Estabilidad de Medicamentos

- Caracteristicas esenciales de calidad:
  - Contenido en sustancia activa
  - Forma farmacéutica y caracteres organolépticos
  - Flora microbiana
  - Toxicidad
  - Biodisponibilidad
- Estables, seguros, eficaces

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)

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.

Alteraciones de los medicamentos

- Inestabilidad Física
- Inestabilidad Química
- Inestabilidad Microbiológica

Inestabilidad Física: alteración de las caracteristicas galénicas

- Consecuencias:
  - Aspecto
  - Regularidad de la dosificación
  - Biodisponibilidad (caducidad biofarmacéutica)
- Vias degradación física:
  - Polimorfismo
  - Crecimiento cristalino
  - Sedimentación
  - Floculación
  - Coalescencia

Inestabilidad química

- Cinética química
- Orden y molecularidad de la reacción

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 ∝ [D]*[W]
- Reaction rate corresponds to the rate of loss of D and is denoted (d[D]/dt)

Stability Calculations

- Reaction rate ∝ [D]*[W]

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

- we let k_2 be the *rate constant*

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

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

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 :

$$-\frac{d[D]}{dt} - k_1[D]$$

where $k_1 = k_2\,[W]$

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

---

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

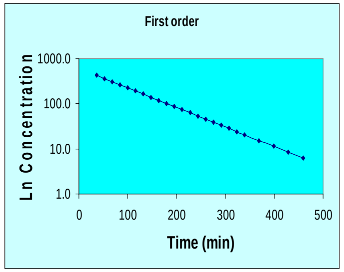
and the reaction is *apparent zero order*

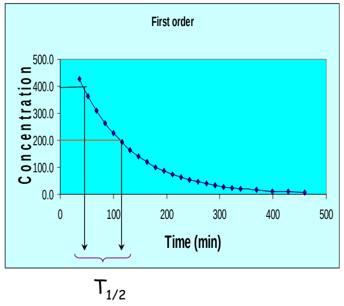
Orden	Ecuación velocidad	Unidades k
0	-dC/dt=k	$C*t^{-1}$
1	-dC/dt=-k*C	t^{-1}
2	$-dC/dt=k*C^2$ -dC/dt=k*C*B	$C^{-1}*t^{-1}$
n	$-dC/dt=k*C^n$	$C^{n-1}*t^{-1}$

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

First-Order Calculations

$$[D] = [D]_0 e^{-k_1 t}$$





First-Order Calculations

- The *half-life*, t½:

is the time for [D] to become [D]/2,

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

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

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,

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

First-Order Calculations

- Example:

aspirin (acetylsalicylic acid)

at pH 2.5 the (pseudo-first-order) rate constant is 5 x $10^{-7}s^{-1}$ at 25ºC.

half-life

$$t_{1/2} = \frac{0.693}{5 \text{ x } 10^{-7}} = 1.39 \text{ x } 10^{6} \text{ s}$$

shelf life

$$t_{90} = \frac{0.105}{5 \text{ x } 10^{-7}} = 2.1 \text{ x } 10^{5} \text{ s}$$

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,

$$\int_{[D]_0}^{[D]} d[D] = -\int_0^t k_0 dt$$

- $[D] = [D]_0 - k_0 * t$

Zero-Order Calculations

- $[D] = [D]_0 - k_0 * t$
- Half life

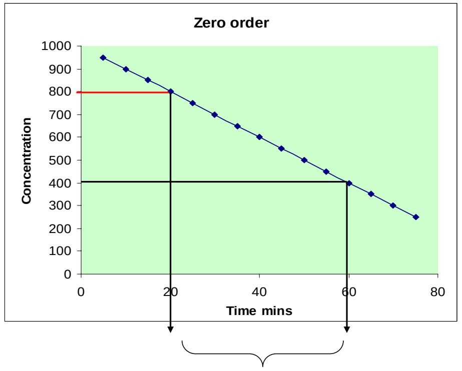
$$t_{1/2} = \frac{0.5[D]_0}{k_0}$$

- Shelf-life

$$t_{90} = \frac{0.1[D]_0}{k_0}$$

Zero-Order Calculations

$D] = [D]_0 - k_0 * t$



$$t_{1/2} = \frac{0.5[D]_0}{k_0}$$

Zero-Order Calculations

- Example: aspirin (acetylsalicylic acid)

at pH 2.5 the (pseudo-first-order) rate constant is
$5 \times 10^{-7} s^{-1}$ at 25ºC.
Aspirin solubility 0.33 g/100 mL.
for an aspirin suspension: zero-order rate

$k0 = 5 \times 10^{-7} s^{-1} \times 0.33$ g/100 mL =
$k0 = 1.65 \times 10^{-7}$ g/(100mL * s)

Dose of aspirin: 650 mg/teaspoon(5 mL) = 13 g/100 mL.

shelf life

$$t_{90} = \frac{(0.1)(13)}{1.65 \times 10^{-7}} = 7.9 \times 10^{6} \text{ s} = 91 \text{ days}$$

TEMPERATURE EFFECTS

Activation Energy Calculations

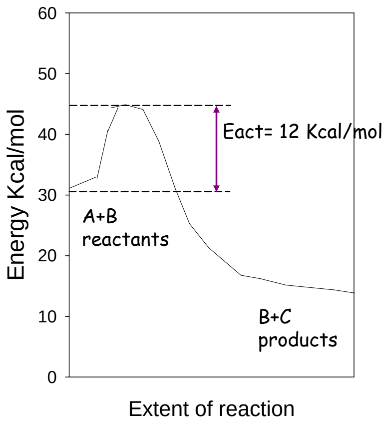
- Reaction rates are proportional to the number of collisions per unit time.
- the number of collisions increases as the temperature increases.
- The reaction rate constant is observed to have an exponential dependence on temperature described by the Arrhenius equation

k = A exp(-Ea/RT)

- k :reaction rate constant
- A :constant
- Ea: activation energy of the chemical reaction
- T : the absolute temperature (t ºC + 273.16ºC).

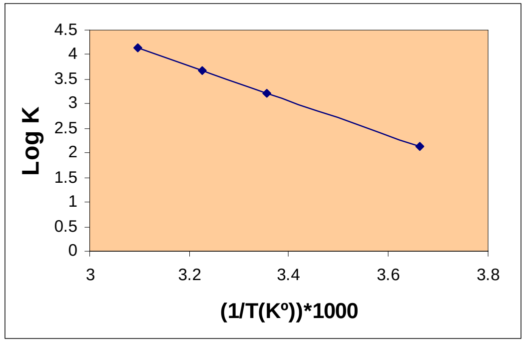
log k = log A - Ea/2.303RT

TEMPERAT



TEMPERATURE EFFECTS

Typical Arrhenius plot of log k against 1/T,



Slope= $3.51*10^3$
Ea= $3.51*10^3*(2.303)*(1.987)$=16.1 Kcal/mol

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

TEMPERATURE EFFECTS

- *Example:*

Sulfacetamide.

first-order rate constant in the pH-independent region (5-11)

K= 9 x 10^{-6} s^{-1} at 120ºC.

Ea= 22.9 kcal/mol at pH 7.4.

Calculate the shelf life at 25ºC.

$$\log\frac{k_2}{k_1}=\frac{-E_a}{2.303R}\left(\frac{1}{T_2}-\frac{1}{T_1}\right) \Rightarrow \log\frac{k_{25}}{k_{120}}=\frac{-22900}{(2.3)(1.987)}\left(\frac{1}{298}-\frac{1}{393}\right)$$

$$\frac{k_{25}}{k_{120}}=8.7\text{ x }10^{-5} \Rightarrow k_{25} = (8.7 \times 10^{-5})\,(9 \times 10^{-6}\text{ s}^{-1}) = 7.85 \times 10^{-10}\text{ s}^{-1}$$

$$t_{90}=\frac{0.105}{7.85\text{ x }10^{-10}\text{ s}^{-1}}=1.34\text{ x }10^{8}\text{ s} \Rightarrow \boxed{4.25\text{ years}}$$

TEMPERATURE EFFECTS

Example

The following rate constants were determined for 5-fluorouracil decomposition at pH 9.90.

t (ºC)	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 (25ºC) and determine the rate constant and shelf life at this temperature.

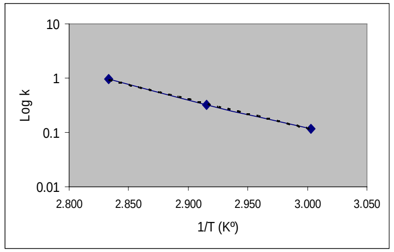
TEMPERATURE EFFECTS

Answer: (a) from the Arrhenius plot of the data we obtain

The slope

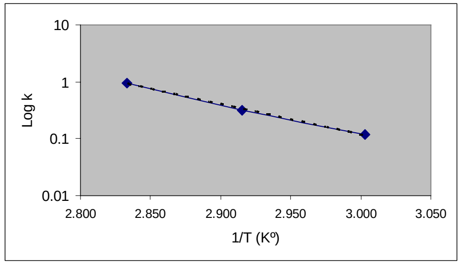
B= -12.31=Ea/R

Ea = 24.5 kcal/mol



TEMPERATURE EFFECTS

(b) From extrapolation of the graph to 25°C (1/T = 0.00335), we obtain log k25°C = -8.86. k25°C = 1.38 x 10-9 s-1
t90 = 7.6 x 107 s = 2.4 years



Note that Ea is always positive.

Q10-Value Calculations:

Consider the ratio of rate constants kT2/kTl at two temperatures T1 and T2. Consider T1=T2+10°

The quantity Q10 is defined as

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

The Q10 factor can be calculated from the next equation:

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

Q10-Value Calculations:

- ❑The activation energies for drug decompositions usually fall in the range 12 to 24 kcal/mol.
- ❑Next table gives values of Ea corresponding to three rounded values of Q10.
- ❑These values of Q10 = 2, 3, or 4 to represent low, average, and high estimates of Q10 when Ea is unknown

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

Q10-Value Calculations:

For an arbitrary change in temperature, ΔT = T2 - T1,

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

Q10-Value Calculations:

For an arbitrary change in temperature, ΔT = T2 - T1,

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

Multiplying the exponential term by

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

gives

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

Q10-Value Calculations:

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

$$= \exp\left[\frac{E_a}{R}\,\frac{10}{(T+10)(T)1}\right]^{[\Delta T/10][(T+10)/(T+\Delta T)]}$$

$$Q_{\Delta T} = Q_{10}^{\,[\Delta T/10][(T+10)/(T+\Delta T)]}$$

This equation is exact. However, since T ≈ 300K, (T + 10)/(T + ΔT) ≈ 1,

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

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) ΔT = +25,

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

= 5.7, 15.6, 32 for Q10 = 2, 3, 4, respectively

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

Q10-Value Calculations:

(b) a 25 to 0°C temperature change.

Answer:

ΔT = -25,

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

= 1/5.7, 1/15.6, 1/32 for Q10 = 2, 3, 4, respectively

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

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.

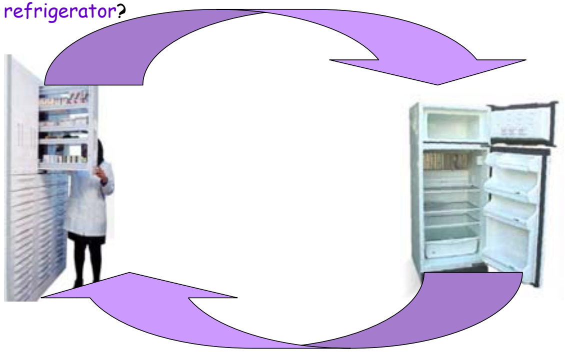
Example: Using Q10 = 2, 3, 4, calculate the half-life change from 70°C to 25°C for methyl paraben at pH 4.
We have ΔT = 25 - 70 = -45,
Q-45= 1/23, (Q10=2)
Q-45= 1/140, (Q10=3)
Q-45= 1/512, (Q10=4)

Since k70°C = 1.6 x 10-6 s-1 (from the monograph) then
t½ (70°C) = 4.3 x 107 s = 501 days

t½ (25°C) = 31 yr (Q =2)
= 199 yr (Q = 3)
= 709 yr (Q = 4)

SHELF-LIFE ESTIMATION METHODS

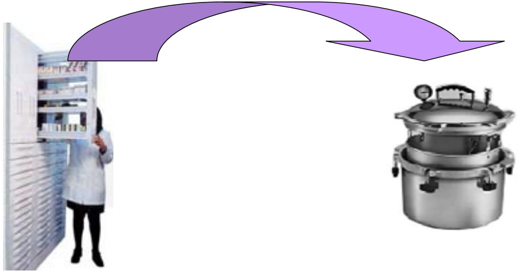
The expiration date is given for room temperature. What is the expected extension of the shelf life in a refrigerator?



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

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 Ea values available, we use the Q10 values of 2, 3, and 4 to make such estimates.

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

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

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 t90(T2) is independent of the order.
a positive ΔT (T2 > T1) reduces the shelf life,
a negative ΔT(T2 < T1) increases it.

SHELF-LIFE ESTIMATION METHODS

- *Example A.*

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.

ΔT = -20ºC,

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} \Longrightarrow t_{90}(5^o) = \frac{18}{Q_{10}^{(-20/10)}}$$

t90 (5ºC) = 18 * 2^2 = 72 h (Q = 2)
= 18 *3^2 = 162 h (Q = 3)
= 18 * 4^2 = 288 h (Q = 4)

conservative estimate would be 72 h and a likely estimate 162 h.

SHELF-LIFE ESTIMATION METHODS

- *Example B.*

A newly reconstituted product is labeled to be stable for 24 h in a refrigerator. What is the estimated shelf life at room temperature?

t90 (5ºC) = 24 h

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} \Longrightarrow t_{90}(25^o) = \frac{24}{Q_{10}^{(20/10)}}$$

t90 (25ºC) = 24/4 = 6 h (Q = 2)
= 24/9 = 2.7 h (Q = 3)
= 24/16 = 1.5 h (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.

SHELF-LIFE ESTIMATION METHODS

If the product has been stored for a known length of time at another temperature:

1. compute the time interval at the specified temperature that would give the equivalent decomposition to that which occurred at the actual storage temperature and
2. subtract this value from or add it to the label date for a new expiration date.

SHELF-LIFE ESTIMATION METHODS

Example

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?

Answer

One month at room temperature would be equivalent to

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} \rightarrow \quad t_{90}(T_2) \cdot Q_{10}^{(\Delta T/10)}$$

1 $*2^2$ = 4 months	(Q = 2)
1 $*3^2$ = 9 months	(Q = 3)
1 $*4^2$ = 16 months	(Q = 4)

that is, 4, 9, or 16 months at 5ºC.

The most likely estimate is 9 months, hence if the product is returned to the refrigerator, only 3 months would be left.

SHELF-LIFE ESTIMATION METHODS

Example.

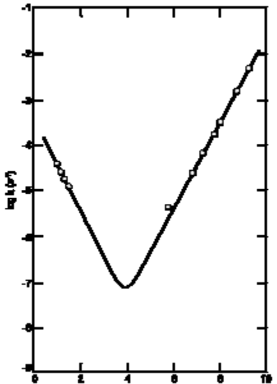
The ampicillin monograph in the *Physicians' Desk Reference* (1) states that the reconstituted suspension is stable for 14 days in a refrigerator. If the product is left at room temperature for 12 h, what is the reduction in the expiration period?

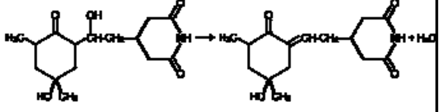
$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} \rightarrow \quad t_{90}(T_2) \cdot Q_{10}^{(\Delta T/10)}$$

0.5 $* 2^2$ = 2 days	(Q = 2)
0.5 $* 3^2$ = 4.5 days	(Q = 3)
0.5 $* 4^2$ = 8 days	(Q = 4)

The expected reduction is thus 4.5 days.

Influencia del pH

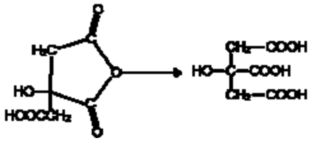


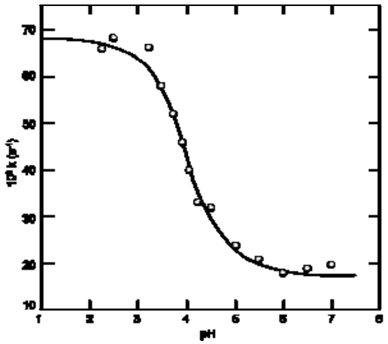


Example:pH-Rate profile for the dehydration of streptovitacin A at 70°C

Influencia del pH

Example1





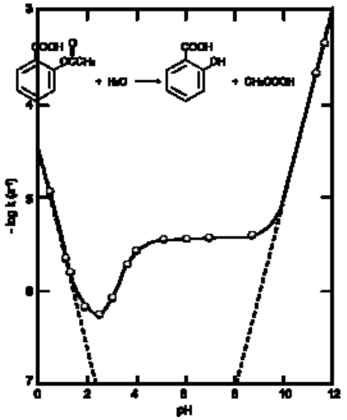
pH-Rate profile for hydrolysis of citric acid anhydride at 25°C

D. pH EFFECTS (2). Sigmoid Curves

Example2: Hydrolysis of aspirin.

where k3 > kl and k" > k'.
The rate equation is

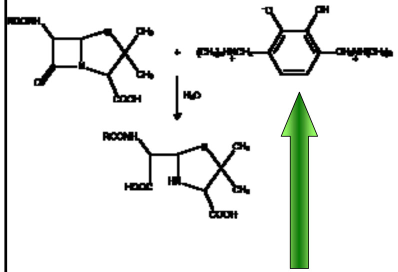
rate = k1[RCOOH][H+] + k'[RCOOH] + k"[RCOO-] + k3[RCOO-][OH-]
The pKa of aspirin is 3.6, so the plateau region of the curve (pH 4 to 8) is accounted for primarily by the k" term, that is, hydrolysis of the anion. This reaction is responsible for the instability of aspirin in solution dosage forms

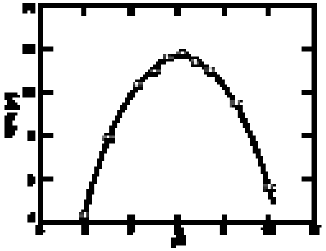


pH-Rate profile for aspirin hydrolysis at 25°C

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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Vías de degraddación química

- Hidrólisis
- Oxidación
- Racemización
- Descarboxilación
- Polimerización
- Descomposición enzimática

Inhibición de la oxidación

- Proteger de la luz
- Evitar presencia oxígeno
- Uso agentes antioxidantes

Antioxidantes sistemas hidrófilos

- Combinaciones inorgánicas de azufre: sulfitos (olor y sabor desagradables)
- Combinaciones orgánicas de azufre: (olor y sabor desagradables)
- Ácido ascórbico: tópicas, 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, citríco, 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.