Review article

The impact of lipophilicity on environmental processes, drug delivery and bioavailability of food components

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A B S T R A C T
Lipophilic properties of the compound allow to predict its fate in living organisms and to propose the models of chemicals transport and accumulation in the ecosystem. Lipophilicity is also useful as the characteristic of chemicals in respect to their optimal attributes for specific biological and non-biological tasks. The lipophilicity descriptors define the potency of endo- and xenobiotics to metabolic transformations and their affinity to target proteins. Therefore, the lipophilicity optimization allows to find the optimal structure of drugs in quantitative structure-activity relationship (QSAR) studies. Additionally, lipophilicity governs the transport of chemicals in the environment and the food delivery systems of bioactive compounds. This review focuses mainly on the lipophilicity importance in the environmental and human life sciences, its multidisciplinary character and applications, availability of reliable partition/distribution coefficients and methods of their assessment.

1. Molecular characteristic by lipophilicity – models and descriptors
Lipophilicity is a physicochemical property of a compound, which consists of two major structural contributions: a bulk term reflecting cavity formation, hydrophobic and dispersive forces and a polar term reflecting more directional electrostatic interactions and hydrogen bonds. It is generally accepted that the first contribution is called hydrophobicity and the second – polarity. Thus, lipophilicity describes the balance between these two contributions and is measured by the compound's distribution behavior in a biphasic system: a non-polar (organic phase) and a polar (mostly aqueous phase) \cite{1}. According to IUPAC definition, lipophilicity is the affinity of a molecule or a moiety for a lipophilic environment \cite{2}.

On the other hand, lipophilicity is one of the core compound properties that are required for the estimation of absorption, distribution, and transport in biological systems, besides the solubility, stability, and acid–base character. Solubility is usually phrased as the saturation solubility in a defined solvent at a specified temperature. The definition of stability should be adjusted to the environmental characteristics important for the assessment of survival rate of the compound, whereas acid–base character is determined by a value of logarithmic acid dissociation constant (pKa) of the compound \cite{1,3}.

The concepts of hydrophobicity and lipophilicity are widely used in relation to the sorption of organic compounds from water \cite{4}. The hydrophobic effect relates to the tendency of non-polar compounds to prefer a non-aqueous environment to an aqueous one. The preference of water to reform an ordered structure creates the driving force for this process. The second concept, lipophilicity, is an extension of the hydrophobic effect and it includes the advantageous solute–solvent interactions that contribute to the distribution of a solute between two media: water and an organic solvents. Other solubilizing media, such as biomembranes can also participate in this distribution \cite{1,3,4}.

The models of hydrophobicity or lipophilicity take on a broader
meaning in chemistry and biochemistry due to the importance of these processes in the environment and natural sciences. The hydrophobic effect is regarded to be one of the driving forces for the passive transport of pharmaceuticals through membranes of organisms and as a component of drug-receptor binding [3,5]. The protein binding, biodistribution and metabolism of drugs may also be modified by their lipophilicity. It is generally known that the lipophilic compounds are the preferred objects for metabolism and they often lead to high clearance rates [1,4]. The studies of bioavailability and bioconcentration have attempted to evaluate the extent to which environmentally relevant chemicals enter the organisms and accumulate in the food chain in relation to compounds lipophilicity [6–8]. The distribution of compounds between water and soil and/or sediment also strongly correlates with the compound’s lipophilicity [4] what make possible the management of hazardous waste disposal, the correct use of crop-protecting agents in agriculture and, above all, in environmental risk assessment.

Lipophilicity is characterized by partition coefficient, P or $K_{\text{OW}}$, expressed as $\log P$ or $\log K_{\text{OW}}$ [3,9]. Therefore, the value of $\log P$ allows to predict the biological activity of chemicals in the body as it describes compounds ability to reach its intended target (Fig. 1) [10,11]. The systematic research on lipophilicity was organized by Hansch and Fujita who introduced the octanol-water system to model compound’s partitioning into cells [12,13]. Hansch pioneered mathematical methods for the correlation studies on the relations between physicochemical properties of molecules and their biological activities, known as QSAR investigations [14]. The majority of QSAR models including octanol-water partition coefficient and optimum $\log P$ value for the compound penetration through biological barriers were established [12,15]. The development of rapid methods for the lipophilicity assessment such as reversed-phase or biomimetic chromatographic techniques allows to establish the lipophilicity libraries [16]. We also observed the deeper insight into the pathway of chemicals from the environment to living organism and many new analytical approaches and tools for lipophilic properties analysis. Therefore, we present here the involvement of these properties into the penetration, metabolism, elimination and final environmental fate of chemicals coexisting with us.

### 2. The role of lipophilicity in the permeation properties of xenobiotics

Lipophilicity influences absorption, distribution, metabolism and excretion (ADME) processes of xenobiotics affecting their therapeutic potential and adverse effects (Fig. 2) [10]. Prior to reaching pharmacological target, compound’s lipophilicity determines the affinity for a lipophilic environment facilitating its transport through membranes in a biological system and the formation of complexes between compound and receptor binding site [1,17].

#### 2.1. Absorption

##### 2.1.1. Solubility and lipophilicity descriptors

Solubility is critical for the absorption and is highly dependent on the balance between hydrophobicity and polarity [1,2]. The quantitative descriptor of lipophilicity is $\log P$, which is defined as the ratio of the concentrations of a neutral compound in octanol and aqueous phases under equilibrium conditions [1,9–11] (Eq. 1).

$$\log P = \log \frac{c_{\text{oct}}}{c_{\text{wat}}}$$

Distribution coefficient ($\log D$) takes into account all forms of a compound: neutral and ionized, present at a given pH [3,18] (Eqs. 2, 3).

$$\log D_{\text{acids}} = \log P - \log (1 + 10^{pK_a - \text{pH}})$$

$$\log D_{\text{bases}} = \log P - \log (1 + 10^{\text{pK}_a - \text{pH}})$$

Considering above, the general solubility ($\log S$) equation is expressed below, where the melting point (MP) describes the lattice energy that is lost on dissolution (Eq. 4) [1,9–11].

$$\log S = 0.5 - \log P - 0.01(\text{MP} - 25)$$

According the Eqs. 3 and 4 the solubility of an ionizable compound increases exponentially with the difference between pH and pKa [19]. In a study by Gleeson, it was found that reducing $\log P$ below 3 made the dependence of solubility on ionization much less significant [20]. The variety of parameters related to lipophilicity is presented in Table 1. They are commonly used descriptor of the compounds in relation to
Lipophilicity of drugs and other xenobiotics influences their ADME properties and determines their bioavailability and final biological effects.

Table 1
Partition coefficients used to evaluate the lipophilic character of compounds.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>logD</td>
<td>Octanol-water distribution coefficient</td>
<td>[18]</td>
</tr>
<tr>
<td>logKAGP</td>
<td>Partition coefficient determined on α1-acid glycoprotein based column</td>
<td>[3]</td>
</tr>
<tr>
<td>logKAO</td>
<td>Air-octanol partition coefficient</td>
<td>[79]</td>
</tr>
<tr>
<td>logKAS</td>
<td>Air-soil partition coefficient</td>
<td>[62]</td>
</tr>
<tr>
<td>logKAW</td>
<td>Air-water partition coefficient</td>
<td>[8]</td>
</tr>
<tr>
<td>logKASL</td>
<td>Partition coefficient determined on human serum albumin based column</td>
<td>[3]</td>
</tr>
<tr>
<td>logKSL</td>
<td>Partition coefficient determined on immobilized artificial membrane column</td>
<td>[3]</td>
</tr>
<tr>
<td>logKGA</td>
<td>Octanol-air partition coefficient</td>
<td>[9]</td>
</tr>
<tr>
<td>logKOC</td>
<td>Organic carbon-water partition coefficient</td>
<td>[58]</td>
</tr>
<tr>
<td>logKOW, logP</td>
<td>Octanol-water partition coefficient</td>
<td>[3,9]</td>
</tr>
<tr>
<td>logKSW</td>
<td>Soil-air partition coefficient</td>
<td>[21]</td>
</tr>
<tr>
<td>logKWS</td>
<td>Soil-water partition coefficient</td>
<td>[21]</td>
</tr>
<tr>
<td>logKWSL</td>
<td>Water-air partition coefficient</td>
<td>[80]</td>
</tr>
<tr>
<td>logKWSL</td>
<td>Water-soil partition coefficient</td>
<td>[22]</td>
</tr>
<tr>
<td>logS</td>
<td>Solubility</td>
<td>[19]</td>
</tr>
</tbody>
</table>

layer in the brain controls the exchange of drugs, nutrients, hormones, metabolites and immune cells between blood and brain in both directions. The gaps between capillary endothelial cells in most parts of the brain are sealed by tight junctions and thus have severely limited permeability. The majority of xenobiotic BBB penetration is through passive diffusion and generally higher lipophilicity provides better central nervous system (CNS) penetration. However, too high lipophilicity can result in the increased non-specific plasma protein binding. Thus, the highest uptake demonstrates CNS penetrated xenobiotics with moderate lipophilicity values logP/logD from 1.7 to 2.8 [25,26].

2.1.4. Skin permeability

The transdermal permeation rate of xenobiotics is limited by the stratum corneum, which comprises of 10–15 layers of flat keratin-filled cells, closely packed in a nonpolar lipid matrix. A molecule can permeate through the skin via either the transcellular or intercellular pathway. The transcellular route requires that the molecule directly passes through both the phospholipid membranes and the cytoplasm of the keratinocytes encountering layers of different lipophilicity. In contrast, compounds crossing the skin by intercellular route must pass through the small spaces between the cells of the skin, making the route more tortuous. This pathway is more common among xenobiotics, which are usually lipophilic compounds. In contrast, transcellular route is not considered as the preferred way of transdermal transport. This is because of low permeability of keratinocytes and the obligation to partition several times from the more hydrophilic keratinocytes to the lipid intercellular layer [27]. Mathematical models for skin absorption of chemicals have been proposed, where lipophilicity, molecular weight and hydrogen bonding characterize the properties for permeation. The maximum skin permeability expressed as optimal logP ranges from 2.5 to 6.0 [11].

2.2. Distribution

After the absorption xenobiotics delivered into the living organism are specifically transported into various tissues according to individual tissue characteristics and compound properties. The distribution is determined by pH, lipid contents and cell membrane function, that can be expressed by different pattern distribution of acidic and basic compounds.

Absorbed xenobiotics are reversibly bound to plasma proteins (human serum albumin (HSA), α1-acid glycoprotein (AGP)) and are transported in the bloodstream. Plasma protein binding affects the disposition profile in terms of both clearance (CL) and volume of distribution (VD), because only free chemical is available for elimination and distribution into peripheral tissues [4,10,17]. HSA contains at least two different binding sites in the form of hydrophobic pockets and naturally serves as a transporter of a variety of different ligands [28]. Acidic compounds show correspondingly higher binding in comparison to basic and neutral compounds due to an ion-pair interactions with a basic residue within HSA [29]. The correlation between HSA...
binding and logP for numerous biologically active compounds has been demonstrated with similar affinity for neutral and ionized molecules with acids displaying the greater affinity [30].

The VD is a parameter used to quantify the distribution of a xenobiotic between plasma and the rest of the body [10]. This parameter, along with CL, allows for the determination of the half-life of a drug and thus influences dosing interval. Ionization state has the most dramatic effect on the VD. Basic molecules have the highest VD values whereas acidic molecules the lowest. The reason for that is higher plasma protein binding for acidic compounds and the tendency of basic compounds to interact with phospholipid membranes [20]. Lipophilicity is particularly important for the distribution of a drug in vivo. The increasing of logP will generally lead to an increase in the VD of neutral and basic compounds in the body, whereas this effect has not been seen for acids and zwitterions [31].

2.3. Metabolic transformations

Majority of xenobiotics are lipophilic what makes them difficult to eliminate. After reaching the liver, as well as in other organs they can be subjected to metabolic transformations. This process aims to increase hydrophilicity making the foreign compound easily excreted via bile and urine. Although metabolism is generally a detoxication process, in some cases the reactive intermediates may be formed which are much more toxic than the parent compound. Xenobiotics may undergo one or two phases of metabolism. In phase I a polar reactive group is introduced into the molecule mainly with the participation of cytochrome P450 isoenzymes (P450) and to a lesser extent of flavin-containing monoxygenases (FMO) and hydrolases. Then, phase II conjugating enzymes such as UDP-glucuronosyltransferases (UGT), sulfotransferases (SULT) and glutathione-S-transferases (GST) introduce much more
bulky substituents, such as sugars, sulphates, or amino acids which cause a significant increase in water solubility of the compound (Fig. 5) [32]. Generally, the binding sites of xenobiotic metabolizing enzymes are lipophilic in nature and hence more readily accept lipophilic molecules, as it was described for P450. Depending on P450 isoenzyme, the average log $P$ of their substrates ranges from 1.1 to 3.7. Metabolic stability of a compound in relation to lipophilicity can be improved in phase II transformations by the introduction of substituents with low lipophilicity or isosteric atoms/functional groups, which imparts increased polarity to the molecule [33].

2.4. Elimination and clearance

Phase I and II metabolites and in some cases unchanged xenobiotics are excreted by membrane efflux transporters in the process called III phase metabolism. Owing to high solubility in water, hydrophilic species generally can be excreted outside the body through urine without chemical modification [34]. Drug and toxicant transporters are expressed in a variety of organs including liver, intestine, kidney and brain. ATP binding-cassette (ABC), transporters localized on the canalicular membrane of hepatocytes, such as P-glycoprotein, multidrug resistance-associated protein (MRP) 2 and breast cancer resistance protein (BCRP) is the major family of proteins responsible for the excretion of drugs into the bile. Renal reabsorption and excretion are mediated by organic cation transporter (OCT) 2, organic anion transporters (OAT) 1 and 3 situated on the basolateral side of renal proximal tubule cells as well as by MRP1 and MRP2 localized on the apical side (Fig. 5) [35]. These membrane transporters involved in xenobiotic absorption, disposition and excretion can be major determinants of the pharmacokinetic, safety and efficacy profiles of chemicals that have
penetrated living organism [36].

The key measure of xenobiotic elimination is the CL, which may be defined as the theoretical volume of fluid from which chemicals are completely removed in a given period of time by the eliminating organ. The kidney and liver serve as the major organs responsible for the removal of xenobiotics [35]. Renal elimination of very polar compounds can contribute to a significant proportion of the total CL, whereas more lipophilic compounds are efficiently reabsorbed in the kidney tubule and tend to undergo metabolism, which results in less lipophilicity [35,37]. Studies on intravenous pharmacokinetic parameters in humans for the sets of xenobiotics exhibited rather weak but statistically significant nonlinear relationship between logP and the in vivo CL [20].

3. Lipophilicity in pathological response

In addition to described above ADME parameters, lipophilicity is also one of the key factors determining compound binding affinity to target proteins, which are responsible for the final biological effect. The analysis of drug affinity to a given molecular target indicates that within oral drugs, different target classes have significantly different average logP value [3]. The investigation of the relationship between target class and the physicochemical properties of ligands revealed distinct differences in the distribution of lipophilic properties between sets of compounds active against different target gene families. For example, ligands for the nuclear hormone receptors are the most lipophilic and generally more lipophilic compounds within a series will be more potent against their target. Thus, medicinal chemistry optimization needs to be balanced and multidimensional [3,38].

Xenobiotic ability to act with multiple molecular targets and to exhibit distinct physiological effects is called “promiscuity”. In general, more lipophilic molecules are less selective and have greater ability to bind to any target and unwanted effects leading to toxicity can be more lipophilic [4]. The key processes that affects transport of many organic compounds in the environment. One of important physicochemical parameters that define the contaminants’ ability to exchange between different environmental compartment and their preferred accumulation media and lipophilicity can be affected [7,42,45]. As a consequence, it may impact on sorption processes in soil and volatility of compounds from water environment, as well as affect transformations by hydrolysis, photolysis, biodegradation, oxidation and reduction. Solubility also influences washout chemicals from atmosphere by rain [51,52]. The properties of compound affect partition coefficient values that allow to understand their fate in the human body, to build models for biological partition processes and to predict in vivo distribution of potential bioactive molecules (i.e. nutraceuticals) [3,12,42,44]. Improving the uptake of highly lipophilic bioactive compounds through design food-based delivery systems can also be supported by lipophilicity studies of functional food ingredients [6].

5. The impact of lipophilicity on environmental fate of compounds

Chemicals released into environment can occur far away from the release point and have rather unexpected effects [46], for instance, freons get to the stratosphere and contribute to the disappearance of ozone layer [47], polychlorinated biphenyls (PCBs) were detected in Norwegian fish [48] organochlorinated pesticides were found in polar bear bones [49] and trichloroethylene was present in groundwater [50]. Therefore, tools to predict chemicals’ fate are of crucial importance (Fig. 6).

The contaminants’ movement through ecosystems is controlled by two factors: physicochemical properties of individual compound and characteristic of various compartments of natural environment. Therefore, the partitioning of these compounds through sediment, water or air depends on their molecular size, polarity and structure. The most important property is solubility in water, because it may impact on sorption processes in soil and volatility of compounds from water environment, as well as affect transformations by hydrolysis, photolysis, biodegradation, oxidation and reduction. Solubility also influences washout chemicals from atmosphere by rain [51,52]. The properties of compound affect partition coefficient values that allow to define the contaminants’ ability to exchange between different environmental compartment and their preferred accumulation media [53]. Partition coefficients related to soil, water and air environment are summarized in Table 1. The values of these coefficients for chemical compounds are mainly determined using the standard testing guidelines (e.g. the Organization for Economic Cooperation and Development (OECD) guideline) and other empirical methods [54]. Examples of such methods for the most important partitioning processes in the environment are summarized and briefly discussed in Table 2. However, due to the time-consuming, laborious and relatively high costs of experimental determinations, partition coefficients are more often estimated by computation methods applying different algorithms based on structural, atomistic, topological, electrotopological, or other considerations on a drawn chemical structure. Recently, the calculation methods based on solvation free energy, such as the conductor-like screening model for real solvents (COSMO-RS) and the polarizable continuum model (PCM), have been developed and applied for prediction of compounds partition between various environmental compartments. A detailed description of these methods has been presented by Mackay et al. [55].

The transfer between the atmosphere and water reservoirs is one of the key processes that affects transport of many organic compounds in the environment. One of important physicochemical parameters that
describes this mobility is Henry's Law constant (H), which is a ratio of vapor pressure substance above a solution (p) to its aqueous solubility (S) (Eq. 5) [56].

\[ H = \frac{p}{S} \text{[Pa·m}^{-3}\text{·mol}^{-1}] \]  

(5)

In atmospheric chemistry, Henry's Law constants are classified into two types: 'Henry's Law solubility constant' and 'Henry's Law volatility constant' (K_{AW}). Both types are needed to explain distribution of compounds between the air and aerosol particles or liquid cloud droplets. Furthermore, in other environmental research areas, these constants are necessary to evaluate the vaporization of pollutants during wastewater treatment processes or from environmental waters [56,57].

The transport of compounds between air and soil is another important process determining the environmental fate and human exposure. The main processes occurring in this exchange are dry deposition (association with particles, vapor adsorption), wet deposition (disposal of vapor- and particle-sorbed compounds) and volatilization from the soil. Soil is fundamental reservoir for chemicals in the terrestrial environment. However, the removal processes, such as leaching to groundwater, biodegradation or migration to atmosphere also occur [9,46]. To describe the pathway of compounds found in soil, various coefficients related to K_{OW} are used: K_{OA}, K_{AO}, K_{OC}, K_{AC}, K_{AS}, K_{WS} and K_{SW} (see Table 1 and Fig. 6) [21,54,58].

An exposure pathway is only operative when the compound can pass from an environment to a living organism under different pathways: bioaccumulation, bioconcentration and biomagnification. Bioaccumulation refers to the accumulation of contaminants in living organism and occurs when an organism absorbs a toxic substance from the environment at a rate greater than that, at which the substance is lost. Bioconcentration describes the uptake and accumulation of a substance from water alone, whereas biomagnification is defined as a durable increase of substance concentration in organism together with increasing trophic position within food chain [59]. In this three cases, K_{OW} is a useful index for assessment of the potential of substance migration from water residues, soils and among food chain. It has been estimated that bioaccumulation occurs for chemicals with K_{OW} > 2000 (logK_{OW} > 3.3), whereas easily bioaccumulative compounds with a tendency to biomagnification at different trophic levels exhibit logK_{OW} > 5 [59–62]. Lipophilic compounds are accumulated in the adipose tissue of organisms where they can have long elimination period. Furthermore, lipophilic xenobiotics that accumulate in female's body may also migrate to cub's tissue. For instance, in case of mammals, it is possible to transfer lipophilic compounds from adipose tissue to milk that contains high level of lipids. For this reason, cubs are exposed to these chemicals during the feeding. Moreover, this exposure has already begun in fetal period. The small size of fed cubs causes that even temporary exposure can lead to much higher levels of xenobiotics in their blood and tissues than in the mother’s body [63].

The harmfulness of xenobiotics to offspring can be determined by evaluation of health risk. Its purpose is to accurately determine and assess all possible risks associated with exposure and even to help in finding a way to reduce the exposure. The health risk assessment process includes four main steps: hazard identification, dose-response assessment, exposure assessment, and risk estimation and characterization. To realize each step a lot of data can be used, obtained by epidemiological investigations, laboratory animal tests or computer modeling, where various partition coefficients are taken into consideration [62].

It is suspected that the expression of lipophilic nature of the compound can be significant for estimation of efficiency of their removal during treatment processes as well as for the prediction of wastewater treatment efficiency models. Contaminants elimination by sorption to suspended materials (solids, colloids, and some others), occurs during primary and secondary wastewater treatment stage (sedimentation, coagulation and/or flocculation). This process is not significant for compounds exhibiting logK_{OW} < 2.5, whereas moderate and high sorption may be observed for chemicals with logK_{OW} 2.5–4.0 and > 4.0, respectively [64,65].

6. QSAR in permeation of xenobiotics and environmental fate assessment

It is now clearly recognized that a successful drug candidate requires not only potency and selectivity, but also a suitable pharmacokinetic profile [66]. The studies showed that less lipophilic compounds are developed easier during preclinical and clinical investigations, implying the role of lipophilicity in QSAR approach [67]. The majority of QSAR models includes lipophilicity expressed as logP [68] as it is one of the major factors in research aimed at rational design of new therapeutic agents [4].

To express the probability of a compound to become a pharmaceutical drug the term drug-ability is used. Among a lot of approaches
<table>
<thead>
<tr>
<th>Type of partition coefficient</th>
<th>Method of determination</th>
<th>Comments</th>
<th>Application</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{AW}$</td>
<td>Gas stripping method</td>
<td>very low $K_{AW}$ values are difficult to assess, especially if the solute is polar or surface active, very long stripping time may be needed, aerosol particles of water should be avoided if the air-phase concentration is measured</td>
<td>polybrominated diphenyl ethers (PBDEs), PCBs, mercaptans, dimethyl sulfide</td>
<td>[81–83]</td>
</tr>
<tr>
<td>$K_{OA}$</td>
<td>Generator column/fugacity meter technique</td>
<td>direct measurement of $K_{OA}$, time-consuming, in particular at low temperatures and for low volatile compounds, complex multi-step procedure, requires quantitative analysis (calibration)</td>
<td>chlorinated benzenes, PCBs, polychlorinated napthalenes, PDBEs, dibenzo-p-dioxins and dibenzofurans, organochlorine pesticides</td>
<td>[77,86]</td>
</tr>
<tr>
<td>$K_{OC}$</td>
<td>Gas chromatographic retention time (GC-RT) method</td>
<td>indirect method that required sufficient number of calibration compounds</td>
<td>organophosphate flame retardants, PCBs, PBDEs, polycyclic aromatic hydrocarbons, polychlorinated benzenes, biphenyls and napthalens</td>
<td>[86–88]</td>
</tr>
<tr>
<td></td>
<td>Batch equilibrium method</td>
<td>time-consuming, laborious and very expensive, evaluation of the adsorption of chemicals on different soil types, in some cases more tedious direct analysis of soil, involving stepwise soil extraction is required (i.e. adsorption of the analyte on surfaces of the test vessels, instability of the analyte during test, weak adsorption giving only small concentration change in the solution), problems with analytes characterized by low water solubility (&lt; 0.1 mg/L) and highly charged substances, soil types for adsorption/desorption experiments should be selected and prepared in appropriate way, selection of optimal soil/solution ratios is required</td>
<td>volatile methylsiloxanes, pesticides, organophosphate esters</td>
<td>[89–92]</td>
</tr>
<tr>
<td></td>
<td>High performance liquid chromatography (HPLC) method</td>
<td>high reliability of the method, especially in comparison with computation methods, tests performed on HPLC columns with cyanopropyl stationary phase (dual-nature of stationary phase), real soils can be used as packing material of HPLC column (soil column LC), method cannot fully replace batch equilibrium method, useful for chemicals which are difficult to study in other experimental systems (i.e. volatile substances; substances which are not soluble in water at a concentration which can be measured analytically; substances with a high affinity to the surface of incubation systems), convenient and low-cost method</td>
<td>pesticides, triazines, amides, polycyclic aromatic hydrocarbons, PCBs, alcohols, halogenated benzenes and phenols, benzenonitriles</td>
<td>[93–96]</td>
</tr>
</tbody>
</table>
Lipinski proposed a way to assess whether a chemical compound of a certain biological activity has a chance to be an active therapeutic after oral administration [5]. Lipinski’s rule known as the ‘rule of five’ (Fig. 7) describes the molecular properties that are associated with drug solubility and permeability. These parameters are crucial for ADME as well as for its pharmacodynamic and toxicological profile. Accordingly, Gleeson suggested that compounds with logP < 4 stand a much higher chance of success against a comprehensive set of ADME parameters [20].

Optimum region of lipophilicity for therapeutic agents is proposed within a narrow range of logP 1–3 [38]. However, to be a successful drug candidate, a compound should have a balance of lipophilic and hydrophilic properties. The lipophilicity of a potent drug should be:

1) high enough to enable adequate permeability through biological membranes and to allow binding to molecular target,

2) low enough to enable solubility in aqueous environment and to prevent undesired drug features.

Optimal lipophilicity allows to avoid the extensive metabolism, high plasma protein binding, off-target activity or accumulation to tissues. It is strongly suggested, that the control of drug candidate logP value within indicated range is crucial for ultimate success in drug development [68].

There is a wide range of chromatographic methods for the description of potent therapeutics in the field of their lipophilic properties. They include various reversed phase liquid chromatography approaches such as: (i) thin-layer chromatography [69], (ii) high-performance liquid chromatography (HPLC) in isocratic mode [70], (iii) gradient HPLC [71], as well as the double gradient methods (i.e. pH/methanol gradient) [72], which have been developed and applied by a lot of research groups, including Kaliszanz et al. [71,73]. Chromatographic methods, in contrast to direct partition coefficient experiments, allowed for faster and easier determination and for the comparison of lipophilic properties for large number of xenobiotics [74]. The detailed comparison of various analytical methods for lipophilicity assessment is presented in Table 3.

QSAR models with a variety of lipophilicity descriptors have been developed for various types of biological, pharmaceutical and environmental purposes [68,73,75]. Following the expansion of lipophilicity descriptors a lot of new forms of QSAR approach have been established. The designation of structure-activity (SA) in QSAR has been substituted for example by structure-property (SP) or structure-retention (SR) [76]. There is widely recognized that the QSAR, QSPR or QSRR relations presented in Fig. 8, obtained in purely empirical fashion from a set of descriptors, may give the considerable insight into the control of physicochemical and biological properties of each compound [74]. In environmental chemistry, QSPR models are mainly used to estimate partition coefficients of compounds between various elements of the environment [9,54,77]. Presently, the major goal is to improve the interpretation of the models and their predictive power in a wide range of chromatographic systems. For instance, QSAR studies expanded also into quantitative structure-pharmacokinetic relationships (QSPkRs) [17]. Furthermore, the studies of the lipophilic properties have revealed a wealth of information on intermolecular forces, intramolecular interactions, and specific elements of molecular structure [76,78].

7. Concluding remarks

The understanding of lipophilic properties of the compound allows either to predict the routes of its transport in a variety of biological systems including plant and animal organism or to propose the models of pollutant transport and its accumulation in ecosystem.

We demonstrate here that the solubility and lipophilicity descriptors define not only the permeability potency of xenobiotics or their distribution profile, but also answer in respect to their potency to metabolic transformation. Higher lipophilicity, for example, promote phase I of metabolism of chemicals, whereas products of this transformation are good substrates for phase II of transformation giving the polar substrates suitable for membrane efflux transporters in phase III of metabolism. Lipophilicity is also the key factor determining the ability of the compound to bind to the target proteins, what is responsible for the selective activity or pathological response. Moreover, the optimal value of lipophilicity descriptor is a preliminary condition for finding the optimal structure of a potent drug in QSAR studies. Lipophilicity plays an important role in estimating bioaccumulation in animals and plants, predicting adsorption in soil and sediments, and, above all, in the evaluation of health risk of emerging environmental exposures. Lipophilic properties modulated by the degree of ionization also govern the food delivery systems of bioactive compounds. As a result of multidisciplinary applications, the determination of various partition coefficients as a measure of lipophilicity has now become almost an art, and thus different experimental methods of lipophilicity assessment are still being developed, especially towards providing a fully validate and standardized high-throughput procedures.

In our opinion the future trends in scientific areas focusing on the lipophilic properties of chemical compounds as a key aspect will include the following efforts. First, the improvement of existing experimental methods for determination of partition coefficients. Second, the elaboration of novel approaches that provide reliable and reproducible results in a wide range of lipophilicity, especially for new type of chemicals released to the environment or proposed as potential bioactive ingredients of pharmaceuticals. There is also a question: should there be attempts to unify the parameters defining lipophilicity, e.g. one universal partition coefficient for a given purpose? On the other hand, future prospects in design of new biomimetic HPLC stationary phases may result in introduction of new lipophilicity descriptors, such as various tissue/plasma or tissue/blood partition coefficients. These types of data can be used to develop more sophisticated physiologically-based models that can describe full pharmacokinetic profile of the substance. Therefore, the tendency to unify the lipophilicity parameters is debatable and depends on the type of partition and distribution processes.

The next future trend could be to develop valid, low cost and fast computation methods (e.g. “first-principles” approaches that based only on a few optimized, general parameters and do not require experimental data) and apply them for estimation of lipophilicity of not well-characterized chemicals and complex samples. This approach needs the application of chemometric tools to extract the meaningful and interpretable features from the multivariate HPLC raw data and then may provide new highly descriptive lipophilicity indices to build databases...
Table 3
Methods for determination of lipophilicity of chemical compounds.

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Applicability</th>
<th>Lipophilicity descriptor</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct methods</strong></td>
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<tr>
<td>Shake-flask method (SFM)</td>
<td>simple, reliable, the most realistic method correlated well with partitioning phenomenon, various partition solvents</td>
<td>time-consuming, labor-intensive, high solvent consumption, requires a large amount (10-50 mg) of high purity compounds, emulsion formation (mainly for hydrophobic compounds), impact of relative solubility, adsorption onto vessel walls, sensitivity to impurities, concentration dependent</td>
<td>medium hydrophilic or lipophilic compounds that do not dissociate under the assay conditions (neutral form); $-3 &lt; \log P &lt; 4$</td>
<td>$\log P$</td>
<td>[17]</td>
</tr>
<tr>
<td>Miniaturized SFM</td>
<td>simple, rapid, high-throughput, reliable and the most realistic method, various partition solvents, potential for full automation</td>
<td>compounds in a neutral form (undissociated), extended range of lipophilicity compared to the traditional SFM; $-2 &lt; \log P &lt; 6$</td>
<td>$\log P$</td>
<td>$\log P$</td>
<td>[97]</td>
</tr>
<tr>
<td>Slow-stirring method</td>
<td>simple and reliable method, problem of emulsion formation is eliminated, various partition solvents</td>
<td>time-consuming, labor-intensive, expensive, relatively large amount of pure compounds used, concentration dependent, solvent consumption</td>
<td>compounds in a neutral form (undissociated) with different lipophilicity, especially hydrophobic compounds with $\log P &gt; 5$</td>
<td>$\log P$</td>
<td>[9,98]</td>
</tr>
<tr>
<td>Filter probe method</td>
<td>simple, partially automated and rapid, well adapted to determine the $\log D$ profile as a function of pH</td>
<td>contamination of aqueous phase by octanol is problematic for hydrophobic compounds (prevention by using the water-plug aspiration/injection method), time-consuming set up, expensive equipment</td>
<td>lipophilic compounds in a neutral and dissociated form (ionic substances); $\log P &gt; 0.2$</td>
<td>$\log P$ or $\log D$</td>
<td>[17,99]</td>
</tr>
<tr>
<td><strong>Chromatographic methods</strong></td>
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<tr>
<td>Thin-layer chromatography (TLC)</td>
<td>simple, rapid, cheap, small amount of analyte required, simultaneous analysis of several compounds, does not require quantitative analysis, low consumption of organic solvents (environmental friendly method)</td>
<td>detection requires visualization reagents (post-chromatographic derivatization) or specific properties of the compounds (i.e. UV absorption, fluorescence), problems with repeatable analysis conditions that can be solved by using fully automated TLC system (higher equipment costs)</td>
<td>moderately and highly lipophilic compounds; $4 &lt; \log P$</td>
<td>$R_{f}, R_{max}$, $S$</td>
<td>[69]</td>
</tr>
<tr>
<td>Classical HPLC in isocratic mode</td>
<td>relatively cheap, fully automated, small amount of analyte required, on-line detection, does not require quantitative analysis, independence of measurements from low compound solubility and impurities or degradation products</td>
<td>different retention mechanisms, possible interactions with the surface of stationary phase, time-consuming in some cases, solvent consumption, calibration set necessary, limited pH range for some silane based reversed-phase columns (alternative: polymer-based columns, columns with hybrid organic-inorganic silica or based on bidentate technology are stable over a wide pH range)</td>
<td>moderately and highly lipophilic compounds in a neutral and dissociated form; $0 &lt; \log P &lt; 8$</td>
<td>$\log k$, $\log k_{\text{aq}}$, $S$, $\text{CHI (}\phi_{\text{0}}\text{)}$, $\log P$ or $\log D$</td>
<td>[100]</td>
</tr>
<tr>
<td>Gradient HPLC</td>
<td>fast, fully automated, high-throughput, small amount of analyte required, on-line detection, does not require quantitative analysis, independence of measurements from low compound solubility and impurities or degradation products, relatively low consumption of organic solvents, results correlate well with SFM, simultaneous analysis of dozens compounds (possible using MS detection and fast gradient), useful for inter-laboratory study – good reproducibility (mainly results in CHI scale), simultaneous determination of $\log k_{\text{aq}}$ and $pK_a$ using double pH/methanol gradient method (additionally high screening rate of ~100 compounds/day), allows to create profiles of $\log D = f(\text{pH})$</td>
<td>relatively expensive equipment for LC-MS based approach (costs of detector, especially TOF-MS), calibration set necessary</td>
<td>compounds with wide range of lipophilicity in a neutral and dissociated form; $-3 &lt; \log P &lt; 8$</td>
<td>$\text{CHI (}\phi_{\text{0}}\text{)}, k_{\text{aq}}, \log P$ or $\log D$</td>
<td>[71,99,100]</td>
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</tbody>
</table>

(continued on next page)
Table 3 (continued)

<table>
<thead>
<tr>
<th>Method</th>
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<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomimetic liquid chromatography</td>
<td>rapid (mainly fast gradient methods used), fully automated, high-throughput, on-line detection, does not require quantitative analysis, independence of measurements from low compound solubility and impurities or degradation products, relatively low consumption of organic solvents, useful for inter-laboratory study (mainly results in CHI scale), simulates well biological partition processes and correlates with pharmacokinetic parameters</td>
<td>high cost of the biomimetic columns with immobilized biomolecules (i.e. plasma proteins, membrane lipids, liposomes, etc.), column lifetime, pH range limited to 2.5-7.5 (for longer lifetime of some columns the range of 7.0-7.5 is even recommended), calibration set necessary</td>
<td>moderately and highly lipophilic compounds in a neutral and dissociated form; (0 &lt; \log P &lt; 8)</td>
<td>(k_g, \log k_w, S, \text{CHI} (\phi_0), k_p, \log P, \log D)</td>
<td>[3]</td>
</tr>
<tr>
<td>Electrokinetic chromatography approaches (micellar, microemulsion or vesicular EKC)</td>
<td>rapid, cheap, high-throughput, small amount of analyte required, insensitivity to samples impurities, wide dynamic range, working in full pH range, possibility of automation</td>
<td>poor reproducibility in case of vesicular EKC, determination of solvation parameter model required</td>
<td>moderately and highly lipophilic compounds in a neutral form (undissociated); (-1 &lt; \log P &lt; 7)</td>
<td>(k_g, Ml, \log P)</td>
<td>[101]</td>
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<tr>
<td>Other methods</td>
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<tr>
<td>Potentiometric titration (pH-metric method)</td>
<td>rapid, working in wide pH range (1.8-12.2), well adapted to determine the (\log D) profile as a function of pH, independent of the magnitude of (\log P) various partition solvents</td>
<td>requires a large amount of pure compounds (2-50 mg), relatively expensive equipment</td>
<td>ionizable and soluble compounds with wide range of lipophilicity; (-1 &lt; \log P &lt; 8)</td>
<td>(\log D, \log P^i, \log P^s)</td>
<td>[102]</td>
</tr>
<tr>
<td>Cyclic voltammetry</td>
<td>working in full pH range, results independent of the experimental conditions</td>
<td>limited number of solvent systems used, relatively large amount of sample required (1-10 mg)</td>
<td>low lipophilic and mainly hydrophilic compounds only in dissociated form (ionic compounds); (-8 &lt; \log P &lt; 1)</td>
<td>(\log P^\mu)</td>
<td>[103]</td>
</tr>
<tr>
<td>SPME-based approach</td>
<td>simple, small amount of analyte required, possibility of automation, good correlation with SFM results, solventless extraction (environment friendly method)</td>
<td>limited lifetime of fiber coatings (stationary phase), results dependent on experimental conditions</td>
<td>moderately and highly lipophilic compounds in a neutral and dissociated form; (0 &lt; \log P &lt; 5)</td>
<td>(\log K)</td>
<td>[104]</td>
</tr>
</tbody>
</table>

Abbreviations: CHI(\(\phi_0\)) – chromatographic hydrophobicity index; \(k\) – retention factor; \(k_p\) – apparent capacity factor; \(k_g\) – retention factor extrapolated to pure water as a mobile phase; \(K\) – distribution constant of analyte partitioning between the aqueous and stationary phase; MI – migration index; MS – mass spectrometry; \(P^i\) – partition coefficient of ion pairs; \(P^s\) – partition coefficient of neutral species, \(P^{\mu,i}\) – standard partition coefficient of ion species; \(R_M\) – retardation parameter; \(R_M^{\mu,i}\) – retardation parameter for pure water as a mobile phase; \(S\) – regression slope (directly linked to specific surface area of stationary phase); SPME – solid-phase microextraction; TOF-MS – time-of-flight mass spectrometer.
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References


