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Preface

Drug solubility: how to measure it, how to improve it ☆

Solubility of active pharmaceutical ingredients (API) has always been a concern for formulators, since inadequate aqueous solubility may hamper development of parenteral products and limit bioavailability of oral products. In recent years, the problem has become more acute and more common as pharmaceutical companies cast the drug discovery net ever wider in the anticipation of finding new therapeutic approaches and improving drugs for existing therapeutic areas.

With the advent of high throughput screening for receptor activity, throughput requirements for physicochemical characterization of new APIs have increased commensurately. This challenge has been met by the pharmaceutical industry by improving *in silico* predictions of important physicochemical characteristics such as solubility, ionization constants and partition coefficients and by developing high throughput characterization methods to enhance predictions with experimental data. Additionally, new medium throughput methods have also been developed to more accurately characterize solubility of new APIs before they are taken forward into animal and human studies.

All these developments are described in the first three contributions to this issue. Faller and Ertl review computational models to predict water solubility, with emphasis on the accuracy of the various prediction methods. They also stress the importance of comparing calculated and measured solubility, and provide guidelines as to when to trust the computed value. Alsenz and Kansy summarize current experimental approaches to solubility determination, with emphasis on recent advances in the experimental methods used to determine drug solubility in drug discovery and early development. Methods for both kinetic and thermodynamic (equilibrium) solubility with both high throughput and traditional methods are presented. Avdeef reviews the experimental and computational basis of the pH-dependent measurement of solubility of sparingly-soluble ionizable drugs. Recently described compound-sparing (but still accurate) approaches, suitable for application in preclinical development, and appropriate for the analysis of solubility of "problematic" molecules, are critically examined. A number of useful experimental methods are reviewed, including the miniaturized shake-flask microtitre plate, the micro solubility self-calibrating direct UV, the potentiometric, and the micro dissolution methods.

Rounding out the discussion on assessing solubility is a contribution by the editors on the subject of gastrointestinal (GI) solubility of APIs, since GI solubility may be far greater than the solubility measured in water. The use of aqueous solubility to predict oral drug absorption can therefore lead to very pronounced underestimates of the oral bioavailability, typically for drugs which are poorly soluble and lipophilic. Various methods for estimating intra-lumenal solubilities are presented, with emphasis on the two most widely implemented methods: determining solubility in fluids aspirated from the human gastrointestinal tract, and determining solubility in so-called biorelevant media, composed to simulate these fluids.

Despite the relatively favorable environment, API solubility in the GI tract can, and often does, limit its oral bioavailability by affecting dissolution rates and/or the maximum amount that can be dissolved intra-lumenally. Similarly, for intravenous application, the API must be dissolved in a vehicle in order to meet tolerance and safety demands. In the second part of the issue, the focus is shifted from estimation of solubility to improvement of API solubility and/or dissolution by both chemical (salts and prodrugs) and formulation (crystal engineering, nanosizing, lipid formulation and cyclodextrin complexation) approaches.

Salt formation is a common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Serajuddin presents the physicochemical principles of salt solubility. Whether certain acidic or basic drugs would form salts and, if salts are formed, how easily they would dissociate back into their free acid or base forms depend on interrelationships of several factors, such as S_0 (intrinsic solubility), pH, pK_a, K_{sp} (solubility product) and pH_{max} (pH of maximum solubility) and these issues are illustrated with practical examples. Non-ideality of salt solubility due to self-association in solution is also discussed.

Crystal engineering offers a number of routes to improved solubility and dissolution rate, which can be adopted through an in-depth knowledge of crystallization processes and the molecular properties of active pharmaceutical ingredients. The article by Blagden and colleagues covers the concept and theory of crystal engineering and discusses the potential benefits, disadvantages and methods of preparation of co-crystals,

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metastable polymorphs, high-energy amorphous forms and ultrafine particles. Nanosizing refers to the reduction of the active pharmaceutical ingredient (API) particle size down to the sub-micron range, with the final particle size typically being 100-200 nm. The reduction of particle size leads to a significant increase in the dissolution rate of the API, which in turn can lead to substantial increases in bioavailability. Kesisoglou and colleagues describe the principles behind nanosizing, the production and characterization of nanoformulations as well as the current experience with utilization of such formulations *in vivo*.

Cyclodextrins can form non-covalent dynamic inclusion complexes with a wide variety of APIs in solution, resulting in large increases in solubility and thus improvements in parenteral application on the one hand and in oral bioavailability of poorly soluble APIs on the other hand. A number of cyclodextrin-based products have reached the market based on their ability to (temporarily) camouflage undesirable physicochemical properties. The review by Brewster and Loftsson provides a general background to the use of cyclodextrin as solubilizers as well as discussing in detail the kinetic and thermodynamic tools and parameters useful in the study of drug solubilization by cyclodextrins.

The ability of lipid-based formulations to facilitate gastrointestinal absorption of many poorly soluble drug candidates has been thoroughly documented in the published literature. However, a considerable gap exists between our knowledge of this technology and the know-how required for its application. Hauss provides a comprehensive summary of the development, characterization, and utilization of oral lipid-based formulations, from both physicochemical and biopharmaceutical perspectives.

In the closing contribution, Stella and Nti-Addae review the use of prodrugs to effect improved oral and parenteral delivery of poorly water-soluble problematic drugs, using both marketed as well as investigational prodrugs as examples. Data are presented to illustrate that an increasing percentage of new drug approvals in fact contain prodrugs. They emphasize that prodrug interventions should be considered early in the drug discovery paradigm rather than as a technique of last resort.

The editors wish to thank all the contributors for their excellent and very current synopses of solubility-related research in the pharmaceutical arena. It is clear that pharmaceutical research and researchers are responding extremely well to the challenge of poorly soluble APIs and that we may expect continued rapid progress in the prediction, measurement and improvement of solubility in the years to come.

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