Buffered Isotonic solutions

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Lecture# 2
Pharmaceutical Buffers
Tissue Irritation Prevention

• Solutions applied to delicate tissues (eyes) or administered parentally may cause irritation if their pH is greatly different from the normal pH of the relevant body fluid.

• In case there is a large difference in pH, tissue irritation can be minimized if the volume and buffer capacity of the solution is much lower than volume and buffer capacity of the physiological fluid.
Isotonic solutions

Why do we need isotonic solutions

• In addition to the importance of pH adjustment in pharmaceutical formulations applied to delicate body membranes or parentally, should also be adjusted to approximately the same osmotic pressure as that of the body fluids.

• Isotonic solutions cause no swelling or contraction of the tissues with which they come in contact and produce no discomfort when instilled in the eye, nasal tract, blood, or other body tissues.

• Isotonic sodium chloride is a familiar pharmaceutical example of such a preparation.
Isotonic solutions

what is osmolarity?

• Osmotic pressure is a colligative property that depends on the concentration of the dissolved particles.

• Osmolarity is a way of reporting total number of particles in the solution to determine osmotic pressure.

\[
\text{Osmolarity} = \text{Molarity} \times n
\]

\[n \rightarrow \text{is the number of dissolved particles.}\]

• Osmolarity of 1M NaCl = 1 x 2 = 2 Osmol/L (n =2, 1 Na + 1 Cl)

• Osmolarity of 1M Na\(_2\)SO\(_4\) = 1 x 3 = 3 Osmol/L (n =3, 2 Na + 1 SO\(_4\))

• Osmolarity of non-electrolytes is equal to its molarity.
Isotonic solutions
What does isotonic solution means
Isotonic solutions
What does isotonic solution means

• Tonicity is the concentration of only the solutes that cannot cross the membrane since these solutes exert an osmotic pressure on that membrane.

• Tonicity is not the difference between the two osmolarities on opposing sides of the membrane. A solution might be hypertonic, isotonic, or hypotonic relative to another solution.

• For example, the relative tonicity of blood is defined in reference to that of the red blood cell (RBC) cytosol tonicity.
Isotonic solutions
What does isotonic solution means

• As such, a hypertonic solution contains a higher concentration of impermeable solutes than the cytosol of the RBC; there is a net flow of fluid out of the RBC and it shrinks (Panel A).

• The concentration of impermeable solutes in the solution and cytosol are equal and the RBCs remain unchanged, so there is no net fluid flow (Panel B).

• A hypotonic solution contains a lesser concentration of such solutes than the RBC cytosol and fluid flows into the cells where they swell and potentially burst (Panel C).

• In short, a solution containing a quantity of drug calculated to be isosmotic with blood is isotonic only when the blood cells are impermeable to the solute (drug) molecules and permeable to the solvent, water.
Methods of adjusting the tonicity

- **Class I method**: You calculate the amount of NaCl needed to be added to a solution to make it isotonic.
  1. Cryoscopic method
  2. NaCl equivalent method → the most important method

- **Class II method**: You calculate the amount of Water needed to be added to a solution to make it isotonic.
  1. White-Vincent method
  2. Sprowls method
Methods of adjusting the tonicity
Class I: Cryoscopic method

• The freezing point depression $\Delta T_f$ of drug solution is a colligative property.
• Freezing point depression of a drug solution can be determined theoretically from the equation:
  $$\Delta T_f = K_f \cdot C$$
• For a solution of electrolytes, a new factor (i) is added to fit the experimental results with the theoretical results, and this factor is called the ionization factor (dissociation factor)
  $$\Delta T_f = i \cdot K_f \cdot C$$
  $$\Delta T_f = L \cdot C,$$ where $L = i \cdot K_f$

The L value for isotonic solution with body fluids is named: $L_{iso}$
  $$\Delta T_f = L_{iso} \cdot C$$
Methods of adjusting the tonicity

Class I: Cryoscopic method

\[ \Delta T_f = L_{iso} \cdot C \]

<table>
<thead>
<tr>
<th>Type</th>
<th>( L_{iso} )</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonelectrolytes</td>
<td>1.9</td>
<td>Sucrose, glycerin, urea, camphor</td>
</tr>
<tr>
<td>Weak electrolytes</td>
<td>2.0</td>
<td>Boric acid, cocaine, phenobarbital</td>
</tr>
<tr>
<td>Di-divalent electrolytes</td>
<td>2.0</td>
<td>Magnesium sulfate, zinc sulfate</td>
</tr>
<tr>
<td>Uni-univalent electrolytes</td>
<td>3.4</td>
<td>Sodium chloride, cocaine hydrochloride, sodium phenobarbital</td>
</tr>
<tr>
<td>Uni-divalent electrolytes</td>
<td>4.3</td>
<td>Sodium sulfate, atropine sulfate</td>
</tr>
<tr>
<td>Di-univalent electrolytes</td>
<td>4.8</td>
<td>Zinc chloride, calcium bromide</td>
</tr>
<tr>
<td>Uni-trivalent electrolytes</td>
<td>5.2</td>
<td>Sodium citrate, sodium phosphate</td>
</tr>
<tr>
<td>Tri-univalent electrolytes</td>
<td>6.0</td>
<td>Aluminum chloride, ferric iodide</td>
</tr>
<tr>
<td>Tetraborate electrolytes</td>
<td>7.6</td>
<td>Sodium borate, potassium borate</td>
</tr>
</tbody>
</table>

Methods of adjusting the tonicity

Class I: Cryoscopic method

• Calculate the $\Delta T_f$ for 1% apomorphine HCl solution (M.W. = 312.79 g/mol, $L_{iso} = 2.6$)

$$\Delta T_f = L_{iso} \cdot C$$

$C$ (molar concentration) = $\frac{101}{312.79} = 0.032 \text{ M}$

$$\Delta T_f = 2.6 \times 0.032 = 0.08 ^\circ$$
Methods of adjusting the tonicity

Class I: Cryoscopic method

• In this method, NaCl or some other substance is added to the solution of the drug to lower the freezing point of the solution by $0.52 \, ^\circ \text{C}$, and thus make it isotonic with body fluids.
Methods of adjusting the tonicity
Class I: Cryoscopic method calculation

• The freezing point depression $\Delta T_f$ of drug solution is a colligative property.

1. Calculate the lowering of the freezing point associated with your drug solution (for example, $\Delta T_f = 0.12 \, ^\circ$)

2. 0.9% NaCl lower the freezing point by 0.52 $^\circ$ ($\Delta T_f = 0.52 \, ^\circ$)

3. Calculate the difference between 2 and 1, in this example $= 0.52 - 0.12 = 0.40 \, ^\circ$

4. If 0.9% NaCl lowers freezing point by 0.52, then what is the needed NaCl concentration to lower freezing point by 0.40 $^\circ$

   \[
   \text{Required NaCl concentration} = \frac{0.9\% \times 0.40 \, ^\circ}{0.52 \, ^\circ} = 0.69\%
   \]

   Thus you need to add NaCl to your drug solution to give a final concentration of 0.69% and thus you will get an isotonic solution.
Methods of adjusting the tonicity

Class I: NaCl equivalent method

- The sodium chloride equivalent of a drug (E value) is the amount of NaCl that has the same osmotic effect of 1 g of the drug.
- E value can be obtained theoretically from the \( L_{iso} \) value and the molecular weight of the drug.

\[
E = 17 \frac{L_{iso}}{M.W.}
\]

If you have 1 g of drug in 1000 mL of solution

\[
\Delta T_f = L_{iso} \cdot \frac{1}{M.W.}
\]

E value is the amount of NaCl that will result in the same lowering in the freezing point of 1 g of the drug.

Thus for NaCl the equation should be

\[
\Delta T_f = L_{iso} \cdot \frac{E}{M.W.} = 3.4 \cdot \frac{1}{58.54}
\]
Methods of adjusting the tonicity

Class I: NaCl equivalent method

\[ \Delta T_f = L_{iso} \cdot \frac{1}{M.W.} = \Delta T_f = L_{iso} \cdot \frac{E}{M.W.} = 3.4 \cdot \frac{1}{58.54}. \]

\[ E = 17 \frac{L_{iso}}{M.W.}. \]

Thus by knowing the \( L_{iso} \) and M.W. of your drug you can easily determine the \( E \) value.
Methods of adjusting the tonicity

Class I: NaCl equivalent method

\[ E = 17 \frac{L_{iso}}{M.W.} \]

Calculate the E value of ephedrine sulfate (M.W. = 428.54, and \( L_{iso} = 5.8 \))

\[ E = 17 \frac{5.8}{428.54} = 0.23 \]

This means that 0.23 g of NaCl lowers the freezing point as that of 1 g of ephedrine sulfate.
Methods of adjusting the tonicity

Class I: NaCl equivalent method

In NaCl equivalent method, NaCl or some other substance is added to the solution of the drug to make the concentration of the solution equivalent to 0.9% NaCl, and thus make it isotonic with body fluids.
Methods of adjusting the tonicity
Class I: NaCl equivalent method

A solution contains 1.0 g of ephedrine sulfate in a volume of 100 mL. What quantity of sodium chloride must be added to make the solution isotonic? How much dextrose would be required for this purpose?

The quantity of the drug is multiplied by its sodium chloride equivalent, \( E \), giving the weight of sodium chloride to which the quantity of drug is equivalent in osmotic pressure:

- The ephedrine sulfate has contributed a weight of material osmotically equivalent to 0.23 g of sodium chloride. Because a total of 0.9 g of sodium chloride is required for isotonicity, 0.67 g (0.90 - 0.23 g) of NaCl must be added.
Methods of adjusting the tonicity
Class I: NaCl equivalent method

A solution contains 1.0 g of ephedrine sulfate in a volume of 100 mL. What quantity of sodium chloride must be added to make the solution isotonic? How much dextrose would be required for this purpose?

• If one desired to use dextrose instead of sodium chloride to adjust the tonicity, the quantity would be estimated by setting up the following proportion. Because the sodium chloride equivalent of dextrose is 0.16

\[
\frac{1 \text{ g dextrose}}{0.16 \text{ g NaCl}} = \frac{X}{0.67 \text{ g NaCl}}
\]

\[
X = 4.2 \text{ g dextrose}
\]
Methods of adjusting the tonicity
Class II: White-Vincent Method

The class II method of tonicity adjustment involves the addition of water to the drugs to prepare an isotonic solution, followed by the addition of an isotonic buffered diluting vehicle to bring the solution to the final volume.

White and Vincent developed a simplified equation for calculating the Volume (V) of water in mLs required to prepare an isotonic solution from a given drug amount.

\[ V = W \times E \times 111.1 \]

- \( W \) → Weight of drug in g
- \( E \) → NaCl equivalent value
Methods of adjusting the tonicity
Class II: White-Vincent Method

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- \( W \) → Weight of drug in g
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Methods of adjusting the tonicity

Class II: White-Vincent Method

How to make 30 mL of a 1% solution of procaine HCl isotonic solution with body fluid. E value = 0.21

Weight of drug in the 30 mL = 30 x 1% = 0.3 g

\[ V = \frac{W \times E}{111.1} \]

\[ V = \frac{0.3 \times 0.21}{111.1} = 7 \text{ mL} \]

Thus 7 mL of water should be added to the drug make an isotonic solution and then add 23 mL of isotonic diluting solution to make a final 30 mL of the finished product.
Methods of adjusting the tonicity
Class II: Sprowls Method

Sprowls method is a simplification of White-Vincent method in which values of V for drugs of fixed weight (0.3 g) are computed and construed as a table (0.3 g is the quantity required to prepare 1% solution for 30 mL solution).

This is commonly used for ophthalmic and parenteral solutions.

\[ V = W \cdot E \cdot 111.1 \]

<table>
<thead>
<tr>
<th>Substance</th>
<th>MW</th>
<th>E</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol, dehydrated</td>
<td>46.07</td>
<td>0.70</td>
<td>23.3</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>456.46</td>
<td>0.17</td>
<td>5.7</td>
</tr>
<tr>
<td>Amphetamine sulfate</td>
<td>368.49</td>
<td>0.22</td>
<td>7.3</td>
</tr>
<tr>
<td>Antipyrine</td>
<td>188.22</td>
<td>0.17</td>
<td>5.7</td>
</tr>
<tr>
<td>Apomorphine hydrochloride</td>
<td>312.79</td>
<td>0.14</td>
<td>4.7</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>176.12</td>
<td>0.18</td>
<td>6.0</td>
</tr>
<tr>
<td>Atropine sulfate</td>
<td>694.82</td>
<td>0.13</td>
<td>4.3</td>
</tr>
</tbody>
</table>
Thank you