SOLID STATE STABILITY

Dr.D.VARUN

Professor & Academic Director

SRI INDU INSTITUTE OF PHARMACY

Hyderabad


Co-Crystal Screening
Crystallization Screening
Polymorphism Screening
Salt Screening
Selection of Best Form for Development
Quality Control
Crystallization Monitoring
Patenting
Crystallization Optimization
Method for Polymorph Purity (DS/DP)
Kinetic Stability (DS/DP)

- Solid state stability refers to physical and chemical changes
- Stability of solids formulations imp … more common. first clinical trials carried
- Pham' solids degrade due to….solvolysis, oxidation, photolysis, pyrolysis
- Test on stability of solids begins with investigation of chem structure….indicates the chemical reactivity.

- Unsaturation / electron rich centres….prones to free radical mediated / photocatalized oxidation.
- Phy prop's …solubility,Pka, M.P,crystal form, equilibrium moisture content influences stability…
- Amorphous less stable than crystalline.
- For structural related compounds..M.P indicates relative stabilities
- Solids decompose,either first order / zero order profiles
- Solid state degradations are complex….elucidation difficult

- Stability studies design.. should identify factors that cause degradation

- Common factors….heat , light , oxygen , moisture…
  - * interplay occur
  - * heat and moisture make material to react with oxygen.. degradation rapids
  - *presence of moisture make substance heat liable

- While conduction of stability studies….. stability is influenced by more than one factors….then study one factor at a time, holding others constant

INTERPRETATION OF STABILITY UNDER VARIOUS CONDITIONS

- Solid sate reactions,very slow….stress cond's used at investigation.
- Data at stress cond's extrapolated to predict with app sorage cond's
- High temp's can drive moisture out of sample
- Degradative pathways at elevated temp's not aparent at low temp's
  - * Ergot alkaloids…degrade completely in 1 year at 45*c, at below 35*c it is less than 1 % per year
  - * At 65 % RH, β chlortetracycline ~><~ α form….at or below 65 % RH no transformation occurs.
- Accelerated stability studies…early and rapid prognosis of stability…
- These studies make force formation of degradants in amounts suff for isolation and characterization

- Stability studies are carried in various conditions and environment…
  - Elevated Temperature studies
  - Stability under high humidity conditions
  - Photolytic stability
  - Stability to oxidation

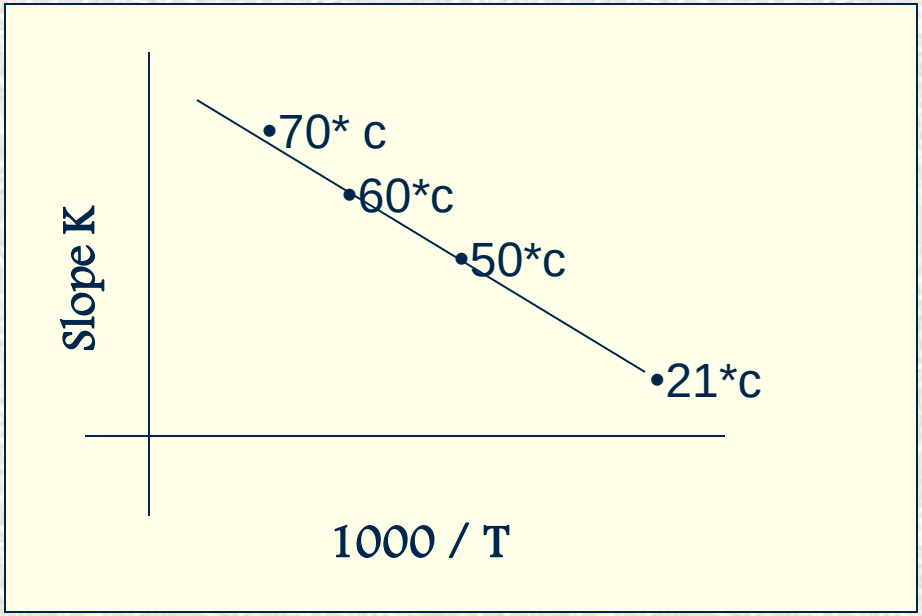
ELEVATED TEMPERATURE STUDIES

- Generally 20,30,40,50,60° c used in conjuction with ambient humidity , occasionally high temp's used

- Samples stored at high temp ..examined for phy & chem changes at frequent intervals …any change when compared to an appropriate control should be noted.

- If substantial change occurs…samples at low temp's observed…If no change after 30days at 60*c …excellent stability

✓ Data at elevated temp's extrapolated with that Low temp's using Arrhenius treatment to determine the degradation rate at low temperatures



- Most solid state reactions are not ammeenable to the Arrhenius treatment, their heterogeneous nature makes elucidation of the kinetics order and prediction difficult.
- Long term lower temperatures studies are therefore an essential part of a good stability programme.
- Even a small loss seen at low temp's has greater predictive value.

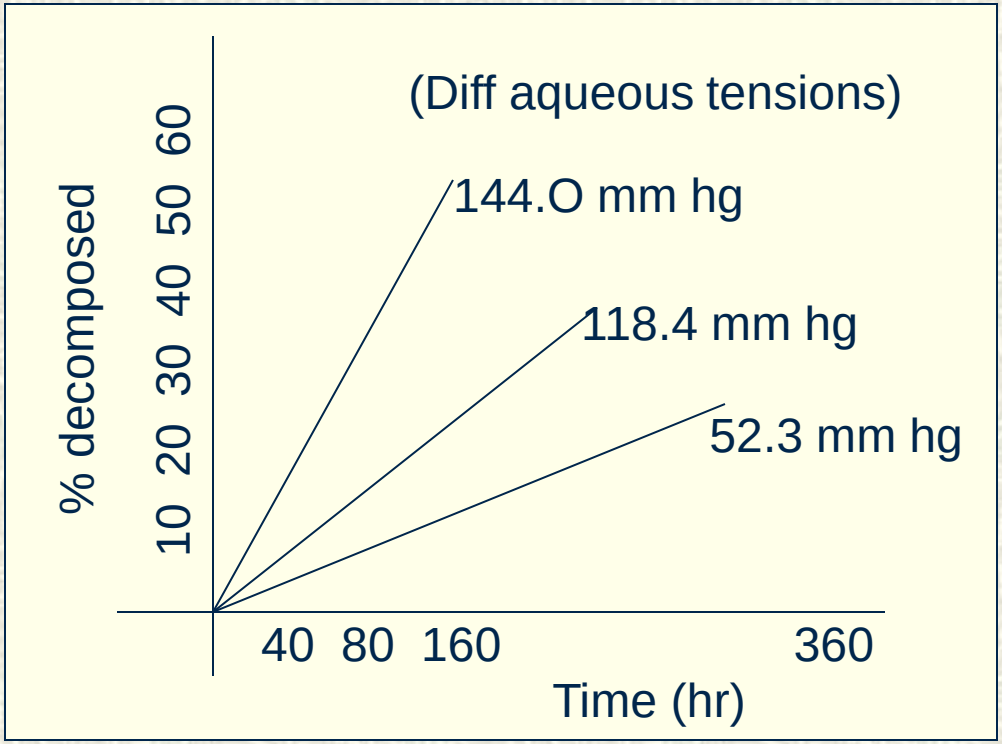
STABILITY UNDER HIGH HUMIDITY CONDITIONS

- In presence of moisture , many drug substances hydrolyze, react with excipients or oxidise
- These reactions can be accelerated by exposing the solid drug to diff RH"s
- Controlled humidity…lab dessicators containing saturated sol's of various salts

closed dessicators placed in oven …for const temp

Data for decorboxylation of P-aminosalcylic acid ..show a dep on ambient moisture

Preformulation data of this reveals if the material is to be protected and stored in controlled hum cond's…or if use of the aqueous based Granulation is to be avoided



PHOTOLYTIC STABILITY

- Fading…on exposure to light
- Extent of degradation is small and limited to exposed surface area
- Presents aesthetic prob..rectified by amber glass,opaque container, Incorporation of dye in pdt to mask discoloration
- Exposure to 400 – 900 fc of illumination for 2 – 4 weeks…provides adequately provide some idea of photosentivity….
  over these periods monitoring is done. and compared to that of original
- Change in appearance. recorded visually, quantified by instruments designed for comparing colors…DIFFUSE REFLECTENCE SPECTROSCOPY
- Analysis of the exposed compounds should be less than 2 %..then safe

STABILITY TO OXIDATION

- sensitivity of each new drug entity to atm oxygen must be evaluated to establish if the final pdt should be packed under inert atm cond's. or to contain antioxidant

- Sentivity is known by ascertaining in high oxygen tensions
  usually 40 % atm oxygen allows for rapid evaluation

- Considered how the sample exposed

- Desicators equipped with 3 way stop cocks are usefull
  samples are packed in desiccator i,e alternatively evacuated and flooded with desired temp
  the process repated 3 -4 times..to ensure essentially 100 % of desired atmosphere.

SIMPLEST DECOMPOSITION MODES OF PURE SOLIDS

•If a solid is placed in a vacuum and exposed to diff temperatures at which it decomposes at a measurable rate….one of the following occurs…

Solid → Solid + Solid

Solid → Solid + Liquid

Solid → Liquid + Liquid

Solid → Solid + Gas

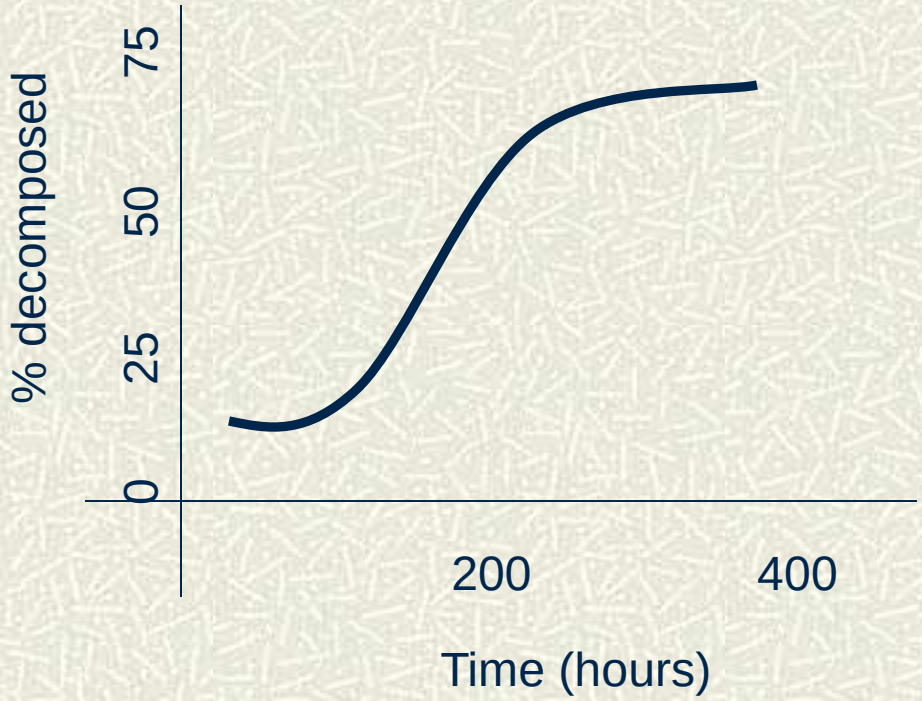
Solid → Liquid+ Gas

Solid → Gas + Gas

SOLID TO SOLID + GAS REACTION

DECOMPOSITION OF p – AMINOSALCYLIC ACID

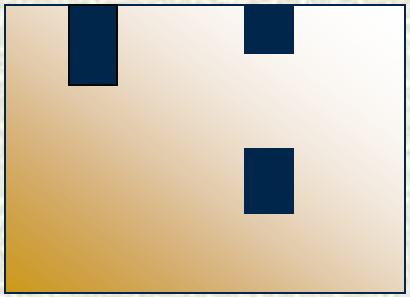
Time (hours)	0	50	100	150	220	260	325
% decomposed	0	4	18	36	60	70	77



- No solids have smooth surfaces….surface imperfections…i,e STEPS at surface / could be crystal defects.

- These are more energetic than remaining..occur more likely at surfaces… Packed with mol's diff from bilk of crystal…
  one less than bulk….decomposition starts there...ACTIVATION SITES

- Once a mol decomposes at activated site...geometry changes…then neighboring mol's starts decomposing

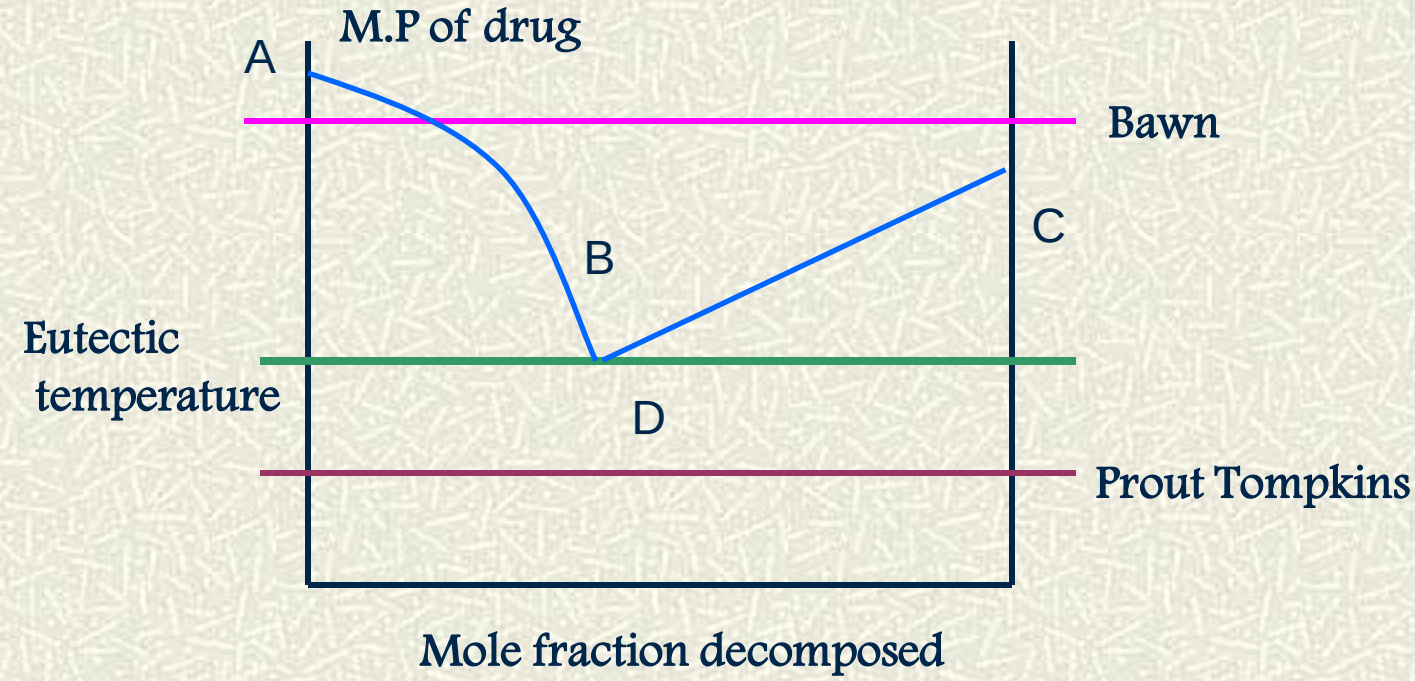


3 active sites

3 chains

Only 1 chain

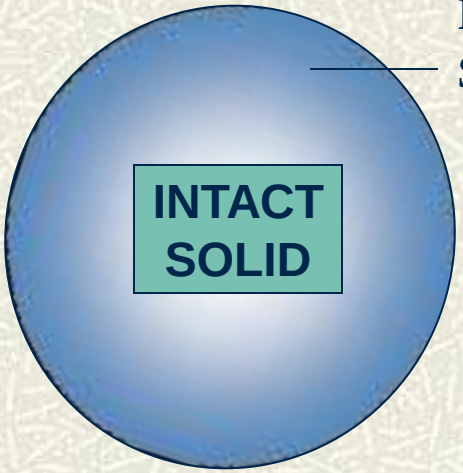
PROPAGATION OF ACTIVE SITE CHAINS FROM 3 SURFACES



BINARY M.P DIAGRAM SHOWING AREAS WHERE VARIOUS KINETICS APPLY

SOLID TO LIQUID + GAS REACTION

- Max decomposition by this type..
- Reaction kinetics…**bawn** kinetics



- At time ' t ' there will be certain amount of liquid decomposition pdt , this amount corresponds to amount of drug decomposed

- The liquid decomp pdt will dissolve parent compound to extent S (mole/drug decomp pdt) .i,e soluble

- Amount present in solid state at time ' t ' is original no of moles (A_O) – amount decomposed ($A_O X$) – the amount dissolved ($A_O X_S$)

$$= A_O - A_O X - A_O X_S$$

THE ' NG ' EQUATION

- NG suggested the following glabal equation for solid state decomposition

$$dx / dt = x^{n} (I - x)\, p$$

on modification,

$$\ln \{ x^{n} / (1-x) \} = -k^{1} (t - t_{1})$$

also written as ,

$$\ln \{ x^{q} / (1 - x) \} = - k (t - t_{1})$$

where , $k = k^{1} / p$

& $q = n / p$