Unit-1
Preformation Concepts

CONTENT

1. **Introduction**
2. **Compatibility Tests**
3. **Sample Preparation**
4. **Analytical Techniques used to detect Drug-excipient Interaction**

INTRODUCTION

- **INCOMPATIBILITY**
  -Definition
  -3 Types
- **OBJECTIVE OF THE STUDY**
  -Why to screen excipients?
    1.need to minimize no of model formulations
    2.provide rational basis for selecting excipients
    3.Formulation stability studies are time consuming.
  -Goal of the study(Identify the excipients that)
    1.are compatible with API
    2.do not have impact on the stability of API
  -Importance
    1.Stabity of formulation can be maximised.
    2.Helps to avoid surprise problems.
    3.Essential for IND submission.
    4.Bridges drug discovery and drug development

COMPATIBILITY TESTS

- **2 Aspects of compatibility tests are**:
  1. Identification of compatible excipients for a formulation.
  2. Identification of stable storage conditions
- **2 Types**:
  1. **Solid state reactions**:
     - much slower and difficult to interpret.
  2. **Liquid state reactions**:
     - easier to detect
     - Acc. to Stability Guidelines by FDA following conditions should be evaluated for solutions or suspensions
       1. Acidic or alkaline pH.
       2. Presence of added substances
       3. High oxygen and nitrogen atmospheres.
       4. Effect of stress testing conditions.

STEPS IN COMPATIBILITY STUDY

- There are THREE steps to consider.
  1. Sample preparation
  2. Storage
  3. Method of analysis

SAMPLE PREPARATION

- **FOR SOLID STATE REACTIONS:**
  - **Sample A**: -mixture of drug and excipient
  - **Sample B**: -Sample A+ 5% moisture
  - **Sample C**: -Drug itself without excipients
- All the samples of drug-excipient blends are kept for 1-3 weeks at specified storage conditions.
- Then sample is physically observed .
- It is then assayed by TLC or HPLC or DSC.
- Whenever feasible, the degradation product are identified by
  - MASS SPECTROSCOPY,
  - NMR or other relevant analytical techniques.
- **To determine Solid state stability profile of a new compound….**
- **To test the Surface Oxidation…..**

SAMPLE PREPARATION

FOR LIQUID STATE REACTIONS:

- Place the drug in the solution of additives.
- Both flint and amber vials are used.
- This will provide information about
  - -Susceptibility to oxidation.
  - -Susceptibility to light exposure.
  - -Susceptibility to heavy metals.
- In case of oral liquids, compatibility with ethanol, glycerin ,sucrose, preservatives and buffers are usually carried out.

STORAGE CONDITION

- The storage conditions used to examine compatibility can very widely in term of temp. & humidity, but a temp. of 50°c for storage of compatibility sample is considered appropriate.

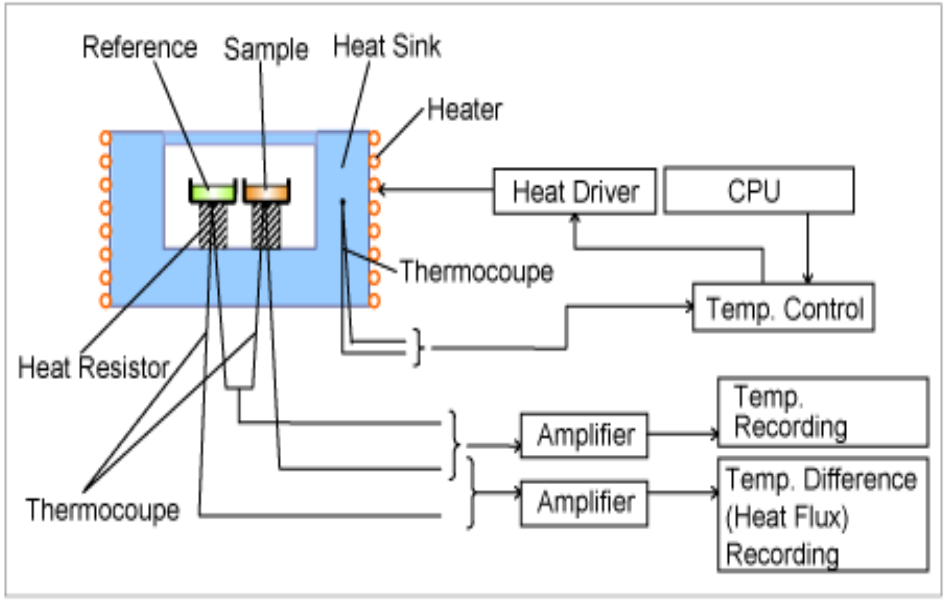
- Some compounds may require high temp. to make reaction proceed at a rate that can be measured over a convenient time period.

ANALYTICAL TECHNIQUES USED TO DETECT DRUG-EXCIPIENT INTERACTION-

1. Thermal methods-
   - DSC- Differential Scanning Calorimetry
   - DTA- Differential Thermal Analysis
   - Isothermal micro Calorimetry
   - Hot stage microscopy
2. Spectroscopic techniques-
   - FT-IR Spectroscopy
   - Powder X- ray diffraction
   - Solid state NMR
3. Chromatography -
   - SIC-Self Interactive Chromatography
   - TLC-Thin Layer Chromatography and HPTLC
   - HPLC-High Pressure Liquid Chromatography
4. Accelerated stability study
4. Miscellaneous-
   - Radiolabelled Techniques
   - Fluorescence Spectroscopy

DSC- DIFFERENTIAL SCANNING CALORIMETRY

- DSC is widely used technique to predict any interaction involving thermal changes.
- METHOD -The preformulation screening of drug-excipient interaction requires (1 : 1) Drug:excipient ratio, to maximize the likehood of observing an interaction. -Mixture should be examined under N2 to eliminate oxidative and pyrrolytic effects at heating rate (2,5 or10 degree C/min) on DSC apparatus.

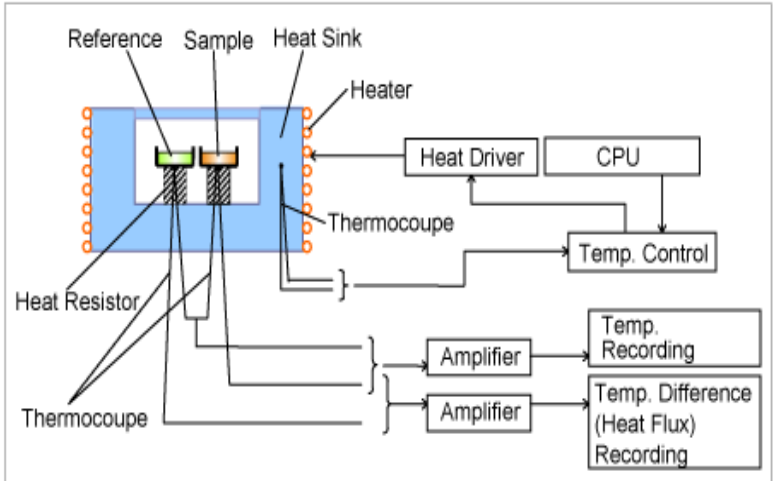


DSC- DIFFERENTIAL SCANNING CALORIMETRY

- the DSC curves of pure components are compared

to the curves obtained from 1:1 physical mixtures.

- An absence, a significant shift in the melting of the components or
- appearance of a new exo/endothermic peak and/or
- variation in the corresponding enthalpies of reaction in the physical mixture indicates incompatibility.



Interaction detected by DSC -

- Elimination of endothermic peak
- Any new peak appeared
- Change in melting point / peak temperature
- Change in peak shape (height and width)
- Change in area of peak or enthalpy

DTA- DIFFERENTIAL THERMAL ANALYSIS

- This technique is useful in the investigation of solid-state interactions and detection of eutectics.
- In this change in temperature between test sample and reference material is measured under controlled and identical condition.
- This differential temperature is plotted against time or temperature.
- Interaction can be identified by comparing DTA curve obtained from the test sample with those of reference material.

If any interaction occur-

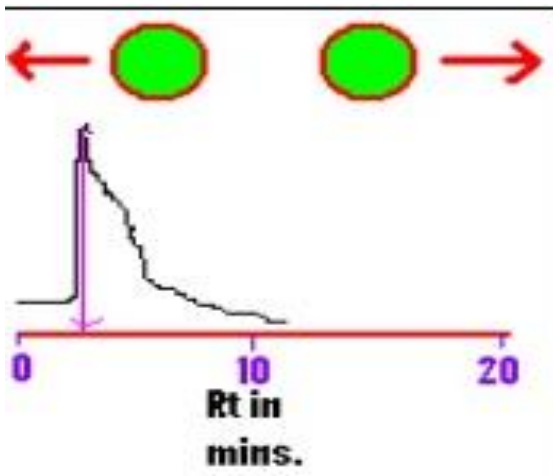
- Thermogram (DTA curve) of a mixture show appearance or disappearance of one or more peaks corresponding to those of the components.

If no interaction occur-

- The thermogram of mixtures show same patterns corresponding to those of the individual components

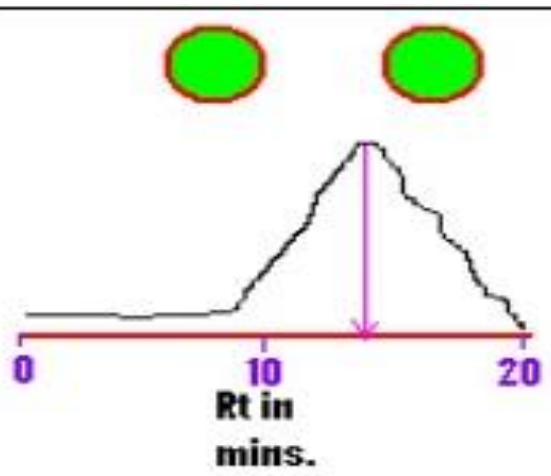
SIC-SELF INTERACTIVE CHROMATOGRAPHY

- SIC is useful for proteinous drug and excipients.
- Principle - For different mobile phases (i.e. different excipients) the injected drug have different interactions (may be repulsive or attractive) with the stationary phase of drug leads to shift in retention time
- Method -It is a modified type of affinity chromatography. Here, drug is made immobilized as the stationary phase & solution to be tested(excipient solution) acts as mobile phase.
- Measure retention time and compare with non-retained marker.
- Eg. INF-Tau(an antiviral drug)- Interactions of it with different types of buffers were studied by SIC. Here, buffer is used to prevent aggregations.



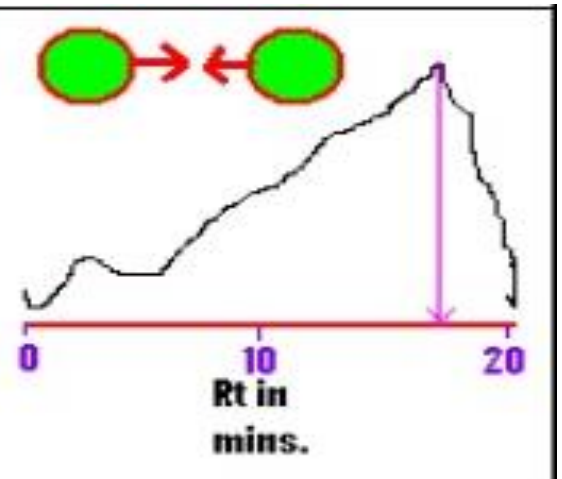
When interaction is repulsive,a sharper peak is obtained at a shorter retention time

Figure (a)



When no net interaction between the immobilized drug,Rt=dead volume of column.

Figure (b)



When attractive interactions,it will have longer retention time& wider peak

Figure (c)

TLC & HPTLC

- TLC is generally used as confirmative test of compatibility after performing DSC because if sample undergo negligible thermal changes, it will difficult to detect by thermal method
- Method- stationary phase consist of powder (silica, alumina, polyamide, cellulose etc.) adhered onto glass, plastic or metal plate.
- Solution of drug, excipient & drug: excipient mixture are prepared & spotted on the same baseline at the end of plate.
- The plate is then placed upright in a closed chamber containing the solvent which constitutes the mobile phase.
- Any change in chromatograph such as appearance of a new spot or a change in Rf values of component is indicative of an interaction.

REFERENCES

- Lachman & Lieberman, The Theory and Practice of Industrial Pharmacy
- N. Fathima, Kajal Ahir, Vandana Patel, Lata Manani, Chirag Patel Drug excipient interaction and its importance in dosage form development, Journal of applied Pharmaceutical Science 2011
- Priyanka Patel, Kajal Ahir, Vandana Patel, Lata Manani, Chirag Patel Drug-Excipient compatibility studies: First step for dosage form development, The Pharma Innovation Journal 2015
- Bapi Gorain, Hira Choudhury, Manisha Pandey, Thiagarajan Madheswaran, Prashant Kesharwani and Rakesh K. Tekade Drug–Excipient Interaction and Incompatibilities 2018