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Solubility of sparingly-soluble ionizable drugs ☆

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Abstract

The experimental and computational basis of the pH-dependent measurement of solubility of sparingly-soluble ionizable drugs is reviewed. 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, potentiometric, and the micro dissolution methods. Several molecules were selected as case studies to illustrate important concepts, with re-analysis of literature data using recently established computational tools.

Keywords: Sparingly-soluble ionizable compounds; pH-dependent solubility; Solubility equations; Aggregation; Complexation; Shake-flask method; Miniaturized shake-flask method; Dissolution template titration method; Micro dissolution method

Contents

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1. Introduction

The experimental and computational basis of the pH-dependent measurement of solubility of sparingly-soluble ionizable drugs is reviewed. New, 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. "Kinetic" solubility methods (nephelometry/turbidity) are beyond the intended scope of coverage in this review.

Several selected molecules which illustrate important concepts are considered in detail, with some literature data reanalyzed and illustrated, using newly-improved computational tools. Exhaustive compilations of experimental results are covered elsewhere [1–5].

Several excellent books and reviews serve as background material for the present discussions: in-depth coverage of solubility [6–8]; phase-solubility methods [9]; salt formation/selection [10–12]; polymorphism/amorphism [13–15]; excipient effects [16]; complex analysis [17]; solubility/dissolution profiling [18,19].

Solubility reactions, being heterogeneous, are often slow to reach equilibrium. Surface-active compounds, when dissolved in water to saturation, can form self-associated aggregates which can complicate the interpretation of the aqueous solubility data. Use of cosolvents (e.g., ethanol, propylene glycol, polyethylene glycol 400, 1-methyl-2-pyrrolidone) can mitigate some of these effects. If measurements are done in the presence of surfactants (e.g., sodium lauryl sulfate, bile salts, mixed micelles, simulated intestinal fluids), or complexing