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Review

Drug delivery: A process governed by species-specific lipophilicities

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ABSTRACT

Drug delivery is a cascade of molecular migration processes, in which the active principle dissolves in and partitions between several biological media of various hydrophilic and lipophilic character. Membrane penetration and other partitions are controlled by a number of physico-chemical parameters, the eminent ones are species-specific basicity and lipophilicity. Latter is a molecular property of immense importance in pharmacy, bio-, and medicinal chemistry, expressing the affinity of the molecule for a lipophilic environment.

This review gives an overview of the types and definitions of the partition coefficient, the most widespread lipophilicity parameter, focusing on the species-specific (microscopic) partition coefficients. We survey the pertinent literature and summarize our recent works that enabled the determination of previously inaccessible species-specific partition coefficients for coexisting, inseparable protonation isomers too. This thorough insight provides explanation why some drugs unexpectedly get into the central nervous system and sheds some light on the submolecular mechanism of pharmacokinetic processes.

The contribution of the various ionic forms to the overall partition can now be quantitated. As a result, there is clear-cut evidence that passive diffusion into lipophilic media is not necessarily predominated by the non-charged species, contrary to the widespread misbelief.

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1. Introduction

Drug delivery is a cascade of molecular migration processes, in which the active principle dissolves in and partitions between several biological media of various hydrophilic and lipophilic character. Targeted delivery is an inevitable goal in drug research to minimize toxicity and side-effects. Since 77.5% of the drugs on the WHO essential medicines list bears ionizable groups (Manallack, 2007), the series of partitions takes actually place via differently charged species. Membrane penetration and other partitions are controlled by a number of physico-chemical parameters, the

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Nomenclature

a_o	activity in the organic phase
a_w	activity in the aqueous phase
D	distribution coefficient
$\Delta G_{tr}^{0,w\to o}$	standard Gibbs energy of transfer from the aqueous to the organic phase
$\Delta_w^o\phi$	Galvani potential difference between the aqueous and the organic phase
$\Delta_w^o\phi^0$	standard Galvani potential difference between the aqueous and the organic phase
K	protonation constant
k	microscopic protonation constant
K_a	acid dissociation constant
$\log(P^N/P^I)$	the difference between $\log P^N$ and $\log P^{0,I}$
$\log(p^{Non}/p^{Zwi})$	the difference between $\log p^{Non}$ and $\log p^{Zwi}$
p	microspecies-specific partition coefficient
p^{Ani}	microspecies-specific partition coefficient of an anionic species
p^{Non}	microspecies-specific partition coefficient of a non-charged species
p^{Zwi}	microspecies-specific partition coefficient of a zwitterionic species
p^{Cat}	microspecies-specific partition coefficient of a cationic species
P^I	partition coefficient of an ion (I)
$P^{0,I}$	standard partition coefficient of an ion (I)
$P^{0,N}$	standard partition coefficient of a neutral (N) solute
pK_a^{oct}	the aqueous pH at which the concentrations of the ionized and the neutral species in the octanol phase are the same
x	mole fraction of a species
$x_{Non}\ p^{Non}$	contribution of the non-charged species to the distribution coefficient
$x_{Zwi}\ p^{Zwi}$	contribution of the zwitterionic species to the distribution coefficient

eminent ones are site-specific basicity and lipophilicity. Latter is a molecular property of immense importance in pharmacy, bio-, and medicinal chemistry, expressing the affinity of the molecule for a lipophilic environment (Avdeef and Testa, 2002; Box and Comer, 2008). The applications of lipophilicity include diverse fields such as drug design for targeted delivery, liquid–liquid extraction of compounds, quantitative structure–activity relationships, and intra- and intermolecular forces of recognition (Testa et al., 1996; Giaginis and Tsantili-Kakoulidou, 2008; Liu et al., 2011).

There are several transport mechanisms that carry the drug from the gastrointestinal lumen to the blood capillaries. The ubiquitous one is the transcellular passive diffusion through the epithelial cells. The ability of drugs to diffuse passively through biological membranes has long been known to be largely influenced by their lipophilicity (Fujita, 1990). Although a recent theory proposed that drug transport is only carrier-mediated and new transporters will be discovered that possess transport characteristics ascribed to passive diffusion (Dobson and Kell, 2008; Kell et al., 2011, 2013), it is more probable that passive and carrier-mediated processes coexist (Sugano et al., 2010; Di et al., 2012; Smith et al., 2014).

2. Thermodynamic definitions

In order to quantitate lipophilicity, the commonly accepted parameter is $\log P$, the logarithm of the partition coefficient. It is the activity ratio of a solute in a single electrical state, being in equilibrium between two immiscible solvents.

The standard partition coefficient of a neutral (N) solute is

$$\log P^{0,N} = \log\frac{a_o}{a_w} = -\frac{\Delta G_{tr}^{0,w\to o}}{RT\ln 10} \tag{1}$$

where a_o (a_w) is the activity of N in the organic (aqueous) phase, $\Delta G_{tr}^{0,w\to o}$ is the standard Gibbs energy of transfer from the aqueous to the organic phase, it represents the difference in solvation energy between the two solvents (Reymond et al., 2001; Mälkiäa et al., 2004). In the thermodynamic description of partition phenomena, the epithet standard (denoted by superscript ^{0}) refers to a 1 mol/dm^3 virtual solution where the solute molecules interact only with the solvent molecules (it is not possible to measure this standard quantity but it can be estimated by extrapolation at infinite dilution).

The partition coefficient of an ion (I) is potential-dependent:

$$\log P^I = \log P^{0,I} - \frac{zF}{RT\ln 10}\Delta_w^o\phi \tag{2}$$

where the standard partition coefficient of I is

$$\log P^{0,I} = \Delta_w^o\phi^0\frac{zF}{RT\ln 10} \tag{3}$$

In Eqs. (2) and (3) ϕ stands for the inner potential of the phase, z is the charge number of the ion (negative for anions). $\Delta_w^o\phi^0$ is the standard Galvani potential difference (the difference of inner potentials) between the aqueous and the organic phase. It is also the standard transfer potential, the standard Gibbs energy of transfer from the aqueous to the organic phase in a voltage scale:

$$\Delta_w^o\phi^0 = -\frac{\Delta G_{tr}^{0,w\to o}}{zF} \tag{4}$$

$\Delta G_{tr}^{0,w\to o}$ is positive for hydrophilic ions, and negative for lipophilic ions.

In order to establish a scale of standard partition coefficients of ions, an extra-thermodynamic assumption is necessary (only the standard partition coefficients of salts can be directly measured experimentally). Usually the TATB (tetraphenylarsonium–tetraphenylborate, $Ph_4As^+ = Ph_4B^-$) assumption is used, based on $\Delta G_{tr,TPA^+}^{0,w\to o} = \Delta G_{tr,TPB^-}^{0,w\to o} = 0.5\Delta G_{tr,TPATPB}^{0,w\to o}$ for all solvents and temperatures. Using a different assumption would only shift the origin of the scale and all its values, but would not change the relative difference between two different ions.

The $\log P^{0,I}$ of H^+ in pure solvents and in mixtures can be found in the literature (Kalidas et al., 2000; Marcus et al., 1988). $\log P^{0,I}$ depends only on T, the solvent pair system and the chemical structure of the ion but it is independent of the nature of the other electrolytes used. $\Delta_w^o\phi^0$ depends on the volume of each phase, the concentration and intrinsic lipophilicity of all the species in the system.

The ion transfer thermodynamics can be studied with the use of electrochemical methodology mainly for solvents with moderate or high relative permittivity, where ion pairing can be neglected, i.e., for polar solvents. These include nitrobenzene and 1,2-dichloroethane, that are immiscible with water and popular with researchers working with liquid membranes, and many solvents that are miscible with water.

Cyclic voltammetry at the interface between two immiscible electrode solutions, typically in the 1,2-dichloroethane(DCE)/water system is often used, however, it cannot discriminate between zwitterionic and non-charged ampholytes, because polarization can affect only globally charged species (Reymond et al., 1999).