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Buffered solutions

Introduction

- Buffers are mixtures of compounds that resists changes in pH upon the addition of small quantities of acid or alkali. التغيير موجود لسا بس اقل من لما ما يكون فيه buffer
- A buffer is composed of a weak acid (HA) and its salt (conjugate base A^-) or a weak base (B) and its conjugate acid BH^+.

Which of the following can form a buffer?

إذا أعطاك:

- $HCl + NaCl$ ❌
- $CH_3COOH + CH_3COONa$ ✅
- $NaOH + NaCl$ ❌
- $NH_3 + NH_4Cl$ ✅

Acid + base ⟶ Acid + base
Conj base   Conj acid

$CH_3COONa + CH_3COOH$

Salt + its weak acid = acidic buffer

Salt + its weak base = basic buffer

Buffer Equation

The pH of a buffer solution can be calculated by use of the *buffer equation*.

E.g. When sodium acetate ($NaAc$) is added to acetic acid (HAc), the salt and the acid have an ion in common.

Salt

weak acid

$HAc \leftrightarrow H_3O^+ + Ac^-$ لانه ضعيف يتأين جزئياً يعني تركيزه عند التأين قليل لذلك نهمل تركيز $[Ac^-]$

$NaAc \rightarrow Na^+ + Ac^-$ يتفكك بالكامل فيعطي تراكيز عالية

$HAc + H_2O \rightleftharpoons H_3O^+ + Ac^-$

التفاعل للحمض

بس اذا ضفنا ملح بزيد تركيز Ac^-

بالتالي ولانه تفاعل بسهمين رح تيغير التوازن يحاول يقلل Ac^-

$HAc + H_2O \rightleftarrows H_3O^+ + Ac^-$

K_a for the weak acid is momentarily (اللحظة) disturbed because the Ac^- supplied by the salt increases the $[Ac^-]$ term in the numerator:

$$K_a = \frac{[H_3O^+][Ac^- \uparrow]}{[HAc]}$$

ال Ka لحمض ضعيف

في محلول

Buffer Equation

To reestablish the constant K_a , $[H_3O^+]$ is instantaneously decreased, by shifting the equilibrium in the direction of the reactants (the ionization of acetic acid is repressed).

$$\uparrow (HAc + H_2O) \leftarrow (H_3O^+ + Ac^-) \downarrow$$

معادلة ال Ka للحمض + الملح المتأين

$$K_a = \frac{[H_3O^+ \downarrow][Ac^- \uparrow]}{[HAc]}$$

زادت من الملح

بينما هي بتقل من الحمض

Since weak acid is slightly ionized, $[HAc]$= [total acid concentration]

Since the salt is completely ionized, $[Ac^-]$ = [total salt concentration]

$$K_a = \frac{[H_3O^+][Salt]}{[acid]}$$

لانه $[Ac^-]$

من الحمض تهمل

لانها صغيرة

By rearranging the equation and using the logarithmic form:

$$pH = pKa + log\frac{[salt]}{[acid]} \quad \begin{matrix}[A^-]\\ [HA]\end{matrix}$$

Buffer Equation

The previous equation is known as the *buffer equation* or the *Henderson–Hasselbalch equation.*

For a weak acid (HA) and its salt (S):

$$pH = pKa + log\frac{[S]}{[HA]}$$

For a weak Base (B) and its salt (S):

$$pH = pKa + log\frac{[B]}{[S]}$$

Buffer Equation

Example

What is the pH of a buffer solution containing 0.1 M acetic acid and 0.1 M sodium acetate?

$$pH = pKa + log\frac{[S]}{[HA]}$$

$$pH = 4.76 + log\frac{[0.1]}{[0.1]} = 4.76$$

Buffer Equation

Example

How many moles of sodium acetate must be added to 100 mL of a 0.1 mol/L acetic acid solution to prepare a buffer with pH 5.2?
(Assume no volume change upon addition.)

•**Given:**

•pH = 5.2, pKa = 4.76

•[HA] = 0.1 mol/L, Volume = 100 mL = **0.100 L**

$$5.2 = 4.76 + \log \frac{[S]}{0.1}$$

$$[S] = 0.1 \times 10^{(5.2-4.76)} = 0.1 \times 10^{0.44} = 0.2754\,\mathrm{mol/L}$$

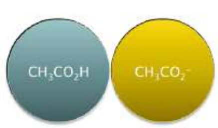
$$\text{Moles of sodium acetate} = 0.2754\,\mathrm{mol/L} \times 0.100\,\mathrm{L} = \mathbf{0.02754\,mol}$$

Buffer capacity سببها وجود **كلا المكونين**:

HA/A^-

- A^- يتعامل مع H^+.
- HA يتعامل مع OH^-.
- لا يتغير pH بشكل كبير لذلك.

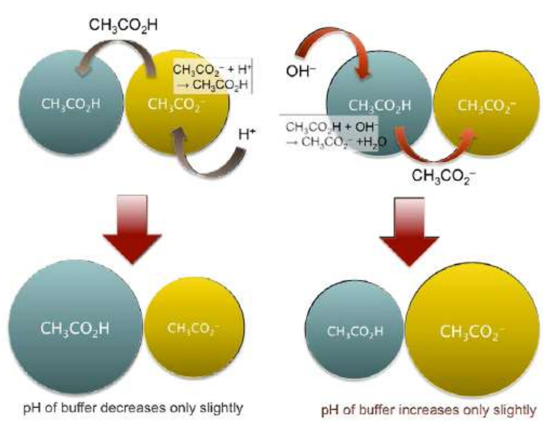
Buffer Capacity



A weak acid and its conjugate base have buffering capacity because A^- ions remove the added H^+ as undissociated weak acid, while HA remove the added OH^- ions as water:

$A^- + H_3O^+ \rightarrow H_2O + HA$ ← اذا انضاف acid بتحول معظمة لماء و base

$HA + OH^- \rightarrow H_2O + A^-$ ← اذا انضاف base بتحول معظمة لماء وحمض



Buffer Capacity

A weak base and its conjugate ~~base~~ acid have buffering capacity because B ions remove the added H^+ as undissociated weak acid, while BH^+ remove the added OH^- ions as water:

w.b Conj. A

$$B + H_3O^+ \rightarrow H_2O + BH^+$$

$$BH^+ + OH^- \rightarrow H_2O + B$$

Buffer capacity is (the quantity of strong acid or base that can be added to change the pH of one **liter** of buffer solution by one pH unit.)

للـ basic buffer:

$$B + H_3O^+ \rightarrow BH^+ + H_2O$$

$$BH^+ + OH^- \rightarrow B + H_2O$$

و:

$\beta = \text{buffer capacity}$

وهي مقدار strong acid/base المطلوب لإحداث تغير pH مقداره 1 لكل liter.

Buffer Capacity

اسماء علماء ← (Koppel and Spiro and Van Slyke) devised an approximate equation for calculating buffer capacity (β):

معادلة مرجحة لكنها غير دقيقة

$$\beta = \frac{\Delta B}{\Delta pH} \qquad \frac{\frac{mol}{L}}{pH} = mol \cdot L^{-1} \cdot pH^{-1} = \frac{mol}{L\,pH}$$

ΔB: number of moles of strong acid or base per liter of buffer.

ΔpH: change in pH.

When one of the buffer components is depleted (ينفد) completely, the solution lose its buffering capacity and can no longer resist the change in pH

$$\beta = \frac{\Delta B}{\Delta pH}$$

و:

- β كبيرة → buffer أقوى.
- β صغيرة → buffer أضعف.
- إذا انتهى أحد مكونات buffer → تفقد الـ buffering capacity.

المعادلة الدقيقة:

$$\beta = 2.3C\frac{K_a[H_3O^+]}{(K_a + [H_3O^+])^2}$$

حيث:

$$C = [Acid] + [Salt]$$

و:

$$[H_3O^+] = 10^{-pH}$$

وأعلى buffering capacity تكون عند:

$$pH = pKa$$

Buffer Capacity

Koppel and Spiro and Van Slyke developed a more exact Equation for calculating buffer capacity:

معادلة دقيقة ←

$$\beta = 2.3C\frac{K_a[H_3O^+]}{(K_a + [H_3O^+])^2}$$

$C = [AH] + [A^-]$

$[Acid] + [Salt]$

C is the total buffer concentration (the sum of the molar concentrations of the acid and the salt).

This equation allows the calculation of buffer capacity at any pH (even when no acid or base has been added to the buffer).

The equation shows that an increase in the concentration of the buffer components (C) results in a greater buffer capacity (β).

⭐ استنتاج مهم جدًا للامتحان

عندما:

$$[H_3O^+] = K_a$$

$[OH^-] = K_b$

فإن:

$$pH = pKa$$

أو $[salt = acid]$

وفي هذه الحالة تكون الـ buffer capacity عند **أعلى قيمة**.

والسبب من المعادلة نفسها:

$$\beta = 2.3C\frac{K_aK_a}{(K_a + K_a)^2}$$

$$= 2.3C\frac{K_a^2}{4K_a^2}$$

$$\beta = 0.575C$$

وهذا يحدث عندما يكون:

$$[HA] = [A^-]$$

أي تقريبًا:

$$pH = pKa$$

$\beta \propto C$

العلاقة بين β و بين $[H_3O^+]$ وال Ka مش طردية ولا عكسية انما كل ما قربت نسبتهم من 1 $\frac{salt}{acid}$ بتزيد β

Buffer Capacity

At a hydrogen ion concentration of 1.75 × 10^{-5}, what is the capacity of a buffer containing 0.10 mole each of acetic acid and sodium acetate per liter of solution? (Ka = 1.75 × 10^{-5})

C = [Acid] + [Salt] = 0.1+ 0.1 = 0.20 mole/liter

$$\beta = 2.3C\frac{K_a[H_3O^+]}{(K_a + [H_3O^+])^2}$$

$$\beta = 2.3 \times 0.2 \times \frac{(1.75 \times 10^{-5})(1.75 \times 10^{-5})}{[(1.75 \times 10^{-5}) + (1.75 \times 10^{-5})]^2} = 0.115\ mol/L$$

Buffer Capacity

The buffer capacity depends on:

(a) the value of the ratio [Salt]/[Acid], (buffer capacity increases as the ratio approaches 1)

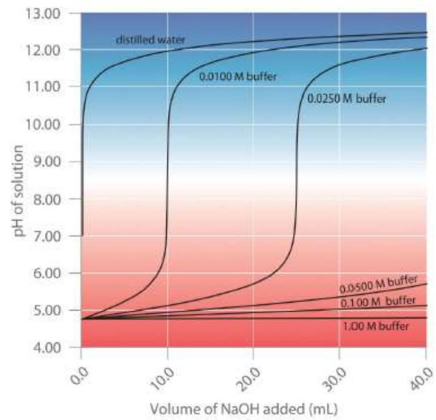
لو عنا مثالين الثنين نسبة $\frac{salt}{acid}=1$

بس واحد قيمتهم اعلى من الثاني

المرة الي قيمتهم كانت اعلى ال β بتكون

اعلى

(b) the magnitude of the individual concentrations of the buffer components (buffer capacity increases as the salt and acid concentrations are increased).

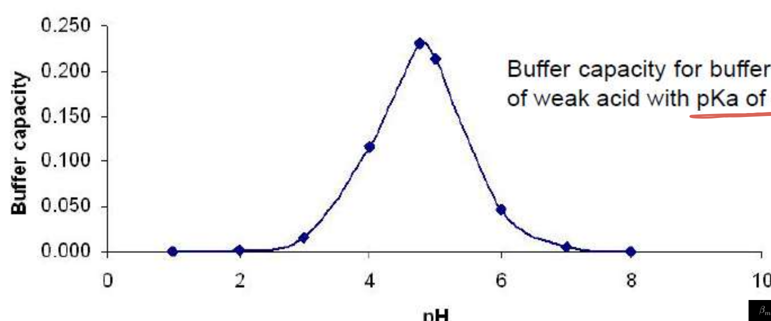


Buffer Capacity

The maximum buffer capacity occurs where pH = pK_a, or, in equivalent terms, where $[H3O+] = K_a$.

$$\beta_{max} = 0.576\ C$$

Where C is the total buffer concentration



$\beta_{max} = 0.576C$

والـmaximum يحدث عندما:

$pH = pK_a$

و:

$[Acid] = [Salt]$

Buffer Capacity

Example

What is the maximum buffer capacity of an acetate buffer with a total concentration of 0.020 mole/liter?

$$\boldsymbol{\beta_{max} = 0.576\ C}$$

$$\beta_{max} = 0.576 \times 0.02 = 0.012 \text{ Mol/liter}$$

Buffer in Biological Systems

Some body fluids have natural buffer capacity:

1. pH of tears is 7-8 with higher buffer capacity so that a reasonably wide pH range of medicines can be tolerated.
2. pH of blood is maintained at approximately 7.4 by buffer component in the plasma (bicarbonate and phosphate buffers) and erythrocytes (hemoglobin and phosphate buffers).

$H_2CO_3 \leftrightarrow HCO_3^- + H^+$

$H_2PO_4 \leftrightarrow HPO_4^{2-} + H^+$

$HbH^+ + O_2 \leftrightarrow + O_2Hb + H^+$

Hb: hemoglobin, O_2Hb: oxyhemoglobin

Pharmaceutical Buffers

Buffer solutions are widely used to adjust pH of aqueous pharmaceutical solutions to ensure:

1. • Prevention of tissue irritation
2. • Optimum therapeutic effect
3. • Maximum drug stability
4. • Maximum drug solubility

Pharmaceutical Buffers

Tissue Irritation Prevention

حساس

- Solutions to be applied to delicate tissues (e.g. eye) or administered parenterally are liable to cause irritation if their pH is greatly different from the normal pH of the relevant body fluid.
- If there is a large pH difference between the solution and body fluid, tissue irritation will be minimal if:
  - The volume and buffer capacity of the solution is low

لما سعة البفر بالدواء تكون قليلة بسرعة
بتخلص والدواء بصير ال pH تبعه نفس
ال pH للجسم وهاد المطلوب عشان ما يضر الجسم

  - The volume and buffer capacity of the physiologic fluid is high.

عشان ما تخلص بسرعة وتقدر تستوعب
تغيرات ال pH من الدواء

حتى نقلل irritation:

Drug → low volume + low buffer capacity

Body fluid → high volume + high buffer capacity

باختصار اللي بخلص السعة اله اول بخسر السيطرة على ال PH

عشان الدواء يكون stable
الافضل المادة تكون على شكل ملح
بدل الايونات اللي ممكن تتفاعل
بس عشان تكون ال Solubility للدواء
افضل لازم يكون Polar بالتالي مش
بشكل ال Salt
لازم يكون مفكوك يعني ايونات
بس هاد يعني انه ال PH رح تبعد عن ال 7
لانه الايونات غالبًا هي حمضية او قاعدية
بالتالي هاد سيئ الجسم لانه ممكن يعمل irritation

الحل انه نخلي المادة مستقرة بس نخلي
ال Capicity للدواء قليلة بحيث اول ما تدخل
الجسم بسهولة تتفكك
ولما تتفكك بتصير Polar يعني اكثر فعالية

Pharmaceutical Buffers

Maximum Therapeutic Effect vs Stability

- The undissociated form of a weakly acidic or basic drug often has a higher therapeutic activity than that of the dissociated salt form because they can penetrate body membranes readily due to their lipid solubility.
- The pH for maximum stability of a drug for ophthalmic use may be far below that of the optimum physiologic effect.
- Under such conditions, the solution of the drug can be buffered at a low buffer capacity and at a pH that is between that of optimum stability and that for maximum therapeutic action.
- When the solution is instilled in the eye, the tears bring the pH to about 7.4, converting the drug to the physiologically active form

Pharmaceutical Buffers

Maximum Therapeutic Effect vs Stability

EXAMPLE 8-10

Mole Percent of Free Base

The pK_b of pilocarpine is 7.15 at 25°C. Compute the mole percent of free base present at 25°C and at a pH of 7.4. We have

$$\underset{\text{Pilocarpine base}}{C_{11}H_{16}N_2O_2} + H_2O \rightleftharpoons \underset{\text{Pilocarpine ion}}{C_{11}H_{16}N_2O_2} + OH^-$$

$$pH = pK_w - pK_b + \log\frac{[\text{Base}]}{[\text{Salt}]}$$

$$7.4 = 14.00 - 7.15 + \log\frac{[\text{Base}]}{[\text{Salt}]}$$

$$\log\frac{[\text{Base}]}{[\text{Salt}]} = 7.40 - 14.00 + 7.15 = 0.55$$

$$\frac{[\text{Base}]}{[\text{Salt}]} = \frac{3.56}{1}$$

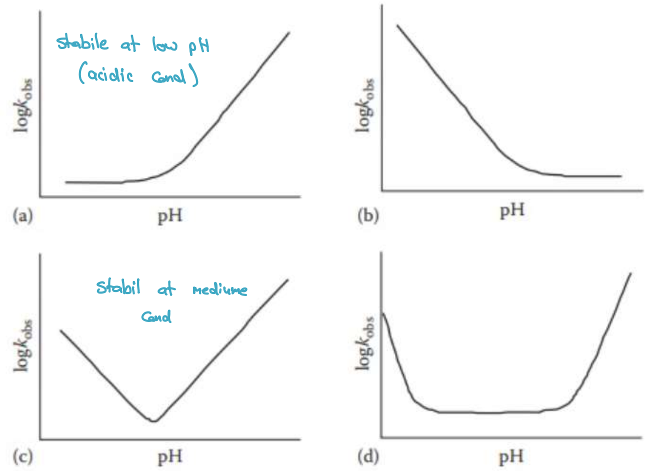
$$\text{mole percent of base} = \frac{[\text{Base}]}{[\text{Salt}] + [\text{Base}]} \times 100$$

$$= [3.56/(1 + 3.56)] \times 100 = 78\%$$

Pharmaceutical Buffers

pH stability profile

- Acid degradation → stability أفضل عند pH أعلى.
- Base degradation → stability أفضل عند pH أقل.
- Both acid + base degradation → أفضل stability في منطقة وسطية.



Typical pH stability profiles. Examples of pH—stability profiles for a drug that degrades under basic (a), acidic (b), or both acidic and basic conditions (c and d).

Pharmaceutical Buffers

Maximum Solubility

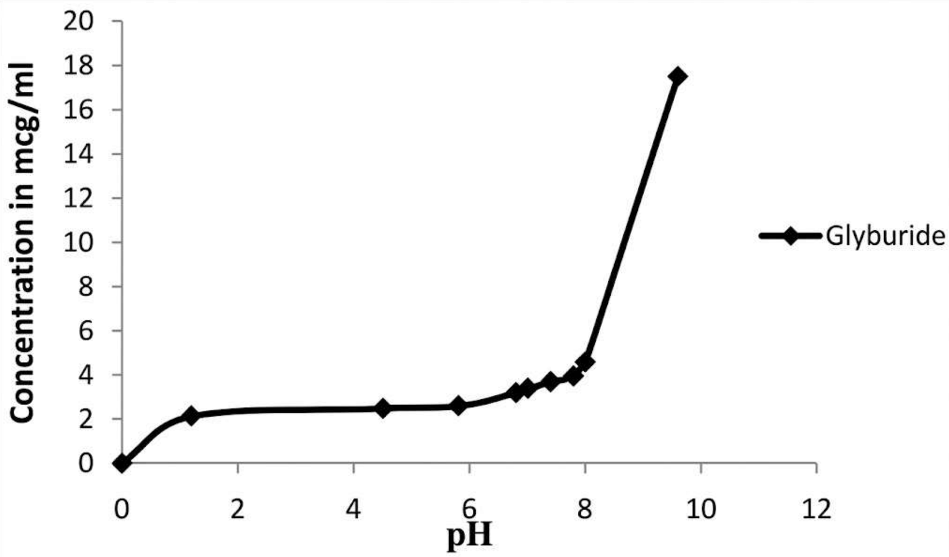
acid → water Soluble polar

base → organic Soluble non polar ~ unionized

- The pH of the solution can affect the solubility of the drug.
- At a low pH, a base is predominantly in the ionic form, which is usually very soluble in aqueous media.
- As the pH is raised, more undissociated base is formed, which has poor water solubility, leading to precipitation of this form from solution.
- Therefore, the solution should be buffered at a sufficiently low pH so that the concentration of the free base is less than its solubility.

Pharmaceutical Buffers

pH Solubility profile



إذا الدواء يذوب
بسوائل non polar

Pharmaceutical Buffers

- The pharmacist may be called upon at times to prepare buffer systems for which the formulas do not appear in the literature.
- The following steps should be helpful in the development of a new buffer.

(*a*) Select a weak acid having a p*K*a approximately equal to the pH at which the buffer is to be used.

(*b*) From the buffer equation, calculate the ratio of salt and weak acid required to obtain the desired pH. The buffer equation is satisfactory for approximate calculations within the pH range of 4 to 10.

$$PH = PKa + \log \frac{Salt}{Acid}$$

Pharmaceutical Buffers

(*c*) Consider the individual concentrations of the buffer salt and acid needed to obtain a suitable buffer capacity.

- A *concentration* of 0.05 to 0.5 M is usually sufficient, and a *buffer capacity* of 0.01 to 0.1 is generally adequate.

(*d*) Other factors of some importance in the choice of a pharmaceutical buffer include:

- availability of chemicals,
- sterility of the final solution,
- stability of the drug and buffer on aging,
- cost of materials,
- freedom from toxicity (borate buffer, cannot be used to stabilize a solution to be administered orally or parenterally.)

(*e*) Finally, determine the pH and buffer capacity of the completed buffered solution using a reliable pH meter.

عند عمل pharmaceutical buffer:

1. اختاري $pK_a \approx desired\ pH$
2. احسبي Salt/Acid ratio
3. اختاري concentrations مناسبة
4. راعي availability, sterility, stability, cost, toxicity
5. **قيسي pH النهائي بالـpH meter**