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Enhancing intestinal drug solubilisation using lipid-based delivery systems ☆

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Abstract

Lipid-based delivery systems are finding increasing application in the oral delivery of poorly water-soluble, lipophilic drugs. Whilst lipidic dose forms may improve oral bioavailability via several mechanisms, enhancement of gastrointestinal solubilisation remains argueably the most important method of absorption enhancement. This review firstly describes the mechanistic rationale which underpins the use of lipid-based delivery systems to enhance drug solubilisation and briefly reviews the available literature describing increases in oral bioavailability after the administration of lipid solution, suspension and self-emulsifying formulations. The use of *in vitro* methods including dispersion tests and more complex models of *in vitro* lipolysis as indicators of potential *in vivo* performace are subsequently described, with particular focus on recent data which suggests that the digestion of surfactants present in lipid-based formulations may impact on formulation performance. Finally, a series of seven guiding principles for formulation design of lipid-based delivery systems are suggested based on an analysis of recent data generated in our laboratories and elsewhere.

Keywords: Drug absorption; Lipid-based delivery systems; Self-emulsifying drug delivery systems; *In vitro* lipolysis; Solubilisation

Contents

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1. Introduction

For drugs to be well absorbed across the gastrointestinal tract (GIT) and provide good oral exposure, a number of potentially limiting factors must be overcome. These include appropriate stability and solubility in the GI fluids, reasonable intestinal permeability, and resistance to metabolism both within the enterocyte and the liver. In recent years, the number of new chemical entities (NCE) for which low aqueous solubility presents the major barrier to absorption has increased and this has been suggested to reflect changes in drug discovery methodologies including the widespread application of e.g. combinatorial chemistry, high throughput screening and cell-based activity assays [1]. Whilst absolute definitions are difficult, up to 40% of the NCE in development have been suggested to be 'poorly water-soluble' [2,14].

Realisation that the oral bioavailability of poorly water-soluble, lipophilic drugs may be enhanced when co-administered with a meal rich in fat [3–8] has led to increasing recent interest in the formulation of poorly water-soluble drugs (PWSD) in lipids as a means to enhance drug solubilisation in the gastrointestinal tract (GIT) [9,10]. Lipid suspensions, solutions and emulsions have all been used to enhance the oral bioavailability of PWSD [11,12] and more recently, there has been increasing focus on the utility of self-emulsifying lipid-based formulations [13,14]. However, despite the proven utility of self-emulsifying lipid-based formulations, relatively few lipid-based products have been commercialised (examples include Neoral® (cyclosporine), Norvir® (ritonavir), Fortovase® (saquinavir) and Agenerase® (amprenavir)). The reasons underlying the lack of application of these technologies are not entirely clear, but likely reflect a limited knowledge of the formulation parameters that are responsible for good *in vivo* performance and the fact that relatively few *in vivo* studies in humans have been reported in the literature when compared with conventional dosage forms. Perhaps most importantly, at least from a developmental standpoint, the lack of effective *in vitro* tests that are predictive of *in vivo* performance has significantly hindered successful development of lipidic formulations. As a consequence, the design of self-emulsifying lipid-based formulations and the choice of formulation components has historically been driven by the solubility of a candidate drug in the dose form, the ease of dispersion of the formulation and the particle size of the resulting emulsion droplets [15–24].

Whilst drug solubility in the formulation (i.e. potential drug load) and the ease of dispersion remain important design criteria, recent studies in our laboratories [25–31], and those of others [32–36], also suggest that assessment of the impact of lipid digestion on the solubilisation capacity of a lipid-based formulation is also required to accurately explain *in vivo* performance [32,37–39]. To this end, this review briefly summarises the historical approaches that have been taken to enhance the oral bioavailability of poorly water-soluble drugs using lipid-based formulations, but concentrates more specifically on relatively recent studies which have explored the potential impact of lipid and surfactant digestion on the functionality of lipid-based delivery systems. Importantly, the current article focusses specifically on the use of lipid-based formulations to enhance drug solubilisation in the GIT — it is clear that lipids may also have an impact on stability, permeability, transporter function and lymphatic transport, however, these aspects are well addressed elsewhere in this theme issue [40,41].

1.1. Intraluminal lipid processing

The patterns of intraluminal lipid processing are key determinants of luminal lipid and drug solubilisation and are briefly summarized below. Further details of lipid digestion, absorption and metabolism are available in the following reviews [42–49].

Processing of exogenous (i.e. food or formulation-derived) lipids generally begins in the stomach where triglycerides (TG) are hydrolysed to di-glycerides (DG) and fatty acids (FA) by the acid-stable lipases, i.e. lingual lipase and gastric lipase. Gastric lipase, secreted by the gastric mucosa, has an optimum pH range of 3 to 6 and shows a preference for sn-1 and sn-3 ester bonds [46,50]. Lingual lipase, secreted by the salivary glands, has an optimum pH of 4 but is still active at pH 6–6.5 and preferentially hydrolyses TG in the sn-3 position [43,47]. Acid lipases have a greater affinity for medium chain triglycerides (MCT) when compared with long chain triglycerides (LCT) and do not hydrolyse phospholipids (PL) or cholesterol esters (CE) [48,51,52]. Acid lipases are also inhibited by long chain fatty acid digestion products, (which are mostly protonated at gastric pH), and therefore digestion via acid lipases accounts for only approximately 10 to 30% of the overall hydrolysis of ingested TG in food [53]. Of the acid lipases, lingual lipase is most important in rats and mice whereas in humans, rabbits, guinea-pigs and baboons, gastric lipase predominates [54].

The stomach is the primary site of initial lipid emulsification in the GIT. Crude emulsification (lipid droplets of 1–100 μm in size) is facilitated by a combination of gastric agitation and gastric emptying, and promoted by the presence of dietary PL, proteins and polysaccharides and the amphipathic products of partial TG lipolysis which together act to stabilise the oil/water interface [55,56].

The presence of lipids in the duodenum stimulates the secretion of bile salts (BS), PL (primarily phosphatidylcholine (PC)) and cholesterol (Ch) from the gall bladder and pancreatic fluids (containing pancreatic lipase/co-lipase) from the pancreas [57,58]. Some PL and Ch adsorbs to the surface of the emulsion droplets and in association with the TG digestion products and bile salts present in the duodenum produce stable, small particle size oil droplets [43,46]. Subsequently, the process of lipid digestion is completed under the action of the pancreatic lipase/co-lipase complex [59–61], although recent data also suggests a role for other pancreatic enzymes in the digestion of (at least) some polyethoxylated lipidic excipients [62]. Lipase/co-lipase binds at the surface of the oil droplets to produce one molecule of 2-monoglyceride (MG) and two FA molecules for each TG molecule [42]. Physiological concentrations of BS and PL inhibit pancreatic lipase activity [63–65] and under these conditions co-lipase is essential to allow pancreatic lipase to bind to the surface