STABILITAS OBAT 3

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Kestabilan dalam kehidupan

- Surah Al-Qashash ayat 77:

وَابْتَغِ فِيْمَآ اٰتٰىكَ اللّٰهُ الدَّارَ الْاٰخِرَةَ وَلَا تَنْسَ نَصِيْبَكَ مِنَ الدُّنْيَا وَاَحْسِنْ كَمَآ اَحْسَنَ اللّٰهُ اِلَيْكَ وَلَا تَبْغِ الْفَسَادَ فِى الْاَرْضِ ۗ اِنَّ اللّٰهَ لَا يُحِبُّ الْمُفْسِدِيْنَ

“Dan carilah pada apa yang telah dianugerahkan Allah kepadamu yaitu kebahagiaan negeri akhirat, dan janganlah kamu melupakan bahagianmu dari kenikmatan duniawi, dan berbuat baiklah kepada orang lain, sebagaimana Allah telah berbuat baik kepadamu, dan janganlah kamu berbuat kerusakan di (muka) bumi. Sesungguhnya Allah tidak menyukai orang-orang yang berbuat kerusakan”.

TUGAS KELOMPOK

(Per 19-11-202410.30 WIB)

- KELOMPOK 1
- KELOMPOK 2
- KELOMPOK 3
- KELOMPOK 4
- KELOMPOK 6
- KELOMPOK 7
- KELOMPOK 10
- KELOMPOK 12
- KELOMPOK 16

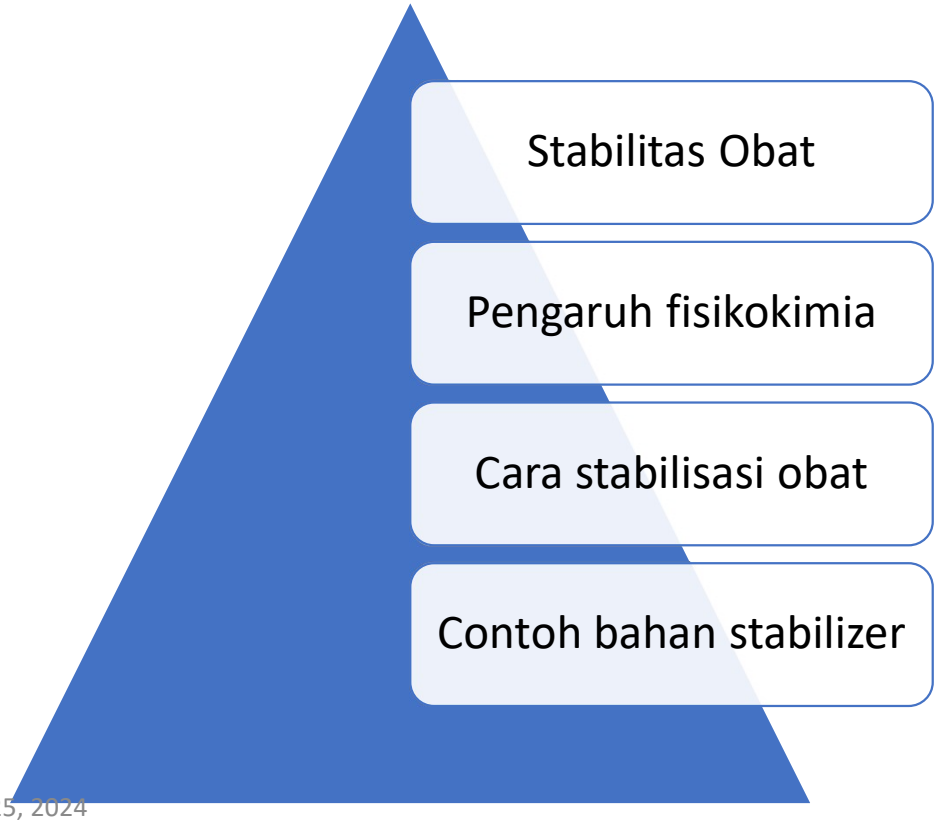
TUGAS KELOMPOK

(Per 19-11-202410.30 WIB)

KELOMPOK 5

OUTLINE STABILITAS OBAT 3

- **Pokok Pembahasan Stabilitas Obat 3**



Stabilitas Obat

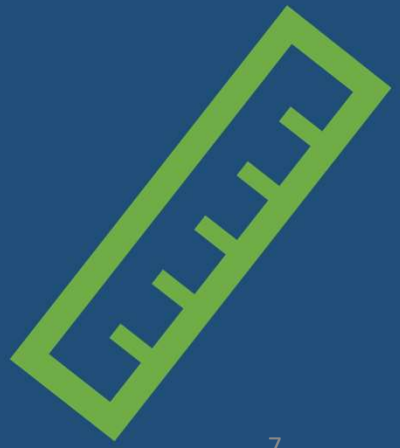
- **Stability:** is the capacity of a drug product to remain within specifications established to ensure its identity, strength quality and purity.

- **Instability may cause**

- Undesired change in performance, i.e. dissolution/ bioavailability
- Substantial changes in physical appearance of the dosage form
- Causing product failures

Efek tidak diinginkan yang potensial dari ketidakstabilan produk farmasi

- hilangnya zat aktif,
- naiknya konsentrasi zat aktif,
- BA berubah,
- hilangnya keseragaman kandungan,
- menurunnya status mikrobiologis,
- hilangnya elegansi produk dan ‘patient acceptability’,
- pembentukan hasil urai yang toksik,
- hilangnya kekedapan kemasan,
- menurunnya kualitas label dan
- modifikasi faktor hubungan fungsional.



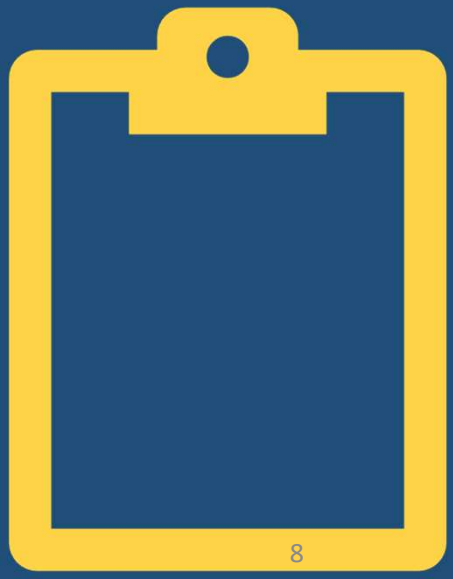
Istilah-istilah dalam Stabilitas Obat

EXPIRATION DATE

Waktu yang tertera pada kemasan yang menunjukkan batas waktu diperbolehkannya obat tersebut dikonsumsi karena diharapkan masih memenuhi **spesifikasi** yang ditetapkan

SHELF LIFE (Waktu simpan)

Periode penggunaan dan penyimpanan, yaitu waktu dimana suatu produk tetap memenuhi **spesifikasinya** jika disimpan dalam wadahnya yang sesuai dengan kondisi penjualan di pasar



Jenis Spesifikasi

- Spesifikasi ‘release’ adalah spesifikasi yang harus dipenuhi pada waktu pembuatan, misalnya 95%-105%.
- Spesifikasi periksa atau spesifikasi waktu simpan atau spesifikasi umur produk, adalah spesifikasi yang harus dipenuhi sepanjang waktu simpannya, misalnya 90-110%
- Waktu simpan minimum, adalah periode waktu yang dibutuhkan suatu produk yang berada pada batas spesifikasi ‘release’ pada saat pembuatan untuk mencapai batas spesifikasi periksa

Criteria for Acceptable Levels of Stability

Type of Stability	Conditions Maintained Throughout the Shelf Life of the Drug Product
Chemical	Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
Physical	The original physical properties,including appearance, palatability, uniformity, dissolution and suspendability are retained.
Microbiological	Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.
Therapeutic	The therapeutic effect remains unchanged.
Toxicological	No significant increase in toxicity occurs.

<1191> STABILITY CONSIDERATIONS IN DISPENSING PRACTICE

Types of stability studies:

- **Physical**
- **Chemical**
- **Microbiological**

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:**

- **pharmaceutical elegance**
- **drug content uniformity**
- **drug release rate**

Physical stability (Cont.)

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

Physical stability (Cont.)

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 solution**	**Change in appearance and in bio-availability**

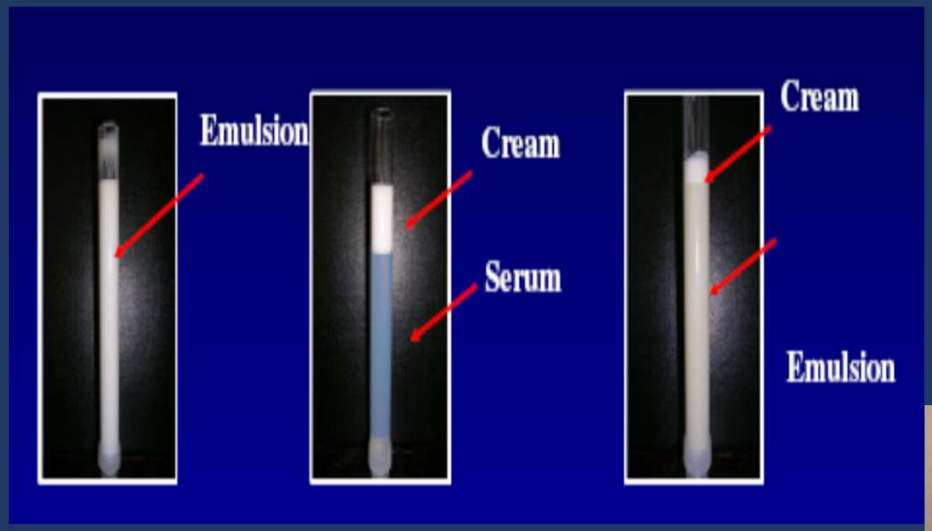
Physical stability (Cont.)

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 (Cont.)

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 (Cont.)



Coalescence

Physical stability (Cont.)

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 (Cont.)

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 (Cont.)

Formulation	Likely physical instability problems	Effects
Capsules	**Change in:** **a) Appearance** **b) Dissolution** **c) Strength**	**Change in drug release**

Chemical stability:

- **Chemical stability implies:**

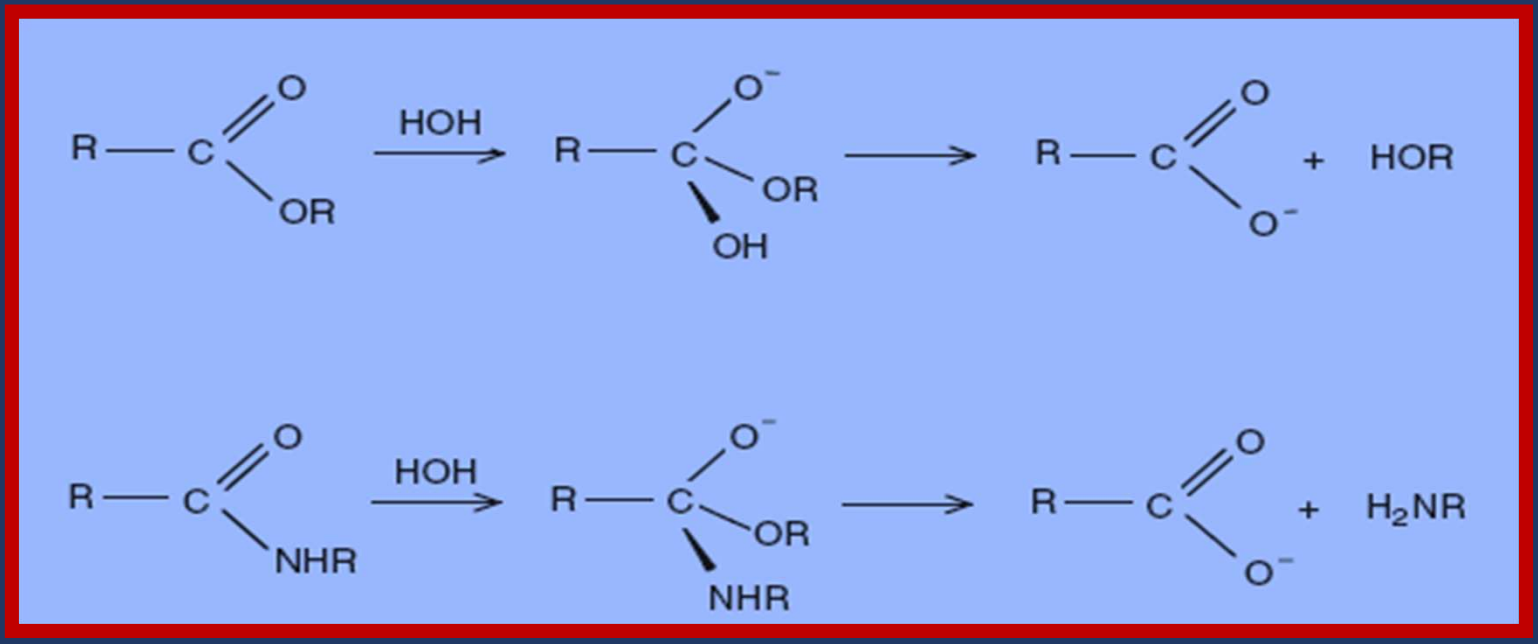
The lack of any decomposition in the chemical moiety that is incorporated in the formulation as the drug, preservatives or any other excipients.

This decomposition may influence the physical and chemical stability of the drug

Mechanisms Of Degradation

1- Hydrolysis:

Hydrolysis means “splitting by water”

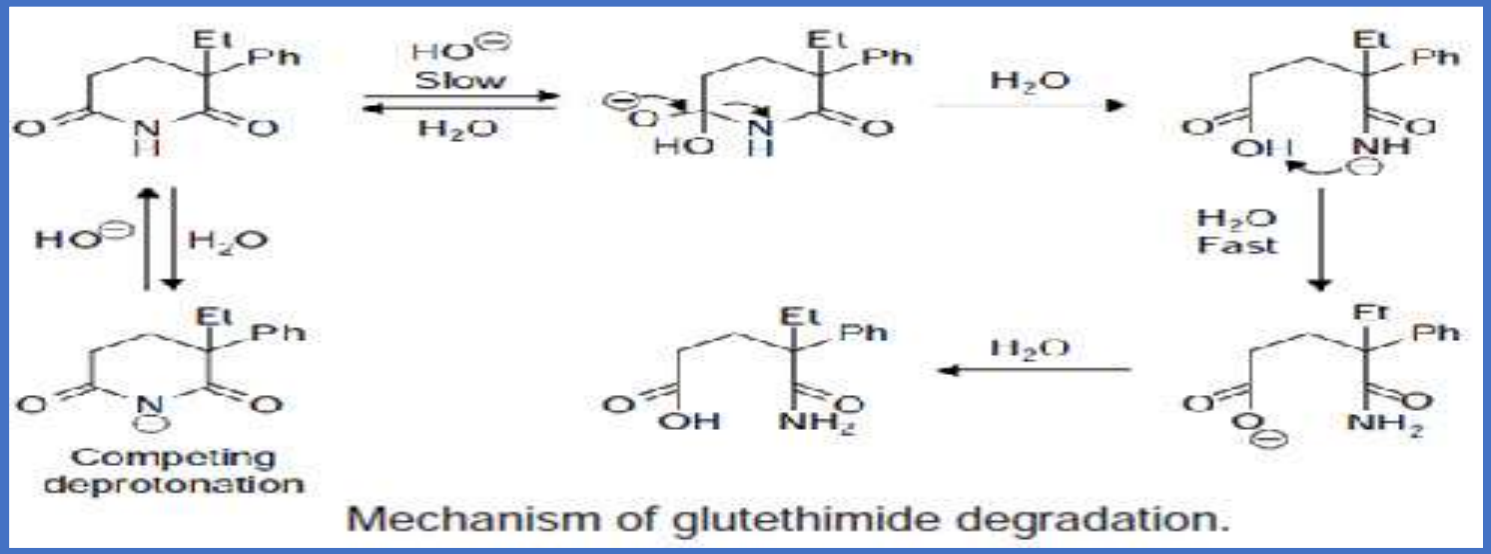


Some Functional Groups Subject to Hydrolysis

Drug type	Examples
Esters	Aspirin, alkaloids Dexamethasone sodium phosphate Nitroglycerin
Lactones	Pilocarpine Spironolactone
Amides	Chloramphenicol
Lactams	Penicillins Cephalosporins

Some Functional Groups Subject to Hydrolysis

Drug type	Examples
Imides	Glutethimide
Malonic ureas	Barbiturates



Mechanism of glutethimide degradation.

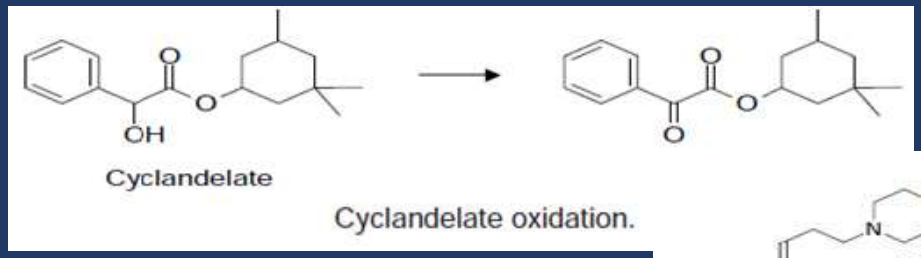
Method of protection from Hydrolysis:

- Replace liquid dosage forms with solid dosage forms e.g., tablet; may also make emulsion and suspension
- Lyophilize liquid dosage forms and reconstitute prior to administration.(Lyophilization (Freeze drying) i.e. sublimation or evaporation of water from solid state to gaseous state).
- Control of pH: optimum pH for stability can be obtained from pH-rate profile
- Complex formation
- Reduced temperature
- Reduced factors which may increase rate of hydrolysis, such as buffer species, solvent polarity, nucleophilic agent, and ionic strength of the system

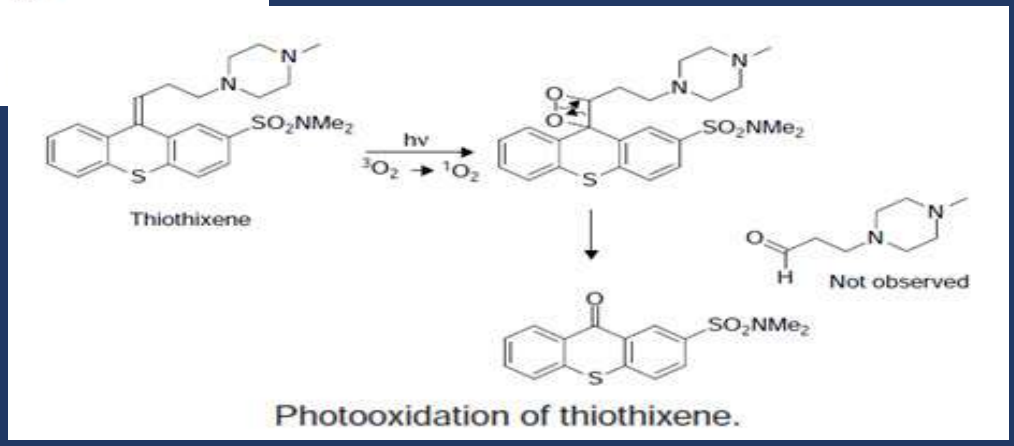
Mechanisms Of Degradation

2- Oxidation

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



Cyclandelate oxidation.



Photooxidation of thiothixene.

Oxidation: phenols, enols, unsaturated alcohol, arylamine

Mechanism: reaction of free radical chains

Induction: $RH \longrightarrow R^{\bullet} + H^{\bullet}$ (light, heat)

Transmission: $R^{\bullet} + O_2 \longrightarrow RO_2^{\bullet}$

(propagation) $RO_2^{\bullet} + RH \longrightarrow ROOH + R^{\bullet}$

$ROOH \longrightarrow RO^{\bullet} + {}^{\bullet}OH$ (metal ion)

Termination: $RO_2^{\bullet} + x \longrightarrow$ inactive product

$RO_2^{\bullet} + RO_2^{\bullet} \longrightarrow$ inactive product

Some Functional Groups Subject to Autoxidation

Functional group	Examples
Catechols	Catecholamines (dopamine)
Ethers	Diethylether
Thiols	Dimercaprol (BAL)
Thioethers	Chlorpromazine
Carboxylic acids	Fatty acids

Methods for delayed oxidation:

- **Reduce oxygen content**
- **Adding antioxidant**
  1. **true and oxygen scavenger antioxidant**
  2. **reducing agent**
- **Adjusting pH**
- **Reduce metal ion**
  1. **decrease metal ion content**
  2. **adding chelating agent**
- **Lower Temperature**
- **Avoid light**

Method of Protection From oxidation:

1- Exclusion of O_2

→ Sealing of ampoules under inert N_2 gas or Argon

→ Deoxygenate (boil) water

→ Use hermetic strip for tablets and capsules

2- Protect from light:

→ Protect from UV and visible light have ionizing radiation leading to oxidation and formation of free radicals called photolysis

3- Use of chelators:

→ Chelators such as EDTA and citric acid are used to remove metal ions from the solution

4- Use of antioxidants such as water soluble ascorbic acid (Vit-C) and water insoluble antioxidant - Vitamin-E. They are called O_2 scavengers because they are more readily oxidized than active drugs.

Mechanisms Of Degradation

3- Photolysis

It means: decomposition by light

e.g. Sodium nitroprusside is administered by intravenous infusion for the management of acute hypertension.

If the solution is protected from light, it is stable for at least 1 year; if exposed to normal room light, it has a shelf life of only 4 hours.

Mechanisms Of Degradation

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

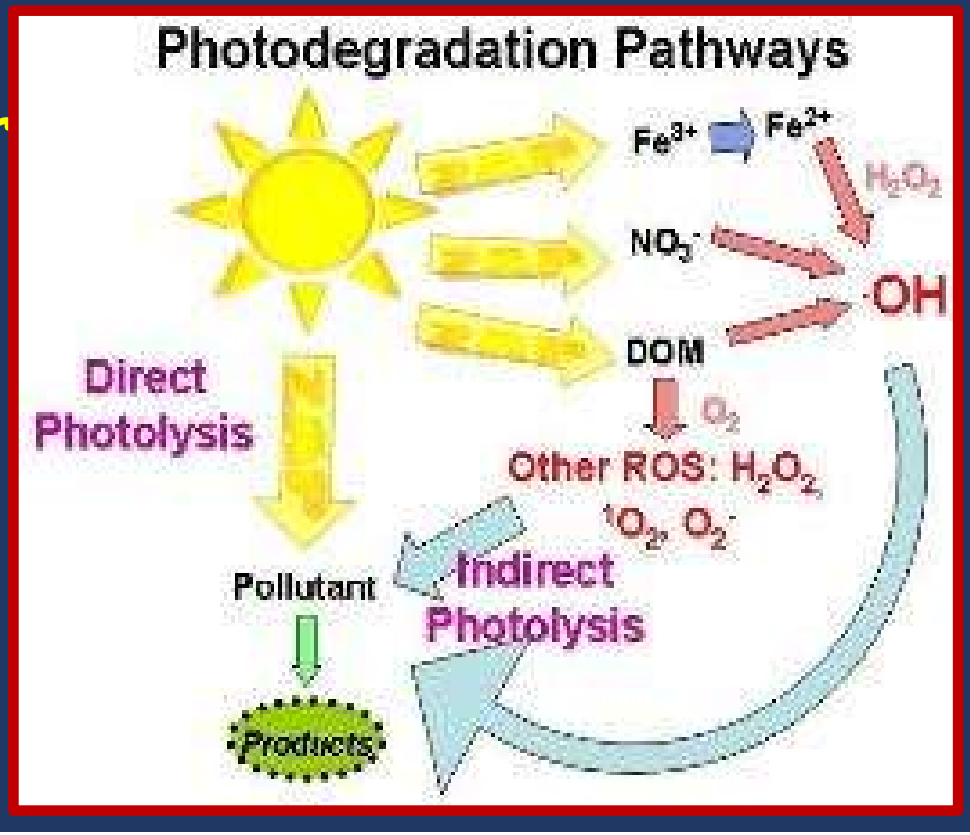
Type of radiation	Wavelength	Energy ($Kcal\ mol^{-1}$)
U.V.	50 – 400	287 – 72
Visible	400 – 750	36 – 1
I.R.	750 – 10,000	< 1

Conventional tungsten filament light bulbs are safe and do not contribute to photolysis.

PHOTOLYTIC STABILITY

- Many drugs fade or darken on exposure to light and this leads to an aesthetic problem which can be controlled by using:

1. Amber Glass Container
2. Opaque Container
3. Incorporating a Dye
4. Cardboard outers
5. Aluminium foil over wraps



Photolysis and the Role of Excipients

- **Sunlight (both in the UV and visible regions) may degrade drug products and excipients; and consequently photolabile APIs can raise many formulation (& phototoxicity) issues.**

- **The addition of light absorbing agents is a well known approach to stabilising photolabile products.**
  - **Order of effectiveness: pigments > colorants > UV absorbers**

- **However, beware variable performance between grades/sources.**
  e.g. Surface-treated titanium dioxide is inferior to the untreated excipient as an opacifier.

Microbiological stability

- **Microbiological stability implies that:**

The formulation has not suffered from any microbiological attack and is meeting the standards with respect to lack of contamination/sterility.

Microbiological stability

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, Streptococci**

To prevent contamination to the formulation during storage

(1) suitably designing the containers

(2) usually using single dose containers

(3) sticking to proper storage conditions

(4) adding an antimicrobial substance as preservative.

Preservatives used in pharmaceutical preparations:

Preparation	Preservative	Concentration (% w/v)
Injections	**Phenol** **Cresol** **Chlorocresol**	**0.5** **0.3** **0.1**
Eye drops	**Chlorhexidine acetate** **Benzalkonium chloride**	**0.01** **0.01**
Mixtures	**Benzoic acid** **Methyl paraben** **Alcohol**	**0.1** **0.1** **12-20**

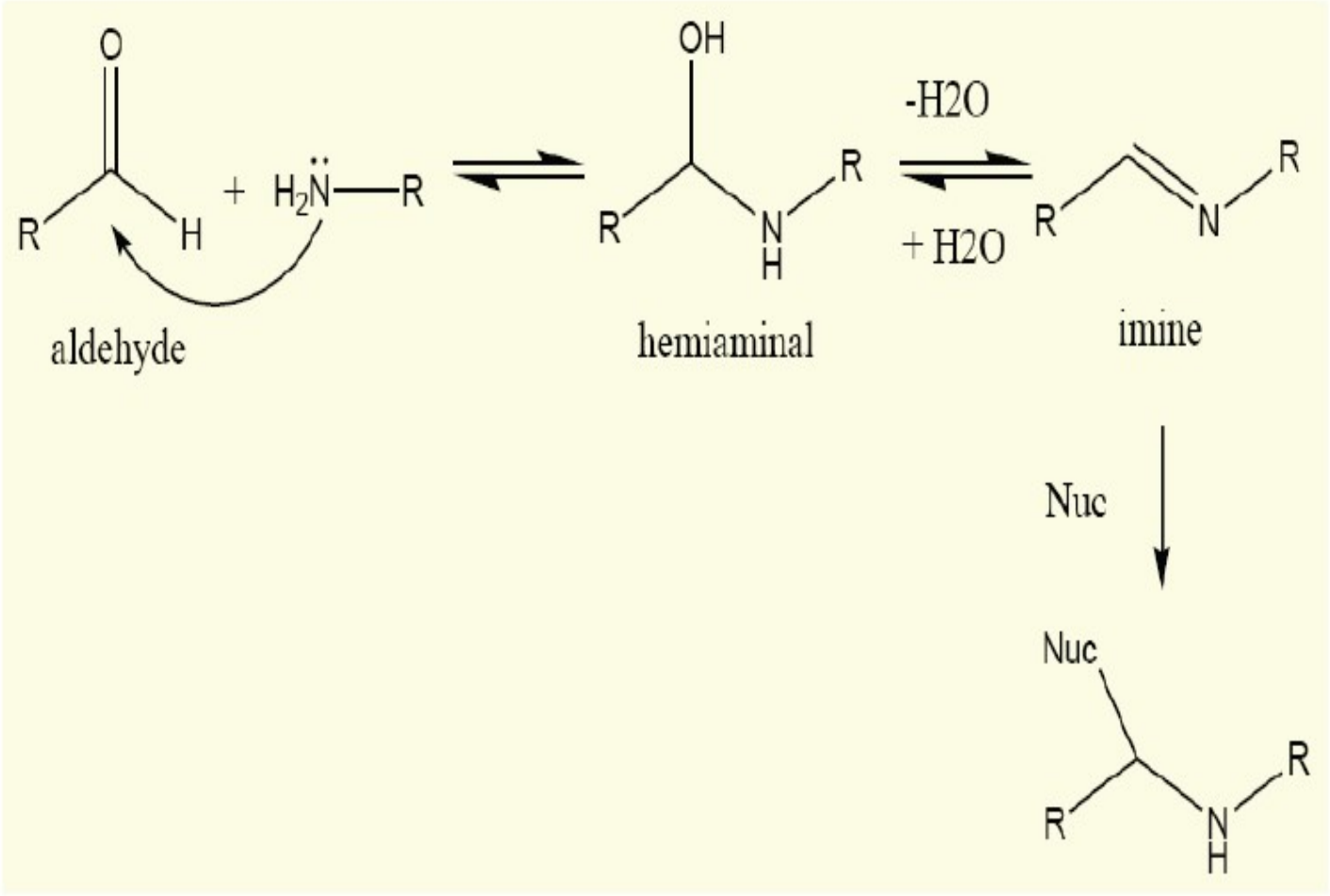
Preservatives used in pharmaceutical preparations:

Preparation	**Preservative**	**Concentration** (% w/v)
Creams	**Parabens** **Chlorocresol**	**0.1-0.2** **0.1**
Tablets	**Methylparaben**	**0.1**

Excipients - API Interactions

- **Whereas excipients are usually biologically inactive, the same cannot be said from a chemical perspective.**
  Excipients, and any impurities present, can stabilise and/or destabilise drug products.
- **Considerations for the formulation scientist:**
  - **the chemical structure of the API**
  - **the type of delivery system required**
  - **the proposed manufacturing process**
- **Initial selection of excipients should be based on:**
  - **expert systems; predictive tools**
  - **desired delivery characteristics of dosage form**
  - **knowledge of potential mechanisms of degradation, e.g. Maillard reaction**
- **The objective of drug/excipient compatibility considerations and practical studies is to delineate, as quickly as possible, real and possible interactions between potential formulation excipients and the API.**

This is an important risk reduction exercise early in formulation development.


O
R
H
+ H2N—R
aldehyde
OH
R
N
H
R
hemiaminal
-H2O
+ H2O
R
N
R
imine
Nuc
Nuc
R
N
H
R

Drug-excipients compatibility study:

Compatibility study is the most important part of any pre-formulation testing of proposed dosage form, and it is necessary that it should be carried out before the development of first formulation of proposed dosage form with a new drug or new formulation of existing API.

This is required due to the following reasons:

- **Formulation stability studies are time consuming and expensive**
- **Need to minimize the number of model formulations**
- **Provide rational basis for selecting excipients used in model formulations**

The main objective behind the compatibility testing is:

1. to find out most appropriate excipients(s) for the particular API in dosage form under consideration and also those excipient(s) that should be avoided for particular API, and
2. to ascertain appropriate excipient(s) which may be reasonably used with drugs in proposed dosage form so that process control and hence product quality should not be compromised.

As suggested by Carstensen (1993):

→ **for tablet formulation, the ratio of drug-excipient(s) should be 20:1 and 1:5 by weight for lubricants and other excipient(s), respectively.**

Indomethacin exhibit different polymorphism, and different forms have different solubility and it may have different bioavailability.

A list of excipients and their incompatibilities with API's:

S.No.	Excipient	API's
1	Lactose	Acyclovir, aceclofenac, ketoprofen, metformin, amlodipine, ceronapril, lisinopril, oxprenolol, fluconazole , primaquine, romethazine, fluoxetine seproxetine maleate, picotamide, etamsylate, aminophylline, clenbuterol, baclofen, ranitidine, doxylamine and thiamine chloride HCl.
2	Mannitol, Pearlitol (80%Mannitol+20% Maize Starch)	Quinapril, primaquine, omeprazole and promethazine
3	Starch	Seproxetine maleate and clenbuterol
4	Sodium Starch Glycolate	Clenbuterol
5	Dextrose	Pefloxacin
6	Magnesium Stearate	Acyclovir , aspirin, ibuproxam, indomethacin, ketoprofen, glipizide, chlorpropamide, glimepiride, glibenclamide, captopril, fosinopril, moexipril, oxprenolol, quinapril, cephalexin, rythromycin, nalidixic acid, oxacillin, penicillin g, primaquine, promethazine, albendazole, β-lapachoneclopidogrel, temazepam

A list of excipients and their incompatibilities with API's:

7	Stearic Acid	Doxylamine
8	Polyvinyl Pyrollidone(PVP)	Indomethacin, ibuproxam, ketoprofen, atenolol, oxprenolol, sulfathiazole, haloperidol, ranitidine, doxylamine, temazepam, clenbuterol.
9	Dicalcium Phosphate Dihydrate(DCPD)	Ceronapril, oxprenolol, quinapril, metronidazole, β-lapachone, parthenolide, famotidine and temazepam.
10	Eudragit RS and RI	Diflunisal , flurbiprofen and piroxicam
11	Eudragit RL 100	Ibuprofen
12	Eudragit E100	Ranitidine
13	Microcrystalline Cellulose(MCC), Avicel P^H 101	Enalapril, isosorbide mononitrate and clenbuterol
14	Cellulose Acetate	Isosorbide mononitrate
15	Hypromellose Acetate Succinate (HPMCAS)	Dyphylline
16	Hydroxy Propyl Cellulose	Trichlormethiazide
17	PEG	Ibuprofen, ibuproxam, polysorbate, ketoprofen, phosphomycin and clopidogrel.

A list of excipients and their incompatibilities with API's:

18	Sodium Lauryl Sulphate	Chlorpropamide, clopidogrel and chlordiazepoxide.
19	Chitosan	Diclofenac and Piroxicam
20	Magnesium Oxide	Ibuprofen
21	Silicon Dioxide	Enalapril
22	Sodium Carbonate	Adefovir and dipivoxil
23	Sodium Bicarbonate	Ibuprofen
24	Plasdone	Glimepiride
25	Ascorbic acid	Atenolol
26	Citric acid	Atenolol
27	Butylated hydroxyanisole	Atenolol
28	Succinic acid	Phosphomycin

Thank You..