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Bridging the gaps between academic research and industrial product developments of lipid-based formulations

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ABSTRACT

Lipid-based formulations, including self-emulsifying drug delivery systems (SEDDS), are an interesting formulation technology that enables the clinical use of compounds for which a low aqueous solubility may be a limitation. From an academic perspective, the technology is interesting on several levels: what drives solubility, what determines bioperformance, what is the potential for solidification etc. From an industrial perspective, >35 lipid-based formulations are available and there is an unknown number of projects in the pipeline. Hence, while there is scientific interest from both academic and industrial perspectives, the agendas/needs in the two settings are different. From an industrial perspective, risks are associated with uncertainty; hence the more that is known about a technology the better – knowledge that in principle can be generated in both the academia and industry. This focuses on the development of lipid-based formulations and the knowledge gaps that could be investigated – with the hope that all stakeholders in the field of lipid-based formulations, including academia, industry, CRO's, lipid excipient manufacturers etc., would share their insight, so that this technology can be even further developed. Some of the gaps discussed include the selection of compounds suited for lipid-based formulations, which potential modifications that could be investigated, e.g., lipophilic salts, what is a relevant definition of accelerated stability studies, how best to construct an industrial development program of a lipid-based formulation, etc.

Contents

Abbreviations: BSC, biopharmaceutical classification system; cGMP, current Good Manufacturing Practice; CRO, contract research organisation; CMO, contract manufacturing organisation; FDA, Food and Drug Administration; GRAS, generally recognised as safe; HPMC, hydroxypropyl methylcellulose; ICH, International Conference on Harmonization; IVIVC, in vitro in vivo *correlation*; PEG, Polyethyle glycol; P-gp, P-glycoprotein; SEDDS, self-emulsifying drug delivery systems; SMEDDS, self-microemulsifying drug delivery system..

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1. Introduction

The majority of drug molecules in pharmaceutical pipelines are class II or IV according to the biopharmaceutical classification system (BSC), i.e., compounds with a high/low permeability or a low aqueous solubility, respectively [1–4]. These compounds were discovered and optimised through a modern drug discovery process including high-throughput screening, computational modelling, etc. While this process has a proven ability to identify high potency compounds, it has also led to the selection of compounds with suboptimal physico-chemical and pharmaceutical properties. Such suboptimal properties, e.g., low aqueous solubility, often translate into poor or variable absorption and pharmacokinetic profiles when administered orally in conventional dosage forms, such as tablets or capsules.

Thus, the use of conventional dosage forms to deliver this class of molecules is not always sufficient to produce the required drug exposure. Several technologies have therefore been developed to enhance bioavailability, including amorphous solid dispersions, nanoparticle systems and lipid-based drug delivery systems, thereby improving the dissolution rate and/or the apparent solubility of such compounds [5]. While each of these different systems has potential and limitations, commercial products exist using these technologies, i.e., technical and regulatory paths have been defined for all. For compounds with the poorest solubility, amorphous solid dispersions and lipid-based drug delivery systems are often used [5,6]. Lipid-based drug delivery systems are formulated as a solution of the compound in an excipient, which allows presentation of the drug molecule to the patient so that slow dissolution of poorly aqueous soluble compounds can be circumvented. Also, post-administration biological conversion of the lipid-based excipients can help to keep the compound solubilized, providing optimal absorption conditions [7,8]. Lipid-based drug delivery systems are a well investigated and established technology in the field of pharmaceutics (e.g. [9–25]). Further, lipid-based drug delivery systems offer several ways to solve some of the pharmaceutical issues observed with the pipeline compounds, and they should be considered when defining the formulation strategy for a new molecule.

The pharmaceutical ecosystem is highly complex and include small to large pharmaceutical companies, biotechnology companies, open innovation clusters, equipment suppliers, contract research organisations (CROs), contract manufacturing organisations (CMOs), excipient suppliers, universities and university spin-off companies, etc. While these terms are used on a day-to-day basis in the pharmaceutical industry, there may be less awareness of the use and links between the academic parts of the pharmaceutical ecosystem. The pharmaceutical industry should be understood broadly as those organisations that in principle can be very small to very large, which develop pharmaceutical products for use in humans or animals. A CRO is a person or an organisation that makes a contract with another company to conduct one or several experiments. From an industrial perspective, CROs are used because they have specialised knowledge or equipment, or simply to reduce the work load of the pharmaceutical company. CMOs are organisations that manufactures either active pharmaceutical ingredients or drug products according to cGMP for a pharmaceutical company, i.e., they are organisations that are used because they have specialised technologies, specialised equipment or as a flow over when there is a high work load in the pharmaceutical company. Excipients are produced by specialised companies and, as for pharmaceutical products, they must be approved by regulators for use in humans. The excipient supplier thus supports the pharmaceutical business with their special products, together with their insight into their use and function.

Different links exist between these organisations and they all fulfil different needs in the pharmaceutical ecosystem/market space, however, they all provide a contribution to serve the patients needing a cure, treatment or relief for their illness. While these links are obvious on an industrial scale, they contribute to both the scientific and commercial development within a specific area, such as lipid-based formulations and their subclasses, as self-emulsifying drug delivery systems (SEDDS). Understanding the science of this field is naturally important to develop the area; however, understanding the ecosystem and the individual stakeholders can boost this development even further. The present review will therefore focus on some of the important elements within SEDDS drug development, while providing a perspective of the industrial and academic interests in order to identify scientific synergies that can be used to advance progress this field of formulation science.

2. Compounds suited for lipid-based drug delivery systems

Lipid-based systems are used to increase the solubility of a compound in the gastrointestinal tract, thereby providing a formulation option for poorly aqueous soluble drugs. The ability of a specific formulation to deliver a real enabling benefit will vary according to the properties of both the drug and the defined formulation.

2.1. Basic physico-chemical properties

Compounds with a low aqueous solubility, i.e., belonging to BCS class II and IV, are normally those relevant for consideration as lipid based formulations. Classification to BSC class II and IV based upon solubility may arise for different reasons, e.g., a very high dose or the inherent physico-chemical properties of the compound. As formulated by the Yalkowsky equation, there is a correlation between solubility (S), melting point (MP in K) and log P [26]:

$$\text{Log S} = 0.8 - \log \text{P} - 0.01(\text{MP} - 25) \quad (1)$$

where P is the partition-coefficient (P). Some poorly water-soluble compounds have limited aqueous solubility due to their tight crystal lattice (compounds referred to as “brick dust”). Other compounds have limited aqueous solubility due to their high affinity for the lipid phase, i.e., highly lipophilic compounds (having a high log P), but with a much lower melting point (the so-called “grease-ball” compounds). Not all compounds can be placed into these two classes, but a continuum exists and most drug compounds do not fit in either extreme. A common perception is that if the molecule has the characteristics of a grease ball and traditional formulation approaches do not provide adequate bioavailability, solubility enhancement through the use of lipid-based excipients and/or surfactants may be a potential formulation strategy. If the compound is a “brick-dust” molecule, the suitability for a lipid-based formulation may be lower, since its solubility in triglyceride-based lipid excipients may not be high enough; however, a higher solubility in surfactants and co-solvents may mean that there are still options within the wider categories of lipid-based formulations. Despite these generalised perceptions, not all compounds with poor aqueous solubility and/or a high log P will have a good solubility in excipients that are suitable for lipid-based formulations. However, the more diverse the excipient in the formulation, the greater the chance that it is possible to find a vehicle that may solubilise the compound, i.e., looking beyond just simple triglyceride-based oil solutions.

SEDDS is one type of lipid-based formulation wherein there is an oil component that solubilizes the compound and a surfactant component that helps the oil phase to remain in a sub-micron sized dispersion after exposure to the gastric fluids, leading to higher amounts of the compound in a state suitable for absorption in the gastrointestinal tract. A big advantage of an SEDDS over other lipid-based systems is its ability to incorporate a wide range of excipients, including co-solvents, comprising a system that provides both the needed solubility, ensures a chemically and physically stable formulation, and facilitates a strong enhancement of bioavailability. Further, different commercial presentations are possible for the formulation type, so it can be developed into a conventional tablet or a hard or softgel capsule, providing the

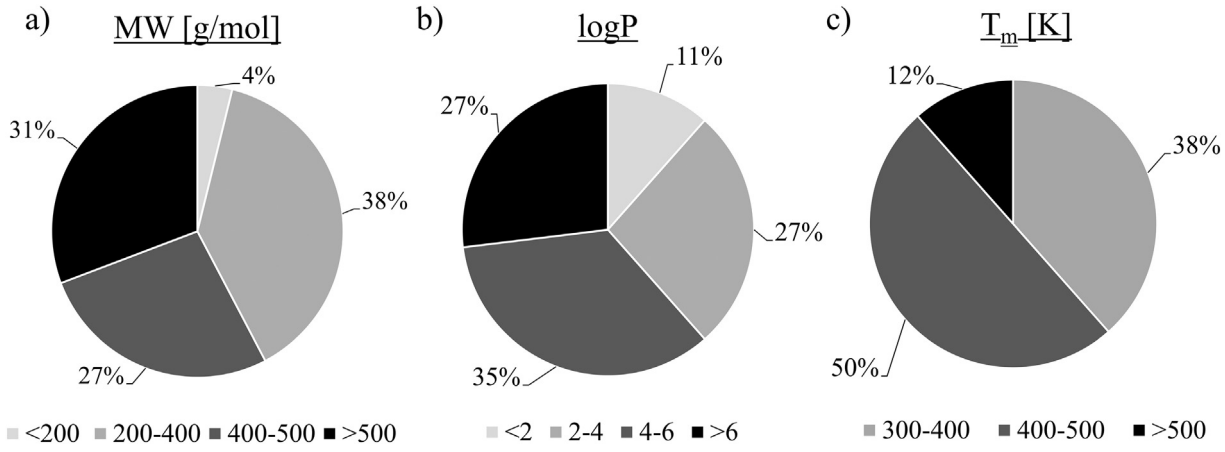

Fig. 1. Physico-chemical properties of drugs in FDA approved lipid-based formulations. The different panels are explained in the main text (reproduced from Ditzinger et al. [6] with permission).

advantages of novel drug delivery system, which is favourable from a treatment and a patient compliance point of view.

Alskär et al. [27] recently investigated the solubility of a broad number of compounds in different excipients suited for lipid-based formulations. These authors [27] concluded that melting point measurements could be good indicators of lipid solubility. A melting point <150 °C was a good indicator of a reasonable solubility in glyceride-based lipids and was suggested as the baseline for the selection of compounds for lipid-based formulations. They found no correlation between the melting point and the solubility in co-solvents [27]. So if a brick-dust compound were to be formulated, there is no guarantee that this could be done in a lipid-based formulation using high levels of co-solvents. This finding is contradictory to the perception described above, but is data based. The solubility in different excipients was found to be linked, i.e., measurements in PEG 400 could be used to estimate solubility in other ethoxylated excipients such as cremophor EL, polysorbate 80, or carbitol. From an industrial perspective, this is useful information to define the screening matrix of vehicles used in the pre-formulation studies in which the potential for formulating a compound in a lipid-based formulation is determined.

In cases where it is not possible to achieve the desired solubility in lipids, there are several options to adjust the properties of the molecule as a prodrug formation [28,29], ionic liquid [30–32], or the formation of lipophilic salts [33]. Lipophilic salts are very appealing, as they falls within the classical delivery approach, from both an industrial and regulatory paradigm and is therefore an approach that would be easy to implement in an industrial setting. While the concept of lipophilic salts has been demonstrated, additional investigations would provide a better understanding of the options and pitfalls this approach might offer. Elements for consideration could be the counter ion selection, characterisation of the lipid solutions, i.e., does the salt dissociate (and if it does, what is the implication for its stability?), what are the biopharmaceutical perspectives and in which classes of lipid-based formulations does the approach fit best? The answer to these and other relevant scientific questions could be usefully conducted at the interface between industrial and academic research, given that this option could be quickly implemented in pipeline projects.

2.2. Physico-chemical properties of compounds marketed in lipid-based formulations

The observations described by Alskär et al. [27] are interesting when developing a new drug compound, but it is also interesting to know the properties of compounds already marketed as lipid-based formulations, in order analyse of cases that were successful. The link between simple physico-chemical properties, i.e., molecular weight, log P and melting point have recently been investigated by Ditzinger et al. [6], see Fig. 1.

Ditzinger et al. [6] reported a large variability in the melting point of drugs already approved in lipid-based formulations by the U.S. Food and Drug Administration (FDA), ranging from approximately 330 to 623 K, with a relatively even distribution over this temperature range. The log P's of the same compounds ranged from 0.8–7.5 and molecular weights ranged from <200 to >500 g/mol, i.e., marketed compounds from a very diverse molecular space are formulated in lipid-based systems. The conclusion was in accordance with the analysis of Savla et al. [34], who also analysed the FDA-approved compounds in lipid-based formulations. This suggests that the very general rules described above work well as a rule of thumb; however, they may not necessarily predict if a successful commercial product can be achieved. Given the broad range of doses (0.25 μg-250 mg/capsule) and types of lipid-based formulations [34] (from simple oil solutions to complex SEDDS compositions), it may be less surprising that the melting point cannot be used as a predictor for a potential lipid-based formulation. The rule of thumbs for compounds suitable for a lipid-based formulation should therefore be used with the addition of good scientific judgement. For lipid-based formulations as for other formulation strategies, the approach needs to be fitted and adjusted to the patient and the compound. Early evaluation of a compound's potential to be formulated in a lipid-based formulation can be easily incorporated as a part of the compound's developmental assessment, or by including the determination of the solubility in a handful of relevant excipients in the first pre-formulation studies of o new compound. In addition to this, generation of solubility data in different lipid-based excipients, including surfactants and co-solvents is suggested, together with additional computational exploration of the available data to identify which key structural components might support a good solubility in lipid-based excipients. Additional benefits might result from the inclusion of elements, such as the dose factor, in some of these analyses.

2.3. Compounds for lipid suspensions

Lipid-based formulations often present the compound in a solubilized state, even though drug suspensions in lipids have been used successfully to increase exposure [35–39]. The compounds tested in lipid-based suspensions thus far include griseofulvin, phenytoin, progesterone and danazol - all compounds with a decent lipophilicity and solubility in lipids. In contrast, no systematic investigations have so far been made for compounds with limited solubility in lipids, as brick dust molecules, and the possibility of increasing their bioavailability using lipid-based suspensions. Furthermore, the investigations conducted so far have used simple vehicles (single component systems), so there is a

lack of insight into which formulation factors could be used to optimise the exposure from lipid suspensions, e.g., how should a SEDDS be optimised as a suspension? Also, important parameters such as particle size in the suspension and the physical stability of the lipid suspensions should be considered. All these questions can be covered as a part of an industrial development project in case a compound fits this formulation space. However, the likelihood of getting these systems evaluated in a clinical program significantly increases if there are some fundamental investigations and perceptions available in the literature that can be used to evaluate the formulation risk. This does not mean that the pharmaceutical industry cannot innovate, but in order to do so there needs to be a clear benefit that may not be solved by other technical solutions. In the brick dust area, amorphous solid dispersions are a well-established technology.

2.4. Lipid formulations to enhance dose accuracy

Besides using lipid-based formulations to enhance bioavailability, the formulation strategy could also be used to obtain a high dose precision for high potency, low dose compounds, which may be difficult to achieve using classical solid dosage forms. It is not known if this was the motivation for marketing ergocalciferol and calcitriol (highest dose 0.5 μg/capsule) [34], but it could have been. In this area, only a very limited solubility in the lipid excipients is required. From an academic perspective, there are limited perspectives in this use of lipid-based formulations. Hence in order to ensure that there is an awareness of the possibility of utilizing lipid-based formulations for this purpose, other stakeholders in the pharmaceutical ecosystem should communicate this possibility, e.g., the CROs that specialise in lipid-based technologies.

2.5. Scientific gaps in identifying compounds for lipid based formulations

Many companies generate pre-formulation and developmental packages for their compounds when entering development [40–42]. This is done in order to not only evaluate the developmental risks of the compound and to provide input into the project plan and tentative timelines and costs but, also to provide initial guidance for the scientific disciplines that will handle the compound in the development phase. One of these investigations includes stressed stability investigations, which is used as a flag of potential excipient compatibility issues [41]. A common perception of compounds that are sensitive to oxidation is that lipid-based formulations may be less optimal as they may contain traces of peroxides that can catalyse their degradation, which may make it hard to obtain sufficient shelf-life of the drug product to support the clinical studies – or the two years stability normally required for a commercial product. Theoretically this perspective is correct, but there are no published insights into how predictive those highly stressed forced degradation studies are. In practice, antioxidants can be added to the formulations to prevent this degradation and investigating this should a standard approach in any industrial formulation work of a lipid-based formulation. Nevertheless, accurate screening methods are still important and the link with the stability obtained from the more representative and less stressful conditions such as ICH stability conditions, i.e., the predictability of this test with respect to lipid-based formulations is largely unknown. Furthermore, several excipient suppliers deliver highly purified grades of lipid excipients, so technically there are also means to circumvent the potential issue. An example of optimisation of the stability of lipid- based formulations was published by Monteagudo and co-workers [43], but in general limited investigations are available in this field. From an academic perspective this may be an interesting case to investigate, but for the investigations to really add value, it would be good if industry could share some of the recent compounds to conduct investigations in a relevant chemical space rather than to focus on older model compounds.

Within an industrial setting, several parameters are involved in the formulation strategy for a new drug molecule. Solubility studies are naturally one of the key investigations, so if a high solubility in lipid-based excipients is found and stress stability studies demonstrate that the compound is relatively stable to oxidation, then using lipids as an excipient strategy should be considered. The choice of a lipid-based formulation would greatly depend on the organisation's experience, as well as defined scientific and manufacturing platforms established within the company. As such this gap does not belong in the interface between academic institutions and the pharmaceutical industry, but between the pharmaceutical industry and the specialised CRO/CMOs operating in the space.

3. Classes of lipid-based drug delivery systems

Drug absorption from lipid-based formulations is complex, dynamic and highly driven by the biochemical conversion of some of the main components in the lipid-based formulations. The understanding of lipid digestion, intestinal lymphatic transport, mixed micelles etc., is an important component in the full understanding of a lipid-based formulation [8,25]. These elements will not be discussed here, but the interested reader is referred to some of the excellent reviews in the literature (e.g. [25,44]. From an industrial perspective, the continuous academic efforts to characterise and understand these important biochemical processes are naturally appreciated and should be highly encouraged.

The composition of a lipid-based formulation can have an influence on the in vivo performance, so an understanding of a number of parameters is important for the development of a successful lipid-based formulation. These include the physico-chemical properties of the compound and the formulation, gastrointestinal physiology and conditions (such as permeability, dissolution rate, absorption) to ensure that drug precipitation does not have a negative effect on performance upon dispersion and/or digestion of the formulation in the gastrointestinal tract. Precipitation upon dilution of a lipid-based formulation is a major concern for many industrial researchers, as it undermines the advantages of a lipid-based system. It is therefore important to consider that the compound can precipitate both as an amorphous form [45,46] as well as submicron-sized particles. These may still get absorbed in vivo after re-solubilisation leading to improved bioavailability, which is why lipid-based formulations should be evaluated from a holistic viewpoint.

3.1. The lipid classification system

Lipid-based formulations comprise several different systems, including solutions, emulsions, micellar systems, SEDDS, and self-microemulsifying drug delivery systems (SMEDDS). In order to classify these many different systems, Pouton [19] suggested a lipid classification system (see Table 1), in which different formulations are classified into 4 main classes.

Table 1
Lipid formulation classification system, based upon [19].

Type	Excipients in formulation (% w/w)			
	Oils: triglycerides or mixed mono and diglycerides	Water-insoluble surfactants (HLB* <12)	Water-soluble surfactants (HLB >12)	Hydrophilic co-solvents (e.g. PEG, glycerol, ethanol)
I	100	–	–	–
II	40–80	20–60	–	–
IIIA	40–80	–	20–40	0–40
IIIB	<20	–	20–50	20–50
IV	0	0–20	30–80	0–50

* HLB = hydrophile-lipophile balance.

Table 2
characteristics of different type of lipid classes classified by the lipid classification system.

Type	Dispersibility	Digestibility	Initial solvent capacity	Solvent capacity upon dispersion	Solvent capacity upon digestion
I	Pure oil Limited or no dispersion	Digestible	Poor	No impact	Increased
II	SEDDS Moderate dispersion needed to form an emulsion	Likely to be digestible	Intermediate	No impact	Possible loss
IIIA	SMEDDS Rapid dispersion to form micro- or nanoemulsions	May be digestible	Slightly above intermediate	Possible loss	Possible loss
IIIB	SMEDDS Rapid dispersion to form micro- or nanoemulsions	Poorly digestible	High	Possible loss	Possible loss
IV	Oil free Rapid dispersion forming a micellar solution	Not digestible	High	Likely loss	No impact

The different types of lipid-based formulations have different characteristics (Table 2). Type I lipid-based formulations contain oils (triglycerides or mixtures of di- and monoglycerides). These lipid excipients must be digested to facilitate the absorption process, converting the excipients into mixed micelles within the gastrointestinal tract. Type I formulations are typically biocompatible and simple, containing GRAS (generally recognised as safe) listed excipients. In an industrial setting, Type I would be the first and last if solubility were achieved. Lipid digestion often does not lead to the loss of solubilisation capacity after dispersion or digestion, i.e., the compound does not go through a phase of supersaturation with the risk of precipitation and loss of bioavailability.

Type II lipid-based formulations consist of a mixture of lipids and water-insoluble surfactants (HLB < 12). These may self-emulsify into crude oil-in-water (o/w) emulsions upon contact with the gastrointestinal fluids. This provides a larger surface area where pancreatic lipase can interact, leading to a faster digestion rate than with type I lipid formulations, and possibly a higher bioavailability than can be obtained from a simple oil solution. As oil is still the main component, digestion is still important, and depending on the surfactant selected, there may be a loss of solvation capacity after digestion.

Type III lipid-based formulations (class IIIA and IIIB) contain water-soluble surfactants (HLB > 12) and co-solvents. These formulations spontaneously self-emulsify upon contact with the aqueous environment in the gastrointestinal tract, i.e., SEDDS when the dispersion is a milky emulsion (droplet size approximately >200 nm) or as SMEDDS when a transparent emulsion with a slightly bluish appearance is formed in water. As the formulations may contain significant proportions of co-solvents, there is a risk that the solvent capacity may be lost upon dispersion and digestion, since the co-solvents may migrate into the aqueous phase.

The last class of lipid-based formulations, type IV, does not contain oil and is based on water-soluble surfactants and co-solvents. The fine dispersions formed when these are dispersed in an aqueous medium can lead to rapid drug release and absorption. The solvent capacity of these systems may be lost upon dispersion, leading to a supersaturated solution and the risk of precipitation in the gastrointestinal tract.

The lipid classification system presented by Pouton [19] is well cited and therefore seems to be generally well accepted, but there are elements that such a simplified classification cannot cover. Furthermore, there are compositions described that do not fall into any of the four classes. Müllertz and co-workers [15] agreed with the usefulness of the lipid classification system, but argued that the Small's lipid classification system should be incorporated and that the empirical HLB reference should be changed. Small [47] suggested a physico-chemical system to classify lipid-based excipients into non-polar and polar lipids, based on their interaction with bulk water and their behaviour at the water–air interface. Non-polar lipids do not spread on water to form a monolayer on the surface and are insoluble in bulk water, e.g., paraffin oil. Small [47] divided polar lipids into three different classes, described as insoluble non-swelling, insoluble swelling and soluble. The soluble polar lipids are further divided into two sub-classes depending on whether or not they form liquid crystalline structures at higher lipid concentration in bulk.

The insoluble non-swelling lipids are the most hydrophobic of the polar lipids (e.g., triacylglycerides). These lipids do not swell by hydration, but form stable monolayers at water–air interfaces. Among the insoluble swelling polar lipids are phospholipids and 2-monoacylglycerides. Similar to the insoluble non-swelling lipids, they form stable monolayers at water–air interfaces and are insoluble in water. However, above their phase transition temperature, they can incorporate water between their polar head groups creating a swollen lipid structure (liquid crystalline state). The group of soluble lipids contains soluble amphiphiles that show lyotropic mesomorphic behaviour at higher lipid concentrations in water. They form an unstable monolayer in the water–air interface and form micelles when the concentration is above their critical micellar concentration (CMC). This group of lipids/surfactants contains both hydrophilic and lipophilic surfactants as described by the HLB system. The third class of lipids according to Small's description [47] are the polar lipids, which form micelles on their own, as well as unstable monolayers, but not liquid crystalline structures at higher lipid concentrations. All surfactants in Small's classification system possess a high capacity to solubilise non-polar and insoluble non-swelling and swelling polar lipids. While it may be fair to include a classification based upon the properties of the lipids and thereby refine the classification, the overall perspectives of Pouton's [19] suggested lipid classification still stand.

From an industrial perspective these kinds of classification systems are valuable because they can be used quickly to identify important development points for discussion, e.g., the risk of precipitation. Classification systems, like flow diagrams, can be adjusted internally within the companies to capture organisational experience and best practices. These elements become very important when there is a change in chemistry, if there is a longer period where a formulation technology is not applied. In this period, it is important that academia keeps developing new insights into this field despite more limited industrial interest. This is also the space where there is a business opportunity for specialised CROs to build up a unique scientific platform, which they can offer to the pharmaceutical industry for those compounds that may still be suited for a lipid-based formulation strategy. Lipid-based formulations have some focus in the pharmaceutical industry, but a longer period with brick dust molecules formulated as amorphous solid dispersions have led to strategical decisions to move lipid-based formulations from an in-house platform to strategic outsourcing to CROs.

3.2. Supersaturated lipid systems

Type III and IV lipid-based formulations both have potential supersaturation following dispersion in the gastrointestinal tract and digestion of the formulation due to their higher levels of water soluble co-solvents. The usefulness of using precipitation inhibitors as a formulation component was elegantly demonstrated in a study by Gao

et al. [48], in a SEDDS of paclitaxel. In vivo studies in rats showed that addition of hydroxypropyl methylcellulose (HPMC) resulted in a 10-fold increase of paclitaxel oral bioavailability compared to the same SEDDS without HPMC. As HPMC is not soluble in the lipid vehicle and was present as a suspension. However, Gao and Morozowich [49] demonstrated that a HPMC capsule could be used instead of a suspension. The authors [49] demonstrated that the absorption of compound X in dogs was similar when HPMC was suspended in the vehicle and encapsulated in a gelatine capsule, or if the formulation was encapsulated in an HPMC capsule. Given the large numbers of amorphous solid dispersions in the pharmaceutical industry, screening for precipitation inhibitors has been developed and redefined in many companies. Thus, the approach of combining a lipid-based formulation with a precipitation inhibitor would likely be accepted in most pharmaceutical companies as they are familiar with the science. As mentioned above, HPMCs are not soluble in lipid-based vehicles, which is less optimal because it complicates the processing. This hybrid formulation system is very interesting from an industrial perspective, as it may enable the use of high quantity co-solvent systems while maintaining a high bioavailability. However, a lot of systematic work can also be considered, such as the solubility of relevant polymers in lipid-based excipients. Is there a link between the screening methodology used to identify relevant precipitation inhibitors for amorphous solid dispersions and their ability to function as such in lipid-based formulations? These and other topics are suitable academic research projects that would provide the basis for industrial investigation and application over a longer term.

4. Commercial lipid-based formulations

Müllertz et al. [15] and more recently Savla et al. [34] investigated the compositions of commercially available lipid-based formulations. Of the 25 formulations classified by Müllertz et al. [15] 13 were lipid-based type I, three were class III and nine were class IV. Savla and coworkers [34] classified 26 formulations and classified 16 as type I, three as type II five as type III and two as class IV. There was not a complete overlap between the formulations classified in the two studies. Salva et al. [34] also included the new drug application year in their analysis. The first application for a type I lipid-based formulation was submitted in 1941 (Drisdol®), type II in 1983 (Sandimmune®), III in 1995 (Neoral®), and type IV in 1999 (Agenerase®). Following this, all types of lipid-based formulations have been approved, hence there is not a move towards more and more complex lipid-based formulations. It is interesting to note that most commercial formulations are type I according to Pouton's [19] lipid classification system, showing that formulation simplicity is preferred from an industrial perspective. This preference is not necessarily as attractive from an academic perspective as there is a much smaller space for exploration and new findings, so clearly there is a gap between the two parts of the pharmaceutical ecosystem. However, it is not necessarily a reflection of an unsuccessful link, but rather the different success criteria in the two different settings.

From the analysis conducted by Salva et al. [34], it is clear that the soft gelatine capsule is the most popular dosage form for the administration of lipid-based formations. Of the 36 evaluated formulations, 25 were in soft gelatine capsules, six in hard gelatine capsules and 5 as oral solutions. This clearly indicates that soft gelatine capsules are the optimal encapsulation approach, an encapsulation with a unique manufacturing process [50,51]. Soft gelatine capsules are more compatible with hydroscopic excipients, such as liquid propylene glycol (PEG) [12], however, softgel capsules are less suited for filling at higher temperatures, which is relevant for semi-solid excipients like Gelucire 44/14, where hard gelatine capsules can be used for the encapsulation. Insights into excipient compatibilities have been presented in the literature (e.g. [44,52]). Kuentz and Röthlisberger [53] published a compatibility method based upon texture analysis. However, despite the importance of this area for commercialisation of lipid-based formulations, there few published studies. Added insight can come from all areas of the pharmaceutical ecosystem, i.e., academic partners can initiate studies with comparability as the focus, the pharmaceutical companies, CROs specialised in lipid-based formulations, lipid excipient producers or hard or softgel capsule producers can share their experience from some of their development programs, which will together provide evidence for a lower risk associated with lipid-based formulations.

Commercial production of pharmaceutical products is kept within the ecosystem that makes products on a large scale, i.e., pharmaceutical companies and CMOs specialised in the field. As mentioned above, pharmaceutical companies operate with core pharmaceutical technologies or platform technologies and strategically define which technologies to maintain internally with respect to competence and equipment. The availability of small scale hard gelatine capsule filling and sealing/banding is available in house in many companies, whereas large scale hard gelatine capsule filling and all scale softgel filling is often defined for outsourcing, since it requires specialised equipment.

Excipient companies and the academic partners have started to be active in suggesting how to get lipid-based formulations produced by conventional pharmaceutical production equipment, in particular through discussion of solidification of lipid-based formulations. Solidification of lipid-based formulations can be used to solve compatibility issues and ease production, together with other benefits [54]. These solidification approaches include physical adsorption onto a solid carrier, hot melt extrusion, freeze drying, and spray drying approaches, where the physical absorption approach is a particularly active research topic using mesoporous silica, clay and similar inorganic structures [54–56]. Despite the absence of commercial products in which lipid-based formulations have been solidified or any public information of the approach being used in clinical trials, it can only be a matter of time before this will happen, given the possibilities that the technology contains, both from a production perspective and the benefit of combining a lipid-based formulation with an excipient that can stabilise an amorphous compound.

5. Defining a composition for a lipid-based formulation

Flow diagrams are frequently used to capture organisational knowledge and experience. So far there are few flow diagrams showing how to make a lipid-based formulation made publicly available by a pharmaceutical company or with employees from a company as co-authors, either because there is a reluctance to share or as they are simply do not exist. Williams et al. [44] is an exception, where a flow diagram was suggested for solution based systems (see Fig. 2), and Müllertz and coworkers [15] have provided a modified version of a decision tree to develop a lipid-based formulation. The flow diagram shown in Fig. 2 to a large extent came out as part of consortium efforts to standardize the in vitro lipolysis assay and naturally places this as a central investigation. Furthermore, the flow diagram is largely a representation of an academic perspective, so a purely industrial flow diagram for lipid-based formulations is still not available in public domain.

As discussed above, drug solubility in the lipid vehicle is perceived as one of the first steps, so pre-formulation studies investigating the thermodynamic solubility of the compound over a broader range of lipid excipients and co-solvents is seen as the starting point. Defining a system that can contain a therapeutic dose is often an issue, which is why a relatively broad screen of different classes of excipients suited for lipid-based formulations is conducted. Different excipients may produce the desired solubility, so an industrial development program may include more concept formulations, which are brought forward to a decision point, e.g., stability data, bioavailability, or capsule compatibility. These systems may be simple solutions in oils or more complex formulations, such as SEEDS in which multiple components are included in the formulation. In general, a simple system is desired from an industrial perspective, with fewer excipient suppliers, fewer critical quality attributes to test, etc. Generation of pseudo-phase diagrams makes sense from an optimisation perspective and can help to define

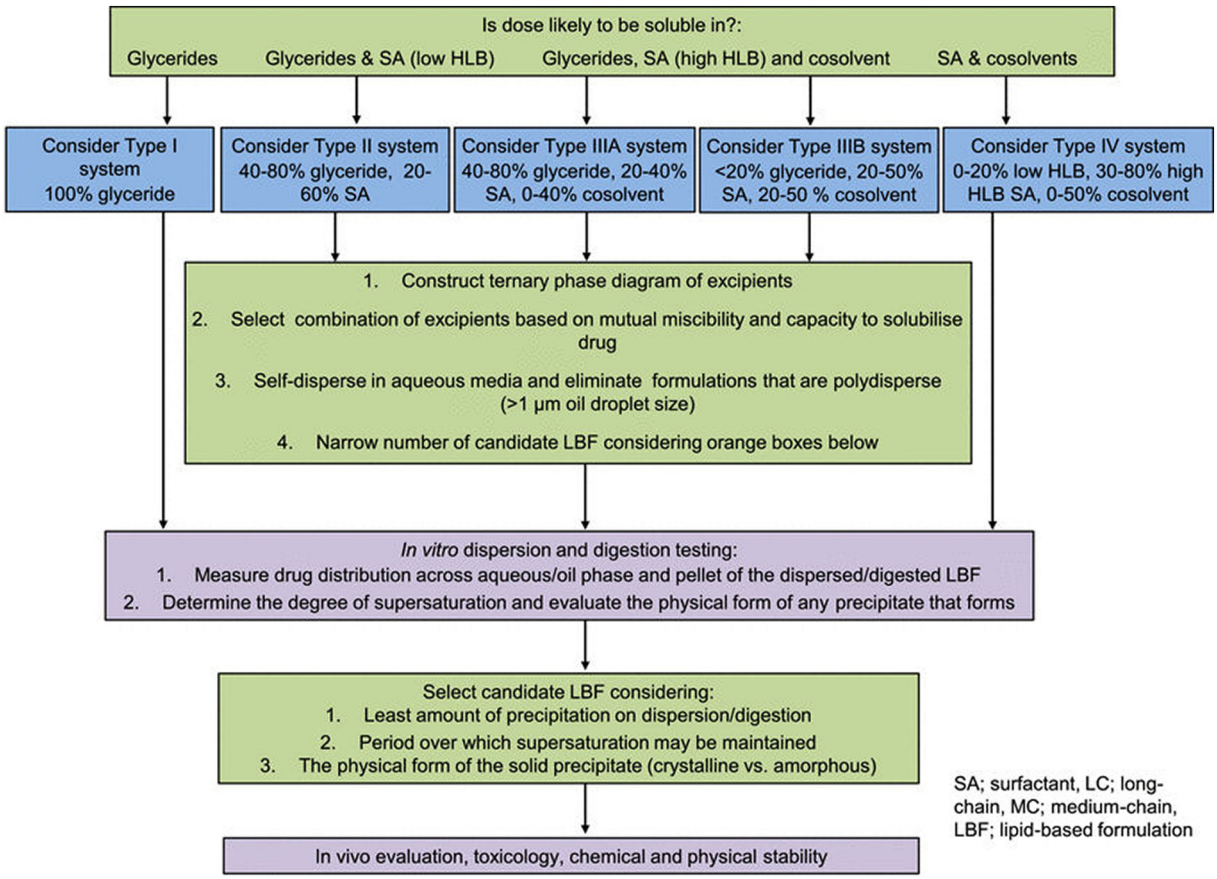

Fig. 2. A flowchart suggesting a general guide to lipid-based formulation design (reproduced from Williams et al. [44] with permission).

the formulation space for a specific molecule, but the availability of relevant in vitro characterisation methods to rank the different concepts under development is one of the major obstacles in the early formulation selection process faced by an industrial formulation scientist working with a new compound. Some frequently used in vitro tests include dispersion of the lipid formulation into water or simulated intestinal fluids and investigation of dispersibility of the formulation in aqueous media, droplet size after formed dispersion, in vitro digestion models etc. [57], where the in vitro lipolysis model has received a lot of academic interest and a much work has been published with a suggested standardised setup [58–64]. From a scientific perspective, the in vitro lipolysis model, i.e., a method in which digestion in the small intestine is mimicked, is very interesting for the evaluation and ranking of the digestible systems, but it also provides information about the digestive processing of pharmaceutically relevant excipients. The model mimics the behaviour and the distribution of the compound during digestion of the formulation, providing an insight into what happens with the compound during this process, i.e., will it precipitate, and if so, will it form a crystalline or amorphous precipitate? Feerney et al. [25] made a meta-analysis of the in vitro in vivo *correlation* (IVIVC) for the ability of the lipolysis model to predict the in vivo performance of lipid-based formulations. Overall, it was concluded that obtaining an IVIVC was highly compound-dependent. Of the eight evaluated compounds a correlation was found in only half of the cases.

Griffin and coworkers [57] investigated a different range of in vitro tests with different levels of complexity to investigate which of these methods best predicted the in vivo performance of three prototype fenofibrate lipid-based formulations. Three SEDDS formulations were investigated: a long chain mono/di/triglyceride Type IIIA SEDDS, a medium chain mono/di/triglyceride Type IIIA SEDDS, and a Type IIIB/IV SEDDS containing only surfactant. The authors reported that the ability of the in vitro dilution and dispersions tests to predict the in vivo bioavailability was demonstrated for Type IIIA and Type IIIB/IV formulations. For the surfactant-only Type IIIB/IV formulations, the extensive precipitation observed during in vitro lipolysis testing was not consistent with the in vivo findings. The authors concluded that the use of the in vitro lipolysis model provided additional information about lipolysis-triggered precipitation, but it was less predictive of in vivo findings than the simpler in vitro dilution and dispersion methods. While the in vitro lipolysis model therefore seems academically interesting and a lot of insight has been generated, there is a need for guidance on when and where to use which in vitro characterisation methods from an industrial perspective.

In the flow diagram from William et al. [44] (Fig. 2), in vitro characterisation is followed by a suggestion to evaluate the in vivo performance, in addition to chemical and physical stability. For lipid-based systems, as well as other bio-enhancing technologies, the question as to which animal to select for non-clinical evaluation has not been addressed yet to the best of my knowledge. In order to answer this question, access to in vivo data from different types of lipid-based formulations used in different animal species as well as from humans will be needed, which could easily be done if pharmaceutical companies where willing to share some of these data. As the types of lipid-based formulations and even SEDDS comprise a very broad category of formulations, there is a risk that, for example, the digestible systems are better tested in one species than the formulations containing a high quantity of co-solvents. However, at present this is not mapped and made available in the literature.

Some of the excipients used in lipid-based formulations influence the efflux mediated by P-glycoprotein (P-gp, ABCB1, MDR1). It was reported that some non-ionic surfactants could reverse multi-drug resistance in cancer cells [65–67]. Later investigations showed that surfactants such as polysorbate 80, cremophor EL [68,69], vitamin E TPGS (α-tocopheryl polyethylene glycol 800 succinate) [69], polysorbate 20, Myrj 52 and Brij 30 [70], could increase the permeability

Table 3
Overview of the industrial focused scientific gaps related to lipid based formulations discussed in this work.

Topic	Gaps	Suggested place to perform the research
Lipophilic salts	Counter ion selection, dissociation in lipid based formulations of the counter ion, stability implications, biopharmaceutical considerations when using lipophilic salts.	Academia and industry
Solubilisation	What physical chemical drivers are important for solubilisation by excipients that can be incorporated into lipid based formulations	Academia
Lipid suspensions	Better biopharmaceutical understanding of lipid suspension, what classes of lipid formulations works best as suspensions, what is the particle size influence in lipid suspensions, what classes of compounds work in lipid suspensions, what are the stability considerations.	Academia and industry
Predictive stability testing	The use of accelerated studies to predict potential stability issues for compounds to be incorporated into a lipid-based formulation could be better systemised, but also investigations of relevant accelerated studies to predict the drug product stability of lipid-based formulations	Industry
Formulation composition	Defining a relevant lipid composition for a compound is not clearly exemplified in the public domain. Description of development stories and how to define the composition can provide an insight that can lead to a lower risk perception	Industry and specialised CRO's
Biopharmaceutical understanding of lipid based formulations	Lipid-based formulations are due to the natural digestion a complex system, which is bio-activated upon intake. Continuous investigation of these processes to develop the insight and understanding into the processes can help support the formulation development.	Academia
Lipid formulation classification systems	Systems that can describe and systemise the different types of lipid-based formulations linked to current knowledge	Consortium
Simple lipid based formulations	There is a tendency to focus on the more advantageous lipid- based formulations; however, the use of simple systems is preferred if possible. There is limited research into these simple formulations, hence investigation of these with current characterisation methods would increase the knowledge of these systems	Academia
Precipitation inhibitors in lipid based formulations	The use of co-solvents in lipid-based formulation induces the risk of supersaturation upon dilution of the formulation in the intestine – potentially leading to precipitation. It has been demonstrated that this can be circumvented by the addition of precipitation inhibitors; however, additional systematic investigations into this field would benefit the approach, e.g., how to select the inhibitor – can screening approaches already used for definition of solid dispersion be used? Is there a stability implication of the precipitation inhibitors, what inhibitors are soluble in which excipients etc.?	Academia and industry
Capsule compatibility	The lipid composition needs to be encapsulated before being brought to the patient – what simple methods can be defined to support the selection of a soft gelatine capsule, a hard gelatine capsule or a solidification approach?	Specialised CROs or capsule producer
Solidification of lipid based formulations	Both the biopharmaceutical as well as the technical aspects of lipid solidification are relevant topics for continued investigations. What is the biopharmaceutical impact of the different approaches for solidification, what is the loading capacity, what is the stability consideration etc.?	Excipient producer and industry
Flow diagrams to define a lipid based formulation	Flow diagrams support the industrial scientist by trying to put present knowledge into a simplified flow that can help making the right reflections during the development work. Refinement of the available flow diagrams to industrial settings should be considered	Consortium
In vitro characterisation methods of lipid based formulations	What in vitro characterisation is relevant for lipid-based formulations to select the best composition of the compound, but also focus on which relevant quality methods that can be defined.	Consortium
In vivo characterisation of lipid based formulations	What animal species to select for the investigation of lipid based formulations? Are there species more suited for simple solutions versus SEDDS?	Consortium
Lipid excipients influence of in- and efflux transporters	Lipid excipients may influence intestinal in- or efflux transports, more systemised investigations of the field would be beneficial to understand if this could be a means to increase or reduce the variation for compounds with a transporter affinity	Academia

of P-gp substrates in cell cultures. These surfactants could easily be considered as a part of a lipid-based formulation. Few studies have investigated if surfactants administered orally could increase the bioavailability of P-gp substrates, such as digoxin [71–74], doxorubicin [75], and etoposide [76,77] and a clear effect of co-administering Tween 20 with digoxin has been reported [73]. When selecting compounds in the discovery phase P-pg substrates are normally screened out if possible, but a systematic clarification of what lipid-based formulations could do for these compounds, e.g., as a function of lipid formulation type are in general absent.

Evaluation of chemical and physical stability must be adapted to each compound and formulation composition, but case stories describing methods most suited to evaluate the stability are relevant. Descriptions of how to evaluate the solubility at ambient temperature of semi-solid systems and how best to test physical stability are examples where additional focus is beneficial.

Throughout this work, suggestions of research that can increase the industrial applications of lipid-based formulations have been made, and these are shown in Table 3. The general thinking behind these suggestions is focused on closing some of the scientific gaps that are important

for an industrial formulation program, where more insight could lower the perceived risk of lipid-based formulations, thereby using the advantages that these systems provide.

6. Conclusions/future perspectives

The pharmaceutical ecosystem consists of several different players, each with their goals and expertise serves the ecosystem differently. There are several synergies between the different stakeholders in this ecosystem, but in addition of the different focus of the different organisations, there are also gaps in the knowledge generated and shared. This work has focused mostly on the gaps in academic research and the needs of industrial product development. In general, the topics suggested can be considered as potential research topics that could be picked up by academic organisations, but some of the topics may better be evaluated in a consortium-like structure containing organisations from the entire ecosystem. Progressing the knowledge about lipid-based formulations will most likely increase the number of commercially available lipid-based formulations and it is therefore in the interest for all stakeholders in the ecosystem. For paediatric formulations, there is for example, the European Paediatric Formulation initiative (EuPFI) [78] and for the development and validation of biopharmaceutical tools, Oral Biopharmaceutical Tools (OrBiTo) [79], both constructed as consortiums. It would be interesting and highly beneficial if the industry could go into similar programs for different formulation technologies and share the data that is already available.

A lot of progress has been made to characterise and understand how lipid-based formulations behave and it is still a very attractive technology to enhance the oral bioavailability for compounds where that need is present. There are many topics where additional research and scientific discussion would be beneficial in order to ease/increase the industrial focus/interest in developing lipid-based formulations. These include in vitro characterisation methods, capsule compatibility, in vivo models, but continuous focus on potential innovations within lipid-based formulations is also highly desirable, as systematic evaluations of lipid suspensions, lipid soluble salts, combining lipid-based formulations with precipitation inhibitors, solidification of lipid-based formulations, and whatever good ideas may arise in the future.

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