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LIPID-BASED LIPOPHILIC FORMULATIONSFOR ORAL DRUG DELIVERY

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ABSTRACT

In the last decade to deliver challenging compounds such as lipophilic drugs there has been a growing interest in lipid-based formulations. This review stress the varios mechanisms of how lipid-based excipients and formulations interact with the absorption process. Using this pertinent formulation approach case studies are presented in which enhanced bioavailability was demonstrated in vivo. It is indicated that lipid-based delivery of challenging drugs requires a improvement in consecutive steps and these prepared formulation improvement is crucial for best possible provision of resources. Hence, lipid-based excipients as with respect to known biological effects, are first evaluated in viewof drug solubility, phase behaviour. Mixtures can be subsequently studied in more advanced biopharmaceutical tests and are screened in simple dilution tests. Different technology are offered to encapsulate the fill in soft or hard capsules after lipid-based formulation principle is identified and also possible to formulate lipid-based systems as a solid dosage form. One has to assure that the final dosage form does not impair the biopharmaceutical potential of the lipid formulation principle, Even though such solid lipid technologies seem very attractive.

INTRODUCTION

Suitable biopharmaceutical compound properties are fundamental for successful development of a new drug. Most researchers nowadays consider the develop ability of a drug when proposing compounds for candidate selection. Issues of permeability and poor water solubility are still very common among new drug candidates. Compound properties, which are unfavourable for drug absorption, cannot be eliminated in the lead optimization

phase. To formulate biopharmaceutically challenging drugs, this emphasize the importance of pharmaceutical technology. Different methods are used to cope with poor permeability or water solubility. As a key technology to formulate lipophilic compounds, this review focuses on lipid-based drug delivery systems (LBDDS)as there are many different types of lipid-based formulations, a categorization was introduced by Colin Pouton.[6,7] LFCS, i.e. lipid formulation classification system is divided in four categories (Table 1). Generally, formulations of all categories are isotropic systems, which are mostly consist of mixturesor single excipients like oil and these formulations do not disperse easily by themselves. Bile salts, phospholipids as well as lipolysis products are needed by some formulations to reduce interfacial tension so that some dispersion can occur in the gastro-intestinal tract. This is called self-emulsifying drug delivery systems (SEDDS).[8] LFCS type II, are different from type IIIA, depending on the nature of surfactant. Type II systems comprises one or more water insoluble surfactants, where the IIIA systems are more hydrophilic. Comprising more co-solvents or surfactants at the costs of less oil,type IIIB systems are even more hydrophilic. And a category IV LBDDS, does not include any oil at all and consists of only co-solvents and surfactants. Type IIIB formulations are self-microemulsifying drug delivery systems (SMEDDS). There are nano-emulsions obtained from low-energy dispersion such as spontaneous emulsification.[11] Microemulsions which are formed spontaneously are apparently homogenous, surfactant containing systems of low viscosity. These are designed on a nano-scale with the help of oil-swollen micelles or of a bi-continuous structure. The thermodynamic stability of microemulsions, differentiating them from other nanoemulsions, and are kinetically stable.Care is needed with the terminology, as it seems that the distinction of different nano-systems is not likely to be of biopharmaceutical relevance.

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

Excipient in formulation	*Content of Formulation (%,w/w)*				
	Type I	**TypeII**	**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

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

Effects of lipid-based excipients

For the in vivo performance of any oral dosage form, the physical state of a lipophilic drug is important. Because no dissolution step is needed, the drug is generally solubilized in LBDDS. It is notenough if solubilization capacity is lost upon aqueous dilution and dispersion as this is a crucial advantage for the delivery of lipophilic drugs. It is generally assumed that re-dissolution is too slow compared to the intestinal transit time, when once a drug precipitates. Such precipitation is therefore causes incomplete drug absorption. It is observed in few cases that a precipitated drug still has time for re-dissolution. Kinetics of the process depends on how much drug precipitated as well as on drug solubility in relation to the dose. At an early development stage Physiologically based modeling can help to better assess such effects.[14,15] In a dynamic way together with re-dissolution and absorption such computer models consider drug release and precipitation. Thus, for more realistically mimics the in vivo situation, an absorption sink is given in silicon. Because of this absorption sink,the amount of precipitated compound can be more in vitro than observed from simple in vivo drug precipitation.[16] Precipitation in crystalline state is certainly more crucial for redissolution than amorphous precipitation. If this was a rather many drugs precipitate in amorphous form or whether exceptional case during their digestion from lipid-based formulations, future research will have to show. Ideally, LBDDS maintains adequate solubilization and delivers a drug in solubilized form within the gastro-intestinal passage. Foster supersaturation that is often sufficient for drug absorption and/or can presence of the lipid-based excipients often increases drug solubility in vivo. There are further mechanisms by which LBDDS typically promote compounds, HIV-protease inhibitors, immunosuppressants, hormones, cardiovascular drugs or H2-receptor antagonists, apart from the effects of drug release and solubility.[19] When the efflux pump is inhibited by excipients, substrates are expected to have increased permeability. Excipients in the group of medium-chain glycerides, polyethylene glycols, polysorbates, polyethoxylated castor oil or block copolymers of the type Pluronic, were found with inhibiting effects on efflux pumps.[19,20] The surfactants with their amphiphilic structure inhibit P-gp. Moreover, xenobiotic efflux transporters such as the breast-cancer- resistance protein (BCRP) may affect due to Amphiphilic excipients.[19] For example, the influence of Pluronic P85 and Tween 20 on the oral absorption of topotecan is observed by Sugiyama's group evaluation.[21] However, adding Pluronic P85 or Tween 20 to

topotecan nearly doubled the AUC in wild-type mice where the drug previously displayed limited absorption because of BCRP efflux. in increasing oral bioavailability in mice, the surfactants were less effective of the type BCRP (_/_) that were not expressing the intestinal transporter. This results to conclusion that, such studies are needed to differentiate how excipients promote oral drug absorption in the individual. A lot of lipid-based excipients affect drug absorption by various mechanisms. Increased drug solubilization is the result of surfactants that affect efflux pumps. Excipients can affect both cytochrome P450 as well as a P-gp metabolism of a drug in the intestine.[8] Finally, production and secretion of intestinal lipoproteins is improved by surfactants, for example, chylomicrons.[22] For those drugs that are transported via the lymphatic pathway, this modulation in chylomicron production is of relevance. Excipients such as.

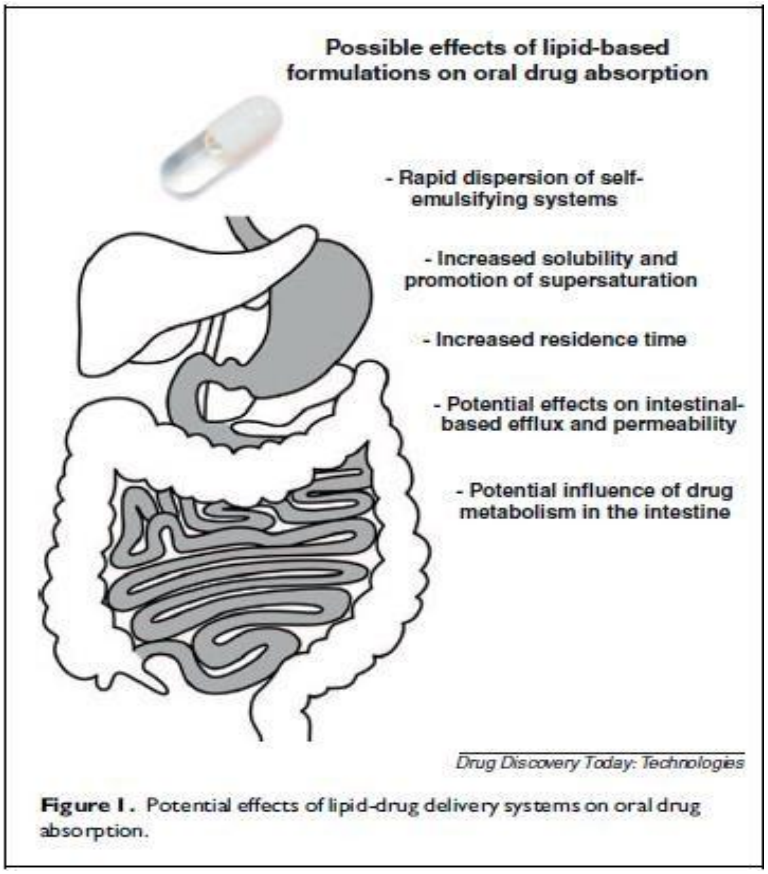

Figure 1. Potential effects of lipid-drug delivery systems on oral drug absorption.

CremphorEL or Pluronic block copolymers were shown to polysorbate 80 increased this production, while chylomicron reduce production.[23] These factors clearly expressed that additives in LBDDS are essentially multi-functional. It is challenging to predict the resulting biopharmaceutical effect of lipid- based excipients or formulations because there are several mechanisms involved. In most cases, on absorption of lipophilic drugs, lipid based systems

exhibit positive effects. Even though other drugs can also profit from lipid-based systems, this compound class is therefore the focus of this review. For example, the afore mentioned excipients effects on permeability are certainly of interest for any drug with permeability issues. More soluble compounds might derive a protective effect from chemical or enzymatic degradation in lipid-based systems. It can be summarized that drug absorption is promoted by lipid-based excipients demonstrate several mechanisms. Therefore an empirical process is the development of complex lipid mixtures. There are not more resources needed for developing an LBDDS compared with other oral formulations, hence, the experiments can be organized in a well structured manner. It is interesting to study some cases demonstrating what can be achieved in vivo before considering this structured development of lipid-based systems.

In vivo performance of selected lipid-based formulations

Studies using lipophilic drugs is shown in Table 2 which lists a series of LBDDS case.[24,25] Most compounds belonged to class II of the Biopharmaceutical Classification System (BCS) and had a comparatively low relative molecular weight (MW).[25] For example, using a SMEDDS compared toa tablet of the drug atorvastatin indicated that, the AUC in beagle dogs was increased about 50%.[26] The comparison was made with a tablet that is on the market that was already an optimized solid formulation, this increase was remarkable. The AUC was increased several times using the SEDDS for Carvedilol.[27] Drugs that exhibit a very low aqueous solubility, such pronounced effects are in fact often seen with them. As Cyclosporine allow aqueous solubility, therefore no lipid formulation was developed for the market. Long-chain triglycerides, ethanol and polyoxyethylated glycolyzed glycerides is shown by the original S and immune product. A coarse emulsion in contact with water is formed due to SEDDS. This SMEDDS not only exhibited other positive pharmacokinetic effects but also increased AUC compared to Sandimmune.[28–30] The SMEDDS demonstrated a reduced inter and intra-subject variability of pharmacokinetics and better dose linearity was achieved. This provide a rationale in its own right for improvement of lipid-based formulations. For a study with different itraconazole formulations food effects is important factor.[31] The drug was administered to rats with a special lipid-enriched meal and in fasted state, fed state. In each condition, a SEDDS and the solid formulation Sporanox were administered. Sporanox displayed a markedly reduced bioavailability in presence of lipid-rich food compared to high AUC regardless of the feeding condition. It was concluded that to achieve high bioavailability, SEDDS is a useful formulation approach for itraconazole, while avoiding a

food effect. Some care should be taken while studying lipid formulations in rats. Physiologically the rat is known for a continuous bile flow and so the amounts of lipid formulation studied are often comparatively high for this species. The rat serve as a model for the human situation and the effects should be interpreted qualitatively. Two more case studies are given in Table 2 lists: one study administered simvastatin to dogs while the second investigated ketoprofen in rats.[32,33] When using SEDDS as compared to a reference formulation, both cases demonstrated again the markedly improved oral bioavailability. In the case of the ketoprofen study, the reference formulation was an aqueous suspension with 0.5% methylcellulose, which is a usual preclinical formulation. Resulting illustration was that lipid-based formulations have a high potential for optimizing drug absorption in early drug development. To find preclinical formulations with adequate exposure it is often a substantial hurdle. In formulation of comparatively high doses, poorly water-soluble drugs creates challenges. Such high doses are mandatory for toxicological studies to examine safety boundaries for new drugs. Before used in clinical trials or on market, Lipid formulations can therefore provide an enabling technology for such drug candidates regardless of the formulations. In early drug development, retrospective data analysis can provide a learning tool for lipid-based formulation. However, the example is a study, in which pharmacokinetic data were gathered from preclinical and clinical formulation screening, as well as from different toxicological studies.[34] The research compound calculated log P ffi 8.9 was very high and its(molecular weight of 531) exhibited very low aqueous solubility (<1 mg/mL). Rats were used in an extensive screening of lipidbased formulations study. In spite of the numerous study results, a direct comparison of excipients or formulation parameters was not easy. Therefore, with respect to the dose-normalized AUC, a partial least square (PLS) analysis was conducted. A key finding was that pure oils or aqueous surfactant solutions of the drug were having low exposure than SEDDS and SMEDDS. In theselection of excipients significant trends were observed: i.e. general advantage to use a co-solvent like ethanol or Transcutol and differences among the surfactants were found. Lecithin as well as Cremophor EL, Capmul MCM resulted in markedly above-average AUC values, and Tocophersolan (TPGS) shown significantly lower AUC. Some of the findings were highly specific for the drug studied, was not determined. Observed differences were recognized to in vivo effects, as all formulations formerly established the absence of any unfavourable drug precipitation in dilution tests. A simple tool for early formulation assessment was provided by aqueous dilution tests. Before any in vivo study, it is one of several activities that are needed. For effective development of preclinical or clinical drug delivery systems these formulation

activities should be carried out in a highly structured manner. Thus, a next section of this review proposes which criteria are used to select the most promising mixtures for subsequent in vivo studies and a strategy of how to elucidate formulation candidates.

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

Drug name and molecular weight	API characteristics	LBDDS	BA study result	Ref.
Atorvastatin MW=~ 558.6	Solw ~= 10 mg/mL log P ffi 5.7; pKa ~= 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	Solw ~= 0.6 mg/mL log P ~= 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	Solw < 10 mg/mL log P ~= 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	Solw < 10 mg/mL log P ff~= 6.5; pKa ~= 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	Solw ~= 51 mg/mL log P ~= 3.2; pKa ~= 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	Solw ~= 0.8 mg/mL log P ~= 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]

Structured development of lipid-based systems

Proposing and screening of formulation candidates

However, the list of lipid-based additives is fairly long, formulation development generally starts with excipients selection. Fatty acids and semi-synthetic excipients as well as Natural oils, phospholipids and fats can be used. The semi-synthetic polyethylene glycol (PEG) derivatives of glycerides or fatty acids are most abundant in the latter group. Such excipients are listed as part of several review articles on lipidbased formulations and an outstanding summary was provided by Gibson.[35]

The excipient mixing behavior must be studied to propose candidate formulations. Identification of suitable mixing ratios for homogenous formulations is done by construction of phase diagrams. Experimental results of phase behaviour, it is possible to organize data in the form of a computer expert system and must be gathered early on.[36] A flow chart for the development of lipid-based formulations is shown in Fig. 2. Some research laboratories may prefer to first screen for drug solubility before phase behaviour is studied in more detail, however, both activities are indeed equally crucial. At this stage it is worth mentioning that, exact thermodynamic solubility values are not needed. For selection of excipients, a first solubility approximation seems to be sufficient. From turbidity measurements, first solubility assessment in excipients can be obtained. It was recently explored in a high-throughput approach to finding lipid-based formulations that the advantage of measuring turbidity is the potential for miniaturization of mixing and solubility experiments.[37] It makes sense to further consider biological effects of the additives from whichever strategy is used to propose candidate formulations. There are many unknowns but some of the biological information on excipients is available in the literature. To fill the existing knowledge gaps and help in profiling lipid- based excipients considerable research effort is needed.

Fig.2 express that the drug-containing systems are studied with respect to their aqueous dilution behaviour when candidate formulations are proposed. Formulations may be either in simulated intestinal fluids or diluted in water. The rationale for such, screening tests is to consider potential drug precipitation after characterize the drug containing systems. Those mixtures that lead upon dilution to crushing out of drug are typically excluded from further development. At a comparatively low dilution level, such a precipitated drug is best observed. Phase transitions that occur close to or below 1:5 (formulation to water, w/w) followed by testing of low aqueous dilution.[38] In addition to a high aqueous dilution such as 1:200 (w/w)

mixtures this range should be studied, which simulate a dilution under physiological conditions. The number of viable formulations was narrow down these dilution studies. 'Advanced' in vitro tests are further investigated by only selected systems (Fig. 2).

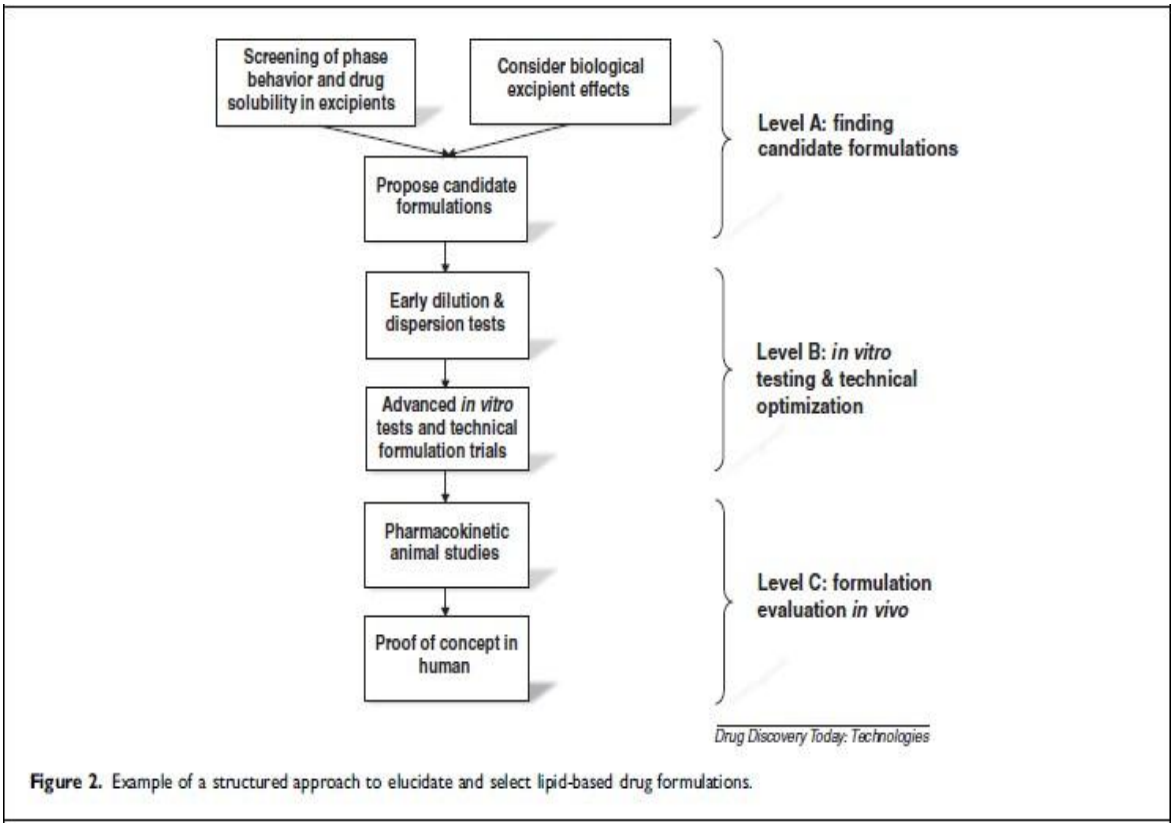

Figure 2. Example of a structured approach to elucidate and select lipid-based drug formulations.

compendial dissolution equipment is used to perform Release testing, and simulated intestinal fluids is recommended for biorelevant testing.[39] To take digestion into account, in vivo situation is certainly considered. And for this, in vitro lipolysis testing of formulations was recommended.[40,41] If formulation components are digested and whether or not this is relevant for drug precipitation, this important test reveals. Following lipolysis, the amount of precipitated drug is quantified; the medium is ultracentrifuged to determine the amount of drug in the evolving pellet. The extent of drug precipitation after lipolysis was shown to be foretelling for the grade of formulation performance in vivo.[42] Nevertheless, harmonization of the test protocols is required and in vitro lipolysis testing still has the character of a research method. Information for optimization of experimental design of lipid-based systems was shared from Research consortiums. A research consortium is a key objective of study of the different experimental factors, which should bring in vitro lipolysis testing to an industrial-quality level.[43]

The final dosage form and comparison of different technologies

For producing the final on-market dosage form of lipid-based systems different options exist. In early developmental stage this dosage form must be considered so that modifications of the composition can still be made. Aspects like the compatibility of fill mass with shell material or the anticipated filling process, must be taken into account. Mostly, the process involves a rotary die filling of soft gelatin capsules; but, other techniques have increasingly gained importance over the last few years. Hard gelatin capsules have become an industrial focus, apart from using alternative materials other than gelatin for soft capsules. Nowadays it is possible to liquid-fill hard gelatin capsules on different batch scales. Either by banding or by employing a 'liquid encapsulation by microspray' (LEMS) principle sealing of the capsules is done.[44] An advantage over the soft capsule technology that generally requires a specialized contract manufacturer is liquid-filled hard capsules can be produced in-house. They withstand much higher filling temperatures of up to 70˚C as compared to ~40˚C for soft gelatin is another benefit of hard capsules. When using hygroscopic excipients, soft gelatin capsules can have advantages of shell compatibility. In addition, the two-piece hard capsules can lead to failures due to leaking out of capsule fill mass due to an inadequate filling. Higher doses can be incorporated into soft gelatin capsules due to more fill mass, because they are entirely filled as opposed to hard capsules that essentially have a head space. In short, no technology is generally deemed superior to another because soft and hard capsules both have their pros and cons. The specific project needs the selected technology and this is also true for solid lipid-based formulations. For the formulation principle that offers an alternative to incorporation of a liquid or semi-solid mass into a capsule, different technologies exist.

Adsorption on a carrier is a classical method to convert lipid-based systems to a solid dosage form.[45] Nanoparticulate excipients are mostly used as the employed solid carriers have a high surface area. Adsorption onto the carrier is processed in a high shear mixer. Using this mixer waxy excipients are combined with a conventional granulation process by Melt granulation, is further used for an alternative technique. As the drug is usually in a coarse crystalline form, is the advantage of yielding much higher drug load. In contrast, the physical state of the drug can be amorphous so adsorbates have the biopharmaceutical advantage of higher surface area. It is rationale for using lipid-based excipients in melt extrusion or spray drying when the drug in amorphous form or as a solid dispersion.

To provide a detailed overview of all the technologies for solid lipid-based systems is the

scope of this article. There are so many dedicated review articles available that cover these solid technologies in detail.[46,47] Fundamental importance for solid lipid-based systems is, the importance of dose and physical state of the drug. For this reason, a high dose can be combined with a fast release of the drug, as solid dispersions using lipid excipients seem highly attractive. However, the solid dispersions must be tested in vitro to determine whether or not they can keep the drug solubilized upon dilution, like other liquid systems. Moreover, several mechanisms of enhancing drug absorption are displayed by lipid-based excipients. To contain as much lipid as possible, it can therefore be important for the final dosage form. By filling soft and hard capsules, high lipid load can simply be achieved. Technically straightforward i.e. classical techniques further were shown to have a scale-up, 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. Summarised that, the choice of the dosage form must balance biopharmaceutical considerations with technical aspects and costs.

CONCLUSIONS

To improve the biopharmaceutical performance of lipophilic drugs compared to a conventional dosage form, lipid-based formulations have unique importance. Effects like better linearity of exposure or less variability within and between subjects may be observed, but there is typically an increase of oral bioavailability as well.

It was concluded that in several steps, a lipid-based formulation should be best developed. In candidate formulations first result should be screening of oil solubility, phase behavior and consideration of biological excipients effects. Further before more advanced biopharmaceutical methods and in vivo studies are performed, screening of dilution behavior is meaningful. According to the specific requirements of the final dosage form, a formulation can subsequently be adapted.

In this study, LOP–NLC for oral administration was successfully prepared by a high shear homogenization method. The LOP–NLC was optimized using the central composite rotatable design– response surface methodology. LOP–NLC under the optimized conditions with low surfactant and lipid concentrations were of small homogeneous particle size (159.5 nm) with high encapsulation efficiency (97.77 %). The oral bioavailability of LOP is expected to improve due to the higher intestinal lymphatic uptake of LOP-NLC. The NLC prepared thus offer a potential approach to enhance the oral bioavailability of poorly water-soluble drug.

Based on these findings, we will further study the precise and specific mechanisms of improvement of oral absorption of the drug in this formulation.

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