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Good formulation technology

Lipid-based formulations for oral delivery of lipophilic drugs

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In the last decade there has been a growing interest in lipid-based formulations to deliver challenging compounds such as lipophilic drugs. Following a brief clarification of the nomenclature, this review stresses the different mechanisms of how lipid-based excipients and formulations interact with the absorption process. Case studies are presented in which enhanced bioavailability was demonstrated *in vivo* using this pertinent formulation approach. It is emphasized that lipid-based delivery of challenging drugs requires a development in consecutive steps. Such a structured formulation development is crucial for optimal allocation of resources. Thus, lipid-based excipients are first evaluated in view of drug solubility, phase behavior, as well as with respect to known biological effects. Mixtures can be screened in simple dilution tests and are subsequently studied in more advanced biopharmaceutical tests. Once a lipid-based formulation principle is identified, different technologies are presented to encapsulate the fill mass either in soft or hard capsules. It is also possible to formulate lipid-based systems as a solid dosage form. Even though such solid lipid technologies seem very attractive, one has to assure that the final dosage form does not impair the biopharmaceutical potential of the lipid formulation principle.

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Introduction

These days it is well understood in the drug discovery phase that suitable biopharmaceutical compound properties are pivotal for successful development of a new drug. In the late 1990s Christopher Lipinski was a pioneer in presenting his rule of five to medicinal chemists [1,2]. More rules followed and most researchers nowadays consider the developability of a drug when proposing compounds for candidate selection. Drug-likeness can be defined as a balance of molecular properties and structural features, which describe how 'drug like' a compound is compared to those of approved drugs [3–5]. However, there is often a need to compromise with high drug activity and other considerations of potential safety and pharmacokinetics. As a consequence, poor water solubility and issues of permeability are still very common among new drug candidates. It seems that compound properties, which are unfavorable for drug absorption, cannot just be eliminated in the lead optimization phase. This emphasizes the importance of pharmaceutical technology to formulate biopharmaceutically challenging drugs. Different techniques exist to cope with poor watersolubility or poor permeability. This review focuses on lipid-based drug delivery systems (LBDDS) as a key technology to formulate lipophilic compounds.

Because there are many different types of lipid-based formulations, a categorization was introduced by Colin Pouton [6,7]. The lipid formulation classification system (LFCS) differentiates four categories (Table 1). Formulations of all

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Table 1. Lipid formulation classification system according to Pouton [7]

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

categories are generally isotropic systems, which mostly are mixtures, but may as well consist of only a single excipient like oil. Triglyceride oil alone or mixtures with its partial glycerides are type I LBDDS. Such formulations do not disperse easily by themselves. Following administration, it needs bile salts, phospholipids as well as lipolysis products to reduce interfacial tension so that some dispersion can occur in the gastro-intestinal tract. This is different to so-called self-emulsifying drug delivery systems (SEDDS) [8]. Only gentle agitation is needed to spontaneously produce a rather fine emulsion. Such formulations include surfactants in addition to the oil component(s). Depending on the nature of this surfactant, LFCS type II systems are differentiated from type IIIA. While type II systems are comprises one or more water insoluble surfactants, the IIIA systems are generally more hydrophilic. The latter formulations can be mixtures of oil, hydrophilic surfactants and co-solvents. Type IIIB systems are even more hydrophilic, comprising more co-solvents or surfactants at the costs of less oil. Finally, there is a category IV LBDDS, which does not include any oil at all and typically consists of only surfactants and co-solvents.

Type IIIB formulations are generally called self-microemulsifying drug delivery systems (SMEDDS). Some authors prefer to use the term self-nanoemulsifying drug delivery systems (SNEDDS) [9,10]. Moreover, there are nano-emulsions that are obtained from low-energy dispersion such as spontaneous emulsification [11]. This terminology needs clarification as was recently pointed out in an expert review [12].

Microemulsions are apparently homogenous, surfactant-containing systems of low viscosity which are formed spontaneously. First described by Schulman, the topic of microemulsions has often been reviewed, for example, Moulik and Rakshit [13]. Microemulsions are structured on a nano-scale by consisting either of oil-swollen micelles or of a bi-continuous structure. The term 'micro' is a rather old notion in colloidal science but it is well established across different scientific disciplines.

The thermodynamic stability of microemulsions is of major importance, differentiating them from other nanoemulsions, which are only kinetically stable. Even though care is needed with the terminology, it seems that the distinction of these different nano-systems is not likely to be of biopharmaceutical relevance. Because drug absorption takes place on a comparatively short time scale, a kinetically stable nano-system is probably equally effective as a microemulsion that is truly stable from a thermodynamic viewpoint.

Mechanisms of lipid-based formulations to improve oral drug absorption and case studies

Effects of lipid-based excipients

The physical state of a lipophilic drug is important for the *in vivo* performance of any oral dosage form. Because the drug is generally solubilized in LBDDS, no dissolution step is needed. This is a crucial advantage for the delivery of lipophilic drugs, but it is not enough if solubilization capacity is lost upon aqueous dilution and dispersion. Once a drug precipitates, it is generally assumed that re-dissolution is too slow compared to the intestinal transit time. A typical consequence of such precipitation is therefore incomplete drug absorption. However, precipitation may not automatically imply erratic drug absorption. There are cases in which a precipitated drug still has time for re-dissolution. Kinetics of the process depends on drug solubility as well as on how much drug precipitated in relation to the dose. Physiologically based modeling can help to better assess such effects at an early development stage [14,15]. Such computer models consider drug release and precipitation in a dynamic way together with re-dissolution and absorption. Thus, an absorption sink is given *in silico* which more realistically mimics the *in vivo* situation. Because of this absorption sink, the amount of precipitated compound can be less *in vivo* than observed from simple *in vitro* drug precipitation [16]. Finally, it was demonstrated very recently that the drug cinnarizine precipitated in an amorphous form during *in vitro* lipolysis testing [17]. Such precipitation in amorphous state is certainly less crucial for re-dissolution than crystalline precipitation. Future research will have to show if this was a rather exceptional case or whether many drugs precipitate in amorphous form during their digestion from lipid-based formulations.

Ideally, LBDDS delivers a drug in solubilized form and maintains adequate solubilization during the gastro-intestinal passage. Presence of the lipid-based excipients often increases drug solubility *in vivo* and/or can foster supersaturation that is often sufficient for drug absorption.

Apart from the effects of drug release and solubility, there are further mechanisms by which LBDDS typically promote

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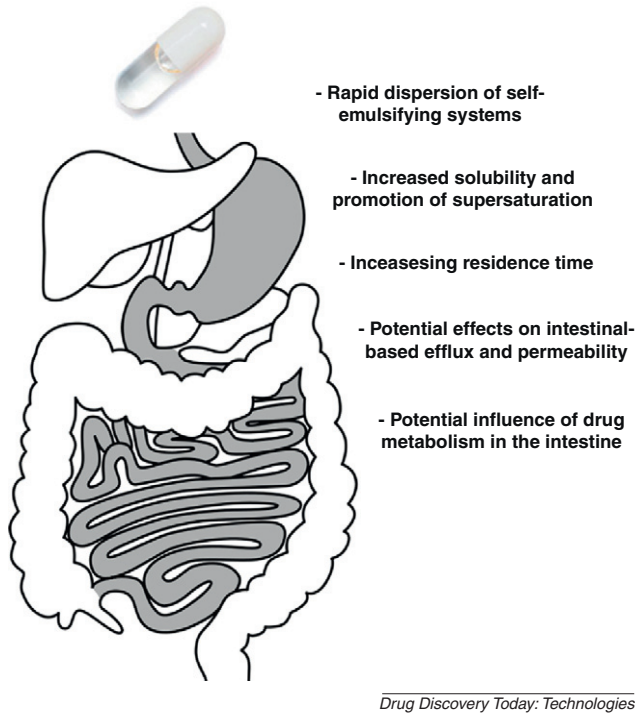

Figure 1. Potential effects of lipid-drug delivery systems on oral drug absorption.

oral bioavailability. Fig. 1 shows mechanisms of potential effects of LBDDS on oral drug absorption. Thus, lipid-based excipients can, for example, impact drug permeability. Many lipid-based excipients such as glycerides, fatty acids and ionic and non-ionic surfactants are known permeability enhancers [18]. This effect can be due to increased membrane fluidity, or alternatively, excipients can open tight junctions. Another mechanism of permeability enhancement is the interaction with efflux transporters. A well-known efflux transporter at the apical membrane of human intestine is, for example, P-glycoprotein (P-gp). Substrates for P-gp can be found in many drug groups such as anti-cancer compounds, HIV-protease inhibitors, immunosuppressants, hormones, cardiovascular drugs or H_2-receptor antagonists [19]. Substrates are expected to have increased permeability when the efflux pump is inhibited by excipients. Excipients with inhibiting effects on efflux pumps were found in the group of medium-chain glycerides, polyethylene glycols, polysorbates, polyethoxylated castor oil or block copolymers of the type Pluronic [19,20]. Especially the surfactants with their amphiphilic structure were shown to inhibit P-gp. Amphiphilic excipients further affected other xenobiotic efflux transporters such as the breast-cancer-resistance protein (BCRP) [19]. For example, an interesting study by Sugiyama's group evaluated the influence of Pluronic P85 and Tween 20 on the oral absorption of topotecan [21]. The drug previously displayed limited absorption because of BCRP efflux; however, adding Pluronic P85 or Tween 20 to topotecan nearly doubled the AUC in wild-type mice. The surfactants were less effective in increasing oral bioavailability in mice of the type Bcrp (−/−) that were not expressing the intestinal transporter. As a conclusion, such studies are needed to differentiate the individual mechanisms of how excipients promote oral drug absorption.

Many lipid-based excipients affect drug absorption by different mechanisms. Surfactants that affect efflux pumps often influence drug solubilization as well. Moreover, excipients can, for example, affect both P-gp as well as a cytochrome P450 metabolism of a drug in the intestine [8]. Finally, some of the aforementioned surfactants exhibit a further impact on production and secretion of intestinal lipoproteins, for example, chylomicrons [22]. This modulation in chylomicron production is of relevance for those drugs that are transported *via* the lymphatic pathway. Excipients such as CremphorEL or Pluronic block copolymers were shown to reduce chylomicron production, while, for example, polysorbate 80 even increased this production [23]. These considerations clearly show that additives in LBDDS are basically multi-functional.

Because there are several mechanisms involved, it is challenging to predict the resulting biopharmaceutical effect of lipid-based excipients or formulations. In most cases, lipid-based systems exhibit positive effects on absorption of lipophilic drugs. This compound class is therefore the focus of this review even though other drugs can also profit from lipid-based systems. For example, more soluble compounds might derive a protective effect from chemical or enzymatic degradation in lipid-based systems. In addition, the aforementioned excipient effects on permeability are certainly of interest for any drug with permeability issues.

It can be summarized that lipid-based excipients demonstrate several mechanisms by which drug absorption is promoted. The development of complex lipid mixtures is therefore mostly an empirical process. Fortunately, the experiments can be organized in a structured manner so that there are not more resources needed for developing an LBDDS compared with other oral formulations. Before considering this structured development of lipid-based systems, it is interesting to study some cases demonstrating what can be achieved *in vivo*.

In vivo *performance of selected lipid-based formulations*

Table 2 lists a series of LBDDS case studies using lipophilic drugs [24,25]. Most compounds had a comparatively low relative molecular weight (MW) and belonged to class II of the Biopharmaceutical Classification System (BCS) [25]. A first example of the drug atorvastatin indicated that the AUC in beagle dogs was increased about 50% using a SMEDDS compared to a tablet [26]. This increase was remarkable, especially because the comparison was made with a tablet

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Table 2. Case studies of self-emulsifying formulations of poorly water-soluble drugs

Drug name and molecular weight	API characteristics [24,25]	LBDDS	BA study result	Ref.
Atorvastatin **MW ≅ 558.6**	$Sol_w \cong 10$ μg/mL log $P \cong 5.7$; p*Ka* ≅ 4.5 BCS II(10–80 mg) High presystemic clearance and first pass metabolism	SMEDDS (Labrafil M19CS, Cremophor RH40, propylene glycol)	Study in beagle dogs: ~1.5 times AUC increase compared to a tablet	[26]
Carvedilol **MW ≅ 406.5**	$Sol_w \cong 0.6$ μg/mL log $P \cong 3.8$ BCS II (3.125–25 mg) Severe first pass metabolism	SEDDS (Labrafil M1944CS, Tween 80 and Transcutol)	Study in beagle dogs: ~4 times higher AUC compared to the tablet	[27]
Cyclosporine **MW ≅ 1202.6**	$Sol_w < 10$ μg/mL log $P \cong 3$ BCS II (10–100 mg) Incomplete absorption and high liver metabolism	'Sandimmune' oil formulation *vs.* SMEDDS 'Neoral' (corn oil glycerides, Cremophor RH40, propylene glycol, vit. E, and ethanol)	Clinical studies of SMEDDS *vs.* standard oil formulation → 'Neoral' resulted in higher AUC, better dose-linearity, reduced food effect and less variability	[28–30]
Itraconazole **MW ≅ 705.6**	$Sol_w < 10$ μg/mL log $P \cong 6.5$; p*Ka* ≅ 3.7 BCS II (100 mg)	Standard 'Sporanox' formulation or an SEDDS (Pluronic L64, Transcutol, and tocopherol acetate)	Different feeding condition (rats) → Sporanox resulted in lower AUC following lipid-rich diet, but SEDDS revealed a consistent high AUC	[31]
Ketoprofen **MW ≅ 254.3**	$Sol_w \cong 51$ μg/mL log $P \cong 3.2$; p*Ka* ≅ 4.5 BCS II (25–50 mg)	Aqueous suspension *vs.* SEDDS (medium chain triglycerides, diglycerylmonooleate, Cremophor RH40 and ethanol)	Rat study: ~1.5 times higher AUC of SEDDS compared to aqueous drug suspension	[32]
Simvastatin **MW ≅ 418.6**	$Sol_w \cong 0.8$ μg/mL log $P \cong 4.7$ BCS II (5–80 mg)	Tablet *vs.* SMEDDS (Capryol 90, Cremophor EL, and Carbitol)	Study in beagle dogs: ~1.5 fold higher AUC from SMEDDS	[33]

that is on the market that was already an optimized solid formulation.

For Carvedilol, the AUC was increased several times using the SEDDS [27]. Such pronounced effects are in fact often seen with drugs that exhibit a very low aqueous solubility. Cyclosporine also has allow aqueous solubility and it is therefore not surprising that a lipid formulation was developed for the market. The original S and immune product consisted of long-chain triglycerides, ethanol and polyoxyethylated glycolyzed glycerides. This SEDDS formed a coarse emulsion in contact with water. A much finer dispersion was achieved by the microemulsion concentrate Neoral. Interestingly, this SMEDDS not only increased AUC compared to Sandimmune but also exhibited other positive pharmacokinetic effects [28–30]. Better dose linearity was achieved and the SMEDDS demonstrated a reduced inter- and intra-subject variability of pharmacokinetics. Such reduction of variability or reduction of a food effect can actually provide a rationale in its own right for development of lipid-based formulations.

Food effects were hence the topic for a study with different itraconazole formulations [31]. The drug was given to rats in fasted state, fed state and following a special lipid-enriched meal. For each condition, the solid formulation Sporanox and a SEDDS were administered. The latter formulation always resulted in high AUC regardless of the feeding condition. By contrast, Sporanox displayed a markedly reduced bioavailability in presence of lipid-rich food. It was concluded that SEDDS is a useful formulation approach for itraconazole to achieve high bioavailability, while avoiding a food effect.

Some care is, however, needed when studying lipid formulations in rats. The amounts of lipid formulation studied are often comparatively high for this species and physiologically the rat is known for a continuous bile flow. The rat may still serve as a model for the human situation, but effects should be interpreted rather qualitatively. Table 2 lists two more case studies: one study investigated ketoprofen in rats, while the second administered simvastatin to dogs [32,33]. Both cases demonstrated again the markedly improved oral bioavailability when using SEDDS as compared to a reference formulation.

The reference formulation in the case of the ketoprofen study was an aqueous suspension with 0.5% methylcellulose, which is a typical preclinical formulation. This example illustrates that lipid-based formulations have a high potential for optimizing drug absorption in early drug development. It is often a substantial hurdle to find preclinical formulations with adequate exposure. Poorly water-soluble drugs are especially challenging to formulate at comparatively high doses. However, such high doses are required for toxicological studies to investigate safety margins for new drugs. Lipid formulations can therefore provide an enabling technology for such drug candidates regardless of the formulations that are later used in clinical trials or on market.

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Retrospective data analysis can provide a learning tool for lipid-based formulation in early drug development. One example is a study, in which pharmacokinetic data were gathered from different toxicological studies, as well as from preclinical and clinical formulation screening [34]. The research compound (molecular weight of 531) exhibited very low aqueous solubility (<1 μg/mL) and its calculated log $P \cong 8.9$ was very high. An extensive screening of lipid-based formulations was conducted in the rat. Despite the numerous study results, a direct comparability of excipients or formulation parameters was not easy. A partial least square (PLS) analysis was therefore conducted with respect to the dose-normalized AUC. A key finding was that SEDDS and SMEDDS reached higher exposure than pure oils or aqueous surfactant solutions of the drug. Significant trends regarding the selection of excipients were observed: it was of general advantage to use a co-solvent, that is, ethanol or Transcutol and differences among the surfactants were found. Cremophor EL, Capmul MCM as well as lecithin resulted in markedly above-average AUC values, while significantly lower AUC was exhibited with systems comprising Tocophersolan (TPGS). It was not determined whether some of the findings were highly specific for the drug studied. However, observed differences were attributed to *in vivo* effects, because all formulations previously demonstrated the absence of any unfavorable drug precipitation in dilution tests.

Aqueous dilution tests provide a simple tool for early formulation assessment. It is one of several activities that are needed before any *in vivo* study. These formulation activities should be carried out in a highly structured manner for effective development of preclinical or clinical drug delivery systems. Thus, a next section of this review proposes a strategy of how to elucidate formulation candidates and which criteria are used to select the most promising mixtures for subsequent *in vivo* studies.

Structured development of lipid-based systems

Proposing and screening of formulation candidates

Formulation development generally starts with excipient selection; however, the list of lipid-based additives is fairly long. Natural oils, phospholipids and fats can be used as well as fatty acids and semi-synthetic excipients. In the latter group, the semi-synthetic polyethylene glycol (PEG) derivatives of glycerides or fatty acids are most abundant. Lists of such excipients are part of several review articles on lipid-based formulations and an excellent overview was provided by Gibson [35].

To propose candidate formulations, the excipient mixing behavior must be studied. Phase diagrams are constructed to identify suitable mixing ratios for homogenous formulations. Experimental results of phase behavior must be gathered early on and it is even possible to organize data in the form of a computer expert system [36]. Fig. 2 proposes a flow chart for the development of lipid-based formulations. The screening of phase behavior is on the same level as the screening of drug solubility in excipients. Both activities are indeed equally crucial; however, some research laboratories may prefer to first screen for drug solubility before phase behavior

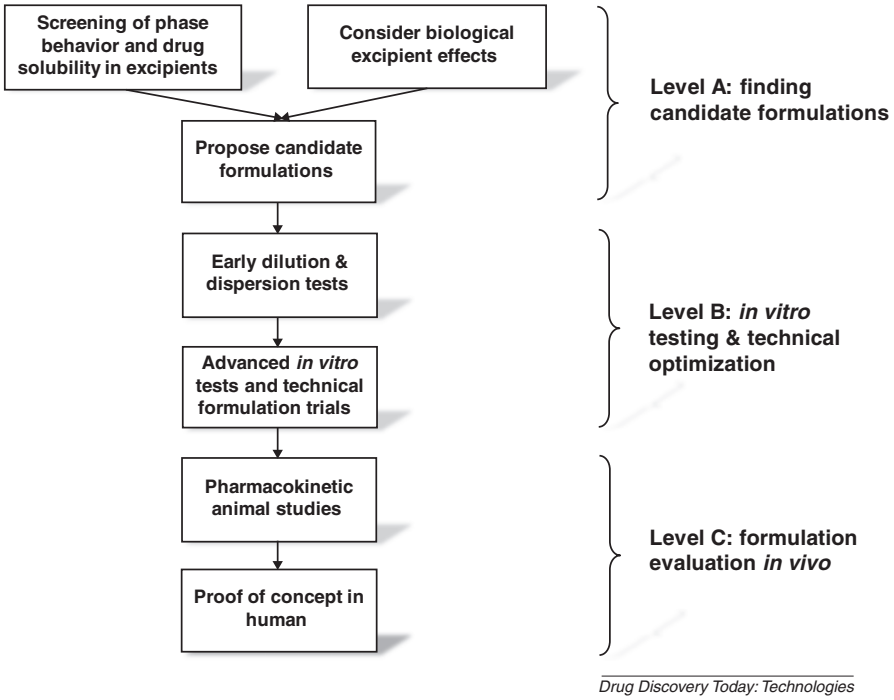

Figure 2. Example of a structured approach to elucidate and select lipid-based drug formulations.

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is studied in more detail. It is worth mentioning that at this stage, exact thermodynamic solubility values are not needed. A first solubility approximation seems to be sufficient for selection of excipients. Such first solubility assessment in excipients can be obtained from turbidity measurements. The advantage of measuring turbidity is the potential for miniaturization of mixing and solubility experiments, which was recently explored in a high-throughput approach to finding lipid-based formulations [37]. Whichever strategy is used to propose candidate formulations, it makes sense to further consider biological effects of the additives. Such effects range from tolerability to interactions with efflux transporters or to a potential influence on lipoprotein assembly. Some of the biological information on excipients is available in the literature but there are many unknowns. Considerable research effort is needed to fill the existing knowledge gaps and help in profiling lipid-based excipients.

Fig. 2 shows that once candidate formulations are proposed, the drug-containing systems are studied with respect to their aqueous dilution behavior. Samples may be either diluted in water or in simulated intestinal fluids. The rationale for such screening tests is to first characterize the drug-containing systems and then to consider potential drug precipitation. Mixtures that lead to crushing out of drug upon dilution are typically excluded from further development. Such a precipitated drug is best observed at a comparatively low dilution level. Testing of low aqueous dilution makes further sense because of phase transitions that occur close to or below 1:5 (formulation to water, w/w) [38]. This range should be studied in addition to a high aqueous dilution such as 1:200 (w/w) mixtures, which simulate a dilution under physiological conditions. These dilution studies narrow down the number of viable formulations. Only selected systems are further investigated in 'advanced' *in vitro* tests (Fig. 2).

Release testing can be performed in compendial dissolution equipment, and for biorelevant testing the use of simulated intestinal fluids is recommended [39]. Even closer to the *in vivo* situation is certainly to take digestion into account. For this purpose, *in vitro* lipolysis testing of formulations was introduced [40,41]. This important test reveals if formulation components are digested and whether or not this is relevant for drug precipitation. The amount of precipitated drug is quantified when following lipolysis; the medium is ultracentrifuged to determine the amount of drug in the evolving pellet. The extent of drug precipitation upon lipolysis was indeed shown to be predictive for the ranking of formulation performance *in vivo* [42]. However, *in vitro* lipolysis testing still has the character of a research method and harmonization of the test protocols is required. Research consortiums can be an effective means of information sharing for optimization of experimental design of lipid-based systems. Study of the different experimental factors is therefore a key objective of a research consortium, which should bring *in vitro* lipolysis testing to an industrial-quality level [43].

The final dosage form and comparison of different technologies

Different options exist for producing the final on-market dosage form of lipid-based systems. This dosage form must be considered early enough in development so that modifications of the composition can still be made. Aspects such as the anticipated filling process or, for example, the compatibility of fill mass with shell material must be taken into account. In most cases, the process involves a rotary die filling of soft gelatin capsules; however, other techniques have increasingly gained importance over the last few years.

Apart from using alternative materials other than gelatin for soft capsules, hard gelatin capsules have become an industrial focus. It is nowadays possible to liquid-fill hard gelatin capsules on different batch scales. Sealing of the capsules is either done by banding or by employing a 'liquid encapsulation by microspray' (LEMS) principle [44]. Liquid-filled hard capsules can be produced in-house, which is an advantage over the soft capsule technology that generally requires a specialized contract manufacturer. Another benefit of hard capsules is that they withstand much higher filling temperatures of up to 70°C as compared to ~40°C for soft gelatin. Apart from these advantages of hard gelatin, other aspects are in favor of the soft gelatin technology. Soft gelatin capsules can have advantages of shell compatibility when using hygroscopic excipients. Moreover, an inadequate filling of the two-piece hard capsules can lead to failures due to leaking out of capsule fill mass. Finally, more fill mass and therefore higher doses can be incorporated into soft gelatin capsules, because they are entirely filled as opposed to hard capsules that essentially have a head space.

In summary, soft and hard capsules both have their pros and cons so that no technology is generally deemed superior to another. The technology selected depends on the specific project needs. This is also true for solid lipid-based formulations. Different technologies exist for this formulation principle that offers an alternative to incorporation of a liquid or semi-solid mass into a capsule.

A classical method to convert lipid-based systems to a solid dosage form is adsorption on a carrier [45]. The employed solid carriers must have a high surface area and so nanoparticulate excipients are mostly used. Adsorption onto the carrier is, for example, processed in a high shear mixer. Melt granulation using this mixer is further used for an alternative technique that simply combines waxy excipients with a conventional granulation process. It has the advantage of yielding much higher drug load as the drug is usually in a coarse crystalline form. By contrast, adsorbates have the biopharmaceutical advantage of higher surface area and the physical state of the drug can be amorphous. Having

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the drug in amorphous form or more generally as a solid dispersion is also the rationale for using lipid-based excipients in melt extrusion or spray drying.

It is beyond the scope of this article to provide a detailed overview of all the technologies for solid lipid-based systems. There are dedicated review articles available that cover these solid technologies in detail [46,47]. However, some general comments can still be made in line with previous considerations. The importance of dose and physical state of the drug is of fundamental importance for solid lipid-based systems. In this respect, solid dispersions using lipid excipients seem highly attractive, because a high dose can be combined with a fast release of the drug. However, like other liquid systems, the solid dispersions must be tested *in vitro* to determine whether or not they can keep the drug solubilized upon dilution. Moreover, lipid-based excipients display several mechanisms of enhancing drug absorption. It can therefore be important for the final dosage form to contain as much lipid as possible. High lipid load can simply be achieved by filling soft and hard capsules. These classical techniques further were shown to have a scale-up that is technically straightforward, while this is often not the case for melt granulation or adsorbates. However, the latter techniques can result in tablets and they might have an edge over capsules when the 'cost of goods' are assessed. This indicates that choice of the dosage form must balance biopharmaceutical considerations with technical aspects and costs.

Conclusions

Lipid-based formulations were shown to improve the biopharmaceutical performance of lipophilic drugs compared to a conventional dosage form. There is typically an increase of oral bioavailability, but other effects like better linearity of exposure or less variability within and between subjects may be observed as well.

It was outlined that a lipid-based formulation should be best developed in several steps. A screening of oil solubility, phase behavior and consideration of biological excipient effects should first result in candidate formulations. Further screening of dilution behavior is meaningful before more advanced biopharmaceutical methods and *in vivo* studies are performed.

It makes sense to first identify the most promising formulation principle from a biopharmaceutical perspective. A formulation can subsequently be adapted according to the specific requirements of the final dosage form. The alternative approach to start development with a specific dosage form technology is often accompanied by the danger that the selected formulation may not reach the full biopharmaceutical potential of lipid-based drug delivery.

Conflict of interest

The author declares no conflict of interest.

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