**Measurement of Solubility:**

N.B. –

 The solvent and solute must be pure.

 A saturated solution must be obtained before any solution is removed for analysis.

Clinical Relevance of Solubility:

 Solubility can affect bioavailability and therapeutic response.

 Need enough drug in solution to reach concentrations that are therapeutically meaningful.

 Stability of drug.

 Formulated drug product disintegrates into dispersed drug particles, which undergo dissolution into

solubilised drug which passes a membrane (must be permeable to drug) and is absorbed.



Increasing no. drugs BCS Class II and IV (poorly soluble drugs). 90% and higher = high permeability. Below

90% - low permeability.

API = Active Pharmaceutical Ingredient, NCE= New Chemical Entity (still in developmental stages).

Measurement of Solubility:

N.B. –

 The solvent and solute must be pure.

 A saturated solution must be obtained before any solution is removed for analysis.

 The method of separating a sample of saturated solution from undissolved solute must be satisfactory (temp., volatile solvents).

 The method of analysing the solution must be reliable (UV, HPLC, Refractometry, etc.)

 Temp. must be adequately controlled.

**Static Methods-** determination of solubility is performed when an equilibrium state is reached.

o Flask Method- shake and excess of a finely powdered substance with the solvent at the required temp. until equilibrium is reached. Filter and assay (quantification of substance).

Variation- heat an excess of solid with the solvent and allow to cool to the required temp.

o Preparation of a Number of Mixtures- containing a fixed amount of the solute in variable volumes of the solvent (or varying quantities of the solute in a fixed volume of solvent) and shaking them at the required temperature until equilibrium is reached.

 Determination of approximate solubility prior to flask or other method

 Volatile solvents

Mixtures are shaken and visually checked for undissolved particles.

Approximate solubility is determined and a further method is chosen

**Dynamic Methods**- the concentration of the solute in solution is checked periodically before attaining a plateau which is considered to be an equilibrium.

 Solubility profiles of high energy solids (such as polymorphic/amorphic forms)/anhydrous forms undergoing solvation during dissolution.

o Turbidimetry- the solute is dissolved in an organic solvent. Portions of this solution added slowly to water/ an aqueous buffer. The mixture will remain clear unless the aqueous buffer solubility is reached and precipitation occurs. Volume added against turbidity (extrapolate back to the point where precipitation began).