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Unlocking the full potential of lipid-based formulations using lipophilic salt/ionic liquid forms☆

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ABSTRACT

Lipid-based formulations (LBF) are widely used by industry and accepted by the regulatory authorities for oral drug delivery in the pharmaceutical and consumer healthcare market. Innovation in the LBF field is however needed in order to meet the demands of modern drugs, their more challenging problem statements and growing needs for achieving optimal pharmacokinetics (i.e., no food-effects, low variability) on approval. This review describes a new lipophilic salt / ionic liquid approach in combination with LBF, and how this salt strategy can be used to better tailor the properties of a drug to LBFs. The potential advantages of lipophilic salts are discussed in the context of dose escalation studies during toxicological evaluation, reducing the pill burden, increasing drug absorption of new drugs and in life-cycle management. Commentary on lipophilic salt synthesis, scale-up, LBF design and the regulatory aspects are also provided. These topics are discussed in the broad context of bringing the widely recognized advantages of LBFs to a broader spectrum of drugs.

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1. Introduction

Lipid-based formulations (LBFs) are widely used in drug development to improve the oral absorption of the growing number of poorly water-soluble drugs belonging to Biopharmaceutics Classification System (BCS) Class II or IV [1–4]. Drugs that are well-suited to LBFs for oral absorption enhancement include those described as “grease ball” type drugs. Such drugs typically exhibit solvation-limited absorption and thus changes to the local solubilization environment in the GI tract resulting from the use of LBFs can greatly improve drug solubility. This is in contrast to “brick dust” type drugs, where strong solid-state forces are most limiting to absorption. For brick dust drugs, an amorphous formulation approach, such as a spray dried dispersion, is typically pursued since accessing the amorphous form greatly depresses the strength of solid-state forces meaning increased aqueous solubility [5–7].

In addition to improving drug solubilization, a LBF can also increase drug absorption by by-passing the drug dissolution step, recruiting endogenous solubilizers to effectively shuttle drug to the site of absorption, and by promoting the uptake of certain drugs into the lymphatic system [8]. In addition to their capacity to boost drug absorption, LBFs possess a range of other advantages that have led to their application in other areas of need, specifically: (i) to provide acceptable content uniformity of high potency/low dose drugs, (ii) to achieve a fast onset of action, (iii) to offer taste-masking, (iv) to enable the delivery of drugs with low melting points, (v) to produce modified release profiles, (vi) to increase drug permeability and (vii) to meet the market needs of a consumer preference [3,9–12], and often a combination of these. Notably, in these broad LBF applications, the drugs may be water-soluble, therefore belonging to BCS Class I and III.

A non-exhaustive list of currently marketed products that utilize LBF technology is included in Table 1. This table highlights this breadth of LBF application which expands across all BCS Classes and a range of finished dosage forms.

A drug within a LBF can either be completely dissolved within the formulation or partly dissolved/suspended in the crystal form [9]. Within the industry, it is common to refer to these scenarios as a “lipid solution” or a “lipid suspension”. The drug physical form in the marketed examples in Table 1 speaks to an industry preference toward lipid solutions "dissolved" in Table 1. Lipid suspensions are still widely found on the market and in development, though they are normally overshadowed by the performance, physical stability and process advantages associated with lipid solutions [13].

That said, the ability to develop a lipid solution that can be progressed into clinical stages of development is not guaranteed. Indeed, a common problem in lipid solution development is the difficulty in identifying a LBF into which the drug can dissolve to reach a target concentration. This is defined by the maximal drug solubility in the LBF, while the target concentration is dependent on the target drug dose and the target drug: formulation ratio. Three, interconnected factors ((i). Maximal drug solubility in the LBF, (ii). Target dose and (iii). target drug: formulation ratio) need to be understood by formulators when attempting to develop a lipid solution formulation.

The solubility of the drug in a LBF vehicle (i) is key to the likelihood of developing a viable lipid solution formulation. For example, in instances where solubility in a range of lipidic excipients is low, a lipid

Table 1
Summary of some marketed oral LBFs grouped together by LBF application.

Drug name	Trade name	BCS Class	Finished dosage form	Market	LBF application	Drug physical form
Isotretinoin	Absorica®	II	Hard capsule	Rx	↑ Absorption	Crystalline
Cyclosporine A	Neoral®	II	Softgel	Rx	↑ Absorption	Dissolved
	Gengraf®	II	Hard capsule	Rx	↑ Absorption	Dissolved
	Gengraf®	II	Oral solution	Rx	↑ Absorption	Dissolved
Sirolimus	Rapamune®	II	Oral solution	Rx	↑ Absorption	Dissolved
Saquinavir	Fortovase®	IV	Oral solution	Rx	↑ Absorption	Dissolved
Bexarotene	Targretin®	II	Softgel	Rx	↑ Absorption	Crystalline
Nimodipine	Nimotop®	II	Softgel	Rx	↑ Absorption / fast onset	Dissolved
Testosterone undecanoate	Restandol Testocaps®	II	Softgel	Rx	↑ Absorption	Dissolved
Progesterone	Prometrium®	II	Softgel	Rx	↑ Absorption	Crystalline
Nintedanib	Ofev®	II	Softgel	Rx	↑ Absorption	Crystalline
Enzalutamide	Xtandi®	II	Softgel	Rx	↑ Absorption	Dissolved
Fenofibrate	Fenogal®	II	Hard capsule	Rx	↑ Absorption	Dissolved
Drobabinol	Marinol®	II	Softgel	Rx	↑ Absorption /low melting drug	Dissolved
EPA, DHA	Lovaza®	II	Softgel	Rx	Low melting drug	Dissolved
Valproic acid	Depakene®	I	Softgel	Rx	Low melting drug	Dissolved
Levothyroxine	Tirosint®	III	Softgel	Rx	Low dose	Dissolved
Dutasteride	Advodart®	II	Softgel	Rx	Low dose	Dissolved
Doxercalciferol	Hectorol®	I/II	Softgel	Rx	Low dose	Dissolved
Azithromycin	Zmax®	III	Oral suspension	Rx	Sustained release	Crystalline
Ibuprofen	Advil®	II	Softgel	CH	Consumer drivers/fast-onset	Dissolved
Naproxen	Aleve®	II	Softgel	CH	Consumer drivers/fast-onset	Dissolved
Cetirizine	Zyrtec®	III	Softgel	CH	Consumer drivers/fast-onset	Dissolved
Loratidine	Claritin®	II	Softgel	CH	Consumer drivers/fast-onset	Dissolved

Rx – prescription drug market.
CH – consumer healthcare market.

solution can only be developed if the target dose is low or if there is scope to utilize larger, or multiple dosage units. Drug solubility in the most lipophilic lipidic excipients (e.g., oils, mixed glycerides, surfactants, cosolvents) is predominantly determined by drug-related properties including the strength of the solid-state forces and hydrogen bonding [14,15]. Other, non-drug related factors can also play a role in determining whether the maximal solubility value can be reached, for example the range of available lipidic excipients that may be used, which can be constrained by dosage form type, market segment and target population.

The target drug dose (ii) is determined by the pharmacological potency of the molecule and oral bioavailability, with higher doses most often reflecting low potency. Unless there is scope to decrease the dose by increasing drug bioavailability, the dose is fixed and cannot be modified by the formulator. In the context of developing a lipid solution, a high dose will therefore usually translate to a need for a high target drug solubility in lipidic excipients.

The target drug: formulation ratio (iii) defines the ideal dosage form size and number of dosage units per dose. The practicality of using a large number of dosage units (i.e., high pill burden) or large dosage form size is tempered by a number of drawbacks including the negative impact on compliance, increased risk of formulation induced adverse effects and basic administration challenges for example in the elderly where there is a high incidence of dysphagia [16,17]. There may be exceptions where multiple dosage units may be used in light of treatment benefits, for example, in certain disease states or in acute conditions, though this tends to be the exception rather than the rule. The consumer healthcare market is on the other side of the spectrum where consumer preference is geared toward small, easy swallow dosage forms [18].

The success of developing a lipid solution can be clearly constrained by several factors, and these constraints can be sufficient to stop the progression of a project very early during development and even before the LBF performance benefits can be explored in vivo. Strategies to improve drug solubility, and therefore drug loading, in LBFs may therefore unlock the broader use and evaluation of LBFs for more drugs.

From the perspective of a formulator, the only other viable option to improve drug solubility in LBFs (beyond changing the nature of the formulation) is to consider approaches that alter the drug's physical properties – most commonly via a decrease in the strength of intermolecular forces in the crystal lattice. One example here is to use the amorphous form of the drug. This approach is commonly combined with polymeric solid dispersion formulations (that serve to stabilise the amorphous form both in the solid state and in solution) to improve the aqueous solubility of poorly water-soluble compounds particularly where strong crystalline forces limit solubility and dissolution [1,5]. Applying the same philosophy to improve drug solubility in lipids, however, is challenging and unlikely to achieve the long-term physical stability needed for LBF development. In most cases, reversion on storage to the more stable and, ultimately, less lipid-soluble crystalline form is likely.

Lipophilic salts are an alternative and promising approach to achieving higher solubility in lipids. The design, manufacture and properties of lipophilic salts will be discussed later in this review. However, in brief, lipophilic salt forms of a drug typically exhibit depressed melting points relative to the free acid or base or traditional salt form and, as a result, exhibit substantially improved solubility in lipidic excipients without any structural changes to the drug. As a snapshot example, the relative solubility difference in a model LBF of erlotinib hydrochloride (marketed form, melting point = 244 °C), erlotinib free base (melting point = 157 °C) and erlotinib lipophilic salt (docusate form, melting point = 71 °C) is depicted in Fig. 1. Despite exhibiting low aqueous solubility and a cLog P of 3.1, the hydrochloride salt form of erlotinib has very low solubility in the model LBF and as such ~90 g of formulation was required to dissolve a single dose. This translates to 110 size 00 capsules. In contrast, the same erlotinib dose can only be delivered in a single capsule using a lipophilic salt approach [19].

The remaining content of this review describes the strategy of lipophilic salt formation to modify drug solubility in lipids in favour of the formulator, and how this approach may unlock new opportunities for LBF application in a range of therapeutic classes and market segments.

2. Broad applications of lipophilic salts and ionic liquids

Salt formation has been widely used in drug development to improve the processing, stability or biopharmaceutical characteristics of acidic and basic drugs [20–22]. In these applications, the counterion is usually small and hydrophilic and either organic or inorganic, for example; hydrochloride, maleate, mesylate, and phosphate salts of basic drugs, and calcium, magnesium, potassium and sodium salts of acidic drugs [23]. Some classical examples include hydrochloride salts of tricyclic antidepressants (amitriptyline, imipramine, nortriptyline etc.) to increase melting points to enable solid dosage form development, sodium or potassium salts to increase solubility and to promote faster absorption of NSAIDs (naproxen, ibuprofen, diclofenac etc.) [11,24].

An alternative salt formation approach gaining interest over the last few years is the pairing of ionizable drug with asymmetric, bulky and often lipophilic counterions such as alkyl sulfates, branched alkyl sulfates and fatty acids/amines, depending whether the drug is a base or

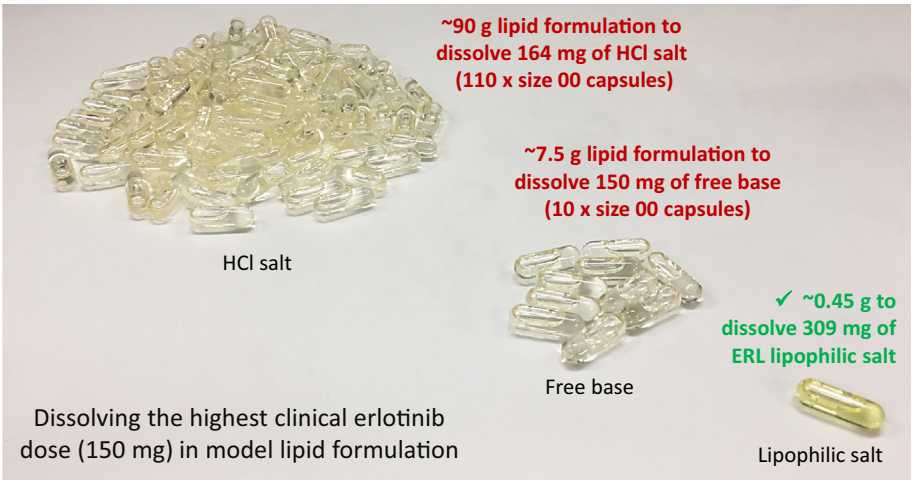

Fig. 1. Photograph illustrating the significant impact of lipophilic salt formation on the drug solubility within a LBF vehicle. In this example, the drug is erlotinib and only the lipophilic salt form (docusate) can be delivered in a single capsule at the target clinical dose. Reproduced from [19]. https://pubs.acs.org/doi/abs/10.1021/acs.molpharmaceut.8b00858. Further permissions related to the material excerpted should be directed to the ACS.

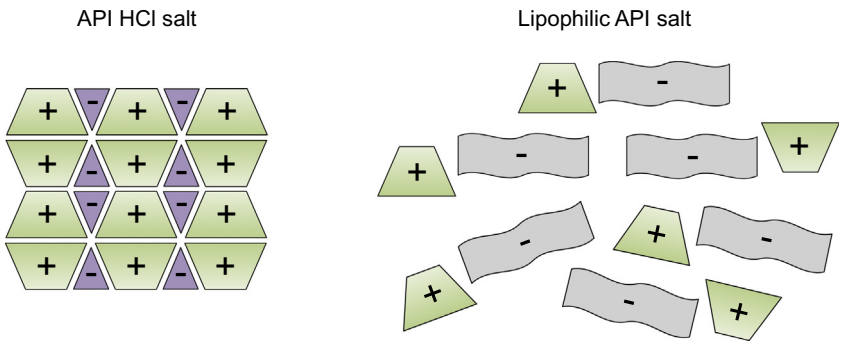

Fig. 2. Picture depicting the change in ionic packing in a conventional hydrochloride salt of a weakly basic drug and a lipophilic salt of the same drug.

an acid. A primary feature of these salts is a depressed melting point relative to the free form of the drug and significantly depressed melting when compared to conventional salt forms.

The formation of a tightly packed crystalline structure in conventional, high melting point salts is driven by strong electrostatic interactions between oppositely charged ions that results in high enthalpy that offsets the reduction in entropy. In contrast, due to a more disordered state, low melting salts have higher entropy. Stability in this more disordered state can be achieved if electrostatic forces between anions and cations are sufficiently weak to offset the higher entropy. Common features of anions and/or cations designed to minimize the strength of electrostatic forces and generate low intermolecular forces therefore include (i) larger ions, to increase inter-charge distance and to introduce asymmetry, and (ii) lower charge density (due to charge delocalization) to decrease charge magnitude [25]. Along with electrostatic forces, the hydrogen bonding potential between ions can also be intentionally minimized to further reduce melting temperatures, for example, by using hydrophobic ions such as alkyl sulfates or alkyl amines (Fig. 2).

Salts with a melting point of <100 °C have been described as "ionic liquids" (ILs) [26]. Those ILs that are liquid-like at ambient conditions are further described as "room temperature ionic liquids". Such materials were first described by Paul Walden in 1914 who reported that the salt, ethylammonium nitrate, had a melting point of 12 °C and was physically stable in the liquid-state at room temperature.

The broad interest in IL applications in the pharmaceutical sciences field has been reviewed extensively elsewhere [27–29], and includes their use as functional excipients in transdermal or oral drug delivery as well as the isolation of ILs to modify drug properties. Focusing first on applications where the drug itself forms part of the IL either as the anion or cation; Balk et al., [30] described IL forms of diclofenac, ibuprofen, ketoprofen, naproxen and sulfadiazine using the counterion tetrabutylphosphonium (TBP), showing that the IL forms of these drugs exhibited increased aqueous solubility and dissolution rate; Shadid et al., [31] described a cholinium salt of sulfasalazine that showed increased aqueous solubility enabling higher doses to be administered parenterally in a saline solution; Wiest et al., [32] used the acidic drug selurampanel to form 36 different salt forms, of which 25 could be classed as ILs. Following increases in in vitro solubilization and extensions of the supersaturation period, three IL salts were dosed to Wistar rats and shown to increase exposure by up to 2-fold, with the greatest increase evident using a dication salt (i.e., drug: counterion ratio of 2:1); Stoimenovski et al., [33] reported liquid forms of ranitidine and propantheline to potentially combat crystalline polymorphism issues associated with these drugs; Wang et al., [34] described ILs formed between two drugs, namely diphenhydramine and naproxen or ibuprofen. Due to the poor wettability of these ILs, they were directly loaded onto a mesoporous carrier resulting in fast dissolution properties; Ferraz et al., [35] described primaquine-based ILs with cinnamate derivatives that showed superior antiparasitic properties when compared to the parent drug; Cojocaru et al., [36] described a prodrug approach to convert neutral paracetamol to an ionizable form and formed respective ILs with the docusate counterion; Furukawa et al., [37] described ILs of ibuprofen and ester forms of the amino acid proline which showed improved permeation through the skin and Miwa et al., [38,39] have described the etodolac – lidocaine IL in clinical trials in a transdermal patch for improved skin penetration.

An alternative application of ILs is to use this atypical salt approach to better tailor the drug to a particular formulation approach with the overall goal of aiding drug delivery. It is this application in relation to LBFs that is the focus of this review article, since IL forms of many drugs show markedly higher solubility in lipid vehicles. Importantly, the utility of salts in this regard is not limited to IL forms, since any depression in melting point between 100 °C and the melting point of the free acid/base can translate to increased solubility in lipids [40,41]. The utility of a salt approach to improve solubility in lipids therefore extends beyond the IL definition. Taking this into consideration, the term "lipophilic salts" offers a broader classification to cover all salts that exhibit enhanced lipid solubility over the respective free acid/free base forms. In addition to increasing solubility in lipids, lipophilic salts can also be used in amorphous polymer formulations, such as spray dried dispersions (SDD) [42] or polymeric nanoparticles (NP) [43] made, for example, by precipitation or emulsion processes. The advantages of lipophilic salts in these formulations include the ability to moderate aqueous solubility of basic drugs in the low pH environment of the gastric media (therefore limiting supersaturation and resulting crystallization upon transfer to the higher pH environment of the intestine), to increase drug solubility, particularly of those drugs with a strong tendency to crystallize, in the polymer matrix of SDD or NP, allowing increased drug loading in these formulations.

The lipophilic salt approach should also not be confused with ion pairing approaches that typically employ an aqueous titration method to complex a drug with an oppositely charged counterion, and where the highest yield of the isolated complex can sometimes be formed when the counterion is in excess [44,45]. As described later in the review, lipophilic salts are formed in a 1:1 M ratio of drug and counterion, with the use of excess counterion only in instances where the drug has multiple ionization centres.

The term lipophilic salt can also be distinguished from other drug – excipient/drug complexes that may form in a 1:1 M ratio, for example deep eutectics [46] and cocrystals [47,48]. While these materials may exhibit a depressed melting point relative to the starting materials, the lack of proton transfer (which is essential for salt formation) provides a useful means of discrimination.

3. Lipophilic salt opportunities in LBF drug delivery: Addressing the unmet need and unlocking broader LBF application

As mentioned in the Introduction (see section 1), LBFs have broad applications in drug delivery, principally in enhancing the absorption of poorly water-soluble drugs. In this section, how transformation of a drug into a lipophilic salt form can expand LBF application into challenging Target Product Profiles (TPP) is discussed, namely those TPPs that

call for a high target drug loading and when the drug exhibits intrinsically low solubility in lipidic excipients. To convey the potential advantages of combining lipophilic salts and LBFs in a practical context, they are discussed against a back-drop of specific drug development steps, namely early drug toxicological evaluation, improving drug absorption, reducing the pill burden and in life-cycle management.

3.1. Improving drug loading in LBF solubility to enable toxicology evaluation

Drug toxicology evaluations are commonly initiated in rodents where the goal is to monitor for drug induced adverse events across a range of oral exposures, achieved by increasing the administered drug dose [49]. Where a drug shows low aqueous solubility, maintaining exposure with increasing drug dose can be challenging [50].

LBFs are widely used in toxicology evaluations to overcome this issue [51]. Their wide use is due to their effective ability to increase exposure, the wide availability of LBF excipients, the simplicity of preparation at a small-scale and administration, and the fact that commonly used excipients have well-defined LD_{50} values in a range of animal models, that are commonly in the >1000 mg/kg range [1,52].

In instances where the drug shows low solubility in LBF vehicles, high formulation volumes are needed to achieve high drug doses, for example >100 mg/kg. The relationship between drug solubility in a LBF and required formulation volumes–with respect to target oral dose–is shown in Table 2. A commonly employed cut-off for the maximum formulation volume to be administered to rodents is 10 mL/kg [53], with the complication that at higher doses, there is an increased risk that the formulation vehicle will cause an adverse toxicity signal, thus masking any potential effects of the drug. Using this 10 mL/kg cut-off, it is apparent that a drug solubility in excess of 100 mg/mL in the LBF vehicle is required to achieve drug doses up to 250–500 mg/kg (Table 2). Furthermore, while doses up to 10 mL/kg of formulation may not directly induce adverse events, there is still the risk that high formulation volumes may change intestinal function, gastric emptying and overall gastric transit time, as observed by Borrowitz et al., [54] and Nickerson et al., [55].

Table 2
Relationship between drug solubility in a LBF vehicle and the required LBF volume to be administered in toxicology studies across a 25 to 500 mg/kg dose range. Those values in italics are above the ideal cut-off of 10 mL/kg that can be reliably and safely administered to rats.

Drug solubility in LBF vehicle (mg/mL)	Drug loading in LBF vehicle (mg/mL) (at loading of 80% of the solubility value)	Target drug dose (mg/kg)	Dose of formulation required (mL/kg)	Actual formulation volume (mL) to achieve the target dose[a]
10	8	25	3.125	0.9375
		50	6.25	1.875
		100	*12*	*3.75*
		250	*31.25*	*9.375*
		500	*62.5*	*18.75*
50	40	25	0.625	0.1875
		50	1.250	0.375
		100	2.500	0.75
		250	6.250	1.875
		500	*12.5*	*3.75*
100	80	25	0.3125	0.0938
		50	0.625	0.1875
		100	1.25	0.375
		250	3.125	0.9375
		500	6.25	1.875
250	200	25	0.125	0.0375
		50	0.25	0.075
		100	0.5	0.15
		250	1.25	0.375
		500	2.5	0.75

[a] For 300 g rat. Values in italics refer to doses above the 10 mL/kg cut-off.

The use of a lipophilic salt approach can be employed to realize drug loadings in excess of 100 mg/g or 200 mg/g, and enable toxicology evaluation in rats by allowing for lower formulation volumes to be administered. Indeed, Sahbaz et al., [40] reported an increase in cinnarizine solubility in a model SEDDS (containing medium-chain triglycerides, glyceryl monocaprylate, polyoxyl 35 castor oil and ethanol) from 43 mg/g using the free base form to >330 mg/g when using the decylsulfate lipophilic salt form. In the same study, itraconazole solubility in another model SEDDS (containing corn oil, glyceryl monolinoleate, polyoxyl 35 castor oil and ethanol) increased over 40–fold from 2.7 mg/g to 115 mg/g using the docusate lipophilic salt form. Using the drug atazanavir, Morgen et al., [56] used a lipophilic salt approach to increase solubility in a SEDDS containing medium-chain triglycerides, glyceryl monocaprate and polysorbate 80. In comparison to the free base, 2-naphthalene sulfonate and docusate salt lipophilic salt forms of the drug were more soluble in the SEDDS by 5.7–fold and 3.7–fold, respectively. Williams et al., [19] used a lipophilic salt approach to increase the lipid solubility of the kinase inhibitors, erlotinib, gefitinib, cabozantinib and ceritinib. The solubility of free base and existing traditional salt forms in commonly explored SEDDS type formulations (containing glyceryl monocaprylate, propylene glycol monocaprate and polyoxyl 35 castor oil) was at best 30 mg/g. Using the docusate lipophilic salt form however, there were substantial increases in lipid solubility; 15–fold in the SEDDS for erlotinib (150 mg/g), ceritinib (150 mg/g) and cabozantinib (150 mg/g) and up to 7.5–fold for gefitinib (150 m/g). On dosing to rats, it was possible to achieve a 100 mg/kg erlotinib dose using a dose of 1000 mg / kg (~300 mg per rat) with no evidence of adverse effects, supported by histology of the rat gastric and intestinal mucosa [19]. In each of these studies, the counterions used were selected based on previous use in pharmaceutical formulations and/or known (good) toxicity profiles. Further toxicology evaluation of lipophilic counterions is however needed, particularly during chronic administration studies. This is discussed more in a later section (see section 6).

A lipid suspension approach could also be explored to avoid high formulation doses when drug dose is high and lipid solubility is low. Alternatively, the recently described “chase dosing” [57] approach could be employed where a dose of crystalline drug is quickly followed by a LBF concentrate. As the drug will remain in the crystalline form in these approaches, however, there is the risk that solid-state barriers to solubility and absorption will compromise oral absorption.

3.2. Enabling LBF pill burden reductions

As a high pill burden will usually result in decreased treatment compliance [16,58], a goal during drug product development is to achieve the delivery of the target clinical dose as a single dosage unit. There are some exceptions, but they are usually limited to instances where the benefits of treatment significantly out-weigh the inconvenience of having to take multiple tablets or capsules, for example, in cancer or HIV therapy. For a single drug therapy, the most common reasons for a high pill burden include a high drug dose and/or the bulking effect of excipients, for example polymers in solid dispersions or lipidic excipients in LBFs.

The use of a lipophilic salt form leads to an increased solubility in LBF vehicles, translating to a high drug loading and a reduction in the number of final dosage forms that might be required per dose or the size of the dosage form. To capture the impact of this increase in lipid solubility on the LBF pill burden the parameter “Lipid Based Formulation Dose Number” ($LBFD_o$) has been proposed [19] which can be described by:

$$LBFD_0 = \frac{D/W}{S * X} \quad (1)$$

where D is the highest target dose (mg) per dosage unit, W is the lipid formulation mass (mg) per dosage unit, S is the solubility (mg/g) in

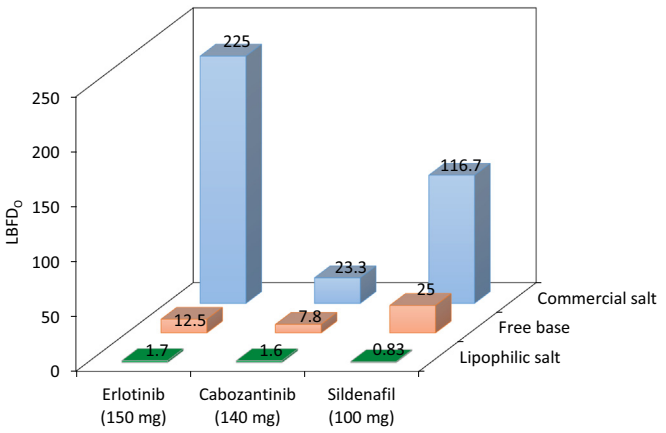

Fig. 3. The Lipid Formulation Dose Number ($LBFD_o$) for a single clinical dose of erlotinib, cabozantinib and sildenafil, either as the marketed salt form, free base or lipophilic salt form. LBFDo values close to 1 are desirable since this indicates a high possibility that the dose may be delivered in a single capsule. See Eq. (1) in the main text for a detailed description of this parameter.

the LBF and X is the drug saturation level in the formulation (expressed as the fraction of the solubility value). $LBFD_o$ therefore captures the relationship between the highest drug concentration in the formulation (if the daily dose was to be delivered in a single dosage unit) and drug solubility in the formulation. $LBFD_o$ values below or close to 1 are desirable for LBF development as they point to the possibility of delivering the target dose in a single dosage unit. Equally, increasing $LBFD_o$ corresponds to an increase in daily pill burden. To illustrate this, $LBFD_o$ numbers have been calculated using experimental LBF solubility data for the current maximum clinical dose for erlotinib, cabozantinib and sildenafil [19,59], and shown in Fig. 3. This illustrates a general trend of decreasing $LBFD_o$ on switching from the marketed salt, to the free base and to the lipophilic salt form. In each example, the same LBF was used for the various forms of the drug in order to make effective comparisons based on respective LBF solubility. Since the $LBFD_o$ is a surrogate for the likely number of capsules to deliver the target dose, it is clear from Fig. 3 that a single capsule option is only feasible for the lipophilic salt forms of all three drugs.

As with the development of a lipid solution in any product development project, monitoring physical stability (signs of drug precipitate in the vehicle) over prolonged duration is needed to provide assurances for long-term stability and acceptable shelf-life. Previous reports have described at least 3 months physical stability of lipophilic salt containing LBFs when stored under ICH long-term conditions (25 °C/60% RH) [19,41]. In these examples, drug loading is typically far in excess of the solubility of the free base form.

The use of a lipophilic salt approach can decrease the pill burden that may be associated with LBFs when the drug exhibits low solubility in commonly used lipidic excipients. If a high dose underpins a high pill burden and if the high dose stems from low absorption, there is also an opportunity that the dose will be lowered if absorption can be increased.

3.3. Lipophilic salts combined with LBFs to enhance oral absorption

The overall benefits of increasing oral drug exposure include (i) reduced dose, (ii) reduced food effects, (iii) reduced variability and (iv) reduced effect of drug-drug absorption related interactions, for example, proton-pump inhibitors or H_2 antagonists decreasing the absorption of weakly basic compounds. LBFs can effectively improve the oral absorption of poorly water-soluble drugs, as evidenced by the examples provided in Table 1. The previous sections have also described how lipophilic salt forms of drugs can lead to substantial increases in drug solubility in LBF vehicles, translating to lower formulation volumes. In addition to this, a performance synergy between lipophilic salts and LBFs can also exist, which in turn may lead to improved absorption from the fasted state.

The first publication to describe this benefit when combining lipophilic salts and LBFs (Sahbaz et al. [40]) employed cinnarizine and itraconazole. In the case of cinnarizine, the lipophilic salt (decyl sulfate salt) was dissolved in a LBF containing medium-chain lipidic excipients and dosed to rats at a dose of 125 mg/kg cinnarizine free base equivalents. The exposure obtained from this formulation was over 3.5-fold higher than the exposure obtained using an aqueous suspension of the free base and nearly 2-fold higher than that of a suspension of cinnarizine free base in the same LBF [40]. This boost in exposure when combining lipophilic salts and LBFs was attributed to the fact that dissolving the drug in the lipid vehicle using the LS approach was able to by-pass traditional dissolution—which is likely to have limited exposure when using a suspended crystalline form of cinnarizine in the same LBF. A lipid solution formulation could also be attained by dissolving cinnarizine free base in the LBF, however, the lower lipid solubility of the free base would have dictated a much higher formulation dose, ~3.5 mL/kg compared to ~1 mL/kg when using the lipophilic salt form.

The benefit of using a dissolved lipophilic salt/LBF formulation on oral absorption was more pronounced for itraconazole [40]. In this case a SEDDS containing long-chain lipids and suspended itraconazole free base yielded negligible exposure in rats (Fig. 4), yet the same formulation containing the lipophilic salt (docusate) in solution yielded an exposure level that was 2–3 fold higher than that of the currently marketed amorphous drug formulation (Sporanox®). This aspect highlights the performance benefit of using lipophilic salts in combination with LBFs. The in vivo data was also supported by in vitro solubilization experiments that showed that the solubility of itraconazole in dispersed and digested SEDDS increased from <0.02 mg/mL when using the free base form to >1 mg/mL (50-fold) when using the lipophilic salt form. Of further note in this study was the negligible exposure seen when dosing the same SEDDS containing a 1:1 physical mixture of itraconazole and the free counterion (docusic acid) (Fig. 4). Taken together, these results indicate that only the lipophilic salt form of itraconazole was able to harness the solubility and absorption enhancing potential of LBFs.

In another study, Morgen et al., [56] explored a lipophilic salt strategy in order to boost drug solubility in a LBF vehicle to enable toxicology evaluation of atazanavir in rats. The lipophilic salt, atazanavir 2-naphthalene sulfonate dissolved in the LBF vehicle yielded higher in vitro solubilized concentrations when the LBF was diluted in 0.01 N HCl when compared to the same LBF containing atazanavir. In rats, the lipophilic salt containing LBF gave similar exposure to the free base aqueous suspension but with reduced variability. Williams et al., [19] focused on employing the lipophilic salt approach to four model kinase inhibitors. There are now over 40 FDA approved kinase inhibitors for the treatment of cancers and various auto-immune diseases, yet drugs in this class are plagued by instances of low aqueous solubility, low and variable absorption and food-affected pharmacokinetics [60,61]. Using simple “off-the-shelf” LBFs to provide an initial proof-of-concept, it was possible to achieve at least 100 mg/g drug loading in LBF when using docusate lipophilic salt forms of erlotinib and cabozantinib [19]. On administration to rats, the use of erlotinib docusate containing SEDDS enabled dose-escalation up to 100 mg/kg while limiting the formulation dose to <1 mL/kg. The cabozantinib docusate SEDDS gave rise to a significant increase in exposure compared to a crystalline aqueous suspension of the free base (Fig. 5a & b). While the performance of this formulation could be matched when using the same SEDDS vehicle containing a suspension of crystalline free base, the suspension gave rise to increased variability and the vehicle used was not representative of a typical lipid suspension formulation. Supporting in vitro testing confirmed the solubilization synergy between the lipophilic salt form and the LBF, with a ~2-fold boost to solubility under simulated intestinal

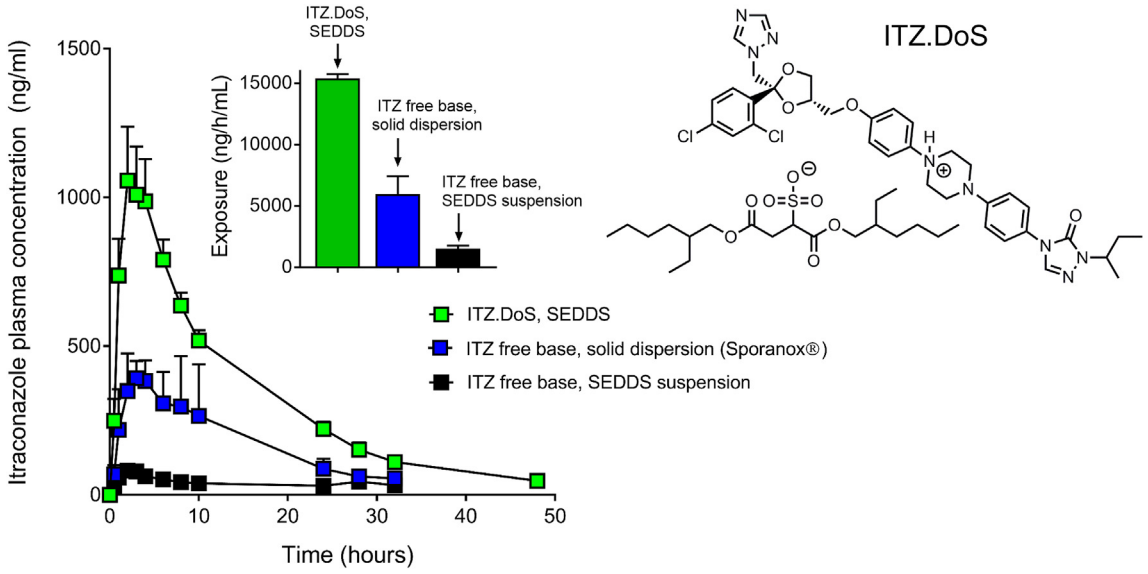

Fig. 4. Itraconazole (ITZ) plasma concentration versus time data after oral administration of ITZ free base (FB) as a suspension in the SEDDS lipid-based formulation, and as the commercial Sporanox® formulation compared to administration of ITZ docusate lipophilic salt as a solution in the SEDDS. All formulations were dosed at 20 mg/kg. Data are mean ($n \geq 4$) ± SEM. Insert: ITZ exposure over 48 h, measured as area under the plasma level time curve from 0 to 48 h, plus the structure of itraconazole docusate. Adapted from [40].

conditions when compared to the same conditions using the free base of both drugs.

The literature studies reviewed above thus show that transforming drugs into lipophilic salts is a viable strategy to give larger numbers of drugs access to the absorption enhancing benefits of LBFs. The underlying mechanisms for the performance benefit of the combination of lipophilic salts and LBF likely reflect firstly, the ability to deliver high drug concentrations molecularly dispersed (dissolved) in a LBF thereby avoiding the potentially absorption rate limiting step of dissolution. In addition, the lipophilic salt showed increased solubility in dispersed and digested LBFs when compared to the free base or free acid, indicating that the presence of the lipophilic counterion can play an important role in promoting drug absorption. The extent to which a lipophilic counterion improves solubility in the GI tract will be dependent on the extent of drug ionization, with maximal solubility gain in lipid-based colloids when both drug and counterion are fully ionized. An additional factor worth mentioning is that the higher lipid solubility of the lipophilic salts across a range of lipidic excipients unlocks the use of a broader range of lipidic excipients. Critically, for enhancing oral absorption, long-chain lipids are often more effective in solubilizing drug in the GI tract and promoting drug absorption than medium-chain lipid formulations or simple cosolvent systems [62–64]. But long-chain lipids have been historically limited by lower drug loading capacity in comparison to e.g., medium-chain lipidic excipients and cosolvents. The use of lipophilic salts may help to overcome this solubility limitation.

3.4. Applications toward NCEs and in life-cycle management

The development of New Chemical Entities (NCEs) can be severely hampered in instances where the drug exhibits low aqueous solubility, and where this limits oral absorption. In these instances, it is common to search for enabling formulations, including LBFs that improve aqueous solubility and, in turn, absorption [1,7]. For low aqueous solubility NCEs that also show low solubility in LBF, investigations of new

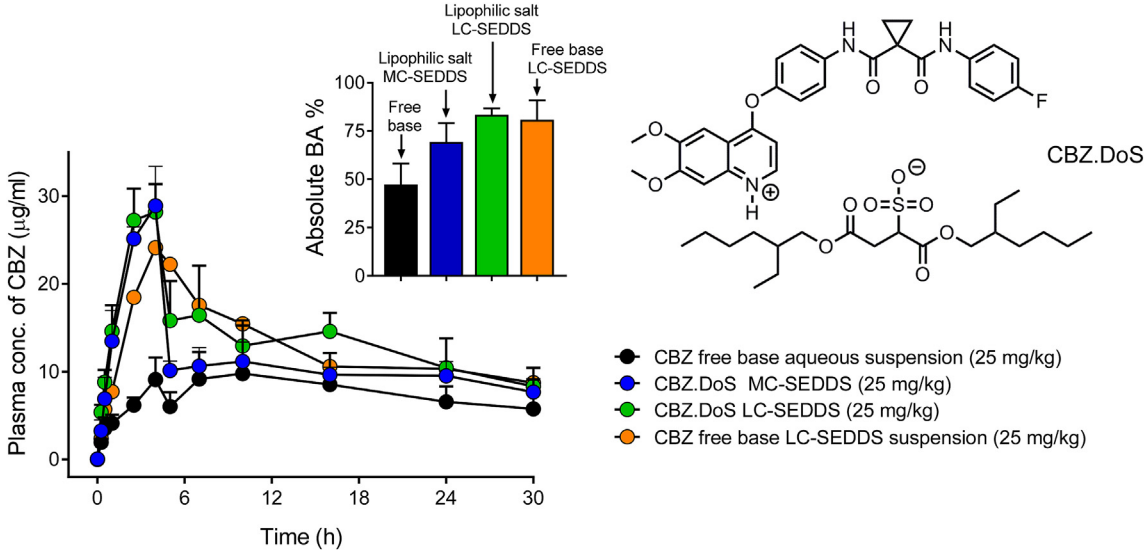

Fig. 5. In vivo exposure in rats of cabozantinib (CBZ) after oral administration of a MC-SEDDS and LC–SEDDS formulation containing cabozantinib docusate (CBZ.DoS) in comparison to an aqueous suspension and LC-SEDDS suspension of cabozantinib free base. Data are expressed as mean ($n \geq 3$) ± SD. The structure of cabozantinib docusate and total CBZ exposure, expressed as absolute bioavailability (BA), is also shown with respect to the formulation type. Adapted from [19].

lipophilic salts might usefully be explored early in development to enhance the utility of LBF development strategies. Indeed, lipophilic salt evaluations could be conducted in parallel with conventional salt screening approaches [22]. In this case, rather than eliminating counterions based on a lack of crystallinity (which is conventional practice in current salt screening), the solubility of such salts could be assessed in an organic solvent or in a simple lipidic excipient such as a monoglyceride. Where a lipophilic salt form of an NCE exhibits improved solubility in lipidic vehicles when compared to the free drug, a LBF development program could therefore be considered. The lipophilic salt form of the NCE would then be developed in a manner analogous to any other salt form; with detailed pharmacokinetic and non-GLP/GLP toxicology testing of the drug and new salt form performed preclinically in parallel with process development to enable the larger scale synthesis of the lipophilic salt form to support stability and clinical testing. Some of the scale-up considerations for lipophilic salts are discussed later in a later section (see section 4).

LBFs are also used in Life-Cycle Management (LCM) projects where the goal is to utilize a formulation strategy to address, for example, a current pharmacokinetic or patient use issue. Some LCM examples include new formulations to optimize delivery and/or pharmacokinetics such as a modified release dosage form to reduce dosing frequency (e.g., Concerta® for methylphenidate hydrochloride formulations), a new taste-masked paediatric formulation (e.g., ATI-1501 (metronidazole) taste-masked oral suspension), or an enabling formulation to increase drug absorption in the fasted state to either eliminate a food-label restriction, reduce dose, or reduce the pill burden (e.g., Absorica® for isotretinoin and Yonsa® for abiraterone acetate).

As described earlier, kinase inhibitors represent a drug class plagued by low absorption and food-effects. Generally, the requirements for rapid development for anti-cancer drugs dictates that drugs in non-enabling formulations with un-optimized pharmacokinetics and food-label restrictions are overrepresented [61], leading to evidence of non-compliance and increases in safety issues [65,66]. While others have questioned the (lack of) effort by pharmaceutical companies to address these issues during development [60,67,68], it is important to recognize that anti-cancer drugs are very commonly, if not always, fast tracked to the market, and that this can place a strain on formulators limiting the ability to deeply explore alternative formulation approaches. For these products, downstream LCM is often employed to address incidences of un-optimized pharmacokinetics (that may be addressed by a formulation approach) without delaying the initial approval and patient access to the newest medicines. In the case of kinase inhibitors, lipophilic salts forms may provide a means to access the full absorption enhancing benefits of LBFs without increasing the risk of increasing pill burden [19].

Applications to the FDA to reformulate approved drugs falls under the 505(b)(2) regulatory approval pathway. This pathway allows for fewer clinical and toxicity studies in order to obtain approval for a new drug product. New salt form applications also fall under the 505(b)(2) pathway [69]. Some past 505(b)(2) new salt form applications include amlodipine, clopidogrel, permetrexed, diclofenac, perindopril and esomeprazole, examples that will be discussed in a later section (see section 6) in the context of lipophilic salts.

LBFs are also used in LCM projects where the goal is to extend the application of the drug into other market segments, with the common example being liquid filled-capsules in consumer healthcare. Notable examples here include the analgesics ibuprofen (e.g., Advil®), naproxen (e.g., Aleve®), diclofenac (e.g., Voltaren®/Zipsor®) and the antihistamines loratadine (e.g., Claritin®) and cetirizine (e.g., Zyrtec®). Notably, liquid-filled formulations of these drugs were only developed after they became Over-the-Counter (OTC) drugs (available from pharmacies without a prescription) and driven by strong consumer preference. The development of liquid-filled capsules in these examples was aided by high lipid solubility of the drug (e.g., ibuprofen) and/or low dose (e.g., cetirizine). In contrast, examples of approved OTC drugs that are only available in tablet form include the anti-histamine fexofenadine. The fact that there is no fexofenadine liquid-filled capsule product on the market in part reflects the low solubility of the commercial hydrochloride salt and free base form in a range of lipidic excipients and LBFs (<20 mg/g) [70] in combination with a high dose requirements. Lipophilic salt forms of fexofenadine isolated using a lauryl sulfate counterion, however, have been shown to be significantly more lipid-soluble, with the potential for fast dissolution [70]. Sildenafil tablets containing the citrate salt form are available OTC in New Zealand, Poland and more recently, the UK [71]. Both the free base and the citrate salt form of sildenafil however exhibit very low lipid solubility, precluding the development of a liquid LBF. In contrast, recent studies have shown that isolation as a lipophilic salt form is able to facilitate dissolution of a 100 mg sildenafil dose in a LBF contained in a single size 0 capsule [59].

Balk et al., [30] described tetrabutylphosphonium salt forms of several NSAID drugs that are used OTC, including naproxen, ibuprofen and diclofenac. In each case, these salt forms exhibited significantly lower melting points compared to the free acid form. Similarly, Sahbaz et al., [72] described new salt forms of several NSAID drugs including tolfenamic acid, meclofenamic acid, ibuprofen and diclofenac. The counterions investigated ranged from various alkyl amines through to permanently charged ammonium cations such as benzalkonium derivatives. The lipophilic salts so formed exhibited significant depression in melting point such that it was possible to isolate liquid salt forms ("room-temperature ionic liquids"). These new salt forms were significantly more lipid soluble than the free acid forms – for example, the solubility of diclofenac free acid in a LBF was 63.2 mg/g whereas the benzalkonium salt form was miscible with the LBF. In vivo evaluations were also performed using tolfenamic acid based salts dissolved in LBFs, although in this case dosing at higher doses led to altered plasma profiles in rats and some GI irritation when compared to the equivalent suspension formulations of tolfenamic acid. This evidence of toxicity has not been observed for lipophilic salts for weakly basic drugs, and illustrates the complexities of lipophilic salt generation for acidic drugs where lipophilic cations are required to form the salt [72].

In July 2018, the FDA released two potential new approaches through which safety and effectiveness for a non-prescription drug can be demonstrated with the goal of approval of a wider range of drug products for the OTC market [73]. Against the backdrop of the increase in OTC drug product approvals that is likely to follow this regulatory announcement, the combined use of LBFs and lipophilic salts may enable the development of a wider range of single-unit (usually a prerequisite in the consumer health care market) liquid-filled capsule products.

4. Lipophilic salt design, synthesis and scale-up considerations

4.1. Identifying suitable drug candidates for lipophilic salt formation

When considering potential drug candidates for conversion to lipophilic salts, several factors must be considered, many of which mirror those in traditional salt form selection. The first and most obvious is that the drug must have the potential to be ionized so that it may form an ion pair. Most potential drug candidates do not hold a permanent charge, and therefore exist as protic salts, meaning a high degree of ionization in the salt complex is required in order to form a stable species and prevent dissociation of the salt. This is achieved by judicious choice of drug and counterion pairs that result in large ΔpK_a values, ensuring a high degree of proton transfer between the ions. However there is some discussion in the literature regarding the benefits of partially ionized drug lipophilic salts in regards to favourable membrane diffusion, since not having a permanent charge allows the neutral form of an drug to permeate more easily [74]. The general rule is that the more basic (or acidic) a drug, the greater the selection of available counterions that are likely to form a stable ion pair. When considering

Table 3
Summarizing the physicochemical properties of drugs that have shown positive increases in lipid solubility as lipophilic salts.

Drug	Therapeutic class	pK_a	Melting point (°C)[a]	Log P	Commercial salt form	BCS Class
Amiodarone [b]	Antiarrhythmic	6.6	156	8.7	HCl	II
Amlodipine [70]	Calcium channel blocker	9.1	140	3.0	besylate	I
Atazanavir [56]	Antiretroviral	4.6	204	3.9	n/a	II
Cabozantinib [19]	Antineoplastic	5.5	216	5.2[c]	(*S*)-malate	II
Ceritinib [19]	Antineoplastic	9.8	180	5.8[c]	n/a	IV
Cinnarizine [40]	Antihistamine	8.4	118–120	5.8	n/a	II
Dextromethorphan [75]	Antitussive	9.8	111	3.6	HBr	II
Erlotinib [19]	Antineoplastic	5.4	157	3.1[c]	HCl	II
Fexofenadine [70]	Antihistamine	9.5	152	5.6	HCl	III
Gefitinib [19]	Antineoplastic	5.3, 7.2	196	3.7[c]	n/a	II
Halofantrine [75]	Antimalarial	8.2	78	8.9	HCl	II
Itraconazole [40]	Anti-fungal	3.7	170	5.7	n/a	II
Lumefantrine [76]	Antimalarial	8.7	133–140	9.2	n/a	II
Metformin [70]	Antidiabetic	12.4	92	−1.37	HCl	III
Ranitidine [70]	Histamine H_2 antagonist	8.1	75	0.3	HCl	III
Sildenafil [59]	Vasodilator	6.5[a]	195	1.9	citrate	II
Tolfenamic acid [72]	NSAID	5.1	207	5.2	n/a	II
Meclofenamic acid [72]	NSAID	3.8	257–259	5.0[c]	Na salt	II

[a] As free base or free acid form.
[b] Internal unpublished dataset.
[c] Calculated Log P.

whether a drug is a good candidate for lipophilic salt formation, pK_a is therefore one of the key determining factors.

The melting point of the free base/acid form of the drug is also important. Although a reduction in melting point due to lipophilic salt formation is expected, a high initial melting point (e.g. >250-300 °C) is indicative of very strong intermolecular solid-state forces, and this may preclude the sufficient disruption of these forces by the presence of a counterion. Additionally, high melting points are also associated with poor drug solubility in the organic solvents employed during the synthetic transformation of the drug to the salt form (see section 4.3).

Despite these restricting factors, a plethora of drugs remain as suitable candidates for lipophilic salt formation. Indeed, Table 3 includes selected lipophilic salt forms that have shown positive utility in combination with LBFs, namely an increase in drug loading and/or improvements to drug absorption in vivo. Examples in this table include both weakly acidic and weakly basic drugs with varying lipophilicities and a wide range of melting point values. This list also contains drugs from the four BCS classes, indicating that the lipophilic salt approach is not limited to drugs that show low aqueous solubility.

The impact of melting point and pK_a value on ideal drug candidates for lipophilic salt formation is further exemplified in Fig. 6 for a range of weakly basic drugs. For each of the specified drugs in Fig. 6, lipophilic salts have been successfully isolated, and these salt forms all exhibited significantly improved solubility in lipidic vehicles. The "high risk" region is representative of basic drugs that exhibit very low pK_a values (i.e., < 4) and/or high melting points (i.e., >250 °C), and thus can be used to initially guide lipophilic salt feasibility based on experimental data relating to the drug.

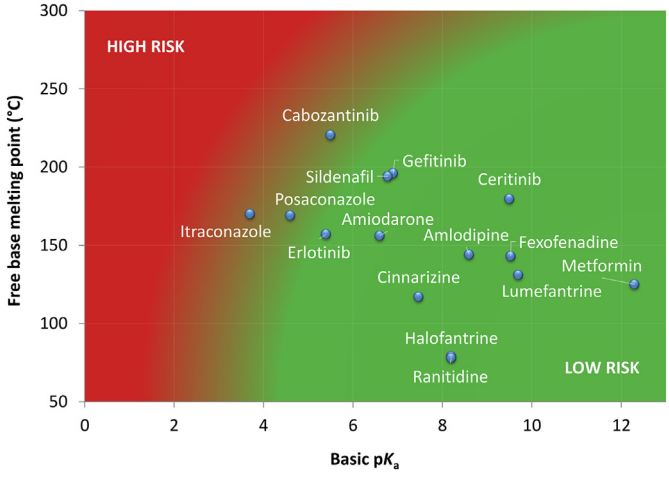

Fig. 6. Risk heat map of several basic or weakly basic drugs determined by factoring melting point of the free base form and pK_a value. Basic drug molecules with a low pKa value (i.e., <4) and/or high melting point values (>250 °C) are challenging drug molecules for the lipophilic salt approach.

4.2. Identifying appropriate counterions for lipophilic salt formation

Counterion selection is another key aspect of developing a lipophilic salt with desirable properties for use with LBFs. The ultimate goal of counterion selection is: i) to form a stable salt complex which is stable under the required conditions, ii) to reduce the crystal lattice energy of the drug lipophilic salt in order to promote dissolution and iii) to increase lipophilicity sufficient to aid lipid solubility in the delivery vehicle.

The stability of the salt complex is largely dependent on the drug-counterion pK_a difference, ΔpK_a. General salt theory suggests that a ΔpK_a difference for a drug and the counterion form should be at least 2 units to prevent the risk of dissociation [77,78], though larger delta pK_a values may be required in some instances since the relationship is not always clear cut [79]. For example, a caprylate salt of ranitidine slowly dissociated on storage whereas the oleate salt of ranitidine did not [70]. This suggests that other factors beyond ΔpK_a can play a role in determining the stability of a salt complex, such as the presence of moisture.

In order to reduce crystal lattice energy, counterions are often selected with structural characteristics that cause deliberate disruption to molecular packing. Examples of such properties include asymmetry, branched alkyl chains, reduced heteroatom count and containing predominantly saturated hydrocarbon frameworks. These aspects allow high degrees of rotational freedom maximizing disruption of lattice energy [80].

Though steric bulk is often desirable in counterions destined for use in lipophilic salts, there is... The larger the counterion paired with the drug, the greater the increase in molecular weight of the salt form and the greater the reduction of drug per unit mass of complex. This counterion "bulking effect" can therefore be limiting to the total amount of drug that can be loaded in a formulation and will also reduce the amount of formulation that can be dosed. Structural properties of the counterion to be generally avoided include aromaticity, H-bond

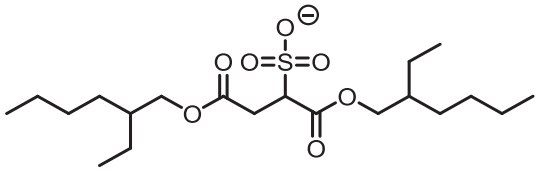

Fig. 7. Chemical structure of the docusate ion.

donors/acceptors, and long linear alkyl chains, as these factors tend to increase intermolecular forces and increase melting point [74,81].

One counterion that is widely represented in the drug lipophilic salt literature is the docusate ion, shown in Fig. 7. Docusate has been shown to form stable salts with a range of weak bases, resulting in salts with low melting points and high solubilities in excipients and formulations [82–85]. Conversion of a small series of small molecule kinase inhibitors to their docusate lipophilic salt forms was discussed earlier (see section 3.1). Synthesis of the lipophilic salts was achieved utilizing biphasic reaction conditions, in this work the docusate salts of erlotinib, gefitinib, cabozantinib and ceritinib were prepared in excellent yield and purity [19]. In all cases a significant melting point reduction was observed relative to the free drug indicating reduced lattice energy.

The utility of the docusate anion can perhaps be explained by several key aspects of the molecule, namely (i) the strong acidity of the sulfonate group and ability to delocalize the charge across the three oxygen atoms, (ii) branched, hydrophobic structure, (iii) presence of ester functional groups to promote hydrogen bonding interactions with lipidic excipients and (iv) chirality to promote chain flexibility.

With the above considerations in mind, it is prudent to combine rational selection of counterions with a small experimental screen in order to observe the properties of these salts relative to the drug free acid/base form or commercial salt form. Counterions with particular structural features will be expected to improve the properties of different drugs to varying degrees in response to differences in the inherent properties of the counterion but also structural compatibility with the drug. In line with the goals outlined above, initial screening tests may include measurement of the reduction in melting point (or glass transition temperature) relative to the free acid/base form, and solubility tests in a range of lipidic excipients.

Toxicity is an important consideration when selecting a counterion, in much the same way as it is in a conventional salt approach [21]. For this and other reasons it becomes prudent to utilize counterions that appear in the Generally Regarded As Safe (GRAS) list [86] where possible or where there has been widespread and documented safe use of the counterion in pharmaceutical products. The toxicity and regulatory considerations of lipophilic salts are further discussed in a later section (see section 6).

4.3. Lipophilic salt synthesis

Though several synthetic methods to access lipophilic salts (and ILs in general) have been reported the most commonly utilized method, particularly for drug ILs, is the metathesis reaction [87]. The metathesis method involves formation of a desired salt through interchange of ions pairs, and the formation relies on either differential polarity or solubility to form the desired ion pair. The former can be achieved utilizing biphasic conditions, whereas the latter can be performed under monophasic conditions. The monophasic method is commonly the method of choice due to ease, reliability, scalability and high yields.

In the classical biphasic reaction system, the reagents are all dissolved in a mixture of water and an organic solvent that is immiscible with water. The lipophilic drug/counterion pair selectively partitions into the organic layer whereas the highly polar by product (commonly sodium chloride) partitions into the aqueous phase on stirring. The partitioning behaviour then drives the reaction to completion. After the metathesis is complete, simple aqueous workup delivers the pure lipophilic salt. Residual impurities are largely removed through water washes of the organic solution, and complete removal of halides can be confirmed through use of a silver nitrate halide test.

Biphasic metathesis methodology has been used successfully to generate a large variety of drug lipophilic salts [19,40,70]. The reaction commonly generates pure products after aqueous workup without the need for chromatographic purification. Fig. 8 lists some example biphasic reactions (and associated yields) for a variety of counterions and BCS Class I, II and III drugs, starting from commercially available salt or free base forms.

Modifications to the biphasic metathesis method have been developed to avoid the formation of sodium chloride as a by-product. For example, Petrovski and co-workers reported the use of Amberlite® resin to form the hydroxide salt of various counterions, a method first reported by Ohno et al., [88]. These were reacted with the ampicillin ammonium salt, giving ampicillin salts and generating both water and ammonia as side products which could be easily removed [88,89]. This methodology was also utilized by Marrucho et al., in the synthesis of a variety of cholinium-based lipophilic salts of various acidic drugs [90]. Cholinium sulfasalazine has also been generated under similar conditions [91]. The carbonate anion can also be used as an alternative to hydroxide, forming water and carbon dioxide as by products. The latter method was successfully utilized to generate a series of anti-inflammatory choline based lipophilic salts [92].

Biphasic metathesis is preferred when the lipophilic salt has favourable organic solubility and there is a large polarity difference between the possible ion pairs (starting materials and products). Complications therefore arise when utilizing biphasic conditions for drugs or counterion species that have high water solubility as the extraction process is often inefficient and can result in mixtures of ion pairs. In these examples, monophasic metathesis may be explored. In the case of monophasic metathesis, both the drug and counterion salts are dissolved together in a moderately polar organic solvent (e.g. methanol or acetonitrile) and allowed to mix. The solution is then concentrated to give a residue from which the lipophilic salt is selectively extracted utilizing a solvent which dissolves the lipophilic salt, and precipitates the sodium chloride (or other salt by-product) which can be easily removed by filtration.

By way of example, metformin HCl—a highly water soluble drug—was converted to the docusate salt via monophasic metathesis [70]. The biphasic system resulted in poor recovery of the lipophilic salt, presumably due to the final product preferentially partitioning into the aqueous phase. Switching to methanol as the organic solvent followed by concentration to give a residue, then extraction with acetonitrile resulted in good yield and purity of the desired docusate salt [70].

A modification to the monophasic metathesis reaction has been reported by Scott [93]. This method involves the use of silver salts of the counterion, which upon treatment with the halide salt of the drug under aqueous conditions leads to precipitation of the highly insoluble silver halide, which can be removed via filtration. Though this procedure is attractive at the bench scale, the cost of silver salts is likely to curb progression to a larger scale.

Several procedures have been reported for the synthesis of lipophilic salts which are a hybrid of mono- and biphasic metathesis. Such methods are often employed when the starting materials (drug and counterion salt) have moderate to good water solubility. In such cases, the reagents are mixed as aqueous solutions (sometimes small amounts of methanol are added to aid dissolution) and generally the lipophilic product will separate from solution. Isolation occurs by decanting the aqueous solution or by addition of organic solvent in order to extract the product [83,94,95].

The most common synthetic alternative to the metathesis reaction to access drug lipophilic salts involves direct acid base reaction of the drug with the counterion. This procedure has the advantage of operation simplicity as no by-products are formed. Lipophilic salts of atazanavir formed via direct protonation have been reported by Morgen

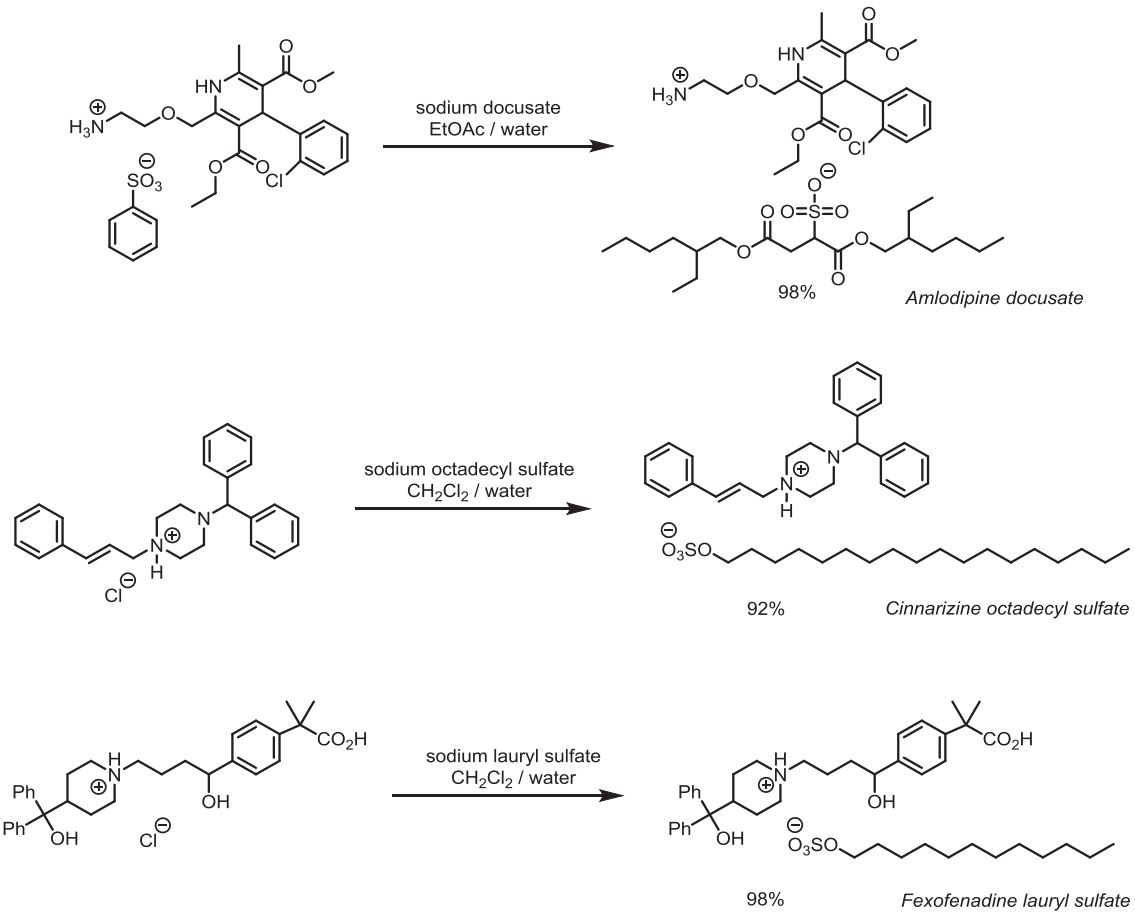

Fig. 8. Examples of the synthesis of lipophilic salts utilizing the biphasic metathesis reaction. EtOAc = ethyl acetate. CH_2Cl_2 = dichloromethane. Reactions are described in more detail in Sahbaz et al., [40] and Williams et al., [70].

et al., [56]. In Sahbaz et al., [72], direct protonation was used in the synthesis of a series of lipophilic salts of weakly acidic drugs. Acid-base reactions can also be utilized to form lipophilic salts in cases where the counterion has a permanent charge (i.e., proton transfer to the counterion itself cannot occur). Thus, reaction of tetrabutyl phosphonium hydroxide with salicylic acid gave the salt tetrabutylphosphonium salicylate and water as a by-product, in quantitative yield [95]. Numerous reports have appeared in the literature describing solvent free formation of drug lipophilic salts through direct protonation [95,96]. For example, Duarte and co-workers performed acid-base reactions by solvent-free physical mixing in order to generate drug lipophilic salts [97].

4.4. Physicochemical characterization of lipophilic salts

Chemical and physical characterization of lipophilic salts is an important part of the counterion screening process, with the primary techniques outlined in Table 4. Proton (^{1}H) NMR spectroscopy is a powerful tool for the chemical characterization of lipophilic salts, providing information regarding the degree of protonation of the drug or counterion substrate. The change in chemical shift for signals close to the site of ionization can provide information regarding the ionicity of the ion pair [98], which can be used to infer degree of ionization and therefore relative stability of the ion pair (Fig. 9). Additionally, integration of proton signals from the drug and counterion can be used to determine whether the product is a pure species and that the molar ratio of drug to counterion are equivalent. Other chemical techniques often utilized in the characterization of drug lipophilic salts include ^{13}C NMR spectroscopy, 2D NMR techniques (including COSY, HMBC, HSQC and NOESY), Raman IR, elemental analysis and high resolution mass spectrometry. As a common by-product of lipophilic salt formation is sodium chloride, methods should be undertaken to probe or quantify trace amounts, for example using a silver nitrate solution, either visually or by the Volhard procedure [99]. Other analytical techniques often utilized include ion chromatography and ion selective electrodes [100,101].

With respect to the physical properties of lipophilic salts, a polarized light microscope may rapidly reveal whether the salt is crystalline or amorphous, which can then be later verified by XRPD. A hot-stage microscope allows visual observation whilst increasing and decreasing temperature, to identify the approximate melting temperature (in the case of crystalline salts) or the approximate solid-to-liquid phase

Table 4
List of chemical and physical characterization techniques that may be applied for lipophilic salts.

^{1}H, ^{13}C and 2-dimensional nuclear mass spectroscopy (NMR)
Elemental analysis
Liquid chromatography mass spectrometry (LC-MS)
High-resolution mass spectrometry (HRMS)
Differential scanning calorimetry (DSC)
Thermogravimetric analysis (TGA)
Polarized light microscopy
Hot-stage microscopy
Raman spectroscopy and microscopy
Infra-red spectroscopy and microscopy
Solid-state NMR
X-ray powder diffraction (XRPD)
Variable temperature XRPD
Karl-Fischer titration

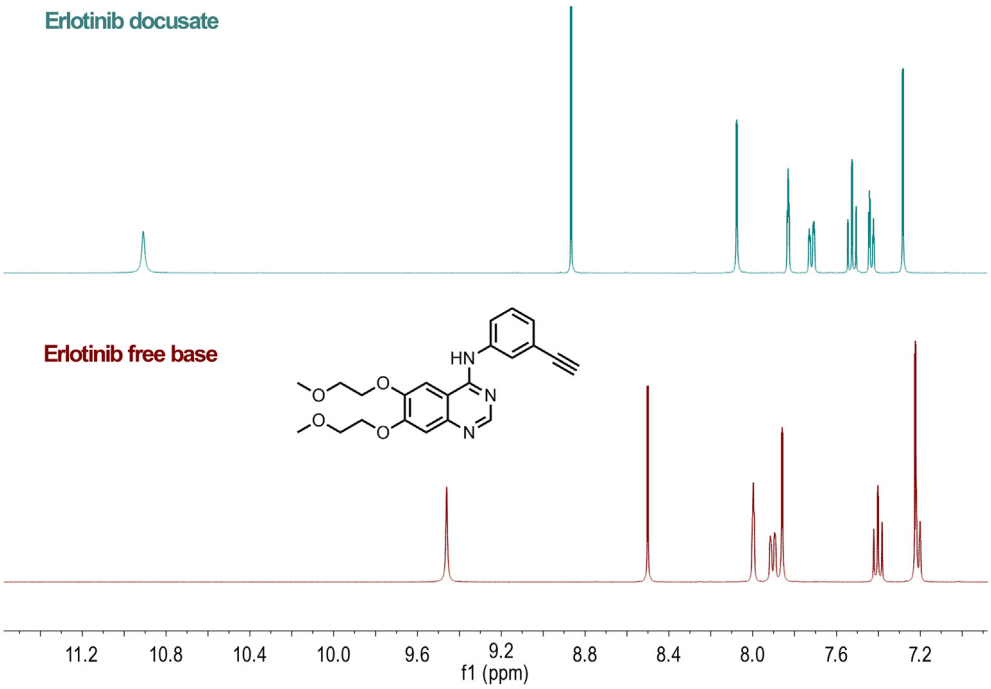

Fig. 9. Exemplar ^{1}H NMR spectroscopy results showing the distinctive spectra for free base and lipophilic salt forms of erlotinib.

transition (in the case of amorphous salts), and subsequent comparison to the thermal behaviour of the free acid/base form of the drug. The respective melting point or glass transition temperature can then be determined by DSC. The possibility of multiple phase-transitions on heating, for example, polymorphic transitions can also be detected on heating on a hot-stage, then probed further using for example DSC or variable temperature XRPD. Solid state NMR techniques may also be useful for characterization of crystal lattice properties. Thermogravimetric analysis (TGA) can be used to determine thermal stability and used in combination with Karl-Fischer tests to identify whether hydrates or other solvates may be present.

In instances where the lipophilic salt is isolated as an amorphous powder or viscous oil, it is advisable to explore the possibility that one or more crystalline forms of the drug exist. Techniques that can be used to screen for crystalline lipophilic salts include those widely used and described previously for small molecules [102].

4.5. Lipophilic salt scale-up synthesis considerations

The philosophy of lipophilic salt scale-up is generally consistent with the scale-up principles of the drug itself or any other pharmaceutical salt form. For example, the synthesis should be first optimized at the smaller laboratory scale before synthesis trialled at the larger kilogram scale. These optimization activities are usually performed by process chemists, who will look to optimize each step of the reaction to meet the specific requirements of the different stages during large-scale production. While it is unlikely that the synthetic route will be finalized for commercial production at this very early stage, it is generally desirable that the key aspects of this method are compatible with pre-existing equipment or new equipment that can be readily integrated within the manufacturing site. The process chemists will therefore focus on manufacturability, process robustness and process design, with a view that the final product prepared via large-scale production consistently meets quality and performance specifications. These final product specifications may include target physical form, target particle size, yield, impurity level, storage condition etc.

With the target specifications in hand, the process chemist will then divide process development work into two distinct but interconnected streams – unit operation and quality control. For unit operation, factors like type of equipment for each operation, process parameters, and safety issues will be considered. For quality control, specifications for raw materials and In-Process Controls (IPCs) will be defined, while the stability of intermediates and/or drug will be studied to support choice of storage condition and packaging etc.

A finalized process will consist of a reliable procedure that can be followed by an operator coupled with analytical methods for quality control purposes. After each batch's production, the final drug product needs to be tested in relation to the target, specifications to ensure that only qualified material be released for formulation study/production. Examples of such tests include potency (HPLC), impurity assessment (HPLC) and organic solubility levels (GCMS). During the process development and scale-up production, ICH guidance and/or cGMP are followed, and this adherence is especially critical for final drug manufacture [103].

5. Lipophilic salt formulation development and testing

5.1. Rational LBF design and development

Robust LBF development involves an in-depth understanding of a range of physicochemical and biopharmaceutical drug properties, for example, the Target Product Profile, the properties of lipidic excipients and their behaviour in the GI tract, and downstream considerations namely formulation manufacture, stability and regulatory acceptance [3,9,10,104].

As a drug will exhibit a number of unique intermolecular interactions with a LBF when undispersed in the capsule shell and when in the gastric contents of the stomach or while the LBF is being digested in the GI tract, it is likely that a LBF developed for a certain drug will not be optimal for another. A rational LBF design approach should therefore be adopted for each new drug in development in order to maximize the utility of the formulation platform. Judicious design of tailor-made LBFs relies on skilled experts, access to up-to-date experimental techniques and, increasingly, the use of digital tools and databases to rapidly identify initial LBF candidates and to better understand the underlying drug-LBF structure at the molecular scale. Employing a rational design

approach also has the potential to save time and money, for example, by relying less on preclinical studies to screen candidate LBFs.

The initial framework of the LBF design is guided by drug's stability, physicochemical and biopharmaceutical properties, and the TPP. An experimental screen of potential lipidic excipients is then performed to identify those toward which the drug demonstrates the highest affinity and highest solubility. Excipients are selected based on structure and function (in relation to drug properties), regulatory acceptance and commercial availability. The results of the excipient screening phase is used to design a series of initial candidate LBFs. In silico tools such as the Lipidex® software platform [105] can facilitate this transition from excipient screening into the testing phase, and minimize the trial and error approach of screening dozens of different formulations. Databases such as Lipidex® contain key data for various combinations of excipients such as phase diagrams for 1-, 2- or 3-excipient LBFs, and based on a series of drug-specific inputs, can be employed to rapidly identify candidate LBFs that meet criteria such as target dispersibility (e.g., the ability to form a microemulsion), the capacity to solubilize the target dose or the inclusion of excipients that may impact intestinal efflux transporters [106].

The LBF testing phase should include the many dimensions of a robust and viable LBF, including formulation performance, stability and processability. LBF performance testing sets out to understand the properties of the LBF and the fate of the drug following oral administration, and to identify LBF that will demonstrate optimal in vivo performance. The likelihood of in vivo utility is typically assessed through a combination of in vitro dispersion tests (in conditions simulating the fasted/fed stomach) and digestion tests (in conditions simulating the upper small intestine) [2,63,107,108]. The goal of these in vitro tests is not to closely predict LBF behaviour in vivo, rather to "stress" performance and to identify those formulations that meet specific performance criteria, i.e., consistent performance across a range of (stressful) conditions [63,107]. This approach increases the likelihood of progressing the most robust LBFs into preclinical and clinical studies.

The physical and chemical stability of a LBF, together with capsule compatibility testing should be monitored and optimized where appropriate, and ideally performed in parallel with LBF performance testing. In the case of lipid solutions, physical stability assessments include the visual and microscopic inspection of formulations for any evidence of solid drug particles that may have formed during prolonged formulation storage in accordance with ICH quality guidelines. Evidence of physical instability in a LBF on storage is a risk factor to poorer formulation performance, and requires either a decrease in drug loading, a change in formulation composition or the progression of alternative LBF formulations. In instances where a drug shows evidence of chemical degradation, this can often be ameliorated by the inclusion of antioxidants, the use of alternative / high purity excipients or other formulation approaches such as the use of semi-solid LBFs [109].

Common tests employed during routine assessment of capsule compatibility have been described previously for hard shell two-piece capsules [9,110,111] and soft gelatin capsules [13]. With respect to the large scale hard capsule filling or softgel encapsulation of LBFs, these processes have also been extensively reviewed elsewhere [9,13]. In short, key physical attributes of the fill formulations that are considered during scale-up primarily include the melt temperature of the formulation (if semi-solid), the measured viscosity at the proposed manufacturing temperature and any chemical sensitivities such as a need to protect from UV light etc.

5.2. Extra design considerations during the development of lipophilic salt containing LBFs

When drug loading is very high, as is possible when employing lipophilic salt derivatives, there is a greater likelihood that the drug will impact LBF performance and physical properties either via direct interaction with the excipients or simply because higher drug loadings dictate lower quantities of the excipients in a fixed dose mass. Indeed, the use of a drug at a high loading in a LBF may significantly impact how well the LBF disperses in aqueous conditions, the extent to which supersaturation is generated on dispersion and/or digestion in the stomach and small intestine and overall formulation viscosity. The philosophy of LBF design and development should thus be re-examined for lipophilic salt forms, even if a developed formulation pre-exists for the free base/acid form of the drug.

Within the context of in vitro dispersion and digestion testing of LBFs, there has been an increased emphasis in the recent literature on characterizing the physical form of drug precipitates formed during these tests. This emphasis stems from a realization that the formation of a high-energy precipitate (amorphous or high energy crystalline polymorph) may still drive drug absorption in vivo, since the precipitate may rapidly redissolve as sink conditions are replenished following drug absorption [108,112,113]. Such considerations are also necessary for lipophilic salt containing LBFs, particularly since the use of very high drug loadings can result in significant supersaturation and the potential for drug precipitation [19].

An extra consideration for lipophilic salts is the characterization of the chemical form of the precipitate to determine whether the precipitate contains the intact lipophilic salt complex or the dissociated drug. From this information, a formulator will be able to determine the primary driver of drug precipitation, namely non-optimized solubilization of the lipophilic salt or dissociation to the less soluble free acid or base, and modify the LBF and/or lipophilic salt accordingly. As described in a previous section (see section 4.4), various spectroscopy techniques may be used to analyse the chemical form of drugs during in vitro formulation testing. Raman spectroscopy should be considered since the strong Raman spectra exhibited by many drugs can result in a low likelihood of interference from background materials that may be present, for example, digested and undigested lipids. This technique however requires an ability to effectively discriminate between the Raman spectrum of the free acid/base form and a salt form. A second technique is ^{1}H NMR spectroscopy, which provides more definitive characterization of the material that precipitates from solution as the free acid/base form of the drug and the lipophilic salt typically have very distinctive spectra. One complication, however, is that precipitates require a washing step prior to analysis to remove residual lipids that may be present and are likely to obscure drug and/or counterion signals. This requires the identification of solvents that can remove formulation components without dissolving the precipitated drug.

A LBF/water partitioning test for LBFs containing lipophilic salts has been recently described [70]. This method was developed to capture whether the drug is preferentially solubilized in the oil phase or in the aqueous phase as a function of changing pH, and to understand the impact of the counterion on this oil/water partitioning tendency. For example, in the case of amlodipine free base, >90% of the drug was found in the aqueous phase across the pH 2–7 range whereas for the more lipophilic docusate and lauryl sulfate salt forms, >50% was present in the oil phase over this pH range [70]. While this information reveals that a lipophilic salt can be used to effectively shelter drug from the aqueous environment in the GI tract, it can also be used to pinpoint the pH at which a water-lipid phase equilibrium starts to shift and how this can be impacted by a lipophilic counterion.

Alongside the accelerated capabilities of high-performance computing, there has been considerable progress in using molecular dynamics simulations (MDS) to more effectively model complex molecules including drugs, lipids and surfactants in both the dispersed and digested state [114,115]. It seems likely that the greater application of in silico platforms in LBF design and development, for example MDS, will provide unique insights into LBF behaviour and ultimately guide and inform LBF design and development. For example, Suys et al. recently employed MDS to provide insight into the colloidal properties of polyoxyl 35 castor oil (Kolliphor® EL) and compared this information to that obtained via experimental techniques such as dynamic light

scattering, cryo-transmission electron microscopy and small-angle x-ray scattering (SAXS) studies [116]. Polyoxyl 35 castor oil is high HLB non-ionic surfactant that is widely used in LBFs, and is considered a compositionally complex molecule. Using recently updated MDS forcefields, Suys et al. were able to effectively replicate the morphology of hydrated polyoxyl 35 castor oil molecules in dilute solution, opening the door for future MDS studies of more complex LBFs containing this excipient [116]. Notably, growing interest in MDS application in formulation design is occurring alongside a growing number of publications where MDS has been used in the broader IL field, for example in predicting IL properties in solution [117] and thermal properties [118].

6. Brief comments on the regulatory aspects of lipophilic salts

Safety and efficacy testing of a lipophilic salt form of a NCE is likely to mirror that taken when developing any salt form of a drug. In the US, a NCE is submitted as a NDA (New Drug Application) under section 505 (b)(1). This NDA submission would contain the Chemistry, Manufacturing and Controls (CMC) evaluation alongside safety and efficacy data relating to that particular salt form of the NCE.

New salt forms of FDA approved drugs typically fall under the section 505(b)(2) [21,69]. The 505(b)(2) approval pathway can be much shorter in duration (i.e., 3–5 years) than the standard development time for a NCE (i.e., up to 15 years). This is because a submission under section 505(b)(2) can rely on pre-existing data associated with the original drug filing (not necessarily performed by the applicant), either described in the literature or in the form of information previously submitted to the agency. In the case of new salt forms that have similar pharmacokinetic and pharmacodynamics properties as the existing branded product (reference listed drug, RLD), a waiver may be sought for pharmacology studies.

The are several past examples where new salt forms of existing drugs have been submitted to the FDA via the 505(b)(2) approval pathway without the need for additional safety and pharmacology studies, or via the analogous “hybrid application” covered under EU Article 10 of Directive 2001/83/EC. These examples include amlodipine, clopidogrel, diclofenac, permetrexed, perindopril. New salt forms of these drugs were developed to circumvent existing intellectual property, to alter solubility and dissolution rate or to block the entry of competitor products.

A recent example is the case of esomeprazole strontium. Esomeprazole was initially FDA approved as a magnesium salt (Nexium®). A new NDA for a delayed release capsule product containing the esomeprazole strontium salt was submitted in 2010 by Hamni USA Inc., and this was later approved in 2013. The delay in approval followed a request from the FDA for additional nonclinical toxicology data since the strontium counterion is used clinically (as strontium ranelate) and had generated some toxicity concerns at higher doses. After the submission of nonclinical toxicology data showing no difference between the magnesium and strontium salt forms, the product was approved by the FDA.

Based on this analysis, the use of a lipophilic salt counterion at a concentration that lies within pre-existing usage in food or pharmaceutical products may well be viewed favourably by the regulatory authorities. There may, however, be instances where novel counterion structures are explored or where the usage level is higher than current precedence. In these examples, the sponsor would need to evaluate the risk versus benefits of this type of approach, factoring in the target population (adults vs. paediatrics) and application (e.g., chronic use in cardiovascular disease vs. cancer therapy), and may wish to engage in early dialogue with the regulatory authorities on safety testing requirements.

7. Summary

LBFs continue to be widely used by the pharmaceutical industry to address a range of biopharmaceutical challenges (most commonly poor absorption due to low aqueous solubility) for NCEs or for marketed drugs, or to meet consumer market drivers for innovative formulations. Limiting the broader application of LBFs in some cases however is low drug solubility in lipidic vehicles, which can be particularly challenging if coinciding with a high dose requirement. In this review, the approach of transforming a drug into a lipophilic salt form to overcome this limitation has been described. Lipophilic salt formation is an extension of the conventional pharmaceutical salt approach, but where the goal is to improve solubility in lipid vehicles (rather than to increase solubility in water) to enable high drug loadings, broader lipid excipient selection and improved drug solubilization in the GI tract. The advantages of the lipophilic salt form have been described for a range of ionizable drugs using GRAS listed molecules as the salt counterions. These include the expanded utility of LBFs toward weakly basic drugs that exhibit poor, variable absorption from the fasted state and a high propensity for food-effects, or in consumer applications where market drivers call for high dose, single unit liquid capsule formulations. Lipophilic salt synthesis at the small scale can be adopted as part of an extended salt screen during early drug development, particularly where there is indication that an enabling formulation approach will be needed to address low drug solubility water. Lipophilic salt forms can also be explored later in development, though as with all new salt forms, this likely will require repetition of some toxicological and stability tests. At the larger scale, the synthetic steps during lipophilic salt preparation are mostly within the scope of existing API synthetic processes, enabling the scale-up of the technology. The design and development of LBFs containing lipophilic salts requires some additional considerations due to the likelihood of high drug loadings and the possibility of salt dissociation in the GI tract (particularly for very weak bases), though the increased excipient flexibility due to the higher lipid solubility of the lipophilic salt form is overall advantageous to LBF development.

Acknowledgements and disclose statement

This review article describes intellectual property in the use of ionic liquids/lipophilic salts in drug delivery that has been assigned to Lonza. Authors H.D.W, L.F, A.I, Z.S, P.B, M.M.M, G.H and H.B are from Lonza.

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