POLYMORPHISM

Dr.D.VARUN

Professor & Academic Director

SRI INDU INSTITUTE OF PHARMACY

Hyderabad

POLYMORPHISM

- Polymorphism is defined as existence of one or more crystalline forms of a single compound…….characteristic of solid substances

- Eventually the work on the diffraction of x-rays by crystalline solids led to the dev of the tech , used directly to study the structures and do structural justification….

- Polymorphs are chemically identical, diff in arrangements, exhibit diff prop

- Possess diff energy levels, effect dissolution rate, solubility, deformation, particle size and shape

- If crystallization conditions are changed, mol's start to form crystal with diff packing arrangements from that of original conditions

  Conditions~~~diff solvent, change in stirring,diff impurities

- Lower free energy…..more stable form…,detestable to stable

- Diff in polymorphs are due to diff in crystalline structures,… diff in physical properties ,could be solubility

- Red mercuric oxide…mixing dil sol's of mercuric oxide & KI Crystallizes as octahydral crystals when washed with cold water, drying below 40°C.when heated to 126°C..changes to yellow laminar crystals..on cooling, yellow form revert to red form…ALLOTROPHY

- For a given material……

heat capacity , conductivity volume,density, viscosity,surface tension,diffusivity,crystal hardness,crystal shape,color,refractive index, electrolytic conductivity,melting/submilation, properties,latent heat of fusion,heat of solution, solubility,dissolution rate,enthalpy of transitions, phase diagrams,stability,hygroscopicity,rate of ractions….

effected by the nature of polymorphs

- Diff solubities,diss rates…led to non-equi bioavailability for diff forms…..evaluation of particular polymorph……. investigated early at the stages of development

THEORITICAL CONCEPTS

•The full specification of a polymorphic system is specified by the thermodynamic properties of the phases involved

•A solid phase has a uniform structure and comp throughout.. & is separated by of other phases of defined boundaries , undergoes a phase transition when a solid phase gets unstable.

^ the course of these changes r known by diff in free energy at the transition associated with str/comp change

^ classical thermodynamics provides bases

^during phase transition, free energy of the sys remains cont….while the entropy, vol and heat capacity undergoes discont change

^ phase transitions (being of same order)
classified as derivative of GIBBS FREE ENERGY (G)…
that exhibits a discontinous change of transition.

$$G = H - TS$$

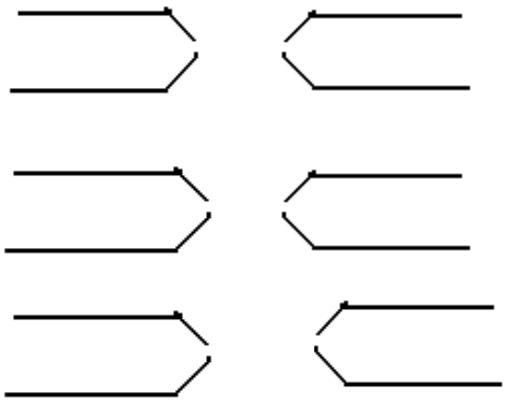
$$= E + PV - TS$$

- Generally lower free energy…..stable (under exp conditions)
  G metastable > G stable……..

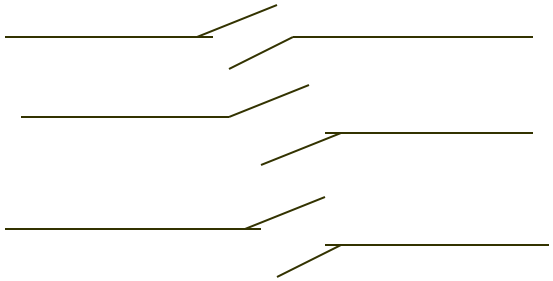
- Milling and compaction differs

- Change in packing arrangement……diff crystals…changes in prop of solid

COMPARISION OF POLYMORPHS



- More spaced
- Diff densities
- Easy to remove
- Lower m.p
- Breaks easily by smaller forces



- Less spaced
- Diff densities
- Difficult to remove
- Higher m.p
- Breaks with greater forces

Polymorphs are either…….

- *ENANTIOTROPIC*

-> Have thermodynamic conversion temp….
one is stable above and other is stable below this temp.
-> Under diff temp's and pressures,reverse transformation alternatively.
-> Processing , dissolution,recrystallisation,storage cond convert this to alternatives(metastable ←→stable)
> Less common..

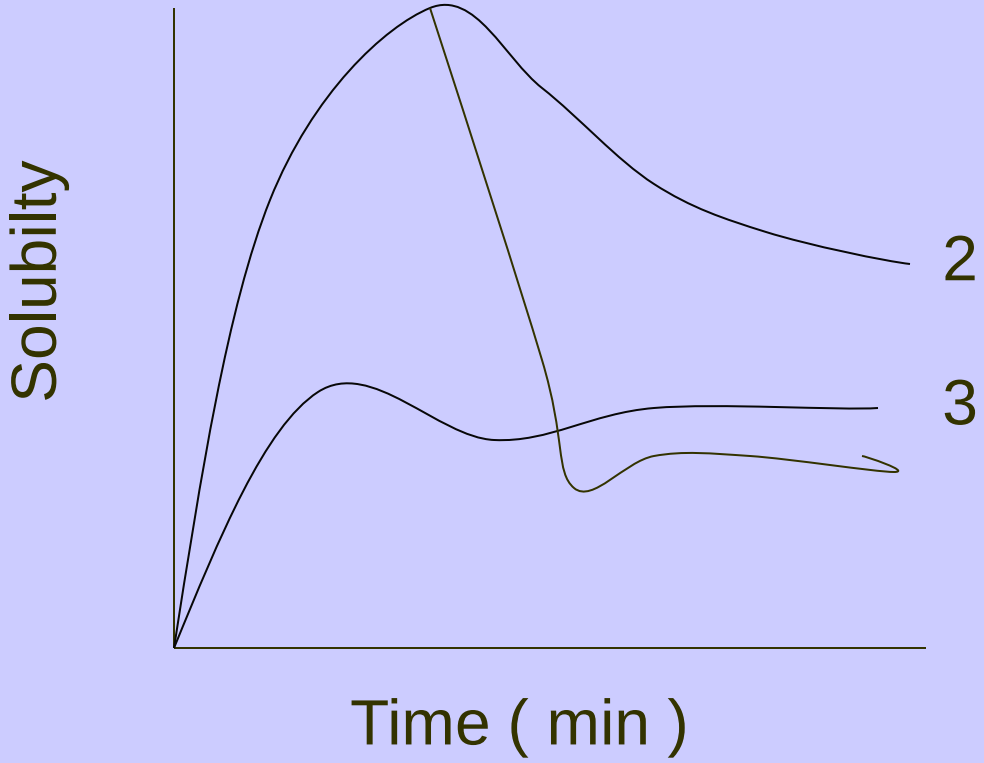
- *MONOTROPIC*

-> No conversion temp below the M.P of polymorph pair,that Crystals are monotropic
-> One is thermodynamically more stable,exists,given a chance
-> True stable..high m.p..all other metastable…..mostly occurs

High melting point = Strong lattice = Hard to remove molecule = Low Dissolution rate

low melting point = Loose lattice = Easy to remove molecule = High Dissolution rate

SOLUBILITY TIME RELATIONSHIP FOR SULPHAMETHOXYDIAZINE



PACKING POLYMORPHISM

when molecules of drug are stacked in diff motifs to occupy Points of diff lattices…….

CONFORMATIONAL POLYMORPHISM

if the molecule is not rigid and can exist in distinct Conformational states……..

SOLVATOMORPHISM

crystalline solids in which solvent mlecules have become Included in structure through existence of positional substitutions At positions that are site specific and are related to other solvent Molecules through transitional symmetry

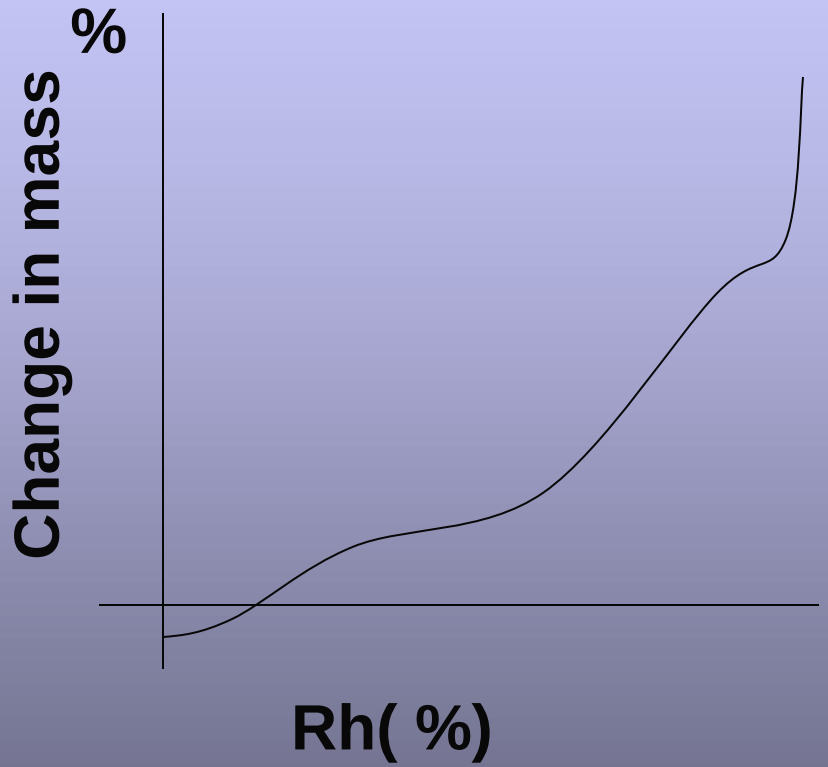
GLASS TRANSITION TEMPERATURE

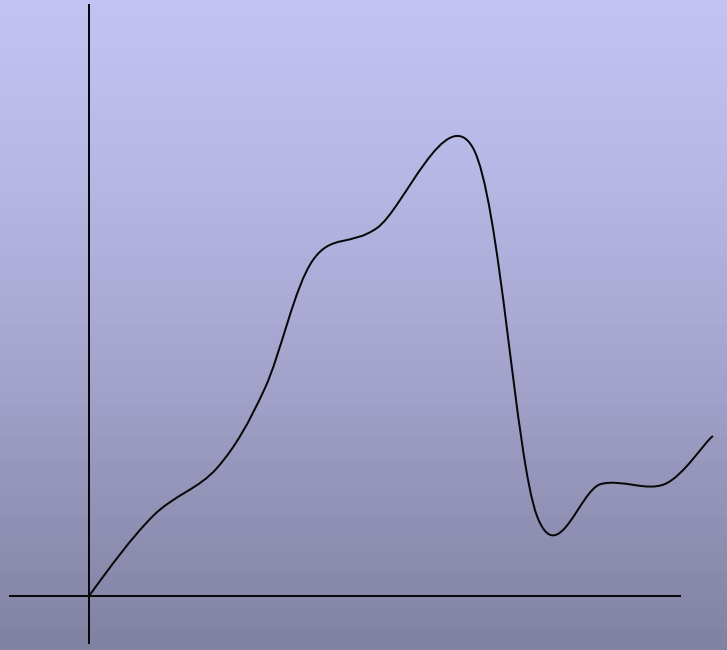
- Tg

* If sample stored
  - ~ below Tg , amorphous form is brittle ..as glassy state
  - ~ above Tg , becomes rubbery
  - ~ Tg below temp , increases molecular mobility allows rapid conversion to crystalline forms.

* Tg….here molecules in glass stale…changes in mobility
* Tg… lowered by adding small molecules (PLASTICIZER) fits between glassy molecule giving geater mobility water….Tg lowered by water vapour
* Amorphous forms are able to absorb more w v absrption..one mol to bulk of other..diff from adsorption that con's at the surface

Water sorption isotherms





Crystalline lactose monohydrate

Amorphous lactose

SOLVATES AND HYDRATES

- Compounds having tendency to trap a fixed molar ratio of Solvent mol's in crystalline state…..SOLVATES
- Solvent is water…..HYDRATES
- Hydrates…..
  - monohydrate….1 mol water for each crystalline mol(host) 50 % drugs occur
  - dihydrate….. 2 mol water for each host 20% drugs occur
  - trihydrate….. 3 mol water for each host 8% drugs occur
  - hemihydrate….1 mol water gor 2 hosts 8% drugs occur
- Solvates.. Not preferred for formultions..organic vapours. unnecessary imp…toxic
- Hydrates. .diff prop from anhydrous, ~~~~~.PEUDOPOLYMORPHSM

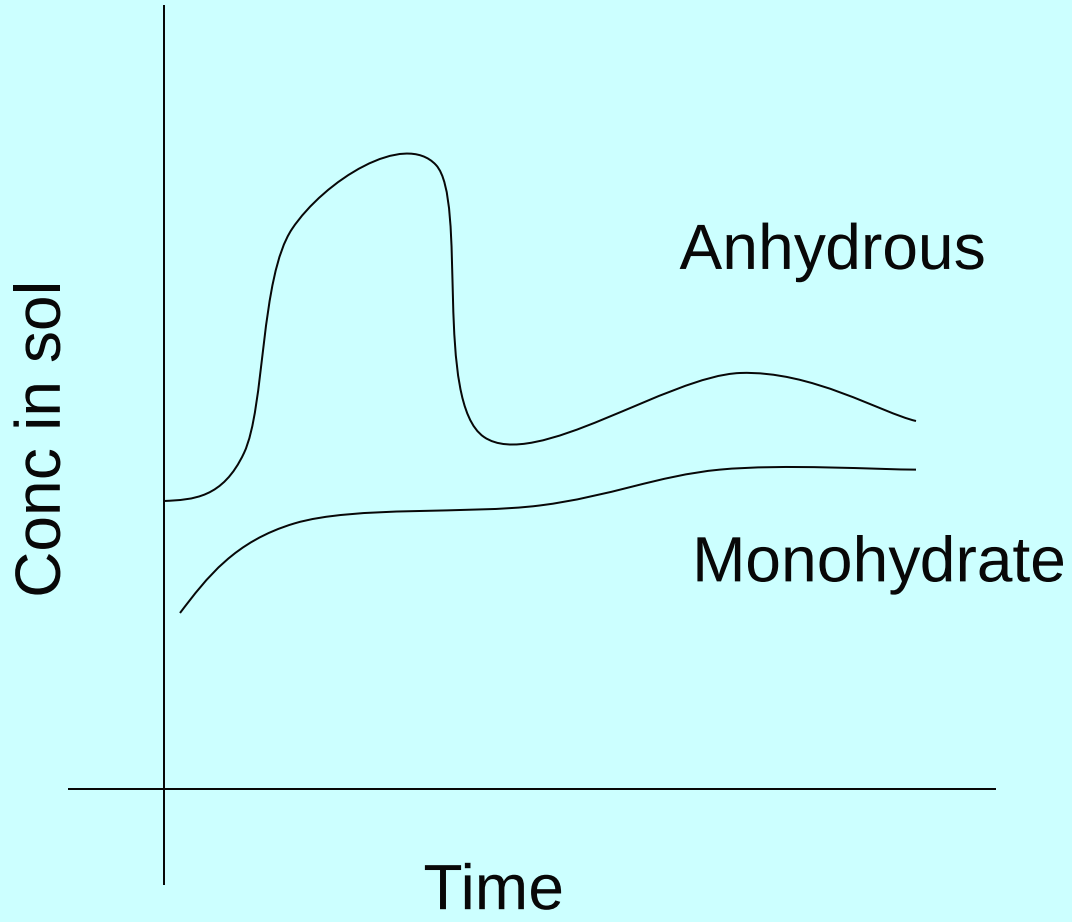
HYDRATE FORM

- Faster and slower dissolution rate
- Less solubility initially
- Saturated and stable form is producd due to intermolecular bonding between the moleculles

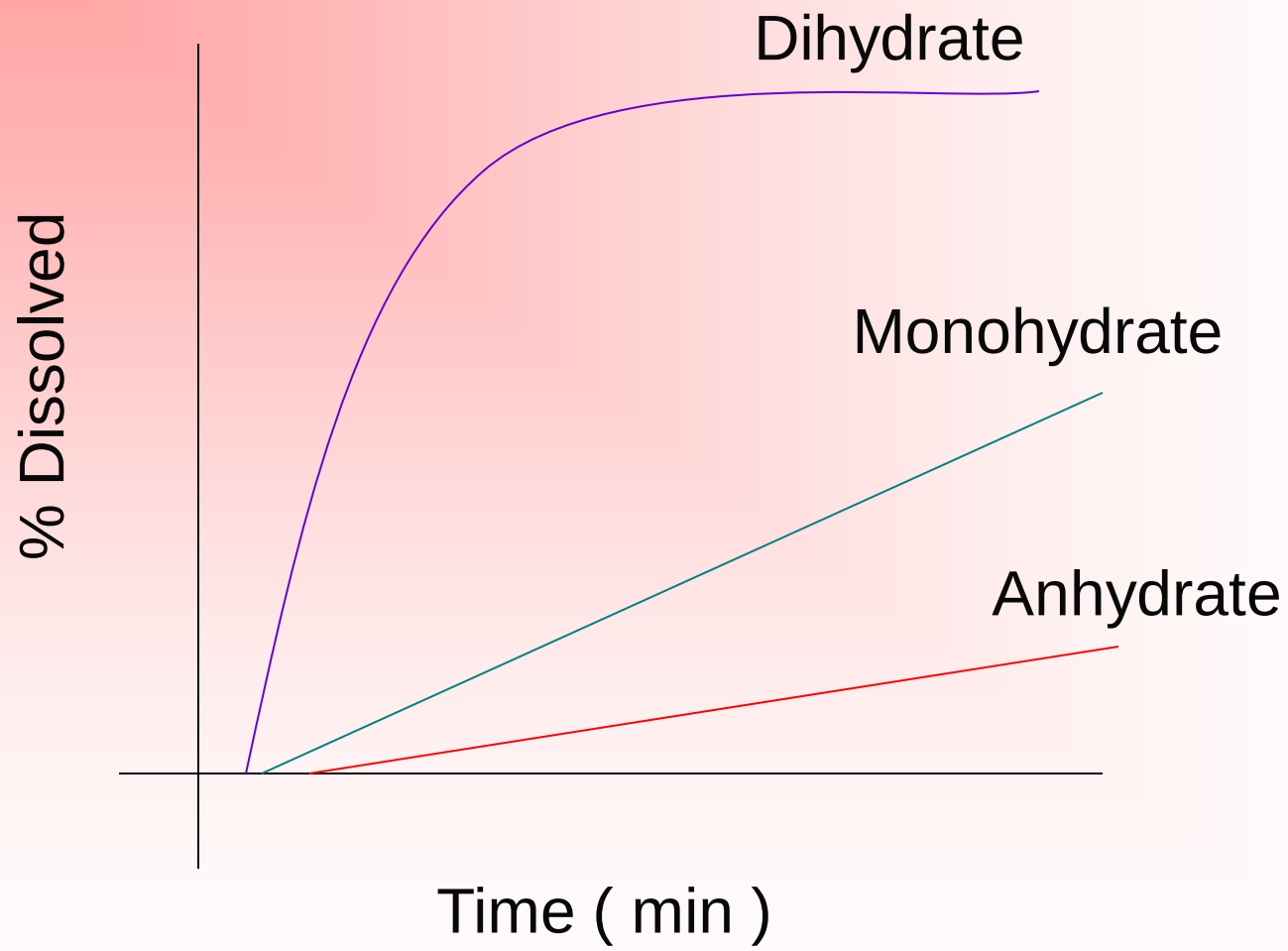
ANHYDROUS FORM

- More dissolution rate
- High solubility initially, raises to high conc and falls again
- Supersaturated and meatstable form is produced initially

DISSOLUTION OF THEOPHILLINE



DISSOLUTION BEHAVIOUR FOR ERYTHROMYCIN



PREFORMULATION ASPECTS OF CRYSTAL PROPERTIES AND POLYMORPHISM

- Diff polymorphs of a solid differ from each other w.r.t many Physical properties….

  solubility,dissolution,true density,
  crystal shape,compaction behaviour,
  flow properties and solid state stability.

- Monitering of solid state property is very must

- Active search of polymorph to circumvalent tha stability, bio-availability and processing problem