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Review

Lipid-based formulations for oral administration of poorly water-soluble drugs

Huiling Mu[a,*], René Holm[a,b], Anette Müllertz[a,c]

[a] Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark
[b] Biologics and Pharmaceutical Science, H.Lundbeck A/S, Ottiliavej 9, DK-2500 Valby, Denmark
[c] Bioneer:FARMA, Danish Drug Development Center, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark

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ABSTRACT

Lipid-based drug delivery systems have shown great potentials in oral delivery of poorly water-soluble drugs, primarily for lipophilic drugs, with several successfully marketed products. Pre-dissolving drugs in lipids, surfactants, or mixtures of lipids and surfactants omits the dissolving/dissolution step, which is a potential rate limiting factor for oral absorption of poorly water-soluble drugs. Lipids not only vary in structures and physiochemical properties, but also in their digestibility and absorption pathway; therefore selection of lipid excipients and dosage form has a pronounced effect on the biopharmaceutical aspects of drug absorption and distribution both *in vitro* and *in vivo*. The aim of this review is to provide an overview of the different lipid-based dosage forms from a biopharmaceutical point of view and to describe effects of lipid dosage forms and lipid excipients on drug solubility, absorption and distribution.

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Contents

1. Introduction

Oral drug administration is desirable due to good patient convenience and consequently better compliance. To be absorbed from the gastrointestinal (GI) tract, a drug needs to be dissolved in the GI fluids; this is a problem for the increasing number of poorly water-soluble drug candidates that are in development in the pharmaceutical industry. However, it seems that a high permeability is maintained for most of these compounds, rendering them class II drugs in the Biopharmaceutics Classification System (BCS) (Amidon et al., 1995; Lipinski, 2000; Lipinski et al., 1997; Yu et al., 2002). Thus the solubility and/or dissolution rate in the GI tract often is the limiting step for the absorption of these drugs.

The interests on lipid-based drug delivery systems (LBDDS) have increased over the past two decades as a function of identification of these pharmaceutically difficult candidates, and increased even further after successful launch of lipid-based oral pharmaceutical products, including in particular cyclosporine A, marketed as

* Corresponding author. Tel.: +45 35336187.
E-mail address: huiling.mu@sund.ku.dk (H. Mu).

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Sandimmune™ and Neoral™. One of the advantages of LBDDS is that drug molecules are pre-dissolved in lipid excipients, avoiding a potentially rate limiting dissolution step in the GI tract, thereby achieving an increased and consistent bioavailability (Chakraborty et al., 2009; Drewe et al., 1992; Gershanik and Benita, 2000; Hauss, 2007; Kohli et al., 2010; Porter et al., 2008; Strickley, 2004).

To develop LBDDS, several complex biological processes have to be taken into account, such as digestion of lipid excipients, formation of different colloid phases during lipid digestion, and transfer of the drug between these colloid phases. Several reviews of lipid-based formulations are available, each focusing on different aspects of lipids in drug delivery (Chakraborty et al., 2009; Fricker et al., 2010; Gursoy and Benita, 2004; Hauss, 2007; Kuentz, 2011; Kohli et al., 2010; Müllertz et al., 2010; Porter et al., 2007, 2008; Pouton, 2000, 2006; Rahman et al., 2011; Shukla et al., 2011; Singh et al., 2009a, 2011; Yanez et al., 2011). Pouton (2006, 2000) proposed a Lipid Formulations Classification System (LFCS) and categorised lipid-based formulations into four different types according to their compositions. Porter and colleagues summarised lipid delivery systems with focus on self-emulsifying delivery system (SEDDS) and assessment of lipid-based formulations using *in vitro* lipolysis (Porter et al., 2008), and provided a good overview on lipid digestion and drug solubilisation in the small intestine as well as lymphatic transport (Porter et al., 2007). Lipid excipients have been reviewed by Hauss in context of their applications in lipid-based formulations (Hauss, 2007) and application of phospholipids in oral drug delivery has been reviewed by Fricker et al. (2010). Singh et al. have made a general review covering SEDDS and solid dispersions (Singh et al., 2011). In a recent review a rational strategy for the development of lipid and surfactant based drug delivery system was suggested (Müllertz et al., 2010). In connection to this the LFCS proposed by Pouton was evaluated and considerations suggested in particular reflecting the differences between triglycerides (TG) and partial glycerides.

This review presents the recent progress on liquid lipid-based dosage forms, with emphasis on the formulation forms from a biopharmaceutical point of view. This includes simple considerations on drug selection and lipid digestion related with lipid structure, and an overview of different lipid-based dosage forms, from simple lipid solutions to advanced SEDDS and solidifying lipid formulations.

2. Selection of compounds for lipid-based formulations

Compounds with a low aqueous solubility, *i.e.* belonging to the BCS class II and IV, are frequently discussed in relation to LBDDS. Compounds may fall into BCS II and IV for different physical chemical reasons; therefore it can be helpful to identify the aetiology of the poor solubility. A number of poorly water-soluble compounds are regarded as "brick dust" and cannot be formulated as LBDDS because of their tight crystal lattice; another group of compounds possesses high lipophilicity ($\log P$) and much lower melting points, the so-called "grease-balls". Obviously, a continuum exists between these two simplified classes of poorly soluble compounds, with most drug molecules not fitting either extreme. If the molecule has the characteristics of a grease-ball and traditional formulation approaches do not provide adequate bioavailability, solubility enhancement through the use of surfactant and/or lipid based excipients may be useful. If the compound is a "brick-dust" molecule, it typically has a low solubility in lipids, but may have considerable higher solubility in surfactants and co-solvents. Therefore not all compounds with poor aqueous solubility and/or a high $\log P$ will have a good solubility in excipients that are suitable for LBDDS.

Müllertz et al. (2010) recently summarised a number of commercial formulations. Of the 25 formulations classified 13 were LFCS class I, three were class III, and nine were class IV. A few simple descriptors for the compounds and their melting points are presented in Table 1, demonstrating that the simple classification into grease-balls and "brick-dust" is not always predictive in the selection of the type of lipid-based formulations. Rane and Anderson (2008) recently provided a review of the different theoretical models developed to predict the solubility of compounds in lipids or lipid mixtures. At present, no model is capable of predicting the solubility of a drug molecule in lipids, but if new theories can be developed that takes the specific and non-specific interactions between the compounds and the lipid excipients into the consideration, they may hold potential for future predictions.

When defining the formulation space for LBDDS the use of Design of Experiments (DoE) is a good and systematic approach. Output parameters often include drug solubility, colloid structures of the aqueous dispersions, and in the case of SEDDS droplet size of the formed emulsion. When incorporating the solubility as an output in DoE, higher solubility may be achieved in the formulation mixtures than in individual excipients (Holm et al., 2006a), even though drug solubility in lipid mixtures can be estimated as a simple weighted average of the drug solubility in individual ingredients (Sacchetti and Nejati, 2012). If the solubility of a compound is low, the solubility should generally be screened. Therefore preformulation measurements of solubility in excipients and mixtures hereof are the most useful parameters to determine if lipid-based formulation is a feasible strategy for a given compound.

3. Physicochemical properties of lipids

Lipids are generally defined as compounds containing fatty acids and can be separated into different classes (Cast and Hamilton, 1999; Castera, 1995; Mu, 2005). Small (1968) has classified lipids based on their interactions in aqueous systems and their behaviour in the water–air interface. Free fatty acids (FFA), diglycerides (DG), and TG are classified as class I polar lipids because they possess some surface solubility and can form stable monolayers on the surface (Small, 1968). Monoglycerides (MG) and phospholipids are classified as class II polar lipids, which can form well-defined liquid crystalline phases in the bulk (Small, 1968). Shimada and Ohashi (2003) studied the interfacial and emulsifying properties of DG and MG; they found that addition of DG to TG reduced the interfacial tension, and addition of MG to TG had a more profound effect in the reduction of the interfacial tension. Pitzalis et al. (2000) characterised the ternary phase diagrams of MG and DG in water and found that MG formed a lamellar phase and two types of bi-continuous cubic phases, which further confirms that MG is different from TG in the formation of microstructures in aqueous media. Even though MG, DG, and TG are normally classified as neutral lipids in food science and lipid chemistry (Christie, 1985; Heinz, 1996), their polarity is increasing in the order of TG, DG, and MG (Christie, 1985; Mu et al., 2000). Therefore TG, DG and MG are different not only in their structures, but also different in their surface activities and polarities.

In addition to the differences of their physicochemical properties, the *in vivo* digestion processes of TG, DG and MG are also different. Digestion of lipids already starts in the stomach; preduodenal lipases partially hydrolyse TG to 1,2(2,3)-DG and FFA, with up to 30% of TG being digested in the stomach, depending on the fatty acid composition of the TG (Armand, 2007; Hamosh, 1979; Hamosh and Scow, 1973; Smith et al., 1986). 1,2(2,3)-DG are further digested in the small intestine by other lipases such as pancreatic lipase to 2-MG and FFA (Christophe, 2004; Mu and Høy, 2004; Tso, 1985). The intramolecular structure of TG affects lipid digestion and

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