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Review

Lipophilicity study of some non-steroidal anti-inflammatory agents and cephalosporin antibiotics: A review

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ABSTRACT

Lipophilicity properties have long been considered a vital component of drug discovery and development, providing insight into the role of molecular properties in the biological activity of known and new compounds. An extensive survey of the literature published in analytical and pharmaceutical chemistry journals has been conducted. Separation, optical, electrochemical and calculation methods which were developed and used for determination of lipophilicity non-steroidal anti-inflammatory agents and cephalosporin antibiotics in drugs and biological materials, have been reviewed. This review covers over 100 miscellaneous methods. Presented review highlighted some recent developments and new techniques that have been used in the lipophilicity detection of two different kinds of drugs.

Contents

Abbreviations: ^{13}C NMR, carbon nuclear magnetic resonance; ^{1}H NMR, proton nuclear magnetic resonance; ADME, absorption distribution metabolism elimination; AID, adjuvant induced disease; AUC, plasma–time curve; BBB, blood–brain barrier; BMC, biopartitioning micellar chromatography; BSA, bovine serum albumin; CHI, chromatographic hydrophobicity index; COX, cyclooxygenase; CSF, cerebrospinal fluid; D, distribution coefficient; DCE, 1,2-dichloroethane; Dex-PEG, dextran-polyethylene glycol; DMPC, dimyristoylphosphatidylcholine; DMSO, dimethyl sulfoxide; E_f, enhancement factor; f_u, unbound fraction; HOMO, highest occupied molecular orbital; HPLC, high performance liquid chromatography; HSA, human serum albumin; IAM, immobilized artificial membrane; ILC, immobilized liposome chromatography; K, the association constant; log k_w, logarithmic chromatographic retention factor; log k_{IAM}, chromatographic retention factor; LSER, linear solvation/free energy relationship; LSS, linear solvent strength; LUMO, lowest unoccupied molecular orbital; LUV, large unilamellar vesicle; M, concentration [mol L^{-1}]; MEs, microemulsions; MI, migration index; MOPS, morpholinepropanesulfonic acid; MS, mass spectroscopy; MW, molecular weight; NSAIDs, non-steroidal anti-inflammatory drugs; o/w, octanol–water; o-NPOE, o-nitrophenyl octyl ether; PP_{ow}, octanol–water partition coefficient; P_{app}, apparent partition coefficient (permeability coefficient); PG, 1,2-propanediol; pK_a, dissociation constant; PSA, prostate specific antigen; QMAR, quantitative migration-activity relationship; QRAR, quantitative retention activity relationship; QSAR, quantitative structure activity relationship; QSPR, quantitative statistical property relationship; QSRR, quantitative structure retention relationship; QSTR, quantitative structure toxicity relationship; r, correlation coefficient; RBCs, red blood cells; R_M, R_{MW} retention values; RP-HPLC, reversed phase high performance liquid chromatography; RP-LC, reversed phase liquid chromatography; RP-TLC, reversed phase thin layer chromatography; S, the slope; SUV, small unilamellar vesicle; TEM, transmission electron microscopy; TLC, thin layer chromatography; UV, ultraviolet; VIS, visible.

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1. Introduction

The distribution of a solute between two phases in which it is soluble has been an important subject for experimentation and study for many years. In one form or another, this technique has been used since earliest times to isolate natural products such as the essences of flowers. The first systematic study of distribution between two immiscible liquids which led to a theory with predictive capabilities was carried out by Berthelot and Jungfleisch [1]. These investigators accurately measured the amounts present at equilibrium of both I_2 and Br_2 when distributed between CS_2 and water. They also measured the amounts of various organic acids; H_2SO_4, HCl, and NH_3 when distributed between ethyl ether and water. From these early investigations came the first appreciation of the basic fact that the ratio of the concentrations of solute distributed between two immiscible solvents was a constant and did not depend on the relative volumes of used solutions. It was concluded from these early observations that there was a small variation in partition coefficient with temperature, with the more volatile solvent being favored by a temperature decrease. In 1891, Nernst made the next significant contribution to the subject [2]. He stressed the fact that the partition coefficient would be constant only if a single molecular species were being considered as partitioned between the two phases. This association and dissociation of solutes in different phases remains the most vexing problem in studying partition coefficients. During the early years of the twentieth century a great number of careful partition experiments were reported in the literature, most of which were carried out with the objective of determining the ionization constant in an aqueous medium of moderately ionized acids and bases. As early as 1909, Herz published formulas which related the partition coefficient (P) to the number of extractions necessary to remove a given weight of solute from solution [3]. From 1940s the mechanical technique of multiple extraction was vastly improved, and countercurrent distribution became an established tool for both the separation and characterization of complex mixtures [4]. During the two decades bracketing the turn of the century, while the partition coefficient was being studied by physical chemists as an end in itself, pharmacologists became quite interested in the partition coefficient through the work of Mayer and Overton who showed that the relative narcotic activities of drugs often paralleled their oil–water partition coefficient. However, the correlation of so-called nonspecific narcotic activity with partition coefficients did not lead to any really useful generalizations in understanding the mechanism of drug action in the broad sense. Consequently, the interest of both groups in partition coefficients declined greatly.

Molecular lipophilicity is a major physicochemical property which affects the oral absorption, permeability, cell uptake, protein binding, blood–brain penetration, and metabolism of bioactive substances. The ability to predict drug absorption through the gastro-intestinal barrier is a key issue in the selection of new drug candidates for oral delivery. Passive diffusion, driven by a concentration gradient, is the main mechanism of drug uptake through the intestinal epithelium. It can occur between cell junctions (paracellular transport) or through the cytoplasm (transcellular transport). Lipophilic compounds cross the plasma membrane easily and are, therefore, mainly transported transcellularly. Cell membranes are relatively impermeable to hydrophilic compounds, so these are transported predominantly via the paracellular route. Excessive lipophilicity is also a common cause of poor solubility of substances and can lead to incomplete absorption after oral administration. It is also generally believed that very lipophilic compounds have greater affinity for plasma–protein binding and are easily transported across the blood–brain barrier (BBB).

Lipophilicity is one of the parameters of chemical substances which influence their biological activities. It is a prime parameter in describing both pharmacodynamic and pharmacokinetic aspects of drug action. In biological systems lipophilicity largely determines the solubility of drugs in biological fluids, penetration through the biological membranes, rate of absorption, affinity to plasma and tissue proteins, distribution into the specific body compartments or in organism. Lipophilicity is defined by the partitioning of a compound between a non-aqueous and an aqueous phase.

Lipophilicity, widely expressed by the logarithm of n-octanol–water partition coefficient ($\log P$) or distribution coefficient ($\log D$) for ionizable compounds, plays an important role of several ADME (absorption, distribution, metabolism and elimination) aspects, as well as in the pharmacodynamic and toxicological profile of drugs [5]. The logarithm of n-octanol–water partition coefficient (P_{ow}) is generally accepted as a useful parameter in structure activity relationship studies for the prediction of biological or pharmacological activity compounds. The partition coefficient is a ratio of concentrations of un-ionized compound between the two solutions. To measure the partition coefficient of ionizable solutes, the pH of the aqueous phase is adjusted such that the predominant form of the compound is un-ionized. The logarithm of the ratio of the concentrations of the un-ionized solute in the solvents is called $\log P$.

$$\log P_{\text{octanol/water}} = \frac{\log [\text{solute}]_{\text{octanol}}}{[\text{solute}]_{\text{un-ionized water}}}$$

The distribution coefficient (D) is defined as the ratio of the concentration of compound in the lipid phase to the concentration of all species in the aqueous phase at a given pH. Estimation of $\log D$ from $\log P$ and pK_a describes equation:

$$\log D_{\text{acids}} = \log P + \log \left[\frac{1}{1 + 10^{\text{pH}-pK_a}} \right]$$

$$\log D_{\text{bases}} = \log P + \log \left[\frac{1}{1 + 10^{pK_a-\text{pH}}} \right]$$

Approximations when the compound is largely ionized: For acids with $(\text{pH} - pK_a) > 1$, $\log D_{\text{acids}} \approx \log P + pK_a - \text{pH}$
For bases with $(pK_a - \text{pH}) > 1$, $\log D_{\text{bases}} \approx \log P - pK_a + \text{pH}$

Approximation when the compound is largely un-ionized:

$$\log D \approx \log P$$

The most common procedures for the measurement of lipophilicity are the “shake-flask” and “stir-flask” techniques. In these methods, the solute concentration in each phase of water–organic mixture is determined by spectrophotometric or chromatographic methods. Among them, separation (chromatographic systems, membranes), optical and electrochemical techniques are using. Apart from the experimental methods, the lipophilicity of novel drugs can be estimated using various chemical software products, based on the different mathematic methods.