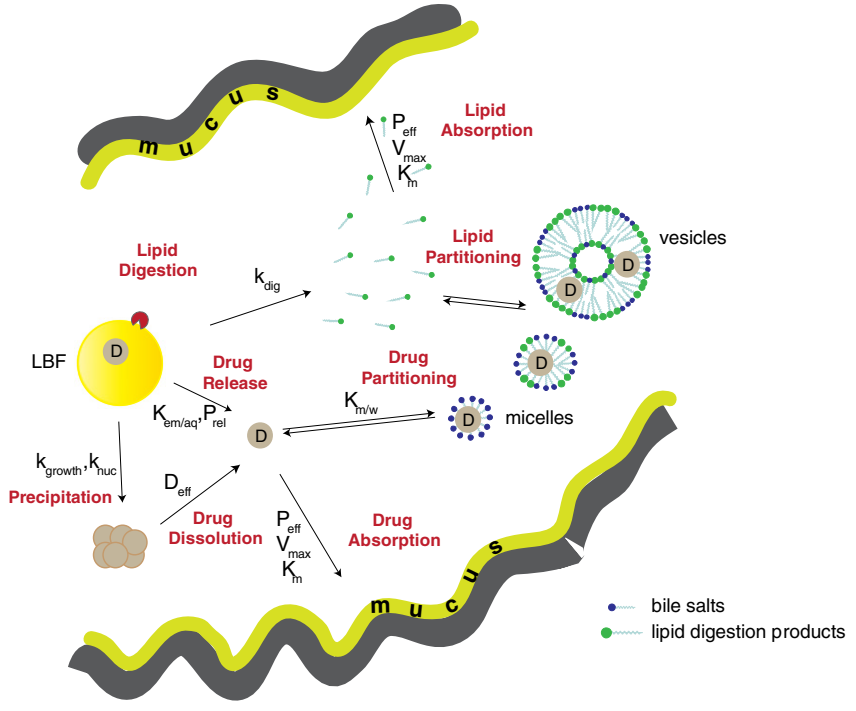

Fig. 1. Processes affecting oral drug absorption when a drug is dosed formulated in a LBF in the GI tract. Kinetic parameters utilized to model each process are also indicated in black and described in Section 4.