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Technical Note: Solubility Measurements

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The solubility of any active pharmaceutical ingredient (API) in aqueous solutions is key information that should be obtained as early as possible in the development of a new product. Solubility data is used in all steps of product development and in classifying the API according the Biopharmaceutics Classification System (BCS). If the API has high solubility in aqueous systems (BCS1 or BCS3) and it is formulated in a rapidly dissolving solid oral dosage form, there is a possibility, with appropriate justification, of requesting a waiver of in vivo bioavailability or bioequivalence studies (*1*).

Solubility data is a key parameter in selecting the composition and volume of medium to be used in dissolution or in vitro release testing.

The U. S. Pharmacopeia is proposing the new General Chapter <1236> *Solubility Measurements* (*2*). This chapter provides an overview of the concepts and equations related to thermodynamic equilibrium and solubility. Also, it discusses the methods to empirically estimate the intrinsic solubility of compounds.

The factors that affect solubility and solubility measurements are:

- **pH**: The solubility of ionizable acids and bases is pH dependent because the charged moiety has much higher aqueous solubility. Because ionizable molecules can differ in the number and type of ionizable groups, it is important to explore solubility across a range of pH values.

- **Salts and counterions**: Ionizable compounds can also form salts with oppositely charged counterions. The reduction in the solubility of the charged molecule with increasing counterion concentration is referred to as the common-ion effect, and it may affect the solubility at low and high pH when the pH adjuster has a common ion.

- **Cosolvents**: Water is often a poor solvent for many APIs, but water is miscible with other solvents, such as ethanol, propylene glycol, and so forth, that may provide good solubility for these substances. Low concentrations of the poor solvent, typically water, in the cosolvent mixture can dramatically reduce the solubility of the solute. For this reason, solutions containing cosolvents are particularly prone to precipitation when diluted due to the significant change in solubility.

- **Surfactants**: Above the critical micelle concentration (CMC), the number of micelles in a solution increases linearly as the concentration of surfactant increases. If the API is able to partition into the micelle, its solubility will increase linearly as the number of micelles increases.

- **Complexing agents**: Complexing agents may form complexes with low-solubility APIs and enhance their solubility. The solubility enhancement is expected to increase linearly as the concentration of the complexing agent increases.

- **Surface area (dissolution rate)**: The Noyes-Whitney equation (*2*) indicates that smaller particles will have greater surface area and will dissolve more quickly. To reach the equilibrium solubility as quickly as possible, the surface area should be kept as high as possible (i.e., smaller particles) and the diffusion layer thickness kept as small as possible (i.e., good mixing).

- **Surface energy (nanoparticles)**: When particle size approaches the nanoparticle range, the surface energy of the particle may affect the solubility.

This proposed new chapter also recommends the experimental conditions for the saturation shake-flask method used in the determination of equilibrium solubility. This method is considered by most to be the most reliable and widely used method for solubility measurement. The medium employed for solubility measurements should be selected to be relevant to the application: biorelevant media for absorption and bioavailability studies, dissolution media for dissolution studies, an appropriate buffer that allows control of ionic strength and counterion types over a wide pH range for research purposes.

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For the determination of apparent solubility, the methods described are potentiometric titration and turbidimetry.

Because solubility should be determined as early as possible in product development, it is necessary to use methods that can determine apparent solubility with as little compound as possible and with the necessary high-throughput. Thus, the chapter makes some recommendations on the use of a miniaturized version of the shake–flask method.

The chapter lists the composition of several biorelevant media that can be used in solubility measurements. For human applications, the media are fasted-state simulated gastric fluid (FASSGF), human fed-state simulated gastric fluid (FESSGF), fasted-state simulated intestinal fluid (FASSIF-V2), human fed-state simulated intestinal fluid (FESSIF-V2), and simulated colonic fluid (SCOF2). For studies involving dogs, the media are fasted-state simulated gastric fluid (FASSGFC pH 1.2–2.5), fasted-state simulated gastric fluid (FASSGFC pH 2.5–6.5), and fasted-state simulated intestinal fluid (FASSIFC). For bovine studies, media with pH 2.5, 3.5, 5.0, and 6.8 with and without short-chain fatty acids are suggested.

The proposed version of the chapter addresses the biorelevant media for dogs and cattle. For other animal species such as swine, poultry, and cats, the information available in the public domain does not give enough detail on the composition of the gastrointestinal fluids of these animals. As more data and information are gathered, the scope of this general chapter will be expanded to include these other animal species.

REFERENCES

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