Solubility in Pharmaceutical Chemistry

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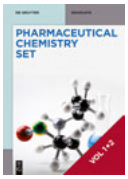

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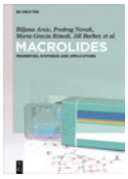

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Solubility in Pharmaceutical Chemistry

Edited by
Christoph Saal, Anita Nair

DE GRUYTER

Editors
Dr. Christoph Saal
Merck KGaA
Frankfurter Str. 250
64293 Darmstadt
Germany
E-Mail: christoph.saal@merckgroup.com

Dr. Anita Nair
Merck KGaA
Frankfurter Str. 250
64293 Darmstadt
Germany
E-Mail: anita.nair@merckgroup.com

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Contents

List of contributors

Annette Bauer-Brandl
Department of Physics, Chemistry and Pharmacy
University of Southern Denmark
Odense
Denmark
annette.bauer@sdu.dk

Wolfgang Beckmann
Bayer AG
Research & Development, Pharmaceuticals
Material Science
42096 Wuppertal
Germany
wolfgang.beckmann@googlemail.com

Joerg Berghausen
Fabrikstrasse 14.2.02-10
Novartis Campus
4002 Basel
Switzerland
joerg.berghausen@novartis.com

Martin Brandl
Department of Physics, Chemistry and Pharmacy
University of Southern Denmark
Odense
Denmark
mmb@sdu.dk

Sandrine Desrayaud
Fabrikstrasse.28.6.73.01
Novartis Campus
4002 Basel
Switzerland
sandrine.desrayaud@novartis.com

Stephanie Dodd
Novartis Institutes for BioMedical Research
250 Massachusetts Avenue
Cambridge, MA
United States of America
stephanie.dodd@novartis.com

Jennifer Dressman
Goethe University Frankfurt
Frankfurt
Germany
dressman@em.uni-frankfurt.de

Bernard Faller
Novartis
Institutes for BioMedical Research
Fabrikstrasse 14.2.02-01
Novartis Campus
4002 Basel
Switzerland
bernard.faller@novartis.com

David Elder
Hertford
Hertfordshire SG14 2DE
United Kingdom
davidelder2110@gmail.com

René Holm
Drug Product Development
Janssen Research and Development
Johnson & Johnson
Turnhoutseweg 30
2340 Beerse
Belgium
and
Department of Science and Environment
Roskilde University
4000 Roskilde
Denmark
rholm@ITS.JNJ.com

Marc Laisney
WSJ-386-10.48.58
Novartis Campus
4002 Basel
Switzerland
marc.laisney@novartis.com

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James L. McDonagh
IBM Research UK
Hartree Centre
STFC Daresbury Laboratory
Sci-Tech Daresbury
Keckwick Lane
Daresbury Cheshire WA4 4AD
United Kingdom
james.mcdonagh@uk.ibm.com

John B. O. Mitchell
EaStCHEM School of Chemistry and
Biomedical Sciences Research Complex
University of St Andrews
North Haugh
St Andrews KY16 9ST
United Kingdom
jbom@st-andrews.ac.uk

David S. Palmer
Department of Pure and Applied Chemistry
University of Strathclyde
Thomas Graham Building
295 Cathedral Street
Glasgow
Scotland G1 1XL
United Kingdom
david.palmer@strath.ac.uk

Christos Reppas
Department of Pharmacy
National and Kapodistrian University of
Athens
157 84 Zografou
Athens
Greece
reppas@pharm.uoa.gr

Christoph Saal
Merck KGaA
Frankfurter Str. 250
64293 Darmstadt
Germany
christoph.saal@merckgroup.com

Rachael E. Skyner
Diamond Light Source Ltd.
Diamond House
Harwell Science and Innovation Campus
Fermi Ave
Didcot OX11 0DE
rachael.skyner@diamond.ac.uk

Klara Valko
School of Pharmacy
Bio-Mimetic Chromatography Ltd
Unit 5B BTC Bessemer Drive
Stevenage, Herts SG1 2DX
United Kingdom
and
UCL School of Pharmacy
29-34 Brunswick Square
London WC1N 1AX
United Kingdom
k.valko@ucl.ac.uk

Maria Vertzoni
Department of Pharmacy
National and Kapodistrian University of
Athens
157 84 Zografou
Athens
Greece
vertzoni@pharm.uoa.gr

David Elder

1 Solubility – definition and basic physicochemical considerations

1.1 Introduction

Solubility is often regarded as one of the most important attributes of a drug substance [1]. However, solubility of a solid active pharmaceutical ingredient (API) in a solvent (or mixed solvent) is a complicated phenomenon, and it is generally considered to be a dynamic equilibrium between the opposing forces of dissolution and reprecipitation. Under certain scenarios the equilibrium solubility may be exceeded to produce a supersaturated solution, which is metastable in nature [2]. The first stage in the process leading to a solution in an aqueous or organic solvent is disintegration of the crystal lattice and hydration or solvation of the API molecules. The thermodynamic driving force for this process is defined by the concentration gradient and resulting chemical–potential gradient between the solid (μ^{s}) and solid–liquid interface (μ^{l}). Then, the hydrated or solvated molecules diffuse from the "solid–liquid interface into the solution bulk phase" [3]. Similarly, the thermodynamic driving force for this latter process is defined by the concentration gradient and resulting chemical–potential gradient between the solid–liquid interface (μ^{l}) and the solution phase (μ^{sol}).

Solubility can be simplistically defined as the "amount of a substance that will dissolve in a given amount of another substance" [4]. This is often further refined as the amount of a solute that will dissolve in a given amount of solvent at a specified temperature and pressure. The latter caveats of temperature and pressure are important as most solutes become more soluble as the temperature increases, but the exact relationship is usually not simple [3].

However, these definitions omit an important factor, which is the nature of the solid-state form of the API. Dependent on the type of solubility measurement selected, this can change, as is typically seen with kinetic solubility or usually remain the same, that is, equilibrium solubility (see Table 1.1). IUPAC [5] tries to address this deficiency by defining solubility as "the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent". The term "designated" implies no change in solid-state form, but this isn't implicitly stated. Solubility may be expressed in units of concentration, mole ratio, mole fraction, percentage, that is, 1% w/v, molality, or indeed other units [5].

Interestingly, changes in temperature play slightly different roles in the initial dissolution process depending on the intrinsic solubility of the API. For highly soluble compounds, it affects the diffusion rate constant and an increase in the intrinsic

David Elder, Hertford, Hertfordshire, SG14 2DE, UK

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Table 1.1: Definitions of differing types of solubility.

Type of solubility measurement	Definition[1]
Kinetic	The concentration of a solute in solution when an induced precipitation first appears; this precipitate is often a thermodynamically metastable solid-state form.
Thermodynamic or equilibrium	A saturated solution in equilibrium with the thermodynamically stable solid-state form. No phase change occurs during the experiment if the thermodynamically stable solid-state form is introduced into the assay.
Intrinsic	The thermodynamic solubility at pH where API is in its neutral form (S_0).
Apparent	The solubility measured under given assay conditions.
Biorelevant (see Chapter 6)	The solubility measured using biorelevant media, for example, SGF, SIF, but more typically using FeSSGF, FaSSGF, FeSSIF, or FaSSIF media. Measurements are often performed at controlled body temperature, that is, 37 °C ± 1 °C

[1]Performed at controlled room temperature, that is, 25 °C ± 1 °C, unless specified otherwise.
SGF, simulated gastric fluid; SIF, simulated intestinal fluid; FeSSGF fed state simulated gastric fluid; FaSSGF, fasted state simulated gastric fluid; FaSSGF fed state simulated intestinal fluid; FaSSIF, fasted state simulated intestinal fluid.

thermodynamic driving force. In contrast, for poorly soluble APIs, it affects the surface reaction rate constant as well as the intrinsic thermodynamic driving force [3].

The pharmacopoeias such as the USP (United States Pharmacopoeia) [6] tend to describe solubility using much broader based terminology, for example, very soluble, freely soluble and soluble (see Table 1.2), which are based on the amount of solvent (in mL) needed to dissolve a specified amount of solute (1 g). The same

Table 1.2: USP definitions of solubility [6].

Descriptive term	Solubility (g/mL)
Very soluble	<1 part solvent needed to dissolve 1 part solute
Freely soluble	1–10 parts solvent needed to dissolve 1 part solute
Soluble	10–30 parts solvent needed to dissolve 1 part solute
Sparingly soluble	30–100 parts solvent needed to dissolve 1 part solute
Slightly soluble	100–1,000 parts solvent needed to dissolve 1 part solute
Very slightly soluble	1,000–10,000 parts solvent needed to dissolve 1 part solute
Practically insoluble	>10,000 parts solvent needed to dissolve 1 part solute

terminology and definitions that are used in the USP are equally applicable in other pharmacopoeias, for example, European Pharmacopoeia and British Pharmacopoeia. Although all the pharmacopoeias provide information on the solubility of majority of the test articles in specified solvents (typically water and certain stated organic solvents), the broad-based nature of these definitions renders this information to be less than useful for more than just a characterization of the respective substance.

1.2 Why is solubility important?

Generally, solubility plays a major role within pharmaceutical research and development with regard to different areas:

- Discovery, that is, utility in assay formats, for example, high-throughput screening (HTS)
- API manufacturing
- Formulation development for preclinical, clinical, and commercial formulations
- Drug bioavailability for per-oral drugs

1.2.1 Drug discovery

During "hit" identification and lead discovery phases of drug discovery, it is necessary to start to develop compound screening assays. This typically involves either (i) HTS of the company's entire compound library using biochemical or cell-based assays to screen for activity against the drug target and other proteins to get an understanding of selectivity of research compounds, (ii) fragment-based screening using small molecular weight (MW) compound libraries, or (iii) a tissue-based screening approach [7]. In all cases, compound solubility in DMSO (dimethyl sulfoxide) or, to a lesser extent, ethanol is required. These solvents are typically used because of their near universal solubilizing power and water miscibility [8]. Handling research compounds that are dissolved in such solvents facilitates compound handling to a large extent. Instead of handling and weighing of solid material, compounds can just be dosed by pipetting. This reduces time required for compound handling, allows for automation, and reduces consumption of research compounds.

The various compound libraries are typically stored as frozen DMSO solutions at storage conditions varying between −20 and 4 °C, at various concentrations (2–30 mM) [9]. These frozen solutions are then diluted further with buffers or water to perform the subsequent assays, which are typically performed at 1–10 μM concentrations. However, it is important to be aware of the final DMSO concentrations in these assays, as biochemical assays can be performed at DMSO concentrations of up to 10% v/v, whereas cell-based assays are much less tolerant and need DMSO concentrations of <1 % v/v.

However, sometimes the compound can show poor DMSO solubility [10]. Approximately, 10–20 % of compounds in compound libraries are not soluble in DMSO at the preferred concentrations [11]. In much the same way that the in silico prediction of aqueous solubility is useful in early-phase screening programmes, similar efforts to predict DMSO solubility have been undertaken [12]. In addition, DMSO solubility can change on storage. A combination of storage time, freeze–thaw cycling, DMSO hygroscopicity, and intrinsically low DMSO solubility can result in drug precipitation – often as a less soluble crystalline solid-state form [10]. Indeed, some researchers have advocated that concentrations of drugs in compound libraries should be reduced to 1 mM to address precipitation issues [13], whereas some researchers have also advocated automated storage in single-use mini-tubes [11].

Finally, DMSO has a non-linear effect on aqueous solubility of research compounds. Therefore, for a typical early-phase solubility assay utilizing 0.5–1.0 mL of aqueous buffer, only 10–50 µL of DMSO stock solution can be meaningfully added to the aqueous buffer component before the results become meaningless [14].

1.2.2 API manufacturing

Solubility in non-aqueous solvents at different temperatures is critical in selecting an appropriate solvent system for crystallization of the drug substance, which is a major factor in defining the purity and solid-state form, for example, polymorph, hydrate, solvate, co-crystal, or pharmaceutical salt of the drug substance [15]. These aspects will also be discussed in chapter 9 of this book. Also working with supersaturated solutions during API manufacturing without being aware of this can lead to uncontrolled precipitation of the API or precursors that can be difficult to control and lead to real manufacturing challenges. Nonetheless, the selection of the optimal solvent(s) and crystallization conditions for novel APIs is typically still mainly trial and error. However, in silico approaches aimed at optimizing solvent selection have seen greater utilization [16]. For example, a non-random two-liquid segment activity coefficient (NRTL-SAC) model was utilized for solvent selection as part of optimizing the crystallization process design. NRTL-SAC was used to screen crystallization solvents with the objective of optimizing API solubility and minimizing solvent usage. The NRTL-SAC model parameters for the candidate molecule are first identified from a small set of solubility experiments in selected solvents. The solubility behaviour of the API in other solvents and mixed solvents was then modelled. The optimal solvent systems were validated in the laboratory and utilized for process scale-up [16]. A more in-depth discussion of solubility in API manufacturing as well as in silico prediction of solubility will be given in chapter 10 of this book.

1.2.3 Formulation development for pre-clinical, clinical, and commercial formulations

Increased solubility can be achieved using several different formulation strategies. As high concentrations of the API are desirable in early animal experiments such as pharmacokinetic (PK) studies or pharmacodynamic (PD) studies, especially in toxicological studies that require administration of high doses and in human trials, realizing appropriate solubility of the API by formulations is key. As an example, high solubility of the API by a formulation can reduce the required administration volume and accordingly allow formulations that are more convenient to administer.

1.2.3.1 Using buffer systems to optimize solubility

pH also affects the solubility of ionizable drugs as it influences the degree of ionizability and the amount of drug present in the neutral and charged forms. The former is much less soluble than the latter based on Henderson–Hasselbalch equation [1]. Modification of the formulation pH is the simplest and most common approach to increasing the solubility of poorly soluble drugs [17]. Solubility enhancements of several orders of magnitude ($\geq 10^3$) can be readily achieved by modifying, then controlling the formulation pH (using buffer systems), at values of >3 pH units away from the respective pK_a [18]. Typically, strong acids or bases, for example, HCl or NaOH, will be used for making large changes in formulation pH, and buffer systems will be used to control the pH at the designated value. Citrates, acetates, phosphates, glycine, and TRIS (tris(hydroxymethyl)aminomethane) are commonly used buffer systems [17, 19]. The pH of maximal solubility isn't always the pH of optimal stability, and selection of the optimal formulation pH can involve "trade-offs" between solubility and stability.

1.2.3.2 Use of co-solvents to optimize solubility

Co-solvents are water-miscible solvents that enhance aqueous solubility. The most commonly used co-solvents for formulations are glycerine, propylene glycol, polyethylene glycol 400, DMSO, and ethanol. Typically, solubility increases in a logarithmic fashion with increasing fraction of the co-solvent. However, there may be physicochemical, regulatory, or safety considerations that constrain the absolute amount of the co-solvent within the formulation, particularly for paediatric use [17–19]. The EMA has recently published useful background information on propylene glycol and ethanol [20, 21].

Co-solvents are used in about one-sixth of all FDA-approved injectable products [22], and this figure is almost certainly higher now, given the increase in the numbers

of poorly soluble APIs over the last two decades. Many of these injectable formulations are intended for infusion use and must be diluted with isotonic media, for example, saline and dextrose, prior to use. This significantly affects the ability of the co-solvent to maintain the drug in a solubilized form, with the inherent risk of precipitation.

1.2.3.3 Use of surfactants

Drugs with high lipophilicity can have poor wetting properties, and solubilization can be facilitated by surfactants. In addition, surfactants can solubilize poorly soluble drug molecules by micelle formation or by acting as co-solvents [23, 24]. Non-ionic surfactants are widely used, and some typical examples are polysorbate 20 and 80 (Tween 20 and 80), sorbitan monooleate 80 (Span 80), polyoxyl 40 stearate, solutol HS-15, polyoxyl 35 castor oil (Cremophor EL), polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), D-α-tocopherol polyethylene glycol 1000 succinate (TPGS), and various polyglycol glycerides [18, 19]. The latter class of surfactants, for example, Softigen 767, Labrafil M-1944CS, Labrafil M-2125CS, Labrasol, and Gellucire 44/14, are useful in preparing lipid-based formulations that can significantly enhance solubility and thereby oral bioavailability using the various "self-emulsifying" systems, for example, self-emulsifying drug delivery systems [23–25]. Microemulsions, which are thermodynamically clear dispersions, can also be used to solubilize hydrophobic APIs [18, 19].

For drugs that are both hydrophobic and lipophilic, where a food effect may be encountered, a useful formulation strategy is to develop a softgel product [26, 27]. Here the drug is typically dissolved (although suspensions may be applicable if the dose is high) in a wide range of non-ionic surfactants, oils, and co-solvents. As such, solubility in these various lipidic vehicles will be important to ongoing development activities [26, 27]. However, accurate prediction of lipid solubility is complicated because interfacial effects can play a fundamental role in these formulations and the solubility can be affected by the lipid microstructure, that is, emulsions, oily solutions, micro-emulsions, nano-emulsions, and so on; as well as by the more fundamental physicochemical properties of the oil, surfactant, co-solvent, and the API [28].

1.2.3.4 Use of complexing agents

Complexation between a solute and a complexing agent can enhance the APIs aqueous solubility. The complexation reaction is dependent on relative size of the solute and the complexing agent, charge, and lipophilicity. Complexing agents form non-covalent inclusion complexes with the hydrophobic API or the most non-polar part of the API molecule within the complexation agent. In contrast to co-solvents, this has the advantage compared to other approaches that after dilution, a

1:1 complex will not precipitate. Complexation agents are typically pharmacologically inert and readily dissociate in the system or gastrointestinal tracts [29]. Cyclodextrins (CDs) are commonly used complexation agents [30]. They are α-(1–4) linked oligosaccharides comprising α-D-glucopyranose sub-units and they form a relatively hydrophilic outer surface (facilitating aqueous solubility), with a relatively hydrophobic inner surface that can accommodate the hydrophobic API. There are three types of CDs (α, β, and γ), which are comprised of 6, 7, or 8 sub-units, and form cavities with diameters of 5.0 ± 0.3, 6.25 ± 0.25, and 7.9 ± 0.4 Å, respectively [28]. The β-form is the most commonly used, but covalent modifications (hydroxypropyl-β-CD or sulfobutylether-β-CD) can dramatically enhance the aqueous solubility [28]. For example, 400 mg/mL solubility with itraconazole (<5 μg/mL solubility in water) is achievable [29]. Common development themes for using CDs are low CD:drug ratios (<2:1), low dose (<100 mg), low drug solubility (<1 mg/mL), medium drug hydrophobicity (calculated log *P*, clog *P* > 2.5) and moderate binding constants (<5000 M^{-1}) [31].

1.2.4 Drug bioavailability for per-oral drugs

Aqueous solubility is also linked with the drugs' biopharmaceutical properties as discussed in Chapter 4 of this book. Thus, for oral drug products, solubility is required in biorelevant media, that is, gastric and intestinal fluids before a molecule can pass across a biological membrane of the intestine via either passive permeability or active transport. As such, without adequate biorelevant solubility, molecules can show solubility-limited absorption, with resultant non-linear kinetics [1] or insufficient bioavailability. The correlation of in vitro drug product solubility and in vivo bioavailability was first developed by Amidon et al. [32]. They developed a four-class system linking solubility and permeability properties to in vivo bioavailability. The four classes are shown in Table 1.3.

Table 1.3: 4-Box model for solubility and permeability: biopharmaceutical classification system (BCS) [32].

I	High solubility/high permeability	III	Low solubility/high permeability
II	Low solubility/high permeability	IV	Low solubility/low permeability

Compounds showing pK_a in the pH range of 1–8 tend to show pH-dependent solubility across the gastrointestinal (GI) tract. Tsume et al. [33] proposed a sub-classification of BCS II drugs into IIa and IIb. Both exhibit pH-dependant solubility; the former are weak acids, for example, naproxen and ibuprofen, that are poorly soluble at gastric pH but show good solubility at intestinal pH. In contrast, class IIb drugs are weak

bases, for example, ketoconazole, that show the inverse solubility relationship. Interestingly, class IIb drugs are prone to supersaturation and/or precipitation as they move from the gastric into the intestinal compartments [34]. This will also be addressed in chapter 11 of this book.

1.3 In silico approaches

It is just over 20 years since the publication of Lipinski's seminal paper on experimental and computational, i.e., in silico approaches to estimate the solubility and permeability of drug candidates [35]. The iconic "Rule of 5" forecasts that absorption from the GI tract will be adversely impacted by several physicochemical parameters, including when the clog *P* is greater than 5, when MW is greater than 500 g/mol, when there are more than 5 H-bond donors or more than 10 H-bond acceptors. The related concept of "drug-likeness" importantly focused on both biological potency and physicochemical attributes, using tools such as lipophilic efficiency [36] or ligand efficiency [37]. This is important, as historically, biological potency was always seen as the most important parameter, and limited efforts were undertaken to try and simultaneously optimize the physicochemical attributes. Drug-likeness and related concepts are now widely used across the pharmaceutical industry to try and reduce the very high attrition rates currently seen with unprecedented pharmacological targets. Unfortunately, both combinatorial chemistry and HTS tend to favour leads with higher MW, higher clog *P*, and lower solubility [38].

As such, successful drug discovery strategies need to be a balance between optimizing both the "hydrophobicity-driven potency and hydrophilicity-driven biopharmaceutics properties" [38, 39]. Accordingly, an over-reliance on potency optimization resulting in non-optimal physicochemical properties will yield inferior ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties and reduce the likelihood of clinical success [40]. Although the sub-optimal physicochemical characteristics can often be addressed using sophisticated formulation strategies [41, 42], and deficiencies in these properties can often still be rate limiting to the progression of drug candidates, particularly with respect to ADMET properties. Therefore, computational methodologies that can qualitatively predict certain physicochemical properties, for example, solubility, before a compound is even synthesized, based on molecular structural attributes are an essential requirement within drug discovery.

In silico approaches have also been applied to predicting solubility of the API in various organic solvents or mixtures of solvents [12, 43–45]. Computational models for predicting DMSO solubility showed a twofold decrease in the number of nonsoluble compounds. However, a significant, that is, four- to ninefold increase was observed if only the most reliable predictions were considered. The structural

features that influenced DMSO solubility were also assessed [43]. Models for predicting API solubility in various organic solvents (up to 85) have been described. The premise is that the relative partitioning of a solute between water and an immiscible organic solvent is given by the ratio of the solubilities in these solvents. Therefore, the solubility in an organic solvent can be predicted using the partition coefficient and solubility in water [44]. In addition, solubility prediction in mixed solvents, that is, water/co-solvent 1, water/co-solvent 1/co-solvent 2, using partial solubility parameters have been reported [45]. Within this book we have dedicated chapter 3 to the in silico prediction of solubility.

1.4 Relationships between solubility and physicochemical properties

There are significant numbers of in silico methods reported within the literature for predicting solubility from underlying molecular properties. However, these computational methodologies need to be able to cope with significant numbers of compounds and filter out "non-drug-like" compounds and/or attributes to focus chemistry initiatives on programmes with improved physicochemical attributes, thereby enhancing productivity. Importantly, it should be clearly appreciated that these early discovery methodologies will provide qualitative and not quantitative outcomes [46].

The intrinsic difficulties inherent in solubility prediction were graphically highlighted by the recent solubility challenge. An academic research group [47] measured the equilibrium solubility of 100 "drug-like" molecules under defined conditions, that is, fixed temperature(25 ± 2 °C), media (KCl buffer), and ionic strength (0.15 M). Utilizing this "training data set" they publicly requested other research groups to predict, using their own preferred computational approach(es), the intrinsic solubility of a further 32 "drug-like" compounds. The "training set" was selected to represent a broad chemical space with MW ranging from 115 (proline) to 645 (amiodarone), which had pK_a in the range of 1–12. The intrinsic solubility of the "training set" covered about seven orders of magnitude ranging from poorly soluble, that is, amiodarone to highly soluble compounds such as acetaminophen, with a relatively even distribution of intermediate values.

The authors received over 100 entries to the solubility challenge [48]. Participants used the full spectrum of available computational tools and approaches. Therefore, this solubility challenge provided an over-arching view of the industry's ability to accurately predict aqueous solubility. However, the authors felt constrained in their ability to recommend an optimal approach. Rather they highlighted several methodologies that were equally successful at predicting aqueous solubility. Several participants in the solubility challenge were surprised that the simpler methodologies were

better than the more complex approaches [49]. Some authors [50] went further claiming that any perceived advantages of these complex approaches were debatable, preferring instead a simple clog *P* correlation [51]. Hewitt et al. [49] highlighted that data quality was fundamental to the predictivity of any computational model. Indeed, even the "high-quality" data set provided by the organizers of the solubility challenge elicited concerns and questions concerning data quality. As such it is critical to recognize and understand the applicability domain, that is, the chemical space, where the model works best. Understandably, predictions made outside of this domain will be less reliable, but no "hard-and-fast" guidance can be provided.

Despite the impressive size of some of the participants' training sets, that is, in one case 46,000 compounds of known solubility, their methods still performed suboptimally for both soluble and insoluble compounds [52]. Interestingly, Kramer et al. [53] demonstrated enhanced solubility predictions with their meta-classifier approach, notwithstanding the fact that their "training set" was based on kinetic rather than equilibrium solubility. The authors showed a high prediction accuracy for the solubility of three quarters of these unknown compounds, but typically and perhaps unsurprisingly, they also showed a high bias, probably because their training set used small levels of DMSO as a co-solvent. However, despite this high level of predictivity, their model still only correctly predicted about one-third of the insoluble compounds in the data set. Finally, the accuracy of these in silico models needs to be further improved so that they mimic better the experimental determinations [40].

By far the biggest impediment to accurate solubility predictions is still the unpredictable nature of the solid-state forms, that is, presence of polymorphs, solvates and hydrates [54]. In other words, how to effectively model enthalpy and entropy within the system, that is, moving from an ordered, structured low entropy solid-state form to a disordered, unstructured high entropy solution state. Thus far, polymorphs still cannot be reliably predicted [55] and accordingly their effect on solubility cannot be accurately predicted by in silico tools. Case studies have shown that the reported solubility can be affected by a factor of 2 or more by factors such as temperature, differences in solid-state form, impurities, and water (in the case of solubility in anhydrous organic solvents) [56]. For more in-depth discussions, see chapters 9 and 10 of this book.

1.5 Solubility theory

Yalkowski and co-workers [57] derived the general solubility equation (GSE), to try and better model solubility:

$$\log S_o = -\log P - 0.01 * (\mathrm{MPt} - 25) + 0.5 \tag{1.1}$$

where S_o is the intrinsic solubility mg/mL, P is the octanol/water partition coefficient, and MPt is the melting point.

The GSE describes the influence of solvation energy, which the system gains after dissolution, arising from the log *P* term. Similarly, the crystal lattice energy that must be overcome prior to dissolution is addressed by the melting point term. Thus, the general concept as qualitatively introduced in Section 1.1. is defined quantitatively by the GSE.

However, the melting point term is only partially successful in helping to address solid-state complexity and its impact on aqueous solubility. It is also evident from the GSE that log *P* is the major variable in the GSE equation [57]. Indeed, medicinal chemists can usually modify log *P* far more easily than the melting point. This is because the melting point is more difficult to predict or indeed to control. The melting point today is not typically measured anymore during early discovery initiatives, as it was the case during the old days of medicinal chemistry. Consequently, optimizing log *P* tends to be the focus in many discovery organizations. Most marketed drugs have clog *P* of about 2.5 and it is probably no coincidence that this value also corresponds to the upper limit of "good solubility" predicted by the GSE [58]. Regrettably, poor aqueous solubility is therefore the logical outcome of introducing overly hydrophobic characteristics into potential new drug candidates.

The GSE limitation of clog *P* of >2.5 is probably the worst-case scenario as it does not accurately reflect the positive impact that ionization can have in improving aqueous solubility; therefore, replacing log *P* with log $D_{\mathrm{pH\ 7.4}}$ produces a more predictive GSE:

$$\log S_{\mathrm{pH\,7.4}} = -\log D_{\mathrm{pH\,7.4}} - 0.01 * (\mathrm{MPt} - 25) + 0.5 \tag{1.2}$$

Hill and Young [38] evaluated a large data set of ca. 20,000 compounds, utilizing measured log $D_{\mathrm{pH\ 7.4}}$, together with calculated values for hydrophobicity (i.e. clog *P* and clog $D_{7.4}$), accurate kinetic solubility measurements at pH 7.4, MW, and the number of aromatic rings in the molecules. The authors showed pronounced differences between the measured and calculated hydrophobicity with compounds of decreasing solubility. Indeed, poorly soluble compounds, that is, <30 μM showed a particularly bad correlation, that is $R^2 = 0.11$. This correlation improved slightly, that is, $R^2 = 0.32$, as the solubility increased from 30 to 200 μM, with the optimal correlation occurring with compounds exhibiting "good" solubility, that is, >200 μM, with $R^2 = 0.462$. Interestingly, these data supported the perspective that calculated log $D_{7.4}$ (or clog *P*) might be a better predictor of hydrophobicity rather than using the measured value [38].

Recently, the undesirable effects of aromaticity on aqueous solubility have been reported. These include the aromatic portion [59, 60], the number of aromatic rings [61, 62], and the percentage of sp^3 hybridized atoms [63] within the molecule. Molecules with limited lipophilicity are more likely to display poor aqueous solubility due to solid-state issues, i.e. 'brick dust molecules'; whereas highly lipophilic compounds are typically solubility limited due to inadequate solvation (poorly wetting),

i.e. 'grease ball molecules' [60]. Numerous scenarios were modelled, and they showed that for compounds with a melting point of >250 °C and clog *P* of >2, the GSE establishes that solid-state considerations will prevail (over 50%); whereas, when the clog *P* is increased above 6, then the solid-state issues decrease markedly (about 25%). Thus, planar, flat and rigid molecules with extended ring systems have a high-likelihood (86%) of demonstrating reduced aqueous solubility [60]. How molecular planarity reduces aqueous solubility and how solubility can in turn be improved by modifying planarity has been evaluated by Ishikawa [64]. This is explainable by considering the increased lattice energy and consequently higher melting point that is arising from enhanced π- π stacking of the planar aromatic systems. Hill and Young [38] also demonstrated extended correlations between the number of aromatic ring systems and clog $D_{\mathrm{pH\,7.4}}$ (as opposed to log *P*) and ultimately aqueous solubility. Consequently, they proposed a solubility forecast index (SFI):

$$\mathrm{SFI} = \mathrm{clog}\, D_{\mathrm{pH\,7.4}} + \text{number of aromatic rings} \tag{1.3}$$

In those cases where SFI < 5, there is typically good aqueous solubility and the authors contended that each aromatic ring system was equivalent to one extra log unit of clog $D_{\mathrm{pH\ 7.4}}$. They noted that the average number of aromatic ring systems in marketed oral products is 1.6 [38] and thus the average SFI would be 2.4.

Two key parameters that impact solubility but are not directly covered by these various "solubility" eqs. (1.1)–(1.3) are (i) purity and (ii) particle size. In the former case, impurities can affect the melting point term in eqs. (1.1) and (1.2), by introducing disorder into the crystal lattice and changing the chemical potential of the solid phase [65]. However, the nature of the impurities can also radically influence outcomes. Some impurities can increase solubility, whereas and perhaps counter-intuitively (given the above explanation), others can decrease solubility. Perhaps the best-known example of an impurity significantly decreasing aqueous solubility was that of ritonavir. The presence of a newly emerging, but poorly purging impurity was responsible for a four- to fivefold decrease in aqueous solubility. The impurity was a cis-geometrical isomer, whereas up to that point ritonavir in its known polymorph had exhibited trans-geometry. The impurity that was less soluble than the parent acted as a template during the crystallization process for the formation of a new conformational polymorph, which had cis-geometry [66]. Therefore, if the source, grade, or purity of either the solute or the solvent is modified in any way, then the solubility of the solute can be affected.

Particle size reduction is a well-known strategy for improving the bioavailability of poorly soluble compounds [26]. This approach increases the surface area that is available for dissolution and also increases the available surface energy. This in turn increases the dissolution rate, but typically not the solubility, at least not markedly unless the particle size is <1 μm [67].

The effect of particle size on solubility constant can be quantified as follows, using a modification of the Kelvin equation [68]:

$$\mathrm{Log}\,(^{*}K_A) = \frac{\mathrm{Log}\,(^{*}K_{A\to 0}) + \gamma A_{\mathrm{m}}}{3.454\ RT} \tag{1.3}$$

where $^{*}K_A$ is the solubility constant for the solute particles with the molar surface area A, $^{*}K_{A\to 0}$ is the solubility constant for substance with molar surface area tending to zero (i.e. when the particles are large), γ is the surface tension of the solute particle in the solvent, A_{m} is the molar surface area of the solute (in $\mathrm{m}^2/\mathrm{mol}$), R is the universal gas constant, and T is the absolute temperature [69].

Nonetheless, particle size is rarely reported as being an important parameter in the determination of solubility. Indeed, accurate measurement of the equilibrium solubility of nano-sized drugs is often complicated by the inability to separate out a supernatant fraction, even after ultra-filtration or centrifugation, due to the presence of very small, suspended particles [26, 67]. Light scattering and turbidity measurements have been utilized to address this issue [67, 70].

1.6 Approaches to measuring solubility during different phases of research and development

Once the new chemical entity (NCE) has been initially synthesized in appropriate quantities, solubility can be measured the first time. Procedural approaches for solubility measurements at this early discovery stage vary from organization to organization. Solubility could be measured for every NCE developed by the organization or alternatively solubility could be measured upon request. However, whatever the process, solubility measurements will be required for a very large number of NCEs and therefore efficient procedures must be in place. There are two main purposes of measuring solubility at this stage [71]:

- The initial solubility measurement tries to answer the fundamental question: is the compound dissolved in the assay medium or has it precipitated out? This question is relevant for many types of assays, for example, biochemical and cellular assays that demonstrate the intrinsic activity of the compound. The same question also applies to assays that support non-clinical safety testing, which are now initiated at much earlier stages of research. In this case, low solubility of an NCE might result in a false negative and consequently hide safety-related risks of a compound or a whole series or scaffold.
- Second, solubility is an important parameter for compound optimization. The goal should be to deliver NCEs with appropriate solubility to ensure sufficient bioavailability and to simplify formulation development and clinical progression.

From a technical standpoint, delivering the required throughput to fulfil both objectives require a high degree of automation. The key to this – as for many other assay formats – is to use pre-dissolved compounds as described in Section 1.2.1. Typically, 10 mmol solutions in DMSO are utilized. This avoids handling of the solid material, which might be non-crystalline, oily, sticky, or highly electrostatic. This overcomes a potential tricky weighing stage and instead compound handling can be carried out by simple volumetric dispensing, that is, pipetting steps. Accordingly, it becomes feasible to implement solubility determinations on robotic systems that carry out manipulation such as volumetric dispensing, compound precipitation, and solid–liquid phase separation by filtration or centrifugation. Typically, these liquid handling systems can be combined with highly sensitive analytical systems, for example, high-performance liquid chromatography (HPLC) or ultra-HPLC (UPLC) utilizing generic methodologies and can be applied to automated solubility assessments with throughputs of 10–100 of compounds per day [65, 72–75]. See further discussions on the analytical approaches in Chapter 7.

However, one must bear in mind that this type of kinetic solubility does not answer the critical question "to what extent does my compound dissolve?" but instead provides the answer to the related question "to what extent does my compound precipitate?" As most drugs are intended for oral administration using solid dosage forms, the first question is more relevant during later research and development phases. The key differentiating point between kinetic solubility obtained using the pre-dissolved compound and thermodynamic solubility obtained using the solid compound is that metastable phases, that is, metastable polymorphs or amorphous phases, are often generated by the former technique. Solubility by the kinetic assay refers to these metastable forms, whereas the thermodynamically stable form will typically be used for further development. In a kinetic solubility assay, the compound will have only very limited time to precipitate out and accordingly will be mainly amorphous in nature. Consequently, solubility will be significantly higher compared to thermodynamic solubility, which typically utilizes the stable crystalline phase [76, 77].

Kinetic solubility is designed to facilitate high-throughput measurements, rather than necessarily providing accurate estimations of the true solubility. Consequently, turbidimetric or similar methods are often used, which allows the rapid determination of solubility using small amounts of compounds (5–50 μg) [78]. The main – and in many cases only – difference between kinetic and thermodynamic solubility assays is the use of DMSO stock solutions, rather than solid material. Handling steps for the solid materials can be difficult to automate and typically become more labour intensive and can constrain throughput of thermodynamic solubility assays. Assessment of solubility by the kinetic or thermodynamic solubility assays is typically limited to generic conditions such as one pre-defined buffer system, typically at neutral pH.

To get a physiologically more relevant understanding – especially for orally administered drugs, thermodynamic solubility can be measured using biorelevant conditions simulating the prevailing conditions within the GI tract. Initially, a pH-solubility profile

is typically generated using different buffers simulating the different pH conditions encountered during the transit of the GI tract. However, a recent Innovative Medicines Strategy (IMI) Innovative tools for oral biopharmaceutics (OrBiTo) collaborative survey challenged the consensus that this is "typically" generated. Margolskee et al. [79] showed that in over one-fifth of cases, pH-solubility measurements are not performed. pH solubility evaluations use simple inorganic or organic buffer systems and they allow investigations of the pH-dependent solubility of the compound. A typical example was recently reported by Sieger et al. [80]. A robotic 96-well-plate automated method was utilized. A small quantity of accurately weighed solute (1–10 mg) was added to the appropriate well, and aqueous buffers (0.5–1.0 mL) of varying pH (typically in the physiological range, i.e. pH 1.2–6.8) were added. The wells were then shaken for 24 h, the contents filtered using 0.45 μm polytetrafluoroethylene (PTFE) filters and assayed using UV spectroscopy. Other standard approaches include the miniaturized shake-flask method [81], potentiometric titrations [82], and small-scale dissolution baths [83].

The standardized saturation shake flask (SSF) methodology for equilibrium solubility determinations was harmonized and validated by Baka et al. [84] and Völgyi et al. [85]. This approach involves accurately weighing the solute and adding it to an excess of buffered medium at controlled room temperature (25 ± 1 °C). The sample is vigorously stirred for 6 h and then left for a further 18 h to sediment, giving a total "incubation" time of 24 h, before centrifuging and sampling the supernatant and measuring the concentration. However, the total incubation time is often defined by the intrinsic dissolution rate of the solute, which in turn is dependent on morphology, crystallinity, particle size, wettability, quantity of solute added, and the intensity of the agitation [86]. In all cases, the equilibrium time must be shown to be appropriate and, sometimes, very long incubation times are needed. This can range from several days or longer. The CheqSol, that is, *Ch*asing *Eq*uilibrium *Sol*ubility approach represents a systematic method to assess the time required for equilibrium to be established [82, 87]. Long times that are required to reach equilibrium bring their own challenges, that is, analyte stability, pH stability, evaporation of solvent, even in some cases microbial contamination of the aqueous buffer. The reader is referred to the excellent review article of Brittain [87] for a more detailed overview of recommended approaches to improve data quality.

An additional approach that can be used to reduce long equilibration times for solutes with low dissolution rates is the facilitated dissolution method (FDM) [88]. This approach employs a small volume, that is, ≤1 % v/v of a second organic solvent that is totally immiscible in the aqueous phase, for example, *iso*-octane, octanol, and dichloromethane. The organic solvent partially solubilizes the solute thereby rapidly facilitating its equilibrium with the aqueous phase. As long as the system continues to contain three phases, aqueous, non-aqueous, and undissolved solid, the thermodynamic solubility is unaffected by the presence of the non-aqueous phase. The solubility of the solute in the water-immiscible organic phase used in the FDM approach

should be at least two orders of magnitude greater than the corresponding solubility in the aqueous phase [86]. For lipophilic solutes, octanol is the best solvent; for less lipophilic solutes, 1,2-dichloroethane is the preferred solvent. Aliquots of the separated aqueous layer are removed, diluted as appropriate, and measured using UV-spectroscopic or HPLC methods. Takács-Novák et al. [86] demonstrated that the FDM method gave similar outcomes to the standard SFF approach. They also commented that the FDM approach can identify those scenarios where the inadequate equilibrium has been attained using the classical SSF method, that is, SSF > FDM, and where the quality of the data from the latter approach should be questioned.

1.7 Application of biopharmaceutical solubility approaches

The GI tract is a complicated biological system with discreet compartments, pronounced changes in pH, ionic strength, and the presence of naturally occurring surfactants, that is, bile acids [89, 90]. As such, even the aforementioned approaches to determine pH-dependent solubility do not provide the complete picture of solubility behaviour of the drug substance that will underpin drug absorption considerations.

Consequently, biorelevant solubility and phase stability, that is, inter-conversion between different salt forms (and polymorphs) in the GI tract should also be assessed. For example, conversion of the free base form of a weak base to the corresponding hydrochloride salt may take place within the acidic conditions found within the stomach. Alternatively, conversion of the designated salt into the less or more soluble hydrochloride salt can occur. Hydrolysis of the designated salt into the less soluble free base (or free acid) form can also occur in these biorelevant media. Although most of the transitions are reported in the literature within the context of dissolution assessments, they are equally or more germane due to the extended duration of the equilibrium solubility experiment, that is, ≥24 h (see Table 1.4 for overview). See chapter 11 on the relationship between solubility and dissolution rate.

Accordingly, there must be a sound knowledge of the phase-stability or conversion of the designated solid-state form during the equilibrium solubility exercise [91]. However, evidence of phase-conversions is still useful information as it almost certainly has biorelevant implications (see Chapter 9). In addition, the solubility of hydrochloride salts can be less than the corresponding free base [92], and other salts of that NCE due to the common ion effect in gastric media [93, 94]. Some examples of such phase transitions are provided in Table 1.4.

Indeed, the challenge of accurately measuring solubility of pharmaceutical salts has necessitated the development of novel computational approaches not dependent on explicit solubility equations, such as p-DISOL-X™ [91, 95, 96]. Salt solubility can also be dependent on experimental design [95]. The reader is referred to

Table 1.4: Overview of typical physical transitions that can be observed in biorelevant solubility determinations.

Typical physical transitions	Overview	Media utilized	Reference
Conversion of free form to salt	Haloperidol[1] free base converted to hydrochloride salt	pH 1.2	[93, 94]
	CI-1041 free base converted to less soluble hydrochloride salt	pH 1.2 (with tween 80)	[97]
Conversion of salt to hydrochloride salt	Haloperidol mesylate salt converted to hydrochloride salt	pH 1.2	[93, 94]
	E2050 dihydrochloride converted to mono-HCl salt	Water (various pH)	[98]
Disproportionation	Haloperidol mesylate salt converted to free base	pH > ca. 5	[93, 94]
	Compound A converted to parent over a 10-h period	SGF (pH 1.2)	[91]
	Compound A converted to metastable form of parent over a 30-min period	FaSSIF (pH 5.0)	[91]
	Bromocriptine mesylate partly converted to amorphous free base	Phosphate buffer (pH 6.5), FaSSIF (pH 6.5)	[99]
	Flurbiprofen tromethamine converted to flurbiprofen once the concentration of salt exceeded 4.3 mM	Water (pH 6.15)	[100]

[1]pH max of haloperidol system was ca. 5. pH max is the pH of maximum solubility for that salt system. At pH max, both salt and free form (base or acid) can coexist in the solid state.

the excellent review article of Brittain [87] for a more detailed overview of this issue; in particular, the case study covering the various haloperidol salts: hydrochloride, phosphate, and mesylate.

Equilibrium solubility is more appropriate than kinetic solubility for later stage development, where API supply is not constrained. However, from a biorelevant solubility perspective, kinetic solubility or indeed dissolution testing (see Chapter 11) can have some advantages. Or rather the time-based, that is, temporal nature of thermodynamic solubility should also be studied. This is because residence times in the stomach and small intestine are typically significantly less than 24 h (see Table 1.5). If the solubility is time dependant or changes with time, this will be biorelevant but will be not be captured using the classical 24-h-based equilibrium solubility methodologies.

Table 1.5: Residence time in stomach and small intestine compartments[1].

GI compartment	Residence time (fasted state) (h)	Residence time (fed state) (h)
Stomach (fundus) [101][1]	0.4	1.04
Stomach (antrum) [101]	0.32	1.58
Small intestine (proximal) [102]	2.00	–
Small intestine (distal) [102]	1.50	–
Small intestine	3.2 [103]	4.76 [103]

[1]Only the stomach and small intestine have been reported. The colon is significantly less important from an absorption perspective, having reduced the surface area and blood volumes.

There are two scenarios where the equilibrium solubility could change significantly over the designated 24-h time period. The first scenario is where there is a change in the solid-state form, typically from a more soluble (metastable) to less soluble (stable) form, that is, polymorph, salt, or co-crystal. Changes to more soluble forms have also been reported. He et al. [91] described μDISS solubility assessments of a zwittterionic NCE (compound A) over a 10-h period in SGF and 1.5 h in FaSSIF. The NCE was a sulfate salt with pK_a of 3.9 (basic) and 7.1 (acidic). In SGF, the authors observed 10-fold higher solubility over a 5-h time course compared to the parent. Thereafter, there was a gradual decrease in aqueous solubility until it equalled that of the parent. The authors showed that after 10 h, the salt had converted to the parent NCE. In contrast, in FaSSIF the initial solubility of the sulfate was 10-fold higher compared to the parent and after 30 min it decreased to fivefold higher and retained this value for the rest of the experiment. Interestingly, in FaSSIF media the residual solid was found to be a higher solubility, metastable polymorph of the parent. The relative bioavailability of the salt was assessed in fasted dogs and the exposure was fivefold greater than the parent. The authors indicated that if the equilibrium solubility had been measured at completion, that is, 24 h, these transitions would have missed. A second example of in situ conversion was recently reported for bromocriptine mesylate in pH 6.5 phosphate buffer and pH 6.5 FaSSIF using μDISS approach [99]. In this case, the undissolved solid was partially amorphous free base.

The second scenario is where the API is poorly wetting over GI-relevant timescales (<4 h), but it will adequately wet and thereby solubilize over an extended 24-h time period.

This is a relatively common phenomenon for “grease ball molecules”, but it is typically under reported [104]. The use of surfactants to facilitate wetting of these hydrophobic APIs is well established, both in dosage form development and dissolution testing [19]. Certain researchers have used wetting kinetics as an alternative approach towards understanding the enhanced dissolution rate of poorly soluble drugs [105]. However, this issue rarely receives any focus within the scope of solubility testing. An additional reason for using biorelevant media, for example,

FaSSIF and FeSSIF, is that they contain naturally occurring surfactants, for example, bile acid salts, which facilitate wetting of hydrophobic APIs. However, even here the time course of the biorelevant solubility determination should be assessed. For a more in-depth discussion on biorelevant media, see Chapter 6. Interestingly, in a recent IMI OrBiTo collaborative initiative, biorelevant solubility information was missing in nearly three quarters of cases [79].

Finally, methods to predict drug absorption and bioavailability have been improved significantly over the last decade. This includes approaches that go beyond allometric scaling [106] and use Biopharmaceutical Classification System (BCS) approaches [32]. During the last few years, the BCS has been refined into the Development Classification System (DCS) [107]. These systems address solubility, permeability, and the dose of the drug. The DCS approach additionally considers dissolution rate and distinguishes between solubility-limited absorption and dissolution-limited absorption, thus providing insights in formulation strategies for poorly soluble compounds. The use of PK simulation software has also become widespread [108] and allows a more detailed understanding of the behaviour of the research compound in humans and animals, including dissolution, solubility, and an understanding of how a drug might precipitate in the GI tract.

1.8 Conclusion

Solubility is one of the most important physicochemical parameters that is used across pharmaceutical research and development. Although solubility is relatively easy to define, it can be difficult to predict using computational methods primarily due to solid-state constraints, for example, enthalpy and entropy considerations. In parallel, experimental methods to assess solubility have been improved and automated during recent years and currently allow measurement of solubility for large numbers of compounds. This holds especially true for measurement of kinetic solubility. The use of kinetic and thermodynamic solubility should be clearly distinguished as the erroneous use of kinetic solubility for compound optimization can be misleading.

However, in later stage of development when API availability is increased, thermodynamic (or equilibrium) solubility, typically over 24 h, becomes significantly more relevant. Additionally, to gain a deeper understanding of the role of solubility in drug absorption in animals and humans, methods and media to mimic in vivo behaviour, that is, behaviour in biorelevant media, have become more and more widespread and easier to use over the recent years. Similarly, just as the transit times in the gastric and small intestinal compartments influence absorption, the temporal aspects of thermodynamic solubility should also be assessed. For example, the solubility should be measured after times such as 1, 4, and 24 h. There is

also a significant overlap between solubility and dissolution. This is particularly important for poorly wetting hydrophobic APIs, where the time course of solubility, which is often dictated by the wetting of the API surface, can significantly influence drug absorption.

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Annette Bauer-Brandl and Martin Brandl

2 Solubility and supersaturation

2.1 Introduction and fundamental considerations

Solubility and supersaturation are classical issues – for example in chemical engineering – regarding crystallization processes of chemical compounds. This aspect is addressed in detail in Chapter 10 of this book. Solubility and supersaturation are also relevant for pharmaceutical drug delivery: Supersaturable drug delivery systems are often used to increase the bioavailability of poorly soluble drugs that are administered as oral solid dosage forms (see Chapter 8). In order to understand their properties in a biopharmaceutical context, transient states of supersaturation need to be considered in settings, where dissolution media gradually change their compositions as is the case during passage through the digestive system. Under these circumstances, a clear distinction between solubility and supersaturation can become difficult, and the impact on dissolution rate, drug absorption rates, and bioavailability can be confusing. This chapter is intended to promote the understanding of these questions.

2.1.1 Definitions and significance of solubility and supersaturation

2.1.1.1 Classical definitions of solubility and supersaturation

2.1.1.1.1 *Solubility*

Solubility of a solute (e.g., a drug substance) refers to the qualitative and quantitative composition of its saturated solution. This means that the solution is in a dynamic equilibrium between the solid particles of the solute in the form of a suspension in a given solvent that is kept under constant conditions (with respect to temperature, solvent composition, etc.). The solubility is expressed as the proportion of the designated solute in the designated solvent system.

The equilibrium refers to a certain solid-state form of the solute. If the suspensions contained different crystalline polymorphs of the compound or the same compound in its amorphous state, each of them would strive towards its individual equilibrium according to different solubilities for different solid-state forms. For the same reason that there is an equilibrium between the solid state of the solute and the solvent, the solubility depends widely on solvent composition. If a pure solvent contains any compounds in

Annette Bauer-Brandl, Martin Brandl, Department of Physics, Chemistry and Pharmacy University of Southern Denmark, Campusvej 55, DK-5230 Odense M.

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addition to the solute, again the equilibrium will be different. Examples of such additives that are frequently used in a pharmaceutical context are buffer salts, cosolvents, polymers, and surfactants.

2.1.1.1.2 Supersaturation

A supersaturated solution has a higher concentration of a given solute in a given solution as compared to the equilibrium state. A supersaturated solution is thus necessarily unstable.

Such instability of supersaturated states is frequently found in the literature designated as "metastability" (which translates to "beyond stability"). This term is designated to those cases where the "metastable" conditions can be preserved for some time. This time is not specified and may range between seconds and hundreds of years and beyond. Thus, IUPAC [1] in general suggests avoiding the term "metastable", because it relates a thermodynamic term (stability) with a kinetic property.

With respect to the solubility of drugs, it is worth to not only consult literature in chemistry but also in the pharmaceutical field, for example, FDA Guidelines for ANDAs [2]. The term "true thermodynamic solubility" is used for the condition "which is reached after infinite time". This definition is perfectly in line with the classical (IUPAC) definition of solubility, namely, the state that is reached at infinite equilibrium time. The term "solubility" is clearly distinguished from the term "apparent solubility", which literally means the solubility that is observed. However, when it comes to apparent solubility and supersaturation in a pharmaceutical context, FDA defines it as follows:

"Apparent solubility refers to the concentration of material at apparent equilibrium (supersaturation)."

This use of the terms is difficult to bring in line with the aforesaid. The difficulty arises from the IUPAC definition of supersaturation that is an instable state. Such instable states may be observed (i.e., they are apparent) for quite long-time periods, but still they are not at equilibrium.

The following text refers strictly to the IUPAC definition. However, when discussing apparent solubility and its impact on biopharmaceutics, the intention of the FDA wording will become more obvious.

2.1.1.2 The concept of differential solubility

Consider an apparatus containing a solution in a flowing system, for example, along a process line of a crystallization plant in chemical industry. For practical reasons, different parts of this system may be exposed to slightly altered conditions. Examples thereof are temperature gradients or concentration gradients that are generated by physico-chemical conversions or the gradual introduction of additives. Depending on

stirring effectiveness, local differences in additive or temperature distributions induce local (small) differences in solubility. Such conditions may be denoted as "differential solubility" because here the infinite solubilities are connected to the global solubility value in the same system. It is acknowledged that differential solubility addresses the borderline between thermodynamic solubility and kinetic effects (gradually changing conditions) if the differences are very small. Therefore, differential solubility may have very limited effect in terms of solubility enhancement factors. However, if these small gradients persist over a long-time period, they will lead to considerable solute transport by dissolution and diffusion processes. In such a dynamic system where the composition of solutions changes with both time and location, possibly supersaturated transitional states may also be generated. They are much more difficult to describe quantitatively as compared to homogeneous systems. In most cases the existence of differential solubility is therefore disregarded, unless it leads to supersaturation followed by precipitation of the solute and thus its significance becomes obvious.

2.1.1.3 Significance of solubility, differential solubility and supersaturation for oral drug delivery systems

Solubility restricts the amount of a drug substance that will be dissolved at equilibrium, for example, from an oral dosage form, in a closed system. Typical closed systems in this context are shaked flasks in which solubility is measured experimentally, and for dissolution studies in single-vessel set-ups (including certain transfer models).

After the oral intake of a dose of a drug, high drug concentrations occur in the gastrointestinal fluids as compared to the concentration of the drug in the rest of the body, e.g. in the blood circulation or in tissues. High concentration gradients between the gastro-intestinal tract and the blood lead to high transfer rates for the passive transport processes of drug molecules from the inner lumen of the gastrointestinal tract into the blood stream. This process is called (passive) *drug absorption*. The higher the concentration gradient, the faster is the absorption. During the time period over which the concentration gradient is maintained, the amount of drug that is transported over the intestinal wall (but not metabolized) can be accumulated to be defined as the drug fraction absorbed. It is often denoted as "bioavailability" and expressed in percent of the full dose given reaching systemic circulation in unchanged form. In this view on transport processes, to enhance oral bioavailability, increasing drug concentrations in the gastro-intestinal tract as much as possible appears as a straightforward formulation approach for poorly soluble drugs, if possible even above the solubility limit. In other words, it is advantageous to choose those formulations that may induce supersaturation. Such formulations are designated as "supersaturable" or "supersaturating" formulations. Experimental data of such systems is accessible through dissolution studies.