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Oral lipid-based formulations ☆

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Abstract

Poor drug solubility remains a significant and frequently encountered problem for pharmaceutical scientists. The ability of lipid-based formulations to facilitate gastrointestinal absorption of many poorly soluble drug candidates has been thoroughly documented in the published literature. However, a considerable gap exists between our knowledge of this technology and the know-how required for its application. This commentary provides a comprehensive summary of the development, characterization, and utilization of oral lipid-based formulations, from both physicochemical and biopharmaceutical perspectives. The characteristics of currently available lipid excipients are reviewed in context of their application to the basic lipid-based formulation modalities. The fundamental concepts of in vitro and in vivo evaluation of lipid-based formulations are summarized followed by a forward-looking summary of unrealized opportunities and potential limitations to more widespread use of this technology.

Keywords: Lipid-based formulations; Drug solubility; Lipid excipients; Lipid digestion; Drug absorption; Surfactant; Drug delivery

Contents

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1. Introduction

It has been estimated that anywhere from 40 to as much as 70 percent of all new chemical entities (NCE) entering drug development programs possess insufficient aqueous solubility to allow consistent gastrointestinal absorption of a magnitude sufficient to ensure therapeutic efficacy [1]. The poor and variable absorption afforded these compounds by conventional formulations can be complicated by a significant, positive food effect, potentially resulting in unexpected toxicity while making development more costly and difficult [2–4]. Solubilization of a drug in the gastrointestinal tract (GIT) is dependent upon the complex interplay of multiple factors, including the presence of food, and thus is an inherently variable phenomenon often resulting in erratic absorption of poorly soluble drugs [5]. By eliminating the variables of pre-absorptive gastrointestinal (GI) solubilization and the effects of dietary status from the equation, lipid-based formulations not only improve but normalize drug absorption, which is particularly beneficial for low therapeutic index drugs [3]. These formulations can also enhance drug absorption by a number of ancillary mechanisms, including inhibition of P-glycoprotein-mediated drug efflux and pre-absorptive metabolism by gut membrane-bound cytochrome enzymes [6,7], promotion of lymphatic transport, which delivers drug directly to the systemic circulation while avoiding hepatic first-pass metabolism [8,9], and by increasing GI membrane permeability [10]. Although the manufacturing processes used for lipid-based formulation products are considerably slower than those of conventional tablets or capsules, this disadvantage is offset by the minimization of other process support activities required to develop and manufacture conventional dosage forms. For example, hard gelatin or HPMC encapsulated lipid formulations are prepared from a single bulk solution that can be filled, sealed and converted into the package-ready, final dosage form in as little as 10 min. And there is no need for coating to address product appearance or to provide taste-masking properties, thus eliminating the need for a complex series of additional operations. In comparison, development of conventional solid dosage forms requires the identification of a stable, crystalline form of the drug substance which often necessitates lengthy and sometimes fruitless searches for salts or developable crystalline forms of the drug. Finally, since the liquid-filling process used to prepare lipid-based dosage forms is essentially dust-free after the initial preparation of the bulk filling solution, the need for the installation, running and maintenance of costly containment facilities and the associated clean-up procedures required for highly-potent drug substances is minimized.

This review will provide a high-level summary of the development, characterization, and utilization of oral lipid-based formulations, from both physicochemical and biopharmaceutical perspectives.

2. Currently marketed oral lipid-based formulation products

As determined in a recently published survey by Strickley, oral lipid-based formulations have been marketed for over 2 decades and currently comprise an estimated 2–4% of the commercially available drug products surveyed in 3 markets worldwide [11,12]. These products accounted for approximately 2% (21 products total) of marketed drug products in the United Kingdom, 3% (27 products total) in the United States of America, and 4% (8 products total) in Japan. Strickley's survey revealed that the most frequently chosen excipients for preparing oral lipid-based formulations were dietary oils composed of medium- (e.g., coconut or palm seed oil) or long-chain triglycerides (e.g., corn, olive, peanut, rapeseed, sesame, or soybean oils, including hydrogenated soybean or vegetable oils), lipid soluble solvents (e.g., polyethylene glycol 400, ethanol, propylene glycol, glycerin), and various pharmaceutically-acceptable surfactants (e.g., Cremophor® EL, RH40, or RH60; polysorbate 20 or 80; D-α-tocopherol polyethylene glycol 1000 succinate (TPGS®); Span 20; various Labrafils®, Labrasol®, and Gelucires®). These formulations, which took the form of either bulk oral solutions or liquid-filled hard or soft gelatin capsules, were applied in instances where conventional approaches (i.e., solid wet or dry granulation, or water-miscible solution in a capsule) did not provide sufficient bioavailability, or in instances in which the drug substance itself was an oil (e.g., dronabinol, ethyl icosapentate, indometacin farnesil, teprenone, and tocopherol nicotinate). The total daily drug dose administered in these formulations, which range in complexity from simple solutions of the drug in a dietary oil up to multi-excipient, self-emulsifying drug delivery systems (SEDDS), range from less than 0.25 μg to greater than 2000 mg. The amount of drug contained in a unit-dose capsule product ranges from 0.25 μg to 500 mg and for oral solution products, from 1 μg/mL to 100 mg/mL. The total amount of lipid excipient administered in a single dose of a capsule formulation ranges from 0.5 to 5 grams, but can range from as low as 0.1 mL to as high as 20 mL for oral solution products. Some of these products tolerate room temperature storage for only brief