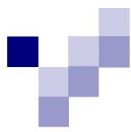
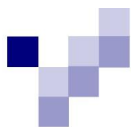


Buffered and Isotonic Solutions



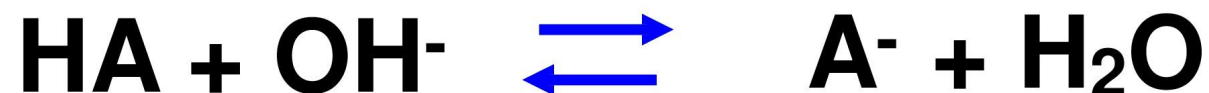
Contents

- **The Buffer Equation**
- **Buffer Capacity**
- **Buffers in
pharmaceutical and Biologic Systems**
- **Buffered Isotonic Solutions**
- **Methods of Adjusting Tonicity and pH**

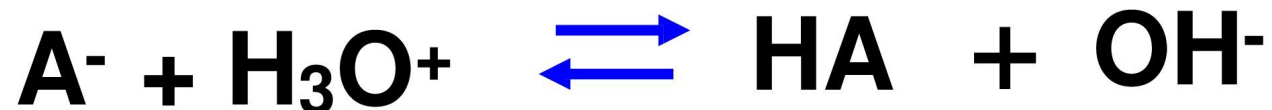


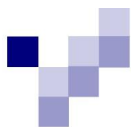
Buffered Solutions

- **Combination of a weak acid and its conjugate base**



- **Combination of a weak base and its conjugate acid**





The Buffer Equation

- A Weak Acid and Its Salt



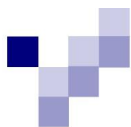
$$K_1[\text{HAc}][\text{H}_2\text{O}] = K_2[\text{H}_3\text{O}^+][\text{Ac}^-]$$

salt

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{Ac}^-]}{[\text{HAc}]}$$

acid

$$-\log[\text{H}_3\text{O}^+] = -\log K_a - \log[\text{acid}] + \log[\text{salt}]$$



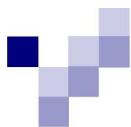
The Buffer Equation

- A Weak Acid and Its Salt

$$\text{pH} = \text{pK}_a + \log \frac{[\text{salt}]}{[\text{acid}]}$$

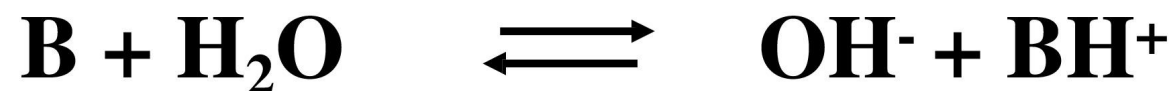
Dissociation exponent

Buffer equation or Henderso



The Buffer Equation

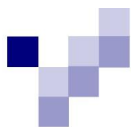
- A Weak Base and Its Salt



$$K_b = \frac{[\text{OH}^-][\text{BH}^+]}{[\text{B}]}$$

salt

base



Common ion effect

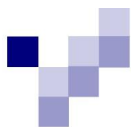
* when Sod. acetate is added to acetic acid...

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

is momentarily disturbed since the acetate ion supplied by the



The ionization of HAc is repressed upon the addition of the c



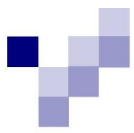
The Buffer Equation

- A weak base and its salt

$$[\text{OH}^-] = K_b \frac{[\text{base}]}{[\text{salt}]}$$

$$\downarrow \quad [\text{H}_3\text{O}^+] \cdot [\text{OH}^-] = K_w$$

$$-\log[\text{H}_3\text{O}^+] = -\log K_w - \log 1/K_b - \log[\text{salt}]/[\text{base}]$$



The Buffer Equation

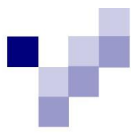
- **A Weak Acid and Its Salt**

base]

salt]



*** Buffers are not ordinarily prepared from weak bases |**



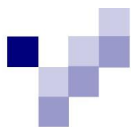
pH 에 영향 주는 인자

1. Altering the ionic strength

- ① Addition of neutral salts
- ② Dilution (alter activity coefficients)

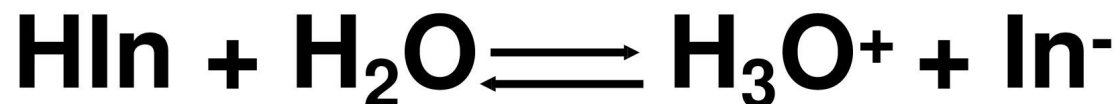
2. Temperature

The pH of the most basic buffer was found to cha



pH indicator

- Acid indicator의 경우



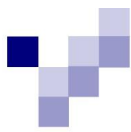
Acid color

Alkaline color

$$K_{In} = \frac{[\text{H}_3\text{O}^+][\text{In}^-]}{[\text{HIn}]}$$

← base acid

←



PH indicator

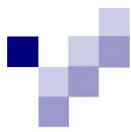
- $\text{pH} = \text{p}K_{In} + \log \frac{[\text{base}]}{[\text{acid}]} \longrightarrow 1/10 \sim 10/1$

* From experience, one cannot discern a change from the acid color to

* The effective range of the indicator is...

$$\text{pH} = \text{p}K_{In} + 1$$





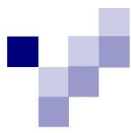
Buffer capacity

- ...the magnitude of the resistance of a buffer to pH changes

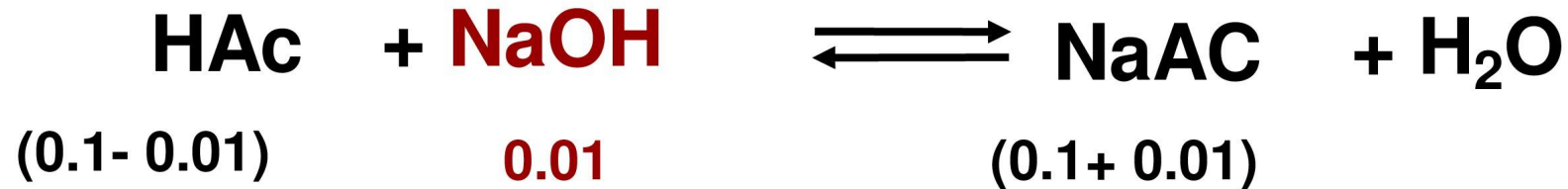
$$\beta = \frac{\Delta B}{\Delta \text{pH}}$$

buffer capacity
= buffer efficiency
= buffer index
= buffer value

ΔB : small increment in gram equivalents/Liter of strong



Buffer capacity (근사식 이용)



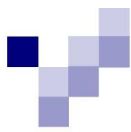
- Before the addition of NaOH

$$\text{pH} = \text{pK}_a + \log \frac{[\text{salt}]}{[\text{acid}]} = 4.76$$

- After the addition of NaOH

$$\text{pH} = \text{pK}_a + \log \frac{[\text{salt}] + [\text{base}]}{[\text{acid}] - [\text{base}]} = 4.85$$

$$\longrightarrow \beta = \frac{\Delta B}{\Delta \text{pH}} = \frac{0.01}{0.09} = 0.11$$



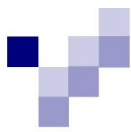
Buffer capacity

- A more exact equation for buffer capacity (1914, 1922)

$$\beta = 2.3 \cdot C \cdot \frac{K_a \cdot [\text{H}_3\text{O}^+]}{(K_a + [\text{H}_3\text{O}^+])^2}$$

c : total buffer conc.(sum of the molar conc. of the ac

β ---- at any $[\text{H}_3\text{O}^+]$



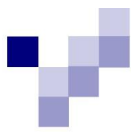
Maximum Buffer capacity

- β_{\max} occurs where $\text{pH} = \text{pK}_a$ ($[\text{H}_3\text{O}^+] = K_a$)

$$\beta_{\max} = 2.303 \cdot C \cdot \frac{[\text{H}_3\text{O}^+]^2}{(2 [\text{H}_3\text{O}^+])^2} = \frac{2.303}{4} \cdot C$$

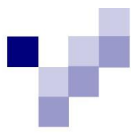
$$\beta_{\max} = 0.576 \cdot C$$

($\text{pH} = \text{pK}_a$)



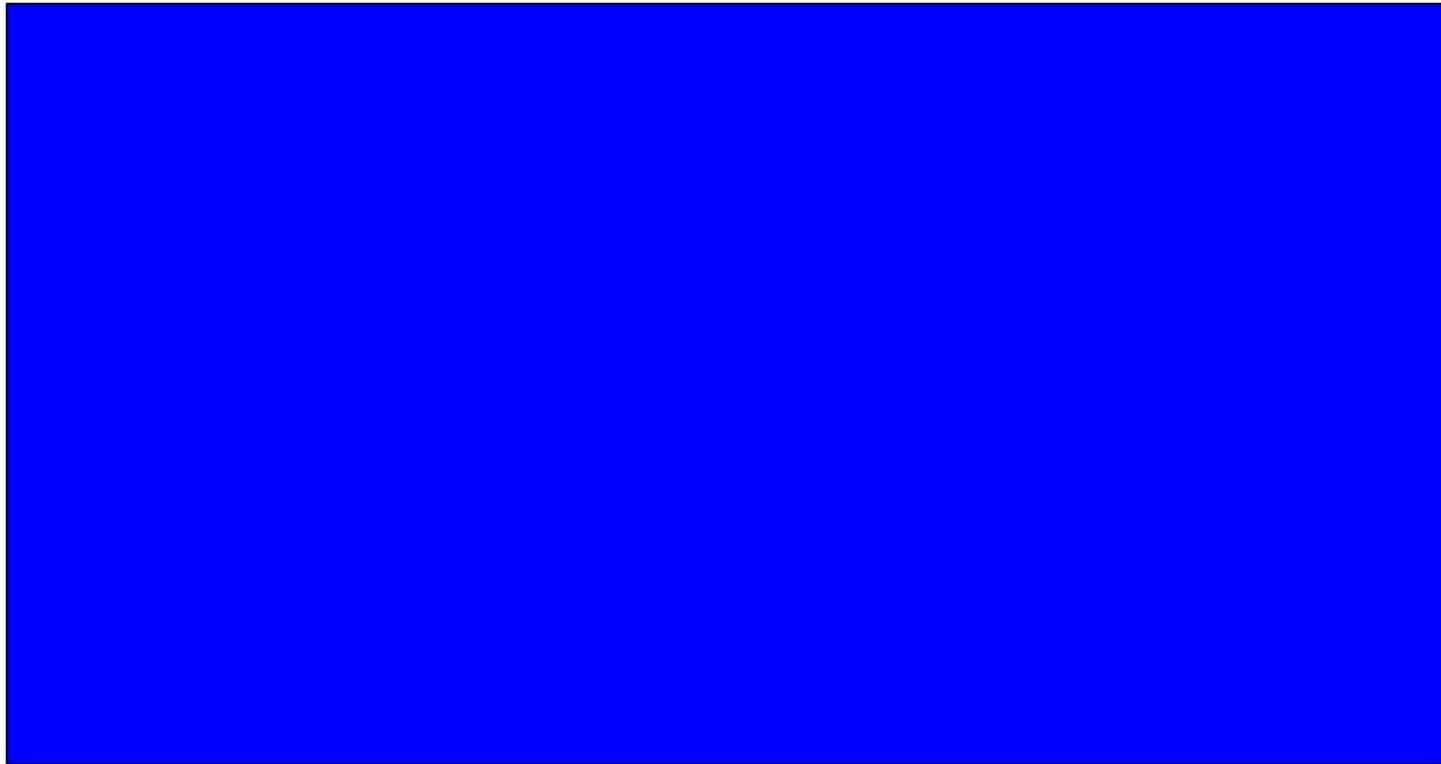
Characteristics of Buffer Capacity

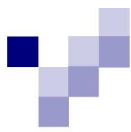
- ...is not a fixed value, but rather **depend on the amount**
- ...depends on the value of the ratio $[\text{salt}]/[\text{acid}]$ and m_a
- **The greatest capacity (β_{max}) occurs where $[\text{salt}]/[\text{acid}] :$**
- **Because of interionic effects, buffer capacities do not in**



Universal Buffer

- Total buffer capacity of a universal buffer (combina





In Vivo biologic buffer systems

- **Blood**

- ① **Primary buffers : Plasma ;**

- NaHCO_3 -- H_2CO_3 , NaHPO_4 -- NaH_2PO_4 , protein**

- ② **Secondary buffers : Erythrocytes ; hemoglobin-oxyhemoglobin, K_2Hf**

- **Lacriminal fluid**

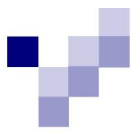
- **pH: 7.4 (range 7 – 8 or slightly higher)**

- **Urine**

- **pH: 6.0 (range 4.5 – 7.8)**

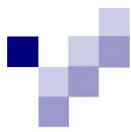
- **below normal...hydrogen ions are excreted by the kidney.**

- **above pH 7.4...hydrogen ions are retained by action of the kidney.**



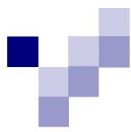
Pharmaceutical buffers

- **ophthalmic soln.**
- **colormetric determination of pH**
- **research studies in which pH must be**



Pharmaceutical buffers

- **Clark-Lubs mixtures and pH**
 - (a) HCl & **KCl**, pH 1.2 - 2.2
 - (b) HCl & potassium biphthalate, pH 2.2 - 4.0
 - (C) NaOH & potassium biphthalate, pH 4.2 - 5.8
 - (d) NaOH & KH_2PO_4 , pH 5.8 - 8.0
 - (e) H_3BO_3 , NaOH & **KCl**, pH 8.0 - 10.0



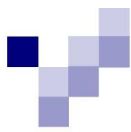
Preparation of pharmaceutical buffer solutions

- **Steps for development of a new buffer**

- ① Select a weak acid having a pK_a approximately equal to the pH
- ② Calculate the ratio of salt & weak acid required to obtain the desired pH
- ③ Consider the individual conc. Of the buffer salt & acid needed

- * Individual conc. : 0.05 ~ 0.5M

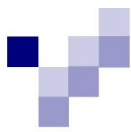
- * buffer capacity : 0.01 ~ 0.1



Preparation of pharmaceutical buffer solutions

- **Steps for development of a new buffer**

- ④ Availability of chemicals, sterility of the final soln, stability of
ex) borate buffer – toxic effect – not be used for oral or parenteral
- ⑤ Determine the pH and buffer capacity using a reliable pH meter

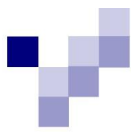


Buffer in pharmaceutical and biologic systems

- Influence of buffer capacity and pH on tissue irritation
 - * Tissue irritation will be minimal when...

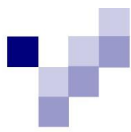
(a) Buffer solution – β , Volume

(b) Physiologic fluid - β   , Volume  



Buffer in pharmaceutical and biologic systems

- **Stability vs. optimum therapeutic response**
 - * **Undissociated form of a weakly acidic or basic drug has a high**
 - * **Molecular form is lipid soluble & can penetrate body membranes**



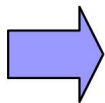
Buffer in pharmaceutical and biologic systems

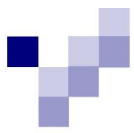
- **pH and solubility**

- * Influence of buffering on the solubility of base

- At a low pH : base is in the ionic form & usually very soluble in a
 - As the pH is raised : more undissociated base is formed when the

Base soln. should be buffered at a sufficiently low pH for sta

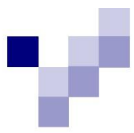




Buffer in pharmaceutical and biologic systems

(Example)

GOAL: Compute the mole percent of free base present



Buffer in pharmaceutical and biologic systems

- Example $C_{11}H_{16}N_2O_2 + H_2O$



$$pH = pK_w - pK_b + \log \frac{[base]}{[salt]}$$

At pH 7.4

$$7.4 = 14 - 7.15 + \log \frac{[base]}{[salt]}$$

[salt]

$$\frac{[base]}{[salt]} = 3.56 / 1$$

$$\text{of base} = 3.56 / (1 + 3.56) \cdot 100 =$$

78%

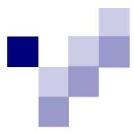
At pH 4.0

$$4.0 = 14 - 7.15 + \log \frac{[base]}{[salt]}$$

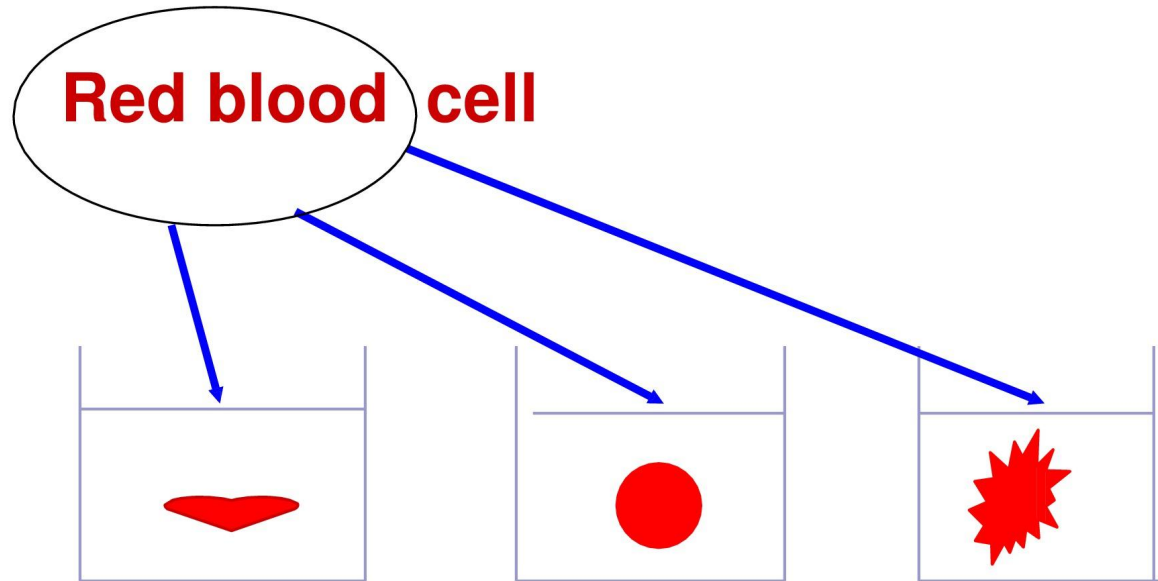
$$\frac{[base]}{[salt]} = 0.0014 / 1$$

$$\text{Mole percent of base} = 0.0014 /$$

0.13%



Buffered isotonic solution

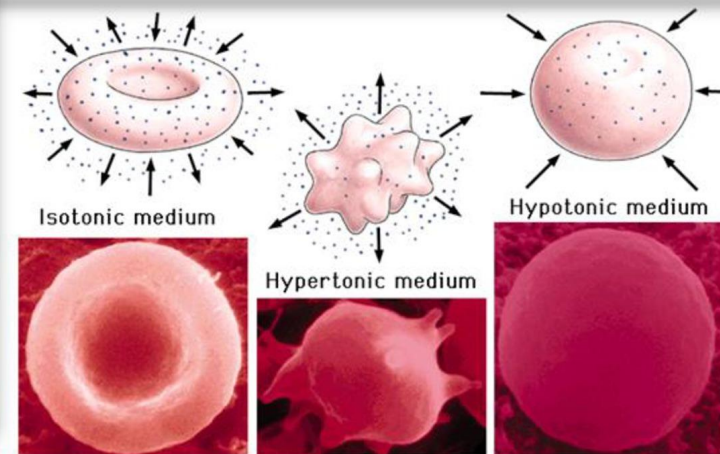
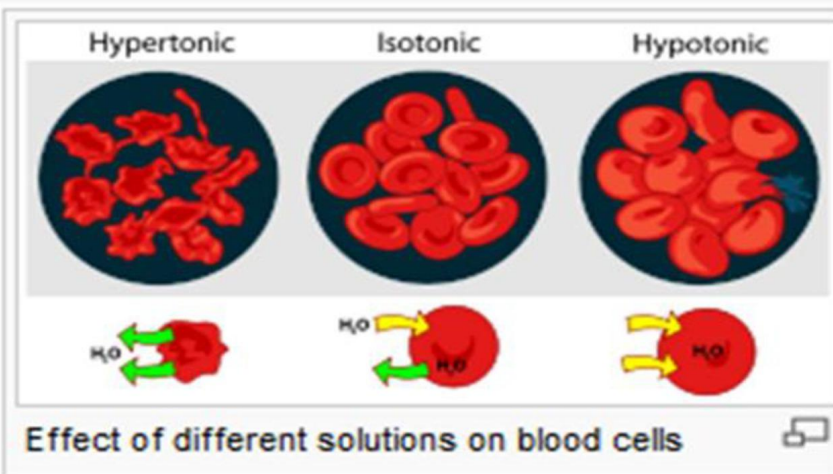


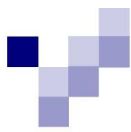
NaCl solution

2.0 % Hypertonic, Isotonic, 0.9 % Hypotonic
Shrink

Types of Tonicity

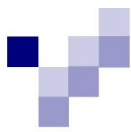
Hypotonic	isotonic	Hypertonic
NaCl 0.2%	NaCl 0.9%	NaCl 2%
solute \gt solute Inside outside	solute $=$ solute Inside outside	solute \lt solute Inside outside
swelling	equilibrium	shrinkage





Buffered isotonic solution

- The term **Isotonic** should be restricted to **solutions having** equal osmotic pressures which
- **Isotonicity value...**the concentration of an aque



Measurement of tonicity

- **Hemolytic method**

- ...apply red blood cells

- ...based on the fact that a hypotonic soln. liberates oxyhemoglobin in dir

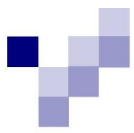
- **determine colligative properties (chapter 5)**

- ...modifications of the Hill-Blades Technique

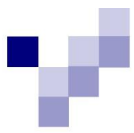
- ...based on a measurement of the slight temp. differences arising from c

$T_f = 0.52 \text{ } ^\circ\text{C}$ (Freezing point lowering of human blood



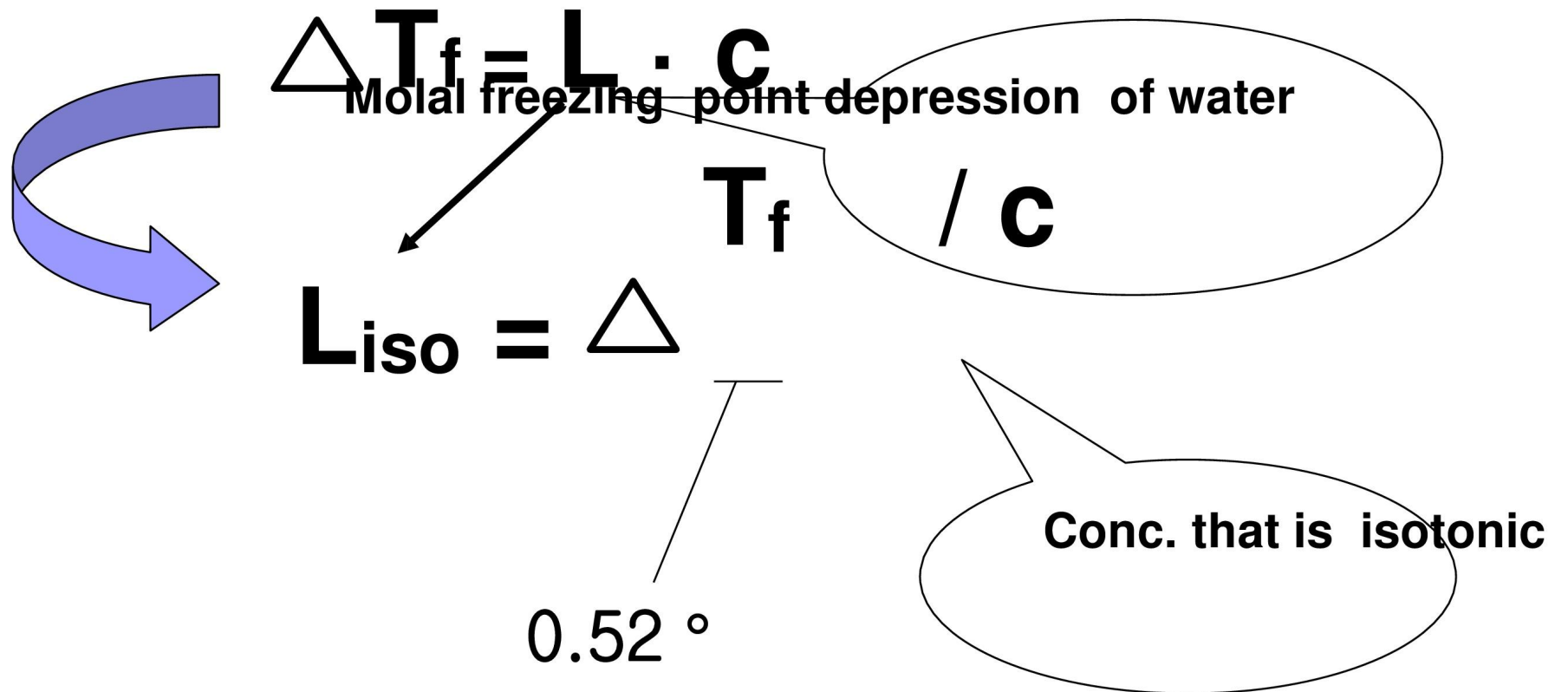


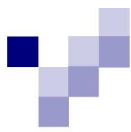
Calculating Tonicity Using L_{iso} values



Calculating Tonicity Using L_{iso} values

- The Van't Hoff expression (Chapter 6)





Method of adjusting tonicity and pH

Class I ...add **Sod. Chloride** to lower the freezing point of soln. to -0.52°

- ① **Cryoscopic method**
- ② **Sodium chloride equivalent method**

Class II ...add **Water** to form an isotonic soln.

- ① **White-Vincent method**
- ② **Sprol's method**



Class I methods

● Cryoscopic method (빙점강하도법)

(Example)

How much NaCl is required to render 100mL of a 1% soln. of apomorphine HCl

→ ΔT_f of NaCl soln : 0.52° (Isotonic with blood)
0.9%

ΔT_f of apomorphine HCl soln : 0.08° (from table)
1%

to reduce the freezing point by an additional 0.44° (0.52-0.08)

→ ΔT_f of NaCl soln : 0.58°
1%

$$1(\%)/X = 0.58/0.44 ; X = 0.76 (\%)$$

|| Dissolve 1 g apomorphine HCl + 0.76g NaCl / make 100mL soln

2-NaCl equivalent method

- NaCl equivalent “E”
Amount of NaCl that is equivalent to(i.e., has the same osmotic effect (same f.p.d) as) 1 gm of drug
- 1st calculate E_{NaCl}
- 2nd add NaCl to reach 0.9%

How to calculate E_{NaCl} ?

$$\Delta Tf = L.c$$

$$\Delta Tf_{drug} = L_{iso} \times \frac{wt_{drug}}{M.wt_{drug} \times V_{drug}}$$

$$\Delta Tf_{NaCl} = L_{iso(NaCl)} \times \frac{wt_{NaCl}}{M.wt_{NaCl} \times V_{NaCl}}$$

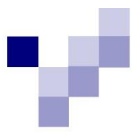
$$L_{iso(drug)} \times \frac{wt_{drug}}{M.wt_{drug} \times V_{drug}} = L_{iso(NaCl)} \times \frac{wt_{NaCl}}{M.wt_{NaCl} \times V_{NaCl}}$$

$$wt_{drug} = 1gm$$

$$wt_{NaCl} = E_{NaCl} \quad M.wt_{NaCl} = 58.45$$

$$L_{iso(NaCl)} = 3.4$$

$$E_{NaCl} = \frac{17L_{iso(drug)}}{M.wt_{drug}}$$



Class I methods

- **Sodium chloride equivalent(E) method**
(염화나트륨당량법) by Mellen & Seltzer

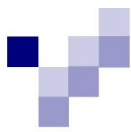
1g drug tonicity = Eg NaCl tonicity

E : weight of NaCl with the same freezing point depression as 1g of th

$$\Delta T_f = L_{iso} \cdot c$$
$$\Delta T_f = \underbrace{L_{iso}}_{3.4} \cdot \underbrace{1g}_{E} / \underbrace{MW}_{58.45}$$

$c = 1 \text{ g} / \text{molecular weight}$

$$E \approx 17 \cdot L_{iso} / MW$$

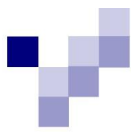


Class II methods

- **White-Vincent method**

•
(Example)

GOAL: make 30mL of a 1% soln. of procaine HCl isotoni

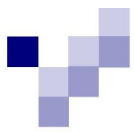


Class II methods

- **Steps for White-Vincent method**

- ① **Weight in grams of drug(0.3 g) • Sod. Chloride equivalent**
- ② **$0.9 \text{ g}/100\text{mL} = 0.063 \text{ g} / V$**
- ③ **$V = 0.063 \cdot \underline{100/0.9}$**
- ④ **$V = 7.0 \text{ mL}$**
- ⑤ **Add isotonic-buffered diluting soln. to complete**


$$V = w \cdot E \cdot 111.1$$



Class II methods

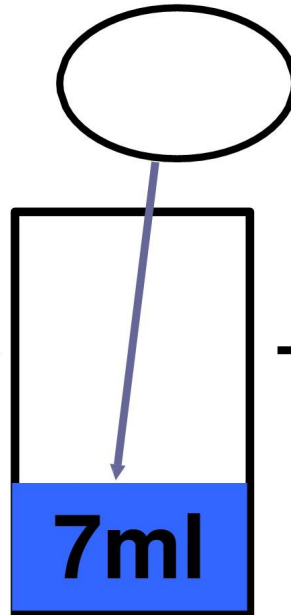
• White Vincent method

make 30mL of 1% soln. of procaine HCl isotonic with body

GOAL:

water

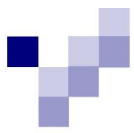
0.9% NaCl
isotonic
0.3g drug
($E=0.21$)



add 0.9% NaCl



Isotonic buffered sol.



Class II methods

- **Sprol's method**

