Solubility Measurement〈*G2-6-190*〉

(溶解度測定法〈*G2-6-190*〉)

Solubility is the upper limit of the concentration at which a solute can dissolve in a solvent. Solubility of excipients or drugs is important information for their property and appropriate handling. This method describes the main points to consider in the measurement of equilibrium solubility, which is commonly stated as the solubility of a solid drug substance. It also outlines standard methods used for drug classification based on the Biopharmaceutics Classification System (BCS), etc.

Dissolution is defined as a state in which solids are homogeneously mixed with a solvent and forming a solution. Equilibrium solubility is defined as the concentration of a solution (saturated solution) where the solute is in dynamic equilibrium between the dissolved and the undissolved states, especially in the presence of excess solute. Transient supersaturation before reaching equilibrium solubility or incomplete dissolution may lead to a concentration (apparent solubility) that is either higher or lower than the equilibrium solubility. Solubility is stated in units of concentration such as molarity, mole fraction, mole ratio, w/w, w/v, etc. This method is not applicable to nanoparticles, materials prepared using particular types of solubilization techniques, materials containing particles that are difficult to remove by sedimentation or filtration, or polymers, all of which are not suitable for evaluation by this method.

The solubility measured by this method is affected by the physico-chemical properties of the material (e.g., surface area, particle size, crystal form, solvate), the properties of the solvent (e.g., pH, polarity, surface tension, presence or absence of surfactants, cosolvents, ion type), and the measurement parameters (e.g., temperature, time, agitation method). Therefore, in solubility measurements, these factors should be taken into consideration, and measurement conditions should be set according to the purpose of the solubility evaluation.

The shake-flask method described below is used for the measurement. Other validated methods may be used.

1. Solvent Selection

Select the appropriate type, pH, and composition (e.g., types and concentrations of buffers or surfactants) of the solvent to suit the purpose. Solvents such as water or methanol, for instance, are used for the evaluation of basic properties of drugs. In addition, the use of solvents in a physiological pH range (pH1.2 – 6.8) reflecting the environment of the relevant site is recommended in the measurement for BCS classification to predict the gastrointestinal absorption or bioavailability of a drug. When a solvent with a different composition from the compendial medium is used based on the purpose, its composition as well as the calculated ionic strength should be reported as necessary with the solubility result.

2. Preparation of Suspension

Add the solvent and the sample to a stoppered flask or vial to prepare a suspension. Prepare three or more independent samples to obtain at least three results of solubility measurements.

The amount of the sample should be sufficient to prepare a saturated solution, while it is not necessary to weigh or measure the exact amounts of the solvent and the sample. To rapidly obtain equilibrium solubility, the surface area of the sample can be made as large as possible by grinding or sieving before adding it to the solvent or by using ultrasonic treatment after the addition to the solvent. Pay attention to changes in the crystal form in this case.

3. Preparation of Saturated Solution

A saturated solution is obtained by removing the undissolved material from the suspension that reaches equilibrium following agitation by a suitable method.

Agitation time should be set to provide sufficient time for equilibrium to be reached, and multiple samplings should be performed at intervals that allow the determination of dissolution equilibrium. When the change in concentrations at multiple time points is found to be small (e.g., less than a 5% change in 24 hours, or less than a 0.2% change per hour[1)]), it can be judged that equilibrium has been reached. To verify that the apparent solubility has reached equilibrium solubility, it is recommended to further agitate the same suspension using the same procedures (e.g., an additional 24 hours.) to confirm the concentration. Note that there is no correlation between the value of equilibrium solubility and the time to reach equilibrium.

To remove the undissolved material, allow the suspension to stand or centrifuge the suspension until the undissolved material to sediment, then withdraw the supernatant liquid, taking care not to incorporate the undissolved material. When necessary, filter the supernatant liquid using an appropriate filter. Pay attention to the adsorption of the material to pipettes, containers, etc. The temperatures during agitation and sedimentation after agitation of the suspension should be set and controlled adequately according to the purpose (e.g., ±0.5°C).

Measure the pH of the solution before the addition of the material and after the completion of equilibration. When the pH of the solution changes as the material dissolves, adjustment of pH may be required according to the solvent type or the purpose of the evaluation. Alternatively, it would be desirable to use a solvent with higher buffer capacity.

4. Measurement of Drug Concentration in Solution and Confirmation of Crystal Form

The concentrations of a solute in solution are measured quantitatively by Liquid Chromatography *<2.01>*, Ultraviolet-visible Spectrophotometry *<2.24>*, or other appropriate methods. When a material degrades in a solvent, it is necessary to distinguish between the material and its degradate in the analysis. The solution is diluted if necessary before analysis to avoid deposition or precipitation of the material during analysis.

It is recommended to check for changes in the crystal form of the material in suspension by using an appropriate method (e.g., X-ray powder diffraction method, Raman spectroscopy, near-infrared spectrophotometry, differential scanning calorimetry). When a change in the crystal form is observed, the interpretation of the data should be made fit for the purpose.

References

1) US Pharmacopeia (2024), <1236> Solubility Measurements.