Review paper **PL 1**

PHARMACEUTICAL SOLUBILITY AS A CRITICAL DETERMINANT OF DRUG QUALITY AND PERFORMANCE

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ABSTRACT

In pharmaceutical research, solubility plays a key part in the assessment of pharmacokinetic risks. Poor drug absorption, reduced efficacy, excessive metabolism, and adverse reactions are frequently related to issues of drug solubility. During early discovery research at pharmaceutical companies, many thousands of molecules are considered. Most are rejected due to perceived unfavorable properties. Pharmaceutical solubility along with permeability link drug quality with its bioavailability and overall performance. For ionizable drugs, solubility depends on pH, ionic strength, ionization, self-association, complex formation, and solid-phase transformations. Studies demonstrate that apparently simple solubility measurements may conceal multiple aqueous and solid-state equilibria. Our research findings obtained within the physicochemical framework developed by Serajuddin and Avdeef, demonstrate that rigorous solubility measurement and mechanistic analysis are essential for salt selection, formulation design, dissolution testing, and reliable assessment of drug quality and performance.

INTRODUCTION

Solubility is often introduced in pharmaceutical development as a single numerical property: the amount of drug that dissolves in a specified medium at a specified temperature [1]. This description is useful, but for many drug substances it is incomplete. A measured solubility is the observable result of several coupled processes, including dissolution of a particular solid form, ionization, association of dissolved species, complex formation with components of the medium, and possible precipitation or conversion to another solid phase. Consequently, the reported value can depend strongly on experimental conditions and on whether equilibrium has actually been established.

The importance of this issue increases as drug discovery produces a larger proportion of molecules with low aqueous solubility. Poor solubility may limit

dissolution in the gastrointestinal tract and thereby reduce or make variable the fraction of an orally administered dose that becomes available for absorption. Solubility is therefore connected not only with formulation development but also with the reproducibility of drug performance. A compound can have favorable pharmacological potency while remaining difficult to develop as a reliable medicine because its physical form and aqueous behavior are inadequately understood.

The objective of this contribution is to illustrate, through selected studies, why pharmaceutical solubility should be considered a mechanistic property rather than a single number. The examples will demonstrate how careful solubility science can contribute to rational drug quality assessment and formulation design.

DISCUSSION

A majority of the new chemical entities (NCE) that emerged as potential drug candidates in pharmaceutical development during the past 2-3 decades are practically insoluble solids consisting of ionizable molecules [2, 3]. Interpreting their solution properties in the course of measuring solubility as a function of pH is of crucial importance as the pH range within human body goes from 1-3 (gastric pH) to 5-8 (intestinal pH). Although solubility determination seems simple and straightforward, optimal experimental design to measure the aqueous equilibrium solubility of an ionizable substance requires a number of critical considerations [4, 5]. The factors affecting the quality of the obtained results are numerous: temperature, purity, and the composition of the starting compound, type and composition of buffer in use, ionic strength, amount of solid phase in excess, amount of substance to total solution volume ratio, carbon dioxide percentage, mixing and sedimentation time, phase separation method, chemical composition and properties of the solid phase in equilibrium with the solution, etc. A multitude of methods can be found in the literature, but today's druglike molecules can pose special challenges, sometimes not adequately addressed in practice. The published literature is replete with incomplete/ambiguous and potentially misleading examples of solubility reports, frequently documented inconsistently.

Based on above considerations, detailed and precise study of compound solubility and the dissolution rate is at the core of the development of bioavailable drug dosage forms and clinically effective pharmaceutical products that would dissolve in gastric and intestinal fluids after oral administration or not precipitate in the blood after intravenous dosing. Furthermore, high quality experimental data can have a major impact on the quality of statistical methods to predict solubility of druglike molecules in an effort to anticipate solubility requirements and risks during structural design in the early stages of drug discovery [1, 6].

A *white paper* on consensus recommendations for improving data quality in equilibrium solubility measurement of ionizable drugs was published [5]

emphasizing the importance of precise solubility measurements. Optimal experimental design requires a number of critical considerations. Briefly, the aqueous medium to which the substance is added ideally contains a buffer to help attenuate changes in pH due to sample addition. To this medium, the substance may be added in a number of ways: (a) as a highly supersaturated aqueous solution, (b) as a saturated hot solution, (c) as a concentrated solution in a water-miscible organic solvent, or (d) as a solid – which may or may not be in a thermodynamically stable crystalline form. The first three approaches are precipitation routes, while the fourth involves dissolution and is most commonly used and best understood. With sufficient added solid and enough time, chemical equilibrium is established, where the crystalline solid substance is in dynamic equilibrium with its solution form. As the dissolution proceeds, the solid phase can re-precipitate as another form with another structure (polymorphic transitions) and even another composition (salt disproportionation, formation of crystal solvates, new salt forms, or loss of solvate from the starting solid). In solution, the substance may undergo ionization, self-aggregation (forming water-soluble dimers, trimers, etc., or micelles in the case of amphiphilic substances), or complexation with some of the buffer components. Both phases of the solubility process are important to consider, as measured solubility depends both on the solid and the solution forms.

Since, as mentioned earlier, most compounds currently synthesized in drug discovery laboratories have poor aqueous solubility, a variety of methods to increase solubility and/or dissolution rate, and thereby increase their bioavailability, have been developed. Still, most of them, like particle size reduction, salt formation, conversion to amorphous form, solid dispersion, and solubilization in lipids or lipid-surfactant mixtures have their own limitations. To mitigate some of the above limitations, a novel method of drug solubilization in aqueous media by acid–base interaction has been developed in the research group of Prof. Serajuddin, [3, 7-11]. This novel approach of greatly increasing the solubility is based on interaction of a model low-soluble basic drug in an aqueous medium with acidic species that would not normally form salts with it.

CONCLUSION

Solubility is one of the most consequential physicochemical properties of a drug substance, but it is also one of the easiest to oversimplify. Our studies [10-14] demonstrate that pH-dependent solubility may involve several simultaneous aqueous and solid-state equilibria, including ionization, complexation, self-association, common-ion effects, and salt interconversion.

For pharmaceutical development, the key message is straightforward: a solubility value is meaningful only when the chemical system that produced it is understood. Rigorous measurement, appropriate equilibrium modeling, and solid-state characterization transform solubility from a descriptive number into a

mechanistic tool. Such an approach can improve salt selection, formulation design, dissolution testing, and interpretation of drug quality and performance.

In this sense, pharmaceutical solubility is not merely a preformulation parameter; it is a central link between the physicochemical identity of a drug and its behavior as a medicine.

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