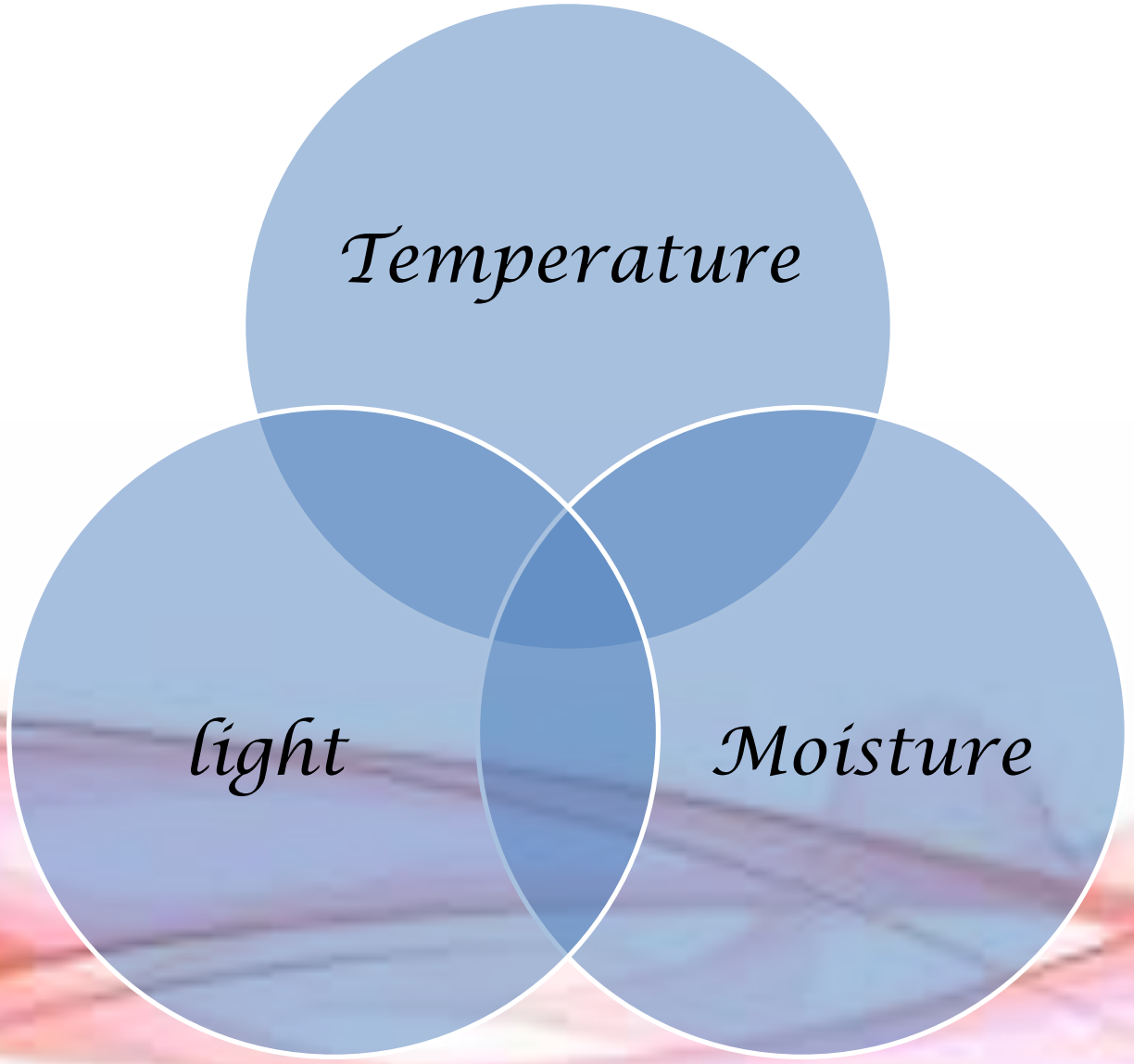
Factors Affecting Stability

- Environmental factors
- Microbial contamination
- Containers and closure

Environmental factors



Temperature

- 3 types of storage temperatures
  1. room temperature
  2. cold temperature
  3. Freeze storage

1. Room temperature:

- Upto 30/25° c

2. Cold temperature/Refrigerator storage:

- Upto 2-8° c

3. Freeze storage:

- Storage between -20 to -10° c

Light(photolysis)

- the shorter the wavelength more the energy is absorbed per mole

It means: decomposition by light

- Various sources of light are sunlight, metal halide lamps, fluorescent lamps, or other indoor lighting sources.

- These reactions can be induced by exposure to photolysis sources emitting in the 290–800 nm region.

- Relationship between wavelength and associated energy of various forms of light.

Type of radiation: board outers	Wavelength	Energy Kcal mol-1
U.V.	50 – 400	287 – 72
Visible	400 – 750	36 - 1
I.r.	750 – 10,000	

Photolysis is prevented by:

- *Suitable packing in amber couloured bottles*
- *Card board outers*
- *Aluminum foil wrappers*

MOISTURE

- *It enhances the hydrolytic degradation*
- *Packing materials such as Glass and Plastic are usually chosen to prevent exposure of drug product to high humid conditions*

Microbial Instability

Sources of microbial contamination

WATER	GRAM-NEGATIVE GROUPS: PSEUDOMONAS, XANTHAMONAS, FLAVOBACTERIUM
AIR	MOULD SPORES: PENICILLIUM, ASPERGILLUS BACTERIAL SPORES: BACILLUS SPP. YEASTS
RAW MATERIALS	MICROCOCCI
STARCHES	COLIFORMS
PIGMENTS	SALMONELLA

Sources of Microbial Contamination

GUMS	ACTINOMYCES
ANIMAL PRODUCTS	SALMONELLA, COLIFORMS
PERSONNEL	COLIFORMS, STAPHYLOCOCCI, STERPTOCOCCI

Packaging And Stability

1.Glass

- Glass is resistant to chemical and physical change and is the most commonly used material.

LIMITATIONS	OVERCOME
1. ITS ALKALINE SURFACE	USE OF BOROSILICATE GLASS
2. IONS MAY PRECIPITATE INSOLUBLE CRYSTALS FROM THE GLASS	THE USE OF BUFFERS
3- PERMITS THE TRANSMISSION OF LIGHT WHICH MAY ACCELERATE DECOMPOSITION.	AMBER COLOURED GLASS

Packing and Stability

2.PLASTICS

The problems with plastic are:

- Migration of the drug through the plastic into the environment.
- Transfer of environmental moisture, oxygen, and other elements into the pharmaceutical product.
- Leaching of container ingredients into the drug.
- Adsorption of the active drug or excipients by the plastic.

Packing and Stability

3.Metals

- Various alloys and aluminum tubes may be utilized as containers for emulsions, ointments, creams and pastes.
- **Limitation:** They may cause corrosion and precipitation in the drug product.
- **Overcome:** Coating the tubes with polymers may reduce these tendencies.

Packing and Stability

Rubber

- *Rubber also has the problems of extraction of drug ingredients and leaching of container ingredients.*

- *The pretreatment of rubber vial stoppers and closures with water and steam reduces potential leaching.*

Types of degradations

CHEMICAL

PHYSICAL

BIOLOGICAL

Chemical Degradation

1- Hydrolysis:

Hydrolysis means "splitting by water"

Some functional groups subject to Hydrolysis

Drug type	Examples
Esters	Aspirin, alkaloids Dexmethasne sodium phosphate Nitroglycerin
Lactones	Pilocarpine Spironolactone
Amides	Chloramphenicol
Imides	Glutethimide
Malonic ureas	Barbiturates

Chemical Stability

2- Oxidation

Oxidation of inorganic and organic compounds is explained by a loss of electrons and the loss of a molecule of hydrogen.

3-Photolysis

Physical Stability

Physical stability implies that:

- *The formulation is totally unchanged throughout its shelf life and has not suffered any changes by way of appearance, organoleptic properties, hardness, brittleness, particle size etc.*

- *It is significant as it affects:*

  1.pharmaceutical elegance

  2.drug content uniformity

  3.drug release rate.

Physical Stability

FORMULATION	LIKELY PHYSICAL INSTABILITY PROBLEMS	EFFECTS
ORAL SOLUTIONS	1- LOSS OF FLAVOR 2- CHANGE IN TASTE 3- PRESENCE OF OFF FLAVORS DUE TO INTERACTION WITH PLASTIC BOTTLE 4- LOSS OF DYE 5- PRECIPITATION 6- DISCOLORATION	CHANGE IN SMELL OR FEEL OR TASTE

FORMULATION	LIKELY PHYSICAL INSTABILITY PROBLEMS	EFFECTS
PARENTERAL SOLUTIONS	1. DISCOLORATION DUE TO PHOTO CHEMICAL REACTION OR OXIDATION 2. PRESENCE OF PRECIPITATE DUE TO INTERACTION WITH CONTAINER OR STOPPER 3. PRESENCE OF "WHISKERS" 4. CLOUDS DUE TO: (I) CHEMICAL CHANGES (II) THE ORIGINAL PREPARATION OF A SUPERSATURATED	CHANGE IN APPEARANCE AND IN BIO-AVAILABILITY

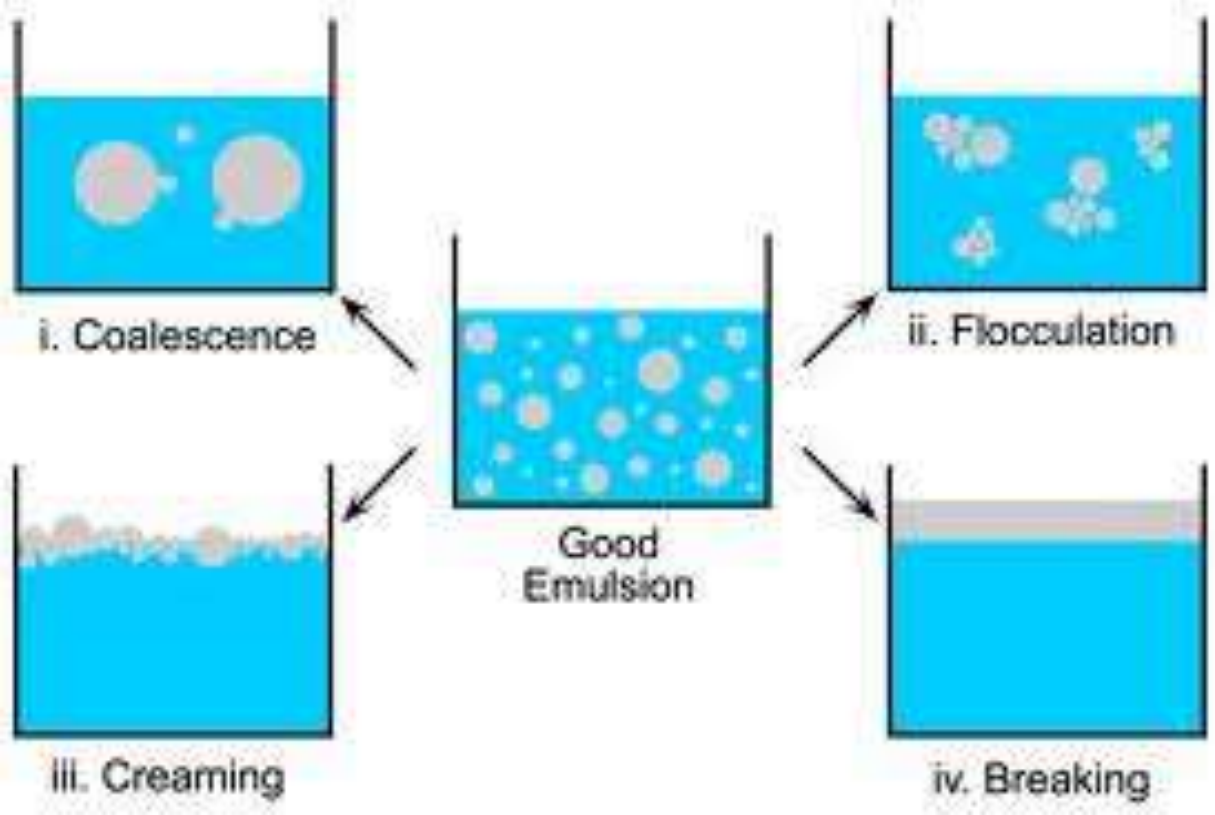
Physical stability

FORMULATION	LIKELY PHYSICAL INSTABILITY PROBLEMS	EFFECTS
SUSPENSIONS 	1- SETTLING 2- CAKING 3- CRYSTAL GROWTH	1-LOSS OF DRUG CONTENT UNIFORMITY IN DIFFERENT DOSES FROM THE BOTTLE 2- LOSS OF ELEGANCE.

Physical stability

FORMULATION	LIKELY PHYSICAL INSTABILITY PROBLEMS	EFFECTS
EMULSIONS 	1- CREAMING 2- COALESCENCE	1- LOSS OF DRUG CONTENT UNIFORMITY IN DIFFERENT DOSES FROM THE BOTTLE 2- LOSS OF ELEGANCE

Physical stability



Physical stability

FORMULATION	LIKELY PHYSICAL INSTABILITY PROBLEMS	EFFECTS
SEMISOLIDS (OINTMENTS AND SUPPOSITORIES) 	1. CHANGES IN: A) PARTICLE SIZE B) CONSISTENCY 2. CAKING OR COALESCENCE 3. BLEEDING	1-LOSS OF DRUG CONTENT UNIFORMITY 2- LOSS OF ELEGANCE 3-CHANGE IN DRUG RELEASE RATE.

Physical stability

FORMULATION	LIKELY PHYSICAL INSTABILITY PROBLEMS	EFFECTS
TABLETS 	CHANGE IN: A) DISINTEGRATION TIME B) DISSOLUTION PROFILE C) HARDNESS D) APPEARANCE (SOFT AND UGLY OR BECOME VERY HARD)	CHANGE IN DRUG RELEASE

Physical stability

FORMULATION	LIKELY PHYSICAL INSTABILITY PROBLEMS	EFFECTS
CAPSULES 	CHANGE IN: A) APPEARANCE B) DISSOLUTION C) STRENGTH	CHANGE IN DRUG RELEASE

Types of Stability Studies

1.Long-Term (Real-Time) Stability Testing

- Stability evaluation of the physical, chemical, biological and microbiological characteristics of a drug product

- duration of the shelf life

Accelerated stability Testing

- Studies designed to increase the rate of chemical degradation or physical change(s) of a drug product by using exaggerated storage conditions with the purpose of monitoring degradation reactions.
- To evaluate the impact of short term excursions and predicting the shelf-life under normal storage conditions.
- The design of accelerated studies may include elevated temperature, high humidity and intense light.

Methods Of Accelerated Stability Testing In Dosage forms

- Freeze Thaw test
- Centrifugal Test
- Shaking test
- Elevated Temperature test

Temperature and humidity control

General storage conditions

STUDY	STORAGE CONDITIONS	MINIMUM TIME PERIOD AT SUBMISSION
LONG TERM	25 ± 2°C / 60% RH ± 5% ZONE I,II. 30 ± 2°C / 35% RH ± 5% ZONE III. 30 ± 2°C / 60% RH ± 5% ZONE IV.	6 MONTHS 6 MONTHS 6 MONTHS
INTERMEDIATE	30 ± 2°C / 60% RH ± 5%	6 MONTHS
ACCELERATED	40 ± 2°C / 75 % RH ± 5%	6 MONTHS

Products packed in semi-permeable containers.

STUDY	STORAGE CONDITIONS	MINIMUM TIME PERIOD AT SUBMISSION
LONG TERM	25 ± 2°C / 40% RH ± 5% ZONE I,II	6 MONTHS
LONG TERM	30 ± 2 °C/ 60% RH ± 5% ZONE III,IV	6 MONTHS
INTERMEDIATE	30 ± 2°C / 60% RH ± 5%	6 MONTHS
ACCELERATED	40 ± 2°C / NMT 25% RH	6 MONTHS

Products intended for storage in a Refrigerator

STUDY	STORAGE CONDITIONS	MINIMUM TIME PERIOD AT SUBMISSION
LONG TERM	5 ± 3°C	6 MONTHS
ACCELERATED	25 ± 2°C / 60% RH ± 5%	6 MONTHS

Products intended for storage in a freezer

STUDY	STORAGE CONDITIONS	MINIMUM TIME PERIOD AT SUBMISSION
LONG TERM	-20 ± 5°C	12 MONTHS