DRUG STABILITY

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REFERENCES

• FDA Guideline 1984, 1987
• Drug Stability, Carstensen JT, 3\textsuperscript{rd} ed, 2000
• Chemical Kinetics, Laidler KJ, 1980
• Chemical Stability of Pharmaceuticals, Connors KA, Amidon GL, Stella VJ, 1986
• IFSCC Monograph number 2, The Fundamentals of Stability testing, 1992
• Physical Pharmacy, Martin, 1993
UNIT OF COURSES


• **Chemical Stability** - Kinetics of Reaction: Rates and Orders of Reaction, Molecularity, Zero-Order, First-Order, Second–Order Reactions, Complex Reactions, Determination of Order

  *Condition of Storage*: Influence of temperature and other factors on reaction rates

  *Decomposition and Stabilization of Medicinal Agents*

  *Accelerated Stability Analysis*

• **Physical Stability**

• **Stability test of pharmaceutical/cosmetics dosage forms**
INTRODUCTION

• **STABILITY**: The ability of a product to remain in compliance with its established specification to be the same as it was produced (identity, strength, quality, purity) and to deliver active ingredients at an effective level specified during shelf-life

• **SHELF-LIFE**: the period of time during which a product remains in compliance with its specification stored under the conditions of the market (period of use and storage)

• **Expiration date**: the period of time printed on the container/package indicating the limit time allowed to be consumed, since the product remains in compliance with its established specification
POTENTIAL ADVERSE EFFECTS OF INSTABILITY IN PHARMACEUTICAL PRODUCTS

• Loss of Active
• Increase in Concentration of Actives
• Alterations in Bioavailability
• Lost of Content Uniformity
• Decline of Microbiological Status
• Lost of Pharmaceutical Elegance and Patient Acceptability
• Formation of Toxic Degradation Products
• Lost of Package Integrity
• Reduction of Label Quality
• Modification of any factor of Functional Relevance
THE GAMUT OF STABILITY CONCERNS

- Bulk Drug Substance and Exipients
- Research and Development Formulations
- Clinical Trial Materials
- Marketed product
- Reformulation, Channel of Manufacturing Site, Trouble Shooting, Complaints
- Product in the Channel of Distribution
- Product in the Control of the Patient
- In Vivo Stability
REASONS FOR STABILITY TESTING

• Concerns for Patient’s Welfare
• To Protect the Reputation of the Producer
• Requirements of Regulatory Agencies
• To Provide a Database that may be of Value in the Formulation of Other Products
MODES OF DEGRADATION

- Chemical
- Physical
- Microbiological
- Therapeutic
- Toxicological
- Drug product stability
STABILITY TEST

• cGMP 1972
• FDA MARET 1984; REVISED FDA 1987
• FDA Guidance for Industry 1998
• ICH (International Conference on Harmonization) Oktober 1993: US, EU, JAPAN
• ICH QIA September 1994
• WHO 1996
• CPMP (The Committee for Propietary Medicinal Products) under EU Okt 1997-April 1998
CHEMICAL STABILITY:
To remain the chemical purity and potency of active ingredients in compliance with its established specifications

KINETICS OF REACTION:
- **Rate of Reaction:** The rate of a reaction is given by $\pm \frac{dC}{dt}$, giving the increase (+) or decrease (-) of a concentration C within a given time interval dt.
- **Order of Reaction:** Amount of atoms or molecules involved in reaction in which concentration determines the rate of reaction.
- **Molecularity:** Amount of molecules involved in elementary reaction.
ZERO-ORDER REACTION:
loss in color of a product, suspension

- $-\frac{dA}{dt} = k_0$

- Integrated between initial absorbance $A_0$ at $t_0$ and $A_t$, the absorbance after $t$ hours:
  \[ \int_{A_0}^{A_t} dA = -k_0 \int_0^t dt \]

- $A_t - A_0 = -k_0 t$

- $A_t = A_0 - k_0 t$

- $t_{1/2} = \frac{1}{2} \frac{A_0}{k_0}$
FIRST-ORDER REACTION

• 2 H₂O₂ = 2 H₂O + O₂
• \(- \frac{dC}{dt} = kC\)
• Integrating between C₀ at t₀ and C at time t, giving:
  \[ \int_{C_0}^{C} \frac{dC}{C} = - k \int_{t_0}^{t} dt \]
• ln C - ln C₀ = - k(t-0)
  \[ \ln C = \ln C₀ - kt \]
  \[ \log C = \log C₀ - kt/2.303 \]
• \( k = 2.303/t \log \frac{C₀}{C} \)
• \( C = C₀ e^{-kt} \)
• \( C = C₀ 10^{-kt/2.303} \)
• \( k = 2.303/t \log \frac{a}{a-x} \)
$\frac{1}{2} C_0$

$C_t$

$t_{1/2}$

-Time

$-\frac{dC}{dt}$
\[ \text{Log } C = -k/2,303 \]
SUMMARY

• Drug Stability is important to be studied for the sake of patient’s welfare to warrant safety, quality and efficacy of medication

• Modes of instability of drugs including chemical, physical, microbiological, therapeutic, toxic degradation

• Can be done for bulk drug substance and excipients, R&D Formulations, Marketed products, Clinical Trial Materials etc

• Potential adverse effect of instability including loss/increase in concentration of active, alterations of BA, lost of content uniformity, decline of microbiological status etc