EFFECT OF VARIOUS ENVIRONMENTAL /PROCESSING FACTORS ON STABILITY OF THE FORMULATION AND TECHNIQUES FOR STABILIZATION OF PRODUCTS AGAINST THE SAME.

PROCESSING FACTORS:-

- BLENDING:-
  - It is **most important step** for manufacturing of solution dosage form. High speed of mixing may introduce air into the product and slow mixing may not form a satisfactory product.
  - For mixing step, both **mixing time and speed should be evaluated** for API and Excipients.
  - Mixing might produce particle size reduction or polymorphic conversion
  - During mixing some other factors like type of agitator, temperature or vaccum etc. can affect the stability.
  - **Say for example**, if during mixing, vacuum is not applied than air bubble will present into the product that might produce oxidation of product.

WAYS FOR STABILIZATION:-

- Use of optimum time and rate of mixing.
- Use of optimum and controlled temperature.
- Application of vacuum.
- Use of closed system.

FOR SOLID DOSAGE FORM:-

- During pharmaceutical powder blending process in case of solid dosage form, electrostatic charges generate due to particle-particle & particle wall collision.
- The effect of electrostatic charging on pharmaceutical powder homogeneity was investigated on 2 binary blending system:- LACTOSE as an excipient with CAFFEINE as an API & MCC as an excipient with CAFFEINE as an API
- 3 different blending procedures were conducted
  1. Conventional without charge control.
  2. Blending with simultaneous charge neutralization.
  3. Blending combined with corona(apparatus) charging process
- It was found that presence of uncontrolled electrostatic charges has an adverse effect on powder blend uniformity. Elimination of charges also appears to have negative impact on blend uniformity. In contrast blending of negatively charged excipient & positively charged API leads to better blend uniformity.

**FREEZE-DRYING PROCESS:-**
- Freeze-drying process also affects the stability of product & there are various substances used for the process of freeze-drying which also leads to either increase or decrease in the stability.
  - A method to produce physically stable formulation.
  - Applicable for multivitamin preparation, antibiotics, hormones and Proteins formulation.
  - Cryoprotectant is added in formulation when product is lyophilized.
  - To act successfully as a protectant, it should have,
    - A high glass transition temperature \( T_g \),
    - A poor hygroscopicity,
    - A low crystallization rate,
    - Contain no reducing groups.

  **Eg:-**
- Freeze drying was found to have destructive effect on the ordered structure of starch & this effect varied with respect to preparation condition.

- Surfactants & sugars possess synergistic effects on the lipoplex stability during freeze drying.

- Impact of bulking agents was studied on the stability of monoclonal antibody. It was found that sucrose acts as a primary stabilizer but when glycine was added, glycine leads to increase in the stability & when mannitol was added instead of glycine again there was increase in the stability though to a lesser extent as compared to glycine.

**POLYMERIC FILM COATING PROCESS:-**
- The key to a successful application of an aqueous film coat to solid dosage forms is a full understanding of the important processing factors influencing the application process. Here we will enlist processing factors that contribute to product performance, since slight variation in processing conditions will impact the properties and therapeutic response of a film-coated drug delivery system.

  **List of processing factors influencing the properties of polymeric film coatings:-**

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<th>Table 1. Processing factors influencing the properties of polymeric film coatings</th>
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<td>1. Inlet and bed temperatures</td>
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<td>10. Influence of tablet shape and pan speed</td>
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WAYS FOR STABILIZATION:
- Use of optimum processing condition for film coating.
- Identification and use of excipients which increased stability of film coated product.

Interactions during Aqueous film coating of Ibuprofen with Aquacoat ECD.

- During the development of a coated ibuprofen formulation a sticking tendency occurred when applying Aquacoat ECD.
- The compatibility of the components of Aquacoat ECD with ibuprofen was investigated by differential scanning calorimetry.
- Cetyl alcohol, a stabilizing excipient in Aquacoat, was found to form a eutectic system with ibuprofen. It was characterized by the construction of a phase diagram with 33 mol% ibuprofen and an onset temperature of 40.5 °C.

MILLING
- The milling process results in a reduction in the particle size of a given material and can be conducted using the mildest conditions possible to render a sample homogeneous, or can use more rigorous milling to reduce the primary particle size.
- The formation of a high energy amorphous material is usually undesirable and given the opportunity, will spontaneously transfer either to a crystalline hydrate or anhydride.
- These physical changes in the state of the drug substance can alter the stability, dissolution characteristics and possibly even the bioavailability of the drug.

WAYS FOR STABILIZATION:
- Use of moderate condition of milling.
- Optimum time of milling.
- Eg:-
  1. The phase transformation of chloramphenicol palmitate associated with grinding and the effect of seed crystals

Thus, as we know that with increase in the concentration of form A of chloramphenicol palmitate the blood level are found to decrease and there is a detection test for presence of form A in Pharmacopoeias, so while grinding no impurity of form A should be present and grinding time should not exceed 150 minutes (to prevent conversion of form B to form A).
2) Formation of physically stable amorphous drug by milling.

**DRUGS**
(KETOPROFEN, INDOMETHACIN, NAPROXAN, PROGESTERON)

**NEUSILIN**
(AMOR. MAGNESIUM ALUMINUM SILLICATE)

**Ball Milling**

**AMORPHIZATION OF DRUG**

**Storage**

**CONCLUSION:** - The amorphous form formed was studied for stability and found that this form is much more stable than normal amorphous form.

AND Similar studies were done on Salbutamol Sulphate & PVP. Experiment was done to improve the stability of SS as SS gets easily converted from amorphous form to agglomerated particles. Stability was induced by the method of co-milling. Co-milling of SS with excipients like pvp was done.

**EFFECT OF COMPRESSION:**
- It is generally assumed that overall amount of energy input into a formulation during compression is not sufficient to induce a phase transformation and for many substances this situation is certainly true. There are numerous examples, for which changes in phase composition do accompany a compression step.

  - Carbamazepine is a drug which shows differences in the dissolution rates that are associated with production of different polymorphs by tablet mfg process.
  - It has 3 different crystalline form – α, β and Dihydrate form.

  - Manufacturing process is
    - **Grinding** (ball mill for 15 and 60 min)
    - **Compression** (single punch machine)
  - It was found that
    - Dihydrate - good compressibility but not stable
      - α - best stability but sticking
      - β - best stability.

- The effects of **milling and compression** on the solid-state Maillard reaction between metoclopramide hydrochloride and lactose were investigated.
- Anhydrous metoclopramide hydrochloride was milled for various times, and then mixed with amorphous lactose. The mixtures were stored at 105°C and 0% RH. The reactivity of metoclopramide hydrochloride towards the Maillard reaction increased with milling time, as the result of increased surface area, formation of amorphous content, and creation of defects.
- Metoclopramide hydrochloride anhydrate and lactose were mixed and the mixtures were compressed into tablets under pressure varied from 70 to 350 MPa. Both tablets and mixtures were stored at 105°C and 0% RH for 9 days.
- For all three types of lactose used, spray-dried anhydrous lactose, spray-dried lactose monohydrate, and amorphous lactose, tablets exhibited higher reaction rate toward the Maillard reaction than the powder mixtures.
- Tablets containing metoclopramide hydrochloride and amorphous lactose prepared at higher pressure showed higher reaction rates than those prepared at lower pressure.

**EFFECT OF LOCAL MOBILITY:**
- Local mobility in amorphous forms of pharmaceuticals can lead to changes in their glass transition temperature effect of which is such that amorphous form converts to crystalline form.

**WET GRANULATION:**
- Wet granulation process, the both wetting phase solvent and drying phase conditions can cause a suitable environment for the transformation to alternate crystalline forms.

> Polymorphic transformations during wet granulation can be divided to

1) Conversion of a metastable form to the stable form;
2) Conversion of the stable form to a metastable form; or
3) Conversion of an unsolvate form to a solvate form.

**WAYS FOR STABILIZATION:**
- Use of granulating liquid which will not produce polymorphic conversion.
- Moderate/Optimum condition for drying.

- The preparation of tablets by THE MELT GRANULATION PROCESS was investigated to enhance chemical stability of a highly water-soluble drug substance, dipeptidylpeptidase IV (DPP-IV) inhibitor (Compound I), that is susceptible to degradation in presence of moisture. Melt granulation with a lipophilic binder (hydrogenated castor oil) improved the stability of the drug, while still maintaining immediate-release characteristics of the drug product.
- With higher binder levels, the sensitivity of the drug to degradation under humidity conditions decreased. It is postulated that the lipophilic binder coated drug particles at the surface protecting them from the influence of moisture. The granules had good flow properties and good compressibility and tablets prepared from them exhibited low weight variation and low friability.
The effect of some processing and formulation variables on the stability of tablets containing a crystalline salt of a triazine derivative was studied. The salt has a relatively low melting point and a low microenvironmental pH due to the weakly basic nature of the parent compound (pK_a = 4.0). This compound decomposes through acid-catalyzed hydrolysis. A full factorial design was used to study the effect of three variables on tablet stability: aqueous wet granulation, ball milling of the salt and filler prior to manufacturing, and the inclusion of sodium carbonate in the formulation as a pH modifier. In addition to the factorial design experiments, a batch of tablets was prepared by wet granulation, using sodium bicarbonate as the pH modifier. Stability of tablets was adversely affected by wet granulation. However, stability was greatly improved by wet granulation in the presence of sodium carbonate. The use of sodium bicarbonate as a pH modifier resulted in only marginal enhancement of tablet stability, suggesting that a higher microenvironmental pH than that provided by sodium bicarbonate is needed to maximize stability. Milling was found to have no effect.

EFFECT OF ADDITIVES:

The amorphous character is common in the polymeric molecules used as excipients. For example, sugars usually exist in the amorphous state e.g. as a result of milling, spray drying or freeze drying. Amorphous sugars are highly hygroscopic and at high RHs they may sorb large amounts of water causing crystallization of that sugar. This process can have significant consequences for the stability of pharmaceutical formulations, because the presence of only small amounts of amorphous material can affect the interaction between the powder and other components of a formulation.

Optimizing the selection of excipients in the formulation could reduce transformation during manufacturing and storage of final dosage forms.

INSTABILITY of APIs and excipients may be broadly classified as:

- **CHEMICAL INSTABILITY** (like Hydrolysis, Oxidation and Deamidation) or
- **PHYSICAL INSTABILITY** (like Polymorphism, Pseudopolymorphism or Crystallization).

WAYS FOR STABILIZATION:

- Avoid use of excipients which produce instability.
- Minimum numbers of excipients should be used.
- Use of excipient with multiple action.

**Eg:-**

- **SURFACTANTS:-**
  - Presence of surfactants may either increase or decrease the stability. LIKE presence of micelles of CETYL TRIETHYLAMMONIUM BROMIDE & CETYL PYRIDINIUM CHLORIDE inhibits degradation of aspirin by hydrolysis which is acid catalyzed reaction in contrast increase the degradation of base catalyzed reaction.
• COMPLEXING AGENTS:-
  ▪ Complexing agents increase the stability. Aromatic esters like benzocaine, procaine & tetracaine can be stabilised in solution form by the addition of 1-5% caffeine because of formation of complex.

• ANTIOXIDANTS & CHELATING AGENTS:-
  ▪ These agents generally increase stability by decreasing the rate of reaction.

EFFECT ON STABILITY IN PRESENCE OF OTHER DRUGS:-
• Sometimes presence of one drug affects either physical or chemical stability of other drug.
  • Eg:-
    1. Yuxingcao injection when mixed with 6 drugs at temp. 25°C & analysed using uv following observation done:-
      • YUXINGCAO + PENICILLIN = PRECIPITATION
      • YUXINGCAO + GANCYCLOVIR= PRECIPITATION
      • YUXINGCAO + OFLOXACIN = NO CHANGE
      • YUXINGCAO + RIBAVIRIN = NO CHANGE
      • YUXINGCAO + CEPHRADIN = NO CHANGE FOR 2 HRS & DECREASE IN CONTENT WITHIN 24 HRS.
      • YUXINGCAO + ACYCLOVIR = DECREASE IN CONTENT WAS OBSERVED.

    2. When fosfomycin sodium & gatifloxacin were mixed & analysed by UV spectroscopy it was found that content & spectra of UV spectra changed significantly.


RADIATIONS:-
• Not common variable.
  • Employed in the sterilization of pharmaceutical product so, its effect on stability of drug should be considered.

WAYS FOR STABILIZATION:
  ➢ Avoid γ irradiation if sterilization by other ways is possible.
  ➢ Formation of various products on γ irradiation of diazepam in a methanolic solution was inhibited by ascorbic acid.


  ➢ The influence of CLO on PLGA radiolysis mechanisms and the identification of possible irradiation markers were investigated.

  ➢ Microspheres were prepared by means of a spray-drying method.

  ➢ Radiolysis mechanisms were investigated by using electronic paramagnetic resonance (EPR) analysis.
Polymer/CLO spin transfer reactions suggest that CLO had a radiostabilising effect on the polymeric matrix.

**ENVIRONMENTAL FACTORS:**

**TEMPERATURE:**
- Study of decomposition of the product at elevated temperature should be done to know the temperature dependency of reaction.
- It helps in predicting the stability of the product at ordinary shelf temperature.
- Rate of reaction is denoted for each 10° C rise in temperature accelerated study is done to decrease the time period for stability study.
- At 37° C it takes 100 days for degradation & for 80° C it takes 25 days for degradation.
- Temperature is one of the primary factors affecting the drug stability.
- As temperature increases a greater available free energy leads to a more rapid reaction and typically a 10° C increase in temperature produces a two to five fold increase in decay.
- It catalyses hydrolysis, oxidation & thermal reaction follows just after initiation of photolytic reaction.
- The most satisfactory method for expressing the influence of temperature on reaction velocity or rate is the quantitative relation proposed by Arrhenius:

\[ K = A \times e^{-\frac{E_a}{RT}} \]

Where,
- \( K \) = specific rate of degradation
- \( A \) = Frequency Factor
- \( E_a \) = Arrhenius Activation Energy
- \( R \) = Gas Constant
- \( T \) = Absolute Temperature

Logarithmically it can be expressed as:

\[ \log K = \log A - \frac{E_a}{2.303 RT} \]

From the graph of \( K \rightarrow 1/T \) one can determine \( E_a \) from slope and \( A \) from intercept.

\[ \text{SLOPE} = \frac{-E_a}{2.303R} \]

\[ \text{INTERCEPT} = \log A \]
Limitations of Arrhenius relationship for prediction of stability of products:

1. At higher temp., there is less relative humidity & O2 solubility, thus hindering the predictability of RT stability of drug sensitive to presence of moisture and oxygen.

2. For dispersed systems, viscosity is decreased as temp. is increased and physical characteristics may be altered, resulting in potentially large errors in prediction of stability.

3. Different degradation mechanisms may predominate at different temperatures, thus making stability prediction marginal at best.

WAYS FOR STABILIZATION:

- Pharmaceutical product should be stored within the temperature range in which they are stable.
- They should not be exposed to extremes of temperature.
- Usually they should be stored at low temperature if they lack sufficient stability at room temperature.
- There are few drugs on which freezing has an adverse effect, so freezing should be avoided unless until it is stable at such temperatures.

HUMIDITY:

- Higher humidity may lead to moisture adsorption.
- As relative humidity is increased stability is decreased for drugs which are highly sensitive to hydrolysis.
- Higher humidity increases ageing process through interaction of drugs with excipients.

It can affect the stability of pharmaceuticals by,

- Hydrolytic degradation
- Isomerization
- Crystallization
- Affecting flow and compaction properties etc.

Three different ways in which water can be located within a solid,

(A) Monolayer adsorbed layer,
(B) Adsorbed layer,
(C) Condensed water.

Figure: Water vapour adsorption and deliquescence of a water soluble solid particle.

- EFFECT OF MOISTURE CONTENT ON THE STORAGE STABILITY OF LIPOPLEX FORMULATIONS CONTAINING THIOBARBITURIC ACID DERIVATIVES WAS FOUND.
- TEMPERATURE CHOSEN WERE RT, 40°C & 60°C FOR 3 MONTHS.
RESULTS:
- AT ROOM TEMPERATURE – CONCENTRATION WAS MAINTAINED.
- AT HIGHER MOISTURE CONTENT – 1.93 LOWER TBA DERIVATIVES.
- AT LOWER MOISTURE CONTENT – LITTLE HIGHER TBA DERIVATIVES

WAYS FOR STABLIZATION:
- Maintenance of controlled humidity condition
- Moisture proof packaging.

OXIDATION - LIGHT:
- BOTH ARE SAME AS DISCUSSED IN PREFORMULATION (PHYSICO-CHEMICAL FACTORS).

pH:
- The change of more than 10 folds in rate constants result in just shift of 1 pH unit.
- So, before formulating the drug in solution, K versus pH should be studied & optimum pH at lowest value of rate constant is to be found out.
- Hydrogen ion catalysis occurs at lower pH & hydroxyl at higher Ph.

WAY FOR STABLIZATION:
- Maintenance of stable pH by use of appropriate buffer salts.

- The effect of salt form on the stability of an ester prodrug of a IIb/IIIa receptor antagonist was investigated. The pH of maximum stability for the ester prodrug is approximately 4. The mesylate salt is thought to provide lower microenvironment pH, closer to the pH of maximum stability, than the acetate salt. Stability of drug product manufactured using the mesylate salt (DMP 755) was studied and compared with that for the acetate salt (DMP 754). Formulations contained disodium citrate as a pH modifier to control formulation pH, since solid state stability for this compound...
is dependent on the microenvironment pH. The pH modifier was not able to achieve adequate microenvironment pH control for the DMP 754 drug product when added using a dry manufacturing process. While DMP 754 required the use of a pH modifier added in solution during wet granulation in order to improve drug product stability, DMP 755 was able to achieve similar results using the dry granulation process. Stability of DMP 755 drug product was independent of effectiveness of the pH modifier. This study showed that the choice of the salt form may provide an alternative for maximizing drug product stability.

**EFFECT OF SOLUBILITY:-**

- Applicable to drugs in solution form.

**Eg:-**

Penicillins are very unstable in aqueous solution because of hydrolysis of β-lactam ring.

**WAYS FOR STABILIZATION:-**

- Stabilised by using insoluble salts of API.
- Formulate the drug in suspension dosage form.

**EFFECT OF IONIC STRENGTH:-**

- The rate of reaction can be influenced by the ionic strength of the solution in accordance with the following equation:

\[
\log k = \log k_0 + 1.02Z_A Z_B \sqrt{U}
\]

Where,

- \(Z_A\) & \(Z_B\) - charges carried by the reacting species in solution
- \(U\) - the ionic strength
- \(K\) - rate constant at infinite dilution.

&

Where,

\[
U = \frac{1}{2} \sum C Z^2
\]
Drugs with positive charge undergoes H\(^+\) ion catalysis & in this increase in ionic strength caused by the addition of salt increases rate of reaction.

If the drug is neutral change in ionic strength will have no effect.

Drugs with negative charge undergoes OH\(^-\) ion catalysis & in this increase in ionic strength caused by the addition of salt decreases rate of reaction.

**EFFECT OF PACKAGING COMPONENTS:-**

- Most commonly employed are

  - **CONTAINERS:**
    - Glass, Plastic, Metal
  - **CLOSURES:**
    - Rubber
  - **CONTAINERS:**

1) **GLASS**

**PROBLEMS:**

a) Release of alkali
b) Release of Insoluble flake

**REMEDY FOR PREVENTION OF RELEASE OF ALKALI:-**

- By decreasing soda content
- Siliconization of surface.
- By replacing sodium oxide with other oxides.
- Surface treatment by sulphur-di-oxide in presence of water-vapor & heat.

**REMEDY FOR PREVENTION OF RELEASE OF INSOLUBLE FLAKE:-**

- Flake formation can be prevented by using borosilicate glass
- Pretreatment of the container with dilute acid.

2) **PLASTIC**

High Molecular Weight Polymers like Polyethylene, Polypropylene, Polystyrene, PVC etc

**PROBLEMS:**

a) Permeation of moisture
b) Leaching
c) ADSORPTION OR ABSORPTION
d) CHEMICAL/PHYSICAL REACTION OF CONTENTS OF CONTAINERS WITH PRODUCTS.

**REMEDY:**

- Lining of the container with an epoxy resin eliminates this problem but has to be evaluated separately for each product.
  (Epoxy lining does not prevent sorption of phenyl mercuric nitrate).

Stability of FENTANYL 5µg/ml diluted with 0.9% sodium chloride injection & was stored in polypropylene syringes....

It was found that above solution was stable for 90 days in controlled ambient conditions when stored protected from light.
3) METALS
Metals commonly used are tin, plastic coated tin, tin-coated lead, aluminum and coated aluminum.

PROBLEMS:
a) Reactivity
   
   1. TIN + CHLORIDE → ERROSION
   2. ALUMINUM + FATTY ALCHOL → WHITE ENCRUSTATION

REMEDY:
⇒ Application of an epoxy lining to internal surfaces of aluminum tubes was found to make them more resistant to attack.

CLOSURES:-

a) RUBBER

PROBLEMS:
a) Sorption of API into rubber.
b) Extraction of one or more components of rubber into vial solution.

Leached extractive in the solution can cause:-
   a. Interference with chemical analysis of drug.
   b. Affects toxicity & pyrogenicity of injectables.
   c. Can cause drug inactivation.
   d. Can cause physical instability so, to prevent such interferences.

REMEDY:
⇒ Epoxy lining applied to rubber stoppers
   - reduction results in amount of extractive leached from stopper but no effect on sorption of preservative from solution.
   - However use of Teflon–Coated rubber stoppers essentially prevents sorption and leaching of the rubber stopper.

NEW STABILIZATION TECHNIQUE:-
SUPERCritical
FLUID:-
• Near the critical points, supercritical fluids possess liquid like densities and gas like transport properties.

• CO2 -choice for pharmaceutical application

   - Dry powders of Stable Protein Formulations from aqueous solutions Prepared using Supercritical CO(2)-assisted Aerosolization
   - Use of a new supercritical carbon dioxide-assisted aerosolization coupled with bubble drying technology.
   - Two model proteins, lysozyme and lactate dehydrogenase (LDH).
   - In the absence of excipients, lysozyme was observed to undergo perturbations of secondary structure observed by solid-state infrared spectroscopy. In the presence of sucrose, this unfolding was minimized.
   - The more labile LDH suffered irrecoverable loss of activity on reconstituting in the absence of carbohydrate stabilizers.
   - LDH could be stabilized through with the addition of sucrose, and almost complete preservation of activity was achieved with the further addition of a surface active agent, such as Tween 20.

PRIOR STUDY QUESTIONS:-

1. Enlist various processing factors affecting stability of formulation?
2. Describe effect of particle size reduction (or milling) on stability of formulation product and stabilization against the same?
3. Describe effect of γ radiation on stability of formulation product and stabilization against the same?
4. Effect of RH on stability and stabilization against the same?
5. What is process induced transformation? Discuss the effect of wet granulation, compression and excipients on the stability?
6. Discuss the effect of temperature, light and RH on the stability and stabilization against the same?
7. Note on the influence of packaging components on the dosage form stability?

NEW STUDY QUESTIONS:-

1. What is the effect of pH & ionic strength on the stability of drug?
2. Write a note on effect of blending on solid as well as liquid dosage form?
3. Explain the effect of freeze drying on the stability?
4. What are the effects of polymeric film coating & amorphous mobility on the stability of drug?
5. Note on effect of additives on stability?
6. Note on effect of presence of other drugs?
7. Explain the effect of solubility on stability with examples & stabilization techniques?
8. Write a note on various stabilization techniques employed for the stability of pharmaceutical dosage form?