DRUG-EXCIPIENT COMPATIBILITY STUDIES

POOL OF CONTENTS:

OBJECTIVES:

☻ **Drug:** active part of dosages form and it is mainly responsible for therapeutic value.

☻ **Excipient:**substances which are included along with drugs being formulated in a dosage form so as to impart specific qualities to them.(jain n.k. sharma s.n. page no.166)

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☻ Incompatibility- general aspects

► Inactivation of drug through either decomposition or loss of drug by its conversion to a less favorable physical or chemical form. (Martin page no.352)

► It affects safety, therapeutic efficacy, appearance or elegance.

► When we mix two or more API and / or excipient with each other & if they are antagonistic & affect adversely the safety, therapeutic efficacy, appearance or elegance then they are said to be incompatible.

☻ Importance of Drug Excipient Compatibility Study:-

- **Stability of the dosage form can be maximized.** Any physical or chemical interaction between drug and excipient can affect bioavailability and stability of drug.

- **It helps to avoid the surprise problems.** By performing DECS we can know the possible reaction before formulating final dosage form.

- **Drug discovery can emerge only new chemical entity**. It becomes drug product after formulation and processing with excipients. By using DECS data we can select the suitable type of the excipient with the chemical entities emerging in drug discovery programs..

- **DECS data is essential for IND (investigational new drug) submission.** Now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval. .

- **Determine a list of excipients that can be used in final dosage form.**
- Example:
    - One would not consider using sucrose or lactose. If the drug substance being consider is a primary amine. This system has the potential for interaction to form a colored compound, readily detected by a color changed.(Remington 19th edition page no.1460)

☻ Types Of Incompatibility

A. **Physical incompatibility:-** It involves the change in the physical form of the formulation which involves color changes, liquefaction, phase separation or immiscibility.

B. **Chemical incompatibility:-** It involves undesirable change in formulation which is due to formation of new chemical comp. with undesirable activity or our formulation undergoes hydrolysis, oxidation, reduction, precipitation, decarboxylation, racemization.

C. **Therapeutic incompatibility:-** It is type of in vivo compatibility. It involves change in therapeutic response of the formulation which is undesirable to patient as well as physician.

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☻ Compatibility tests- general view regarding solid and liquid dosage forms.

Aspects of above tests are-

►Identification of compatible excipients for a formulation

►Identification of stable storage conditions for drug in solid or liquid state.

(A) Solid state reactions:- Solid state reactions are much **slower** and more **difficult to interpret** than solution state reactions, due to a reduced no. of molecular contacts between drug and excipient molecules and to the occurrence of multiple phase reactions.

SAMPLE –A	SAMPLE-B	SAMPLE-C
# Prepare a small mixture of drug and excipient. # Place above mix in vial. # Place a rubber closure on vial and dip the stopper in molten carnauba wax to render it hermetically sealed.	# Sample preparation method is same as SAMPLE-A but 5% moisture is added in mixture.	# Drug itself without any excipient is taken as a sample for solid state stability study.

Procedure: 1. All the samples of drug-excipient blends are kept for 1-3 weeks at specified storage conditions.

2. Then sample is physically observed for (1) caking (2) liquefaction (3) Discoloration (4) odor (5) gel formation.

3. It is then assayed by TLC or HPLC or DSC.

4. 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 weighed sample are placed in open screw cap vials and exposed directly to a variety of temp., humidity & light intensities for up to 12 weeks.**

□ **Sample usually consists of 5-10 mg for HPLC analysisFor polymorph evaluation 10-50 mg by DSC**

□(~2 mg in KBr & ~20 mg in Nujol) for IR

■ To test the surface oxidation, samples are stored in large (25 ml) vials for injection capped with a Teflon lined rubber stopper & headspace filled with dry oxygen.

(B) Liquid state reactions:-

► It is easier to detect liquid state reactions as compared to solid state reactions.

► For detection of unknown liquid incompatibilities, the program set up is same as solid dosage forms.

► Now according to "Stability guidelines" by FDA states that:

Following conditions be evaluated in studies on solutions or suspensions of bulk drug substances:

1) Acidic or alkaline pH.
2) Presence of added substances- chelating agents, stabilizers etc.
3) High Oxygen and Nitrogen atmospheres.
4) Effect of stress testing conditions……

Procedure:

- Place the drug in the solution of additives.
- Both flint and amber vials are used.
- Autoclave conditions are employed in many cases.
  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.

☻ Analytical techniques used to detect Drug-Excipient Compatibility

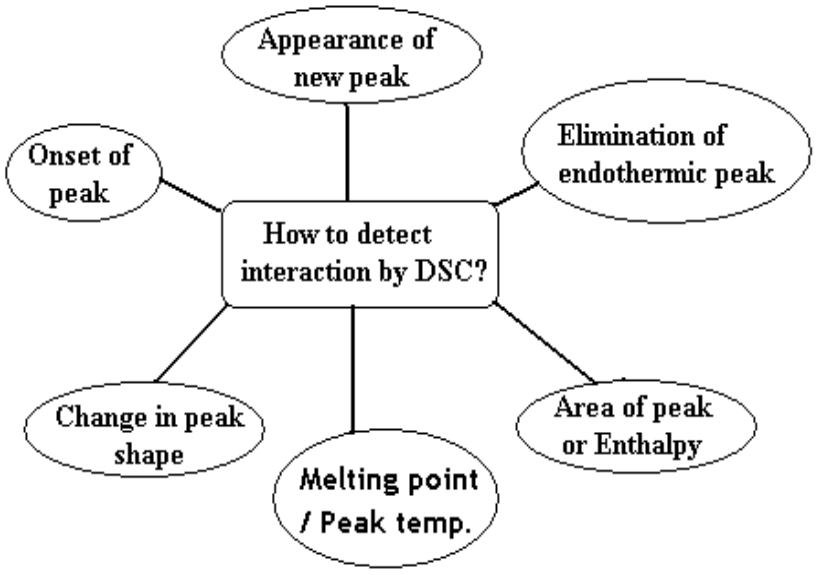
1) Thermal methods of analysis
   I. DSC- Differential Scanning Calorimetry
   II. DTA- Differential Thermal Analysis
2) Accelerated Stability Study
3) FT-IR Spectroscopy
4) DRS-Diffuse Reflectance Spectroscopy
5) Chromatography
   I. SIC-Self Interactive Chromatography
   II. TLC-Thin Layer Chromatography
   III. HPLC-High Pressure Liquid Chromatography
6) Miscellaneous
   I. Radiolabelled Techniques
   II. Vapour Pressure Osmometry
   III. Flourescence Spectroscopy

DSC:- Differential Scanning Calorimetry. DSC is widely used to investigate and predict any physico-chemical interaction between drug and excipients involving thermal changes..

➢ METHODOLOGY

The preformulation screening of drug-excipient interaction requires 5 mg of drug, in 50% mixture (1 : 1) with excipient, to maximize the likehood of observing an interaction.

NOTE: Mixture should be examined under N_2 to eliminate oxidative and pyrrolytic effects at heating rate (2, 5 or 10^0c / min) on DSC apparatus.

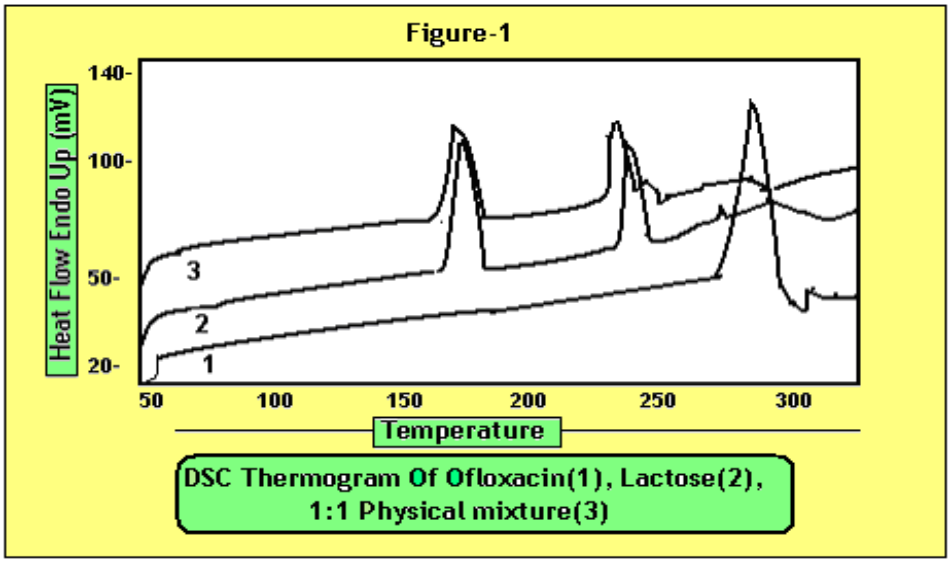


However, some changes in peak shape, peak ht. & width are expected b'coz of possible differences in mixture geometry.

Experimental Drug: Ofloxacin

Experimental Excipients: (1) Lactose, (2) Starch, (3) PVP, (4) Talc

Figure-1

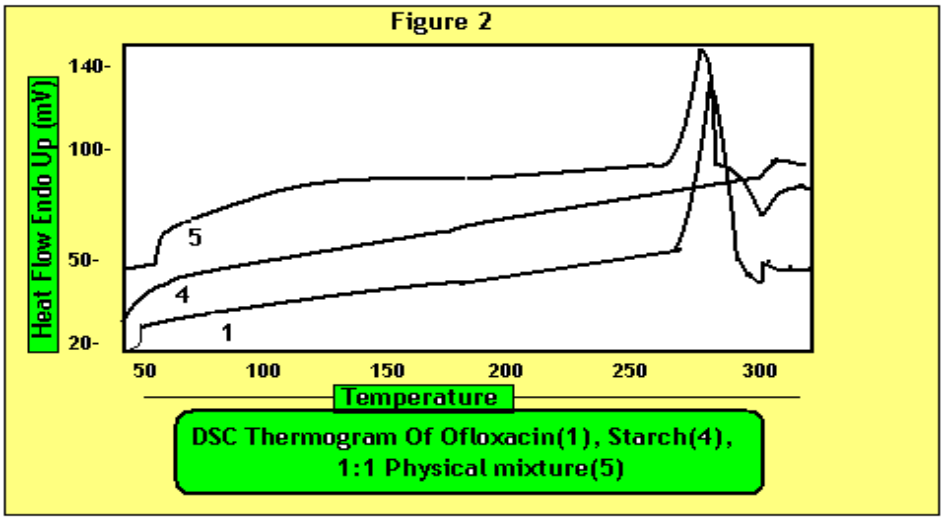


DSC Thermogram Of Ofloxacin(1), Lactose(2), 1:1 Physical mixture(3)

DSC RESULT-- INCOMPATIBLE

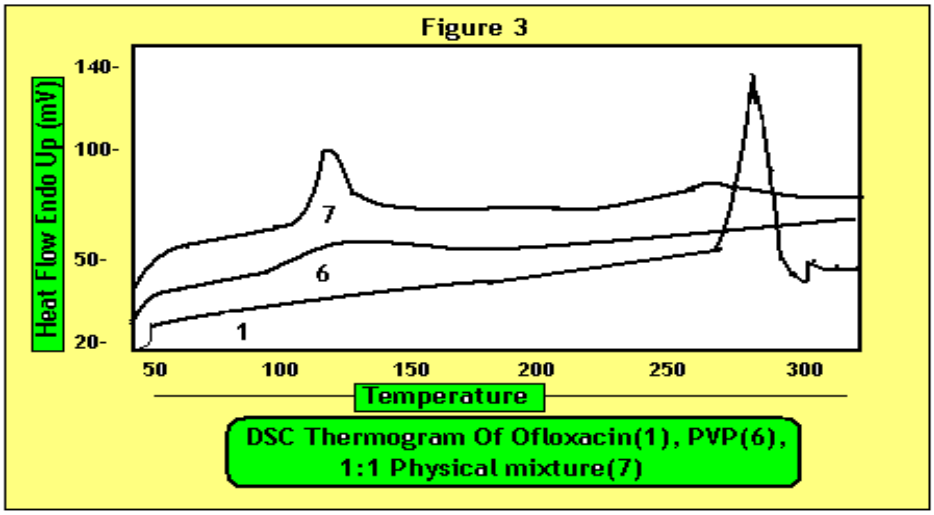
- **Trace 1** of figure 1-4 shows peak at 278.33 ^{0}C. (melting Endothermic peak of Ofloxacin).
- **Trace 3** (Physical mixture of Ofloxacin & Lactose) shows absence of peak at 278.33 ^{0}C and slight

pre shift in Lactose peaks.



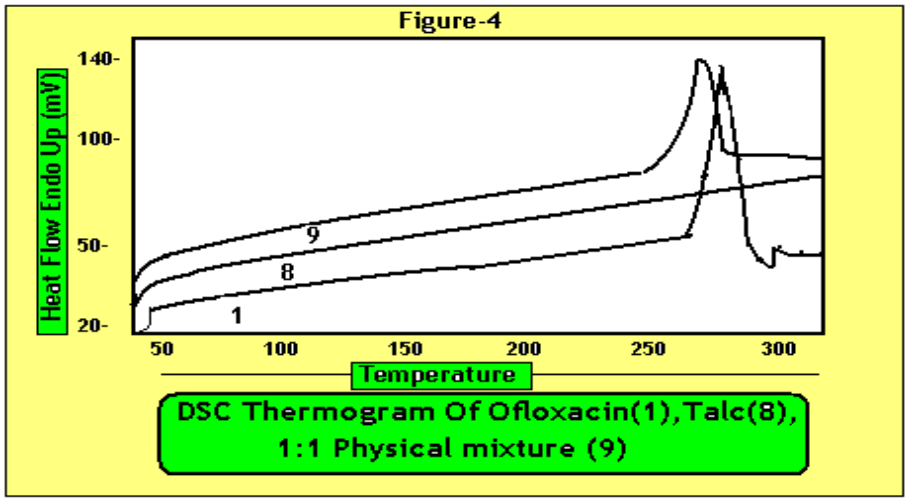
DSC RESULT—COMPATIBLE

- **Trace 5** (Physical mixture of Ofloxacin & Starch) shows an early onset at 268.37 ^{0}C.



DSC RESULT--INCOMPATIBLE

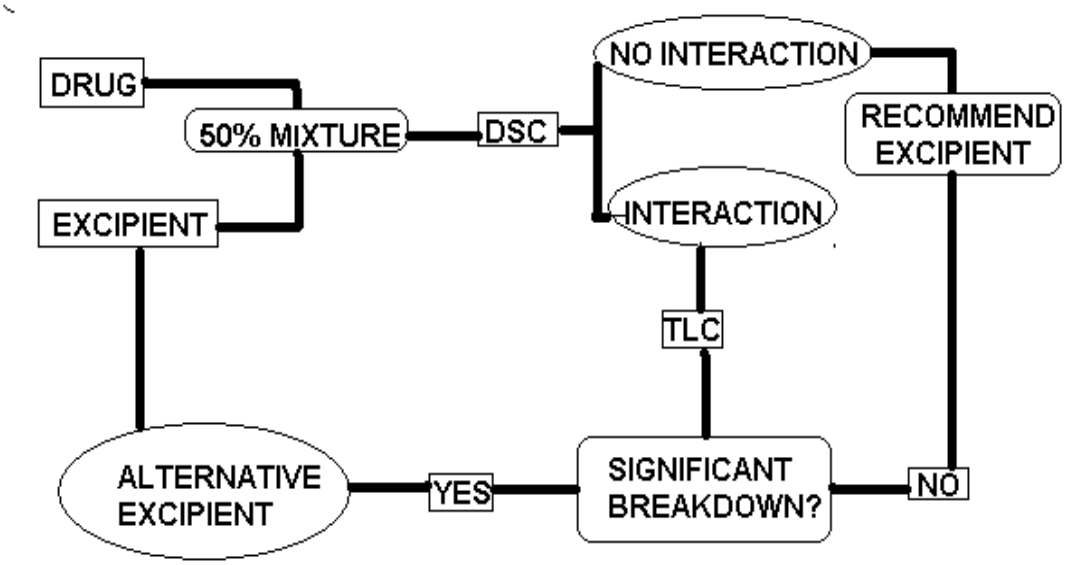
- **Trace 7** (Physical mixture of Ofloxacin & PVP) shows no change in position of endothermic peak for PVP but there is increase in peak area and size & shape of peak for Ofloxacin is also decreased.



DSC RESULT—COMPATIBLE

- **Trace 9** (Physical mixture of Ofloxacin & Talc) shows combine features of each component but there are evident changes in onset.

►DSC Study of Ascorbic acid P'ceutical formulations



IDENTIFY CHEMICALLY COMPATIBLE EXCIPIENT USING DSC WITH CONFIRMATORY TLC

Excipients: Sod. Crosscarmellose, MCC, Lactose

- Thermal stability was performed on ascorbic acid std. samples, binary mix. Of ascorbic acid & excipients, under N2 & air atmospheres.
- IR & X-Ray Diffractometry: No chemical interaction
- However thermal stability of P'ceutical formulations is different.
- Temp. of beginning of thermal degradation for Ascorbic acid is lowered of about 5^0C for MCC & 10^0C for Na-crosscarmellose & Lactose.
- Such facts must be considered for storage planning of tablets.

►ADVANTAGES OF DSC OVER TRADITIONAL METHODS:-

1. fast – (no long term storage of mixture is required prior to evaluation.
2. Reliable
3. Very less sample required (few mg.)

►LIMITATIONS:-

1. If thermal changes are very small, DSC can't be used. Therefore, it should always be supported by some non-thermal methods like TLC or FT-IR or XRPD.

2. DSC can not detect the incompatibilities which occur after long term storage.

For Eg. MCC / ASPIRIN……. DSC shows no incompatibilities between these two. But after long term storage MCC, being hygroscopic, absorb moisture and degradation of Aspirin occur due to moisture.

3. It is important to view results of such incompatibility testing with caution.
   For Eg. Mg-stearate is incompatible with wide range of compounds when tested. Yet because it is used at low conc. (0.5-1%). Such low conc. rarely produces a problem in practice on long term storage & use.

4. Not applicable if test materials exhibit properties that make data interpretation difficult. Such as Eutectic formation, coincident melting & dissolution of one component in the melt of other.

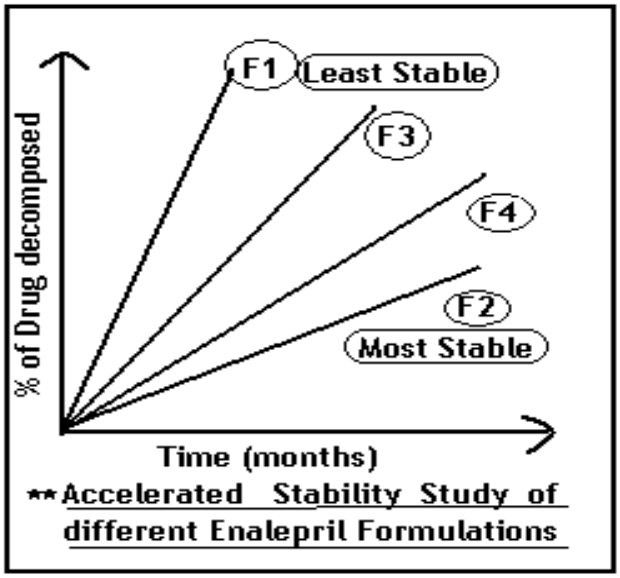
DIFFERENTIAL THERMAL ANALYSIS

Experimental Drug : Enalepril maleate
Experimental Excipients(Directly compressible diluent)**:**

1.Avicel
2.Spray dried lactose
3.Emcompress
4.A-tab

► In all the formulations excipients other than directly compressible vehicle are kept same.

FORMULATION	RESULT OF DTA (interaction)	SHELF LIFE	INFERENCE
F_1 (Avicel)	+	3 ½ month	Least suitable
F_2 (Spray dried lactose)	—	1 yr and 3 month	Ideal
F_3 (Emcompress)	+	8 month	Not recommended
F_4 (A-tab)	+	9 ½ month	Not recommended



**Accelerated Stability Study of different Enalepril Formulations

ACCELERATED STABILITY STUDY

- Different formulations of the same dru are prepared.(Eg. Enalepril maleate As above F_1-F_4)
- Samples are kept at 40^0C / 75 % RH.
- Chemical stability is assessed by analyzing the drug content at regular interval.

- Amt. of drug degraded is calculated. % Drug decomposed VS time (month) is plotted and determine with excipient combination in which drug attains maximum stability.

DIFFUSE REFLECTANCE SPECTROSCOPY:

- **Principle:** In this technique solid drug, excipients and their physical mixture are exposed to incident radiation.
  - A portion of the incident radiation is partly absorbed and partly reflected in a diffuse manner.
- The diffuse reflectance depends on the packing density of the solid, its particle size and its crystal form. Where these factors are adequately controlled, diffuse reflectance spectroscopy can be used to investigate physical and chemical changes occurring on solid surfaces.
- DRS is more useful than HPLC assay to detect surface discoloration due to oxidation or reaction with excipients.

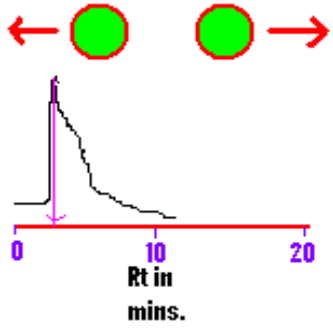
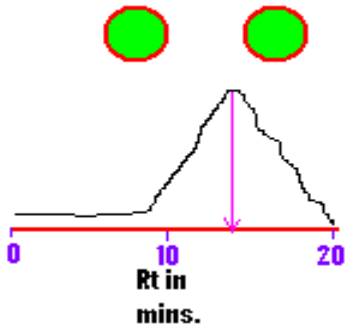
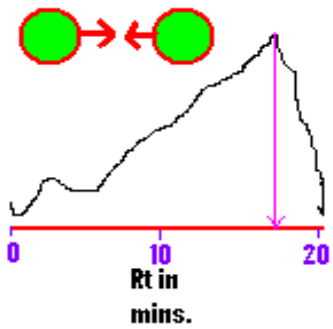
CHROMATOGRAPHY

1. TLC: Thin Layer Chromatography
2. HPTLC: High Performance Thin Layer Chromatography

►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.
►In TLC, Stationary phase consist of powder adhered onto glass, plastic or metal plate.
►Powder commonly used are Silica, Alumina, Polyamide, Cellulose & Ion exchange resin.
►Solution of Drug, Excipient & Drug: Excipient mixture are prepared & spotted on the same baseline at the ed of plate.
►The plate is then placed upright in a closed chamber containing the solvent which constitutes the Mobile phase.
►As the solvent moves up the plate, it carries with it the material.
►The materials that have stronger affinity for S.P. will move at slower rate.
►The material is identified by its Rf value.
►The position of the material on the plate is indicated by spraying the plate with certain reagents or exposing the plate to UV radiation.
►If there is no interaction between drug & excipient, the mixture will produce two spots.
The Rf value of which are identical with those of individual drug & excipient.
►If there is interaction, the complex formed will produce a spot. The Rf value of which is different from those of the individual components.

(3)C: SIC: Self Interactive Chromatography

- **Principle:-** For different mobile phases (i.e. different excipients) the injected drug have different interactions (may be repulsive or attractive) with the SP of drug leads to shift in retention time.

FIGURE(A)	FIGURE(B)	FIGURE(C)
		
When interaction is repulsive, a sharper peak is obtained at a shorter retention time.	When no net interaction between the immobilized drug, Rt =dead volume of column.	When attractive interactions, it will have longer retention time& wider peak.

► **Method**:-

►SIC is a modified type of affinity chromatography.

►Here, drug is made immobilized as the SP and solution to be tested acts as MP.

►Measure, Rt (Retention time) and compare it with non- retained marker.

► **Applications**:-

►SIC is useful for proteinous drug products with excipients.

►EX: INF – Tau – A new anti- viral drug. Interactions of it with different types of buffers were studied by SIC. Here, buffer is used to prevent aggregations.

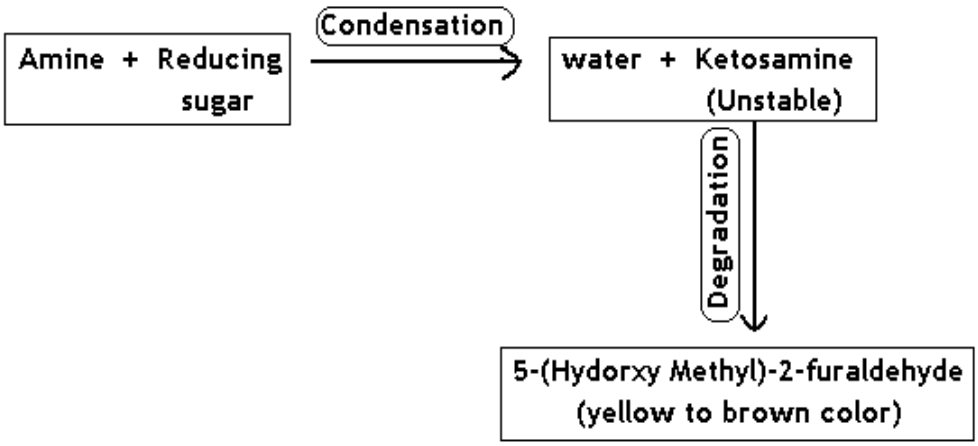
Compatibility studies in different dosage forms

A) Drug-Excipient compatibility studies in solid dosage forms

Example 1:-

Millard reaction:- is a non-enzymatic bimolecular browning reaction between reducing sugar and an amine(1^0/ 2^0)

Mechanism:-



Example 2:

<u>Effect of Excipients on Hydrate formation in wet masses containing Theophylline</u>

- During wet granulation Theophylline Shows Pseudopolymorphic changes that may alter its dissolution rate.

- In the presence of moisture Theophylline monohydrate is formed which has slow dissolution rate.

- Diluents Used:

    - α- Lactose monohydrate ⟹ Minimum water absorbing capacity. So not able to prevent but enhanced Hydrate formation of Theophylline.

    - Silicified MCC ⟹ Highly water absorbing capacity.

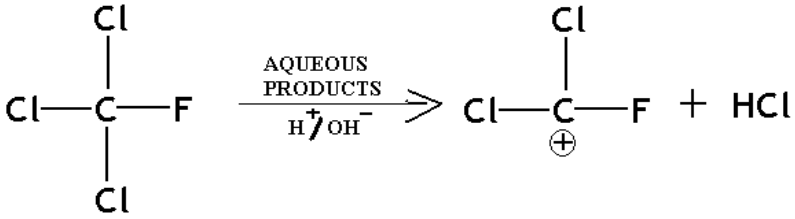
Able to inhibit the formation of Theophylline monohydrate at low moisture content.

B) Drug excipient Compatibility Studies in Aerosols

Example 1:- **Interaction of propellent-11 with aqueous drug products**.

- Propellent 11 is trichloromonofluoromethane.

- Interaction of above with the aqueous drug is as follow.

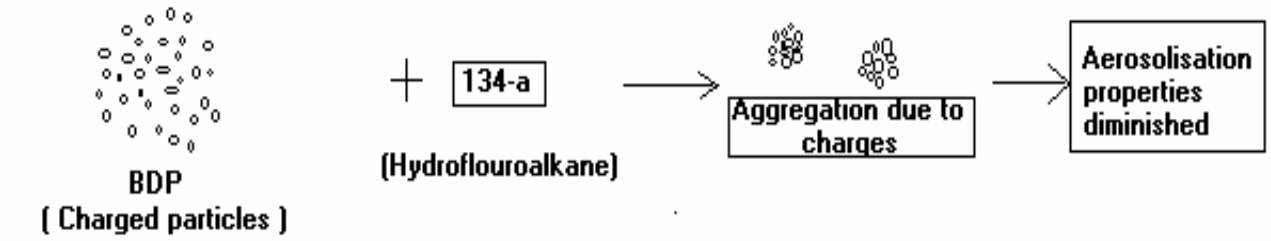


- HCl corrodes the Al-container.

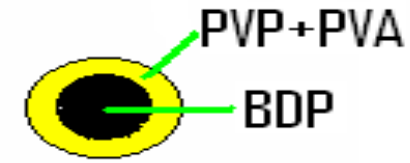
- Therefore, Propellent 11 is incompatible with aqueous products.

Example 2: Beclomethasone- Hydroflouroalkane interactions:

- BDP is a Steroidal drug used in Asthma.



- Manipulation of above interaction: BDP particles coated with amphiphilic macromolecular excipient by Spray drying.



- Therefore, prevention of aggregation & production of physically stable suspension with excellent aerosolisation properties.

C) Drug Excipient Compatibility Studies in Parenteral products

Excipients are added to parenteral formulations to enhance or maintain active ingredient solubility and/or stability. Excipients also are important in parenteral formulations to assure safety, minimize pain and irritation upon injection, and control or prolong drug delivery. These are all examples of positive or synergistic interaction between excipient and drugs.

(I) **Anti-oxidants**:-

A) **Ascorbic acid**: It is incompatible with those drugs which are acid- unstable.
Eg. Penicillin-G, Phenylephrine HCl, Pyrilamine meleate, Salicylamide, Theobromine.

B) **Na bisulfite**: It is a strong Nucleophilic anti-oxidant.

- Epinephrine + Na bisulfite ⇨ Sulphonic acid dvt.
  - It can be prevented by addition of Na-borate which produces complex with Epinephrine and prevent its interaction with Na-bisulfite.
- It is incompatible in Opthalmic solution containing Phenyl mercuric acetate especially when autoclaved.

C) **Edetate salts**: used in stabilization of drugs sensitive to metal catalyzed oxidation and / or photolysis.

- Edetate salts are incompatible with Zn Insulin, Thiomerosal, Amphotericin & Hydralazine HCl.

(II) **Preservatives**:

A) **Phenolic Preservatives**:

- Lente- Insulin + Phenolic preservative ⇨ Break-down of Bi-sulphide Linkage in Insulin structure.

- But when we formulate Protamine- Insulin formulation Phenol plays imp. role. It forms tetragonal oblong crystals which is responsible for prolong action of insulin.

(III) **Surface active agents**:

A) **Polysorbate 80**: Solubilizing agent, Wetting agent, Emulsifying agent.

- One must concern about the residual peroxide present in Polysorbate.
- PS 80 ⇒ Polyoxyethylene sorbitan ester of Oleic acid (Unsatd.F.A)
- PS 20 ⇒ Polyoxyethylene sorbitan ester of lauric acid (Satd.F.A)

  So PS 20 is less prone to oxidation than PS 80.

(IV) **Cosolvents**:

A) **Sorbitol**: Increase the degradation rate of Penicillin in Neutral and Aqueous solutions.

B) **Glycerol**: Increase the mobility of freeze-dried formulation leading to peptide deamidation.

INCOMPATIBLE IMPURITIES

► Chemical impurity profiles of the excipient can be very important in influencing the long term chemical stability performance of the formulated drug product.

Eg.

(1) DCP – Sometimes, IRON may be present in DCP as impurities. & It is incompatible with MECLIZINE HCl . (Fe NMT 0.04%)

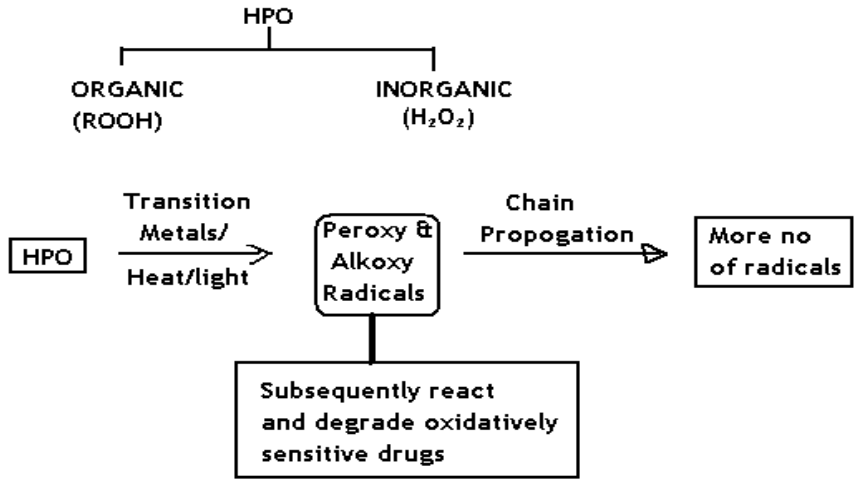
(2) Evaluation of Hydroperoxides (HPO) in common pharmaceutical excipients.

POVIDONE
PEG 400
HPC
POLYSORBATE 80

Contains substantial conc. of HPOs with significant batch to batch OR manufacturer to manufacturer variations.

While MCC, Lactose, High M.wt PEG, Polyxamer contains less amt. of HPOs.

► In solid dosage forms, PVP is commonly used as a bonder for wet granulation & often used at very low conc.



However, the total HPO content is high enough in PVP to promote significant degradation when formulating oxidatively sensitive drugs.

► 5% of **PVP** was shown to be responsible for N-oxide formation of Raloxifen HCl, due to high HPO content.

► So for these excipients, active monitoring and control of HPOs by the supplier may be necessary.

(3) Gelatin is also containing IRON as impurities, Dark spots may occur in the shell due to the migration of water soluble iron sensitive ingredients from fill material into the shell.

P-GLYCOPROTEIN INHIBITOR EXCIPIENTS

- P-Glycoprotein is membrane associated transport protein. It is an efflux pump lies in tissue membranes.
- Research has shown that some excipients have p-Glycoprotein efflux-pump inhibiting properties.
- Thus they increase drug concentration in cells & hence enhance the effect of drug molecules.

EXAMPLES: - 1) PEG-32 lauric glycerides. 2) PEG-50 Stearate
3) Polysorbate-80 4) Polysorbate-20
5) Polysorbate-85 6) PEG-40 hydrogenated castor oil
7) PEG-35 castor oil

Known Incompatibilities

Functional group	**Incompatibility**	**Type of reaction**
Primary amine	Mono & Di-saccharides	Amine-Aldehyde & Amine-Acetal
Ester, Lactone	Basic component	Ring opening, Ester base hydrolysis
Aldehyde	Amine, Carbohydrate	Aldehyde-Amine, Schiff base Or Glycosylamine formation
Carboxyl	Base	Salt formation
Alcohol	Oxygen	Oxidation to Aldehyde & Ketones
Sulfhydryl	Oxygen	Dimerization
Phenol	Metal	Complexation
Gelatin- Capsule Shell	Cationic Surfactant	Denaturation

Excipient	**Incompatibility**	**Type of reaction**
Parabens	Non ionic surfactants (Polysorbate 80)	Micellization (Reduced antimicrobial activity)
	Plastic Containers	Absorption of Parabens

Phenylmercuric Nitrate	# Anionic Emulsifying agents, Suspending Agents, Talc, Na-metabisulfite, Na-thiosulfate	Anti-microbial activity Reduced
	Halides	Incompatible (forms less soluble halogen compds)
PEG	Penicillin & Bacitracin	Anti-bacterial activity reduced
	Phenol, Tannic acid & Salicylic acid	Softening & Liquifaction
	Sulphonamide & Dithranol	Discoloration
	Film coating	Migration of PEG from tablet film coating, leading to interaction with core component

► Why drug itself is taken as one of the sample for Drug- excipient compatibility studies?

1.Organic synthesis of compound may lack the refinement and it is common that there will be several weak spots (of impurities) on a TLC chromatogram of a compound. So, when we get TLC chromatogram of Drug-Excipient mixture after accelerated exposure, there should not be additional or new spots developed and no change in intensity of spots of the drug.

2.Drug stability profile (effect of humidity, temp., $_P$H, oxygen) helps in proper selection of excipients.

Eg. A compound with bulk instability at high humidity should be formulated with anhydrous excipient.

- Similarly $_P$H of maximum drug stability should match with $_P$H of an aqueous suspension or solution of Drug + excipient.

3. It is now required by FDA for IND submission.

► <u>STUDY QUESTIONS:-</u>

1. Enlist the techniques employed in studying drug-excipient compatibility study. How is Accelerated stability study carried out? (Sept: 2006)

2. Excipients can affect absorption &bio- availability: Justify the sentence. (Sept: 2006)

3. A Pharmacist wants to develop SGC formulation of a new drug. What tests he should carry out in order to ascertain drug-adjuvant interaction? Give brief outline & the significance if each test. (Sept: 2004)

4. Enlist the technique employed in DE compatibility screening &detail about accelerated storage testing. Write a note on D.E. interaction in parenterals.

5. Comments:-

A) Drug-itself is taken as a sample in DECS.

B) DSC is one of the important methods to study DECS though not the complete one.

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