ELSEVIER
DRUG DISCOVERY TODAY TECHNOLOGIES
Drug Discovery Today: Technologies
Vol. xxx, No. xx 2018

Editors-in-Chief
Kelvin Lam – Simplex Pharma Advisors, Inc., Boston, MA, USA
Henk Timmerman – Vrije Universiteit, The Netherlands

Automated assays for thermodynamic (equilibrium) solubility determination

Tomás Sou, Christel A.S. Bergström*

Department of Pharmacy, Uppsala University, BMC P.O. Box 580, SE-751 23 Uppsala, Sweden

Solubility is a crucial physicochemical property for drug candidates and is important in both drug discovery and development. Poor solubility is detrimental to absorption after oral administration and can mask compound activity in bioassays in various ways. Hence, solubility liabilities should ideally be identified as early as possible in the drug development process. With the increasing number of compounds as potential drug candidates, automated thermodynamic solubility assays for high throughput screening enabling rapid evaluation of a large number of compounds are becoming increasingly important. This review discusses the current status of the most widely used automated assays for thermodynamic solubility, followed by recent high throughput measurements of properties related to solubility (e.g. dissolution rate and supersaturation) and a brief overview of predictive computational methods for thermodynamic solubility reported in the literature.

Section editor:
György T. Balogh – Compound Profiling Laboratory, Gedeon Richter Plc.

Introduction

Aqueous solubility, a critical physicochemical parameter for any potential drug candidate, is routinely measured in drug discovery and development programmes. Poor solubility is detrimental to absorption after oral administration and can mask compound activity in bioassays in various ways [1], including underestimated activity, reduced hit rates in high-throughput screening (HTS), variable data outputs, inaccurate structure-activity relationship (SAR), and inaccurate in vitro absorption, distribution, metabolism, excretion and toxicity (ADMET) test results [2]. The importance of solubility data in early stage drug profiling during development for prediction of oral absorption has also been widely discussed [3,4]. Hence, solubility limitations should ideally be identified as early as possible prior to carrying out functional assays. Early evaluation of solubility in the drug discovery process is therefore of critical importance.

The solubility of a substance can be broadly defined as the maximum amount of the substance that dissolves in a specified volume of solvent. However, it is important to understand that the solubility of a compound can vary drastically depending on the condition of the solvent (e.g. temperature and pH) and the physiochemical properties of the compound (e.g. ionisation and crystallinity). These critical factors need to be considered during solubility determination in order to generate high quality solubility data that will be useful in the progression of compounds through the discovery and development stages. The functional meaning and concepts of solubility also differ for drug discovery scientists and development scientists and can sometimes be a source of misunderstanding. In drug discovery, solubility assays are often used to prioritise hit selection, to flag compounds with potential liabilities and to validate hits by

*Corresponding author: Christel A.S. Bergström (christel.bergstrom@farmaci.uu.se)

1740-6749/$ © 2018 Published by Elsevier Ltd. https://doi.org/10.1016/j.ddtec.2018.04.004

Please cite this article in press as: Sou T, Bergström CAS. Automated assays for thermodynamic (equilibrium) solubility determination, Drug Discov Today: Technol (2018), https://doi.org/10.1016/j.ddtec.2018.04.004

comparing the dose response values of the compounds with their apparent solubility values during lead optimisation. In development, the formulation and solid state properties of the compound are the key areas to be addressed with solubility assays [5].

The method used for determining solubility should take into account the information required for the specific purpose. Solubility assays determine either the kinetic or the thermodynamic solubility of a compound, depending on the experimental set-up. Traditional solubility assay workflows can be tedious, since they involve multiple steps such as dispensing of solvent and compounds, incubation, separation of residues and sample analysis. Furthermore, these steps are typically performed on a larger scale, using at least several millilitres, instead of microliters, of solvent for each replicate made. To speed up the process and enable the evaluation of a larger number of compounds, HTS has become increasingly important for determining solubility. This review discusses the current status of the most widely used automated assays for determining thermodynamic solubility and solubility-related properties (e.g. dissolution rate and supersaturation), followed by a brief overview of some computational methods reported in the literature for predicting thermodynamic solubility.

Kinetic vs thermodynamic solubility — which assay should I use?

Kinetic solubility

The kinetic solubility of a compound is the maximum solubility of the fastest precipitating species of the compound; this is often measured using a stock solution of the compound dissolved in an organic solvent, typically dimethyl sulfoxide (DMSO), as the starting material. Kinetic solubility values are strongly time- and method-dependent and hence are not expected to be reproducible between different laboratories using different protocols. The precipitate formed, which is rarely determined during the assessment, could be any combination of various possible solid states of the compound, including amorphous, crystalline, salt or co-crystals. Given the level of supersaturation that could occur when an organic solvent is diluted in water, kinetic solubility values are typically higher than the corresponding thermodynamic (equilibrium) solubility values (Table 1). Solubility assays in the early discovery process often determine kinetic solubility.

Thermodynamic solubility

The thermodynamic (equilibrium) solubility is the saturation solubility of a compound at the end of the dissolution process, where the dissolved compound is in equilibrium with

Table 1. Comparison of kinetic solubility with equilibrium solubility (μM) of solid samples (mean± s.d., n = 3) [8].

Compound		DMSO-SP		Intrinsic solid solubility	Ratio[b]	
	pH	10 min[a]	20 h[a]		10 min[a]	20 h[a]
Albendazole	6.5	4.6 ± 0.9	2.7 ± 0.4	2.8	2	1
Amiodarone	10	57.9 ± 14.9	6.6 ± 1.1	0.015	3860	440
Danazol	6.5	25.6 ± 0.6	1.6 ± 0.1	1.2	22	1
Diclofenac	3.0	118.3 ± 25.0	6.9 ± 1.3	2.6	46	3
Dipyridamole	6.5	160.0 ± 34.0	12.4 ± 0.9	10	16	1
Efavirenz	6.5	76.6 ± 0.9	40.1 ± 10.1	29	3	1
Estradiol	6.5	27.5 ± 1.4	29.9 ± 0.6	7.3	4	4
Gefitinib	6.5	263.4 ± 24.2	25.6 ± 0.3	4.5	26	2
Glibenclamide	3.0	6.6 ± 0.2	5.8 ± 0.2	0.12	1414	48
Griseofulvin	6.5	264.2 ± 16.9	101.0 ± 3.6	29	9	3
Indomethacin	3.0	89.5 ± 0.7	7.6 ± 0.7	14.0	6	1
Ivermectin	6.5	1.0 ± 0.3	1.2 ± 0.0	1.2	1	1
Lansoprazole	6.5	296.9 ± 14.2	81.4 ± 8.7	60	5	1
Levothyroxine	6.5	2.2 ± 0.0	1.9 ± 0.2	0.64	3	3
Loratadine	6.5	32.2 ± 1.6	5.8 ± 0.3	13	2	0.4
Mefenamic acid	3.0	2.0 ± 1.4	0.9 ± 0.3	0.25	8	4
Nifedipine	6.5	186.1 ± 13.5	39.0 ± 9.8	56	2	1
Phenylbutazone	3.0	123.7 ± 17.1	47.9 ± 1.7	17	7	3
Phenytoin	6.5	283.5 ± 23.3	127.9 ± 4.3	123	2	1
Pranlukast	3.0	3.1 ± 0.0	3.2 ± 0.1	2.5	1	1
Reserpine	6.5	59.8 ± 2.2	N.D.	N.D. (<0.47)	>14	>6
Simvastatin	6.5	31.8 ± 1.8	24.3 ± 0.7	22	1	1
Tamoxifen	6.5	67.3 ± 8.2	8.2 ± 2.5	0.028	443	11
Tolnaftate	6.5	2.7 ± 0.1	3.2 ± 0.1	N.D. (<0.18)	>15	>18
Trichlormethiazide	3.0	>300	177.3 ± 3.3	295	>1	1

Abbreviations: DMSO-SP = dimethylsulfoxide sample stock solution-precipitation method; N.D. = not detected.
[a] Incubation time.
[b] The DMSO-SP solubility versus the intrinsic solubility measured using solid samples.

Please cite this article in press as: Sou T, Bergström CAS. Automated assays for thermodynamic (equilibrium) solubility determination, Drug Discov Today: Technol (2018), https://doi.org/10.1016/j.ddtec.2018.04.004

Download English Version:

https://daneshyari.com/en/article/8411136

Download Persian Version:

https://daneshyari.com/article/8411136

Daneshyari.com