BIO & PHARMA ANALYTICAL TECHNIQUES

Chapter 12
Stability Test

by
Dr. Siti Umairah Mokhtar
Faculty of Engineering Technology
umairah@ump.edu.my

Chapter Description

- Aims
  - Discuss theory, principles and application of analytical techniques used in material characterization, pre-formulation development, manufacturing process and storage stability.

- Expected Outcomes
  - Explain general facts of stability testing in pharmaceutical industry
  - Differentiate the procedures between types of stability testing
  - Discuss on the significance/importance of stability testing in pharmaceutical industry.

- References
  - ICH Q1R(2) Stability Testing of New Drug Substances and Products
  - ASEAN Guideline on Stability Study of Drug Product (Update revision 2013)

STABILITY

- Stability of pharmaceutical product:
- may be defined as the capability of a certain formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specification.

Importance of stability testing

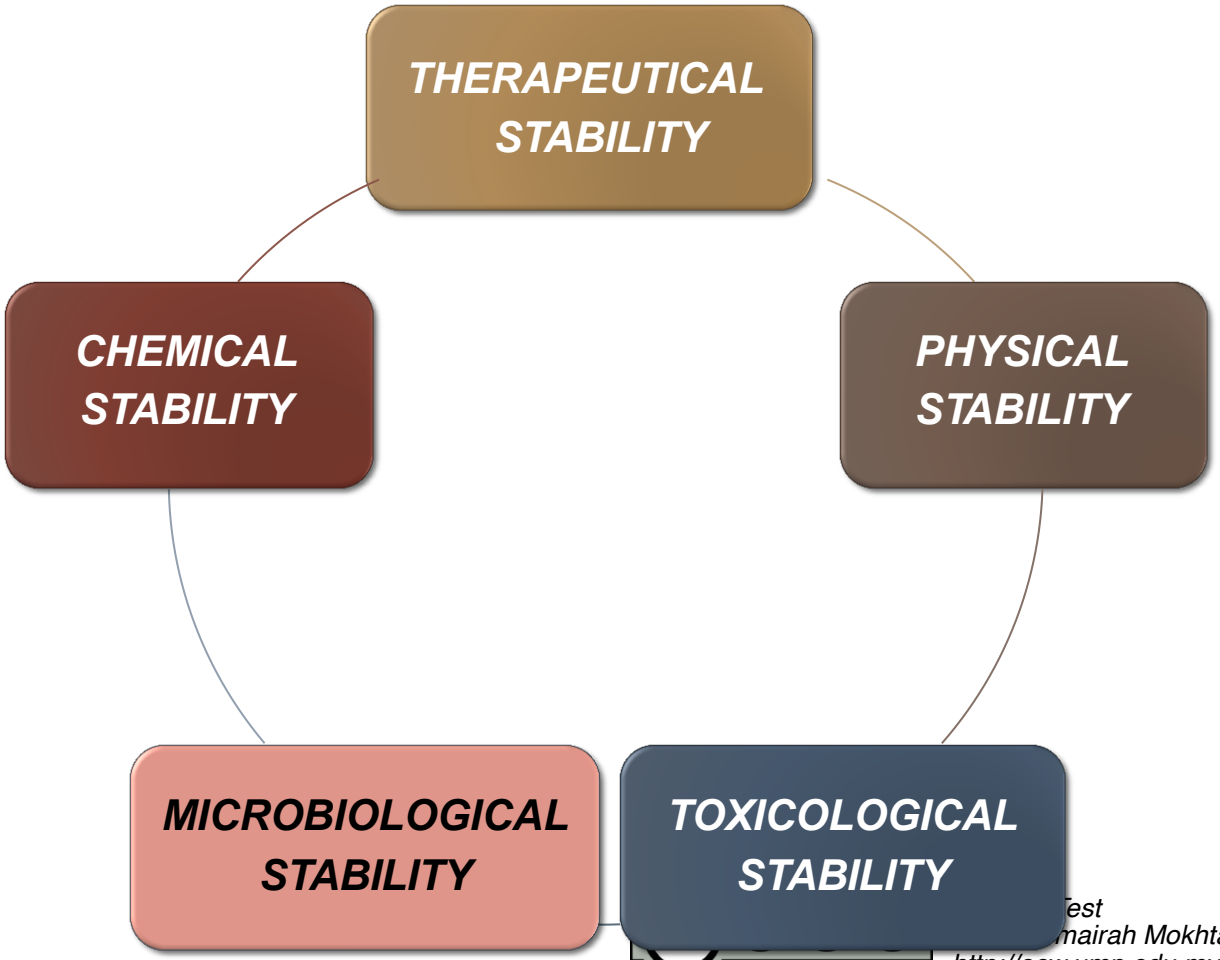
Provide an evidence on how the ***quality*** of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as:

- Temperature, Humidity, Light

Objectives:

1. To determine shelf life of a product.
2. To prepare good storage condition for the product.
3. To provide suitable packaging components (container & closure system).
4. To provide safety point of view of patient

Types of STABILITY



Test
mairah Mokhtar
http://ocw.ump.edu.my/course/view/php?id=611

TYPES OF STABILITY

- **CHEMICAL**

  Each API/final product retains its ***chemical properties***

- **PHYSICAL**

  The API/product retains its physical stability properties e.g. appearance, palatability, uniformity, dissolution and suspendability.

- **MICROBIOLOGICAL**

  The product retains its sterility or ***resistance to microbial growth*** according to specified requirement.

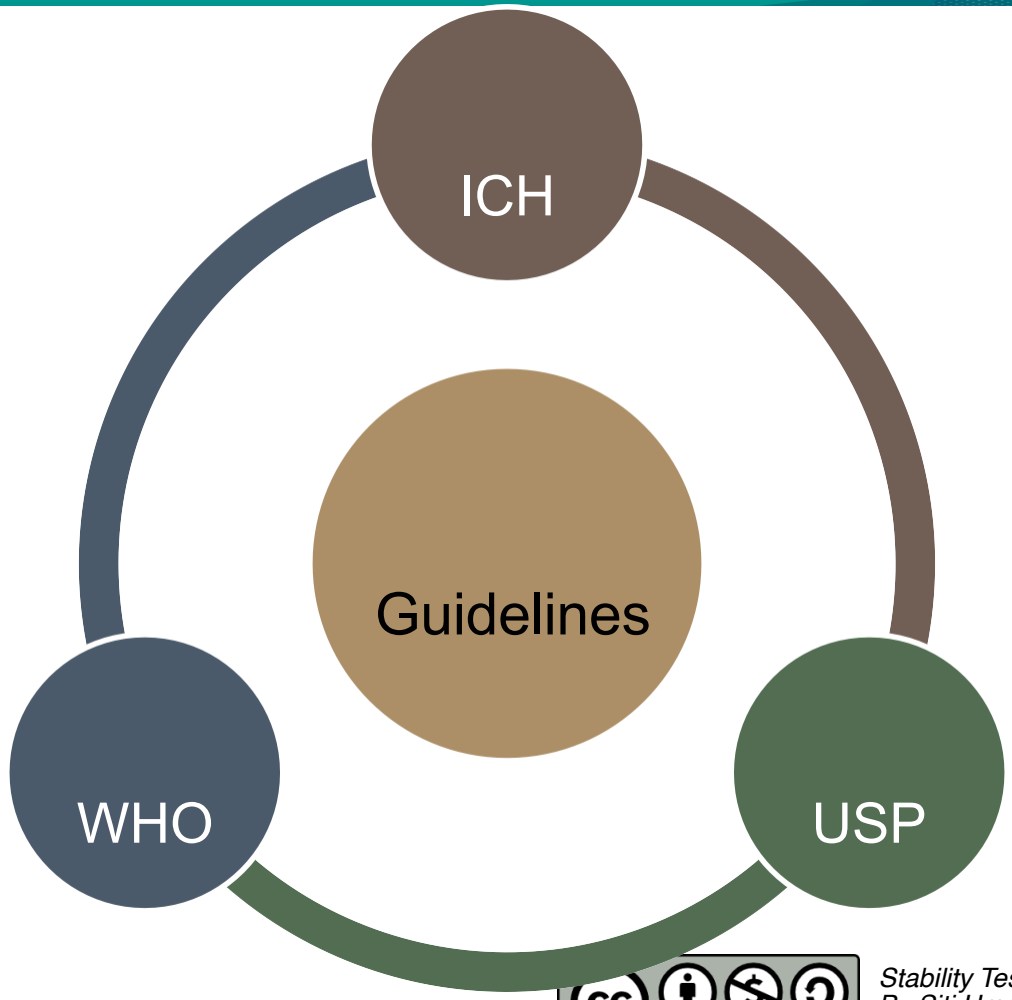
- **THERAPEUTIC**

  Therapeutic activity/clinical use of each product remains unchanged .

- **TOXICOLOGIC**

  Rate of toxicity has no significant increase.

REGULATORY REQUIREMENTS



GUIDELINES FOR STABILITY

1. **ICH guidelines Q1A-Q1F.**
2. **ASEAN** Guideline on Stability of Drug Product
3. **WHO** "Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms"
4. **USP** (US Pharmacopeia)
5. USP <1150> & USP<1151> Pharmaceutical Stability
6. **EMEA** Note for Guidance on Stability Testing of existing active substance and Related Finished products (Draft), February 2002

ICH STABILITY GUIDELINES

ICH GUIDELINES	TITLE
Q1A (R2)	Stability testing of new drug substances and products
Q1B	Stability testing: Photostability testing of new drug substance and products.
Q1C	Stability testing for new dosage forms
Q1D	Bracketing and matrixing designs for stability testing of drug substances and products
Q1E	Evaluation of stability data
Q1F	Stability data package for registration application in climatic zones III and IV

(Source: ICH Guidelines)

PHARMACEUTICAL DEGRADATION

TYPES OF PHARMACEUTICAL DEGRADATION

1. Physical degradation
2. Chemical degradation
3. Microbiological degradation

Stability Test
By Siti Umairah Mokhtar
http://ocw.ump.edu.my/course/view/php?id=611

FACTORS AFFECTING PHYSICAL DEGRADATION

The physical stability properties are retained. E.g. appearance, palatability, uniformity, dissolution and suspendability.

- Loss of volatile contents
- Loss of water
- Absorption of water
- Polymorphism
- Color changes

FACTORS AFFECTING

LOSS OF VOLATILE CONTENT:

- Volatile compounds used such as alcohol ether and camphor oils.
- The compounds **escape from the formulation → leads to degradation of formulation.**
- Ex: Nitroglycerine from drugs evaporate.

LOSS OF WATER:

- **Loss of water from liquid preparation** (O/W Emulsion) → crystallization → increase in potency and decrease in weight → leads to changes in stability
- Ex: Water evaporates from Na_2SO_4 .Borax.

ABSORPTION OF WATER

- Hygroscopic pharmaceutical formulations → **absorb the water from its external environment → degradation.**
- Ex: Gelatin capsule

POLYMORPHISM:

- A stable crystal form is effected → the formation of polymorph, cause instability in formulation. This may lead to *alteration in solubility, dissolution of drug.*
- Ex: Chloramphenicol (amorphous → crystalline)

COLOR CHANGE:

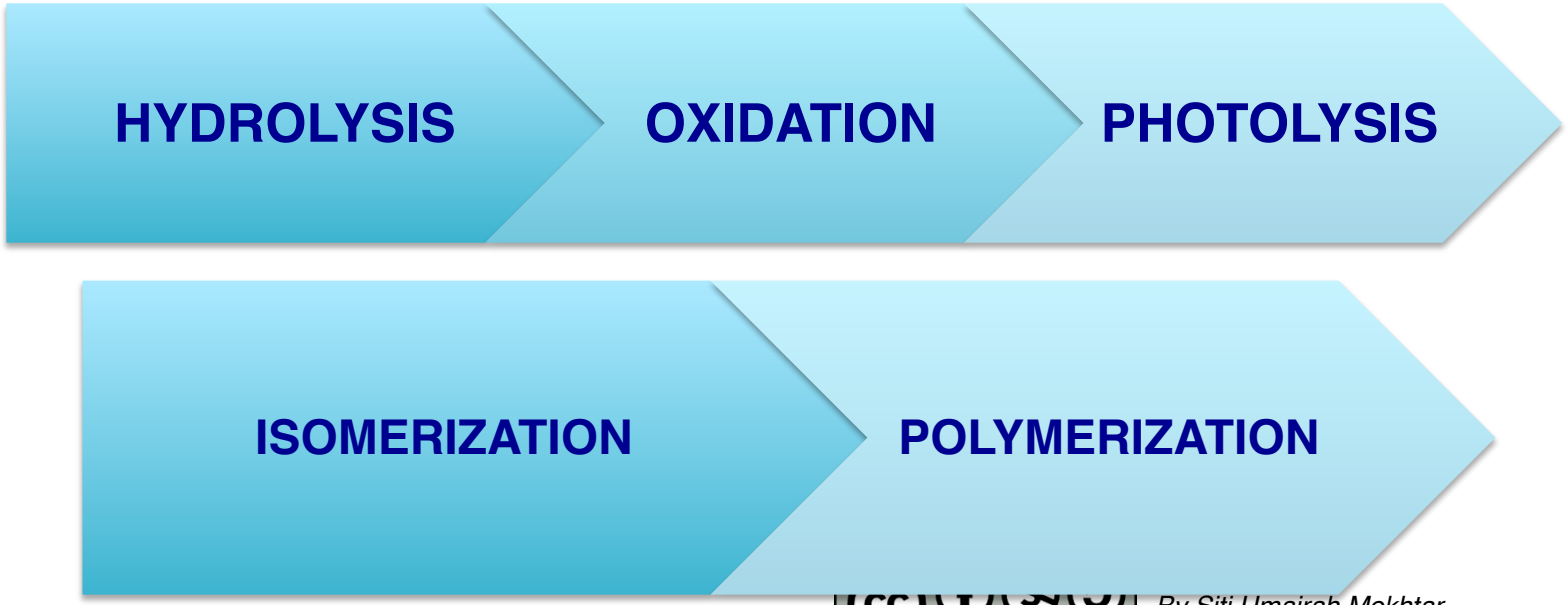
- Loss or development of color may occur .

(Due to change in pH, use of reducing agent, exposure to light)

- Ex: Phenolphthalein. It is colorless in acidic solution and pink in basic.

CHEMICAL DEGRADATION

- Chemical degradation of a dosage form can occurs through several reaction.
- These reactions may lead → lowering of therapeutic agent in the dosage form, formation of toxic product, decreased bioavailability etc.



1. HYDROLYSIS

- For drugs which are affected by the moisture.
- Drugs with functional groups such as esters, amides, lactones or lactams → may be susceptible to hydrolytic degradation.

HOW TO AVOID HYDROLYSIS:

- **Avoids contact with moisture during manufacture.**
- **Packs the products in suitable moisture resistant packs (e.g. strip packs and storage in controlled humidity and T).**
- **Addition of specific complexing agent (for certain drugs; benzocaine, procaine)**
- **Formulate in the dry powder form for reconstitution or dispersible tablets (for penicillin and derivatives)**

2. OXIDATION

- Oxidation is depends by environment (light, trace elements, oxygen and oxidizing agent).
- When exposed to atmospheric oxygen.
- Either the addition of oxygen or removal of hydrogen .

Example of drugs decomposed by oxidation pathways:

- Archis oil, Ascorbic acid, Morphine, Vitamin B12.

Protection against oxidation:

1. Use of antioxidants
2. Use of chelating agents (EDTA)

3. PHOTOLYSIS

- **Exposure to light** → substantial degradation of drug molecule.
- When molecules are exposed to electromagnetic radiation - **absorb light (photons) at characteristic wavelength** → cause increase in energy.

•It can :

➢Cause decomposition

➢Retained or transferred

➢Be converted to heat

➢Result in light emission at a new wavelength (fluorescence, phosphorescence)

- **Protection against photolysis:**

❑ Use of amber colored bottles .

❑ Store the product in dark

❑ Package in cartons.

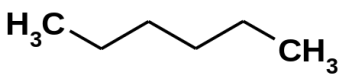
❑ Coat the tablets with polymer films.

4. ISOMERIZATION

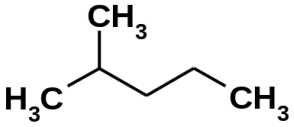
- **DEFINITION:** Process of one molecule is transformed into another molecule which has exactly the same atoms, but the atoms are rearranged (e.g. A-B-C → B-A-C).

- Conversion of *an active drug into a less active or inactive isomer* having same structural formula but different stereochemical configuration.

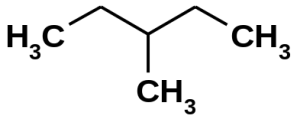
Ex:



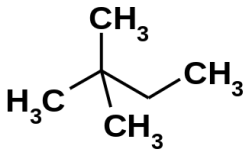
(1)



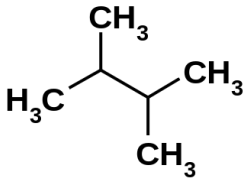
(2)



(3)



(4)



(5)

5. POLYMERIZATION

- **Definition**: Combination of two or more identical molecules to form a much *larger and more complex molecule.*

- Ex. Degradation of *antiseptic formulations* and *aldehydes* is due to polymerization.

PHARMACEUTICAL INSTABILITY

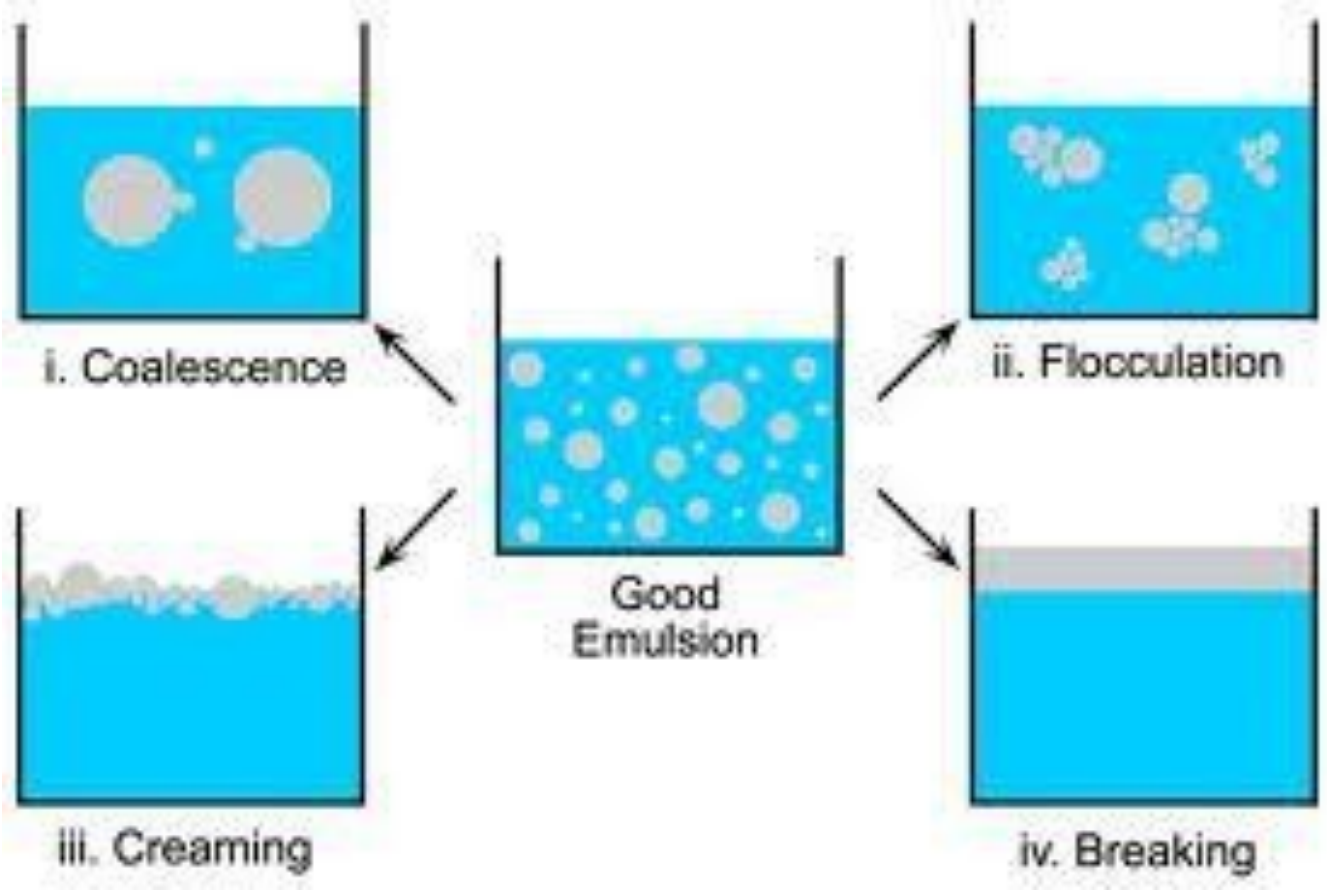
Formulation	Likely instability problems	Effects
Oral solutions	Loss of flavor Change in taste Presence of off flavors due to interaction with plastic bottle Loss of dye Precipitation Discoloration	Change in smell or feel or taste

Formulation	Likely instability	Effects
Parenteral solutions	Discoloration due to photo chemical reaction or oxidation Presence of precipitate due to interaction with container or stopper Clouds due to Chemical changes (hydrolysis)	Change in appearance and in bio-availability

Formulation	Likely instability problems	Effects
Suspensions	Settling Caking Crystal growth	Loss of drug content uniformity in different doses from the bottle

Formulation	Likely instability problems	Effects
Emulsions	Creaming Coalescence	Loss of drug content uniformity in different doses from the bottle

EMULSIONS



Source: http://sparror.cubecinema.com/

Formulation	Likely instability problems	Effects
Semisolids (Ointments and suppositories)	Changes in: • Particle size • Consistency • Caking or coalescence • Bleeding	Loss of drug content uniformity Loss of elegance

Formulation	Likely instability problems	Effects
Tablets	Change in: • Disintegration time • Dissolution profile • Hardness • Appearance (soft and ugly or become very hard)	Change in drug release

MICROBIAL DEGRADATION

- Contamination of a product may sometimes cause a *lot of damage* and sometimes may *not be anything at all*.
- It is depends on the type of microbe and its level of toxicity it may produce.
- If parenteral or ophthalmic formulations are contaminated → cause serious harm.
- Pyrogens - hazardous product released by gram negative bacteria (metabolic products of bacterial growth) → cause coldness and fever if administered accidentally.

PREVENTION OF MICROBIAL DEGRADATION

1. Design the most suitable containers for final products.
2. Use single dose containers
3. Stick to right storage conditions
4. Add an antimicrobial substance as preservative.

What happens if drug is degraded?

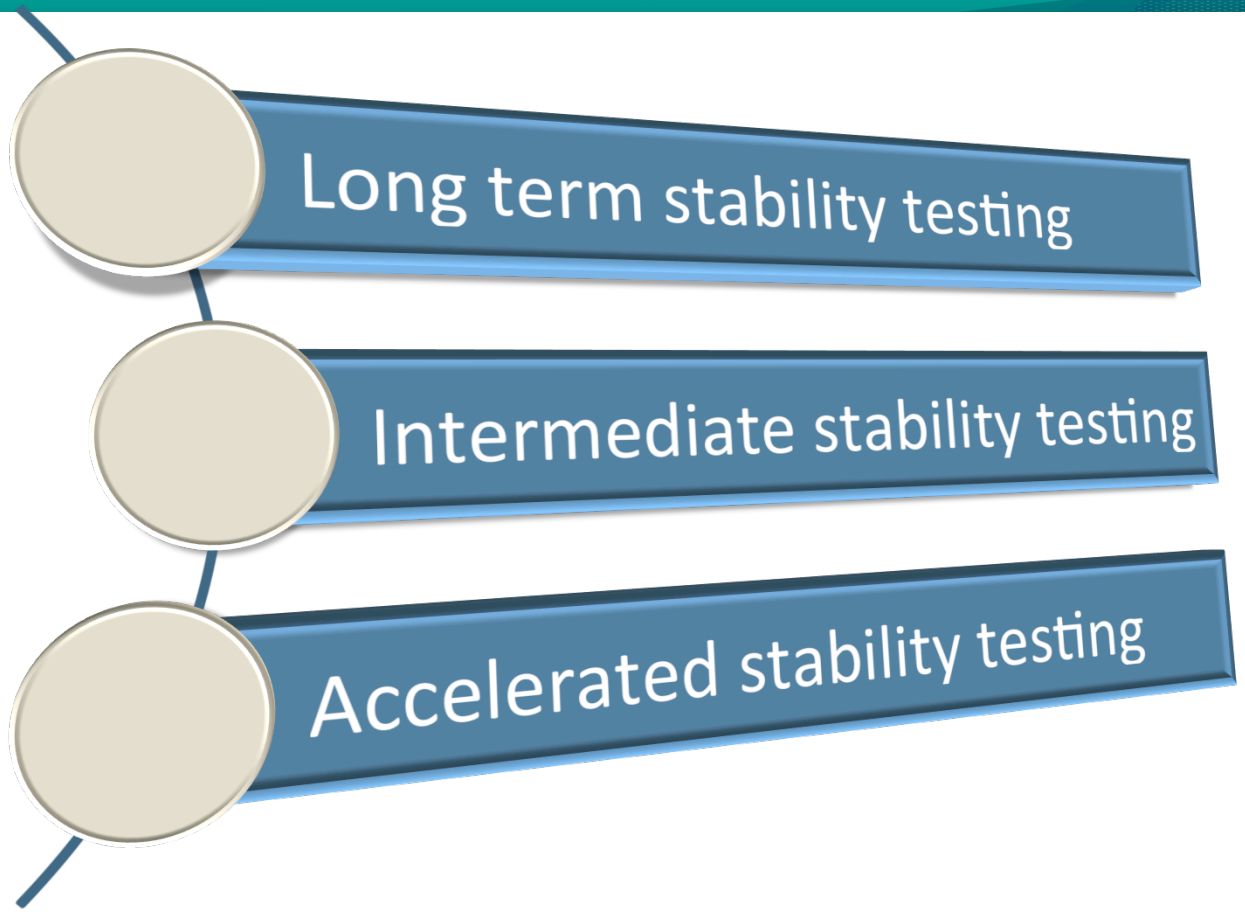
Lowering of concentration/potency

Active to toxic product

Appearance/Loss of elegance

Reduction in bioavailability

TYPES OF REGULATORY STABILITY TESTING



Stability Test
By Siti Umairah Mokhtar
http://ocw.ump.edu.my/course/view/php?id=611

LONG TERM STABILITY TESTING

- Long term stability testing is normally performed for **longer duration of the test period** in order to allow significant product degradation under **recommended storage conditions.**

STUDY	STORAGE CONDITION	MINIMUM TIME PERIOD COVERED BY DATA AT SUBMISSION
Long term	25°C ± 2°C/60% RH ± 5% RH OR 30°C ± 2°C/65% RH ± 5% RH	12 months

*RH: Relative humidity

INTERMEDIATE STABILITY TESTING

STUDY	STORAGE CONDITION	MINIMUM TIME PERIOD COVERED BY DATA AT SUBMISSION
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months

If 30°C ± 2°C/65% RH ± 5% RH is the long term condition, there is no intermediate condition

ACCELERATED STABILITY TESTING

In accelerated stability testing, a product is stressed at several high (warmer than ambient) temperatures.

STUDY	STORAGE CONDITION	MINIMUM TIME PERIOD COVERED BY DATA AT SUBMISSION
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

STABILITY TEST FOR TABLETS

Stable tablets retain their original size, shape, weight, roughness, colour variation, cracking under normal handling and storage conditions throughout their shelf life.

Friability Test	• Physical instability if any in tablet
Hardness Test	• Resistance to crushing
Color Stability	• by colorimeter, reflectometer with heat, sunlight and intense artificial light

STABILITY TEST FOR CAPSULES

- Gelatin capsules are stable in dry conditions - but they rapidly reach equilibrium with the atmospheric conditions under they are stored.
- If too humid - capsule shell softens and becomes sticky.
- If too dry - capsule shell becomes brittle and crack.
- Testing for capsules:
  1. Brittleness
  2. Dissolution
  3. Water content
  4. Level of microbial contamination.

STABILITY PARAMETERS FOR OTHER DOSAGE

DOSAGE FORM	PARAMETER
EMULSIONS	Phase separation, pH, viscosity, level of microbial contamination & distribution of dispersed globules.
ORAL SOLUTION & SUSPENSION	Clarity for solutions, formation of precipitate, pH, viscosity, microbial contamination, rheological properties & distribution of particles.
NASAL SPRAY	Clarity, level of microbial contamination, pH, particulate matter, unit spray medication, content uniformity, droplet and/or particle size distribution.

STABILITY PARAMETERS FOR OTHER DOSAGE

DOSAGE FORM	PARAMETER
TOPICAL	Clarity, pH, suspendibility for lotions, consistency, viscosity, homogeneity, level of microbial contamination/sterility & weight loss
OPTHALMIC	Sterility, particulate matter & extractable.
SUPPOSITORIES	Softening range, dissolution (at 37°C)
PARENTERALS	Color clarity, particulate matter, pH, sterility

Conclusion of The Chapter

1. Stability testing is very important to make sure the API and final product are in good conditions to be supplied to patient.

2. Several factors are affecting the stability of drug substance and/or drug products which needs to be considered.

3. There are 3 stability testing have been applied in industry for stability testing program.

Universiti Malaysia PAHANG
Engineering • Technology • Creativity

Any Question?

Please refer to:

Dr. Siti Umairah Mokhtar

umairah@ump.edu.my