STABILITAS OBAT 4

APT. DYANI PRIMASARI SUKAMDI, M.SC.

Kestabilan dalam kehidupan

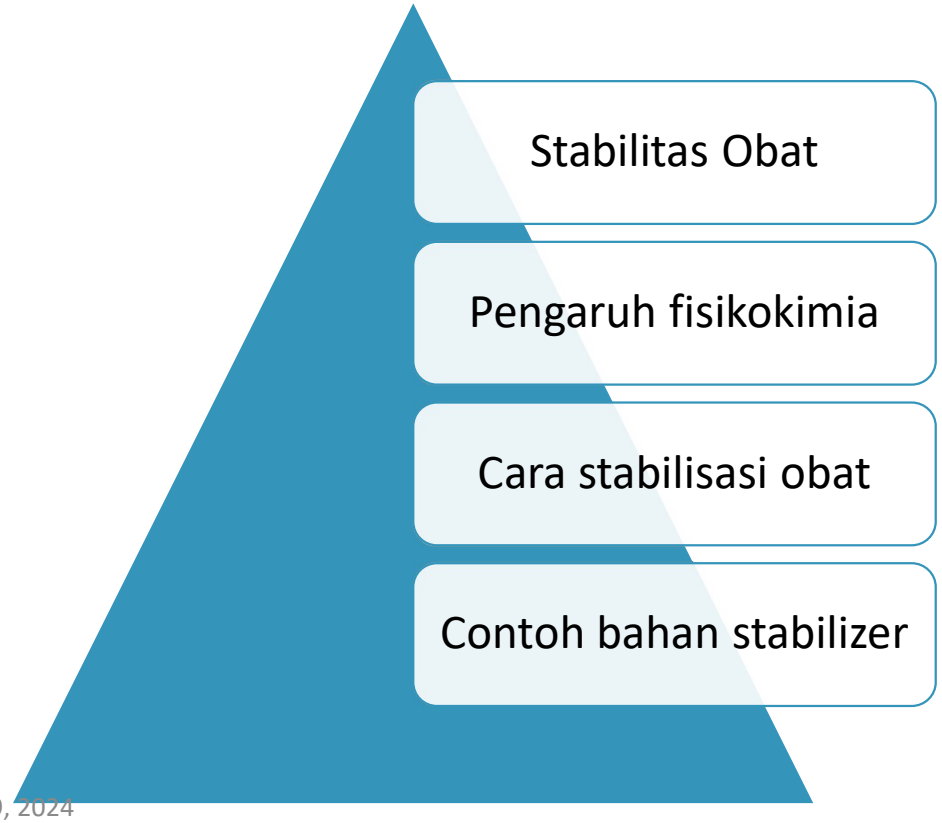
- Surah Al-Qashash ayat 77:

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”.

OUTLINE STABILITAS OBAT 3

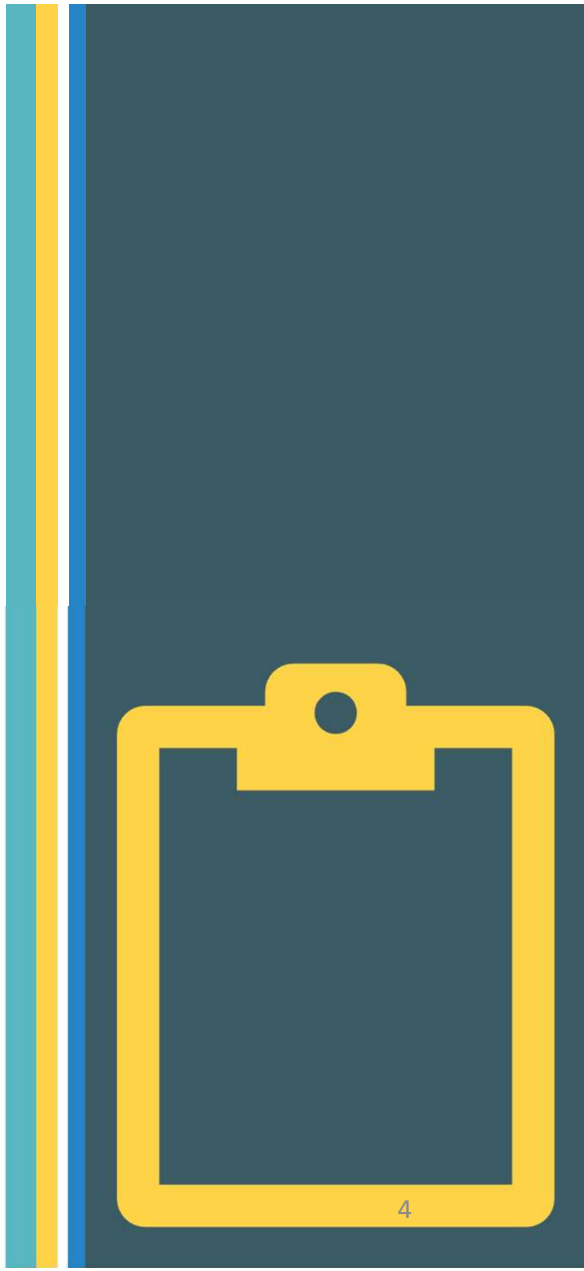
- **Pokok Pembahasan Stabilitas Obat 3**



Stabilitas Obat

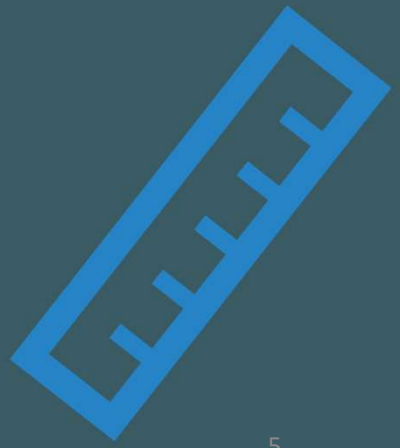
- **Stabilitas:** **kapasitas suatu produk obat untuk tetap dalam spesifikasi yang ditetapkan untuk memastikan identitas, kekuatan, kualitas, dan kemurniannya.**

- **Ketidakstabilan dapat menyebabkan:**
  - **Perubahan kinerja yang tidak diinginkan, yaitu kelarutan/ bioavailabilitas**
  - **Perubahan substansial dalam tampilan fisik bentuk sediaan**
  - **Menyebabkan kegagalan produk**

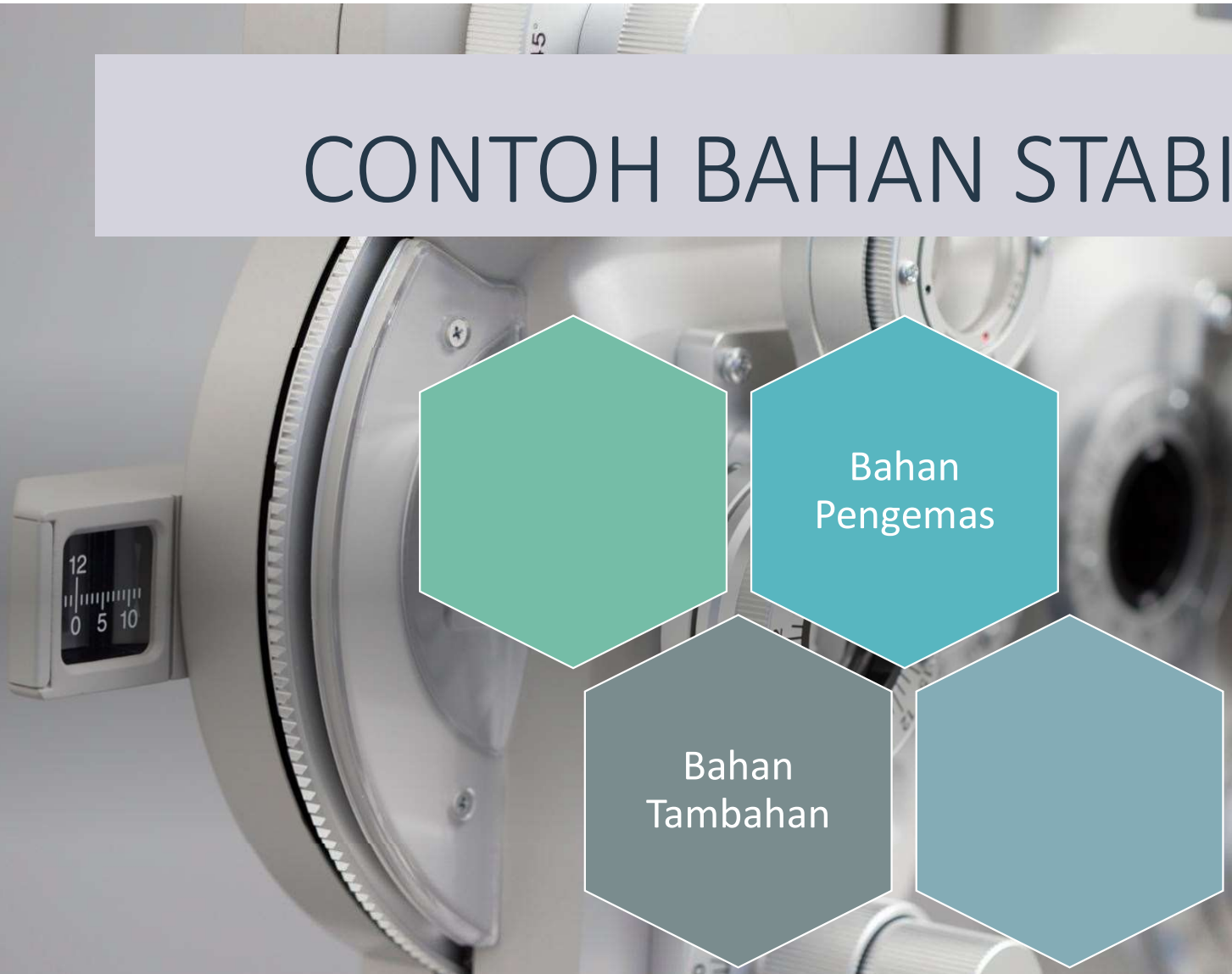


Efek tidak diinginkan yang potensial dari ketidakstabilan produk farmasi

- 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.



CONTOH BAHAN STABILIZER



The effect of packaging on drug stability

Faulty packaging of pharmaceutical dosage forms can invalidate the most stable formulation.

<u>Package:</u>

It is defined as an economical means of providing protection, presentation, identification and convenience for a product until the product is completely used.

<u>Protection from:</u>

(a) Environmental hazards

- **Humidity**
- **Sunlight**
- **Oxygen**
- **Microbial contamination**

(b) Physical hazards such as storage and transit

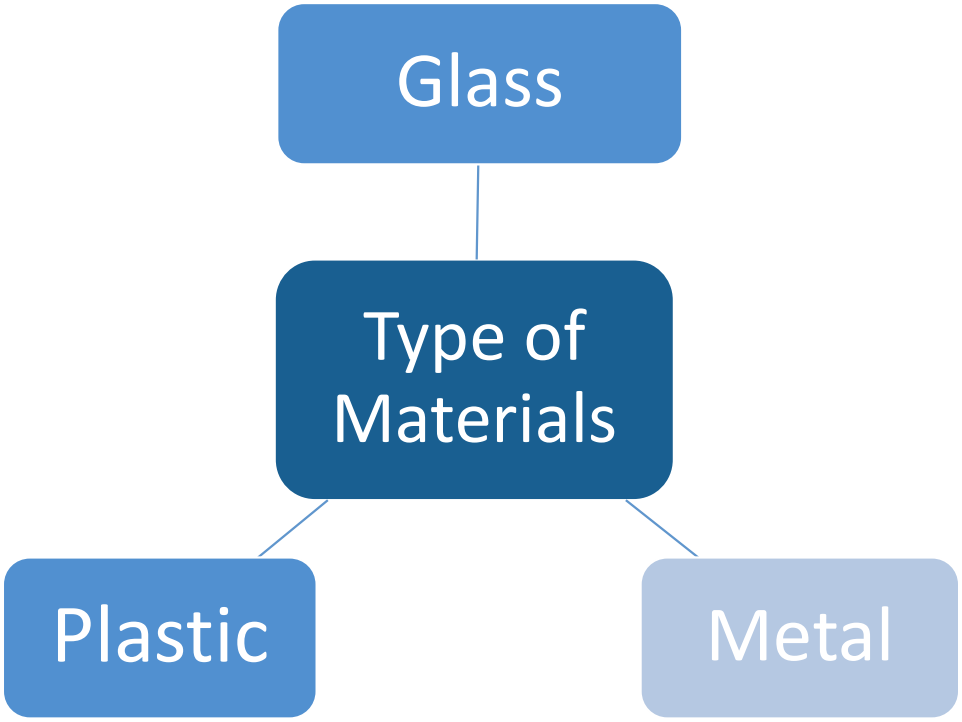
Protection from (cont'd):

Harmful effects caused by the pack itself i.e. product and pack must be compatible.

The pack should not leach out and Material should not absorb constituent from the formulation.

Failure of protection of pharmaceuticals leads to:

- **Product may deteriorate by losing activity**
- **Product may give rise to harmful products.**


Glass
Type of Materials
Plastic
Metal

Types of materials used for containers and closures:

(i) **Glass:**

Most commonly used packaging material.

Advantages:

- Readily available material
  - Inert, i.e. provides excellent product-pack compatibility
- Provides good product presentation

Types of Glass

According to pharmacopoeia (USP, EP, BP):

1. **Neutral or borosilicate glass**
2. **Soda glass with surface treatment**
3. **Soda glass with limited alkalinity**
4. **Soda glass, non-parenteral general-purpose glass**

Properties of Glass

1. **Neutral or borosilicate glass**
   - **Only advocated for injectable products or when chemical reaction may occur because it is inert**
   - **more expensive**
   - **durable**
2. **Soda glass (three types)**
   Suitable for product not affected by the slight alkalinity of the surface

(ii) Plastic

Advantages

- ❑ **Lighter than glass or metal**
- ❑ **Can be used in thinner section**
- ❑ **Less prone to breakage and in case breakage occurs, fragments are less hazardous**

Disadvantages

- ❑ **Low chemical inertness compared to glass**
- ❑ **More permeable than glass**
- ❑ **Low resistance to high temperature compared to glass**
- ❑ **For topical ointments, vaccines and transfusion bottles, flexible plastic called polyolefins are used**

(iii) Metal

Advantages

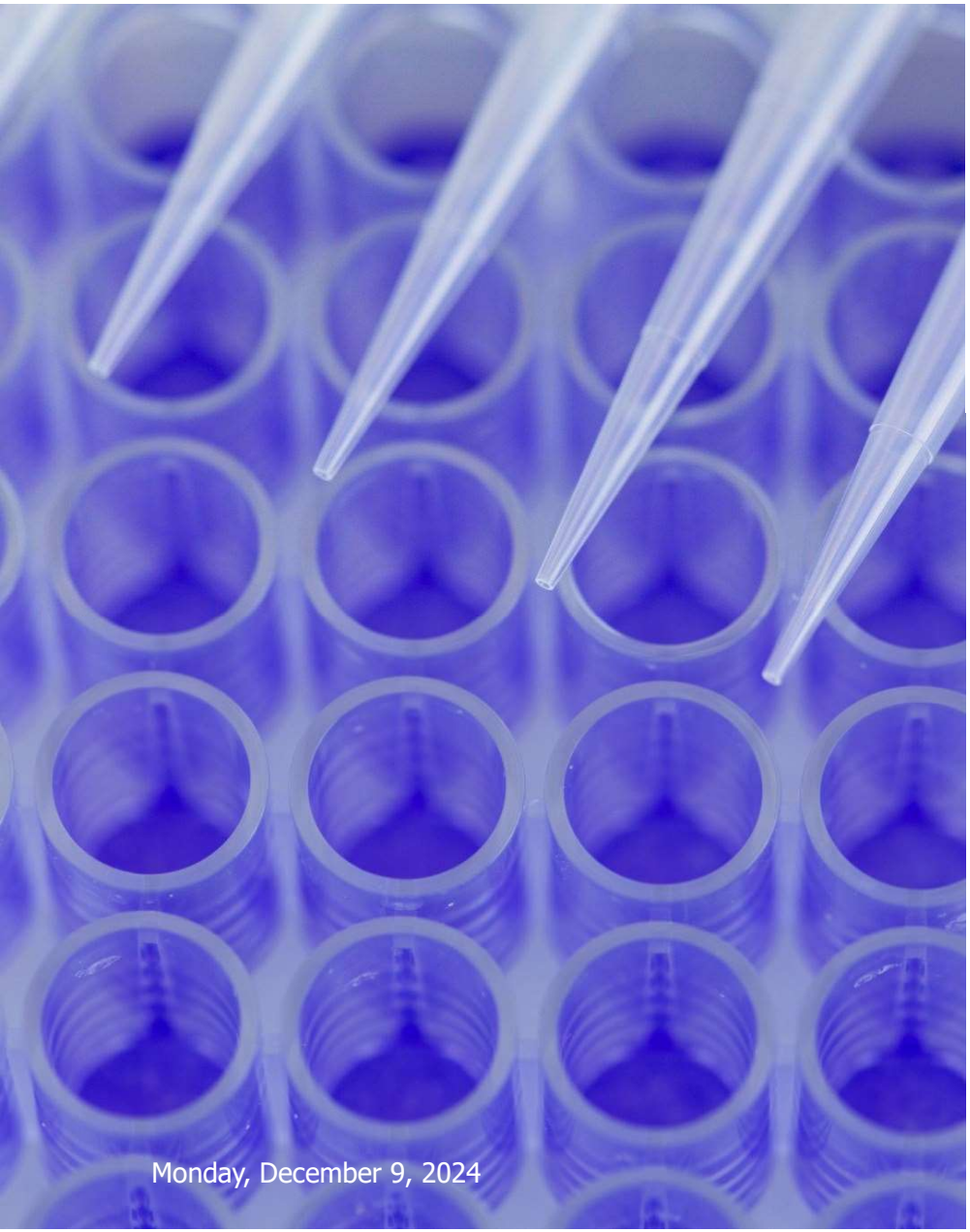
- ❑ **Strong material**
- ❑ **Opaque**
- ❑ **Impermeable to liquids, gases, odors and bacteria**
- ❑ **Resistant to both low and high temperature**

Types of metal materials

- **Aluminum**
- **Tin**
- **Steel**
- **Tinplate**

Disadvantages

- ❑ Chemical reaction with drug products i.e. not inert
- ❑ Corrosion might occur from inside or outside. To overcome corrosion metal substances are coated e.g. Tinplate, made by coating low carbon steel sheet electronically with pure tin
- ❑ Most commonly used metal packaging material is Aluminum because:
  - it can be used uncoated
  - it is light weight
  - it is ductible
  - it is non-toxic
  - resistant to corrosion
  - Sterilizable
  - can be shaped into rigid, semi rigid or collapsible containers



Closures:

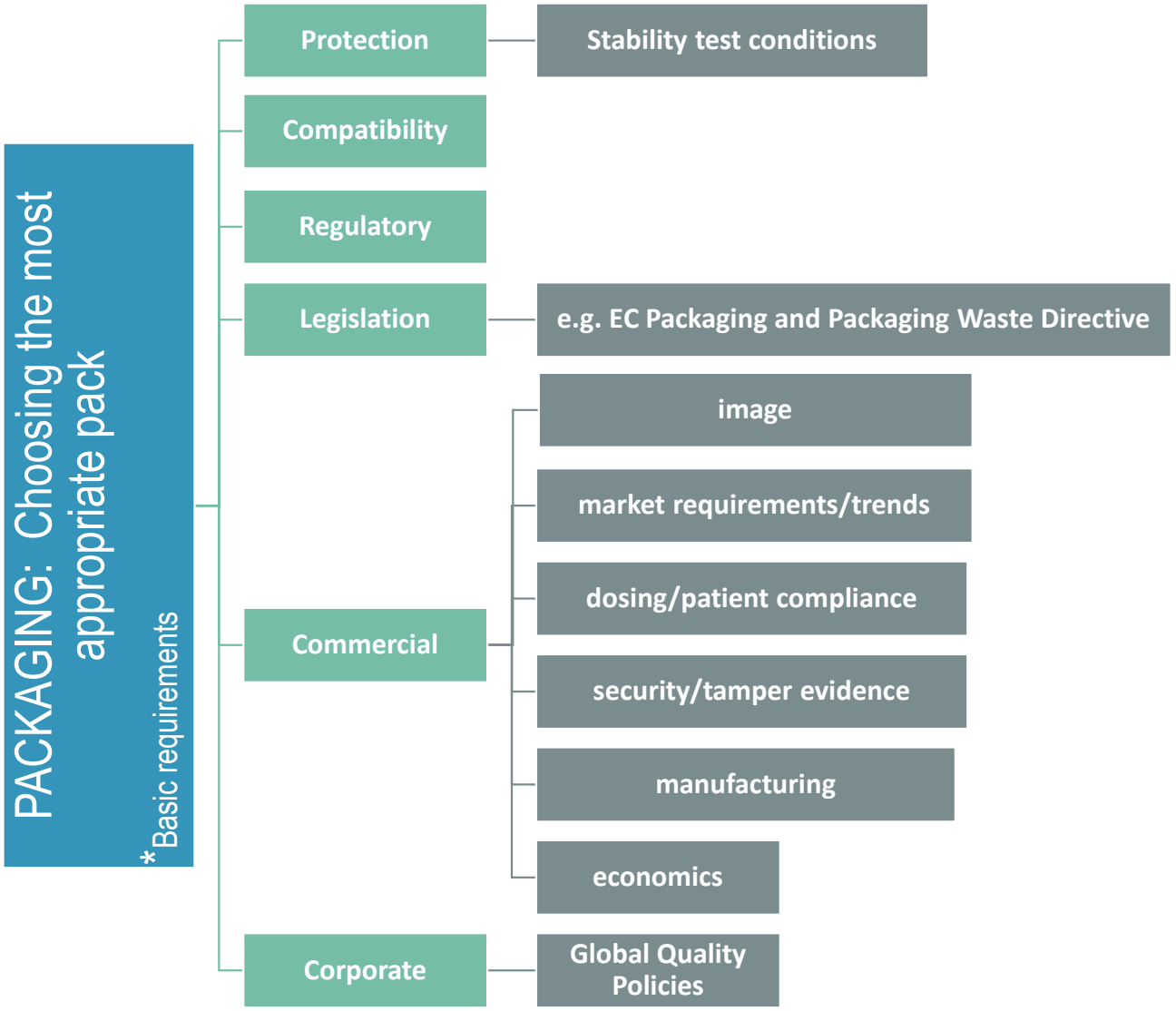
Most effective closure for glass ampoules is sealing by fusion because product is in contact with only one material.

Requirements for Closures:

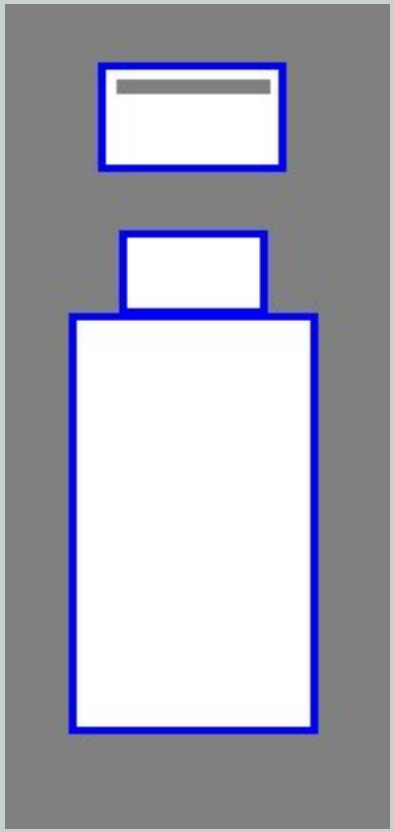
- ❑ Must be compatible with the product. Closures are made of metal, plastic or rubber bungs.
- ❑ Rubber bungs are used for parenterals that require multiple or single piercing for multiple use without any detachment of particles by fragmentation.

Packaging And Stability :

- **The immediate container and closure are particularly important in affecting product stability.**


PACKAGING: Choosing the most appropriate pack
*Basic requirements
Protection
Stability test conditions
Compatibility
Regulatory
Legislation
e.g. EC Packaging and Packaging Waste Directive
Commercial
image
market requirements/trends
dosing/patient compliance
security/tamper evidence
manufacturing
economics
Corporate
Global Quality Policies

PACKAGING: Bottles



- **Glass**
  - type III (solids)
  - type I (for inhaled solutions)
- **Plastic**
  - low density polyethylene LDPE
  - high density polyethylene HDPE
  - po lypropylenePP
  - polyester PET, PETG
  - Cyclo-olefin copolymer (COC)

Packaging: WVTR

- **Laju transmisi uap air/ Water Vapor Transmission Rate (WVTR) melalui wadah ditentukan oleh:**
  - **Ketebalan dinding wadah**
  - **Permeabilitas bahan kemasan**
  - **Perbedaan antara lingkungan kelembapan relative ekstaernal dan internal**
  - **Gaya penggerak untuk fluks air melalui wadah**
- **The theoretical rate of water permeation through a standard 60-cc HDPE bottle when stored at 40°C/75% RH has been determined:**
  - **setara dengan penyerapan 1 mg air per hari.**
  - **Jadi, bahkan jika suatu produk dikemas dalam kondisi uap air rendah, kondisi kelembaban relatif di dalam wadah akan kembali seimbang hingga 50% dalam waktu 1 hari.**

Packaging: Desiccants

- **Desiccants (pengering) digunakan untuk mengendalikan paparan produk terhadap masuknya kelembapan.**
- **Desiccants (pengering) bervariasi dalam kapasitasnya dan laju penyerapan/ penyerapan kelembapan yang masuk.**
- **Silica gel sangat efisien dalam menyerap kelembapan pada tingkat kelembapan relatif tinggi, tetapi relatif buruk pada tingkat kelembapan relatif rendah.**
- **Molecular sieve desiccants - the opposite scenario prevails.**
  - **As a consequence, more molecular sieve is required at higher relative humidities, and the greater the handling precautions that are required during packaging operations.**
  - **Molecular sieve approved in EU for pharmaceuticals, not by FDA in US.**
  - **Based on the calculated WVTR of known container components and the rate of moisture adsorbed by desiccants, the amount of desiccant that would be required to maintain a specified relative humidity over the product's shelf-life can be determined.**

PACKAGING: Choosing the most appropriate pack

Barrier Properties (typical WVTR g/m^2/day 38°C/90%RH)

Cold Form Aluminium	0.00
Aclar ® 33C	0.08
Aclar ® UltRx2000	0.11 - 0.12
Aclar ® 22C	0.22
Aclar ® SupRx 900	0.23 - 0.26
Aclar ® 22A	0.31 - 0.34
PVC/80g PVDC	0.31
Aclar ® Rx160	0.39 - 0.42
Aclar ® 33C	0.42
PVC/60g PVDC	0.47 - 0.6
PVC/40g PVDC	0.7 - 0.75
PP	0.7 - 1.47
PVC	2.4 – 4

Aclar ® is a registered trade mark of Allied Signal

Packaging: OVTR (Oxygen Vapor Transmission Rate (WVTR)

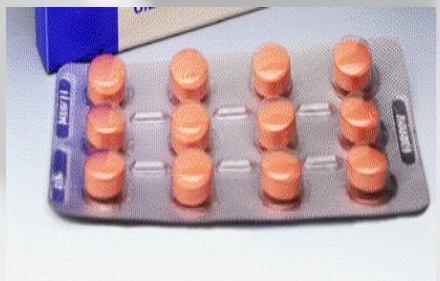
- **Similar considerations are relevant to protection of products that are labile to oxidative degradation.**

- **The permeability of plastic containers to oxygen ingress has also been evaluated (OVTR) and is summarised here.**

Pack	OVTR (g. mm/(m^2. day))
LDPE	241
HDPE	102
Polystyrene	127
Polycarbonate	114
Polypropylene	89
PVC	4
PET	2

PACKAGING: Solid Dose – Blister Packs

- THERMOFORM BLISTERS
  - plastic base web
  - blister formed with aid of heating
  - low to high barrier



- Overlacquer
- Print
- Aluminium
- Primer
- Heat seal lacquer

Lidding Foil – typically 20 micron Al

Film – e.g PVC, PVC/PVDC, PVC/PE/PVDC, PVC/Aclar®

- PVC
- PVDC or Aclar®

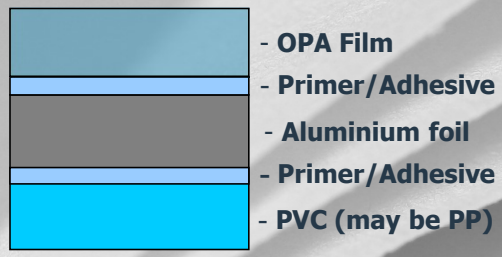
Product contact layers: For PVC or PVC/Aclar® = PVC
For PVC/PVDC = PVDC
For Lid foil = heat seal lacquer

PACKAGING: Solid Dose – Blister Packs

- **COLD FORM BLISTER**
  - blister formed mechanically (no heat)
  - high barrier

Lidding Foil

Foil Laminate – e.g. OPA/foil/PVC, or OPA/foil/PP



Product contact layers:
For base = PVC (or PP)
For lid foil = heat seal lacquer

PACKAGING: Solid Dose – Blister Packs

- **TROPICALISED BLISTER**
  - thermoform blister plus cold form tray
  - once tray opened, in use life determined by primary thermoform blister
  - high barrier before use

Lidding Foil

Film – e.g. PVC, PVC/PVDC

Foil Laminate – e.g. OPA/foil/PVC

Product contact layers:
For PVC = PVC
For PVC/PVDC = PVDC
For Lid foil = heat seal lacquer

Packaging challenges (4FDC)

A 4-API combination anti-TB tablet:

Rifampicin	150 mg
Isoniazid	75mg
Pyrazinamide	400mg
Ethambutol	275mg
TOTAL API weight:	900mg
Tablet weight: 1.3g	

The technical challenges:

- Big tablet
- Problem APIs !!
  - ☹ Rifampicin is vulnerable to oxidative degradation and hydrolysis; it is light sensitive, and it reacts with isoniazid. It also exhibits solid-state polymorphism.
  - ☹ Isoniazid reacts with aldehydes/reducing sugars….& rifampicin → major degradant
  - ☹ Ethambutol (2HCl) is hygroscopic, attracting moisture into the tablet to form a slightly acidic solution that encourages the rifampicin/isoniazid interaction!
  - ☹ ☺ Pyrazinamide…..seems to be OK !

Packaging challenges (4FDC)

The solution:

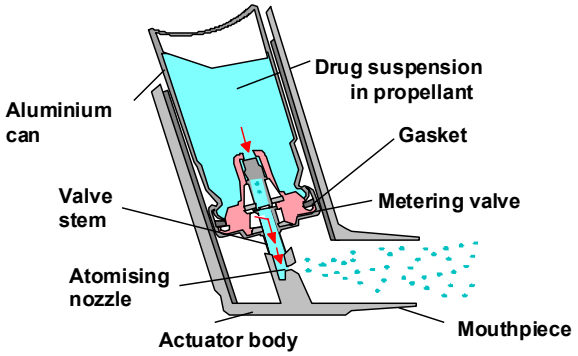
- **Packaging:**
  - **Non-permeable (moisture and oxygen) material**
  - **Do not remove from primary packaging until use**
  - **Avoid repackaging**
  - **Protect from light**

Also:

- **Excipients: no sugar/lactose (isoniazid)**
- **Rifampicin used as “as is” powder (no granulation)**
- **Maintain low water content of tablets (USP ≤ 3.0%)**

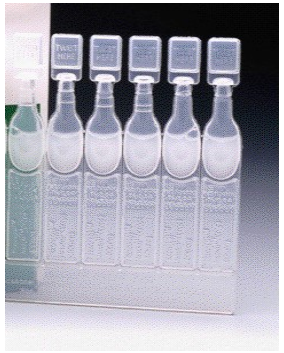
PACKAGING: IH and IN Products

Metered dose inhaler



Dry Powder Inhalers

Nebules



Intranasal

Packaging And Stability:

- **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 colored glass

Packaging And Stability :

- **Plastics**

The problems with plastic are:

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

Packaging And Stability :

- Metals

- Various alloys and aluminium 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.

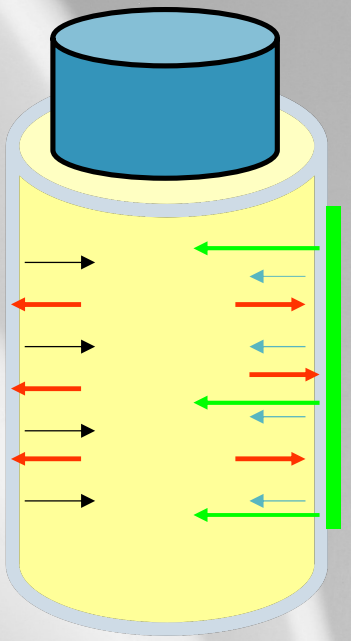
Packaging And Stability :

- **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.**

EXTRACTABLES and LEACHABLES: Definitions



- **Extractable**
  - Senyawa yang dapat diekstraksi dari komponen elastomerik, plastik, atau lapisan wadah dan sistem penutup saat terdapat pelarut yang sesuai.
- **Leachable**
  - Senyawa yang larut dari komponen elastomerik, plastik, atau lapisan wadah dan sistem penutup akibat kontak langsung dengan formulasi produk obat.
  - Dapat berinteraksi dengan komponen produk untuk menghasilkan pengotor yang memerlukan pemantauan stabilitas.

EXTRACTABLES and LEACHING:

Practical examples of Issues

- **Polyaromatic hydrocarbons (PAH) detected in CFC-filled MDIs (c.1990)**
  - **Prompted the first concerted efforts to look for leachables in MDIs**
- **Vanillin detected in solutions for inhalation packed in LDPE containers**
  - **Source: migration through LDPE container wall from cardboard outer packaging.**
  - **Protective Al foil laminate overwrap introduced.**
- **Di-ethylhexyl phthalate (DEHP)**
  - **Plasticizer in PVC; detected, for example, in TPN fat emulsions probably via infusion tubing set**
  - **Neonates have particular sensitivity to DEHP**

EXTRACTABLES and LEACHING: Considerations

- **Clinical concerns:**
  - A potentially sensitive, compromised (especially paediatric) patient population
  - Safety for both acute and chronic administration
- **Regulatory requirements:**
  - FDA requirements
  - Included in CPMP guideline 3AQ10a and CPMP/QWP/4359

Extractables: control of quality of packaging materials and robust relationship with suppliers, e.g. change control.

Leachables: comprehensive stability package – long-term storage condition and accelerated stability assessment for drug product in pack to cover shelf-life of the product

- Consistency in materials/components (Specifications, DMFs)
- Control of packing material and product manufacture
- Control for unintended contaminants

Labeling

Limiting factors	Additional labeling statement, where relevant
Pharmaceutical products that cannot tolerate refrigerating	"Do not refrigerate or freeze"
Pharmaceutical products that cannot tolerate freezing	"Do not freeze"
Light-sensitive pharmaceutical products	"Protect from light"
Pharmaceutical products that cannot tolerate excessive heat, e.g. suppositories	"Store & transport always below 30°C"
Highly hygroscopic pharmaceutical products	"Store in dry condition"

Final thoughts

Preformulation studies are an important foundation tool early in the

development of both API and drug products. They influence….

- **Selection of the drug candidate itself**
- **Selection of formulation components**
- **API & drug product manufacturing processes**
- **Determination of the most appropriate container closure system**
- **Development of analytical methods**
- **Assignment of API retest periods**
- **The synthetic route of the API**
- **Toxicological strategy**

ANY QUESTIONS PLEASE?

Excipients

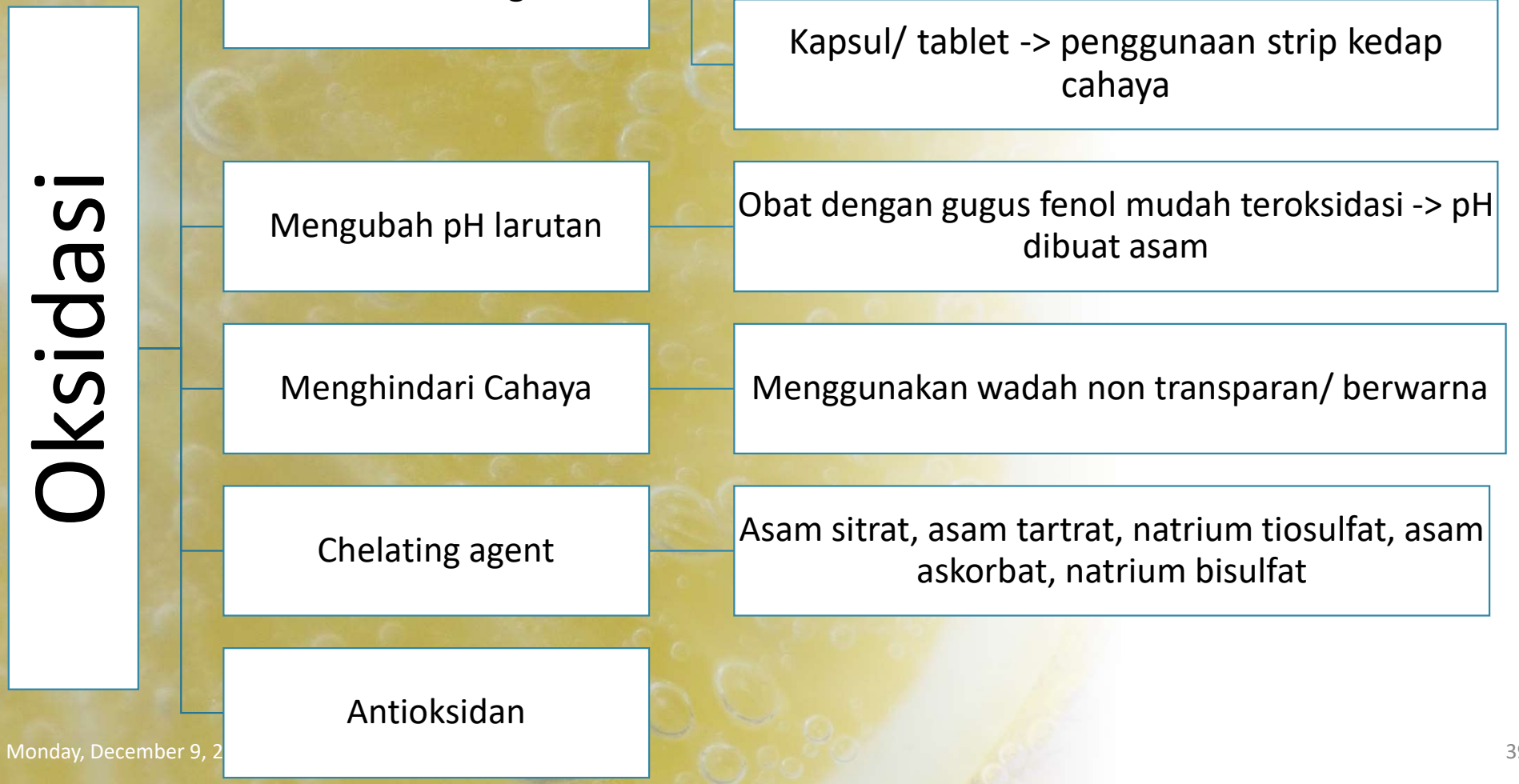
Excipients

Gelatin

Sodium alginat

Pektin, Guar gum

CMC


Oksidasi
Eksklusi Oksigen
Obat suntik -> O2 diganti gas inert
Kapsul/ tablet -> penggunaan strip kedap cahaya
Mengubah pH larutan
Obat dengan gugus fenol mudah teroksidasi -> pH dibuat asam
Menghindari Cahaya
Menggunakan wadah non transparan/ berwarna
Chelating agent
Asam sitrat, asam tartrat, natrium tiosulfat, asam askorbat, natrium bisulfat
Antioksidan

Hidrolisis

- Determinasi pH optimum
- Menekan kelarutan
  - Sitrat, dekstrosa, sorbitol danglukonat
- Membatasi obat kontak dengan air
  - Sediaan solid; ex: Amoxicilin dry syrup

Fotolisis

- Penggunaan kemasan berwarna gelap
- Penyimpanan pada ruang gelap
- Tablet salut -> menggunakan polymer film coating ultraviolet absorber

Thank You..