

Tecnología Farmacéutica.	Estabilidad
Estabilidad de Medicamentos ■ Características esenciales de calidad: – Contenido en sustancia activa – Forma farmacéutica y caracteres organolépticos – Flora microbiana – Toxicidad – Biodisponibilidad ■ Estables, seguros, eficaces	
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Tecnología Farmacéutica.	Estabilidad
Contenido en sustancia activa ■ Periodo de validez: – reducción del 10% en sustancia activa – Toxicidad no aumenta debido a productos de degradación ■ Fecha de caducidad: mes y año ■ Periodo de validez máximo 5 años (RD 736/1987 de 17 de marzo)	
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Tecnología Farmacéutica.	Estabilidad
Estudios de estabilidad ■ Sobre la sustancia activa ■ Fase de preformulación: – Sólido y disolución – Compatibilidad con excipientes – Estabilidad frente a operaciones básicas ■ Especialidad terminada – Ensayos a largo plazo – Ensayos de envejecimiento acelerado.	
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Tecnología Farmacéutica.	Estabilidad
Alteraciones de los medicamentos ■ Inestabilidad Física ■ Inestabilidad Química ■ Inestabilidad Microbiológica	
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Tecnología Farmacéutica.	Estabilidad
Inestabilidad Física: alteración de las características galénicas ■ Consecuencias: – Aspecto – Regularidad de la dosificación – Biodisponibilidad (caducidad biofarmacéutica) ■ Vías degradación física: – Polimorfismo – Crecimiento cristalino – Sedimentación – Floculación – Coalescencia	
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Tecnología Farmacéutica.	Estabilidad
Inestabilidad química ■ Cinética química ■ Orden y molecularidad de la reacción	
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Stability Calculations ■ a typical chemical reaction  D and W, "colliding" to form one or more product molecules, ■ the rate of reaction: proportional to the number of collisions a ■ the number of collisions is proportional to the product of the concentrations of the two species: – Reaction rate $\propto [D][W]$ ■ Reaction rate corresponds to the rate of loss of D and is denoted $(d[D])/dt$	
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Tecnología Farmacéutica.	Estabilidad
Stability Calculations  – Reaction rate $\propto [D][W]$ $-\frac{d[D]}{dt} \propto [D][W]$ – we let k_2 be the <i>rate constant</i> $-\frac{d[D]}{dt} = k_2 [D][W]$	
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Tecnología Farmacéutica. Estabilidad

Stability Calculations

- Order of reaction: sum of the exponents of the concentration terms in the rate equation

$$-\frac{d[D]}{dt} = k_2[D][W]$$


Second order reaction

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Tecnología Farmacéutica. Estabilidad

Stability Calculations

- Order of reaction:

$$-\frac{d[D]}{dt} = k_2[D][W]$$
 - If the water concentration W is held constant (by having a large excess, as in most solutions) then :
$$-\frac{d[D]}{dt} = k_1[D] \quad \text{where } k_1 = k_2[W]$$

and the reaction is *apparent first order* or pseudo first order

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Tecnología Farmacéutica. Estabilidad

Stability Calculations

- Order of reaction:
 - If, now, in addition, we also fix the drug concentration (e.g., by making a suspension), the equation becomes:

$$-\frac{d[D]}{dt} = k_0$$

where $k_0 = k_1[D] = k_2[D][W]$

and the reaction is *apparent zero order*

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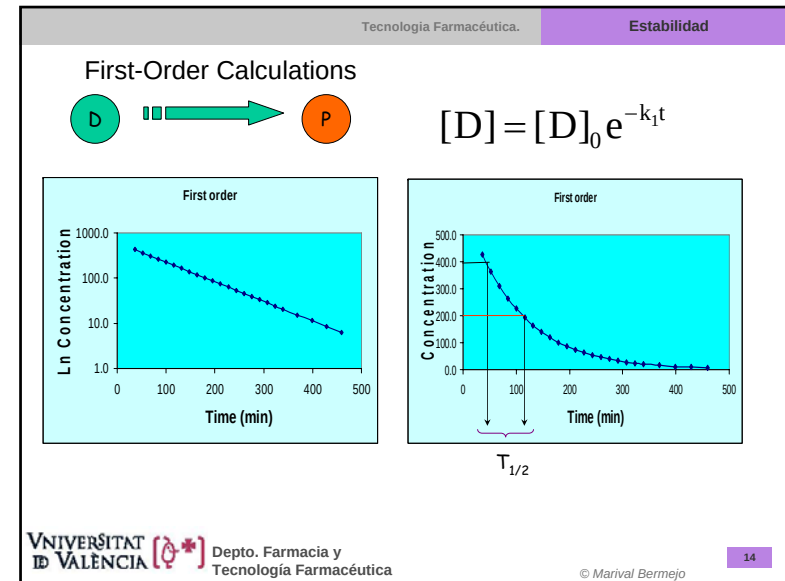
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Orden	Ecuación velocidad	Unidades k
0	$-dC/dt=k$	$C \cdot t^{-1}$
1	$-dC/dt=k \cdot C$	t^{-1}
2	$-dC/dt=k \cdot C^2$ $-dC/dt=k \cdot C \cdot B$	$C^{-1} \cdot t^{-1}$
n	$-dC/dt=k \cdot C^n$	$C^{n-1} \cdot t^{-1}$

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Tecnología Farmacéutica.		Estabilidad
Orden	Ecuación velocidad	Ecuación integrada
0	$-dC/dt=k$	$C = C_0 - k \cdot t$
1	$-dC/dt=-k \cdot C$	$C = C_0 \cdot e^{-k \cdot t}$
2	$-dC/dt=k \cdot C^2$	$\frac{1}{C} = \frac{1}{C_0} + k \cdot t$

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First-Order Calculations

- The *half-life*, $t_{1/2}$:
is the time for $[D]$ to become $[D]/2$,

$$\ln \frac{[D]_0}{2} = \ln [D]_0 - k_1 t_{1/2}$$

$$\frac{\ln 2}{k_1} = t_{1/2} \rightarrow t_{1/2} = \frac{0.693}{k_1}$$

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First-Order Calculations

- The *shelf-life*, t_{90} :
usually taken to be the time for $[D]$ to reach $0.90[D]$, that is,
10% decomposition,

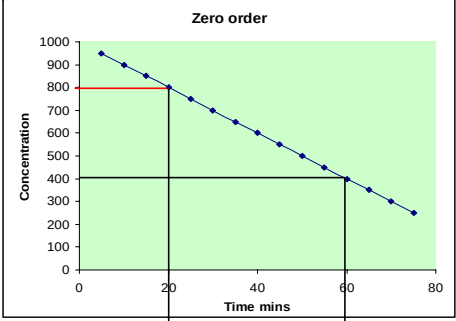
$$t_{90} = \frac{0.105}{k_1}$$

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First-Order Calculations Example: aspirin (acetylsalicylic acid) at pH 2.5 the (pseudo-first-order) rate constant is $5 \times 10^{-7} \text{s}^{-1}$ at 25°C. half-life $t_{1/2} = \frac{0.693}{5 \times 10^{-7}} = 1.39 \times 10^6 \text{ s}$ shelf life $t_{90} = \frac{0.105}{5 \times 10^{-7}} = 2.1 \times 10^5 \text{ s}$	
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Tecnología Farmacéutica.	Estabilidad
Zero-Order Calculations - rate equation with no concentration dependence. $-\frac{d[D]}{dt} = k_0$ - Integrating from $t = 0$ to $t = t$ with $[D] = [D]_0$ at $t = 0$, $\int_{[D]_0}^{[D]} d[D] = -\int_0^t k_0 dt$ $[D] = [D]_0 - k_0 t$	
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Tecnología Farmacéutica.	Estabilidad
Zero-Order Calculations $[D] = [D]_0 - k_0 t$ - Half life $t_{1/2} = \frac{0.5[D]_0}{k_0}$ - Shelf-life $t_{90} = \frac{0.1[D]_0}{k_0}$	
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Tecnología Farmacéutica.	Estabilidad
Zero-Order Calculations $[D] = [D]_0 - k_0 t$  $t_{1/2} = \frac{0.5[D]_0}{k_0}$	
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Tecnología Farmacéutica.	Estabilidad
Zero-Order Calculations Example: aspirin (acetylsalicylic acid) at pH 2.5 the (pseudo-first-order) rate constant is $5 \times 10^{-7} \text{ s}^{-1}$ at 25°C. Aspirin solubility 0.33 g/100 mL. for an aspirin suspension: zero-order rate $k_0 = 5 \times 10^{-7} \text{ s}^{-1} \times 0.33 \text{ g/100 mL} =$ $k_0 = 1.65 \times 10^{-7} \text{ g/(100mL} \cdot \text{s)}$ Dose of aspirin: $650 \text{ mg/teaspoon}(5 \text{ mL}) = 13 \text{ g/100 mL}$. shelf life $t_{90} = \frac{(0.1)(13)}{1.65 \times 10^{-7}} = 7.9 \times 10^6 \text{ s} = 91 \text{ days}$	
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Tecnología Farmacéutica.	Estabilidad
TEMPERATURE EFFECTS Activation Energy Calculations - Reaction rates are proportional to the number of collisions per unit time. - the number of collisions increases as the temperature increases. - The reaction rate constant is observed to have an exponential dependence on temperature described by the Arrhenius equation $k = A \exp(-E_a/RT)$ - k : reaction rate constant - A : constant - E_a: activation energy of the chemical reaction - T : the absolute temperature ($t^\circ\text{C} + 273.16^\circ\text{C}$). $\log k = \log A - E_a/2.303RT$	
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Tecnología Farmacéutica.	Estabilidad
TEMPERAT Energy Kcal/mol Extent of reaction A+B reactants B+C products Eact= 12 Kcal/mol	
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Tecnología Farmacéutica.	Estabilidad
TEMPERATURE EFFECTS Typical Arrhenius plot of log k against 1/T, Log K $(1/T(K^\circ)) \cdot 1000$ Slope= $3.51 \cdot 10^3$ $E_a = 3.51 \cdot 10^3 \cdot (2.303) \cdot (1.987) = 16.1 \text{ Kcal/mol}$	
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TEMPERATURE EFFECTS		
Compound	Reaction	E _a (kcal/mol)
Ascorbic Acid	Oxidation	23
Aspirin	Hydrolysis	14
Atropine	Hydrolysis	14
Benzocaine	Hydrolysis	19
Chloramphenicol	Hydrolysis	20
Epinephrine	Oxidation	23
Procaine	Hydrolysis	14
Thiamine	Hydrolysis	20

Activation Energies for Some Drug Decomposition Reactions

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TEMPERATURE EFFECTS		
■ <i>Example:</i> Sulfacetamide. first-order rate constant in the pH-independent region (5-11) K = $9 \times 10^{-6} \text{ s}^{-1}$ at 120°C. E_a = 22.9 kcal/mol at pH 7.4. Calculate the shelf life at 25°C.		
$\log \frac{k_2}{k_1} = \frac{-E_a}{2.303R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right) \Rightarrow \log \frac{k_{25}}{k_{120}} = \frac{-22900}{(2.3)(1.987)} \left(\frac{1}{298} - \frac{1}{393} \right)$		
$\frac{k_{25}}{k_{120}} = 8.7 \times 10^{-5} \Rightarrow k_{25} = (8.7 \times 10^{-5}) (9 \times 10^{-6} \text{ s}^{-1}) = 7.85 \times 10^{-10} \text{ s}^{-1}$		
$t_{90} = \frac{0.105}{7.85 \times 10^{-10} \text{ s}^{-1}} = 1.34 \times 10^8 \text{ s} \Rightarrow 4.25 \text{ years}$		

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TEMPERATURE EFFECTS		
<i>Example</i> The following rate constants were determined for 5-fluorouracil decomposition at pH 9.90.		
t (°C)	10 ⁶ k (s ⁻¹)	
80	0.96	
70	0.32	
60	0.118	

(a) Determine the activation energy at this pH;

(b) Extrapolate the graph to room temperature (25°C) and determine the rate constant and shelf life at this temperature.

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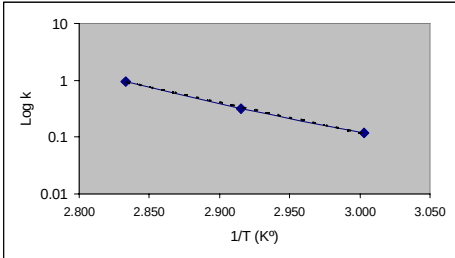
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TEMPERATURE EFFECTS		
<i>Answer:</i> (a) from the Arrhenius plot of the data we obtain The slope B = -12.31 = E_a/R E_a = 24.5 kcal/mol		

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Tecnologia Farmacéutica. **Estabilidad**

TEMPERATURE EFFECTS

(b) From extrapolation of the graph to 25°C ($1/T = 0.00335$), we obtain $\log k_{25^\circ\text{C}} = -8.86$. $k_{25^\circ\text{C}} = 1.38 \times 10^{-9} \text{ s}^{-1}$
 $t_{90} = 7.6 \times 10^7 \text{ s} = 2.4 \text{ years}$



Note that E_a is always positive.

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Tecnologia Farmacéutica. **Estabilidad**

Q10-Value Calculations:

Consider the ratio of rate constants k_{T2}/k_{T1} at two temperatures T_1 and T_2 . Consider $T_1 = T_2 + 10^\circ$

The quantity Q_{10} is defined as

$$Q_{10} = \frac{k_{(T+10)}}{k_T}$$

The Q_{10} factor can be calculated from the next equation:

$$Q_{10} = \frac{k_{(T+10)}}{k_T} = \exp \left[-\frac{E_a}{R} \left(\frac{1}{T+10} - \frac{1}{T} \right) \right]$$

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Tecnologia Farmacéutica. **Estabilidad**

Q10-Value Calculations:

- The activation energies for drug decompositions usually fall in the range 12 to 24 kcal/mol.
- Next table gives values of E_a corresponding to three rounded values of Q_{10} .
- These values of $Q_{10} = 2, 3$, or 4 to represent low, average, and high estimates of Q_{10} when E_a is unknown

Q_{10} (30 to 20°C)	E_a (kcal/mol)
2.0	12.2
3.0	19.4
4.0	24.5

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Tecnologia Farmacéutica. **Estabilidad**

Q10-Value Calculations:

For an arbitrary change in temperature, $\Delta T = T_2 - T_1$,

$$Q_{\Delta T} = \frac{k_{(T+\Delta T)}}{k_T} = Q_{10}^{(\Delta T/10)}$$

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Tecnología Farmacéutica.	Estabilidad
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Q10-Value Calculations:
For an arbitrary change in temperature, $\Delta T = T_2 - T_1$,

$$Q_{\Delta T} = \exp \left[\frac{E_a}{R} \left(\frac{\Delta T}{(T + \Delta T)(T)} \right) \right]$$

Multiplying the exponential term by

$$\frac{10}{10} \frac{T + 10}{T + 10}$$

gives

$$Q_{\Delta T} = \exp \left[\frac{E_a}{R} \frac{\Delta T}{(R + \Delta T)(T)} \frac{10 (T + 10)}{10 (T + 10)} \right]$$

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Q10-Value Calculations:

$$Q_{\Delta T} = \exp \left[\frac{E_a}{R} \frac{10}{(T + 10)(T)} \frac{\Delta T}{10 (T + \Delta T)} \right]$$

$$= \exp \left[\frac{E_a}{R} \frac{10}{(T + 10)(T)} \right]^{\left[\frac{\Delta T}{10} \right] \left[\frac{(T + 10)}{(T + \Delta T)} \right]}$$

$$Q_{\Delta T} = Q_{10}^{\left[\frac{\Delta T}{10} \right] \left[\frac{(T + 10)}{(T + \Delta T)} \right]}$$

This equation is exact. However, since $T \approx 300K$, $(T + 10)/(T + \Delta T) \approx 1$,

$$Q_{\Delta T} = \frac{k_{(T + \Delta T)}}{k_T} \approx Q_{10}^{\Delta T/10}$$

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Q10-Value Calculations:
Example Calculate the factors by which rate constants may change for:

(a) a 25 to 50°C temperature change
(b) a 25 to 0°C temperature change.

Answer:

(a) $\Delta T = +25$,

$$Q_{+25} = \frac{k_{(25+25)}}{k_{25}} = Q_{10}^{(25/10)}$$

= 5.7, 15.6, 32 for $Q_{10} = 2, 3, 4$, respectively

Thus the rate increases between 6-fold and 32-fold, with a probable average increase of about 16-fold.

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Q10-Value Calculations:
(b) a 25 to 0°C temperature change.
Answer:

$\Delta T = -25$,

$$Q_{-25} = \frac{k_{(0-25)}}{k_0} = Q_{10}^{(-25/10)}$$

= 1/5.7, 1/15.6, 1/32 for $Q_{10} = 2, 3, 4$, respectively

Thus the rate decreases to between 1/6 and 1/32 of the initial rate.

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Tecnología Farmacéutica. Estabilidad

Q10-Value Calculations:

- $Q = 4$ provides the largest estimate for the increase in rate with increasing temperature,
- $Q = 2$ provides the smallest reasonable estimate for the decrease with decreasing temperature.

Example: Using $Q_{10} = 2, 3, 4$, calculate the half-life change from 70°C to 25°C for methyl paraben at pH 4.
 We have $\Delta T = 25 - 70 = -45$,
 $Q_{-45} = 1/23$, ($Q_{10}=2$)
 $Q_{-45} = 1/140$, ($Q_{10}=3$)
 $Q_{-45} = 1/512$, ($Q_{10}=4$)

Since $k_{70^{\circ}\text{C}} = 1.6 \times 10^{-6} \text{ s}^{-1}$ (from the monograph) then
 $t_{\frac{1}{2}}(70^{\circ}\text{C}) = 4.3 \times 10^7 \text{ s} = 501 \text{ days}$

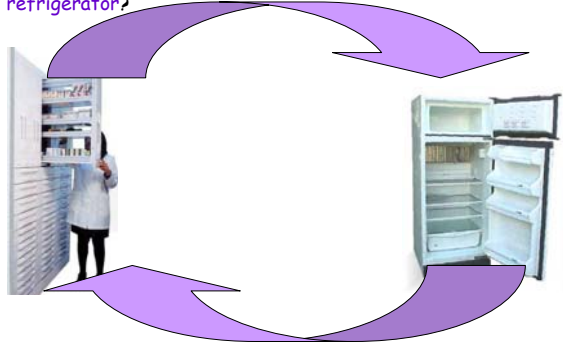
$t_{\frac{1}{2}}(25^{\circ}\text{C}) = 31 \text{ yr}$ ($Q = 2$)
 $= 199 \text{ yr}$ ($Q = 3$)
 $= 709 \text{ yr}$ ($Q = 4$)

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Tecnología Farmacéutica. Estabilidad

SHELF-LIFE ESTIMATION METHODS

The expiration date is given for room temperature. What is the expected extension of the shelf life in a refrigerator?



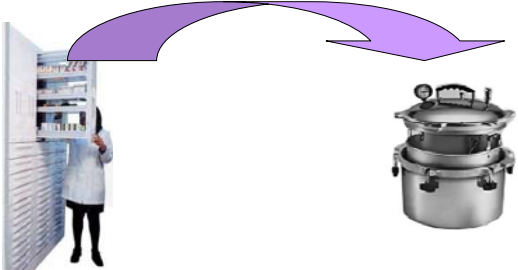
The expiration date is given for refrigeration conditions. How long may the product be left at room temperature?

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Tecnología Farmacéutica. Estabilidad

SHELF-LIFE ESTIMATION METHODS

The expiration date is for room-temperature conditions, and it is desired to heat the product in sterilization. What percent decomposition can be expected at the higher temperature?



Problems of this type require estimates of the effect of temperature on the shelf life. Assuming we do not have exact E_a values available, we use the Q_{10} values of 2, 3, and 4 to make such estimates.

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Tecnología Farmacéutica. Estabilidad

SHELF-LIFE ESTIMATION METHODS

The expiration date is for room-temperature conditions, and it is desired to heat the product in sterilization. What percent decomposition can be expected at the higher temperature?

Zero order $t_{90} = \frac{0.1[D_0]}{k_0}$

First order $t_{90} = \frac{0.105}{k_1}$

$t_{90}(T) = \frac{a}{k_{(T_1+\Delta T)}}$

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Tecnología Farmacéutica.	Estabilidad
SHELF-LIFE ESTIMATION METHODS	
$t_{90}(T_2) = \frac{a}{k_{T1} \cdot Q_{10}^{(\Delta T/10)}}$ or, since $t_{90}(T1) = a/k_{T1}$: $t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}}$ the estimate of $t_{90}(T2)$ is independent of the order. a positive ΔT ($T2 > T1$) reduces the shelf life, a negative ΔT ($T2 < T1$) increases it.	
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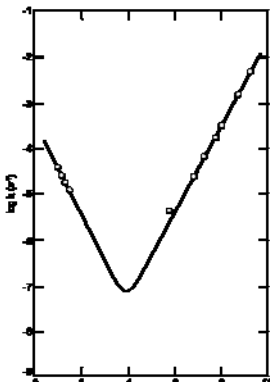
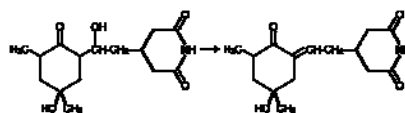
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SHELF-LIFE ESTIMATION METHODS	
■ <i>Example A.</i> The expiration period for a reconstituted product is 18 h at room temperature. Estimate the expiration period when the product is stored in the refrigerator. $\Delta T = -20^\circ\text{C}$, $t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} \rightarrow t_{90}(5^\circ) = \frac{18}{Q_{10}^{(-20/10)}}$ $t_{90}(5^\circ\text{C}) = 18 \cdot 2^2 = 72 \text{ h} \quad (Q = 2)$ $= 18 \cdot 3^2 = 162 \text{ h} \quad (Q = 3)$ $= 18 \cdot 4^2 = 288 \text{ h} \quad (Q = 4)$ conservative estimate would be 72 h and a likely estimate 162 h.	
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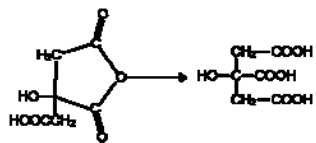
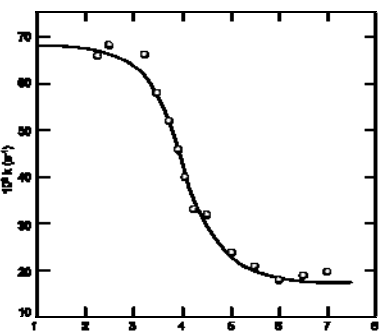
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SHELF-LIFE ESTIMATION METHODS	
■ <i>Example B.</i> A newly reconstituted product is labeled to be stable for 24 h in a refrigerator. What is the estimated shelf life at room temperature? $t_{90}(5^\circ\text{C}) = 24 \text{ h}$ $t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} \rightarrow t_{90}(25^\circ) = \frac{24}{Q_{10}^{(20/10)}}$ $t_{90}(25^\circ\text{C}) = 24/4 = 6 \text{ h} \quad (Q = 2)$ $= 24/9 = 2.7 \text{ h} \quad (Q = 3)$ $= 24/16 = 1.5 \text{ h} \quad (Q = 4)$ Thus a likely value is about 3 h, with a conservative estimate of 1.5 h and a possible value of 6 h.	
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Tecnología Farmacéutica.	Estabilidad
SHELF-LIFE ESTIMATION METHODS	
If the product has been stored for a known length of time at another temperature: - compute the time interval at the specified temperature that would give the equivalent decomposition to that which occurred at the actual storage temperature and - subtract this value from or add it to the label date for a new expiration date.	
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Tecnología Farmacéutica.	Estabilidad
SHELF-LIFE ESTIMATION METHODS <i>Example</i> The expiration date for a product is one year from the current date when stored in a refrigerator. The product has been stored for one month at room temperature. If the product is now returned to the refrigerator, what is the new expiration date? <i>Answer</i> One month at room temperature would be equivalent to $t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} \rightarrow t_{90}(T_2) \cdot Q_{10}^{(\Delta T/10)}$ $1 \cdot 2^2 = 4$ months (Q = 2) $1 \cdot 3^2 = 9$ months (Q = 3) $1 \cdot 4^2 = 16$ months (Q = 4) that is, 4, 9, or 16 months at 5°C. The most likely estimate is 9 months, hence if the product is returned to the refrigerator, only 3 months would be left.	
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Tecnología Farmacéutica.	Estabilidad
SHELF-LIFE ESTIMATION METHODS <i>Example.</i> The ampicillin monograph in the <i>Physicians' Desk Reference</i> (1) states that the reconstituted suspension is stable for 14 days in a refrigerator. If the product is left at room temperature for 12 h, what is the reduction in the expiration period? $t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} \rightarrow t_{90}(T_2) \cdot Q_{10}^{(\Delta T/10)}$ $0.5 \cdot 2^2 = 2$ days (Q = 2) $0.5 \cdot 3^2 = 4.5$ days (Q = 3) $0.5 \cdot 4^2 = 8$ days (Q = 4) The expected reduction is thus 4.5 days.	
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Tecnología Farmacéutica.	Estabilidad
Influencia del pH   Example: pH-Rate profile for the dehydration of streptovitacin A at 70°C	
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Tecnología Farmacéutica.	Estabilidad
Influencia del pH Example1   pH-Rate profile for hydrolysis of citric acid anhydride at 25°C	
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Tecnología Farmacéutica.	Estabilidad
D. pH EFFECTS (2). Sigmoid Curves Example2: Hydrolysis of aspirin. where $k_3 > k_1$ and $k'' > k'$. The rate equation is $\text{rate} = k_1[\text{RCOOH}][\text{H}^+] + k'[\text{RCOOH}] + k''[\text{RCOO}^-] + k_3[\text{RCOO}^-][\text{OH}^-]$ The pKa of aspirin is 3.6, so the plateau region of the curve (pH 4 to 8) is accounted for primarily by the k'' term, that is, hydrolysis of the anion. This reaction is responsible for the instability of aspirin in solution dosage forms pH-Rate profile for aspirin hydrolysis at 25°C	
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Tecnología Farmacéutica.	Estabilidad
D. pH EFFECTS (3). Bell-Shaped Curves Some pH-rate profiles show maxima, often with a "bell shaped" peak. Hydrolysis of penicillin G catalyzed by 3,6-bis (dimethylaminomethyl)-catechol. Catalysis is produced by the monoanion of the catechol derivative,	
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Tecnología Farmacéutica.	Estabilidad
Vías de degradación química ■ Hidrólisis ■ Oxidación ■ Racemización ■ Descarboxilación ■ Polimerización ■ Descomposición enzimática	
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Tecnología Farmacéutica.	Estabilidad
Inhibición de la oxidación ■ Proteger de la luz ■ Evitar presencia oxígeno ■ Uso agentes antioxidantes	
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Antioxidantes sistemas hidrófilos

- Combinaciones inorgánicas de azufre: sulfitos (olor y sabor desagradables)
- Combinaciones orgánicas de azufre: (olor y sabor desagradables)
- Ácido ascórbico: tópicos, parenterales, orales

Antioxidantes sistemas lipófilos

- Naturales: Tocoferoles
- Sintéticos y semisintéticos:
 - Ácido gálico y ésteres del ácido gálico
 - Ésteres ácido ascórbico
 - Butilhidroxianisol(BHA)
 - Butilhidroxitolueno(BHT)

Sinérgicos

- Reforzadores de acción: ácido fosfórico, cítrico, tartárico
- Inactivadores de catalizadores: EDTA

Sobredosificación

- Antibióticos, vitaminas
- Exceso de contenido activo que es necesario tener en cuenta para garantizar la estabilidad, es decir, la compensación de la pérdida de principio activo prevista durante el periodo de conservación.

Inestabilidad biológica

- Conservadores: requisitos
- Tolerancia fisiológica
- Compatibilidad
- Estabilidad química
- Olor y sabor
- Espectro activo

Clasificación conservantes

- Fenoles
- Alcoholes alifáticos y aromáticos
- Compuestos orgánicos de mercurio
- Compuestos de amonio cuaternario
- Ácidos carboxílicos
- Otros.