لجان الدفعات

PHYSICAL PHARMACY

MORPHINE ACADEMY

م الهدف من ال Buffer : مقاومة التغير بال pH.

Buffered solutions

له قاعدة ضعيفة + حمضها المرافق.

له حمض ضعيف + قاعدته المرافقة.

Introduction

- Buffers are mixtures of compounds that resists changes in pH upon the addition of small quantities of acid or alkali.
- 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^+.

ليش بضيف ملح مو قاعدة مرافقة بشكل مباشر؟ انه ليش ضفت مع weak acid ملح ال weak acid؟ ليش ما ضفت مع weak acid القاعدة المرافقة تبع ال weak acid؟

لأنه هذا الحمض تأينه ضعيف أساسًا بالتالي كمية القاعدة المرافقة اللي راح ينتجها جدًا بسيطة. بالتالي انا شو راح أضيف مع هذا الحمض؟ ملح هذا الحمض اللي بتكون من القاعدة المرافقة لهذا الحمض مع حمض مرافق لأي قاعدة ثانية

لذا مصدر القاعدة المرافقة هو ال salt.

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.

→ Ac^- → Ac^- → فعليا مصدرين لل conj. Base

$$HAc \leftrightarrow H_3O^+ + Ac^-$$

$$NaAc \rightarrow Na^+ + Ac^-$$

→ common ion.

كمياتهم متساوية بنفس المحلول.

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

ال K_a بتكون تغيرت بسبب Ac^- لأنه الها مصدرين: weak acid. salt (المختار الأكبر)

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

لكن هل هاي ال K_a راح تضل موجودة بهذا الشكل والمقدار؟ أكيد لا، لأنه لما يرتفع ال Ac^- راح يقل مقدار H_3O^+ بشكل كبير بسبب كمية ال Ac^- الكبيرة بالمحلول بالتالي بتفكك

→ $H_3O^+ \rightleftharpoons H_2O + H^+$ → Ac^- مباشرة رح ترتبط مع ويرجع لشكل HAc (Reacossiation) ⇐ هذا الأشي بيصير مباشرة انخفاض في مقدار H_3O^+ فبترجع ال K_a للوضع الطبيعي.

Buffer Equation

حكيناه

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). → Reacossiation.

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

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

لانها ثابتة لما تتأثر بتتأثر بشكل ضعيف فيادوب ما فرقت شيئا.

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

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

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

حكينا انه مصدره الأكبر من الملح لذا بنهمل الجزء المتأتي من الحمض.

By rearranging the equation and using the logarithmic form:

$$pH = pKa + log\frac{[salt]}{[acid]}$$

→ Base (conj. حتى لو) → Acid

اعتدنا بالسابق المحاضرة انه: سبا: قاعدة. مقام: حمض.

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 → HA and 0.1 M sodium acetate? → source of conj. Base.

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

$$pH = 4.76 + \underbrace{log\frac{[0.1]}{[0.1]}}_{0} = \boxed{4.76}$$

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**

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

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

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

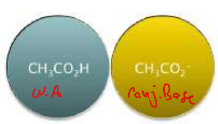
كيف يعني ؟

مقياس لقوة الـ Buffer soln في مقاومة التغير بالـ pH ، وبعض أدق
هو مقدار الحمض القوي او القاعدة القوية القادر على تغيير الـ pH لـ 1 liter من
الـ soln بمقدار 1 pH زيادة او نقصان.

يعني افرض انه عندك 1 liter من Buffer soln
الي مقدار pH = 6 ، كم مقدار الـ S.A الي
انت لازم تضيفه على 1 liter عشان ينزل الـ pH
من 6 ← 5 ؟ او كم مقدار الـ S.B الي المفروض
تضيفها على محلول 1 liter حتى ترتفع الـ pH من
6 ← 7 ؟

كلما زادت كمية الـ S.A او الـ S.B عشان
تقدر تغير الـ pH تبعت الـ Buffer soln ← يعني
انه مقاومة الـ Buffer soln للتغير بالـ pH راح
تكون أكبر وأكبر.

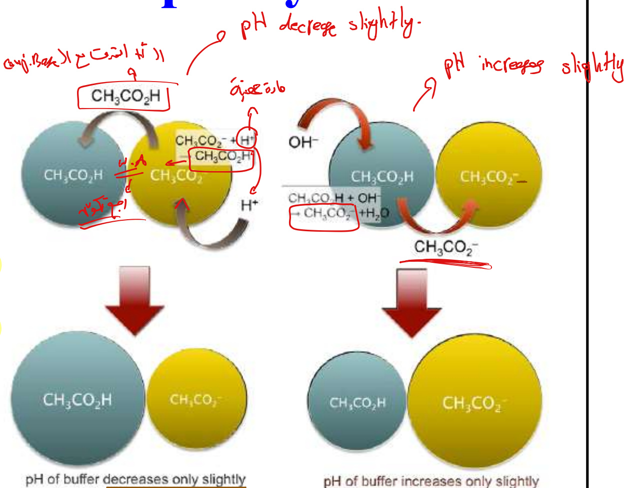
Buffer Capacity



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:

$A^- + H_3O^+ \rightarrow H_2O + HA$

$HA + OH^- \rightarrow H_2O + A^-$



* A^- removes added H^+
* HA removes added OH^-

} weak Acid Buffer

\# B removes added H^+
\# BH^+ removes added OH^- } weak Base Buffer.

Buffer Capacity

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

Buffer soln.

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

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

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.

نقصان او زيادة

النوع	يمسك H^+	يمسك OH^-
HA/A⁻	A⁻	HA
B/BH⁺	B	BH⁺

Buffer Capacity

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

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

ΔB → عدد المولات من S.A او S.B التي انت ضفتهم للمحلول.

ΔpH → مقدار التغير بال pH بعدما انت ضفت ال S.A او S.B

$\boldsymbol{\Delta B}$: number of moles of strong acid or base per liter of buffer.

$\boldsymbol{\Delta pH}$: change in pH.

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

AH ⇌ A⁻ ← H⁺ H⁺ H⁺ H⁺

Reassociation

A⁻ تجمع

حالياً اضفنا كمية لحد ما استهلاك كل ال A⁻ ، وكل ال A⁻ تحولت لـ HA { خرب ال Buffer capacity

لذا كمية ال H⁺ الزائدة الي تتفاعل مع H₂O وتكون H_3O^+ ، وال H_3O^+

بأثر على pH المحلول فتنزل ال pH

ملاحظة ضرورية

ΔB↑ → β↑

ان ال Buffer capacity ال عالية.

لعاذا ضفت كمية كبيرة من S.A وما تغير pH

المحلول فتش لعند ال pH الا بشكل بسيط

يعني

Buffer Capacity

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

عف ومقاومة الرافقة. ⟵ [[S]+[HA]]

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

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).

$\beta \propto C$

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

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

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

يعني مقاومة الـ Buffer للاضطرابات تقل

كلما كانت النسبة بينهم اقل من 1 يعني انه درجة الـ Buffer soln ع انه يقاوم DPH من ناحية معينة راح تبقى أقل

Buffer Capacity

The buffer capacity depends on:

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

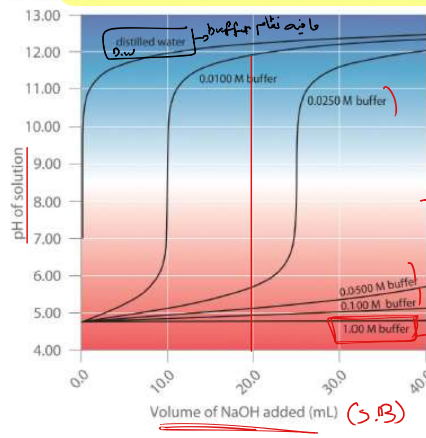
عندما كانت $\frac{[S]}{[AH]}$ اقتربا الى 1 فإن β اعلى.

يعني $[S] = [HA]$

أي $A^- = HA$

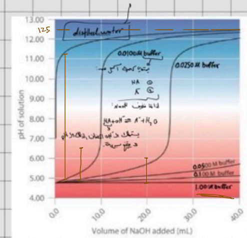
الـ soln راح يكون الها قدرة في انه يحافظ على pH من انها تتغير

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



كلما زدت تركيز الـ Buffer soln صار التغير بالـ pH مرة قليل

الـ pH ثابتة تقريباً



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

$-\log K_a = -\log [H_3O^+]$

$pK_a = pH$ } This is the maximum buffer capacity.

Buffer Capacity

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

$[H_3O^+] = K_a$

$-\log[H_3O^+] = -\log K_a$

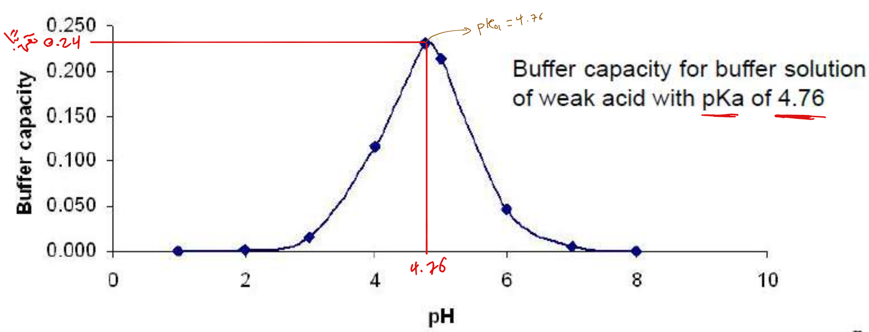
$$\beta_{max} = 0.576\,C$$

Where C is the total buffer concentration

$K_a = \frac{[H_3O^+][A^-]}{[HA]}$ salt

متى $[H_3O^+] = K_a$ ؟

لما تكون قيمة $1 = \frac{[A^-]}{[HA]}$



Buffer capacity for buffer solution of weak acid with pKa of 4.76

Buffer Capacity

Example

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

$\beta_{max} = 0.576\,C$ ([S] + [A])

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

يعني انت محتاج هالقد حتى ترفع الـpH او تقلله بمقدار 1.

Buffer in Biological Systems

Some body fluids have natural buffer capacity:

لذا العين بتتحمل range اكبر من الادوية.

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).

(in plasma) Bicarbonate buffer ← $H_2CO_3 \leftrightarrow HCO_3^- + H^+$ → $\frac{[HCO_3^-]}{[H_2CO_3]}$ → $pH \approx 7.4$

(in plasma + erythrocytes) phosphate buffer ← $H_2PO_4^- \leftrightarrow HPO_4^{2-} + H^+$ → $\frac{[HPO_4^{2-}]}{[H_2PO_4^-]}$

(in erythrocytes) RBCs ← $HbH^+ + O_2 \leftrightarrow + O_2Hb + H^+$

Hb: hemoglobin, O_2Hb: oxyhemoglobin

ملاحظة:

$H_2CO_3 \rightleftharpoons HCO_3^- + H^+$ هذا هو الـBuffer

then $HCO_3^- \rightleftharpoons CO_3^{2-} + H^+$

بتحتوي ع تأيين ثاني بس مش مهم. Ka₂ ($Ka_2 < Ka_1$:لانه اقل)

$H_3PO_4 \rightleftharpoons H_2PO_4^- + H^+$

$H_2PO_4^- \rightleftharpoons HPO_4^{2-} + H^+$ → هذا هو الـBuffer

$HPO_4^{2-} \rightleftharpoons PO_4^{3-} + H^+$

Pharmaceutical Buffers

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

- Prevention of tissue irritation
- Optimum therapeutic effect
- Maximum drug stability
- Maximum drug solubility

للأشياء اللي بيتغير عنا لما اضافنا ع pH.

لكن اذا بنلاحظ فال لـ buffer يُستخدم من اجل تغيير pH الجسم بشكل كامل 98 الجسم محافظا ع pH ثابت بواسطة انظمة الضبطية.

natural physiological pH of the body.

Pharmaceical Buffers

Tissue Irritation Prevention

الأنسجة الحساسة.

- 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.

ومقدار التهيج راح يتناسب مع ΔpH ((طرديًا)).

ΔpH

- If there is a large pH difference between the solution and body fluid, tissue irritation will be minimal if:

drug

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

body

كلما كانت كمية الدوى أكبر ← كلما زادت قدرة الجسم ع انها تعادل ال pH تبعت ال soln.

باختصار: حتى أقلل ال irritation اللي بيصير لما اعطي soln معين ع Body fluid ⇐ بزيد ال β والحجم تبع هذا ال Body fluid وبقلل ال β والحجم تبع هذا ال soln اللي بدي أضيفه عال Body fluid.

Pharmaceutical Buffers

Maximum Therapeutic Effect vs Stability

هدول العاملين مش ممكن تواجدهم سوا بنفس الدوا.

لذا بنوفق حل وسط: بنوفق pH تكون وسط بين pH الـ therapeutic effect و الـ pH المناسبة لل 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.

الـ unionized form الها تأثير علاجي أكبر من الـ ionized form لأنه بتخترق الـ cell membrane لأنه lipid soluble.

∴ undissociated form → better penetration → ↑ Activity.

- 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

Eye drops should have low buffer capacity to allow tears to adjust the pH.

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

unionized form.

$$C_{11}H_{16}N_2O_2 + H_2O \rightleftharpoons C_{11}H_{16}N_2O_2^{+} + OH^-$$

Pilocarpine base — Pilocarpine ion

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

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

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

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

1s → 3.56 B

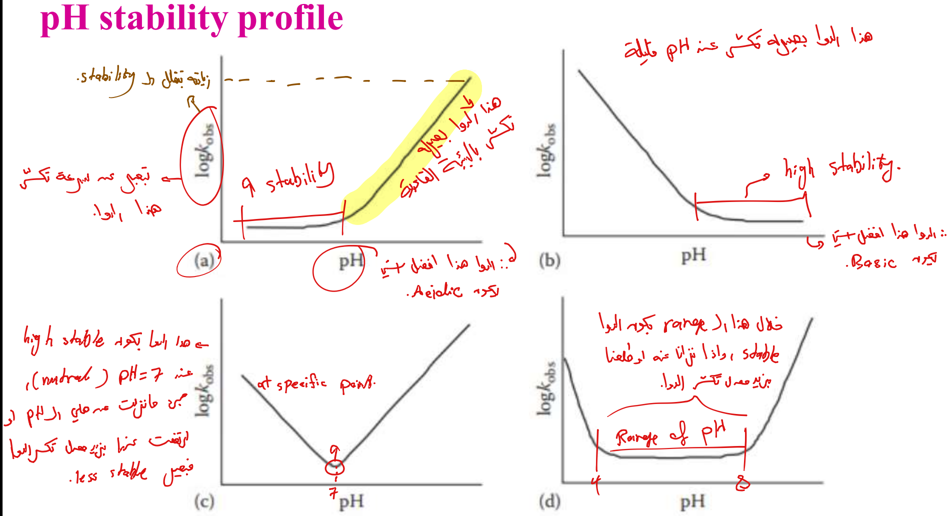
$$\text{mole percent of base} = \frac{[Base]}{[Salt] + [Base]} \times 100$$

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

$\frac{B}{S+B} = \frac{3.56}{1+3.56} = 0.78 \times 100\% = 78\%$

Pharmaceutical Buffers

pH stability profile



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).

Rate of degradation $\frac{1}{\alpha}$ stability.

* اذا كان الدوا بيتحلل بـ basic degradation : $pH\uparrow \Rightarrow [OH^-]\uparrow \Rightarrow$ Rate of Degradation$\uparrow$

* اذا كان الدوا بيتحلل بـ acidic degradation : $pH\downarrow \Rightarrow [H^+]\uparrow \Rightarrow$ Rate of Degradation$\uparrow$

: at ionized state soluble in water

: at unionized state soluble in lipid

لأنه like dissolves like

Pharmaceutical Buffers

Maximum Solubility

- 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.

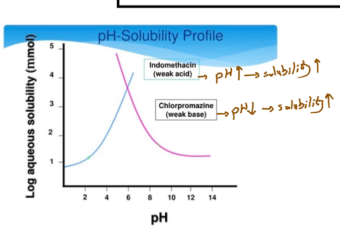
At weak base: $pH\downarrow \rightarrow$ solubility$\uparrow$

لذا غالبا الدوا بتحول لل ionic form

At weak acid: $pH\uparrow \rightarrow$ solubility$\uparrow$

لأنه ما بذوب

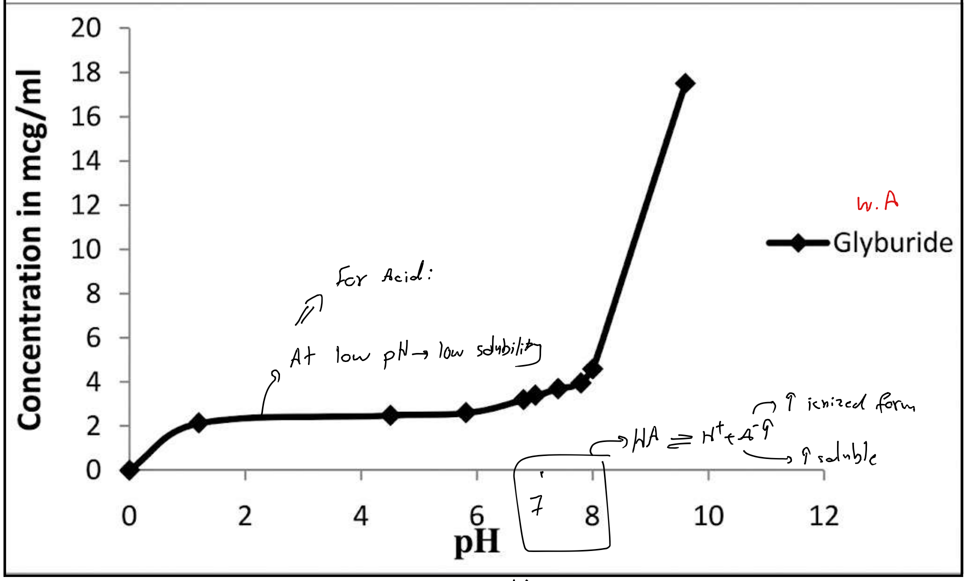
free → unionized form has low solubility



زي مثلاً مي بتذوب 5mg بس من ال Free base ،
فإذا كانت كمية Free base < 5 راح يذوب تماماً واذا
كان Free base > 5 راح يترسب جزء منه ، طيب اذا
هو اصلا اكبر من 5 شو الحل ؟ قلل ال pH حتى يتحول للشكل المتأين
فيصير تركيز BH+ اكبر وتركيز Free B قليل فيذوب تماماً .

Pharmaceutical Buffers

pH Solubility profile



Acidic Basic

اذا بدنا نحضر Buffer جديد

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:

maximum β عشان تعطي ← ***(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.

$$pH = pKa + \log \frac{[salt]}{[acid]}$$

لما المعادلة صحيحة اذا بدي افضل Buffer لل pH بـ Range (4 to 10)

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, هل المواد متوفرة ؟
- sterility of the final solution,
- stability of the drug and buffer on aging, هل راح يضلوا ثابتين مع الوقت؟
- cost of materials,
- freedom from toxicity (borate buffer, cannot be used to stabilize a solution to be administered orally or parenterally.)

يعني لازم المادة تكون مقاومة لل microbs

المحاليل التي ال pH تبعها =7 راح تكون محاليل ملائمة microbs لأنه ال microbs بتحب بيئة الماء والي لا pH ال =7 .

حقن

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

من خلال التجربة مش من خلال الحسابات .