INDUSTRIAL PHARMACY-I

UNIT I-PREFORMULATION

CLASS3

TOPIC: Partition coefficient,Physical form (crystal & amorphous)

Partition Coefficient

Partition coefficient (Log P) value is defined as ratio of unionized drug distributed between aqueous and organic phase. Oil-water partition coefficient gives the idea about drug's ability to cross the lipidic membrane. Lipophilic/hydrophilic balance is one of the most important contributing factors for optimum drug absorption and delivery. Due to lipidic nature of biological membrane, the amount of drug absorbed depends heavily on its lipophilicity. It is the unionized form of molecule that has better lipophilicity and hence it has received so much importance.
LogP=(CoilCwater)equilibriumLogP=CoilCwaterequilibriumE1

If the value of Log P is 0, it indicated that drug has equal distribution in water and partition solvent.
Value of Log P less than 1 is indicative of higher water solubility and value greater than 1 is indicative of higher lipidic solubility.
For optimum solubility and absorption, a proper hydrophilic-lipophilic balance is necessary.
Determination of Log P value in biological system is next to impossible task, so several methods are available to determine partition coefficient of molecule in vitro, which are as follows:
* Shake flask method
* Chromatographic method (HPLC)

* Computation based on software

* Countercurrent/filter probe method

Highly used method is shake flask method that utilizes octanol-water system to determine drug's partitioning behaviors. There are several reasons behind selection of octanol as partitioning solvent, which can be explained as follows:

* Octanol is believed to mimic the lipoidal character of biological membrane as it contains polar head and nonpolar tail.

* Octanol is organic compound that is immiscible with water; however, some of the water is expected to be present in polar head portion.

* Solubility parameter for most of the drugs resembles with that of octanol

Hypordiscriminating solvents more polar than octanol like Butanol and pentanol are used to simulate buccal membrane

Hyperdiscriminating solvents less polar than octanol like Chloroform and Cyclohexane are used to simulate Blood brain barrier system

Rule of 5 States that drug candidate have poor permeability and poor absorption if a drug exceeds two or more following limita

- Logp>5
- >5 hydrogen bond donors(no of NH+.OH-)
- Mol WT>500
- >10 hydrogen bond acceptors(no of N and O s)
- Molar refractivity should lie between 40-130

Drug with high logp high membrane permeability is more partitioned into lipid bilayer but sequestered leads to less absorption

Bulk characterization:

Bulk properties of solid dosage form such as crystallinity, polymorphism, particle size, powder flow property, etc are likely to change during process development.So to avoid misleading predictions of stability or solubility, characterization of preformulation lots is necessary.

CRYSTALLINITY:

Crystal habit describes outer appearance of crystal(platy, equant, needle, bladed, etc.)

internal structure is molecular arrangement with in solid.

Compounds have different crystal habits depending on the environment for growing crystals..Change in internal structure alters crystal habit while chemical change will produce change in structure and crystal habit.

The internal structure is classified in variety of ways into crystalline or amorphous compounds.

Crystalline forms are those in which molecules are packed or arranged in definite order or 3D array and that order repeats again and again throughout the particle

Amorphous forms are thermodynamically unstable and molecules are randomly placed.

A crystalline compound may contain stoichiometric or non-stoichiometric amount of crystallization solvent

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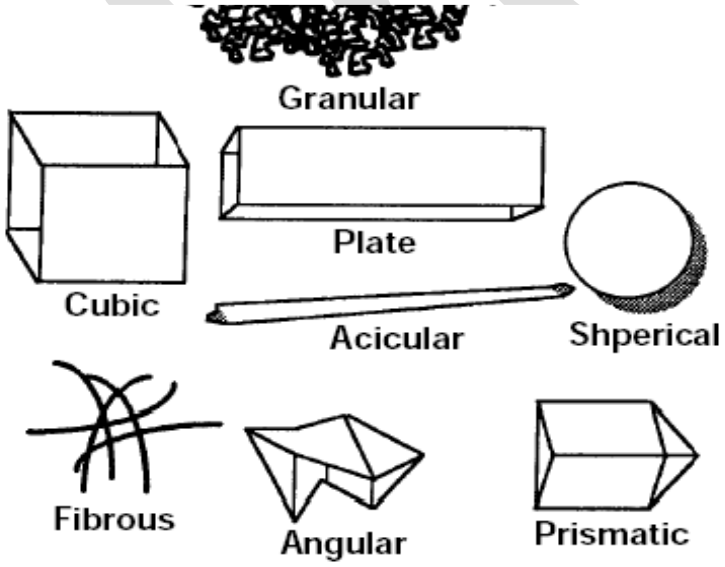


A crystalline compound may contain either as to stioichiometric or nonstoichiometric amount of crystallization solvent.

- ✓ Nonstoichiometric aducts are called as inclusions or clathrates.

- ✓ Stoichiometric aducts are called as solvent molecules.

e.gChloramphenicol palmitate A,B,C & amorphous form are used in suspension then after investigation it was found that form B have increased peak serum level due to more soluble form.

POLYMORPHISM

- ✓ Polymorphism is the ability of the compound to crystallize as more than one distinct crystalline species with different internal structure
- ✓ Formation of different polymorphs depends on solvents, temperature, pressure, rate of cooling, etc
- ✓ Polymorphic transitions can also occur during milling, granulating, drying and compressing operations
- ✓ Different polymorphs vary in physical properties such as dissolution, solid-state stability, compatibility, etc

HYGROSCOPICITY

The tendency of a solid to take up water from the atmosphere, as it is subjected to a controlled RH program under isothermal condition i.e.hygroscopicity.

Deliquescent materials adsorbs sufficient water to dissolve completely.

Changes in moisture level can greatly influence many parameters e.g. chemical stability, flowability, comactibility

Analytical method used for characterization

Sample of bulk drug are placed in open containers with a thin powder bed to assure maximum atmospheric exposure. These samples are then exposed to range of controlled relative humidity environment prepared with saturated aqueous salts solution.

Other method used are TGA ,Karl fischer titration & gas chromatography

Classification of Hygroscopicity

Table Hygroscopicity

Class I non-hygroscopic

Essentially no moisture increases occur at relative humidities below 90%. Furthermore the increase in moisture c
week at above 90% relative humidity (RH) is less than 20%

Class II slightly hygroscopic

Essentially no moisture increases occur at relative humidities below 80%. The increase in moisture content after
above 80% RH is less than 40%

Class III moderately hygroscopic

Moisture content does not increase above 5% after storage at relative humidities below 60%. The increase in mo
storage for 1 week at above 80% RH is less than 50%

Class IV very hygroscopic

Moisture increase may occur at relative humidities as low as 40–50%. The increase in moisture content after sto
90% RH may exceed 30%

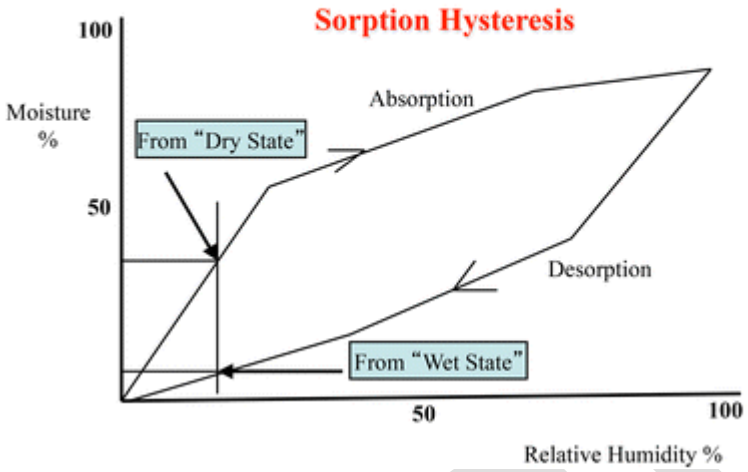
Some materials, e.g. maize, potato and corn starches, have the capacity to retain different amounts of water at the same relative humidity depending upon their moisture exposure history.

For example if a starch powder is dried completely and then exposed to a humid environment it will adsorb and absorb moisture isothermally to a maximum emc at 100% RH. When the moisture saturated powder is placed in a low-humidly environment, desorption takes place more slowly due to the amylase chemical bonding that has occurred during sorption, which resists the rapid desorption of water molecules.

The moisture sorption graph thus displays a hysteresis . At any particular relative humidity, starch powder may have a different moisture content depending upon its exposure history.

Hygroscopicity

Moisture sorption/desorption at different relative humidities



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Characterization of solid form involves –

- ✓ Verifying that the solid is expected chemical compound.
- ✓ Characterizing internal structure
- ✓ Describing habit of crystal.

Analytical method used for characterization

- ✓ Microscopy
- ✓ Differential scanning calorimetry
- ✓ Infrared spectroscopy
- ✓ Thermogravimetric analysis
- ✓ X-ray diffraction

MICROSCOPY

In this technique substances are examined under the microscope.

It gives information about shape, thickness, particle size, etc. of drug molecules.

By this method we can study crystal morphology, difference between polymorphic character of molecule

Differential Scanning Colorimetry

In DSC, the sample & the reference material are subjected to linear heating, but the temperature of two materials should be same,and a graph is plotted.

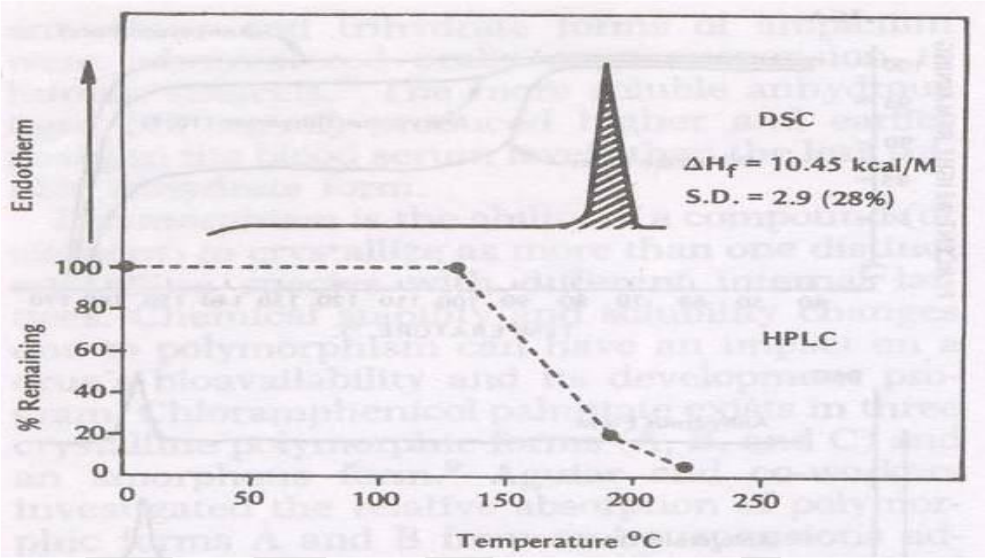
E.g.Doxorubicin.

In both Differential Scanning Colorimetry & Differential Thermal Analysis the heat loss and gain resulting from physical or chemical transition so ccurring in a sample.

Enthalpic changes both endothermic & exothermic are caused by phase transitions.

For example, fusion, sublimation, solid-solid transition & water loss generally produce endothermic effects while crystallization produces exothermic effects

Differential Scanning Colorimetry



Thermal Gravimetric Analysis

It is an excellent analytical procedure for determination of the content of moisture.

TGA helps to determine the temperature at which the material losses weight due to evaporation or decomposition.

E.g.Cefamandole Naftate.

Weight loss begins at 63°C & loss continues at 137°C & at 163°C resulting decomposition.

Determine the temperature at which no loss of weight takes place; this indicates the stability of the compound

X-RAY DIFFRACTION

- ✓ When a beam of nonhomogenous x-rays is allowed to pass through a sample the x-ray beam is diffracted & it is recorded by means of photographic plates.

- ✓ Single Crystal X-ray provides the most complete information about the solid state
- ✓ It is used to differentiate the amorphous and crystalline forms
- ✓ This method is tedious, time consuming & hence unsuitable for routine use

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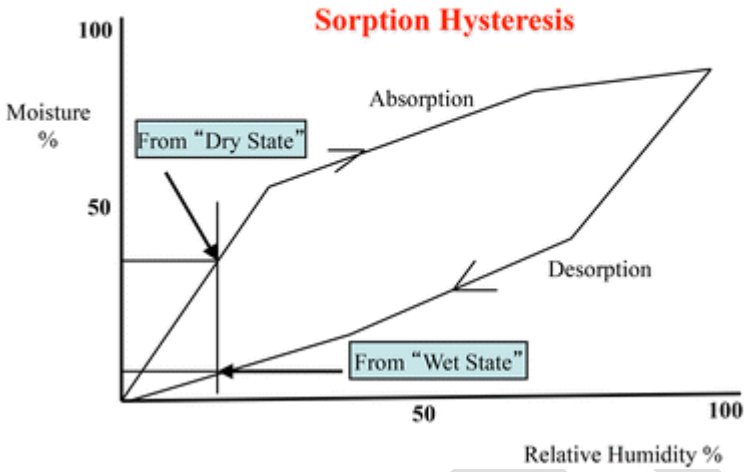

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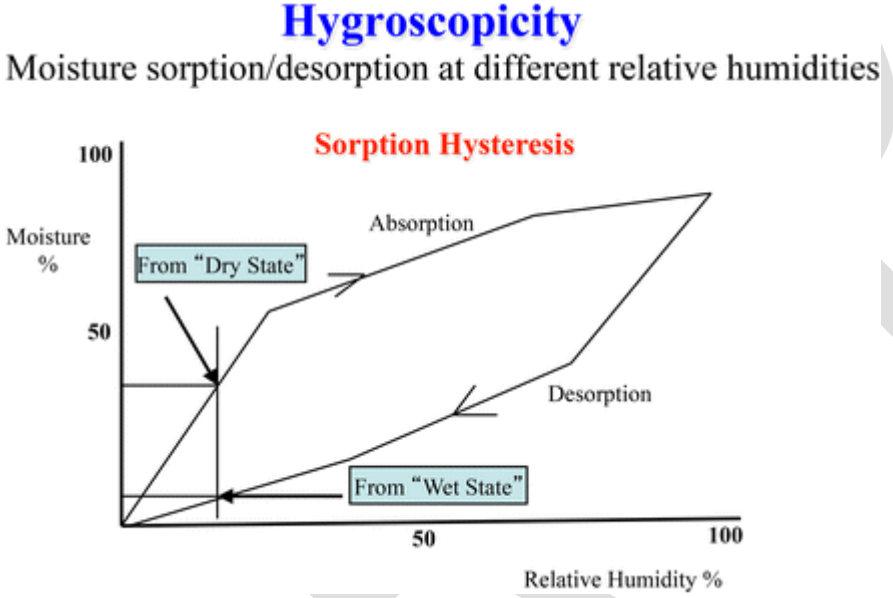

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