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EXPERT OPINION

The influence of lipophilicity in drug discovery and design

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Introduction: The role of lipophilicity in drug discovery and design is a critical one. Lipophilicity is a key physicochemical property that plays a crucial role in determining ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties and the overall suitability of drug candidates. There is increasing evidence to suggest that control of physicochemical properties such as lipophilicity, within a defined optimal range, can improve compound quality and the likelihood of therapeutic success.
Areas covered: This review focuses on understanding lipophilicity, techniques used to measure lipophilicity, and summarizes the importance of lipophilicity in drug discovery and development, including a discussion of its impact on individual ADMET parameters as well as its overall influence on the drug discovery and design process, specifically within the past 15 years.
Expert opinion: A current review of the literature reveals a continued reliance on the synthesis of novel structures with increased potency, rather than a focus on maintaining optimal physicochemical properties associated with ADMET throughout drug optimization. Particular attention to the optimum region of lipophilicity, as well as monitoring of lipophilic efficiency indices, may contribute significantly to the overall quality of candidate drugs at different stages of discovery.

Keywords: ADMET properties, compound quality, lipophilicity, physicochemical properties

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1. Introduction

Drug discovery and design consists of identification and characterization of new targets, synthesis of new lead molecules, screening of new lead molecules for *in vitro* and/or *in vivo* biological activities, and physicochemical characterization of leads. On average, every new drug molecule requires 12 – 15 years to reach the patient and costs a staggering amount of US$ > 800 million [1]. Further, roughly 10% of those compounds that are selected for further clinical study make it to the marketplace as effective drugs, demonstrating that the overall drug development process is far from ideal [2].

To be successful, drug development requires not only optimization of specific and potent recognition by its pharmacodynamic targets, but also efficient delivery to these target sites. To elicit an *in vivo* response, a drug must reach the biophase, crossing several biomembranes by passive and/or transporter-mediated uptake. Biopharmaceutical properties such as solubility, stability, permeability, and first-pass effect, as well as pharmacokinetic properties (clearance rate, biological half-life, extent of protein binding, and volume of distribution) are responsible for the entry of a drug into the body and across various cellular barriers. Recent advances in combinatorial chemistry, molecular modeling, and high-throughput screening have shifted the bottleneck of drug discovery to potency optimization rather than hit and lead discovery [3]. However, lead discovery is still one of the most challenging activities since this includes multiparameter optimization which has a major impact on the fate of the discovery program. This is due to the fact that

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Article highlights.

- Lipophilicity is a key physicochemical property that contributes to the ADMET characteristics of drugs, thus impacting their metabolism and pharmacokinetics as well as their pharmacodynamic and toxicological profile.
- Given its evidenced role as a predictor of eventual compound success, an understanding of lipophilicity and its modulation are essential for the practicing medicinal chemist and for drug discovery and design.
- A review of the literature demonstrates that compounds that display a log P or D between 1 and 3 appear to be optimal for achieving appropriate physiochemical characteristics.
- A comparison of marketed oral drugs with compounds in earlier stages of development shows that high lipophilicity (> 5) frequently leads to compounds with rapid metabolic turnover, low solubility, and poor absorption.
- If lipophilicity is too low, a drug will generally display poor ADMET properties.
- Accurate measurement of log P, attention to the optimum region of lipophilicity and monitoring of lipophilic efficiency indices like LLE and LELP may contribute significantly to the overall quality of candidate drugs at different stages of drug discovery.

This box summarizes key points contained in the article.

the starting points of lead optimization usually determine what is delivered at the end.

It is well-recognized that drugs can be designed for more effective delivery if physicochemical principles are given careful consideration and applied in a constructive fashion during development. Lipinski's rule of 5 (**Figure 1**), for example, describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion (ADME) and states that, in general, an orally active drug has no more than two violations of the following criteria: Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms); not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms); a molecular mass less than 500 daltons (Da); and an octanol–water partition coefficient log P not greater than 5 [4]. Physicochemical properties beyond those consistent with the rule of 5 have also been shown to be important for drug absorption, including the number of rotatable bonds (RBs) in a molecule [5]. According to Veber, compounds with lower molecular flexibility, as measured by the number of rotatable bonds, tend to have better oral bioavailability [5]. In humans, 13 rotatable bonds have been identified as an upper limit to predict ≥ 20% oral bioavailability based on an analysis of 1,014 marketed drugs [6].

Among the aforementioned physicochemical properties, lipophilicity has long been recognized as an important factor for a drug's successful passage through clinical development and on to the marketplace. Lipophilicity refers to the ability of a compound to dissolve in fats, oils, lipids, and nonpolar solvents such as hexane or toluene. Thus, *in vivo*, it reflects the key event of molecular desolvation in transfer from aqueous phases to cell membranes and to protein binding sites, which are mostly hydrophobic in nature. Although the term hydrophobicity is often used interchangeably with lipophilicity and both can be used to describe the same tendency toward participation in the London dispersion force, these terms are not one in the same—silicones and fluorocarbons, for example, are hydrophobic but not lipophilic. In drug discovery, a calculated log P (clog P) is routinely used as an assessment of lipophilicity with measured partition coefficients obtained on key compounds through a project's progression. Recent analyses reporting mean values of lipophilicity between older (pre-1983) and newer (1983 – 2002) marketed oral drugs have demonstrated little variance in these values over the past decade compared to compounds entering the development pipeline in recent years for which there is a noted trend in increasing lipophilicity values [7]. Given the value and influence of lipophilicity on the drug discovery and design process and its evidenced role as a predictor of eventual compound success, an understanding of lipophilicity and how to modulate it are essential for the practicing medicinal chemist and for the development of a successful therapeutic compound.

This review will focus on understanding lipophilicity, techniques used to measure lipophilicity, its impact on individual ADMET (absorption, distribution, metabolism, excretion, and toxicity) parameters and discuss its overall influence on the drug discovery and design process, specifically in the last 15 years.

2. Lipophilicity: an important parameter in drug discovery and design

Lipophilicity is an important parameter in drug discovery and design [8], because it constitutes the single most informative and successful physicochemical property in medicinal chemistry [9]. Lipophilicity contributes to the ADMET characteristics of drugs, contributing to their solubility and permeability through membranes [3,10]; potency [11], selectivity, and promiscuity [8]; impacting their metabolism and pharmacokinetics [12]; and also affecting their pharmacodynamic and toxicological profile [13]. A common finding when comparing marketed oral drugs with compounds in earlier stages of development is that high lipophilicity (> 5) frequently leads to compounds with rapid metabolic turnover [14], low solubility, and poor absorption [4]. If lipophilicity is too high, there is an increased likelihood of *in vitro* receptor promiscuity [8-11,15-17] and *in vivo* toxicity [13,18,19], as well as poor solubility and metabolic clearance. If lipophilicity is too low, a drug will generally display poor ADMET properties.

Although the average lipophilicity value has changed little for oral drugs approved since 1983 (2.6), there is a noted

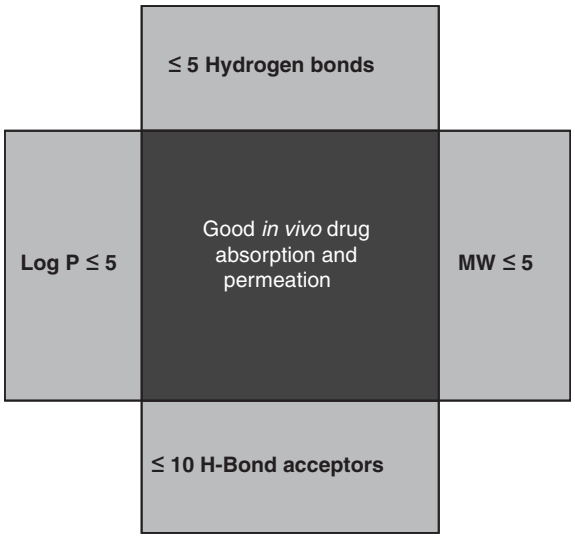

Figure 1. Lipinski's "Rule of 5".

trend that lipophilicity increases as candidate molecules progress through Phase I, II, and III medicinal programs. This undesired shift in log P is noted as a major factor for the well documented inflation of physicochemical properties of drugs [8,20] and is evident in recent medicinal chemistry practice as demonstrated by Walters *et al.* [21]. According to Lipinski, a limit of log P < 5 is a desirable lipophilicity range for compounds reaching Phase II clinical trials [4]; however, Gleeson has suggested that compounds with log P < 4 (and a molecular weight < 400) stand a much higher chance of success against a comprehensive set of ADMET parameters [12]. A recent review of the literature indeed suggests that the optimum region of lipophilicity lies within a narrow range of log D between ~ 1 and 3 [22].

Lipophilic efficiency indices provide a straightforward and meaningful way to control lipophilicity. Leeson and Springthorpe introduced lipophilic ligand efficiency (LLE) or LiPE as a parameter to evaluate the quality of research compounds, linking potency and lipophilicity in an attempt to estimate drug-likeness. Defined as the difference of log P (or log D) and the negative logarithm of a potency measures (pK_d, pK_i, or PXC_{50}), LLE describes the contribution of lipophilicity to potency and can be used in conjunction with log P, log D, or clog D. For a 1 nM inhibitor with a log P = 3, the LLE = 6, while for a 10 nM inhibitor with a log P = 3, LLE = 5, and the optimal target range for LLE is generally considered to be between 5 and 7 [23]. The application of LE and LLE in drug optimization is highlighted by several recent examples, including the design of a potent cyclin-dependent kinase 2 (CDK2) inhibitor [24,25], protein kinase B inhibitor [26], soluble epoxide hydrolase inhibitors [27], CB_2 agonists [28], CB_2 agonists/CB_1 agonists [29], ATP-competitive Akt inhibitors [30], dual PI3K/mTOR inhibitors [31], and HIV non-nucleoside reverse transcriptase inhibitors [32] (for a review see [23]).

The concept of lipophilicity-corrected ligand efficiency (LELP) [33], defined as the ratio of log P and ligand efficiency (LE), is an efficacy index used for log P values typical in many discovery programs and allows both fragments and lead-like and drug-like compounds to be evaluated [33]. Tarcsay *et al.* recently evaluated the performance of LLE and LELP on multiple data sets representing different stages of drug discovery, including fragment and HTS hits and leads, development candidates, Phase II compounds, and launched drugs [34]. In analyzing the impact of LLE and LELP on ADME and safety properties as well as binding thermodynamics, they determined that both indices help to identify compounds of better quality; however, they noted that each metric has distinct characteristics: LLE does not prefer fragment-type hits that might be considered promising for lead discovery and thus would be more applicable in the later development stages; while, LELP incorporates molecular size and penalizes the increase in log P more than in LLE and therefore would be more practical for ADME- and safety-related issues over LLE. Their study findings suggest that monitoring lipophilic efficiency metrics like LLE and LELP could help to control physiochemical parameters, especially log P or log D, while maintaining compound potency throughout optimization, improving compound quality [34].

3. Measuring lipophilicity

Lipophilicity is determined experimentally as partition coefficients (log P) or as distribution coefficients (log D). Log P is a molecular parameter which describes the partition equilibrium of an un-ionized solute between water and an immiscible organic solvent, while log D is the ratio of the sum of the concentrations of all forms of the compound (pH-dependent mixture of ionized plus un-ionized forms) in each of the two phases; thus, lipophilicity reflects the net result of all intermolecular forces involving a solute and the two phases between which it partitions [9]. Larger log P values correspond to greater lipophilicity. The accurate and efficient measurement of lipophilicity is an important requirement in drug design; however, in practice, the calculated value (clog P) is often used instead of the measured log P. clog P values used for screening virtual libraries are often inaccurate and based on methods that predict the measured log D/log P values with a reasonable degree of error which is often systematic [22], particularly if they refer to ionized or partially ionized molecules which interact differently with non-polar lipophilic species and with aqueous environments than neutral molecule. Indeed, Mannhold *et al.* recently analyzed the prediction error of log P calculations on a large independent Pfizer data set, and their analysis demonstrated low prediction accuracy for most of existing log P calculation methods [35]. In this review, when referring to log D (pH 7.4 unless otherwise noted) and log P data from the literature, we will discuss these

values in generic terms regardless of the method of calculation or measurement used.

Two well-described experimental techniques for lipophilicity measurement in isotropic solvent/water systems are the shake-flask method [36] and potentiometric titration [37,38]. The shake-flask method consists of dissolving the sample compound in a mixture of mutually presaturated buffered water and octanol, agitation until equilibrium has been reached, careful separation of octanol and aqueous phases, and measurement of the solute in each solvent by UV/VIS spectroscopy [39]. In potentiometric titration, log P is characterized by comparing an aqueous pKa to an apparent pKa measured in the two-phase system (water–octanol) using a difference curve analysis. Both of these methods yield a good measure of a compound's lipophilicity, but are not without their disadvantages—the former being unsuitable for degradable compounds and less amenable to automation, the latter being limited to ionizable compounds and requiring ionization centers, and both being more labor-intensive compared with some other methodologies (reviewed in [39]).

Because early, pharmaceutical discovery settings emphasize high-throughput measurements, low compound consumption, and method versatility to accommodate diverse compounds, alternative approaches to lipophilicity determination aimed at providing a more rapid and user-friendly approach have been developed in recent years. These include attempts to automate the traditional shake-flask method to a 96-well format and [40], chromatographic methods such as reversed-phase (RP)-HPLC, electrophoretic methods such as microemulsion electrokinetic chromatography (MEEKC), and immobilized artificial membrane (IAM) HPLC-columns (for a review see [3,41,42]). Among the chromatographic methods, RP-HPLC has been at the forefront of lipophilicity determination and is the method of choice for many laboratories. This is attributed to advances in understanding solute interactions in liquid–liquid systems in a non-equilibrium environment and the availability of robust, well-characterized stationary phases and columns and the automation of modern HPLC systems [43]. The chromatographic hydrophobicity index (CHI) developed by Valko *et al.* can be used as an independent measure of hydrophobicity [44] and offers a simple way to evaluate the log P of a drug [45]. In fact, the need to correct chromatographic measurements with the hydrogen bond acidity to get reliable log P values has been demonstrated recently [42,46]. This is a remarkable feature since pure chromatographic methods only offer good estimations of log P for compounds without significant hydrogen bond acidity. Young and colleagues have also demonstrated the value of chromatographic measurements (Chrom log$D_{pH7.4}$), versus other hydrophobicity estimates, in their analysis of 100,000 GlaxoSmithKline compounds [47]. Chrom logDpH7.4 is an estimate of hydrophobicity derived from reverse phase (C-18) HPLC measurements, which has been shown to be more reliable and relevant than traditional octanol–water measurements and predictions [47,48].

Accurately measured data early in the drug discovery process and monitoring of lipophilic efficiency metrics may lead to better control of lipophilicity in the design of future drugs. Mannhold *et al.* suggest that in order to accurately predict log P for a given chemical series, log P should be experimentally evaluated for a representative set of compounds. This suggestion stems from their recent analysis demonstrating the failure of a number of software programs to accurately predict log P for proprietary compounds. The large differences in method accuracy for the analyzed public data set versus in house data sets from Pfizer and Nycomed indicate that these methods have been trained primarily on small organic molecules rather than on drug-like and lead-like compounds that are pursued by the pharmaceutical industry in the drug discovery process. Additionally, using predictive methods to calculate lipophilicity that produce inaccurate results can misinform the drug development process, causing potentially promising compounds to be discarded and/or potentially flawed compounds to move forward. The use of confidence in log P prediction would allow higher resolution and discrimination with regard to selection of reliable and non-reliable predictions, thus increasing design efficiency [35].

4. Absorption

4.1 Solubility

Solubility is critical for absorption and subsequent bioavailability of a drug *in vivo* and is a critical component in lead generation and optimization. Solubility is dependent on lipophilicity (log P). General solubility of a compound can be described as a function of its log P and melting point (MP), where the melting point describes the lattice energy that is lost on dissolution. The general solubility equation is described in **Figure 2** [49,50]. The effect of lipophilicity on solubility is depicted in **Table 1**, which illustrates the relationship between log P and MP and what is considered poor, intermediate, and good solubility [23,51]. Ionization class of a compound also affects solubility with zwitterionic being highly soluble, followed by acidic molecules followed by neutral molecules being the least soluble [12]. However since solubility of ionizable compounds increases exponentially with changes in pH and pKa, the former difference in solubility is more a consequence of ionization [52,53]. In a study by Gleeson, it was found that reducing log P to < 3 brings neutral molecules into the solubility range of ionizable molecules, however this effect from increasing lipophilicity appears to increase solubility more for neutral and basic molecules compared to acids and zwitterions [12]. Thus in general, a reduction in log P should be considered to increase compound solubility [52].

4.2 Permeability

In general, membrane permeability is a major determinant of pharmacokinetic behavior specifically for absorption, distribution, and excretion of drugs [3]. A relationship between

$$\log S = -\log P - 0.01(mp-25) + 5$$

Figure 2. The General Solubility Equation.

Table 1. Solubility calculated based on the general solubility equation (log *P* vs. MP).

log *P*	0	1	2	3	4	5
MP (C°)						
50	0.25	-0.75	-1.75	-2.75	-3.75	-4.75
100	-0.25	-1.25	-2.25	-3.25	-4.25	-5.25
150	-0.75	-1.75	-2.75	-3.75	-4.75	-5.75
200	-1.25	-2.25	-3.25	-4.25	-5.25	-6.25
250	-1.75	-2.75	-3.75	-4.75	-5.75	-6.75
300	-2.25	-3.25	-4.25	-5.25	-6.25	-7.25

Solubility key: Good | Intermediate | Poor

permeability and lipophilicity has been established in numerous drug permeation studies using diverse types of compounds with various biological membranes. These studies have demonstrated that there exists a linear [54], bilinear [54,55], sigmoidal [56-59], parabolic [60], and hyperbolic [61-64] relationships between permeability and lipophilicity, however when taken together this implies that lower permeability correlates with lower lipophilicity [3,22]. In a study using the AstraZeneca Caco-2 model system of absorption, data from 9,571 structurally diverse compounds demonstrated that Caco-2 permeability was diminished in compounds with characteristics like low log D, high MW, and high polar surface area (PSA) [10]. Further analysis of this data revealed that log D and MW were the most critical factors for membrane permeability, with high permeability (> 50% probability of P_{app} of < 100 nm/s) requiring a log D value of > 1.7 for compounds of MW 350 – 400, > 3.1 for MW 400 – 450, > 3.4 for MW 450 – 500, and > 4.5 for MW > 500 [10]. In general, as log D rises, the *in vitro* permeability increases and as molecular mass (size) decreases within a log D bin, the permeability increases. Computational models to calculate absorption have also been developed that use lipophilicity measures in combination with other factors like, PSA (a surrogate for size), to predict absorption and permeability. In these models, compounds with good absorption display a log P with a range of -1 to 5.9 and an optimal PSA of < 132 $Å^2$ [65]. Taken together, the general trend is that an increase in lipophilicity and a decrease in size (PSA and MW) generally encourage permeation of a compound through a membrane.

4.3 Bioavailability

Bioavailability is a composite parameter that is composed of solubility, permeability, and clearance (discussed in Section 6) [12] and since each of these parameters is dependent on lipophilicity, a role (direct or indirect) for lipophilicity is expected. However, a clear and direct role for the effect of lipophilicity on bioavailability is less specific in the literature and it is important to note that most of the studies, including ones mentioned below, measure oral bioavailability. In one retrospective analysis of human bioavailability data [66], compounds found in the log D range of -2 to 3 were found to display increased bioavailability, and in a recent study by Gleeson, the average bioavailability displayed no significant change for compounds with log P < 3 when compared to compounds with log P > 3, independent of ionization type [12]. These studies appear to be in agreement with the general rule of thumb that the optimal range of lipophilicity for achieving good bioavailability is a log P between 0 and 3 [52], which is consistent with the range of lipophilicity where one can achieve a good balance between solubility and permeability [67]. However it is important to note that since bioavailability is a composite parameter, when considering two of the components of this parameter like solubility and permeability, the use of log D (optimally between 1 and 3) is likely more relevant [68]. However there have been studies that have failed to show a direct correlation between log P and bioavailability [69] and these studies suggest that other parameters like PSA, rotatable bonds, and ionization state are better predictors of bioavailability [5,12,69]. This is likely due to the effects of these parameters on other ADMET properties like permeability, again highlighting the complex nature of bioavailability as a composite parameter. In one oral bioavailability study in rats assessing 1100 GSK drug candidates, only two criteria including 10 or fewer rotatable bonds and PSA were suggested to affect bioavailability and that reduced PSA correlated better with increased permeation than lipophilicity [5,12,69].

Oral bioavailability is the product of adsorption and metabolism/clearance. In a study that measured drug absorption compared with first-pass elimination (FPE), lipophilicity showed distinct but opposing trends for the fraction absorbed (Fa) and the fraction cleared during FPE (FPE in this study accounted for the total from gut-wall and hepatic elimination) resulting in a parabolic relationship. In this study, FPE declined as lipophilicity increased, except for compounds with a log D > 5 showing increased gut-wall and hepatic clearance [70]. However in this study, other physiochemical parameters also influenced oral bioavailability.

5. Distribution

5.1 Plasma protein binding

Lipophilicity is important for determining the distribution of a drug *in vivo*. The volume of distribution, also known as apparent volume of distribution, is a measure used to quantify

Table 2. Summary of relationship between ADMET parameter and log *P* and log *D*. This table summarizes the reported optimal log *P* and log *D* values in relation to ADMET parameter.

ADMET Parameter	Log *P*	Log *D*	Notes	Ref.
Solubility	< 3	–	Ionization-dependent	[11]
Permeability	–	Low better	MW-dependent	[9]
	-1 to 5.9	–	PSA-dependent	[55]
Bioavailability	–	-2 to 3		[56]
	0 to 3	–		[42]
	–	1 to 3		[58]
	< 3	–	Ionization-dependent	[11]
Distribution	↑ better	–	Ionization-dependent	[11]
CNS Penetration	↑ better	–	MW-dependent	[11,71]
	> 2	–		[72]
	–	1 to 3		[42]
	Mean 2.8	Mean 1.7		[27]
↑ Clearance	3 to 5		Ionization-dependent	[11]
↑ Renal Clearance	–	↓ better		[74,75]
↓ Clearance	–	< 3	MW-dependent	[76]
	↓ better	–		[61]
Toxicity	> 3	–	PSA-dependent	[12]
Promiscuity	> 3	–	PSA-dependent	[7]
	> 2	–		[16]
hERG inhibition	–	↑ less	Ionization-dependent	[78]
CYP inhibition	↓ less	–	Ionization/MW-dependent	[11,27]
DIPL	–	–	Sum log P2 and pKa > 90	[20,83]

↑: Increasing; ↓: Decreasing value.

the distribution of a drug between plasma and the rest of the body after oral or parenteral dosing and clearance. Thus when considering the volume of distribution of a drug, it is important to understand the ability of the drug to bind specifically or non-specifically to various proteins or tissues, because only free drug is available for distribution throughout the body. Based on this understanding, the ability of a drug to bind to plasma proteins, specifically serum albumin and alpha-acid glycoprotein, affects the measurement of the volume of distribution [22,71]. Plasma protein binding typically shows a sigmoidal relationship with lipophilicity [72]; however, further analysis of these original data by Obah *et al.* revealed that the trend is linear when graphed as a log of the affinity constant [K] [73]. In a study by Valko *et al.*, log P and log k were found to predict drug binding to serum albumin, with similar affinity for neutral and ionized molecules with acids displaying the greatest affinity [74]. Log D was also determined to be a factor that affects non-specific binding in human tissue [75,76]. Additionally, a study by Gleeson determined that increasing log P leads to an increase in the volume of distribution of either a neutral or basic compound in the body [12]. Increasing lipophilicity typically yields increased protein binding because hydrophobic forces drive interactions with plasma proteins. Acidic compounds have higher protein binding relative to bases and neutrals due to an ion-pair interaction with a basic residue within serum albumin [77]. Basic compounds tend to show high affinity for alpha-acid glycoprotein due to an electrostatic interaction with acidic residues [78].

5.2 CNS penetration

Distribution (penetration) of drugs into the central nervous system (CNS) represents a special case scenario due to the fact that the CNS sits behind the blood–brain barrier (BBB). The BBB is composed of brain capillary endothelial cells with vessel walls interconnected with tight junctions and that contain efflux pumps, such as p-glycoprotein (P-gp) that function to keep non-essential molecules out of the brain and thus have limited permeability [3,79]. In general, passive permeation of small, highly lipophilic compounds can occur across membranes of cells that make up the BBB and increasing lipophilicity is likely to enhance BBB permeation. Thus, over the years, consideration of lipophilicity has been relied on heavily in drug design for targeting the CNS; however, in addition to passive transport mechanisms, active influx or efflux mechanisms also influence movement of molecules across the BBB (for a review see [80]), and high lipophilicity can lead to higher binding affinity for certain efflux transporters [79-81]. For example, a relationship between lipophilicity and P-gp efflux ratio in relation to ionization state has been explored [82,83]. These studies show that neutral molecules display a nonlinear relationship with log P and that basic molecules display a linear relationship with increasing log P; however, reliable trends were not established for acidic or zwitterionic molecules due to low sample number. More recently, a study used CNS drugs and tested them in a mouse model where genes that encode the P-gp efflux pumps have been knocked out. This study demonstrated that out of 34 CNS drugs, only 7 showed no evidence of efflux using

brain-to-plasma AUC values in these mice compared to wild-type (WT) mice, 14 showed modest efflux and 3 showed pronounced efflux [73]. These studies demonstrate that active efflux in the CNS via P-gp pumps in this drug set may be modest at best; however, larger drug sets should be tested using this system and since other transporters have also been found in the BBB, the contributions of these mechanisms must also be examined moving forward.

As we have discussed, increasing log P typically leads to an increase in the volume of distribution, and in the case of the CNS, as the log P of a molecule increases, the CNS penetration, on average, increases [12,84,85]. Studies have shown that CNS penetration is also dependent on MW [12,86]. As a molecule gets bigger, it ability to permeate the CNS decreases. However, a study analyzing the effects of log P on the mean log BB (blood–brain permeation) show that the two parameters are independent, thus suggesting that size and lipophilicity have an independent effect on CNS penetration [12]. A recent study of 50 marketed CNS drugs demonstrated that 75% of these drug have a log P of > 2 and that rat brain permeability is related to log P in a non-linear fashion with a plateau of log P values at 2 and 3 [87]. In a separate study, it was also demonstrated that for compounds to cross the BBB they should have a log D between 1 and 3 [52]. Consistent with this, a more recent analysis of 119 marketed, oral CNS drugs found that the optimal physicochemical properties with respect to lipophilicity were a log P of 2.8 and a log D of 1.7 [23].

However, reliance on strict cutoff values for any drug-like attribute, including lipophilicity, when designing and testing CNS drugs may be problematic. A recent study that examined physiochemical drug properties associated with *in vivo* tolerance found that 44% of CNS drugs in this set had a log P ≥ 3 and yet these drugs overcame attrition risks and were marketed [13]. Thus if a log P of > 3 were used as a strict cutoff, drug design of appropriate CNS drugs may be significantly restricted [88]. To address this concern, a CNS multiparameter optimization approach has been developed by Wager *et al.* that considers six physiochemical parameters including lipophilicity, distribution coefficient, molecular weight, TPSA, hydrogen bond number, and most basic center (pKa). This more holistic approach may prove to better predict the drug likeness of future CNS drugs. Nevertheless, this approach is biased to controlling lipophilicity since it is a key element in regulating many of the parameters used in this tool.

6. Metabolism and clearance

Metabolism and subsequent *in vivo* clearance of drugs involve a myriad of enzymes and tissues including the hepatic, renal and biliary systems and is considered the most difficult ADMET parameter to predict. A study by Gleeson (2008) describes the contribution of molecular weight, ionization state, and log P on *in vivo* clearance. In this study using 11,490 GlaxoSmithKline compounds a weak, non-linear but statistically significant, correlation between log P and *in vivo* clearance existed [12]. Most notable are differences in log clearance between ionization states at log P > 5, and less pronounced at log P 3–5 and log P < 3. The contribution of molecular weight was analyzed independent of ionization state and log P here. One conclusion from this study was that given the complexity of the metabolism/clearance parameter, an emphasis on structural considerations rather than, physicochemical properties like lipophilicity, is needed when considering *in vivo* clearance [12]. Still several studies have attempted to determine optimal lipophilicity to predict this parameter and in general, a reduction of lipophilicity is often considered valid for achieving reduced metabolic clearance [14,52,89]. This strategy is consistent with the scenario *in vivo* where in general, metabolism converts lipophilitic drugs into more polar metabolites to facilitate biliary or renal clearance and indeed in several studies, it has been shown that a reduction in log D correlates with improved renal clearance [90,91]. A large study that used *in vitro* permeability data from 16,227 compounds and *in vitro* clearance data from 47,018 compounds to assess the effects of lipophilicity (log D) and MW on absorption and clearance found that generally speaking, as lipophilicity and molecular weight decreases, the *in vitro* clearance prediction improves [92]. In this study, compounds within a log D range of 1.0–3.0 had a higher opportunity to be metabolically stable and that, while the log D range optimal for low clearance was dependent on MW, a log D < 3 was generally desirable in all MW categories. Additionally, similar results have been seen in an analysis on *in vivo* clearance rates on intravenously administered drugs, where lower average clearance values were also seen with low log P values [73].

7. Toxicity and promiscuity

Numerous studies examining physicochemical properties of compounds have found that *in vivo* toxicity and *in vitro* promiscuity are both correlated to lipophilicity [13,18,19,22,23] and are more likely to occur when log P is > 3. A Pfizer study of 245 preclinical candidates that considered the effect of log P and PSA demonstrated that log P > 3 was 2.5 times more likely to be toxic and drugs with a log P < 3 were 2.5 times more likely to be less toxic [13]. Effects of log P and PSA on biochemical promiscuity were also evaluated in a study analyzing CEREP BioPrint profiling data from 108 compounds. In this study, promiscuity increased for log P > 3 [8], with compounds with a high log P and low PSA being 25-fold less specific than those with a low log P and high PSA [13]. Similar results were also obtained in a separate study analyzing BioPrint data from 213 Roche compounds [17], where in this case promiscuity increased in compounds displaying a log P > 2.

Three specific examples of drug-induced toxicity that correlate to lipophilicity include inactivation of the human ether-à-go-go-related (hERG) cardiac potassium channel, drug-induced cellular phospholipidosis (DIPL), and cytochrome 450 superfamily (CYP) inhibition. The hERG cardiac

potassium channel can bind numerous compounds with high promiscuity and potency that can result in its inactivation [93,94]. Increases in drug lipophilicity have been associated with increased promiscuity for hERG binding and inactivation [94]. Binding to hERG can be quantified as a direct function of lipophilicity and is dependent on ionization class [23]. As summarized by Waring *et al.* in a study of 7,685 AstraZeneca compounds, for neutral and basic compounds, hERG potencies for achieving an IC_{50} > 10 μM diminish as log D increases with basic compounds exhibiting the highest propensity to inhibit hERG [94]. The upper limit of log D to predict that > 70% of compounds achieve a hERG IC_{50} > 10 μM were > 4 (log P > 9) for acids, 1.9 for bases (log P = 1.4), 4.0 for neutrals (log P > 3.3), and 4.4 for zwitterions (log P > 2.3) [22]. Meaning that lipophilic basic molecules demonstrate the lowest probability to achieve a hERG IC_{50} of > 10 μM with lipophilitic acids, neutral compounds and zwitterions having a wider acceptable range of log P and log D and being considerably less problematic in this type of drug-induced toxicity [22,95].

DIPL (drug-induced phospholipidosis) describes the excess accumulation of phospholipids in cells *in vivo* that can occur as the result of treatment with many cationic amphiphilic drugs, including antidepressants, anti-anginal, antimalarial, and cholesterol-lowering agents [96-98]. It is important to note that although no study has ever demonstrated a clear correlation between phospholipidosis and the manifestation of toxicity, its impact on the drug development process can be severe and requires serious consideration [23]. *In vivo* DIPL is strongly correlated with lipophilicity, especially for basic compounds. In a study by Ploemen *et al.*, analyzing physicochemical properties of known DIPL inducing drugs, it was demonstrated that the risk of a compound causing DIPL increases if the sum of log P^2 and pK_a^2 is > 90 [22,99]. This observation has been subsequently refined [100] and other models have also been developed [101,102] (for review see [23]) to create computational methods to use physicochemical attributes to predict DIPL. In all cases, lipophilicity remains an important consideration and a component in these computational methods.

The CYP (cytochrome p450) family of enzymes comprise a large and diverse group that primarily function in drug metabolism and account for about 75% of the total number of different metabolic reactions *in vivo* [103]. CYP enzymes convert lipophilic and non-lipophilitic substrates into more polar compounds to assist with their *in vivo* clearance. CYP enzymes are generally considered lipophilic and they have an inherent affinity for lipophilic substrates [52,89,104,105]. Lipophilitic compounds can also inhibit different members of the CYP family of enzymes dependent on their ionization state [12]. A study by Gleeson analyzing the effect of lipophilicity on CYP inhibition (isoforms: 1A2, 2C9, 2C19, 2D6 and 3A4 which make up roughly 60% of hepatic CYPs), found that average IC_{50} values are lower for compounds with log P of < 3 than for those > 3 with the upper limit log P of < 4 [12,23]. In this study, ionization state and MW were also important, but log P and MW were the most significant predictors.

8. Emerging trends

In an effort to capture emerging trends in drug design, several recent studies have analyzed the physicochemical properties of marketed drugs and compared them with drugs in discovery and development. A common trend which has emerged is that there is too heavy a focus in drug discovery on advancing candidate molecules with increased molecular weight (MW) and higher overall lipophilicity [23]. In a study published by Leeson and Springthorpe in 2007, the physicochemical profiles of 592 oral drugs and compounds in development with active compounds from Merck, AstraZeneca, Pfizer, and GlaxoSmithKline (GSK) disclosed in the patent literature between 2001 and 2007 were compared. The authors noted that there was an increase of both the median clog P and MW with time among the 592 approved drugs, and compounds in the patent literature had a median MW of 450 Da and clog P of 4.1; however, the number of drugs approved per year globally decreased between 1983 and 2006 as did the proportion of drugs with a MW of less than 350 Da [8]. Leeson notes that these changes are concerning, as the mean molecular mass of compounds decline as they progress through Phase I, II, and III and more lipophilic compounds tend to be discontinued at each phase ([8,106]. Similarly, in a study by Gleeson that analyzed ADMET and physicochemical data from a diverse set of GSK compounds, ionization state, clog *P*, and MW were reported to be the most useful predictors of potential ADMET problems, with MW and clog *P* identified as the key drivers. Thus, he concluded that molecules with a MW of < 400 and clog *P* of < 4 were more likely to satisfy *in vitro* and *in vivo* ADMET profiling criteria [12].

What are the factors driving the increase in physical properties of recently discovered oral drugs? According to several recent articles, it may relate to a larger number of "less druggable" new targets with the most lipophilic (or largest) ligands that require compounds with increased lipophilicity for high affinity binding to active sites [20,21]. However, compounds that achieve their potency through lipophilic interactions are likely to be less selective and more promiscuous, running the risk of off-target interactions and unwanted toxicity [8,13]. Gleeson *et al.* recently scrutinized the common assumption that compounds with higher *in vitro* potency at their target(s) have greater potential to translate into successful, low-dose therapeutics. Using the ChEMBL database which includes more than 500,000 drug discovery and marketed oral drug compounds, Gleeson and colleagues analyzed a data set of 201,355 compounds for links between *in vitro* potency, ADMET, and physicochemical parameters [11]. Gleeson reported several important findings: first, that oral drugs seldom possess nanomolar potency (50 nM on average); second, that many oral drugs have considerable off-target activity; and third, that *in vitro*

potency does not correlate strongly with the therapeutic dose. These findings suggest that the perceived benefit of high *in vitro* potency may be negated by poorer ADMET properties [11]. Indeed, the idea that greater *in vitro* potency will lead to a more effective therapeutic is embedded in early drug discovery schemes, and according to a recent analysis by Leeson and St-Gallay, many pharmaceutical companies have not altered their drug design practices to reflect optimal physicochemical profiles [20].

9. Summary

There is increasing evidence to suggest that control of physicochemical properties such as lipophilicity, within a defined optimal range, can improve compound quality and the likelihood of therapeutic success. A review of the current literature suggests that lipophilicity is an important consideration for maintenance of candidate compounds within desired ADMET parameters and has specific effects on several important physiochemical properties (see **Table 2**) necessary to achieve desired *in vivo* pharmacokinetics. Thus, particular attention to the optimum region of lipophilicity as well as monitoring of lipophilic efficiency indices may contribute significantly to the overall quality of candidate drugs at different stages of discovery. Further, these data suggest that other physiochemical parameters are also critical and necessary in combination with lipophilicity to achieve desired compound characteristics. Therefore, no one parameter can be solely relied upon; drug design requires optimization among a constellation of parameters to insure success and must be tailored to individual targets.

10. Expert opinion

Indeed, lipophilicity has long been considered a vital component of drug discovery and development and is a crucial physicochemical parameter that strongly influences drug absorption, distribution, metabolism, excretion, and toxicity (ADMET). A review of the literature demonstrates that compounds that display a log P or D between 1 and 3 appear to be optimal for achieving appropriate physiochemical characteristics to ensure downstream drug success. However, there are clearly successful drugs that do not fall within this lipophilic range, and additionally, since this range is a composite based on various methodologies that either predict or calculate lipophilicity with their own error, caution should be exercised when using these general rules of thumb.

Gaining a better understanding of the key technologies used to measure lipophilicity in order to generate more reliable lipophilicity data to inform the drug discovery process has been a major challenge over the past several years. Numerous predictive methods have been developed, yet these methods often introduce substantial variation in their own right [35]. This is further complicated by the fact that the accuracy of the techniques employed to measure lipophilicity and validate these predictive models, including octanol/water partitioning or distribution, have also been questioned recently. Thus, the widespread belief that calculation of a molecule's lipophilicity is straightforward and further, can accurately predict the success of a compound as it progresses through the discovery program is incorrect; rather, it can misinform the drug development process, causing potentially promising compounds to be discarded and/or potentially flawed compounds to move forward. As suggested by Mannhold *et al.*, the use of confidence in log P prediction would allow higher resolution and discrimination with regard to selection of reliable and non-reliable predictions, thus increasing design efficiency [35].

The average lipophilicity value has changed little for approved oral drugs in the last 30 years; however, a shift toward increased lipophilicity and an increase in mean molecular mass has been seen recently in drug candidates resulting in inflation of physicochemical properties of drugs [8,20]. This may be due to the fact that much attention recently has been focused on screening for specific characteristics, like potency, earlier in the drug development process skewing physicochemical parameters away from values associated with more desirable ADMET characteristics and potentially effecting druglikeness downstream [11]. One possible way to mitigate inflation of physiochemical parameters is to rely on composite descriptors like LLE, LiPE and LELP that consider potency and lipophilicity to predict druglikeness earlier in the drug development process. However, accuracy of these predictions needs to be fine-tuned, and this can only be achieved with an improved understanding of the validity of technologies used to measure lipophilicity. In addition, calculated lipophilicity needs to be verified with measurement of actual lipophilicity throughout the drug discovery process. This may appear to be a daunting task, however, with the continued development and validation of high-throughput, low consumption, and versatile measurement methodologies like RP-HPLC, MEEKC and IAM HPLC, this type of approach may prove to be more efficient and economical then in the past; yet, bearing in mind that the use of generic predictive algorithms may still present complications when applied to different series of compounds. Despite these limitations, accurately measured data early in the drug discovery process and continual monitoring of lipophilic efficiency metrics will lead to better control of lipophilicity in the design of future drugs.

Although there is a heightened awareness of the importance of early screening for physicochemical properties, like lipophilicity, the parallel integration of multiple parameters like potency early into the drug design will be essential if improved molecules with greater potential to succeed downstream are to be identified in the future.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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