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Formulation of lipid-based delivery systems for oral administration: Materials, methods and strategies ☆

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Abstract

Oral lipid-based drug delivery systems may include a broad range of oils, surfactants, and cosolvents. This diversity makes comparison of lipid-based formulations difficult. Although the relationship between formulation and drug absorption is understood at a conceptual level, performance *in vivo* cannot be predicted with confidence at present. The Lipid Formulation Classification System (LFCS) identifies the factors which are likely to affect performance *in vivo*. There is now a need to establish performance criteria which will facilitate *in vitro–in vivo* correlation studies. In this review we discuss the properties of excipients, and identify criteria for selection of excipients for lipid-based formulations. Excipients are discussed in the context of the LFCS, our existing knowledge of the fate of these materials during dispersion and digestion, and the likely consequences of their use in formulations. We outline the formulation strategies that can be used for each type of lipid formulation, and suggest a framework for the *in vitro* testing of each type. Finally we address the choice of lipid formulations in relation to the physicochemical properties of the drug.

Keywords: Lipid-based formulations; Self-emulsifying drug delivery systems; Excipients, Lipid Formulation Classification System; Formulation strategies; Surfactants; Self-dispersion

Contents

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1. Introduction

Lipid-based delivery systems range from simple oil solutions to complex mixtures of oils, surfactants, co-surfactants and cosolvents. The latter mixtures are typically self-dispersing systems often referred to as self-emulsifying drug delivery systems (SEDDS) or self-microemulsifying drug delivery systems (SMEDDS) [1]. Formulations which disperse to form transparent colloidal systems are usually referred to as SMEDDS, though in scientific terms this distinction is somewhat arbitrary. Whether these dispersions are thermodynamically stable microemulsions is usually unknown, though the dispersions formed by both SEDDS and SMEDDS are often stable in practice for months. The particle sizes of dispersions formed by SMEDDS are lower than those formed by SEDDS but in our view it is not helpful to assume that low particle size is always better. The performance of lipid-based delivery systems is governed by their fate in the gastrointestinal tract, rather than the particle size of the initial dispersion. This concept can be appreciated by considering the fate of long-chain triglycerides, which have no practical ability to self-disperse but are digested rapidly in the intestine [2]. Subsequent to lipolysis their fatty acid and monoglyceride digestion products are solubilised by bile salt–lecithin mixed micelles, a fine colloidal dispersion which promotes absorption [3,4]. It is likely that the powerful digestive system in the intestine will play a part in determining the fate of all lipid-based delivery systems. Even when non-digestible excipients are used the interaction of a dispersed formulation with bile is likely to change its physical form. Formulators need to have a good understanding of gastrointestinal digestion and are increasingly making use of relevant *in vitro* tests which can predict the fate of the formulation, and most importantly the drug, after oral administration [5,6]. Formulation of SEDDS with glyceride oils dates back to the 1980s when the focus was predominantly on the rate and mechanisms of dispersion and the resultant particle size [7,8]. In the 1990s the influence of digestion on performance was becoming apparent [9–11] and we now have valuable data from *in vivo* studies which have been designed to establish a framework for *in vitro–in vivo* correlation (IVIVC) [12]. Interest in lipid-based formulations has grown quickly over the past decade and a recent book provides a useful summary of the state of the art [13]. However there are few systematic and mechanistic studies addressing the critical area of IVIVC, and these studies are concentrated on a small number of 'model' drugs. An accompanying article discusses the area of IVIVC [12]. Here we focus on how the choice of excipient is likely to influence the fate of the formulation and drug. The reader is referred to a series of valuable recent articles for more detail on the excipients used for lipid-based formulations [14], the contents of existing marketed products [15,16], and liquid formulations that have been tested in bioavailability studies [12,17]. There is also interest in solid or waxy lipid-based products [18–20] which we do not discuss in detail here. Solid or waxy formulations have the advantage that they may reduce the incidence of leakage in soft or hard-gelatin capsule products. If the physical properties are suitable they could also be processed as self-dispersing lipid-based tablets. These formulations introduce some technical difficulties relating to the physical form of the waxes and the drug, and in particular the analysis and tracking of morphological changes that might occur in the product during storage. These issues are beyond the scope of this article but are discussed in an accompanying article [18].

2. The Lipid Formulation Classification System

The Lipid Formulation Classification System (LFCS) was introduced as a working model in 2000 [21] and an extra 'type'of formulation was added in 2006 [1,21]. In recent years the LFCS has been discussed more widely within the pharmaceutical industry to seek a consensus which can be adopted as a framework for comparing the performance of lipid-based formulations. The main purpose of the LFCS is to enable *in vivo* studies to be interpreted more readily, and subsequently to facilitate the identification of the most appropriate formulations for specific drugs, i.e. with reference to their physicochemical properties. Table 1 indicates the fundamental differences between Type I, II, III and IV formulations. Whilst the defining properties of each Type are easy to understand, as yet there are few studies which link the LFCS with *in vitro* or *in vivo* performance. Many of the marketed products are Type III systems but this group is particularly diverse as a result of the wide variation in the proportions of oily and water-soluble materials used. To indicate this issue in previous publications [1,21] this group has been further divided into Type IIIA and Type IIIB, to