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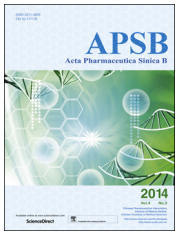

REVIEW

Pharmacokinetic aspects and *in vitro–in vivo* correlation potential for lipid-based formulations

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Abstract Lipid-based formulations have been an attractive choice among novel drug delivery systems for enhancing the solubility and bioavailability of poorly soluble drugs due to their ability to keep the drug in solubilized state in the gastrointestinal tract. These formulations offer multiple advantages such as reduction in food effect and inter-individual variability, ease of preparation, and the possibility of manufacturing using common excipients available in the market. Despite these advantages, very few products are available in the present market, perhaps due to limited knowledge in the *in vitro* tests (for prediction of *in vivo* fate) and lack of understanding of the mechanisms behind pharmacokinetic and biopharmaceutical aspects of lipid formulations after oral administration. The current review aims to provide a detailed understanding of the *in vivo* processing steps involved after oral administration of lipid formulations, their pharmacokinetic aspects and *in vitro in vivo* correlation (IVIVC) perspectives. Various pharmacokinetic and biopharmaceutical aspects such as formulation dispersion and lipid digestion, bioavailability enhancement mechanisms, impact of excipients on efflux transporters, and lymphatic transport are discussed with examples. In addition, various IVIVC approaches

Abbreviations: ADME, absorption/distribution/metabolism/elimination; AUC, area under the curve; BCS, biopharmaceutics classification system; BDDCS, biopharmaceutics drug disposition classification system; CACO, human epithelial colorectal adenocarcinoma cells; C_{max}, maximum plasma concentration; CMC, critical micellar concentration; CYP, cytochrome; DDS, drug delivery systems; FaSSGF, fasted-state simulated gastric fluid; FaSSIF, fasted-state simulated intestinal fluid; FeSSIF, fed-state simulated intestinal fluid; GIT, gastrointestinal tract; IVIVC, *in vitro in vivo* correlation; LCT, long chain triglyceride; LFCS, lipid formulation classification system; log *P*, *n*-octanol/water partition coefficient; MCT, medium chain triglyceride; MDCK, Madin–Darby canine kidney cells; NCE, new chemical entity; P-app, apparent permeability; P-gp, permeability glycoprotein; SCT, short chain triglyceride; SEDDS, self-emulsifying drug delivery system; SIF, simulated intestinal fluid; SMEDDS, self-microemulsifying drug delivery system; SNEDDS, self-nanoemulsifying drug delivery system; Vit E, vitamin E

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towards predicting *in vivo* data from *in vitro* dispersion/precipitation, *in vitro* lipolysis and *ex vivo* permeation studies are also discussed in detail with help of case studies.

1. Introduction

Approximately 40% of the currently marketed formulations and more than 70% of pipeline molecules from top pharmaceutical companies today contain drugs that are poorly soluble[1,2]. However, the superior therapeutic efficacy of these poorly soluble molecules (BCS-II and IV) may be the reason that they cannot be always avoided in drug development, and optimal formulation strategies are required to handle them so as to enhance their availability in systemic circulation. Even though there are conventional approaches available for handling poor aqueous solubility, very often advanced drug delivery systems (DDS) are required for developing a stable and acceptable dosage form. The most important category in advanced DDS is lipid-based formulations such as lipid solutions, lipid suspensions and self-emulsifying lipid formulations[3,4]. The lipid-based formulations in general are well recognized as a frontline formulation technology to handle the poorly water-soluble compounds. These systems can be designed to present and keep the drug substance in a solubilized state thereby preventing the solubilization and subsequent dissolution step of a poorly water-soluble compound. The extensive research work done by Pouton and Porter[5,6] in the area of lipid formulation development has resulted in increased awareness and understanding about lipid formulations in both industry and academia.

The preparation of lipid-based formulations is considered an easy process when compared with other solid oral dosage forms such as tablets and capsules. The excipients used in lipid formulations include lipids (natural/synthetic origin), surfactants (hydrophilic/hydrophobic), hydrophilic solvents and co-solvents. Once prepared, the lipid-based systems can be administered as solutions after dilution with suitable juices or dietary fluids or in the form of liquid-encapsulated soft gelatin capsules or liquid-filled hard gelatin capsules[7]. The general process for development of lipid formulations along with the pharmacokinetic importance of each step is presented in Fig. 1. Due to the wide variety of excipients available for preparing lipid-based formulations, Pouton et al.[8] introduced a lipid formulation classification system (LFCS) in order to harmonize the understanding about these formulations. As per LFCS, the lipid-based formulations can be classified into four different categories: Types-I, II, III (A and B) and IV. The compositions of these formulation types along with their characteristics, advantages, disadvantages and pharmacokinetic aspects are presented in Table 1. Out of these four systems, Type-II formulations are named as self-emulsifying drug delivery systems (SEDDS, coarse emulsions) and Type-III formulations are named as self-microemulsifying drug delivery systems (SMEDDS, microemulsions) due to their ability to form instantaneous emulsions with minimal energy input.

Out of the lipid-based formulations available in the present market, Neoral® and Sandimmun Neoral® are considered to be the first commercial successes[9]. The complete list of all commercially available lipid formulations is outlined by Strickley[10]. The data clearly indicate that despite the multiple advantages and extensive research work in academia and industries, there are very few commercially successful products available in the market today. From one side of the coin, this problem can be attributed to scale-up and stability challenges, marketability concerns, lack of in-house soft gelatin manufacturing capabilities, and non-acceptability of soft gelatin capsules in a few countries. From the other side of the coin, critical problems arise due to the lack of availability of *in vitro* tests that can describe the *in vivo* behavior of the lipid formulations. There are numerous *in vivo* ADME processes involved after intake of lipid-based formulations which make the concepts more complex for designing the *in vitro* tests. Additionally no clear IVIVC relationship has been established for lipid-based formulations, indicating the difficulties in correlating *in vitro* results with *in vivo* behavior. This clearly indicates the need for understanding the pharmacokinetic aspects and other related systemic processes for lipid-based formulations. An extensive literature review revealed that a few articles have described the pharmacokinetic aspects from different perspectives but no single article described all pharmacokinetic and IVIVC aspects of lipid-based formulations in detail. In this context, the objective of the present article is to outline the pharmacokinetic aspects and *in vivo* processing steps occurring after administration of lipid formulations so as to provide a better understanding of the lipid-based formulations from a pharmacokinetic point of view. In addition, multiple IVIVC concepts and methodologies are covered which can further aid in development of successful *in vitro* prediction tests.

2. Pharmacokinetic aspects of lipid-based formulations

2.1. *In vivo drug solubilization and processing*

Even though in the present context lipids are described as core excipients in the lipid-based formulations, they are an essential group of constituents in the food we take everyday. The processing of lipids containing drug is essentially similar to that of the dietary lipids present in food or in any other related source. Ingestion of lipid formulations results in increase in the total amount of lipids available in GI tract. These larger quantities of lipid (>2 g, equivalent to two soft gelatin capsules) are capable of stimulating secretion of additional bile through gallbladder contraction thereby increasing the luminal concentration of bile salts[11]. The increased levels of endogenous bile salts, phospholipids and cholesterol in the presence of lipid and surfactants provide a lipidic microenvironment to form emulsion droplets which will further transform into various components such as vesicular and micellar phases. The poorly water-soluble drug initially dissolved in the formulation will partition into these vesicular and micellar phases. The drug then will partition into the micelles formed due to the combination of bile salts, phospholipids and cholesterol which in turn are called "mixed micelles"[12]. The formation of mixed micelles is an important step for solubilization