Kawakami, K. (2012). "Modification of physicochemical characteristics of active pharmaceutical ingredients and application of supersaturatable dosage forms for improving bioavailability of poorly absorbed drugs." *Adv Drug Deliv Rev* 64(6):480–495.

New chemical entities are required to possess physicochemical characteristics that result in acceptable oral absorption. However, many promising candidates need physicochemical modification or application of special formulation technology. This review discusses strategies for overcoming physicochemical problems during the development at the preformulation and formulation stages with emphasis on overcoming the most typical problem, low solubility. Solubility of active pharmaceutical ingredients can be improved by employing metastable states, salt forms, or cocrystals. Since the usefulness of salt forms is well recognized, it is the normal strategy to select the most suitable salt form through extensive screening in the current developmental study. Promising formulation technologies used to overcome the low solubility problem include liquid-filled capsules, self-emulsifying formulations, solid dispersions, and nanosuspensions. Current knowledge for each formulation is discussed from both theoretical and practical viewpoints, and their advantages and disadvantages are presented.

Kerns, E. H. et al. (2008). "In vitro solubility assays in drug discovery." *Curr Drug Metab* 9(9):879–885.

The solubility of a compound depends on its structure and solution conditions. Structure determines the lipophilicity, hydrogen bonding, molecular volume, crystal energy and ionizability, which determine solubility. Solution conditions are affected by pH, cosolvents, additives, ionic strength, time and temperature. Many drug discovery experiments are conducted under "kinetic" solubility conditions. In drug discovery, solubility has a major impact on bioassays, formulation for in vivo dosing, and intestinal absorption. A good goal for the solubility of drug discovery compounds is >60 μg/mL. Equilibrium solubility assays can be conducted in moderate throughput, by incubating excess solid with buffer and agitating for several days, prior to filtration and HPLC quantitation. Kinetic solubility assays are performed in high throughput with shorter incubation times and high throughput analyses using plate readers. The most frequently used of these are the nephelometric assay and direct UV assay, which begin by adding a small volume of DMSO stock solution of each test compound to buffer. In nephelometry, this solution is serially diluted across a microtiter plate and undissolved particles are detected via light scattering. In direct UV, undissolved particles are separated by filtration, after which the dissolved material is quantitated using UV absorption. Equilibrium solubility is useful for preformulation. Kinetic solubility is useful for rapid compound assessment, guiding optimization via structure modification, and diagnosing bioassays. It is often useful to customize solubility experiments using conditions that answer specific research questions of drug discovery teams, such as compound selection and vehicle development for pharmacology and PK studies.

Narayan, P. (2011). "Overview of drug product development." *Curr Protoc Pharmacol* Chapter 7: Unit 7(3): 1–29.

The process for developing drug delivery systems has evolved over the past two decades with more scientific rigor, involving a collaboration of various fields, i.e., biology, chemistry, engineering, and pharmaceutics. Drug products, also commonly known in the pharmaceutical industry as formulations or "dosage forms," are used for