Lipophilicity and hydrophobicity considerations in bio-enabling oral formulations approaches | a PEARRL review

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Abstract

Objectives: This review highlights aspects of drug hydrophobicity and lipophilicity as determinants of different oral formulation approaches with specific focus on enabling formulation technologies. An overview is provided on appropriate formulation selection by focussing on the physicochemical properties of the drug.

Key findings: Crystal lattice energy and the octanol-water partitioning behaviour of a poorly soluble drug are conventionally viewed as characteristics of hydrophobicity and lipophilicity, which matter particularly for any dissolution process during manufacturing and regarding drug release in the gastro-intestinal tract. Different oral formulation strategies are discussed in the present review, including lipid-based delivery, amorphous solid dispersions, mesoporous silica, nanosuspensions, and cyclodextrin formulations.

Conclusions: Current literature suggests that selection of formulation approaches in pharmaceutics is still highly dependent on the availability of technological expertise in a company or research group. Encouraging is that, recent advancements point to more structured and scientifically based development approaches. More research is still needed to better link physicochemical drug properties to pharmaceutical formulation design.

Keywords: Poorly water-soluble drug, hydrophobicity, lipophilicity, crystal lattice energy, solid-state-limited solubility, solvation-limited solubility, modern formulation approaches

Introduction

The use of modern drug discovery approaches, such as combinatorial chemistry and high throughput screening as well as structural understanding of drug-target binding by X-ray diffraction and molecular modelling, has resulted in an increasing percentage of highly potent lead compounds. However, these compounds present increasing issues for formulation development as they often have high melting points (T_m) and high octanol-water partition coefficients (logP). [1–4] While T_m is a characteristic of crystal lattice energy, logP, as a partition coefficient, denotes a solvation tendency or a lack of the same. These properties are in the chemical space of poorly soluble drugs often associated with hydrophobicity and lipophilicity, respectively. [5] Most importantly, high values of T_m and logP limit aqueous solubility and as a consequence thereof often bioavailability when administered orally in conventional dosage forms. [4,6,7] These limiting factors of drug solubility can be assigned to separate idealised dissolution processes. A molecule first has to overcome crystal lattice energy to interact with solvent molecules in the consecutive process of solvation. Figure 1A depicts the crystal structure of a model compound (cinnarizine), which is used to highlight molecular interactions in the solid state. Figure 1B shows a molecule dissolved in water that requires interactions for the solvation step, hence the ease of this hydration depends on the solute affinity to water.

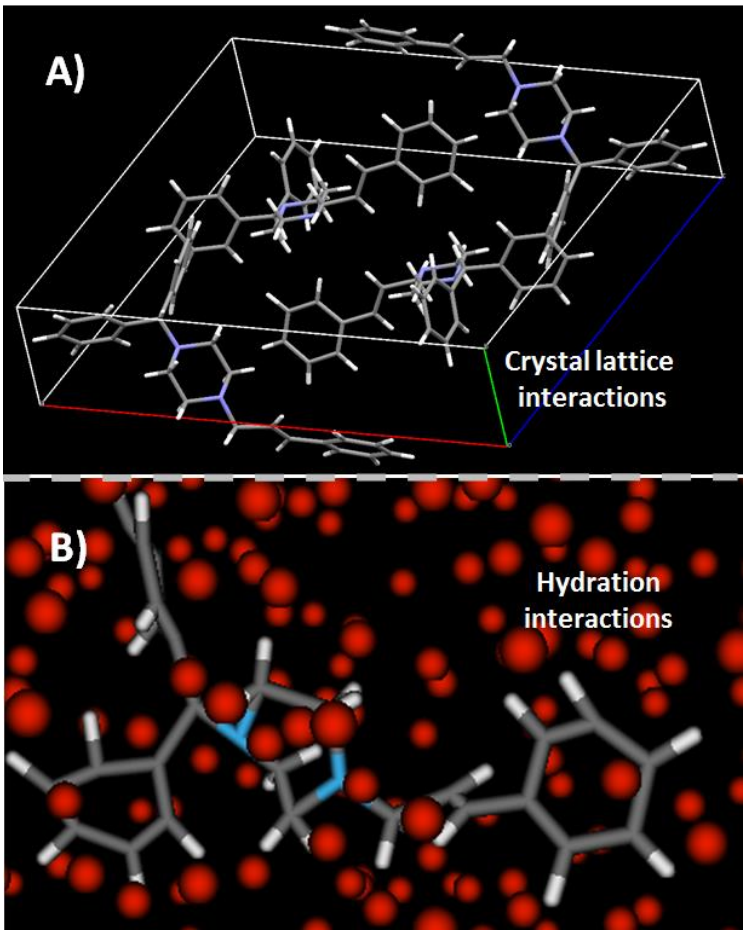

Figure 1 A) Model poorly soluble compound (cinnarizine) is shown as the unit cell of the crystal lattice and upon B) aqueous solvation (water molecules are shown without hydrogens for clarity of presentation).

The general chemical meaning of the word hydrophobicity is the physical characteristic of a molecule that it is repelled by water. Such a rather broad definition of hydrophobicity includes different reasons that cause a molecule to behave in this way. This umbrella use of hydrophobicity leads to some overlap with lipophilicity. A more specific use of hydrophobicity focuses on pharmaceutical compounds that exhibit limited aqueous solubility due to high crystal lattice energy. [5]

This has become a widespread convention in pharmaceutical sciences when poorly soluble drugs are considered. Hydrophobicity in this context has to be clearly differentiated from lipophilicity. Thus, lipophilicity as a scale is conventionally viewed as relative in the given chemical space. For example, values of logP < 2 mark a low range of lipophilicity for poorly soluble drugs, whereas a high regimen

of lipophilicity starts in this chemical space beyond about logP > 6. Such ranges are tentatively assigned and can be subject to change.

In line with these considerations, T_m and logP are generally seen as two important properties of biopharmaceutical drug profiling. [8] Such profiling is required to predict biopharmaceutical issues early on and to propose adequate formulation strategies. The design, development, and characterisation of bio-enabling formulations are among the core objectives of PEARRL (Pharmaceutical Education And Research with Regulatory Links), a European Network, focused on pharmaceutical education and research for faster patient access to breakthrough therapies. This paper addresses the need to review oral bio-enabling formulation approaches from a specific viewpoint of compound lipophilicity and hydrophobicity characteristics.

Theoretical aspects of lipophilicity and hydrophobicity

The molar solubility of a compound x_{eq} can be obtained as a function of temperature, T, by considering the solid-liquid equilibrium, which can be expressed as follows: [9,10]

$$lnx_{eq} = \frac{\Delta H_f}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) - \frac{1}{RT}\int_{T_m}^{T} \Delta C_p dT + \frac{1}{R}\int_{T_m}^{T} \frac{\Delta C_p}{T} dT - ln\,\gamma_{eq} \quad (1)$$

where ΔH_f is a compound's enthalpy of fusion, R is the gas constant, and ΔC_p represents the heat capacity difference between the supercooled melt and the solid. The activity coefficient of the solute in the saturated solution is given by γ_{eq} and estimation of this property is a central task of various thermodynamic theories. A classical and rather simple approach is the regular solution theory of Scatchard-Hildebrand, [11] which has been used by Jain and Yalkowsky to describe drug solubility in octanol, S_o. [12] Such solubility estimation of an organic molecule in an organic solvent, like octanol, appears to be simpler than a direct estimation of a drug's water solubility, S_w. The two properties are linked via the partition coefficient logP as approximated by:

$$\log S_w = \log S_o - \log P \quad (2)$$

Use of the regular solution theory was complemented with further simplifications (for example Walden's assumption of a constant entropy change upon fusion, ΔS_f) to obtain the general solution equation (GSE) for non-electrolytes: [12]

$$\log S_w = 0.5 - 0.01(T_m - 25) - \log P \quad (3)$$

The above GSE has particular importance for the present review because logS_w is a function of a compound's crystal lattice energy and lipophilicity as expressed by T_m in K and logP, respectively. This GSE approach (Equation 3) allows an estimation of how a drug's lattice energy (conventionally seen as hydrophobicity for poorly soluble drugs) and lipophilicity determine solubility. Compounds with high T_m values and moderate or low logP values are often called "brick-dust", whereas a low T_m and high logP values often give molecules the properties of so-called "grease balls". While the brick-dust compounds exhibit a solid-state limited solubility with breakdown of the crystal lattice as most difficult step, the grease-balls have the solvation step in water as the main hurdle for drug dissolution. [5,13] The GSE can provide initial estimates of aqueous drug solubility, but for more precise values it has been suggested to assume a non-constant entropy change between the solid and a supercooled melt. [14]

Hydrophobicity and lipophilicity are not only important characteristics for the different approaches to predict solubility [15] but they are also interesting regarding further pharmaceutical aspects. Accordingly, one field of interest is about which molecular features or moieties lead to brick dust or grease ball characteristics. It has, for example, been observed that structural features related to rigidity or aromaticity were correlated with restricted solubility due to stable crystal structures and thus hydrophobicity. [16] Regarding solvation-limited solubility, it makes sense to consider the molecular features that lead to high partitioning into an apolar phase, e.g. as inferred from the Abraham solvation predictors. [17,18] This approach has recently been used to obtain a better understanding of the molecular drug characteristics that drive solubilisation in biorelevant media. [19] It is clear that an improved molecular understanding of solubility limitations would be of great help in the drug discovery phase when designing and selecting drug candidates. General developability criteria, such as Lipinski's rule

of 5, [20] could be further refined so there is clearly more research to be done in this field. However, the current review approaches hydrophobicity and lipophilicity primarily from a formulator's perspective and provides guidance regarding the selection of excipients and bio-enabling formulation approaches.

Lipophilicity and hydrophobicity regarding different formulation approaches

Lipid-based formulations

The utility of lipid based formulations (LBF) as a bio-enabling formulation approach for poorly water-soluble drugs is well recognised and has fostered the development of several marketed drug products. [21] Oral LBFs are defined as delivery systems, which present the drug in a mixture of excipients consisting of triglyceride oils, partial glycerides, surfactants or co-surfactants and co-solvents. [22] The key advantage of most marketed LBF's as a bio-enabling strategy is the ability to enhance drug solubilisation *in vivo* as the drug is generally dissolved in lipids. [21] Following oral administration, the drug is ideally maintained in the solubilised/supersaturated state in the course of lipid dispersion and digestion. There is a risk of drug precipitation from LBFs, which is especially pronounced with formulations containing high percentages of co-solvents.

The thermodynamic factors governing drug solubility in lipids are illustrated in Figure 2. A drug sublimation helps to emphasise the crystal lattice hurdle and this idealised step comes with the Gibb's free energy change of $\Delta G^{0}_{\text{crystal- gas phase}}$. This is followed by a second idealised step of drug solvation in the lipid vehicle with the free energy change of $\Delta G^{0}_{\text{gas phase- lipid}}$.

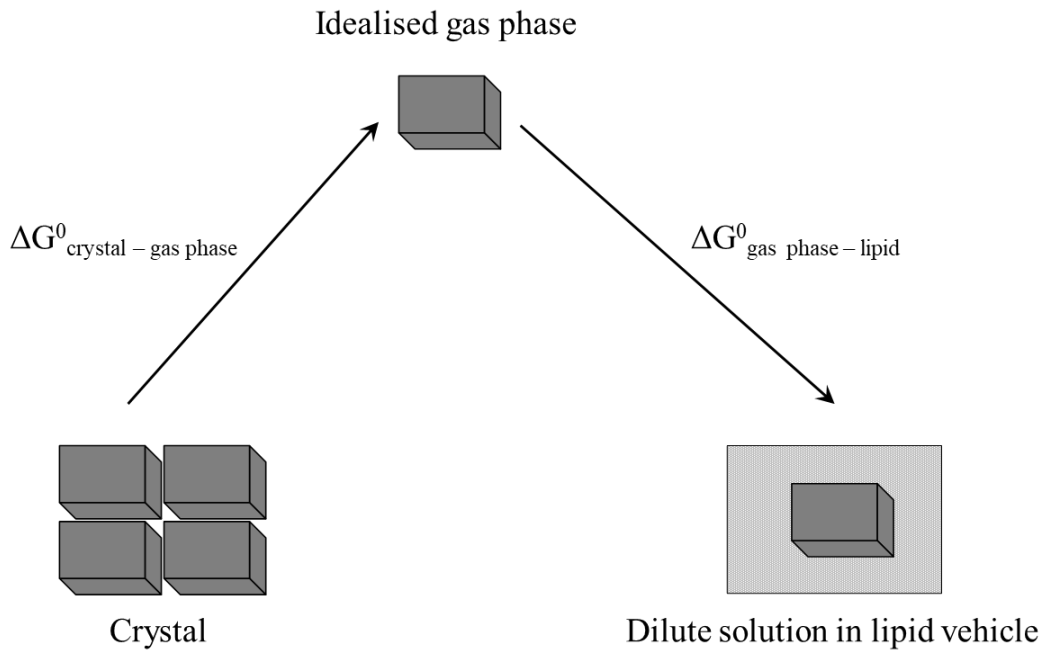

Figure 2. Factors that drive drug solubility in lipids as idealised steps of sublimation from crystal lattice and solvation in lipid vehicle. Details are given in the text. Adapted from Rane and Anderson [23]

In terms of predicting which classes of drugs will be soluble in lipids, grease ball molecules are considered advantageous for LBFs because of their dominant lipophilic characteristics and relatively weak crystal lattice energy, which both favour solubilisation in lipids. In the case of brick dust molecules, drug solubility in lipids will be limited by a high crystal lattice energy. However, compounds with medium hydrophobicity and lipophilicity are not categorisable as clear brick dust or grease balls, as there is often a mixture of solid-state and solvation limited solubility. Within the chemical space of compounds emerging from drug discovery, there is a need of better understanding how lipophilic and/or hydrophobic properties predict drug solubility in LBFs.

Regarding crystal lattice energy, it has been reported that compounds with T_m values below 423.15 K mostly show a reasonable solubility in glycerides. [24,25] These studies further showed a clear trend towards reduced solubility in lipid excipients with increased T_m values of the drug. However, T_m is only one characteristic of the crystal lattice and equals to the ratio of changes in enthalpy of fusion (ΔH_f) and entropy of fusion (ΔS_f). More refined consideration of the solid state can therefore be advantageous.

Accordingly, Persson et al. reported that the accuracy of solubility predictions in lipids slightly increased, when T_m and ΔS_f were both considered. [24] More recently, Gautschi et al. similarly found that T_m alone could not reliably predict drug solubility in C-8 and C-10 triglycerides. [26] Consequently, solubility estimations for lipids solely based on T_m appear to describe only a part of data variability and may only be valid for a rather narrow chemical space. Interestingly, as illustrated in Figure 3, there is a large variability in T_m of drugs approved as LBFs by the FDA, ranging from approximately 330.15 – 623.15 K. However, T_m values should still be considered as an important descriptor in solubility models and a guiding predictor for decisions in formulation design. Therefore, a thorough solid-state characterisation is important to understand the factors that govern drug suitability in LBFs. For example a compound with a high T_m combined with a low ΔS_f is less favourable to dissolve in pure triglycerides (TGs) and therefore unlikely to be suitable for a LBF. [25] However, it is also worth noting that there are further limitations reported on the use of T_m in models to estimate the solubility in ethoxylated excipients, which are commonly used excipients in LBFs. [24,25] Additional work seems to be required to clarify such effects of individual excipient classes.

Apart from overcoming the crystal lattice energy, a favourable solvation process is crucial for the solubility in any solvent. [8] In the case of drug solubility in LBFs, this is generally associated with a high logP value. It has been suggested that a logP of > 4 would be desirable to achieve adequate solubility in pure triglycerides, while an intermediate logP, between 2 and 4, may still show suitable solubility in LBF mixtures containing triglycerides, surfactants and co-solvents. [22] These considerations of lipophilicity can provide initial formulation guidance but aspects of crystal lattice energy as well as dose strength must be also taken into account. Recently an analysis of 36 LBFs (26 different drugs) approved by the FDA showed that the range of logP was 0.8 – 7.5 with a median of 4.9. [22] The distribution of logP for the 26 drugs is illustrated in Figure 3. Moreover, Figure 4 highlights the distribution of molecular weight (MW), logP and T_m of the FDA approved LBFs. The majority of drugs have a logP above 2 which underpins the above mentioned lipophilicity considerations.

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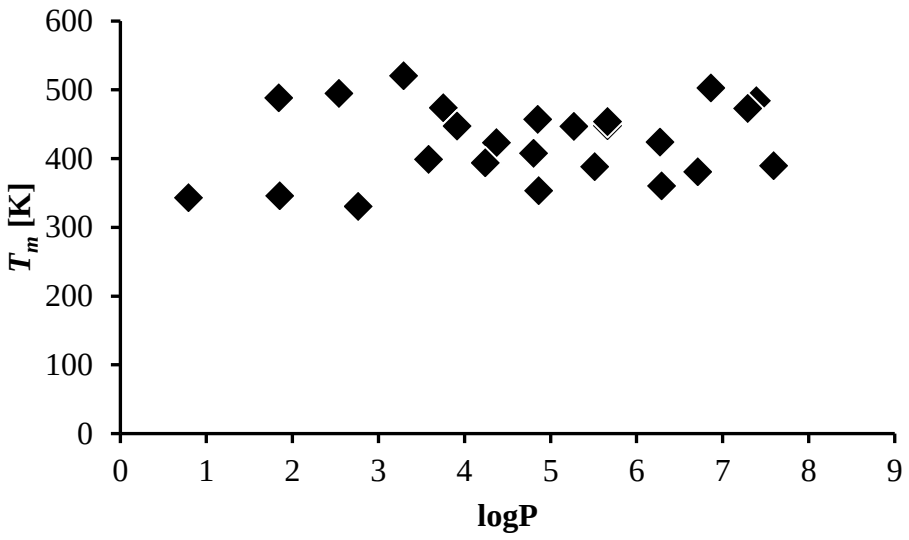

Figure 3 T_m vs. logP of FDA approved LBFs. Only three compounds have a logP below 2, however, a high variability for logP as well as T_m can be observed.

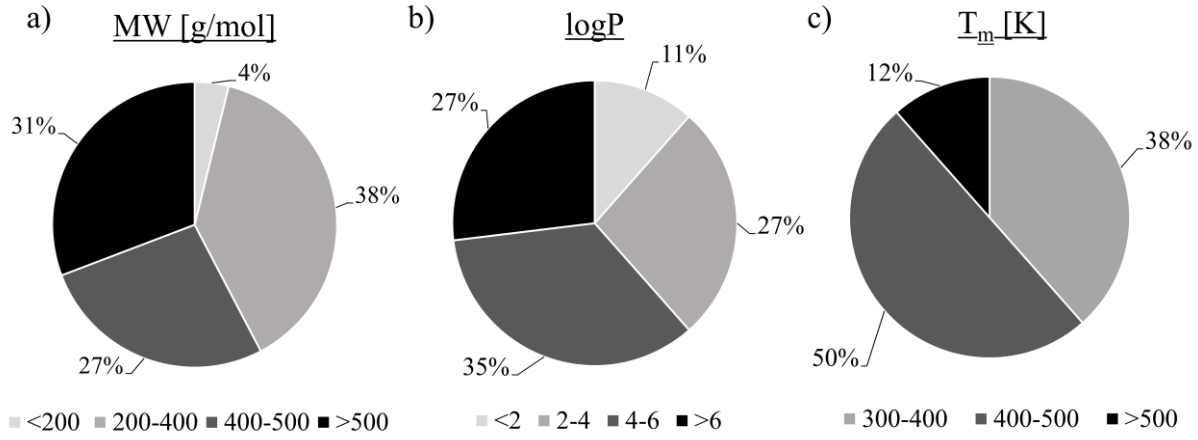

Figure 4 Physicochemical properties of FDA approved LBFs

Delving further into exploring the relationship between logP and lipid solubility, Figure 5 and 6 present the lipid solubility as a function of logP for a range of poorly water soluble drugs from Alskär et al. (halofantrine omitted). [25] Among the 34 model drugs included there was a subtle trend of increased solubility in both medium chain (Captex 355) and long chain TGs (Soybean oil) between a logP of 2 to 5. However, the situation is more complex for logP values larger than 5, where solubility appears to decrease (Figure 5 and Figure 6). A larger dataset is probably needed to draw final conclusions on the relationship between logP and lipid solubility.

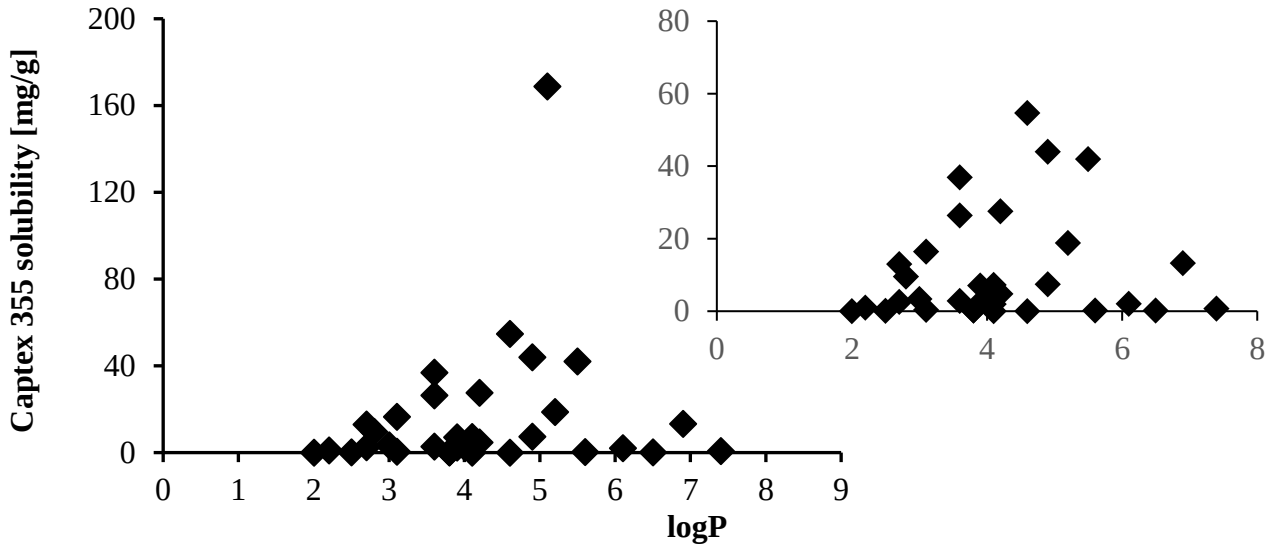

Figure 5 Solubility in Captex 355 plotted against the logP. Dataset from Alskär et al. [25] **Insert: Close up with fenofibrate omitted. The T_m values of all used drugs were below 423.15 K.**

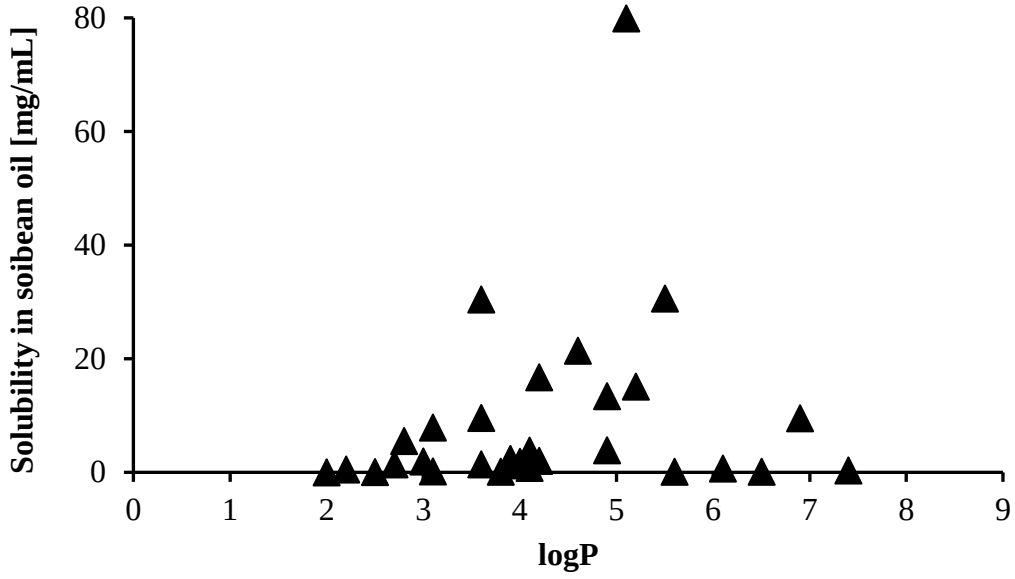

Figure 6 Solubility in Soybean oil (SBO) plotted against the logP. Dataset from Alskär et al. [25] **The T_m values of all used drugs were below 423.15 K.**

In the framework of this solubility analysis in lipids, it should be noted that poor aqueous solubility is only one rationale for LBFs. Also practical aspects like, for example, high potency, hygroscopicity or instability can be reasons to select this formulation strategy. When a biopharmaceutical rationale is given, solubility in a LBF is only one aspect to consider, while it is also important how a drug solubilises upon dispersion/digestion as well as how the absorption step is influenced. LogP has also been used to

predict further biopharmaceutical properties of drugs including the propensity for lymphatic transport, intestinal permeability, potential pre-systemic clearance, susceptibility to efflux pumps or further drug disposition. [27,28] However, such a broad scope was not intended for the current review, but this should be kept in mind to avoid any dogmatic rules of formulation selection that are based solely on drug solubility in LBF.

Besides the drug characteristics, also the choice of excipients merits further discussion. In general, it was shown in two studies that the solubility of a dataset of 10 and 35 structurally diverse compounds followed a general solubility ranking of long chain TG < medium chain TG < surfactant. [25,29] LBFs can be classified depending on the oil, surfactant and co-solvent content, [22,30] with four proposed classification types. Type I contains solely oils as triglycerides (TG), diglycerides (DG), monoglycerides (MG) or a mixture thereof, whereas Type IV formulations don't contain lipids but are mixtures of surfactants and co-solvents. Type II, IIIA and IIIB contain different kinds of lipids, surfactants and co-solvents. [30] The more lipophilic a drug molecule is, the more likely it will dissolve in Type I, II and IIIA formulations. On the other hand hydrophobic drug molecules would be more suited for Type IIIB or IV formulation given the more polar characteristics. [30]

Furthermore, several excipient properties can be used to predict and guide the choice of lipids, surfactants and co-solvents. [31] It was shown that the polarity expressed as the relative permittivity, hydrophilic and lipophilic balance (HLB), ester concentration (in triglycerides), solubility parameter, surface tension, logP, chain length, MW and molecular volume can be helpful to guide excipient selection. [31,32] The polarity describes the capability of a drug or excipient to interact through dipole interactions and possibly also through hydrogen bonding. These molecular interactions are different from the dispersive interactions of the more apolar parts of molecules. In formulation design, it is critical for the excipient selection to know, if the compound of interest needs to form polar and/or non-polar interaction with a given excipient. These molecular interactions of a drug molecule and an excipient can be visualised in molecular dynamics simulations to improve the understanding of where a drug molecule resides in a LBF and in the complex mixture after aqueous dispersion/digestion. [26,33] For example such studies can be used to explain why high solubility in LBFs may not entail high solubility after dispersion

or digestion in the intestinal media. It was for example observed for medium chain TGs that a C8 chain length resulted in the best LBF solubilisation for several drugs, whereas the corresponding digestion phases yielded best solubilisation in favour of the C10 chain length TGs. [26] These observations were similar to a previous study exploring lipid chain length and drug solubilisation. [34] More data are needed to draw final conclusions on drug solubility effects in lipids while keeping in mind that lipid solubility is only one factor of adequate formulation design.

In an effort to overcome inherent solubility limitations for challenging drug candidates, a number of advanced LBF technologies have been investigated. Widespread is the concept of self-nanoemulsifying drug delivery systems (SNEDDS)), which relies on the combination of drug, surfactant, oil and a co-emulsifier resulting in the formation of a nanoemulsion upon aqueous dispersion. More recently, this approach has been advanced to so-called super-SNEDDS that are supersaturated LBFs. [35] This type of formulation is suitable for highly hydrophobic drugs and offers an option to solubilize more active pharmaceutical ingredient (API) than conventional LBF. Formulation of a super-SNEDDS involves heating of the drug lipid mixture, to overcome the drug's crystal lattice energy. After cooling, the drug is maintained in a supersaturated state within the lipid vehicle and such formulations have been found to be kinetically stable, for drugs like simvastatin or fenofibrate. [36,37] Further studies are required to assess whether the kinetic stability is maintained throughout the commercial shelf life of super-SNEDDS formulations.

A recent approach proposed to use lipophilic counter ions to form a more lipophilic salt. [38] This approach increases drug lipophilicity and due to the nature of the specific counter ion, the salt formation could reduce crystal lattice energy and T_m of the free drug. Furthermore, the higher lipophilicity promotes the solute-solvent interaction. For example, the solubility of the lipid salt of atazanavir in an unoptimised LBF vehicle increased 3- to 5-fold compared with the free base. [38] Therefore, formation of ionic liquids (as defined by T_m < 373.15 K for the resulting salt) has the potential to increase drug solubility of hydrophobic compounds in LBFs. [39] Ionic liquids were synthesised by using bulky and highly lipophilic counter ions. In the case of itraconazole a 72-fold solubility increase with a dioctyl sulfosuccinate salt in a long chain LBF was observed. [39] In addition to the improved solubility in the

formulation, the lipophilic salt can also promote drug absorption in the GIT. These approaches therefore broaden applicability of LBFs, but for future market formulations the toxicological and regulatory acceptability of the used counter ions must be assured. [40]

An alternative strategy is to employ lipophilic prodrugs to improve lipophilicity. While the use of lipophilic prodrug strategies is more commonly employed to improve biopharmaceutical properties such as increased intestinal permeability and lymphatic transport, the increased lipophilicity is often favourable regarding solubility in LBF. [7] A study with a range of prodrugs for an anti-cancer drug (SN38) showed a significant increase in solubility in Soybean oil of 11 - 444-fold. [41] However, increasing lipophilicity via a prodrug approach also introduces risks to altered stability and pharmacokinetics, which must be adequately assessed. For example, while a TG ester prodrug of mycophenolic acid showed significant improvement in lymphatic transport and drug concentrations in lymphocytes, an alkyl ester prodrug showed poor metabolic stability and low permeability. [42]

While much focus to date has been on the use of lipid solutions as a bio-enabling strategy for challenging drugs, it has been reported that lipid suspensions may confer similar advantages in terms of improved biopharmaceutical performance. [43,44] Thomas et al. reported, for example, that a lipid suspension of fenofibrate displayed similar oral bioavailability to a comparable lipid solution. [37]. However, the number of studies employing lipid suspension are relatively few and further studies are needed to assess reliability and reproducibility of this formulation approach.

In summary, lattice energy and lipophilicity considerations are important for the choice of the lipid delivery approach and for the selection of excipients. While T_m has proven useful in predicting lipid solubility of drugs, logP does not generally represent a reliable quantitative predictor of solubility. Therefore, the hydrophobic, or solid-state properties of a drug, appear to be crucial relative to their lipophilicity. The presented analysis of drugs marketed as LBFs suggests that poor hydrophobicity alone may not limit commercial development. There are a number of emerging formulation approaches such as ionic liquids, lipophilic prodrugs or lipid suspensions that may offer promise in addressing unfavourable hydrophobicity characteristics. Future work may provide more complex structural and physicochemical factors for guiding the design and development of LBFs.

Amorphous solid dispersions

The formulation approach of amorphous solid dispersion (ASD) was introduced by Chiou and Riegelmann in 1969 because of an increasing number of poorly water-soluble compounds that required a new formulation perspective. Since then this approach has been common practise for solubility enhancement [45] of hydrophobic or lipophilic drugs. [46]

From a thermodynamic viewpoint, an amorphous state has generally higher Gibbs free energy than a crystal. Therefore, an amorphous state is either labile or metastable with a considerable risk of crystallisation in non-stabilised ASDs.

Figure 7 emphasises the differences in Gibbs Energy between amorphous and crystalline material. Moreover, it shows the changes in this energy compared with increasing temperature, going from an amorphous state to the final transition in the liquid molten state, respectively. The two temperatures in Figure 7 mark the transition of an amorphous to the crystalline state. The glass transition temperature (T_g) represents the alteration between an amorphous state and a supercooled liquid. The other change in the solid state can be observed at T_m, when the crystals melt and become liquid.

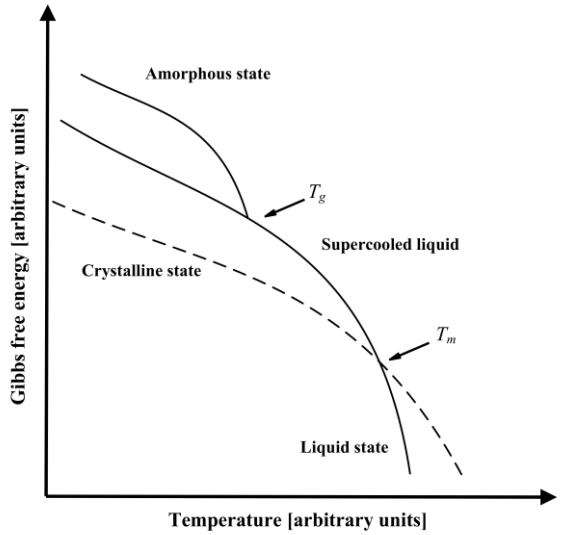

Figure 7 Gibb's Free Energy of amorphous and crystalline material. Adapted from Hancock and Shamblin [47]

Moreover, the difference in Gibbs free energy shown in Figure 7 also results in an enhanced apparent solubility compared to the crystalline form. [48] This so-called amorphous solubility advantage was coined by Hancock and Parks, who associated the difference in free energy to the difference in apparent solubility according to Equation 4. [49]

$$\Delta G_T^{a,c} = -RT \ln\left(\frac{\sigma_T^a}{\sigma_T^c}\right) \quad (4)$$

The different solubility of the amorphous and the crystalline state at a fixed temperature are represented by σ_T^a and σ_T^c, respectively. Consequently, $\Delta G_T^{a,c}$ is the difference in free energy at a given temperature. A higher difference in free energy can be associated with a larger solubility advantage of the amorphous form over the crystalline form. Such increased apparent solubility has to be balanced with the general drawback of potential physical instability of an amorphous state. A possible crystallisation to the original crystal form or any other polymorph has to be monitored by adequate solid state analysis.

Due to the high relevance of identification and quantification of amorphous drug in a solid dispersion, there are several methods commonly applied. A widely used technique is X-ray powder diffraction (XRPD), where an amorphous form shows a halo and absence of any Bragg peaks. [50] This result underlines the lack of long-range order in the solid state. [51] Another common method is differential scanning calorimetry (DSC), where the absence of a melting endotherm and the presence of a T_g indicate an amorphous state. The spectrum of further characterisation methods is very broad including also spectroscopic methods such as Raman or IR-spectroscopy as well as solid-state NMR spectroscopy. However, XRPD and DSC are still the most common methods, because of their rather simple handling and good reproducibility.

Solid dispersions can be categorised according to the physical state of the given phases. [52] The first dispersions were often eutectic mixtures, which were miscible in the molten state. A disadvantage of the eutectic systems is that re-crystallisation occurs at the characteristic eutectic temperature, which typically occurs during the cooling process. Pioneer solid dispersions were prepared with a water-soluble

carrier like citric acid, and a poorly water-soluble drug (e.g. griseofulvin). [45] Depending on the individual composition it is possible to obtain an amorphous solid solution, where a compound is dispersed molecularly in the amorphous carrier [53]. Leuner and Dressman pointed out that solid solutions can be continuous versus discontinuous or substitutional versus interstitial. Systems with an amorphous carrier are generally called glasses where glass solutions can be differentiated from glass suspensions depending on the physical state of the drug and whether one or two phases are present in the system. [53]

Since ASDs have a long tradition, different generations of formulation types have been in use. Those different generations were described in detail by Vo et al. Main differences are given in the types of excipients selected during the pharmaceutical development of solid dispersions (Figure 8). [54]

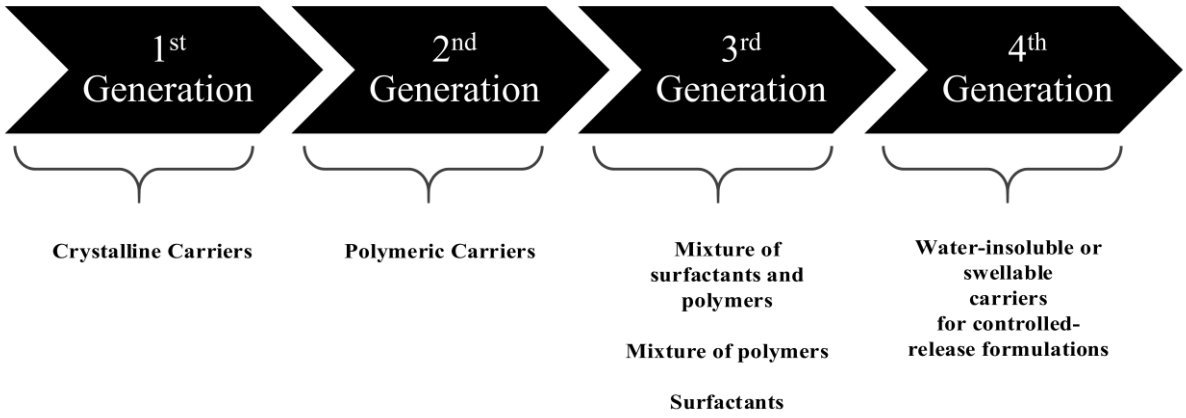

Figure 8 Different generations of solid dispersions. Adapted from Vo et al. [54]

In the first generation of solid dispersions, a crystalline carriers (i.e. mostly small molecular additives) were used for dispersing the drug homogeneously in the solid state, with the disadvantage that a rather fast drug precipitation upon aqueous dispersion was often observed. Therefore, a second generation of improved formulations was proposed that were based on polymeric carriers, which were advantageous with respect to the biopharmaceutical fate of the drug. Such ASDs typically showed a dissolution rate that was widely controlled by the hydration and dissolution of the polymeric matrix. [55] The third generation solid dispersions consisted mainly of polymeric carriers combined either with each other or

with surfactants to improve the aqueous dispersion following oral administration. Interesting is here a combined functionality like, for example, the BASF polymer Soluplus®, which represents a polymer (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) with significant amphiphilic characteristics of a surfactant.

The production of the formulations mentioned above can be mainly divided into melt-based and solvent-based methods. [48] This is critical since the preparation has a substantial effect on the physicochemical characteristics, stability and therefore performance of amorphous ASDs. [56]Considering the marketed solid dispersion products, it is interesting to see that a rather limited number of polymeric carriers and production techniques have been used. [57] While the choice of the formulation components are generally based on physical and chemical considerations and long series of experiments during development, the production methods are often more arbitrarily selected depending on available technological knowledge and equipment. [58] Selection of the manufacturing method based upon the physicochemical drug properties is therefore desirable. Such an approach also may accelerate process development and should finally result in a robust manufacturing of drug product.

Different melt and fusion techniques represent the classical methods to prepare amorphous solid dispersions. [58,59] For the melting of the active pharmaceutical ingredient (API) and a carrier, temperatures should be above the T_m of the API. [60] Raising the temperature above the T_g of the mixture creates adequate molecular mobility for the API to be incorporated in the carrier. [58] Although a variety of method modifications have been introduced throughout the years, ASDs with APIs presenting high T_m values (e.g. quercetin) typically encounter issues of lacking temperature stability of the carrier. These high-melting APIs therefore only have a limited range of available polymers that can be used at the needed process temperatures. Moreover, high shear forces in a process of hot melt extrusion (HME) may facilitate, besides the vigorous mixing and the desirable dispersion of the API in the carrier, the removal of oxygen and moisture. [54,61] This enables the incorporation and usage of APIs that are sensitive to oxidation. However, high shear forces may also compromise the stability of thermo-sensitive APIs, due to possible local high temperatures. [61]

An alternative to any melt method is to prepare a solution of drug and carrier in a solvent. The fate of the solution may vary, from solvent evaporation to amorphous precipitation. The solvent evaporation method includes first the dissolution of API and carrier in a common organic solvent (or solvent mixture) and the subsequent removal of the solvent by heating, spray drying or freeze-drying. [62] The choice of a common solvent for the API-carrier systems may prove to be limiting, as it is challenging to identify a solvent for combinations that vary significantly in polarity. [62] Generally, thermal degradation is not a common limitation in the solvent evaporation methods, as temperatures are kept low. Specifically for thermo-labile compounds, a freeze-drying method is of interest, where the API-carrier solution is frozen and the solvent or solvent mixture is sublimated at temperatures below the T_g of the mixture. [58] A sublimation above this critical temperature comes with increased molecular mobility that can facilitate recrystallisation. Consequently, APIs with extremely low T_g*'s* may not be suitable for this method. In addition, during the removal of the solvent by heating, molecular mobility is critical, as elevated temperatures (above T_g) may facilitate API diffusion from the carrier, thereby creating a phase separation and subsequent crystallisation. This suggests that this method may be less suitable for APIs with a T_g below the boiling point of common organic solvents (e.g. methanol, ethanol, acetone ~60-70°C).

It seems that API lipophilicity has barely been investigated for its effect on different ASD manufacturing methods. Due to the fact that solubility is governed either by lipophilicity (logP) or by the crystal lattice energy (hydrophobicity), [16] it is expected that these molecular properties are relevant for selection and manufacturing of solid dispersions. Finally, the ratio of T_m/ T_g merits consideration because it is an indicator of glass-forming ability that can again be related to molar volume and entropy change upon fusion. [63] The latter entropy change can be estimated from chemical structure. Such *in silico* estimations of glass-forming ability are of high interest, not only for drug discovery, but also in development because T_g is not easy to measure with fast crystallizing compounds. [63]

In line with these considerations of solid dispersion developability, Friesen et al. introduced the classification of several drugs according to the ratio of T_m and T_g plotted against logP. Different groups of active substances were introduced. [64] For drugs with T_m/T_g ratio of maximum 1.25 (group 1), it was considered possible to formulate an amorphous state. Group 2 with T_m/T_g ratios of 1.25 to 1.40 was

estimated to have a limited drug load of 35-50 % (w/w) due to lower amorphous stability. Most challenging compounds in terms of stability exhibit a T_m/T_g range of higher than 1.4 and consequently, a drug load of maximum 35 % (w/w) was proposed. These drugs with a logP smaller than 6 were assigned to group 3, whereas all other lipophilic drugs with logP higher than 6 were viewed as generally problematic regarding dissolution and assigned into group 4 regardless of their T_m/T_g ratios.

For this review, the described categorisation approach was applied to drugs for which formation of a stable ASD was reported in the literature. [63,65,66] The distribution of the MW, the logP and the melting temperature of these drugs is displayed in Figure 9.

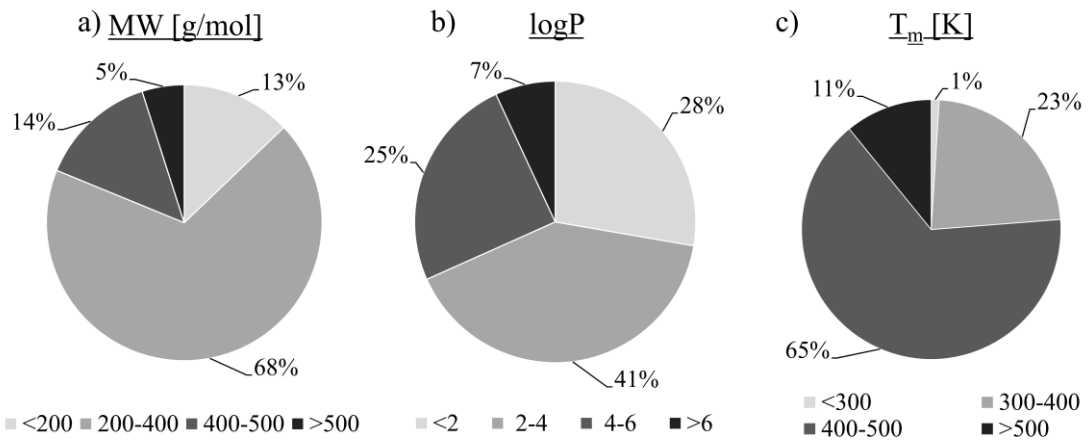

Figure 9 Properties of APIs formulated as ASD [63,65,66]

Figure 9A suggests that most substances successfully formulated in an amorphous state have a MW between 200 and 400 g/mol. This is in accordance with the publications of Edueng et al. and Mahlin et al, who also found a limited occurrence of very small molecules, as MWs above 300 g/mol are more optimal for good glass forming ability. [5,67] The pie chart (Figure 9B) of the logP value reveals a broad distribution with a lowest fraction of highly lipophilic drugs. Furthermore, T_m (Figure 9C) is mostly between 400K and 500K. These distributions of physico-chemical properties cannot only be explained

by ASD rationales as they are likely biased by the natural occurrence of MW, logP and T_m among available drugs.

A novelty compared to the data gathered by Friesen et al. is the inclusion of melt-based amorphisation techniques. [64] If only the subset of marketed drugs in amorphous products is considered, which are not included in Figure 10, a challenging $T_m/T_g > 1.4$ was only observed with etravirine and vemurafenib. [68] This can be compared to glass forming ability, which can be determined by means of a DSC method. [65] Vemurafenib was verified as a fast crystallizing compound, while this is hard to demonstrate for etravirine due to thermal decomposition. [57] Interestingly, etravirine as well as vemurafenib are manufactured in their market products by a solvent-based method. Apart from these drugs, other market compounds are in group 4 due to their high logP > 6, which is the case for itraconazole and everolimus. While Figure 10 shows the compounds found in scientific publications, it emphasises that more melt-based manufacturing methods have been reported in group 4. However, there are also reports on drugs for which melt-based as well as solvent-based techniques were used. Also in group 3, where the majority of the compounds is located, there is not a clear dominance of either the melt or solvent-based method, so clear trends of a preferred method are missing. There is on the other hand currently no established molecular rationale for the selection of a manufacturing method and this choice is greatly influenced by the available expertise of individual formulation scientists.

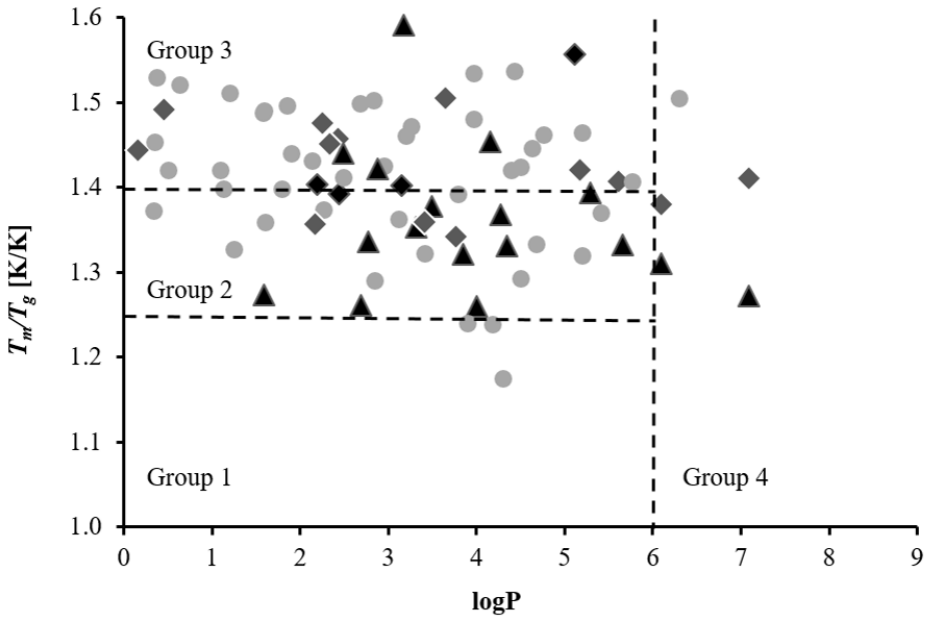

Figure 10 APIs gathered from the literature, [63,65,66] for which solid dispersions were successfully formulated, labelled by their amorphisation method. Diamonds represent melt-based amorphisation. Dots stand for solvent-based amorphisation and triangles are drugs, which were formulated by both approaches. The lines indicate the different groups according to Friesen et al. [64]

For a better evaluation of hydrophobicity and lipophilicity influences, the graph was modified to show T_m versus logP (Figure 11). Furthermore, the graph represents the drugs differentiated by their amorphisation method in accordance with Figure 10.

Figure 11 indicates that melt-based methods were primarily used in research for compounds with logP > 2. Moreover, there are not many substances that have a T_m > 500 K and substances of logP > 6. The distribution of data points shows an accumulation between logP values of 2 and about 5, which may not be specific for the selection of solid dispersion technology, but also reflects the natural distribution of drug lipophilicity for the compounds studied.

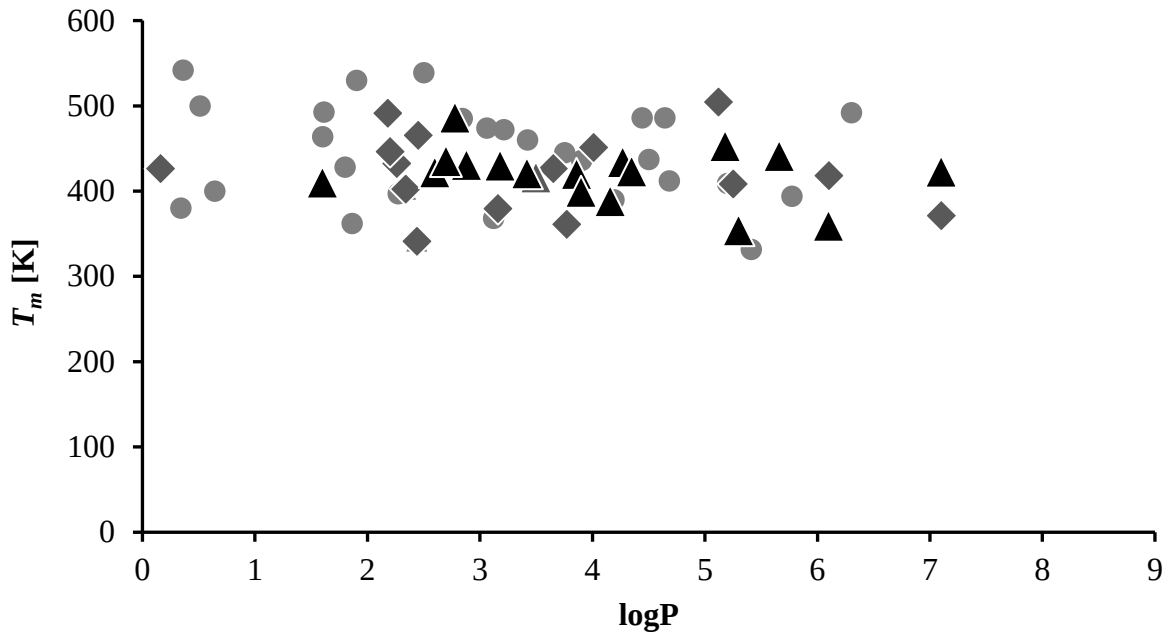

Figure 11 Scatter plot of drug as melting temperature versus the logP values for further evaluation of hydrophobicity (data taken from the literature [63,65,66]). The colours and makers are analogues to Figure 10.

In summary, Figure 11 as a plot of lipophilic and hydrophobic drugs does not reveal pronounced tendencies with respect to the process technique. It seems that melt-based methods are limited regarding high T_m, because of possible degradation issues of drug and excipients. However, also a solvation step can be clearly limited by excessive hydrophobicity. A more recently introduced solvent-based method

is the microprecipitated bulk powder, where amorphous co-precipitation occurs with a polymer, which is based on ionisable groups to facilitate drug-excipient interactions. [69] This broadens the applicability of ASDs for APIs with high T_m values. Currently there is only one drug (i.e. vemurafenib) formulated in this way on the market, but this can change in the future. At least for ionisable compounds, the possibilities for solvent-based approaches can be broadened for compounds with very high T_m values.

This section approached amorphous systems from the viewpoint of hydrophobicity and lipophilicity, but further molecular aspects are relevant for the different quality attributes of amorphous systems. This has become a developing field of research and more information on molecular descriptors applicable to ASD attributes can be inferred from recent publications. [5,70]

Mesoporous silica formulations

Mesoporous silica refers to any number of a variety of materials synthesised to produce a SiO_2 mesoporous structure. [71] Mesoporous silica can be ordered or non-ordered. [72,73] The former include structures such as SBA-15 and MCM-41, [74] whilst the latter include novel, proprietary excipients manufactured by drug delivery specialists, such as the excipients Parteck SLC® (Merck Milipore) [75,76] and Neusilin™ (Fuji Chemical). [77] Such systems have a wide range of applications, including: tissue engineering, [78] catalysis, [79] chromatography , [80] adsorbents in environmental modelling [81] and drug delivery systems for poorly soluble active pharmaceutical ingredients (API). [82] For the latter, it has been widely reported that mesoporous silica can act as a solubility enhancer by 'trapping' API in non-crystalline form within the mesoporous network. [75,76,83–86]

For this purpose, there are various methods of loading crystalline API onto mesoporous silica, which can be grouped into three broad categories: solvent-based, [75] mechanical activation [87] and vapour-mediated. [88] A thorough overview of these loading methods of poorly soluble API onto mesoporous silica is beyond the scope of this review, but the interested reader is referred to a number of publications that provide more details on the different routes to API-loaded silica. [71,87,89–91]

Although a rather broad variety of methods is present in the literature; the solvent-based approach is most commonly employed. This can be attributed to the poor loading efficiencies and time-consuming processes involved in the solvent-free loading methods such as melt and supercritical fluid based processes. [87] These solvent approaches can be grouped into two main categories: solvent impregnation and incipient wetness. During the solvent impregnation loading approach, API is dissolved in organic solvent and added to mesoporous silica. Adsorption of API onto the silica is then initiated through mechanical agitation or sonication of the slurry. Finally, the solvent is removed, which can be achieved using a number of methods including vacuum drying, spray drying, lyophilisation or rotary evaporation. [71,75,92,93] The second approach, incipient wetness, involves the steady addition of small volumes of concentrated API solution onto the silica, so the full amount of solvent is adsorbed into the network and then rapidly evaporated, which leaves the API within the pores. [76,85] Both methods result

in an API-loaded silica, in which the previously crystalline API is now amorphous or molecularly dispersed, which can be confirmed with analytical methods such as DSC or XRPD.

In general, the theoretical maximum drug content that can be loaded onto mesoporous silica is dependent on the surface area, [94] pore volume , [95] and pore geometry of the silica [96] with values as high as 75% reported in the literature. [92] However, such very high-loads are experimentally barely achievable and residual crystallinity is often observed in drug-loads exceeding 50% (w/w). [92] Most cases of API-loaded silica in the literature do not exceed 40% loading.

The loading process can be considered from an energetic perspective of drug adsorption onto the carrier but there is currently insufficient information available. Some hypotheses include: hydrogen bond interactions, [97,98] hydrophobic interactions, [86] capillary action [92] and ionic interactions, [99,100] although the latter depends on the silanol groups on the surface of the silica to be deprotonated and negative.

One of the potential benefits of mesoporous silica relative to alternative amorphous formulations, is the high stability that is achievable. This is due to the very small environment of the mesoporous network (so-called 'nano-confinement') [101] and complimentary interactions (yet to be fully resolved) with the silica surfaces, which lower the free energy of the system further. [102] API-loaded silica can often be stored in open containers and at elevated temperatures and pressures, although this can be API-dependent as well. For example, Muller and co-workers demonstrated stability of an amorphous form at ambient and accelerated conditions for 30 different formulations of API-loaded silica, exceeding the requirements for regulatory stability studies. [103] This could be particularly used for compounds that have high tendency to re-crystallise, e.g. low T_g, where otherwise classical solid dispersions may fail to provide stable formulations. [34,74,104]

Following dispersion in an aqueous medium, such as in the GI tract, the API is displaced from the mesoporous network and has the potential to generate supersaturation. The release mechanism can be considered using diffusion kinetics. However, due to the complexity of the porous network and multiple phases a more refined view will likely emerge in the future when more research have focused on the

topic. Simplified, upon administration to an aqueous environment, there is a diffusion of water into the porous network *via* capillary action. This in turn solubilises the loaded API, which generates a concentration gradient between the inside of the silica and the outside medium. This in turn drives release of API *via* diffusion along a concentration gradient, generating supersaturation and potentially increased absorption. [86]

This kind of release behaviour can be approximated by classical matrix diffusion (Equation 5) **,** which was proposed by Higuchi in 1961 to describe API release from thin ointment films: [105]

$$M_t = A\sqrt{2c_{ini}Dc_s t} \quad (5)$$

where M_t is the amount of drug released from the inorganic carrier; A is the surface area available for release; c_{ini} is initial drug concentration in the carrier; D the diffusion coefficient of drug in the insoluble carrier and c_s is the maximum (saturation) concentration of the drug in the carrier.

The approach can also be expanded to describe the release of any API adsorbed or entrapped within an inorganic and insoluble matrix into an external medium *via* diffusion. [106]

When one considers the above Higuchi equation, the release of API from mesoporous carriers can be described as a diffusion-driven process. Similarly, to loading efficiency, drug release is further dependent on pore surface area, pore volume, and pore morphology. However, there have been a number of examples in the literature, where Higuchi diffusion kinetics successfully modelled release of, for example, ibuprofen from mesoporous materials. [107–109]

There is surely more research needed to more specifically model release from mesoporous materials and to better understand molecular interactions of the loaded API with the porous carrier.

After the previous mentioned compound release, a high energy state of drug supersaturation is typically obtained. Therefore, mesoporous formulations are often coupled with so-called precipitation inhibitors such as polymers like poly(vinylpyrrolidone), which should inhibit a potential crystallisation. This maintenance of initial drug supersaturation forms the basis of the parachute in the spring and parachute

model first proposed by Guzman, and is more generally used in formulations that generate supersaturation. [110]

Mesoporous silica is a relatively novel formulation option for poorly soluble drugs, with no examples of commercially available formulations so far, and limited proof of concept studies in man that are available in public domain. [111] However, there has been a dramatic increase in the interest for mesoporous silica-based formulations in the past decade. A summary of drug properties reported in mesoporous silica formulations is shown in Figure 12.

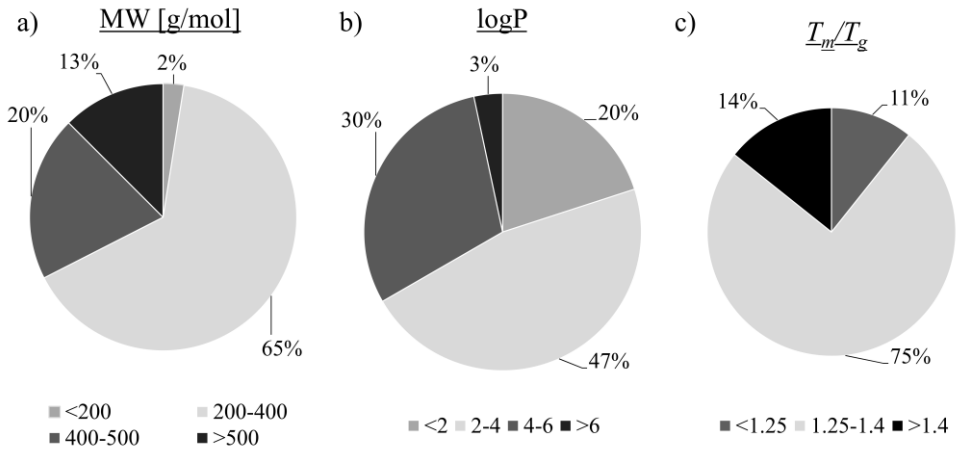

Figure 12 Properties of APIs formulated with mesoporous silica in the literature

For MW, there might be a kind of 'sweet spot'. For very small molecules, there is efficient and deep penetration within the porous network, but microcrystalline domains can rise (extra space for critical nuclei formation), [101] why release can often occur too quickly (high risk of precipitation). [83] On the other hand, molecules that are too large and bulky may have problems accessing the pores efficiently, with only impractically low loading efficiencies being obtainable. Another factor of loading efficiency using larger molecules is the pore geometry of the porous network, with open 3D pore structures such as Parteck SLC® likely being more accessible than the classical ordered 2D mesoporous silica such as MCM-41. Therefore, in the case of MW, it makes sense that the majority of compounds investigated are in the 'middle ground' of 300-500 Da. Further investigation into very small (<200 Da) and very large (>500 Da) molecules would offer interesting insights based on future work. Such additional work may study different quality attributes of amorphous systems. A previous study highlighted, for example, the

importance of MW and T_m for the amorphous solubility advantage, which could be further investigated specifically for mesoporous systems. [112]

For logP, and the hydrophobicity of the molecule, the retrospective analysis of reported mesoporous formulations is less clear. It is likely that the hydrophobicity of a molecule is of great importance in terms of with how it interacts with the surface of the mesoporous silica, and in turn how it is loaded and released. For example, not only polar but also dispersive interactions between API and the silica are expected to play an important role. However, in line with previous considerations of solid dispersions, a very high logP value is problematic with respect to drug dissolution. The logP data of mesoporous formulations show that most of the formulated poorly water-soluble compounds fall in the logP range of 3-5. Thus, in line with the previous comment surrounding MW, future studies on very lipophilic and hydrophobic molecules can only add to the growing understanding of mesoporous silica, and will significantly help towards creating a more rationale selection criteria of the most 'suitable' candidates for this purpose.

Another parameter that can be considered is again the ratio T_m/T_g. A higher T_m/T_g ratio indicates decreased glass-forming ability and decreased stability, which comes with higher propensity for recrystallisation. [64]

Previously, it was highlighted that mesoporous silica can enhance shelf-life stability *via* nano-confinement in combination with complimentary API-pore interactions, making them suitable even for fast crystallisers as critical compounds in class 3 and 4 of the Friesen plot mentioned above. However, it seems based on T_m/T_g values that not many more of these difficult drugs have been formulated using mesoporous silica as compared to other solid dispersions. Thus, current literature trials with mesoporous silica have been carried out with the so-called 'usual suspects', that being the compounds that are known to work well with other amorphous formulations, such as those obtained by spray drying. This represents a gap in the literature. More work should be done to identify a chemical space, where mesoporous silica has particular advantages compared to existing technologies, such as spray-dried dispersions and hot melt extrudates. It is possible that mesoporous silica could be an especially attractive formulation option

for critical compounds with T_m/T_g > 1.4. Further studies with such compounds would be helpful to map, which technical option is the most promising to obtain an optimal amorphous system for a given drug linked to its physicochemical properties.

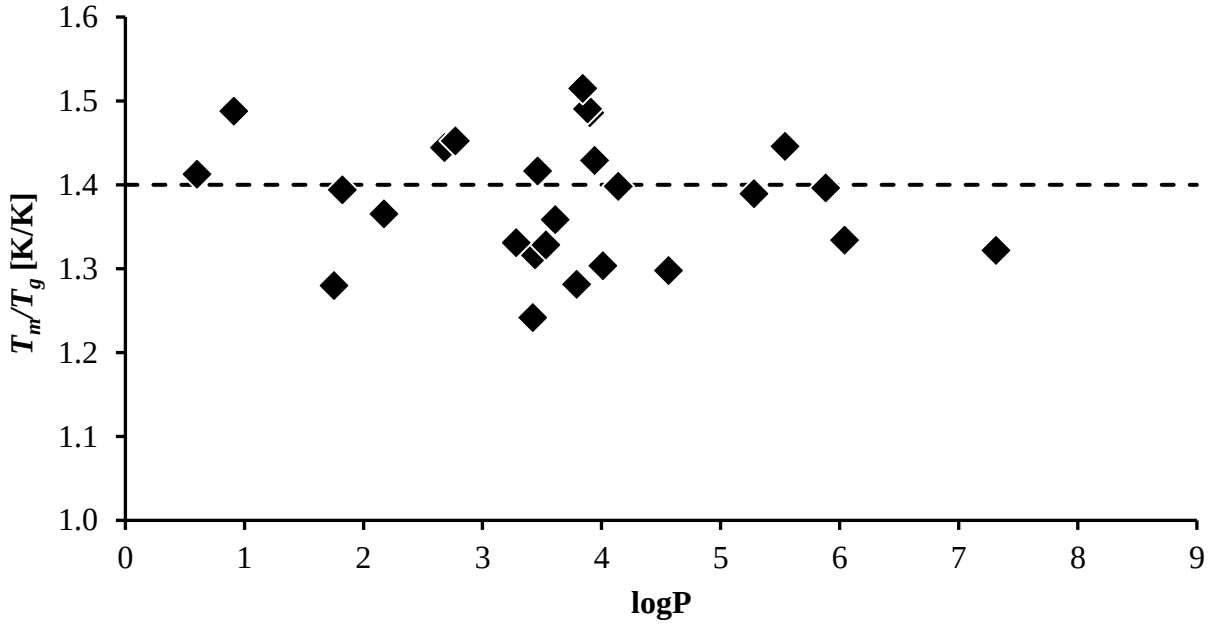

Figure 13 T_m/T_g vs. logP for APIs formulated with Mesoporous Silica. The dotted line indicates the fragile-boundary, above with stability issues can be expected with the amorphous form.

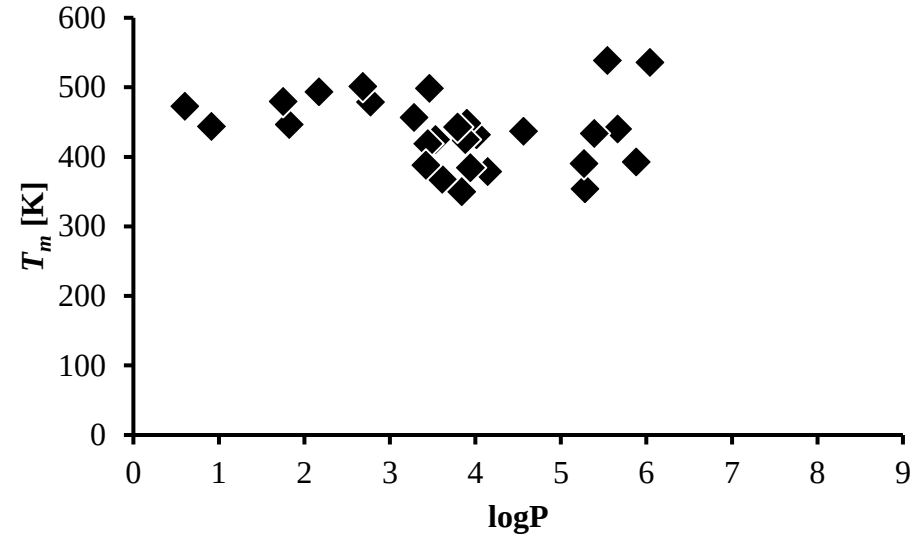

Figure 14 LogP as a function of T_m of compounds in formulations containing Mesoporous Silica.

In line with the previous consideration of hydrophobicity (in terms of T_m) Figure 14 highlights the observation that the commonly used APIs are interestingly confined to within a rather limited chemical space.

This leads to the initial impression from Figures 13 and 14 that, there is currently no pronounced difference to the other solid dispersion approaches even though mesoporous silica is an exciting prospect to add to the formulator's toolbox when considering poorly soluble API. As it stands, more work is required in key areas to better understand: the loading process, the interaction between API and porous surfaces and the release process. More research in this area will allow a more rational selection of mesoporous silica as a viable formulation option, based on a thorough understanding of the chemical drug space that is optimal for this formulation approach. This would avoid some unnecessary formulation screening and lead to a more focused drug development process. It is only when this understanding is established that there will be a shift away from the one-size-fits-all approach in terms of solid dispersions towards more tailored formulation techniques.

Nanosuspensions

The previous sections outlined the different strategies of how to solubilise poorly water-soluble drugs in the dosage form or how to convert their crystalline solid form, into an amorphous state. An alternative approach is to formulate such challenging drugs as nanosuspensions. [113] This formulation technique is of particular interest when high crystal lattice energy is limiting the alternative solubilisation in, for example, lipid-based formulations. This high lattice energy can be so pronounced that drug candidates might be neither soluble in polar nor apolar solvents or excipients. [114] Nanosuspensions can be formed by breaking larger micron-sized particles down (*i.e.* top-down approach) and stabilised by a mixture of polymer/surfactant, as in a wet milling technique. [115] Several examples such as Rapamune (Wyeth), Emend (Merck), TriCor (Abbott Laboratories) and Triglide (Skye Pharma) are already on the market. [116] In earlier phases of drug development, nanosuspensions are often used to formulate poorly soluble compounds because high doses are administered in toxicological studies. It is here an advantage that wet milling is a rather versatile method to enable nanosuspension production with the majority of compounds. However, many of them do not achieve sufficient physical stability and therefore fail with their critical quality attributes (CQA) of the nanosuspension. According to current literature, poorly

soluble drugs with high MW, high T_m values, and with a surface energy comparable to that of a given stabiliser, are able to form stable nanosuspensions. [117] Specific interactions between the functional groups of stabilisers and drug particle surfaces in the stabilisation process have been demonstrated. [118] However, despite of extensive efforts, most formulation scientists still evaluate their suspensions in a trial and error screening of stabilisers, even though some notable guidance has been reported by George et al. [119] The main goal of their study was to correlate the characteristics of the drugs (logP and enthalpy of fusion) with feasibility of forming a stable nanosuspension. According to the data presented, the best candidates were drugs with a high enthalpy of fusion (or T_m so high lattice energy) and high lipophilicity (logP), which can be stabilised either electrostatically or sterically. Thus, a wide range of stabilizing surfactants may result in stable nanosuspensions. On the other hand, drugs with comparatively low enthalpy of fusion (or T_m) and rather low lipophilicity are poor candidates, irrespective of the stabiliser used. High enthalpy of fusion drugs with rather low logP value may require an ionic surfactant as stabiliser. Drugs with lower lattice energies but, which were more lipophilic (high logP), were proposed to be stabilised by an ionic surfactant with rather high HLB value like sodium lauryl sulfate (SLS). This formulation guidance can provide some initial help but more research is needed to rationally design pharmaceutical nanosuspensions. Future research should address mechanisms of stabilisation. Until a more educated approach is available, it seems that the presented considerations of lipophilicity and lattice energy offer at least a starting point for nanosuspension development.

Cyclodextrin formulations

Enzymes belonging to the group cyclodextrin cycloglycosyltransferases (GCRase, EC 2.4.1.19) convert starch into cyclic oligosaccharides, known as cyclodextrins (CDs). These structures are composed of α- (1,4) linked glucopyranose subunits. The α, β, or γCDs, consisting of six, seven, or eight glucose units, respectively, are the most investigated CDs. [120,121] The CD molecule has the shape of a torus due to the chair conformation of the glucopyranose units. Furthermore, the CD molecule has a spatial distribution of polar hydroxyl groups on the outer rim and apolar (relative to water) glucoside oxygens and hydrogens in the cavity. This is why the CD molecule has a hydrophilic outside and a hydrophobic cavity. As a consequence of this structure, CDs have the ability to form inclusion complexes through

molecular encapsulation with a wide range of organic compounds. [120,121] This special characteristic makes CDs valuable in a number of disciplines, including pharmaceutics, where the increased solubility of complexes can be used to increase the apparent solubility of poorly soluble drugs. [122–135]

While natural α- and γCD have good aqueous solubility, natural βCD only has an aqueous solubility of 18.5 g/L, which is believed to be a reflection of the very rigid structure formed through H-bonding of the C2-hydroxyl of one glucopyranose unit with the C-3 hydroxyl of an adjacent unit. [136] In the βCD molecule, a complete set of seven intra-molecular H-bonds can be formed, effectively lowering the thermodynamic driving force for interaction with the solvent. [137] Moreover, CDs can be chemically modified by e.g. hydroxylation, alkylation or sulfoalkylation, thereby breaking this belt of H-bonds around the CD ring, which for βCD increases the solubility significantly. Different chemically modified CDs with improved physical chemical properties have been prepared and commercialised, including, 2-hydroxypropyl β-cyclodextrin (HPβCD), 2-hydroxypropyl γ-cyclodextrin, methyl βCD (mβCD), and sulfobutylether β-cyclodextrin. Due to the low toxicity of the CDs, they can be used for all administration routes (with the exception of parenteral applications of natural βCD). Kurkov and Loftsson recently made a comparative analysis of the more than 30 know CD containing commercial formulations across these administration routes and reported that the most frequently used CD was natural βCD followed by HPβCD. [125] In total, natural and modified βCDs were included in 83.4% of the formulations.

CD inclusion complexes are molecular complexes, which are formed by a reversible complexation that can be described by the following equilibrium;

$$m \cdot D + n \cdot CD \overset{K_{m:n}}{\rightleftharpoons} D_m CD_n \quad (6)$$

where *m* is the number of drug (D) molecules associated with *n* molecules of CDs to form a complex with the stoichiometry of m:n. and $K_{m:n}$ is the stability constant. As the stoichiometry of the complex is often a 1:1 the stability constant can normally be written as;

$$K=\frac{[D-CD]}{[D]\cdot[CD]} \quad (7)$$

The total solubility in presence of a CD is therefore the intrinsic solubility plus the drug fraction complexed with the CD. Across different routes of administration, the compounds included in commercial formulations containing CDs displayed an average MW of 369 ± 130 g/mol. The distribution in MW was not associated with the type of CD used in the formulation, i.e. the lower MW molecules were not predominantly formulated with αCD and the larger compounds with γCD. The logP of the molecules were 3.2 ± 1.8 with a distribution from -0.4 to 7.8, see Figure 15B, with most of the compounds having a log P of 2-4. This places the compounds used with CDs in the mid-range of the logP field, i.e. there is not a trend that this solubilizing approach is used for the real grease balls among drug substances.

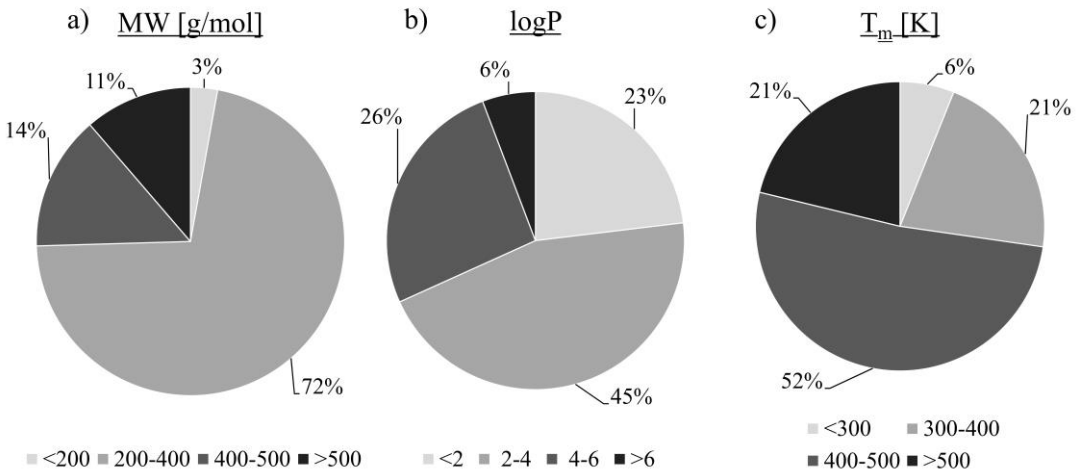

Figure 15 Properties of compounds included in commercial formulations containing cyclodextrins

The compounds formulated with CDs had an average T_m of 436 ± 82 K distributed from 194 K for nicotine to higher than 633 K for mitomycin, with most of the compounds having a T_m in the range of 473 K - 573 K.

When investigating logP as a function of T_m, it is clear that the compounds formulated with CDs tend to have a logP from 2 - 4.5 and a T_m between 473 K and 573 K. Based upon these data, compounds in the mid-range of the spectrum of these limits seem to provide most successful formulations with CDs.

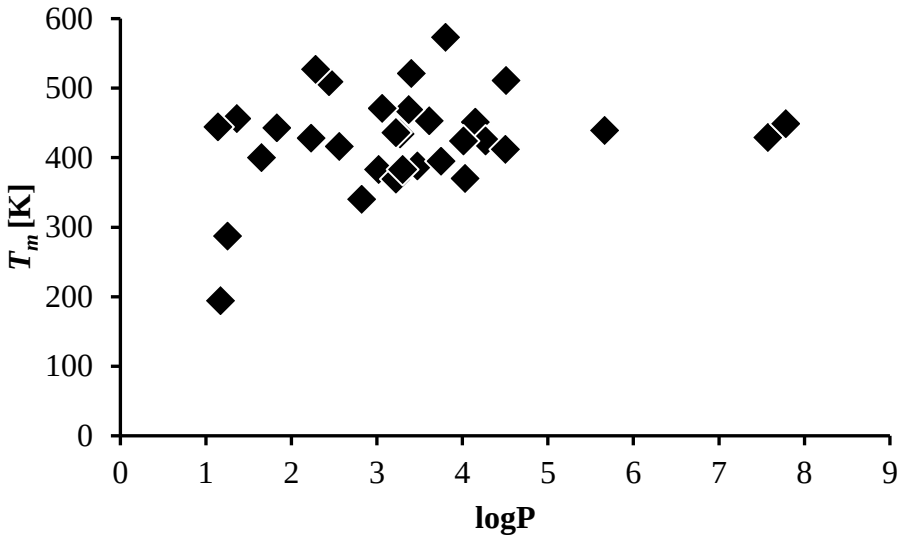

Figure 16 LogP as a function of T_m of compounds included in commercial formulations containing cyclodextrins.

The discriminating power between logP and the T_m revealed some value as a predictor for the useful application of CDs in a formulation. Important for the excipient functionality is the stability constant of inclusion complexation. [125] The observed values for stability constants are usually reported to be between 50 to 2000 M^{-1}. Therefore, an important element is also to define how the molecular usage of the CDs can be optimised, i.e. as high a complexation efficacy as possible. [127] Since the complexation efficacy is defined as a function of the stability constant multiplied with the intrinsic aqueous solubility, different influences on these factors (e.g. ionisation of the drug, addition of co-solvents, addition of polymers etc.) could be used to affect the complexation efficacy. [125] When investigating the Yalkowsky equation presented in the theoretical section (Equation 3), it is clear that both logP and the T_m are part of the equation controlling the aqueous solubility. [12] Consequently, molecules with a relatively low values of logP and T_m would naturally seem to be good candidates to obtain a high complexation efficacy in CDs. However, Chari et al. concluded with a training set of 258 ligands that the most import molecular descriptor to describe the interaction with CDs was primarily logP. [138] Li et al. reported the parameters

of VAMP polarisation YY and VAMP dipole Y component, representing a semi-empirical molecular orbital package in the TSAR software, logP, Balaban topological index, and cosmic electrostatic energy, as the five most important structural parameters influencing the binding constant between drugs and ßCD. [139] Hence, there seems to be a general agreement that logP is a fair descriptor of potential interaction between drug molecules and CDs. Interestingly, T_m has not been mentioned in any of the studies focusing on molecular descriptors. It therefore seems that rather solvation-limited solubility than a high crystal energy of drug candidates would favour the choice of CD formulations. Moreover, geometric molecular fit requirements must be given drugs to achieve successful complexation with CDs.[140]

Conclusions

Since lipophilicity is conventionally understood as a relative scale for given compounds, it should be clearly distinguished from hydrophobicity as a solubility limitation for poorly water-soluble drugs. The properties T_m (or enthalpy of fusion) and logP have to be considered for the selection of a promising bio-enabling oral formulation. It is for example reasonable to assume that very high T_m values can lead to issues of solubility in any solvent-based process and any lipid-based formulation. While this can indeed give a first orientation about the formulation strategy, one should refrain from any absolute statements. Recent developments in lipid-based formulations were discussed that may cope with quite hydrophobic drug bases. Also in the field of solid dispersions and mesoporous silica, a consideration of T_m or T_m/T_g is important to guide initial experiments and to assess the stability of an amorphous state, but such simple approaches have their limits. It seems particularly difficult to obtain clear guidance on the selection of the manufacturing method based on available literature data. Novel approaches like the mesoporous formulations or coprecipitated amorphous formulations are likely to become more important in the future. More work is also expected with respect to molecular modelling that can highlight effects of molecular size and specific interactions for example in cyclodextrin formulations or regarding stability in nanosuspensions. It can be expected that considerations of hydrophobicity and lipophilicity will also be of importance in the future but only for a rough assessment of the formulation

strategy because more refined considerations require additional molecular properties for a rationale and structured development of bio-enabling formulations.

Declarations

Conflict of interest

The authors declare that they have no conflicts of interest to disclose.

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