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Research paper

Kinetic solubility and lipophilicity evaluation connecting formulation technology strategy perspective

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ABSTRACT

Lipophilicity and solubility are important physicochemical properties of pharmaceutical compounds, especially orally administration drugs. In this study, we developed a chromatographic distribution coefficient (LogD) determination method as lipophilicity evaluation and a kinetic solubility procedure with rapid quantitation by HPLC-UV. Both methods are simple and applicable for use of conventional equipment in early stage of drug discovery and development. Actually both data of model drugs were collected and discussed to improve the physicochemical properties using formulation technologies such as solubilization and enteric coating. The parallel measurement and consideration of both sets of data enables not only detail evaluation of the physicochemical properties but also the perspective of the relevant formulation strategies of drugs. Such rational evaluation will facilitate the development of high quality and effective drugs.

1. Introduction

The formulation strategies for new drug candidates closely links to the physicochemical properties of drug substance, solubility, permeability, stability and various molecular and solid material properties [1]. Especially, solubility and permeability are crucial for the oral absorption, which are affected by formulation technologies [2].

The solubility of drugs in aqueous media at physiological pH is a vital factor in drug discovery and development [3]. Low solubility is the cause of low bioavailability and high variability of pharmacokinetics for orally administered drugs, which are linked to insufficient efficacy [4]. From pharmaceutical science aspects, low solubility also raises the risk of solubility changes in polymorphs and necessitates the use of formulation technologies, such as solid dispersions, nanocrystals, and lipid-based solubilized formulations, which are effective leverage for high quality medicine on drug development [5].

There are two main types of solubility that can be evaluated, kinetic and thermodynamic [6,7]. Kinetic solubility is the solubility of a molecule itself and thermodynamic solubility is the solubility of a crystal, which is affected by the crystallinity and the crystal form. Kinetic solubility is the intrinsic molecular solubility that can be improved by changing the chemical structure; some cases, it is an upper limit, however, solubilization formulation technologies can also improve the kinetic solubility. Since kinetic solubility uses DMSO stocks of compounds, high-throughput methods are very applicable to the measurement of kinetic solubility [7,8]. In this work, we use LC-UV to develop a fast quantitation method to use for determination of kinetic solubility. LC-UV can directly measure wide concentration ranges in solutions with various pH values with some additives. In this paper, the combination of fast quantitation using LC-UV and a multi-plate incubation procedure is investigated to measure the kinetic solubility for application in the early stages of drug discovery and development.

Generally, kinetic solubility is closely linked to the lipophilicity of a molecule [9]. Higher lipophilicity is associated with lower aqueous solubility. And, since lipophilicity also links permeability, lipophilicity extensively influences oral absorption [10]. Thereby, too high lipophilicity leads to poor drug-likeness and published reports proposed criteria that limit lipophilicity [11]. Lipophilicity value aligns needful solubilized formulation technologies. High lipophilicity profile usually matches oily and micellar formulation, while low lipophilicity usually matches nanocrystal and solid dispersion [12]. Lipophilicity is commonly expressed as a partition coefficient, LogD, which reflects the distribution coefficient of a

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drug molecule between 1-octanol and aqueous solutions. LogD is determined by direct quantitation of drug concentrations in 1-octanol and aqueous phases after partition of a drug, and also by indirect measurements using voltage differences, electrophoresis, chromatography [13,14] and *in-silico* calculation. Because direct LogD determination requires much workload and complicated procedures, indirect chromatographic determination was adopted for LogD measurement in this study. And, chromatographic determination can also use DMSO stocks of compounds like as kinetic solubility. In a previous study by Masumoto, the retention times in an isocratic mobile phase flow were used to determine LogD [15]. We customized and downsized Masumoto's analytical method and newly developed a LogD measurement method.

We measured the kinetic solubility and LogD of drug molecules using DMSO stocks in parallel and evaluated the relationships between them. The correlation is not necessarily perfect, suggesting that some of the compounds are easily crystallized in solution or form strong intermolecular interactions, such as hydrogen bonds and micelle complexes. Therefore, both of evaluations are important to assess the physicochemical and biopharmaceutical properties. The obtained information is important for not only the selection of drug candidates and the scaffold of the lead compound, but also the formulation strategy to improve the physicochemical properties. Therefore, this study makes a significant contribution to the discovery and development of new drugs with the decision and perspective of formulation strategy.

2. Materials and methods

2.1. Materials

Standard compounds for LogD measurement including anthracene, methylphenylsulfone, and sodium nitrate were purchased from Wako Chemical Co., Ltd (Osaka, Japan), and acetophenone (1-phenylethanone), biphenyl, 4,4-DDE (1,1-bis(4-chlorophenyl)-2,2-dichloroethylene), hexachlorobenzene, and thymol (2-isopropyl-5-methylphenol) were purchased from Tokyo Chemical Industries Co., Ltd (Tokyo, Japan).

Model compounds for test method development for quantitation of solubility and actual kinetic solubility/LogD measurement including lansoprazole ((*RS*)-2-([3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl)-1*H*-benzo[*d*]imidazole, PubChem CID: 3883), hydrochlorothiazide (6-chloro-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide, PubChem CID: 3639), griseofulvin ((2*S*,6′*R*)-7-chloro-2′,4,6-trimethoxy-6′-methyl-3*H*,4′*H*-spiro [1-benzofuran-2,1′-cyclohex[2]ene]-3,4′-dione, PubChem CID: 441140), diclofenac (2-(2-(2,6-dichlorophenylamino)phenyl)acetic acid, PubChem CID: 3033), indomethacin, (2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid, PubChem CID: 3715), albendazole (methyl [6-(propylthio)-1*H*-benzoimidazol-2-yl]carbamate, PubChem CID: 2082), and tamoxifen ((*Z*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-*N*,*N*-dimethylethanamine, PubChem CID: 2733526) were purchased from Wako Chemical Co., Ltd (Osaka, Japan). Our internal compounds, compound A and compound B were gifted from Chemical Development Laboratories or Medicinal Chemistry Research Laboratories in Takeda Pharmaceutical Co., Ltd.

Other reagents and solvents were of reagent grade, and were obtained from Wako Chemical Co., Ltd (Osaka, Japan) and Tokyo Chemical Industries Co., Ltd (Tokyo, Japan).

Analytical columns were purchased from YMC Co. Ltd (Kyoto, Japan) and Shimadzu Corp. (Kyoto, Japan).

2.2. HPLC systems

LogD measurements were conducted using an Alliance 2795 system with a 2487 UV-Vis detector from Waters Corp. (MA, USA). The quantitation for solubility determination was developed and conducted using a UFLC Prominence instrument with a PDA-20A photodiode array detector from Shimadzu Co., Ltd (Kyoto, Japan).

2.3. Relationships between LogD and retention time

The relationship between LogD and retention time is described by the following linear expression:

$$\mathrm{LogD} = \mathrm{aLogk'} + \mathrm{b},$$

where a is the slope, b is the intercept, the retention factor $k' = (RT - T_0)/T_0$, RT is the retention time (min), and T_0 is the dead time of the column (min).

2.4. Test sample preparation for chromatographic LogD measurement

The standard solutions for LogD measurements were mixtures of test compound solutions as follows: 1 mL of 2-mg/mL sodium nitrate in distilled water, 2 mL of 0.5-mg/mL methylphenylsulfone in methanol, 0.4 mL of 0.5-μL/mL acetophenone in methanol, 1 mL of 2-mg/mL thymol in methanol, 0.5-mg/mL biphenyl in methanol, 0.5-mg/mL anthracene in methanol, 1.5-mg/mL 4,4-DDE in methanol, and 2-mg/mL HCB in methanol were added to a 10-mL volumetric flask, and made up to volume with methanol. The sample compounds used to determine LogD were prepared by dilution of 10 mM compound DMSO solution into distilled water:acetonitrile (1:1 v/v) to a concentration of 0.1 mM.

2.5. Actual LogD measurement

Determination of the $\mathrm{LogD_{pH7.4}}$ values of standard compounds as reference was based on the methods in Chemical Substances Control Law from the Japanese Ministry of Economy, Trade, and Industry [16]. Compounds were dissolved in water-saturated 1-octanol and were then mixed with the same volume of Britton–Robinson buffer (pH 7.4) for 5 min. After centrifugation for 20 min, the concentration of each phase was determined by using HPLC-UV. LogD values were then calculated using the following equation:

$$\mathrm{LogD} = \log_{10}\mathrm{Pow},$$

where Pow is the compound concentration in 1-octanol/compound concentration in buffer.

2.6. Kinetic solubility measurement

Kinetic solubility was measured based on the solution–precipitation method [4]. First, the compound solutions in DMSO were added to some biorelevant media in a 96-well filter plate at a concentration of 10 mM so that the added volume was 2.5% of the biorelevant media volume. After incubation without stirring and shaking at 25 °C, the media were filtered by vacuum aspiration. The solubility, as the concentration of the filtrates, was quantified using a Shimadzu UFLC with an external standard solution, which was prepared by the addition of 0.5% of the compound solutions in DMSO into water: acetonitrile (1:1). The incubation time and HPLC conditions are discussed in detail in Section 3 (Results and Discussion). The solubility was calculated