Stability of pharmaceutical preparations

Stability - definition

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

- ***Quality***
- ***Safety***
- ***Efficacy***

Regulations

- Before 1990: USP, FDA, CFR
- After 1990: ICH
  - Stability examinations of novel dosage forms
  - Photostability
  - Stability examinations of biological preparations

International Conference on Harmonisation 1990

- European Medicines Agency (**EMA**)
- European Federation of Pharmaceutical Industries and Associations (**EFPIA**)
- Ministry of Health, Labor and Welfare, Japan (**MHLW**)
- Japan Pharmaceutical Manufacturers Association (**JPMA**)
- US Food and Drug Administration (**FDA**)
- Pharmaceutical Research and Manufacturers of America (**PhRMA**)

Drug Stability

- Five types 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.*

Stability Studies are preformed on ...

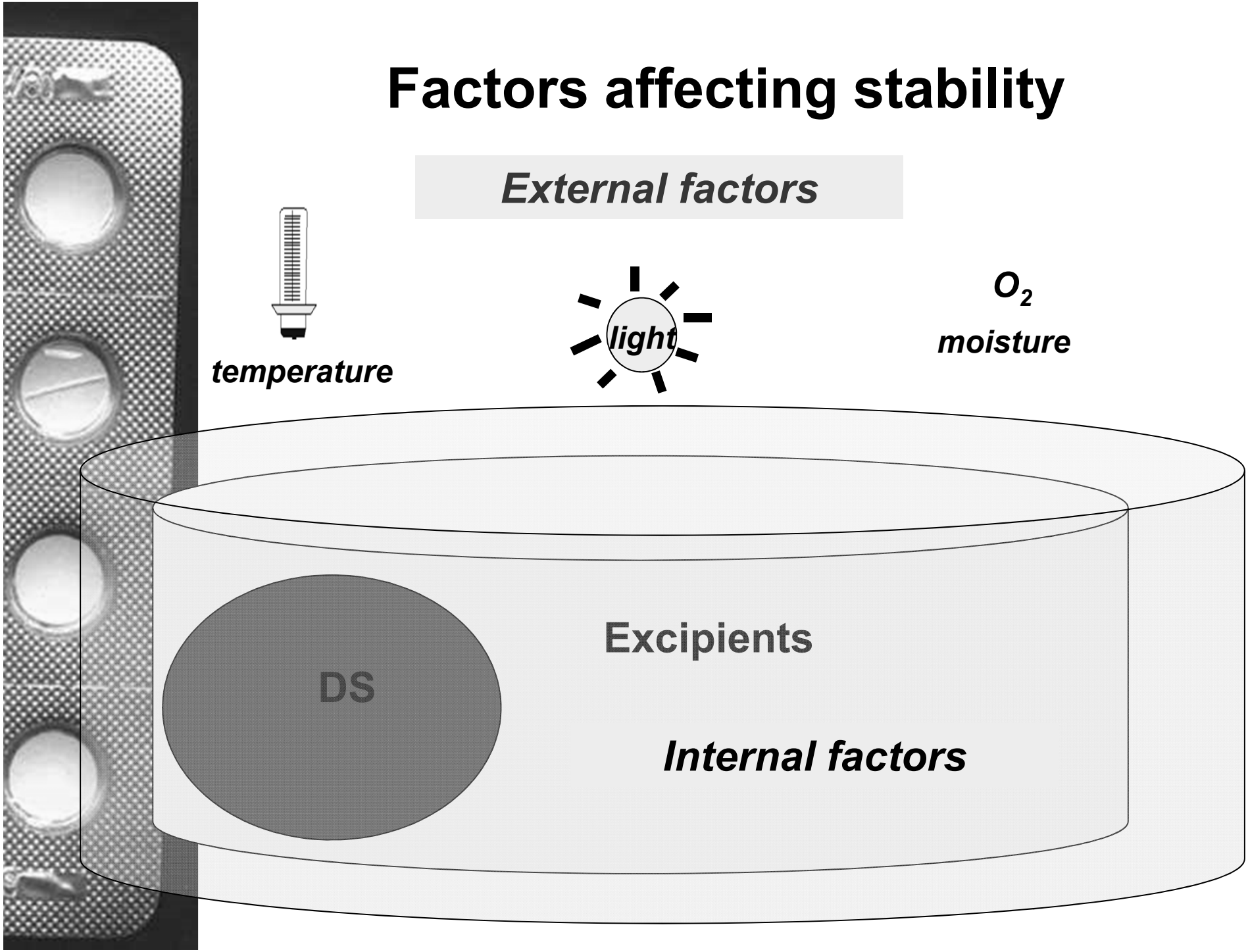
Drug Substances (DS)

The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Drug Products (DP)

The dosage form in the final immediate packaging intended for marketing……. controlled and documented determination of acceptable changes of the drug substance or drug product

Factors affecting stability



Factors affecting stability

External factors

- **Reactive substances**
  - oxygen
  - carbon-dioxide
  - water
  - others (i.e. OH^-, H^+)
  - wrappers
- **Energy**
  - heat
  - light
  - others (pl. radiolysis)
- **Catalyzers**
  - heavy metal ions
  - enzymes

Factors affecting stability

Internal factors

- **Reactive substances**
  - excipients, APIs, stabilizing agents
  - water (residual water content)
- **Catalyzers (Accelerants)**
  - Heavy metal ions
  - pH
  - buffers
  - decomposition products
  - contaminants (pollutants)

List of changes

Physical changes

- Appearance
- Melting point
- Clarity and color of solution
- Moisture
- Crystal modification (i.e. Polymorphism)
- Particle size

Chemical changes

- Increase in Degradation
- Decrease of Assay

Microbial changes

Physical changes

- Solubility
- pK_a
- Melting point
- Crystal form
- Equilibrium moisture content.

- i.e. amorphous materials are **less stable** than their crystalline counterparts.

A relatively dense material may better withstand ambient stresses, aminobenzylpenicillin trihydrate is **more denser** and **stable** than its amorphous form.

Physical changes

Formulation	Likely physical instability problems	Effects
Oral solutions	1- Loss of flavour 2- Change in taste 3- Presence of flavours due to interaction with plastic bottle 4- Loss of dye 5- Precipitation 6- Discoloration	Change in smell or feel or taste

Physical changes

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 changes

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 changes

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 changes

Formulation	Likely physical instability problems	Effects
Semisolids (Ointments and suppositories)	Changes in: 1. Particle size 2. Consistency 3. Caking or coalescence 4. Bleeding	1-Loss of drug content uniformity 2- loss of elegance 3-change in drug release rate.

Physical changes

Formulation	Likely physical instability problems	Effects
Tablets	Changes in: 1. Disintegration time 2. Dissolution profile 3. Hardness 4. Appearance (soft and ugly or become very hard)	Change in drug release

Physical changes

Formulation	Likely physical instability problems	Effects
Capsules	Change in: 1. Appearance 2. Dissolution 3. Strength	Change in drug release

Chemical stability

- Solid state reactions are **generally slow** and it is customary to use stress conditions in investigation of stability.
- Data obtained under stress is then extrapolated to make prediction of stability.
- High temperature can drive moisture out of a sample and render the material apparently stable otherwise prone to hydrolysis.

i.e. - above 65% relative humidity the beta form of chlortetracycline hydrochloride transforms into alpha form.

Effect of light

- Many drugs **fade or darken** on exposure to **light** and this leads to an **aesthetic problem**.

1. Real photochemical reactions
2. Photochemical catalytic reactions
3. Photochemical sensibilized reactions

Effect of packaging material

- Glass
- Plastics
- Metal
- Rubber

Effect of packaging material

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

Effect of packaging material

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.

Effect of packaging material

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.

Effect of packaging material

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.

Decomposition kinetics

- Zero order

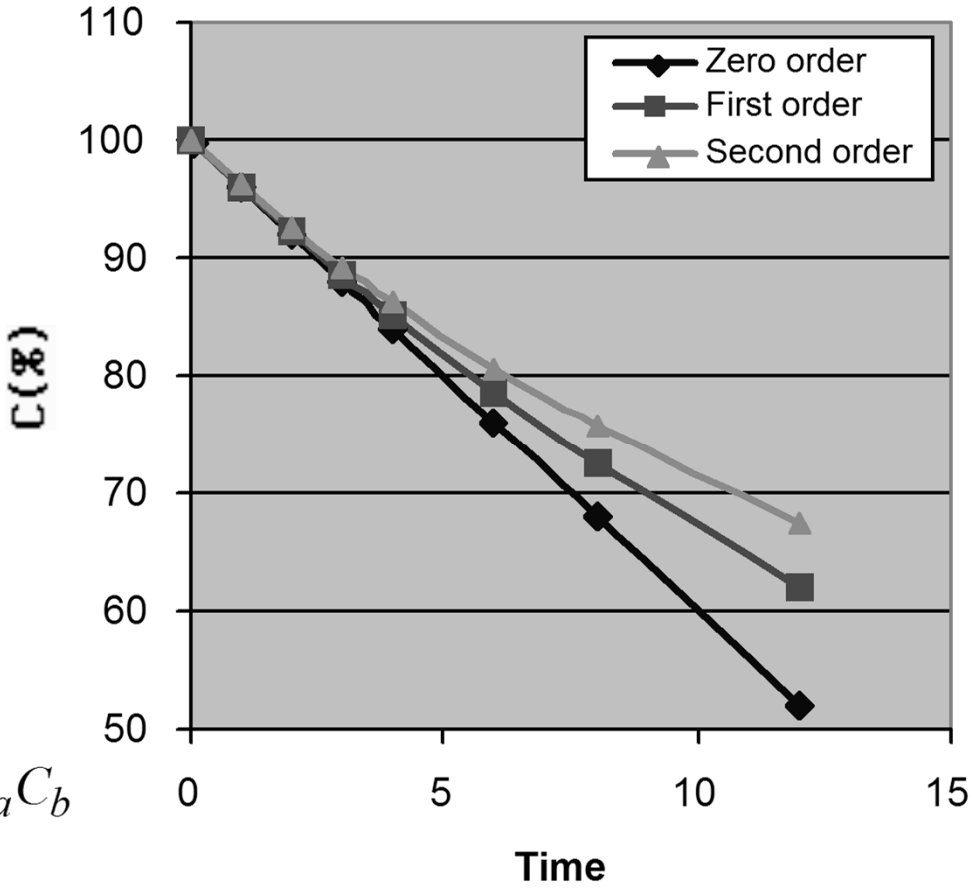
$$f(C) = k$$

- First order

$$f(C) = kC$$

- Second order

$$f(C) = kC^2 \; f(C) = kC_aC_b$$



Arrhenius' equation

Arrhenius' equation is a simple, but remarkably accurate, formula for the temperature dependence of reaction rates.

The equation was proposed by Svante Arrhenius in 1889, based on the work of Dutch chemist J. H. van't Hoff who had noted in 1884 that van't Hoff's equation for the temperature dependence of equilibrium constants suggests such a formula for the rates of both forward and reverse reactions. Arrhenius provided a physical justification and interpretation for the formula.

Arrhenius' equation

Arrhenius' equation gives the dependence of the rate constant of a chemical reaction on the absolute temperature (in kelvin),

$$k = Ae^{-Ea/(RT)}$$

where
A = is the pre-exponential factor (or simply the prefactor),
Ea = is the activation energy, and
R = is the Universal gas constant.

Types of stability tests

- Stability on **pre-formulation batches**
- **Accelerated and long term testing** for registration
- **On-going Stability** testing
- **Follow-up** Stabilities

Aims of stability tests

- Provides evidence on how the drug substance or product quality varies with time under environmental conditions during distribution.
- Helps to recommend storage conditions including establishment of shelf life, expiry date or retest period
- Key assurance of quality of pharmaceuticals.

Stability tests

- **Long term** stability studies
- **Intermediate** stability studies
- **Accelerated** stability studies

Stabillity tests

Long term tests

25°C ± 2°C / 60% RH ± 5% RH

- 1. year→ every 3. month
- 2. year → every 6. month
- 3. year → every year once

Length of study: min. 1 y, (max. 5 yrs)

Stabillity tests

Intermediate studies

30°C ± 2°C / 65% RH ± 5% RH

Length of study:

(min. 6 months, max. 12 months)

Stabillity tests

Accelerated studies:

40°C ± 2°C/75% RH ± 5% R

Length of study: 6 month

Stabillity tests

<u>Long term study (refrigerator):</u>

5°C ± 3°C

Length of study: min. 12 month

Stabillity tests

<u>Accelerated study (refrigerator):</u>

25°C ± 2°C/60% RH ± 5% RH

Length of study: min. 6 months

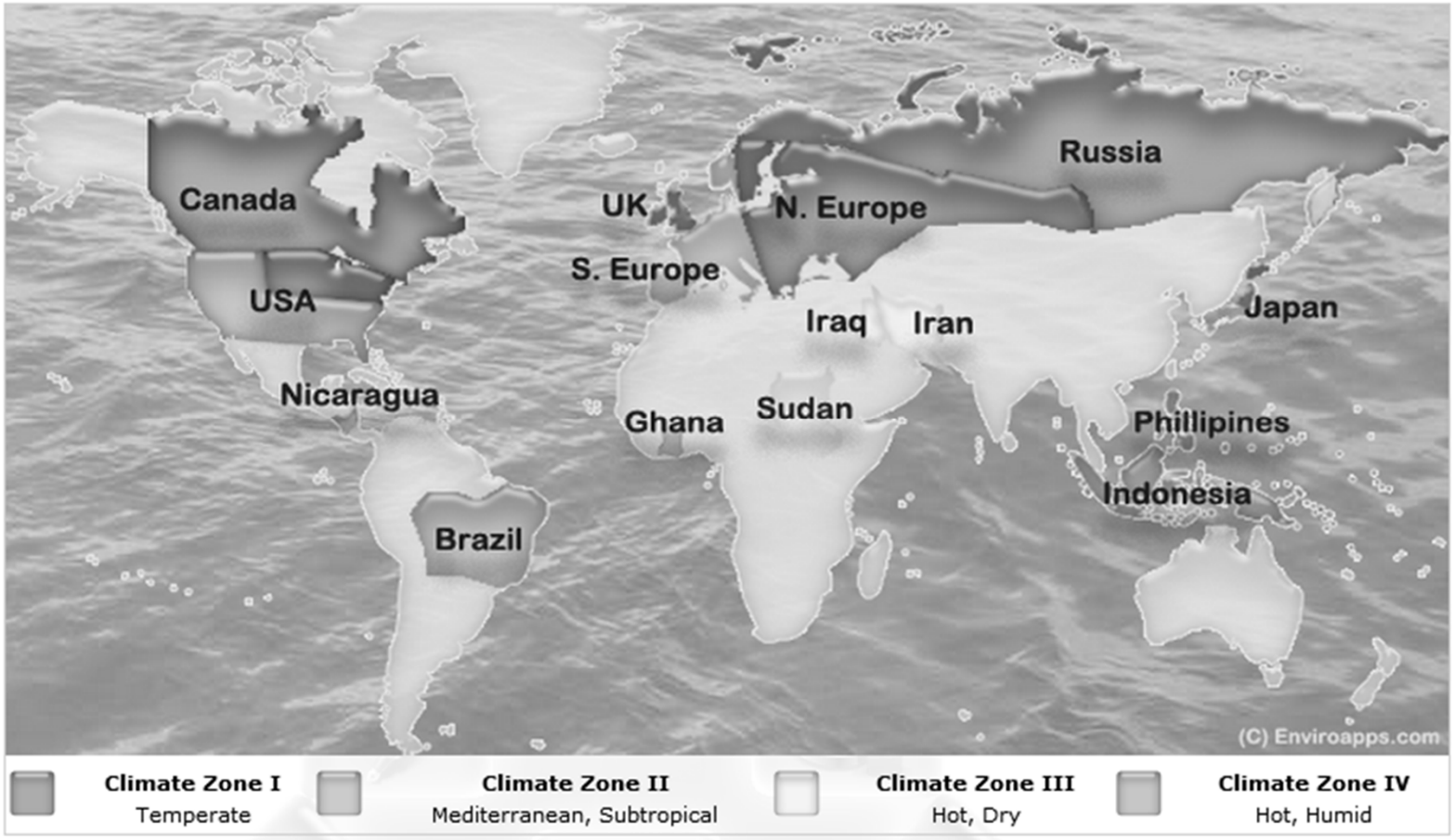
Stabillity tests

Long term study (freeze):

-20°C ± 5°C

Length of study: min. 12 months

Climatic zones



Climatic zones

Climatic Zone Countries	**Calculated data**			**Derived data**	
	Temp. °C	**MKT** °C	**Humidity** % RH	**Temp** °C	**Humidity** % RH
Climatic Zone **I** "**Temperate**" Japan, United Kingdom, Northern Europe, Canada, Russia, United States	**20**	**20**	**42**	**21**	**45**
Climatic Zone **II** "**Mediterranean**, **Subtropical**" Japan, United States, Southern Europe	**26.4**	**22**	**52**	**25**	**60**

Climatic zones

Climatic Zone Countries	**Calculated data**			**Derived data**	
	Temp. °C	**MKT** °C	**Humidity** % RH	**Temp** °C	**Humidity** % RH
Climatic Zone **III** "**Hot, dry**" Iran, Iraq, Sudan	**26,4**	**27,9**	**35**	**30**	**35**
Climatic Zone **IV** "**Hot, humid**" Brazil, Ghana, Indonesia, Nicaragua, Philippines	**26,7**	**27,4**	**76**	**30**	**70**

Stability examinations

Changing parameters of climatic chambers

- Temperature
- Humidity
- Light exposure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Questions

List the five types of stability!

What are the most commonly used four packaging materials?

What is the classification of stability tests?

What is the number of our climatic zone?

Thank you for your attention!