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EXPERT REVIEW

# Transforming Lipid-Based Oral Drug Delivery Systems into Solid Dosage Forms: An Overview of Solid Carriers, Physicochemical Properties, and Biopharmaceutical Performance

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**ABSTRACT** The diversity of lipid excipients available commercially has enabled versatile formulation design of lipid-based drug delivery systems for enhancing the oral absorption of poorly water-soluble drugs, such as emulsions, microemulsions, micelles, liposomes, niosomes and various self-emulsifying systems. The transformation of liquid lipid-based systems into solid dosage forms has been investigated for several decades, and has recently become a core subject of pharmaceutical research as solidification is regarded as viable means for stabilising lipid colloidal systems while eliminating stringent processing requirements associated with liquid systems. This review describes the types of pharmaceutical grade excipients (silica nanoparticle/microparticle, polysaccharide, polymer and protein-based materials) used as solid carriers and the current state of knowledge on the liquid-to-solid conversion approaches. Details are primarily focused on the solid-state physicochemical properties and redispersion capacity of various dry lipid-based formulations, and how these relate to the *in vitro* drug release and solubilisation, lipid carrier digestion and cell permeation performances. Numerous *in vivo* proof-of-concept studies are presented to highlight the viability of these dry lipid-based formulations. This review is significant in directing future research work in fostering translation of dry lipid-based formulations into clinical applications.

**KEY WORDS** dry emulsions · lipid-based drug delivery systems · oral bioavailability · poorly water-soluble drugs · proliposomes · silica-lipid hybrid · solid carriers · solid self-emulsifying systems

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## INTRODUCTION

Oral lipid-based formulations entered the pharmaceutical market as early as 1981 in the form of simple lipid solutions (1). The subsequent commercialisation of lipid and surfactant-based self-emulsifying formulations after 1990 has highlighted the importance of the physicochemical aspect of a lipid-based vehicle in effectively delivering poorly water-soluble, lipophilic drugs *via* the oral route (2). Lipid-based formulations are developed to mimic the food (or post-prandial) effect based mainly on the mechanisms that the ingested lipids, whether digestible or not, enhance the state of drug solubilisation during gastrointestinal (GI) transit by creating a lipophilic microenvironment with a concentration gradient favouring drug transport towards the intestinal absorptive sites (3–5). Commercially available lipid excipients include *fatty acids* (e.g. oleic acid), *natural vegetable oils* (e.g. soybean oil), *semi-synthetic glycerides* (e.g. Miglyol®, Capmul®MCM, Sterotex™), *polyoxyethylene glycols (PEG) derivatives or macrogolglycerides* (e.g. Labrasol®, Labrafil®, Gelucire®), *ethoxylated glycerides* (e.g. Cremophor®), *polyalcohol fatty acid esters* (e.g. Solutol®, Tween®), as well as *cholesterol* and *phospholipids* (e.g. egg and soybean lecithin) (1,6,7). The self-assembling properties of these lipid excipients have been exploited for developing a wide range of differently structured colloidal drug carriers, for examples, emulsions, microemulsions, micelles, liquid crystalline phase carriers, liposomes, niosomes and various self-emulsifying systems. A substantial number of reviews have been devoted to the fabrication of these lipid-based systems and the associated formulation factors that possibly influence the carrier solubilisation capacity and absorption pathway of drugs, such as the state of formulation emulsification or dispersion, lipid digestibility nature, lipid acyl chain length, lipid dose,

and the presence of endogenous/exogenous surfactants (5,6,8,10–18).

This review primarily focuses on the transformation of liquid and semisolid lipid-based systems into solid dosage forms or 'liquisolid' formulations (i.e. free-flowing and compressible powders containing a non-volatile liquid vehicle) (27,28), a current trend in lipid-based formulation design. Solidification is seen as viable means for stabilising lipid colloidal systems while eliminating stringent processing requirements associated with liquid systems. Other practical advantages are (*i*) possible reduction in the volume of administration (e.g. converting a liquid emulsions or suspensions containing >50% water into the dry state that can be filled/processed into single capsule or tablet unit), (*ii*) enhanced precise dosing (e.g. pre-encapsulation of the whole dose into capsules/tablets provides more accurate and precise dosing in comparison to administering a prescribed volume of a suspension using a syringe or spoon), (*iii*) ease of transfer and storage (i.e. liquid formulations are bulky and typically prone to stability and microbial challenges), and (*iv*) better patient compliance (*i.e.* it is generally preferred by adult patients to administer capsules/tablets rather than a liquid formulation) (3,19–21). To date, the marketed oral lipid-based formulations [of which a comprehensive list is summarised in textbooks, e.g. (1)] are based mostly on liquid or semisolid lipids and typically encapsulated in soft or hard capsules, e.g. Neoral® (cyclosporine A) soft gelatin capsules and Solufen® (ibuprofen) hard gelatin capsules (22). An interesting exception is the antibiotic Cipro® (ciprofloxacin) oral suspension, which is formulated as a microcapsule powder for constitution to a suspension with lipid-based diluents composed of medium-chain triglycerides, sucrose, lecithin, water and a flavouring agent; however, the suspension is only stable for 14 days after constitution (1).

The capsule liquid-filling approach, while enabling high drug loading potential (up to 50% w/w), generally requires specialised technology and processing equipment particularly for soft gel mass preparation (i.e. involving third party manufacture) and hard capsule sealing (e.g. using the microspray sealing LEMS$^{TM}$ technology developed by Capsugel) (7,23). Chemical stability of liquid-state formulations has been a major concern with respect to material compatibility, potential leakage and migration of the excipients into the capsule shell (7,24). To enable simpler handling and manufacturing process using more economic and conventional equipment, a myriad of solidification approaches have been developed for fabricating lipid-based formulations into solid forms such as powders, granules or pellets. The techniques employed in liquid-to-solid formulations as well as their associated advantages and drawbacks have been the subject of numerous reviews over the past few years (7,24–26). Commonly employed solidification approaches include *physical adsorption onto solid carriers* (suitable for liquid lipids and producing the so-called 'liquisolid compacts' in the presence of a solid carrier and a coating agent (27,28), *spray-drying* (immediate evaporation of the volatile phase by spraying the liquid/semisolid dispersion into a hot air chamber), *freeze-drying or lyophilisation* (sublimation of the frozen aqueous phase at reduced temperature and pressure), *rotary evaporation* (evaporation of the volatile phase under reduced pressure conditions), *melt extrusion-spheronisation* (passage of semisolid materials through a die under controlled temperature and pressure conditions), and *melt granulation* (high shear mixing of semisolid formulations with a meltable binder) (Fig. 1). Each processing technique shares a common principle that a chemically inert solid carrier is incorporated for adsorbing or enhancing the physical integrity of the liquid and semisolid lipid matrices to facilitate subsequent dry capsule filling or tablet compression. The encapsulation efficiency associated with different solidification techniques was compared by Jannin *et al.* (7) based on data collected from various studies. The technique of physical adsorption was reported to produce the lowest drug loading levels (i.e. maximum 10% w/w), although lipid exposure could be relatively high for this method (i.e. best achievable report of 80% w/w, particularly for highly porous adsorbents). This is because the amount of drug loadable into the solid carriers is likely to be limited by its solubility in the liquid lipid phase. Other techniques, which enable more feasible use of both liquid and semisolid lipids for optimising the drug solubility, could possibly produce >50% w/w drug loading although such a value is not representative of the normal achievable range. Such high drug loading levels could be seen achievable for oily drugs (where drug is the lipid phase itself) or alternatively, in cases where drugs are suspended above the limit of their lipid solubility and sufficiently encapsulated by solid carriers.

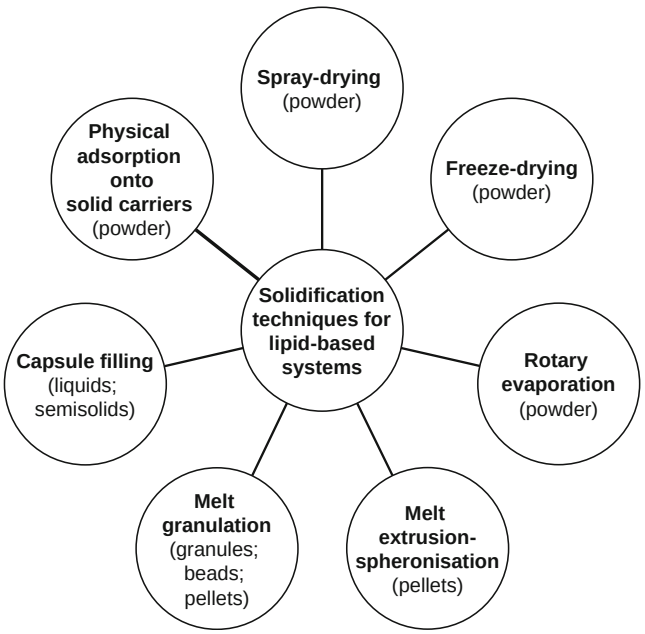


**Fig. 1** Overview of solidification techniques commonly used for transforming liquid and semisolid lipid-based formulations into solid dosage forms.

The following sections are dedicated to provide an in-depth review of the types of pharmaceutical grade excipients commonly utilised as solid carriers for lipid-based formulations, and to systematically review the biopharmaceutical aspects of various dry lipid-based formulations. Case examples are selected from various studies to specifically illustrate the influence of solid carriers on solid-state physicochemical and redisperison properties of various lipid-based formulations, digestion behaviour of the lipid phases, release kinetics and cell permeating properties of the encapsulated drugs. Emphasis is placed on the *in vivo* bioavailability studies to provide insight into the role of solidification in affecting the biopharmaceutical performance of various lipid-based formulations for the oral delivery of poorly water-soluble, lipophilic drugs.

## TYPES OF SOLID-STATE LIPID-BASED FORMULATIONS

This section provides an overview of the currently emerging solid-state lipid-based formulations and the specific characteristics of each formulation type, while detailed *biopharmaceutical assessment* of these systems is addressed in a latter section.

Figure 2 summarises the types of solid-state lipid-based formulations that have been evaluated for oral drug delivery. Attention is paid to four major classes of solid-state lipid-based formulations: dry emulsions, silica-lipid hybrid (SLH) microparticles, solid self-(micro)emulsifying drug delivery systems [S(M)EDDS], and proliposomes or proniosomes. Formulations composed of solid lipids are excluded from discussion given that this formulation type does not require the use of solid carriers for solid-form transformation; these systems have been reviewed in detail elsewhere (10,29–31).

### Dry Emulsions

Pharmaceutical dry emulsions, first described in the early 1960's, were prepared by spray-drying (32) followed by lyophilisation and solvent rotary evaporation techniques which evolved later (19,33–35). Dry emulsions are formed by removal of the aqueous phase of a liquid emulsion containing a water-soluble or insoluble solid carrier, leaving behind a dispersion of the immiscible oil phase within a solid phase (19,21,25,33). The precursor oil-in-water emulsions are typically homogenised to form droplets in the size range of 150 nm up to several micrometers, mostly in the presence of an emulsifying agent, e.g. hydroxypropyl methylcellulose (33), sodium caseinate (19), or Tween® 80 (36). Dry emulsions are more frequently prepared based on water-soluble carriers of polysaccharide (or carbohydrate), protein or polymeric origin (20,33,37), and to a lesser extent water-insoluble silica-based adsorbents (33,34,37). Dry emulsions may be the precursors for conventional unit dosage forms such as filled hard gelatin capsules (109) and compressed tablets (34,37). Compressibility of dry emulsions into tablets is greatly affected by the choice and mass ratio of solid carriers. It has been a great challenge to directly compress dry emulsions prepared based on single solid carrier, especially for polysaccharide-based dry emulsions which often exhibit higher cohesiveness and poorer flowability in comparison to silica-based dry emulsions. Approaches such as granulation and the combined use of both water-soluble and porous insoluble carriers have been shown to enhance the interlocking strength of particles, thus enabling direct compression of dry emulsions into compact tablets (34,37).

### Silica-Lipid Hybrid (SLH) Microparticles

Having close resemblance to dry emulsions, silica-lipid hybrid (SLH) microparticles are fabricated from homogenised Pickering emulsions (i.e. particle-coated emulsions stable against coalescence) or colloidosomes (i.e. microcapsules composed of densely packed colloidal particles) (38). Depending on the size and porosity (or specific surface area) of the silica particles, SLH microparticles are featured by different internal porous matrices (with pore diameters of 3–

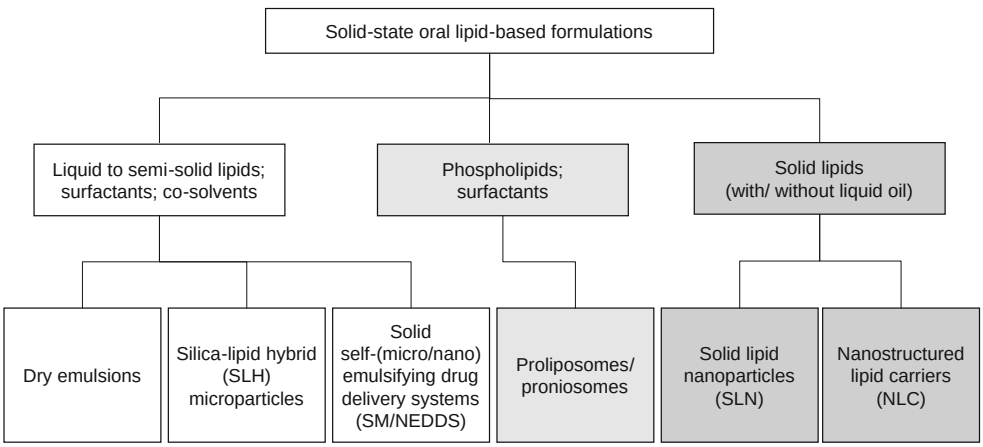


**Fig. 2** Classification of solid-state lipid-based formulations used for oral delivery of poorly water-soluble, lipophilic drugs.

100 nm) rather than the more common core-shell structures (39–41). Such porous features have led to a number of desirable properties which are discussed in the latter section of "Biopharmaceutical Assessment". The choice of emulsifier plays an important role in governing the surface charge (zeta potential) of the precursor droplets and their interactions with silica nanoparticles, hence affecting the resultant encapsulation efficiency of lipid droplets. It has previously been demonstrated that positively charged lipid droplets (emulsified by oleylamine) effectively formed similar porous microparticles at 10-times lower silica:lipid mass ratio than that of negatively charged droplets (emulsified by lecithin); this is facilitated by the electrostatic attractions between the lipid droplets and silica nanoparticles (38,42). The SLH microparticles have been investigated for *in vivo* absorption performance in the form of reconstituted dispersions (39,41,42) and as hard gelatin capsules (40). More recently, compressed tablets of SLH microparticles prepared incorporating mannitol have also been developed and desirably retained the drug release and lipid vehicle digestion performance as in its powdery form (43). While the unmodified SLH microparticles were somewhat cohesive powders resulting in fragile tablets, the incorporation of mannitol (at 1:5 mannitol to silica mass ratio) in the silica-stabilised emulsions prior to spray-drying was essential to enhance powder flowability and making the microparticles suitable for direct compression. The SLH-mannitol tablets ideally met the standard British Pharmacopoeia requirement for tablet friability, hardness and disintegration properties, thus exhibiting feasibility to be processed into viable dosage forms using conventional apparatus.

## Solid Self-(Micro)Emulsifying Drug Delivery Systems

Solid S(M)EDDS, originates from isotropic mixtures of oil, surfactant and sometimes including a co-solvent, have been engineered in the forms of powder, granules, pellets, beads, microspheres and tablets which spontaneously emulsify to form fine oil-in-water emulsions on exposure to an aqueous medium under mild agitation (7,22,25,26). Depending on the types and concentrations of each excipient incorporated, SEDDS (typically prepared without a co-solvent) readily redisperse to form turbid and white emulsions with droplet sizes ≥100 nm; SMEDDS, on the other hand, form thermodynamically stable, clear-to-translucent microemulsions containing droplets of 50 nm or smaller (13,25,44). For solid SMEDDS that contain volatile co-solvents such as ethanol and Transcutol®, cares need to be taken when selecting solid carriers and solidification techniques, bearing in mind that processing under elevated temperature (e.g. spray-drying) and reduced pressure conditions (e.g. freeze-drying and rotary evaporation) may pose challenges in retaining the volatile fractions (45). A recent study has presented the use of liquid and gas chromatography tandem mass spectrometry (LC-MS and GC-MS) methods to analyse the encapsulation and thermal stability of a solid SMEDDS containing Labrasol® (flash point >150°C) and Transcutol® (flash point≈96°C) (46). Spray-drying (at an inlet temperature of 140°C) was found to result in substantial loss of these two components and this was proposed to be one of the reasons for reduced emulsification and redispersion efficiency of the resultant solid SMEDDS.

In terms of final dosage forms, solid S(M)EDDS have been successfully developed into pellets (102,104,114,118) and liquid loadable tablets (103) in addition to hard gelatin capsules (60,67) in a number of preclinical evaluations. The approach of 'liquid loadable tablets' has distinct advantages over the conventional development strategy for compressed tablets in a way that the liquid preconcentrates are adsorbed into a preformed, highly porous tablet matrix (e.g. by immersion for a number of hours) without having to optimise the compressibility and compactibility of the lipid-based formulations. Such an approach has been shown to produce approximately 50–70% SMEDDS loading levels (*c.f.* <40% typically reported for compressed tablets of dry emulsions and SLH microparticles). Porosity of the tablets is one of the key determinants of the maximum loading level of SMEDDS and this could be enhanced by carefully controlling the compression force during tablet preparation (i.e. lower compression forces lead to higher porosities but lower tablet hardness).

## Proliposomes and Proniosomes

Proliposomes and proniosomes, collectively recognised as provesicular systems, are dry powder formulation that disperses to form isotonic liposomal suspensions under agitation conditions in water (47–49). Proliposomes are typically composed of phospholipids and cholesterol, whereas proniosomes are of non-ionic surfactants that are adsorbed onto a water-soluble (e.g. polysaccharide or carbohydrate-based) carrier, which also acts as a cryo-protectant. These pro-vesicular formulations are most frequently prepared by lipid-film deposition using rotary evaporation and freeze-drying. The presence of a cryo-protectant is crucial in preventing fusion of liposomes in the dry state by stabilising the phospholipid head groups *via* hydrogen bonding, thereby avoiding tight packing of the acyl chains of the phospholipid molecules (50,51). Consequently, the constituent lipids are most likely preserved in a liquid crystalline phase and readily redisperse in water to form the initial (multilamellar) vesicular droplets. To avoid oxidative instability, the use of hydrogenated phosphatidylcholine or other non-phospholipid surfactants may be preferred over formulations based on unsaturated phospholipids (which may require processing and storage in a vacuum or nitrogen atmosphere) (48,49). Existing proof-of-concept studies have mostly highlighted the physicochemical stability of these pro-

vesicular formulations and evaluated their biopharmaceutical performance in the reconstituted aqueous dispersion form. Little is known about the final dosage forms that this formulation type could lead to. Nevertheless it seems likely that conventional methodologies such granulation, direct tablet compression and hard capsule filling could be easily adopted, given that these formulations generally do not contain oily lipids and the inert carriers could act as the tableting aids. This research subject may form the priority for future work to enhance the clinical translation of proliposome and proniosome formulations for oral drug delivery.

## TYPES OF SOLID CARRIERS

A solid carrier works by either acting as a direct adsorbent for liquid excipients or by encapsulating the dispersed lipid colloids from the continuous phase prior to drying. Among the commonly used solid carriers are the water-insoluble, highly porous silica-based adsorbents, as well as the water-soluble polysaccharide-based, polymeric and protein-based carriers.

### Porous Silica-Based Adsorbents

Silica-based carriers, well known for their biocompatibility, chemically inert nature and stealthy properties (52,53), have been extensively evaluated for the formation of dry emulsions, SLH microparticles and solid S(M)EDDS. It has yet to find application in the preparation of proliposomes or proniosomes. A plethora of amorphous silica or silicate products characterised by different particle sizes and porosity (or specific surface area) have been made available commercially in addition to in-lab synthesised materials (27). Silica-based carriers have been used directly as physical adsorbents for liquid lipids (by simple blending procedures) or alternatively, *via* incorporation into a dispersion of lipid droplets (which is followed by a drying step). Examples of the commonly used silica products and their associated physical properties, i.e. average particle size, pore diameter, specific surface area and oil adsorbing capacity, are summarised in Table I. These include the Aerosil® series of fumed silica composed of <20 nm primary particles, Syloid® and Sylysia® micronised porous silica gels, Neosyl® precipitated silica, Neusilin® magnesium aluminometasilicate, as well as Florite® and Hubersorb® calcium silicates (Fig. 3). It is evident that some adsorbents with relatively high specific surface area (i.e. 200 $m^2/g$ and above) has enabled an oil adsorption capacity of more than twice the weight of the carrier itself. Larger sized and highly porous inorganic carriers (e.g. Neusilin US2) are advantageous in producing powders with better flowability and compressibility than the smaller sized silica particles (e.g. Aerosil 200) and other classes of non-porous, polymeric and organic carriers (27,34,37). Tablets of dry emulsions and SLH microparticles formulated with silica-based carriers were reported to contain 30–55% of lipid content, and exhibited acceptable tablet friability/hardness and disintegration properties (27,34,37,43). It is noteworthy that the presence of other tableting aids, such as film-forming agents and disintegrants

**Table I** Examples of Silica-Based Excipients Used as Pharmaceutical Solid Carriers

| Silica-based carriers | Particle size, average ($\mu$m) | Pore diameter, average (nm) | Specific surface area ($m^2/g$) | Oil adsorbing capacity (g/100 g) |
|---|---|---|---|---|
| Aerosil 200 fumed silica (Evonik Degussa)[a] | (primary) 0.012 | — | 200 ± 25 | — |
| Aerosil 380 fumed silica (Evonik Degussa)[a] | (primary) 0.007 | — | 380 ± 30 | — |
| Syloid 244FP silica (Grace)[b] | 2.5–5.5 | 16–20 | 320 ± 10 | 380 ± 50 |
| Silysia 350 (Fuji Silysia)[c] | 4 | 21 | 300 | 320 |
| Neusilin US2 magnesium aluminium silicate granules (Fuji)[d] | 44–177 | 5–6 | 300 | 305 ± 35 |
| Neusilin UFL2 magnesium aluminium silicate powder (Fuji)[d] | 3–5 | — | 300 | 305 ± 35 |
| Neosyl GP (Banner Chemical)[e] | 19.5 | >30 | 200 | 285 |
| Florite calcium silicate (Eisai)[f, (27)] | 26 | 150 | 100 | — |
| Hubersorb 5121 calcium silicate (Huber Engineering)[g, (27)] | 25 | — | 50 | 90 |

[a] http://www.aerosil.com/product/aerosil/en/products/hydrophilic-fumed-silica/Pages/default.aspx

[b] http://www.grace.com/EngineeredMaterials/ProductsAndApplications/Coatings/MattingAgents/SYLOIDApplicationsAndCharacteristics/SyloidGradesOverview.aspx

[c] http://www.silysiamont.com; Miura *et al.* Chemical and Pharmaceutical Bulletin. 2011;59(6):686–691

[d] http://www.neusilin.com/product/general_properties.php; http://www.neusilin.com/faq/

[e] http://www.specialchem4polymers.com/tds/neosyl-gp/pq-corporation/12844/index.aspx#

[f] Ito *et al.* International Journal of Pharmaceutics. 2006; 317(2):114–119

[g] http://www.hubermaterials.com/products/product-finder.aspx?type=Silicas+and+Silicates

(e.g. gelatin, microcrystalline cellulose and crospovidone) are essential to facilitate the tablet matrix formation as well as disintegration in aqueous media.

## Polysaccharide-Based Carriers

Polysaccharide (or carbohydrate)-based excipients have a long history of applications in the food and pharmaceutical industries as sweeteners, coating agents, bulking agents, viscosity-enhancers, tablet/capsule binders, diluents and direct compression agents (54). Examples include the lower molecular weight mannitol, sorbitol, sucrose, lactose, trehalose, and the higher molecular weight maltodextrins, cyclodextrins, dextrins, gum acacia and starch sodium octenyl succinate (Table II). This class of solid carrier is particularly popular for use in the formation of pro-vesicular formulations mainly due to the cryo-protecting function as described earlier. However, the crystalline and hygroscopic natures of such solid carriers should be taken into consideration during formulation design. Most polysaccharide-based carriers are prone to partial or complete transformation into the high energy amorphous state when processed using spray-drying, lyophilisation and rotary evaporation (33). Hygroscopic carriers, such as lactose and sucrose, have shown the tendency of re-crystallisation in dry emulsions where changes in their surface composition (i.e. leakage of liquid lipids) have resulted in particle agglomeration; this was proposed to be the reason for enlarged redispersed size distribution during storage at elevated temperature (40°C) and/or relative humidity (75% RH) (21,55,56). Mannitol is a non-hygroscopic isomer of sorbitol and may be preferred for encapsulating moisture-sensitive compounds (54).

## Polymeric Carriers

Amphiphilic polymers, by virtue of their solubility in aqueous media and great solubilising power for lipophilic compounds, have found many applications as emulsifiers and solid carriers in lipid-based formulation design (33,37,57).

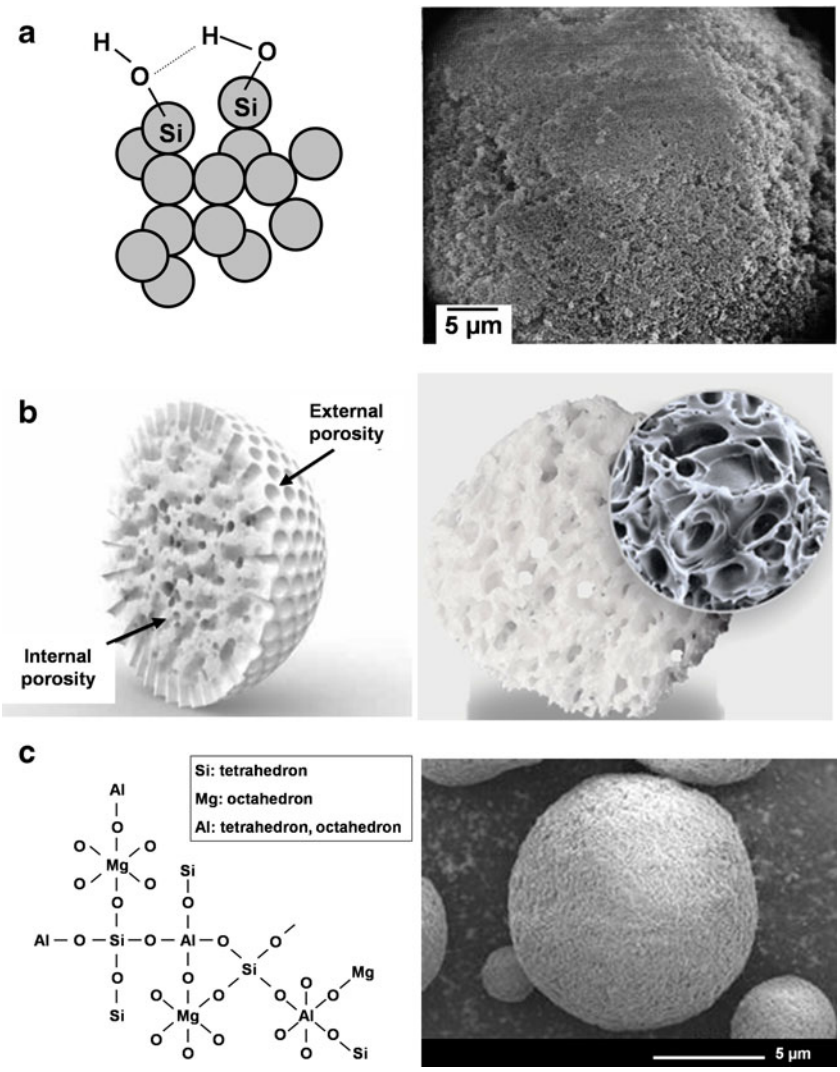


**Fig. 3** Schematic or molecular structures and representative scanning electron microscopic images of (**a**) Aerosil® fumed silica, (**b**) Syloid® micronised porous silica gel and (**c**) Neusilin® magnesium aluminometasilicate. (Reproduced with permission from Medicines Complete, Grace.com and Neusilin.com, respectively).

**Table II** Examples of Polysaccharide-Based Excipients Used as Pharmaceutical Solid Carriers

| Polysaccharide-based carriers | Molecular weight (g/mol) | Specific surface area ($m^2/g$) | Solubility in water (at 20°C) | Melting temperature (°C) |
|---|---|---|---|---|
| Mannitol[54] | 182 | 0.37 | 1 in 5.5 | 166–168 |
| Sorbitol[54] | 182 | 220–400 | 1 in 0.5 | 93–110 |
| Sucrose[54] | 342 | Irregular sized granules | 1 in 0.5 | 160–186 |
| Lactose[54] | 342 (anhydrous) | Irregular sized particles | Freely soluble | 232 |
| Trehalose[54] | 378 (dihydrate) | — | Freely soluble | 97 |
| Maltodextrin[54] | 900–9,000 | 0.31 – 0.54 | Freely soluble | 240 |
| Cyclodextrin (CD) [a, 54] | | (Internal dimension) | | |
| α-CD | 972 | 0.57 nm | 1 in 7 | 250–260 |
| β-CD | 1135 | 0.78 nm | 1 in 50 | 255–265 |
| γ-CD | 1297 | 0.95 nm | 1 in 4.4 | 240–245 |
| Dextrin[54] | 4,500–85,000 | 0.14 | Soluble in boiling water | 178 |
| Gum acacia[54] | 240,000–580,000 | — | 1 in 2.7 | 289–320 |

[a] Brewster *et al. Advanced Drug Delivery Reviews. 2007; 59(7):645–666*

Poloxamers (or Pluronics/Kolliphor), hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose (CMC) sodium and polyvinylpyrrolidone (PVP) are examples of this class of carrier (Table III). The advantageous application of some of these polymers as drug precipitation inhibitors or supersaturation promoters has also been successfully demonstrated, e.g. for a solid SEDDS formulation encapsulated by HPMC in combination with lactose (58). Though efficient as emulsifiers, solid carriers, and drug precipitation inhibitors, some of these polymers may form highly viscous aqueous solutions at increased concentrations which compromise further optimisation in the processing methods. For example, when spray-drying highly concentrated HPMC-containing emulsions, water-cooling may be required to reduce temperature at the atomiser for preventing polymer gelation and nozzle blockage (33). Most polymer-based carriers are hygroscopic and adsorb moisture in a non-linear pattern at elevated temperature and relative humidity (54). The moisture content and hygroscopicity are reportedly lower for poloxamers in comparison with other materials as listed in Table III and thus, may be a preferred choice of carrier for enhancing stability of formulations for moisture-sensitive compounds.

### Protein-Based Carriers

Water-soluble, protein-based carriers also exhibit amphiphilic characters that render their function as both emulsifiers and solid carriers for lipid-based formulations (34,59,60). Protein-based carriers, such as gelatin and glycine, are less frequently reported for the solid-state transformation of lipid colloids presumably due to their inferior compressibility properties. Gelatin swells and is soluble in water (at near to 40°C) and has been more frequently used in the manufacturing of soft and hard capsules for filling of liquid and semisolid lipids. Owing to its film-forming properties, gelatin has been used to encapsulate fish oils and oily vitamins in gelatin beadlets using coacervation technique, which can then be handled as a powdered formulation (54). A more recent study has shown that gelatin, as a single carrying agent, produced solid SMEDDS in the form of well-encapsulated microcapsules based on a lipid:carrier mass ratio of at least 1:1 (60). Similar to some of the polysaccharide-based materials, glycine has been reported to be an excellent lyophilisation aid for emulsions and has found great application in freeze-dried injectable formulations (54,59).

## BIOPHARMACEUTICAL ASSESSMENT

Whilst lipid excipients are generally selected based on the best solubilising capacity and the propensity for lymphatic drug transport, solid carriers are generally screened and chosen to enable the highest possible lipid (and drug) loading efficiency, adequate flowability and mechanical strength for tablet compression, as well as efficient redispersibility which has a great impact on drug release and other biopharmaceutical performance (7,22). It is an important research question as to whether transformation of various liquid lipid-based formulations into the dry state would affect their biopharmaceutical performance in comparison to that observed in the liquid state. The following sections detail the current major findings with respect to the influence of solid carriers on the physicochemical properties and the biopharmaceutical performance of various lipid-based formulations in their solid and redispersed states.

### Solid-State Physicochemical and Redispersion Properties

#### *Physical Properties*

Ideally, a dry lipid-based formulation is expected to readily redisperse in aqueous media (such as the GI fluids) to reform

**Table III** Examples of Synthetic Polymer-Based Excipients Used as Pharmaceutical Solid Carriers

| Polymer-based carriers | Molecular weight (g/mol) | Moisture content (w/w) | Solubility in water | Melting temperature (°C) |
|---|---|---|---|---|
| Poloxamers[54] | | <0.5% | | |
| P124 | 2090–2360 | (Hygroscopic at >80% RH) | Freely soluble | (liquid) 16 |
| P188 | 7680–9510 | | | (solid) 52 |
| Hydroxypropyl methylcellulose (HPMC)[54] | 10,000–1,500,000 | <5% (Hygroscopic at >50% RH) | Soluble (gels at >50°C) | $T_g$ = 170–180 |
| Microcrystalline cellulose (MCC)[54] | 36,000 | <5% (Hygroscopic) | Practically insoluble (slightly soluble in 5% w/v NaOH) | 260–270 |
| Carboxymethylcellulose (CMC) sodium[54] | 90,000 – 700,000 | <10% (Hygroscopic at >20% RH) | Soluble | Browns at 227 |
| Polyvinylpyrrolidone (PVP)[54] | 2,500 – 3,000,000 (solution viscosity indicating k-value from 12–120) | <10% (Hygroscopic at >40% RH) | Freely soluble | 150–180 |

the original colloidal dispersion. Based on the published data, it is inferred that the drying method and the types of solid carrier have vital effects on the solid-state structures and redispersed particles sizes of all kinds of lipid-based formulations. Spray-drying involves atomisation of the lipid dispersions followed by instantaneous evaporation of the continuous phase; this often results in the production of well separated and spherical particles. Supercritical fluid extraction methods have also been shown to produce well-closed, spherical submicron proliposome particles (61). It has been reported for dry emulsions (19–21,33,35,36,55,62), SLH microparticles (39,41,42,63,64), solid SMEDDS (44,58,60,65–68), and proliposomes (69) that spray-dried systems encapsulated by polysaccharide-based and polymeric carriers often exhibited smooth particle surfaces (usually with shallow dents), whereas those prepared with silica-based carriers showed relatively coarse surface appearance (Fig. 4). Alternative drying methods such as lyophilisation, rotary evaporation and coacervation frequently produced irregularly shaped mixtures (42,70). It is envisaged that these different morphologies could have a significant impact on drug release and formulation lipolysis performance, given that the surface area-to-volume ratio of a formulation potentially changes with its shape and structure. Yet, the effect of various drying methods on the biopharmaceutical performance of dry lipid-based formulations has not been systematically elucidated.

Figure 5 shows the typical range of particles sizes of various reconstituted lipid-based formulations fabricated based on different solid carriers and emulsifiers. While dry emulsions and SLH microparticles (top figures) generally reconstituted to form droplet sizes of ≥1 μm with at least 30% size increment than the precursor droplets, solid S(M)EDDS showed better efficiency in reforming submicron droplets (bottom left figure). Depending on the size of carriers and surfactants, the reconstituted particle sizes of proliposomes and proniosomes are highly variable ranging from below 100 nm up to several micrometers (bottom right figures). Based on these observed trends, solid S(M)EDDS may be thought to be more beneficial in terms of redispersion and emulsification. However, these data require careful interpretation, bearing in mind that many studies did not specify the exact phases taken for particle size analysis, i.e. whether the size data corresponded to the whole dispersion (including the lipid phase and solid carriers) or just the separated phase of dispersed lipid droplets. While the reliability of redispersion efficiency as a simple performance indicator of a 'solidified' lipid-based formulation remains ambiguously characterised, other parameters such as the specific surface area of a formulation and its interaction with the lipid-digesting enzymes surely necessitate further investigations to unravel the complicated mechanisms behind the drug release and absorption processes (40).

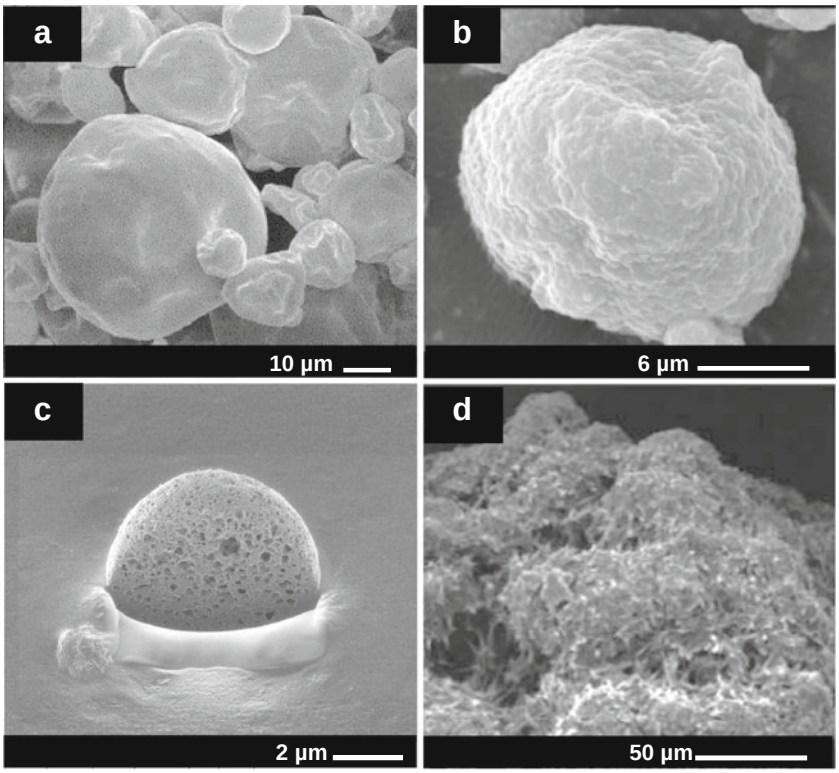


**Fig. 4** Scanning electron micrographs of (**a**) a spray-dried sucrose-HPMC based dry emulsion, (**b**) a spray-dried Aerosil® 200 based solid SEDDS, (**c**) cross section of a spray-dried SLH microparticle, and (**d**) a sorbitol-phospholipid based proliposomes prepared by rotary evaporation. [Reproduced with permission from reference (21,67,82) and (70), respectively.]

### *Chemical Properties*

*Lipid and Drug Loading*. To achieve successful liquid-to-solid transformation, the amount of solid carrier(s) incorporated has to be proportionally higher than the amount of lipids in some cases. This inevitably reduces the overall drug loading level in comparison to the liquid systems. This is less of a problem for pro-vesicular formulations which are mostly prepared using solid excipients rather than oily lipids that require sufficient encapsulation or adsorption. Proliposomes represents a platform strategy to overcome the problem of low drug loading levels as encountered for conventional liposomes, i.e. from typically less than 1% w/v up to more than 10% w/w of drug content (61,71–74). The physical state of an encapsulated drug could change from crystalline to a complete amorphous form with increasing lipid (or surfactant)-to-drug ratio (72,73,100,119). Charged phospholipids could be exploited for enhancing drug entrapment efficiency *via* the formation of more expanded entrapped volume between the lipid bilayers, or based on electrostatic attraction between lipid components and drug molecules in their ionised state (119).

For oily drugs such as Vitamin E (75) and zedoary turmeric oil (76), the use of other lipid excipients is not required and this often enables a drug loading level of at least 40% w/w in the final solid dosage forms. For drugs that exhibit limited solubility in both aqueous solutions and commonly used surfactants and pharmaceutical lipids, the viability of a dry lipid-based dosage form is usually hampered by inadequate drug loading content (typically <10% w/w). In addressing this limitation, the nanostructured SLH microparticles demonstrated a novel dual-step loading mechanism for enhancing the encapsulation of water- and lipid-resistant compounds in a supersaturated, amorphous state (77). For a weakly basic model drug, albendazole, the first step of the approach took advantage of the drug's pH-dependent solubility by solubilising the drug in acidified lipids; this enhanced its apparent solubility from practically insoluble to ~4%. Subsequently, a maximum drug loading of 25% w/w was achieved by electrostatically adsorbing the drug molecules (in its cationic form) to the anionic silica nanoparticles which act as a carrier. This synergistic drug loading approach based on solubilisation and electrostatic adsorption has proved to be useful for encapsulating ionisable molecules in SLH microparticles in a supersaturated state.

A wide range of porous silica-based carriers, endowed with high lipid adsorbing capacity (as summarised in Table I), have received the highest attention in formulating solid SMEDDS and to a lesser extent, dry emulsions. When prepared by simple physical blending, solid SMEDDS powder with a lipid load of 50–70% w/w has been reported to be non-sticky and free-flowing based on Neusilin® particles and silicon dioxide of 3.6 up to 300 µm (78). The effect of carrier particle sizes on the recovery of formulation powder has proved to be significant when prepared using spray-drying. A previous study by Hansen *et al.* (34) has systematically evaluated the influence of Neusilin® carrier types on the powder yield and lipid encapsulation efficiency resulting from spray-drying a medium-chain triglyceride

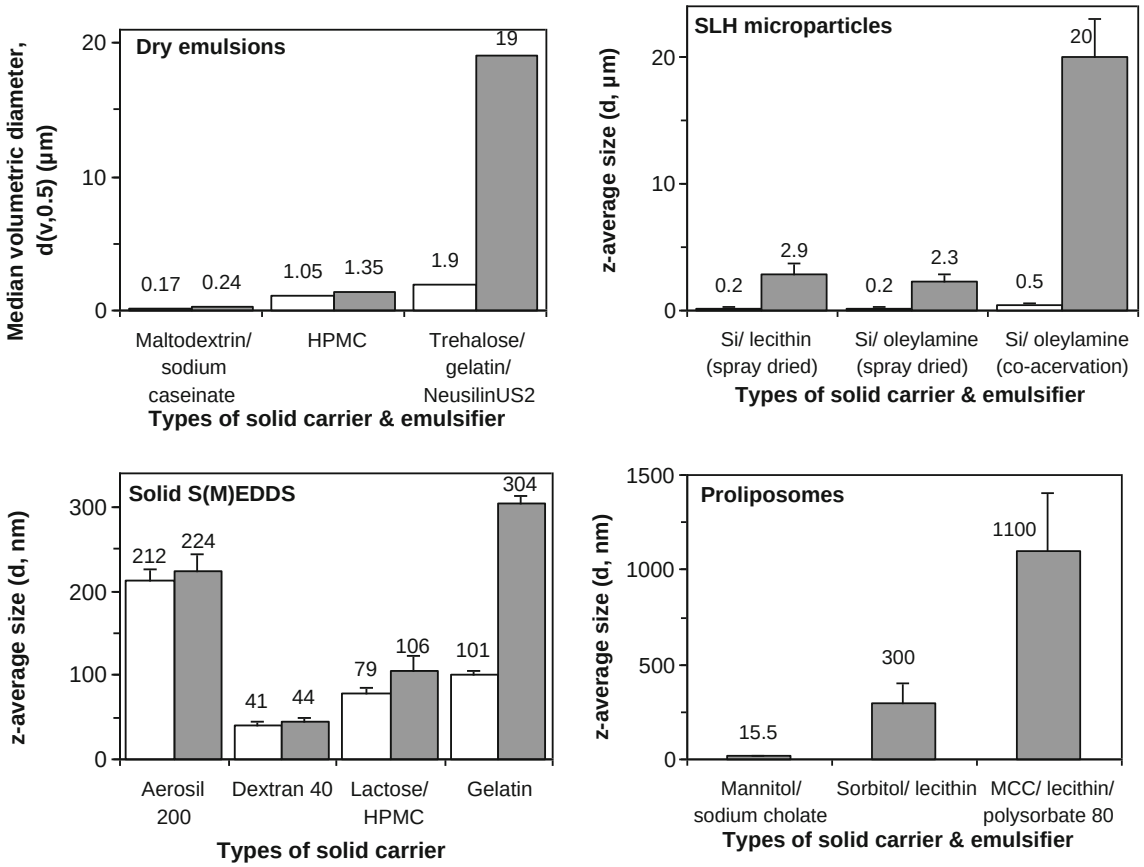


**Fig. 5** The average particle sizes of various reconstituted lipid-based formulations as a function of the types of solid carrier and emulsifier. Data re-plotted based on references (19,37) for dry emulsions, (39,42) for SLH microparticles, (58,60,66,67) for solid SMEDDS, and (72,73,115) for proliposomes, respectively. White bars represent particle sizes of the precursor droplets and grey bars correspond to particle sizes of the reconstituted formulations.

dry emulsion. The smaller sized Neusilin® UFL2 particles (3 μm) were shown to produce relatively higher powder yield and more efficient lipid encapsulation efficiency than the larger sized Neusilin® US2 particles (112 μm) (Fig. 6). The substantial loss of lipids and higher moisture content for the Neusilin US2-based formulations were ascribable to two reasons: firstly the large solid carrier was not optimum for encapsulating the fine lipid droplets and secondly, the process of water removal during spray-drying was less efficient due to greater diffusion path of water from the large sized carrier; consequently a large fraction of lipid droplets, presumably remained uncoated or non-adsorbed, were prone to adherence or deposition in the drying chamber. However, particles of larger sizes may be favourable in producing powders with better flowability (i.e. less cohesive) and increased mechanical strength for formulating into tablets (27,34). As a general guide, a lipid load of up to 40% w/w has been identified as optimum for dry emulsions (based on polymeric and silica-based carriers) to exhibit good tablet compressibility and redispersion into the initial emulsion droplet sizes (27,33,34).

*Protection of Volatile and Photosensitive Compounds.* The potential of dry lipid-based formulations in conferring shelf-life stability and chemical protection of volatile and photosensitive drugs have been reported for dry emulsions containing *l*-menthol and amlodipine (20,35), SLH formulations containing vitamin A (38), solid SEDDS containing coenzyme $Q_{10}$ (79), and proliposomes containing vitamin D3 (61) and beta-carotene (69). Jang *et al.* (20) have specifically assessed the photostability of amlodipine when formulated into various carrier systems; it was reported that the rate and extent of drug degradation was four to ten-times lower for a dextrin-based dry emulsion in comparison to that of an ethanol solution and the pure drug powder. When cross-compared with the photostability results obtained by Ragno *et al.* (80) for other amlodipine formulations, including a conventional tablet formulation, liposomes, cyclodextrins and a polymer-based microsphere formulation, the potential of dry emulsions in prolonging the shelf-life of the amlodipine product is clearly evident (Fig. **7**).

## *In Vitro* Performance

Despite the fact that compendial dissolution studies have mostly demonstrated promising preservation of immediate drug release performance of various lipid-based formulations after

transformation into solid forms, evaluations under simulated digesting conditions are more biorelevant and often show different drug solubilisation or precipitation behaviour. This is because drug release and solubilisation from a digestible lipid-based formulation (including those composed of glycerides and various esters of fatty acids and alcohols) is not simply governed by dispersion of the lipid colloids, but also by enzymatic processing of the lipid excipients (3,5). Lipolysis models, typically comprised of a buffered bile salt/phospholipid micellar medium in the presence of lipid-digesting enzymes (i.e. lipase/colipase), have been extensively utilised for probing the fate of drugs under simulated fasted or fed state gastrointestinal conditions in humans. At present, *in vitro* methodologies commonly used for characterising the performance of lipid-based formulations (both in the liquid and solid states) may encompass one or more of the following procedures: (*i*) determination of lipid carrier digestion kinetics based on titrimetric or spectroscopic assay of free fatty acids liberated (i.e. the major lipolysis end products); (*ii*) chromatographic measurement of the partially digested lipid components such as free fatty acids and mono-/di-/triglycerides; (*iii*) quantification of drugs that remain solubilised (in the oil or micellar aqueous phases) or precipitated (in the pellet phase) in the digestion samples after inhibiting the enzymes' activity and separating the various phases *via* centrifugation; and (*iv*) microscopic analysis of the sequential changes of the digesting formulation phases (4,5,13–15,85). Recently, the enzymatic-mediated lipolysis models have been progressively developed and cross-validated by various research groups in an effort to establish a standardised diagnostic tool for lipid-based formulations (9). Recommended modifications such as reduction in bile salt/phospholipids levels, the use of back titration (at pH higher than the $pK_a$ of fatty acids) as a better indicator of the overall lipolysis extent, and replacement of ultracentrifugation with bench-top centrifugation as a robust phase separation method, are anticipated to enhance high-throughput and cost-effectiveness of the test methodology.

The following section presents important case studies that illustrate the role of solid S(M)EDDS and SLH microparticles in controlling drug release, lipid digestion, as well as their capability in reducing fed *versus* fasted state variations in terms of drug solublisation. Furthermore, lipid excipients that have been reported to enhance intestinal permeation or uptake of poorly water-soluble drugs are also discussed.

### *Controlling Drug Release or Solubilisation*

Ideally, good solidification methodologies would result in either preservation or enhancement of the drug release or solubilisation performance of lipid-based formulations from their dry states. However, this has been shown to be dependent on the physical properties of solid carriers, as well as the molecular interactions between drug molecules, lipids/surfactants and solid carriers.

A recent study by Agarwal *et al.* (78) has investigated the effect of silica-based adsorbents with different chemical nature, specific surface area and particles sizes on the *in vitro* release behaviour of griseofulvin from SEDDS and solid-SEDDS. The preconcentrate was composed of Captex 355, Labrasol and Tween 80 (1:6:9 w/w) and griseofulvin at approximately 1.2% w/w loading. The liquid SEDDS, with an average droplet size of 7.25 nm, significantly enhanced the dissolution rate and extent of griseofulvin (i.e. 86.5% released in 15 min) as compared to the micronised drug powder (8.6% dissolved). Interestingly, SEDDS adsorbed onto Neusilin® UFL2 silicate (5 μm) at 1:1 ratio produced more sustained drug release kinetics but still with 86% dissolution achieved in 30 min (Fig. 8). When the larger sized Neusilin® US2 silicate (80 μm) was used as an

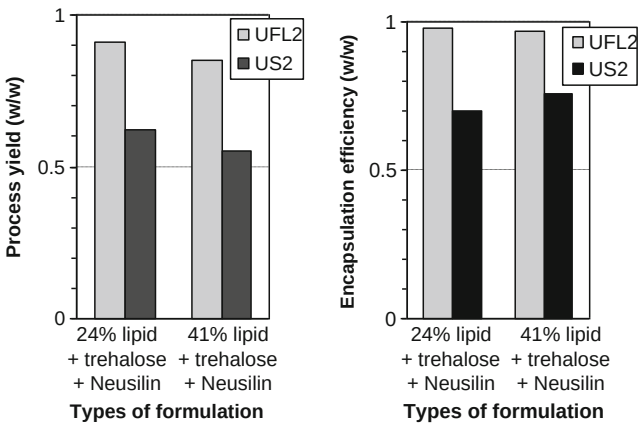


**Fig. 6** Size effects of Neusilin® porous carriers on (*left figure*) the spray-drying process yield, and (*right graph*) the encapsulation efficiency of a medium-chain triglyceride dry emulsion. The particle sizes $d_{50\%}$ for Neusilin UFL2 and Neusilin US2 were 3 μm and 112 μm, respectively (34).

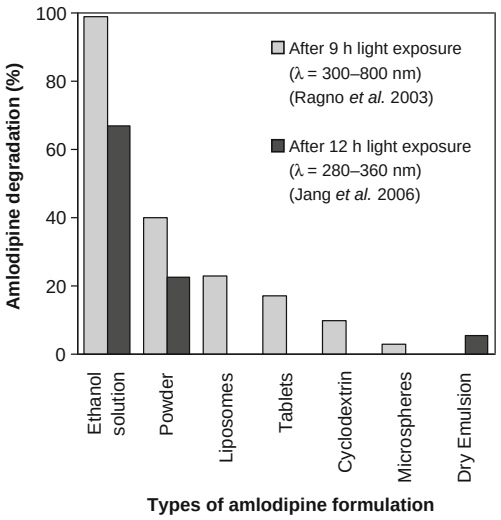


**Fig. 7** Percentage of photodegradation of amlodipine formulated in various pharmaceutical carrier systems. Data re-plotted based on references (20,80).

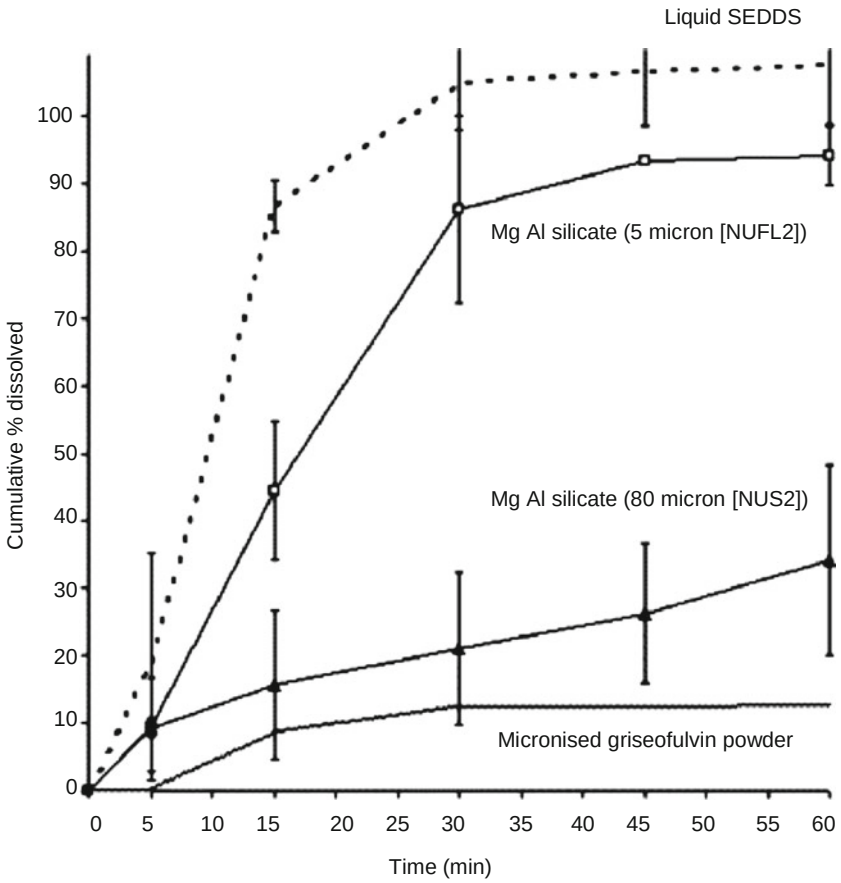


**Fig. 8** Dissolution profiles of various formulations equivalent to 5 mg of griseofulvin filled into hard gelatin capsules of size 000 in 100 ml of water (37°C): micronised griseofulvin powder, liquid SEDDS, and SEDDS adsorbed on magnesium aluminium silicate (5 and 80 $\mu$m) at a 1:1 ratio. [Reproduced with permission from reference (78)].

adsorbent at the same ratio, the release of griseofulvin-SEDDS was significantly reduced to <40% in 60 min. Given that the two Neusilin carriers have equivalent specific surface area (i.e. BET≈300 $m^2/g$), it was suggested that the retarded drug release kinetics was related to the greater pore length present in the Neusilin® US2 particles, which restricted the access of water to rehydrate the encapsulated SEDDS, as well as reduced rate of formulation 'leaching' into the surrounding medium. Comparison was also made across a series of different carriers, including calcium silicate (25 µm, BET≈50 $m^2/g$) and silicon dioxides (3.6, 20 and 300 µm, BET≈150–200 $m^2/g$). Calcium silicate demonstrated the slowest drug release kinetics comparable to the largest silicon dioxide particles (<15% release in 30 min), whereas the remaining two types of silicon dioxides exhibited slightly higher and equivalent release kinetics (<40% release in 30 min). All these solid-SEDDS were inferior in their drug release performance in comparison to the liquid SEDDS which produced complete drug release. Based on these observations, the authors identified a number of important factors that possibly play a role in affecting drug release performance of solid-SEDDS adsorbed onto porous silica-based carriers, specifically (*i*) *pore size and length* (related to particle sizes), where increased pore length (and particle sizes) is expected to diminish the efficiency of formulation hydration and leaching; (*ii*) *specific surface area*, where lower specific surface area may result in adsorption of SEDDS as thin films on the external surface of particles rather than residing inside the pores; and (*iii*) *total area of contact* between formulation liquid and the adsorbent surface, i.e. increased risk of drug nucleation or recrystallisation if drug molecules show higher affinity towards the adsorbent and have larger contact with the exterior of the filling region. It should be bear in mind that the solubility of drug molecules in thin films is likely much reduced in comparison to that in bulk liquid (i.e. in droplets), hence resulting in different adsorption affinity towards the carrier surface. The authors illustrated a number of possible adsorption phenomena related to the solid-SEDDS release performance. Although simplistic, some important features that could affect the retention pattern of SEDDS formulations should not be neglected. Such features include the exact shape or geometry of the carrier pore network (e.g. conical or tortuous) that determines the accessibility of dissolution media, as well as the wetting

properties between the pore wall and the formulation liquid versus that of dissolution media (which could be reflected by contact angle measurements).

In another study using danazol as a model drug, similar findings were also reported for the incomplete desorption and release of liquid SEDDS from the large sized Neusilin® US2 silicate (81). Adsorption of SEDDS based on medium- or long-chain triglycerides onto Neusilin® US2 silicate noticeably reduced danazol solubilisation by approximately 35% in comparison with the corresponding liquid SEDDS, under both digesting and non-digesting conditions. It was verified experimentally that danazol in micellar solution has low affinity towards dispersed Neusilin particles; therefore readsorption of drug molecules onto the carrier (which was <4%) is not a major reason for the reduced aqueous phase solubilisation levels. Incomplete desorption of one or more lipid/surfactant components was most likely to occur based on the observation that both particle size distribution and solubilisation capacity of the redispersed Neusilin-SEDDS was in good agreement with that exhibited by the liquid SEDDS at reduced surfactant (i.e. Cremophor EL)-to-lipid ratios. The authors emphasised the importance of probing the residual adsorbed excipients and specific molecular interactions between polar surfactants and inorganic carrier materials to better understand the performance of solid S(M)EDDS formulations. Equally important is the characterisation and prevention of possible loss of any excipient materials during formulation preparation, particularly the volatile fractions (e.g. ethanol) which may also affect the emulsification and solubilisation properties. Taken together, a desirable formulation design of a solid S(M)EDDS should always balance between the drug solubility in lipids (to minimise the risk of recrystallisation), the carrier adsorbing/desorbing capacity (where complete formulation desorption may be promoted *via* surface modification of the pores, e.g. *via* pegylation), as well as the formulation particle sizes or specific surface area to ensure adequate drug/lipid loading and yet, complete formulation release within a reasonable time period.

### *Controlling Lipid Digestion*

The ability to control digestion behaviour of lipid-based carriers could be advantageous for manipulating the state of drug release and solubilisation during gastrointestinal transit. SLH microparticles with specific internal nanostructures (i.e. matrix or core-shell, spherical or non-spherical) have been successfully developed and used to control digestion kinetics of lipid colloids from the solid state (40,82). These microparticles were engineered from submicron emulsions encapsulated by silica nanoparticles of different sizes and porosity. Spherical, matrix-structured SLH microparticles were produced using mesoporous Aerosil®380 fumed silica nanoparticles (i.e. 50 nm nanoaggregates composed of primary particles of 7 nm; specific surface area 380 $m^2/g$); whereas mixed shape, thick porous-shell SLH microparticles with or without an oil interior were prepared using non-porous Ludox® silica nanoparticles (22 nm; specific surface area 140 $m^2/g$). Both SLH microparticle prototypes were shown to facilitate more predictable and enhanced lipid digestibility in comparison to a coarse oil solution and submicron emulsions. The increased lipid digestibility as promoted by the SLH microparticles could be related to their specific surface area and was ranked in the following order: Aerosil-SLH > Ludox-SLH > pure oil (Fig. 9). This highlights the valuable potential of the nanostructured SLH microparticles for manipulating the release and absorption of lipid food and drugs from the GI tract.

### *Variation in Drug Solubilisation Under Fed Versus Fasted States*

For S(M)EDDS mixtures composed of Captex 355, Capmul MCM and Solutol®HS15 that redispersed to form droplets of approximately 90 nm (formulation with mass ratio 5:3:2) and 35 nm (mass ratio 4:2:4), the solubilisation behaviour of progesterone resulting from digestion of these formulations has been evaluated under both simulated fasted and fed state digesting conditions (83). This study employed the commonly used fasted and fed state simulated intestinal fluids (i.e. FaSSIF and FeSSIF) consisting of bile salt:phospholipids mixed micelles in the molar ratio of 5:1.25 and 20:5 mM, respectively. As shown in Fig. 10 (top figure), both formulations were well solubilised upon dispersion in the mixed micellar media but prone to progressive precipitation as digestion occurred. A similar trend in fasted/fed variation was observed for both formulations, i.e. progesterone was better solubilised in FeSSIF than in FaSSIF with an approximately 20% difference between the two conditions at most time points. SMEDDS

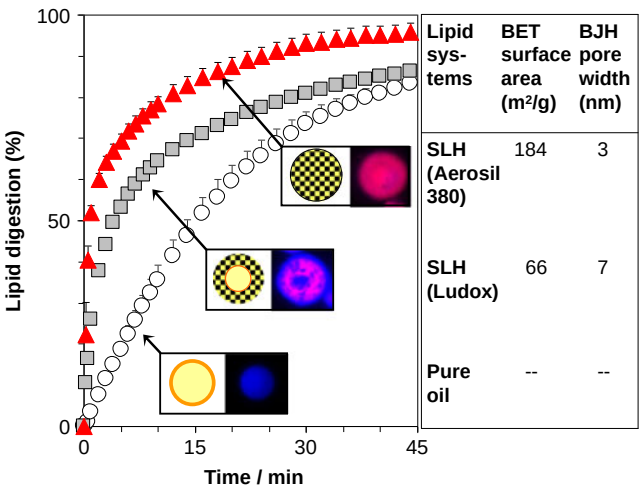


**Fig. 9** Enzyme-mediated lipid digestion profiles of medium-chain triglyceride oil and two SLH microparticles of different internal nanostructures under simulated human fasted-state intestinal conditions at 37°C. The digestion medium contained bile salt:phospholipids mixed micelles in the molar ratio of 5:1.25 mM and 1000 TBU/mL of pancreatic lipase activity [Reproduced with permission from reference (40)].

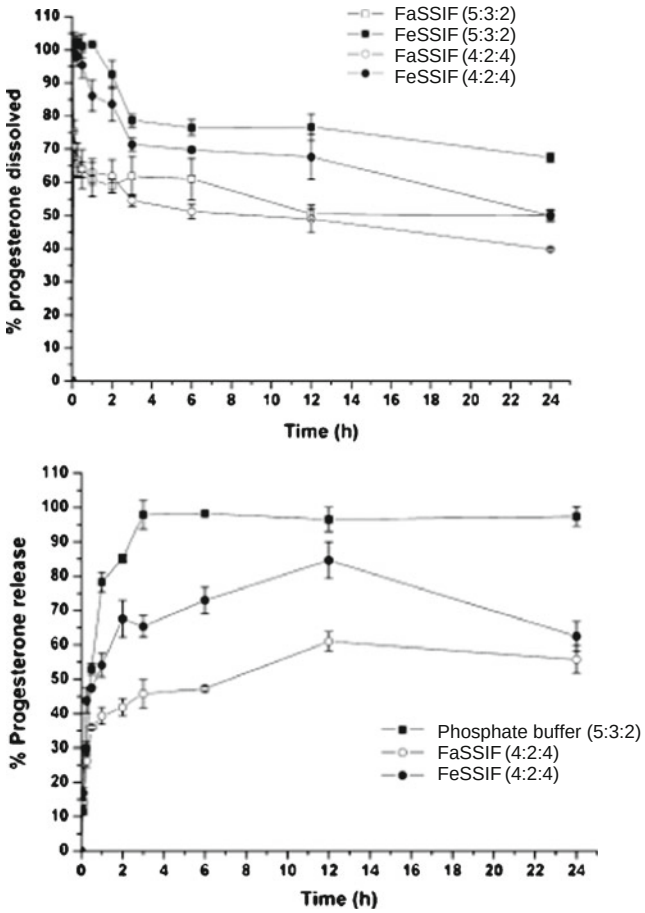


**Fig. 10** Percentage of progesterone solubilised as a function of time from progesterone loaded self-emulsifying mixtures (upper graph) and pellets (lower graph) in 7.5 ml of different media at pH 6.8, 37°C: fasted and fed-state simulated intestinal fluids (FaSSIF and FeSSIF) consisting of bile salt:phospholipids mixed micelles in the molar ratio of 5:1.25 and 20:5 mM, respectively, and phosphate buffer (mean ± standard deviation, $n = 3$). Both FaSSIF and FeSSIF contained 450 IU/mL of pancreatic lipase activity. The self emulsifying formulations were composed of Captex 355:Capmul MCM: Solutol HS15 in the mass ratio as indicated in parentheses. [Reproduced with permission from reference (83)].

with a mass ratio of 4:2:4, although exhibiting better emulsification capacity, has produced slightly lower solubilisation capacity for progesterone. This is plausibly attributed to its lower oil but higher surfactant content; as digestion progressed, this formulation generated relatively lower concentration of digestion products to support drug solubilisation in the mixed micellar media. This SMEDDS formulation was further processed into dry pellets based on MCC using the extrusion/spheronisation technique. Interestingly, the pellet formulation almost retained the equilibrium solubilising capacity of the liquid SMEDDS, but with an increasing solubilisation curves under both FeSSIF and FaSSIF conditions (bottom figure) rather than a precipitating trend as observed in the case of liquid SMEDDS. In this study, the liquid and solid SMEDDS formulations have not been successful in negating the variations between the fasted and fed-state solubilisation, nevertheless promising preservation of the SMEDDS performance after processing into dry pellets has been shown. In fact, such *in vitro* solubilisation/precipitation studies simulate only the pre-enterocyte processes and are limited in detecting mechanisms other than drug solubilisation for influencing the fed-fasted response of a lipid-based drug formulation. The presence of exogenous lipids and other excipients may significantly alter the intestinal cell permeation or cellular uptake of drugs, changes in the intestinal and hepatic metabolism, as well as stimulating drug uptake *via* the lymphatic route (84,85). The establishment of a more powerful *in vitro* model, such as a combined digestion-permeation experimental set-up, may provide a better indication of various mechanisms critical towards the negation of food effects and enhancement in the overall systemic exposure of drugs.

### *Cellular Permeation or Drug Uptake*

In general, the influence of lipid excipients rather than the solidification process or incorporation of solid carriers is thought to be significant in affecting the intestinal permeation of drugs that are vulnerable to the intestinal protective barriers (86–88). The role of various water-soluble or insoluble solid carriers as a permeation or uptake enhancer has yet to be systematically elucidated. Previous *in vitro* investigations suggested that digested lipids and bile salt components can enhance drug permeation by (*i*) increasing the intestinal membrane fluidity (thereby enhancing transcellular transport), or by (*ii*) disrupting the integrity of the tight junctions (thus facilitating paracellular or intercellular uptake) (89). These events are mostly dose- and time-dependent, and such dietary-induced damage has known to be reversible in most cases (90). In addition to this, there have been considerable reports suggesting the inhibitory effects of various lipid and surfactant excipients on the intestinal P-glycoprotein (P-gp) efflux and CYP3A metabolising systems, which eventually leads to an enhanced drug uptake (91). For example, vitamin E TPGS (92–94), Peceol (i.e. glycerol monooleates), Gelucire 44/14 (i.e. PEG, tri- and diglycerides) (95), sodium taurocholate (NaTC) (96), *1*-monopalmitin (i.e. monoglycerides) (97) and the non-ionic surfactant Cremophor EL (i.e. polyoxyethylene-glycoltriricinoleate) (98), have been shown to inhibit P-gp or to down regulate its expression. Other lipid excipients, such as oleic acid and micellar solutions (99), have been specifically identified as potent CYP3A inhibitors.

Likewise, there has been a significant number of studies supporting the use of proliposomal formulations as intestinal uptake or penetration enhancers based on experiments conducted using the conventional Caco-2 cell line, *in situ* rat intestinal perfusion, everted rat intestinal sac and parallel artificial membrane permeability assay (PAMPA). Such

**Table IV** Examples of Studies Examining the Oral Absorption of Poorly Water-Soluble, Lipophilic Drugs From Various Solid-State Lipid-Based Formulations: Dry Emulsions, Silica-Lipid Hybrid (SLH) Microparticles, Solid Self-(Micro)Emulsifying Drug Delivery Systems [S(M)EDDS] and Proliposomes

| Compound | Lipid excipients | Solid carrier | Drying method | Study subject | Rank order of bioavailability parameters ($p < 0.05$) | Ref. |
|---|---|---|---|---|---|---|
| **Dry emulsions** | | | | | | |
| Vitamin E acetate (log $P = 12.2$) | Cottonseed oil | ▪ Silicon dioxide (Aerosil 200) | Spray-drying | Dogs ($n = 2$) | (filled in hard gelatin capsules; under fed state) ***F*** and $\boldsymbol{C_{max}}$: DE ≈ liquid emulsions ≈ drug-oil suspension | (109) |
| 5-PDTT (log $P = 3.7$) | Miglyol 812 | ▪ Maltodextrin | Spray-drying | Rabbits ($n = 3$) | ***F***: DE (3.2-fold) > β-CD<br>$\boldsymbol{T_{max}}$: β-CD < DE (3-fold) | (19) |
| Lu 28–179 (log $P = 8.5$) | MCT | ▪ HPMC (powder);<br>▪ Trehalose/gelatin/ Neusilin US2 (tablets) | Spray-drying | Dogs ($n = 4$) | (filled in hard gelatin capsules except for β-CD solution)<br>***F***: β-CD solution (14%) ≈ DE powder (11%) ≈ DE tablets (10%) ≈ MCT solution (6%)<br>$\boldsymbol{T_{max}}$: DE tablets (3.5 h) ≈ DE powder (3.3 h) ≈ MCT solution (2 h) ≈ β-CD solution (1.8 h) | (37) |
| Amlodipine besylate (log $P = 3.0$) | Labrafil M1944CS | ▪ Dextrin | Spray-drying | Rats ($n = 5$) | ***F***: DE (2.9-fold) ≈ Norvasc® suspension (2.8-fold) > aqueous suspension<br>$\boldsymbol{C_{max}}$: Norvasc® suspension (3-fold) ≈ DE (2.6-fold) > aqueous suspension | (20) |
| Lovastatin (log $P = 4.3$) | Phosal 53 MCT | ▪ Starch sodium octenyl succinate | Spray-drying | Rats ($n = 5$) | ***F***: DE (1.8-fold) > β-CD (1.2-fold) > aqueous suspension<br>$\boldsymbol{C_{max}}$: DE (2.3-fold) > β-CD (1.6-fold) > aqueous suspension | (36) |
| Indomethacin (log $P = 1.0$) | Soybean oil | ▪ α-cyclodextrin (as powder and beads) | Freeze-drying | Rats ($n = 6$) | (filled in hard gelatin capsules; under fasted & fed states)<br>***F***: Naked CD-beads (1.8-fold) ≈ DE (1.5-fold) > Coated CD-beads (1.2-fold) > Indocid®<br>$\boldsymbol{C_{max}}$: DE (1.7-fold) > Naked CD-beads (1.2-fold) > Indocid® ≈ Coated CD-beads<br>$\boldsymbol{T_{max}}$: DE ≈ Indocid® < Naked CD-beads (1.8-fold) < Coated CD-beads (2.3-fold) | (101) |
| **SLH microparticles** | | | | | | |
| Celecoxib (log $P = 3.5$) | Miglyol 812 | ▪ Silicon dioxide (Aerosil 380); | Spray-drying | Rats ($n = 5$) | ***F***: SLH (1.5-fold) ≈ Celebrex® (1.3-fold) > Maltodextrin-DE (1.2-fold) ≈ Lipid emulsions | (39) |

**Table IV** (continued)

| Compound | Lipid excipients | Solid carrier | Drying method | Study subject | Rank order of bioavailability parameters ($p < 0.05$) | Ref. |
|---|---|---|---|---|---|---|
| | | | | | (1.2-fold) ≈ Lipid solution ≈ Aqueous suspension<br>$C_{max}$: SLH (2-fold) > Celebrex® (1.3-fold) ≈ Maltodextrin-DE ≈ Aqueous suspension ≈ Lipid emulsions ≈ Lipid solution | |
| | | ▪ Maltodextrin | | | | |
| | Capmul MCM | ▪ Silicon dioxide (Aerosil 380) | Spray-drying | Dogs ($n = 4$) | (filled in hard gelatin capsules)<br>**F**: SLH fasted (6.5-fold) ≈ Lipid solution fasted (5.0-fold) > Neat drug fed (2.9-fold) ≈ Neat drug fasted<br>$C_{max}$: SLH fasted (11-fold) > Lipid solution fasted (8-fold) > Neat drug fed (6-fold) ≈ Neat drug fasted | (40) |
| Indomethacin (log $P = 1.0$) | Miglyol 812/lecithin | ▪ Silicon dioxide (Aerosil 380) | Spray-drying | Rats ($n = 5$) | **F**: SLH (1.7-fold) > Lipid emulsions (1.2-fold) ≈ Aqueous suspension<br>$C_{max}$: SLH (1.7-fold) > Lipid emulsions (1.3-fold) ≈ Aqueous suspension | (41) |
| | Miglyol 812/oleylamine | ▪ Silicon dioxide (Aerosil 380) | Spray-drying *vs.* Phase coacervation (vacuum filtration) | Rats ($n = 5$) | **F**: Phase coacervated-SLH (1.9-fold) ≈ Spray dried-SLH (1.8-fold) > Lipid emulsions (1.2-fold) ≈ Aqueous suspension<br>$C_{max}$: Phase coacervated-SLH (1.9-fold) ≈ Spray dried-SLH (1.7-fold) > Lipid emulsions (1.3-fold) ≈ Aqueous suspension | (42) |
| **Solid S(M/N)EDDS** | | | | | | |
| Simvastatin (log $P = 4.7$) | Soybean oil/Capryol90/ Tween80/CremophorEL | ▪ Silicon dioxide (Aerosil 200) | Physical blending | Rats ($n = 6$) | **Reduction in total cholesterol level** (at 24 h post-dose): DE > aqueous suspension ≈ placebo treatment | (117) |
| Nimodipine (log $P = 3.1$) | Ethyl oleate/Labrasol/ CremophorRH40 | ▪ Dextran 40 | Spray-drying | Rabbits ($n = 6$) | **F**: Solid SMEDDS (2.6-fold) ≈ Liquid SMEDDS (1.9-fold) > Conventional tablet<br>$C_{max}$: Solid SMEDDS (6.5-fold) ≈ Liquid SMEDDS (5-fold) > Conventional tablet<br>$T_{max}$: Liquid SMEDDS (3-fold) < Solid SMEDDS (1.2-fold) ≈ Conventional tablet | (66) |
| Nitrendipine (log $P = 2.9$) | Miglyol 812/Cremophor RH40/Tween80/TranscutolP | ▪ Silicon dioxide (Syloid 244FP)/ Crospovidone/MCC/ Lactose (as pellets) | Physical blending and extrusion/ spheronisation | Dogs ($n = 6$) | (filled in hard gelatin capsules)<br>**F**: Liquid SEDDS (1.9-fold) ≈ SEDDS pellets (1.6-fold) > Conventional tablet | (102) |

**Table IV** (continued)

| Compound | Lipid excipients | Solid carrier | Drying method | Study subject | Rank order of bioavailability parameters ($p < 0.05$) | Ref. |
|---|---|---|---|---|---|---|
| | | | | | ***C*max**: Liquid SEDDS (3.1-fold) ≈ SEDDS pellets (2.4-fold) > Conventional tablet | |
| Docetaxel (log $P = 3.2$) | Labrafac/Cremophor RH40/Transcutol P | ▪ Lactose/HPMC | Spray-drying | Rats ($n = 5$) | ***F***: Solid SEDDS (8.8-fold) ≈ Liquid $SEDDS_{no\ carrier}$ (6.1-fold) > Aqueous suspension<br>***C*max**: Solid SEDDS (5.1-fold) ≈ Liquid $SEDDS_{no\ carrier}$ (3.4-fold) > Aqueous suspension | (58) |
| Silymarin (milk thistle) (log $P < 2$) | Akoline MCM/Miglyol 812/Tween 80/soy lecithin/propylene glycol | ▪ MCC/Lactose | Physical blending and extrusion/ spheronisation | Rats ($n = 4$) | ***F***: Dispersed SEDDS pellets (207-fold) > Aqueous suspension<br>***C*max**: Dispersed SEDDS pellets (52-fold) > Aqueous suspension<br>***T*max**: Aqueous suspension (5-fold) < Dispersed SEDDS pellets (double peak $C_p$-time profiles) | (118) |
| Cydosporine A (log $P = 2.9$) | Labrafil M2125CS/Propylene glycol/Cremophor RH40/ethanol | ▪ Neusilin US2 (as powder)<br>▪ Neusilin US2/ crospovidone/ magnesium stearate (as liquid loadable tablets) | Physical blending and adsorption | Dogs ($n = 6$) | (filled in gelatin capsules except for SMEDDS tablets)<br>***F*** and ***C*max**: Neoral® ≈ Solid SMEDDS powder ≈ SMEDDS tablets (0.8-fold) ≈ Liquid SMEDDS (0.7-fold) | (103) |
| Dexibuprofen or S(+)-ibuprofen (log $P = 4.0$) | Labrasol/Capryol 90/Labrafil M1944CS | ▪ Silicon dioxide (Aerosil 200) | Spray-drying | Rats ($n = 6$) | (filled in mini hard capsules)<br>***F*** and ***C*max**: Solid SEDDS (2.1-fold) > Pure drug powder | (67) |
| Vinpocetine (log $P = 4.2$) | Akoline MCM/peanut oil/Polysorbate 80 | ▪ MCC/lactose | Physical blending and extrusion/ spheronisation | Rats ($n = 4$) | ***F***: Dispersed SEDDS pellets (2.4-fold) > Dispersed drug-carrier physical mixture<br>***C*max**: Dispersed SEDDS pellets (2.1-fold) > Dispersed drug-carrier physical mixture | (114) |
| | Labrafac/oleic acid/Cremophor EL/Transcutol P | ▪ Gum acacia | Physical blending | Rats ($n = 6$) | (under fasted and fed states)<br>***F***: Solid SMEDDS (1.6–1.9-fold) > drug-poloxamer solid dispersions (1.1–1..2-fold) ≈ conventional tablets ≈ aqueous suspension<br>***C*max**: Solid SMEDDS (1.3–1.5-fold) > drug-poloxamer solid dispersions (1.1–1.2-fold) ≈ conventional tablets ≈ aqueous suspension | (87) |
| Sirolimus (log P = 5.8) | Labrafil M1944CS/Cremophor EL/Transcutol P | ▪ MCC/lactose/sodium carboxymethyl starch | Physical blending and extrusion/ spheronisation | Dogs (n = 6) | (filled in gelatin capsules except for commercial tablets) | (104) |

**Table IV** (continued)

| Compound | Lipid excipients | Solid carrier | Drying method | Study subject | Rank order of bioavailability parameters ($p < 0.05$) | Ref. |
|---|---|---|---|---|---|---|
| | | | | | ***F*** and $C_{max}$: SMEDDS pellets (1.4-fold) > Rapamune® tablets | |
| Coenzyme Q10 or Ubiquinone (log P = 3.6) | MCT/sucrose ester of fatty acid | ▪ HPC | Spray-drying | Rats (n = 6) | ***F*** and $C_{max}$: Solid SEDDS (5-fold) > Aqueous suspension | (79) |
| Flurbiprofen (log P = 3.6) | Labrafil M1944CS/Labrasol/ Transcutol HP | ▪ Gelatin | Spray-drying | Rats (n = 6) | ***F*** and $C_{max}$: Solid SEDDS in hard gelatin capsules (3.6-fold) > Fluben® tablets (cut into small oblong form) | (60) |
| Danazol (log *P* = 4.2) | ▪ (Medium chain, MC) Captex 355/Capmul MCM/ Cremophor EL/ethanol<br>▪ (Long chain, LC) Soybean oil/Maisine 35-1/ Cremophor EL/ethanol | ▪ Neusilin US2 | Physical blending | Rats (*n* = 4) | ***F*** and $C_{max}$: Liquid MC-SEDDS (2-fold) > Solid MC-SEDDS;<br>Liquid LC-SEDDS (2.4-fold) > Solid LC-SEDDS | (81) |
| Zaleplon | Labrafil M1944CS/Transcutol P/Vitamin E TPGS | ▪ Neusilin US2 | Physical blending | Rats (*n* = 3) | ***F*** and $C_{max}$: Solid SEDDS (3.5-fold) > Aqueous suspension | (116) |
| **Proliposomes/Proniosomes** | | | | | | |
| Cydosporine A (log *P* = 2.9) | Egg lecithin/Cremophor EL | ▪ Lactose | Direct spraying under reduced pressure/ film deposition by rotary evaporation | Rats (*n* = 4) | ***F***: Proliposomes (9.6-fold) > Panimun Bioral® microemulsions (7-fold) > Aqueous suspension<br>$C_{max}$: Proliposomes (3.3-fold) > Panimun Bioral® microemulsions (2.7-fold) > Aqueous suspension | (71) |
| Dehydro-silymarin (Water solubility = 51 μg/mL at 37°C) | Soybean lecithin/cholesterol/ sodium cholate | ▪ Mannitol | Rotary film dispersion/ freeze drying | Rabbits (*n* = 3) | ***F***: Proliposomes (2.3-fold) > Aqueous suspension<br>$C_{max}$: Proliposomes (5-fold, double peak $C_p$-time profiles) > Aqueous suspension | (72) |
| Vinpocetine (log P = 4.2) | Soybean lecithin/cholesterol | ▪ Sorbitol | Film deposition by rotary evaporation | Rabbits (n = 6) | ***F***: Proliposomes (3.5-fold) > Aqueous suspension of drug-sorbitol physical mixtures | (115) |
| Zaleplon | ▪ (Neutral) Phospholipon 90H (soy lecithin)/cholesterol<br>▪ (Anionic) Phospholipon 90H/ cholesterol/dicetyl phosphate<br>▪ (Cationic) Phospholipon 90H/cholesterol/stearylamine | ▪ Pearlitol SD200 (spray-dried mannitol) | Film deposition by rotary evaporation | Rats (*n* = 6) | ***F***: Cationic proliposomes (4.6-fold) > Anionic proliposomes (3-fold) > Neutral proliposomes (2-fold) > Aqueous suspension<br>$C_{max}$: Cationic proliposomes (2.9-fold) ≈ Anionic proliposomes (2.4-fold) ≈ Neutral proliposomes (2-fold) > Aqueous suspension | (49) |
| Halofantrine (log *P* = 8.5) | Distearoylphospha-tidylcholine | ▪ Cellulose acetate phthalate | Film deposition by rotary evaporation/ spray coating | Rats (*n* ≥ 5) | ***F***: Proliposomes (1.5-fold) > Drug-lipid physical mixtures (suspension) ≈ Aqueous suspension | (74) |

**Table IV** (continued)

| Compound | Lipid excipients | Solid carrier | Drying method | Study subject | Rank order of bioavailability parameters ($p < 0.05$) | Ref. |
|---|---|---|---|---|---|---|
| | | | | | **$C_{max}$**: Proliposomes (2-fold) > Drug-lipid physical mixtures (suspension) ≈ Pure drug | |
| Diphenyl dimethyl bicarboxylate (fruit extracts) (Water solubility ≤ 4 μg/ml) | Tween 80/cholesterol/ stearylamine | ▪ Sorbitol | Film deposition by rotary evaporation | Rats ($n = 10$) | **Elevation of serum liver enzymes** (i.e. degree of hepatocellular damage): Control (healthy) < Proniosomes (1.5 times) < Aqueous suspension (2.2 times) < Placebo treatment (3.1 times) | (119) |

All studies reported were conducted under fasted conditions where the formulations were administered in the form of reconstituted dispersions or suspensions unless otherwise specified. The partition coefficient (log *P*) of each drug was obtained from the reference quoted or the handbook of Clarke's Analysis of Drugs and Poisons

potential has been exemplified for a number of proliposomal formulations: a proliposome containing progesterone, dimyristoyl-phosphotidylcholine, polysorbate 80 and microcrystalline cellulose (73); a proliposome composed of exemestane, distearoyl-phosphatidylcholine, cholesterol and dimyristoyl-phosphatidylglycerol (100); and another formulation encapsulating zaleplon with hydrogenated soyphosphatidylcholine and cholesterol either in a neutral, anionic or cationic form (49). The latter study has significantly highlighted the role of surface charge of a pro-vesicular system in affecting the intestinal permeation and thereby, increasing the oral bioavailability of zaleplon; this is discussed for further details in the following section.

## *In Vivo* Performance

Case examples of preclinical studies examining the oral bioavailability and efficacy of poorly water-soluble, lipophilic drugs resulting from various classes of transformed solid dosage forms of lipid-based formulations are summarised in Table IV. Details such as lipid excipients, solid carriers, drying methodology, the solid dosage forms investigated (i.e. in the forms of redispersed suspensions, filled hard gelatin capsules, pellets or tablets) and the subject of study are specified for each study. The pharmacokinetics was assessed based on three major parameters, i.e. relative bioavailability ($F$), maximum plasma concentration ($C_{max}$), and the time taken ($t_{max}$) to achieve $C_{max}$. Formulations that have been evaluated against commercial products include amlodipine dry emulsions (20), indomethacin dry emulsions (101), celecoxib SLH microparticles (39), nimodipine solid SMEDDS (66), nitrendipine SEDDS pellets (102), cyclosporine A SMEDDS tablets and proliposomes (71,103), vinpocetine solid SMEDDS (87), sirolimus SMEDDS pellets (104), and flurbiprofen solid SEDDS (60). It is noteworthy that all of these formulations have demonstrated at least bioequivalence (i.e. a difference less than 25%) with the corresponding commercial formulations. An exception is the indomethacin dry emulsion which successfully produced a greater drug bioavailability than Indocid® based on its synergistic solubilising power resulting from formulation lipids and α-cyclodextrins (101). In the following discussion, case studies are selected on the basis that these drugs (with different lipophilicity and solubility properties) have either been investigated for more than one formulation type or have been studied in a more systematic manner (e.g. for food effects, comparison between liquid and solid forms) to illustrate the absorption enhancing capacity of each formulation type after transforming into solid forms.

### *Enhanced Drug Absorption*

*Cyclosporine A (CsA).* The most well-known example of an oral self-emulsifying product is the marketed SMEDDS formulation of the immunosuppressant, cyclosporine A (Neoral®, Novartis),

which is a microemulsion preconcentrate containing corn oil-derived glycerides as lipids, Cremophor RH40 as a water-soluble surfactant, propylene glycol and ethanol as cosolvents, as well as DL-α-tocopherol as an antioxidant (15). Neoral® was shown to outperform the earlier marketed SEDDS formulation (Sandimmun®, Novartis), which contains corn oil, Labrafil M-2125-CS and ethanol, in several ways: (*i*) Neoral® exhibited faster and better absorption independent of the bile flow, specifically with 1.7–2.4-fold greater fasted-state bioavailability with improved dose linearity over 200–800 mg therapeutic dose levels (105,106); (*ii*) Neoral® (at 180 mg CsA) demonstrated insignificant food effects while Sandimmun® (at 300 mg CsA) produced drastically delayed absorption (i.e. 2-times longer $t_{max}$) and 37% increased bioavailability when co-administered with a fat-rich meal (107); it is of note that after dose-normalisation (assuming dose-linear performance for Neoral®), the bioavailability of Neoral® was computed to be 1.9 and 1.2-fold greater than that of Sandimmun® in the fasted and fed state, respectively; (*iii*) Neoral® significantly reduced intra- and intersubject variability in $C_{max}$, $t_{max}$ and bioavailability of CsA in comparison to that of Sandimmun® (i.e. coefficient of variations 3–22% *c.f.* 19–41%) (108). It is apparent that enhanced lipid dispersion and rapid formation of smaller lipid droplets in the GI tract is advantageous in producing more predictable and enhanced absorption of CsA with negated food effects.

To further evaluate the performance of CsA-SMEDDS in its transformed solid form, Sander *et al.* (103) has recently investigated the use of Neusilin® US2 for converting a liquid CsA-SMEDDS (29.9 nm comparable to Neoral® of 26.2 nm) into two different solid dosage forms, i.e. one as an adsorbed powder formulation and the other in the form of liquid loadable tablets with or without crospovidone as the superdisintegrant. With exception for the SMEDDS tablets, all formulations were filled into hard gelatin capsules (size #2 Capsugel) prior to administration to male beagle dogs under fasting conditions. Both solid SMEDDS powder and tablets in the presence of crospovidone successfully produced statistically comparable $F$ and $C_{max}$ with reference to the precursor liquid SMEDDS and the Neoral® preconcentrate formulation (Table IV). The SMEDDS tablets were only able to retain the drug release and solubilisation properties of liquid SMEDDS when a superdisintegrant was incorporated, which facilitated rehydration of the encapsulated liquid SMEDDS by reducing its length of diffusion path to the surrounding medium or *vice versa*. Simlarly, there have been a number of other studies illustrating the importance of disintegrants with swelling properties (such crospovidone, microcrystalline cellulose, croscarmellose, hydroxypropylcellulose and polyvinylpyrrolidone) in facilitating drug release from SMEDDS when processed into the forms of tablets and pellets (102,104,114,118).

For the same drug model, another study conducted by Shah *et al.* (71) has supported the use of a proliposomal formulation in enhancing its oral bioavailability in comparison with a marketed microemulsion product (Panimun Bioral®) and an aqueous suspension. It was shown in a series of photomicrographs that the proliposomal formulation (composed of egg lecithin, Cremophor EL and lactose) rapidly redispersed in water to form multilamellar vesicles within a minute. The average particle sizes of the hydrated proliposomes ranged between 7 and 12 μm, which increased with higher drug loading levels. Despite the relatively large redispersed particle size, this proliposomal formulation demonstrated a 9.6-fold greater bioavailability and a 3.3-fold higher $C_{max}$ in comparison to the aqueous suspension, and these were significantly higher than that of the commercial product.

*Celecoxib (CEL).* Based on a model non-steroidal anti-inflammatory drug, celecoxib, a series of systematic oral bioavailability studies have been conducted for evaluating the *in vivo* viability of the nanostructured SLH microparticles. The investigated SLH formulation was prepared using spray-drying and composed of medium-chain lipid emulsions stabilised by Aerosil® 380 silica nanoparticles. An absorption study conducted in a fasted rat model has shown statistically higher bioavailability and $C_{max}$ for the SLH formulation in comparison to a maltodextrin-coated dry emulsion, submicron lipid emulsions, lipid solution and an aqueous suspension (39). In another dose-dependent drug absorption study, the SLH formulation successfully demonstrated bioequivalence with the marketed product, Celebrex® (administered as a suspension), across a CEL dose range of 5–50 mg/kg (63). The bioavailability and $C_{max}$ values obtained for both SLH and Celebrex® were consistently 2-fold higher than an aqueous suspension over this dose range.

Given that rats do not have a gallbladder and normally produce bile secretions independent of dietary or formulation lipid intake, they are not ideal for evaluating the food effect on drug absorption. The CEL formulations were thus further evaluated for the food effect in a beagle dog model (40). Each formulation was filled into hard gelatin capsules and administered only under fasting conditions for a lipid solution and an SLH formulation, whereas the pure drug was administered under both fed and fasted-states for demonstrating the ordinary food effect on its absorption. The pharmacokinetic parameters revealed a remarkably enhanced food-mimicking effect for the SLH formulation with a 6.5-fold greater bioavailability and 11-fold higher $C_{max}$ in comparison to that of the pure drug under fasting conditions; and the bioavailability increment was 2-fold higher than that of the pure drug under fed-state. Such degree of enhancement in CEL oral absorption is thus far the highest among those reported (or predicted) in dogs and humans (109–111). The major mechanism behind the enhanced absorption was related to the nanostructured silica network for facilitating more efficient lipid processing under digesting conditions and thereby, triggering rapid formation of more solubilising mixed micellar phases for CEL.

Furthermore, the role of hydrophilic silica nanoparticles in preventing recrystallisation of the released drug molecules should also be considered, given that porous adsorbents have been extensively used for direct loading of drugs *via* physical adsorption from a solvent-based solution. It is noted that a recent study has reported negligible effect of Aerosil®200 silica nanoparticles in inhibiting the precipitation of danazol during an *in vitro* digestion study of a SEDDS formulation (112), nevertheless research into this area requires more extensive and systematic investigations.

***Vinpocetin.*** Vinpocetin, a nootropic drug used in the prevention and treatment of cerebro-vascular diseases, is susceptible to hepatic first-pass metabolism (i.e. 75% pre-systemic degradation) which typically results in as low as ~7% fasted-state oral bioavabilability (113). Formulation of vinpocetin as solid-SMEDDS and proliposomes have demonstrated effective oral delivery and enhanced bioavailability in a number of studies conducted in rats and rabbits (87,114,115). All these studies illustrated similar mechanisms whereby microencapsulation of vinpocetin in the lipid matrices significantly improved its dissolution and intestinal permeation, as well as triggering its lymphatic uptake by exploiting the lymphotropic potential of long-chain acyl lipids (e.g. oleic acid, peanut oil). In two of these studies (114,115), although comparison with the pure drug is lacking, the physical drug-carrier mixtures have shown significantly lower bioavailability than the solid-SMEDDS and proliposomes; this implies that the solid carriers (i.e. MCC/lactose and sorbitol) have negligible effects in contributing towards these absorption mechanisms.

The study of Chen *et al.* (87) specifically addressed the food effect on the absorption of vinpocetin from various non-lipid and lipid-based formulations. A solid-SMEDDS composed of Labrafac, oleic acid, Cremophor EL and Transcutol P using gum acacia as a solid carrier was developed. Under both fasted and fed conditions, this formulation was shown to produce significantly higher $F$ and $C_{max}$ in comparison to a drug-poloxamer solid dispersion, a conventional tablet and a pure drug aqueous suspension. The authors also highlighted a higher degree of variation between the fed *versus* fasted-state bioavailability for all the control formulations as compared to that of the solid SMEDDS; however, these differences were lack of statistical significance.

***Zaleplon.*** Zaleplon is a poorly water-soluble pyrazolopyrimidine hypnotic and anticonvulsant drug. Two types of dry lipid-based formulations have been shown to increase the oral bioavailability of zaleplon in fasted rat models, i.e. a solid SEDDS (116) and proliposomes of different surface charges (49). The latter study emphasised the importance of surface charge of a proliposomal formulation in affecting the intestinal permeation and absorption of zaleplon *via* a comparison between 'neutral', anionic and cationic proliposome. The neutral proliposomes was formulated with hydrogenated soyphosphatidylcholine and cholesterol adsorbed onto spray-dried porous mannitol (average zeta potential, $\zeta = 3.1 \pm 2.6$ mV), while the anionic form in the presence of dicetyl phosphate ($\zeta$ = negative $19.1 \pm 2.4$ mV), and the cationic form with stearylamine ($\zeta$ = positive $26.0 \pm 2.2$ mV). Microscopic imaging showed that all proliposome powder formed tubular structures on contact with water, and redispersed on manual agitation to produce multilamellar vesicles of <300 nm. Orally dosed absorption study in rats showed a bioavailability rank order of cationic proliposomes (4.6-fold) > anionic proliposomes (3-fold) > neutral proliposomes (2-fold) > pure drug, while $C_{max}$ values remained comparable across the different formulations. This rank order was shown to be consistent with the effective permeability coefficient obtained for the various systems in a rat intestinal perfusion study conducted in parallel. These results confirmed the effective use of a charged proliposomal system in enhancing the intestinal permeation of drugs, potentially *via* enhanced formulation dispersion and stability, and more importantly *via* mucoadhesion in the GI tract.

### *Reduced Drug Absorption*

***Danazol.*** Different from the findings of Sander *et al.* (103) on cyclosporine-solid SMEDDS (in dogs), another study on a medium-chain (MC) and a long-chain (LC) danazol-solid SEDDS (in rats) has unfavourably shown a ≥2-fold lower $F$ and $C_{max}$ in comparison with the corresponding parent liquid SEDDS (81). Overall, the bioavailability data showed the following rank order: liquid LC-SEDDS ($AUC_{0\rightarrow 8h} = 183.1 \pm 82$ ng.h/mL) > liquid MC-SEDDS ($139.4 \pm 14.7$ ng.h/mL) > solid LC-SEDDS ($76.6 \pm 33.2$ ng.h/mL) > solid MC-SEDDS ($70.7 \pm 18.0$ ng.h/mL). The differences between the liquid and solid SEDDS formulations were statistically significant ($p < 0.05$). Reduction in the bioavailability for both solid MC- and LC-SEDDS were consistent with the *in vitro* drug solubilisation assessment performed under both digesting and non-digesting conditions, which have been described in the earlier section (under "Controlling Drug Release or Solubilisation"). It was also reported that incomplete desorption and release of the liquid lipid excipients, particularly the surfactant component Cremophor EL, has resulted in approximately 2–3-times enlargement in the redispersed droplet sizes in conjunction with the reduction in drug solubilisation. Based on these controversial performances for cyclosporine and danazol, the suitability of Neusilin® US2 as an adsorbent for liquid S(M)EDDS requires careful consideration and optimisation for its formulation desorption issues. The large particle sizes may result in more restricted intra-particle wetting or hydration as described by Agarwal *et al.* (78).

## Conclusion and Future Prospects

While a standard pharmacopoeial protocol has yet to be established for specific evaluation of lipid-based formulations, there is noticeable progress in the development and validation of *in vitro* assessment tools for investigating the biopharmaceutical design of various lipid-based formulations. This inherently leads to substantial notice and interests in taking the conventional lipid-based formulations one step further towards clinical applications by transforming the liquid and semisolid lipid-based formulations into solid dosage forms, which are attractive strategies to confer convenience in the manufacturing and handling processes, prolong product shelf-life, as well as to facilitate the ease of administration.

Four major types of solid-state lipid-based formulations have been identified in this review, specifically dry emulsions, SLH microparticles, solid S(M/N)EDDS and proliposomes/proniosomes. These formulations generally require the use of a water-soluble or dispersible solid carrier (alternatively a cryoprotectant in the case of proliposomes/proniosomes) to be converted into a dry, powdery form. Existing research studies have demonstrated the flexibility of these formulation powders to be further processed into granules, pellets, tablets (in combination with other tableting aids for enhancing compressibility and disintegration), or simply encapsulated in hard gelatin capsules. It is yet challenging to outline clear criteria as to which type of formulation should be preferred over the others in a given case. Cross comparison between these four different formulations for their biopharmaceutical performance in a more systematic manner (e.g. based on the same model drug at a fixed dose regimen, similar experimental set-up, study subjects and dosing conditions) may make it possible to establish a general guide for the selection of solid carriers and lipid phases to address specific delivery challenges in accordance to the drug properties. Importantly, consideration in formulation design of a dry lipid-based formulation is ideally built around a number of key parameters: solubility of drugs in lipid/surfactant excipients; chemical stability, porosity and particle sizes of solid carriers, which in turn control encapsulation efficiency, formulation redispersion, drug release or formulation desorption properties; choice and mass ratio of lipids:solid carriers which have great impact on the formulation powder flowability and compressibility into final dosage forms; and the scaling-up and manufacturing opportunities.

Ideally, good solidification methodologies would result in either preservation or enhancement of the drug release or solubilisation performance of lipid-based formulations from their dry states. The case studies presented herein have supported the promising applications of various lipid-based formulations in the solid-state for enhancing the physicochemical stability of colloidal lipid vehicles and sensitive drug molecules. These 'solidified' lipid-based formulations demonstrated great potential as viable dosage forms for facilitating desirable biopharmaceutical functions, specifically (*i*) *controlling lipid colloid digestion* (where molecular interactions between enzyme-carrier-formulation lipids are yet to be better characterised); (*ii*) *controlling drug release or solubilisation* (where better understanding of formulation adsorption/desorption mechanisms is warranted); (*iii*) *addressing the variation issues between fed and fasted-state performance* (limited evidence have been reported and a more powerful *in vitro* diagnostic tool such as a combined digestion-permeation model may be useful to better predict the fed/fasted responses); and (*iv*) *manipulating cellular uptake of drugs* (further investigations are warranted to exemplify the role of various solid carriers on cellular permeation or uptake of drugs). The significant number of promising preclinical data accumulated from various studies is envisaged to foster the translation of these functional solid-state lipid-based formulations into clinical trials and practice.

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