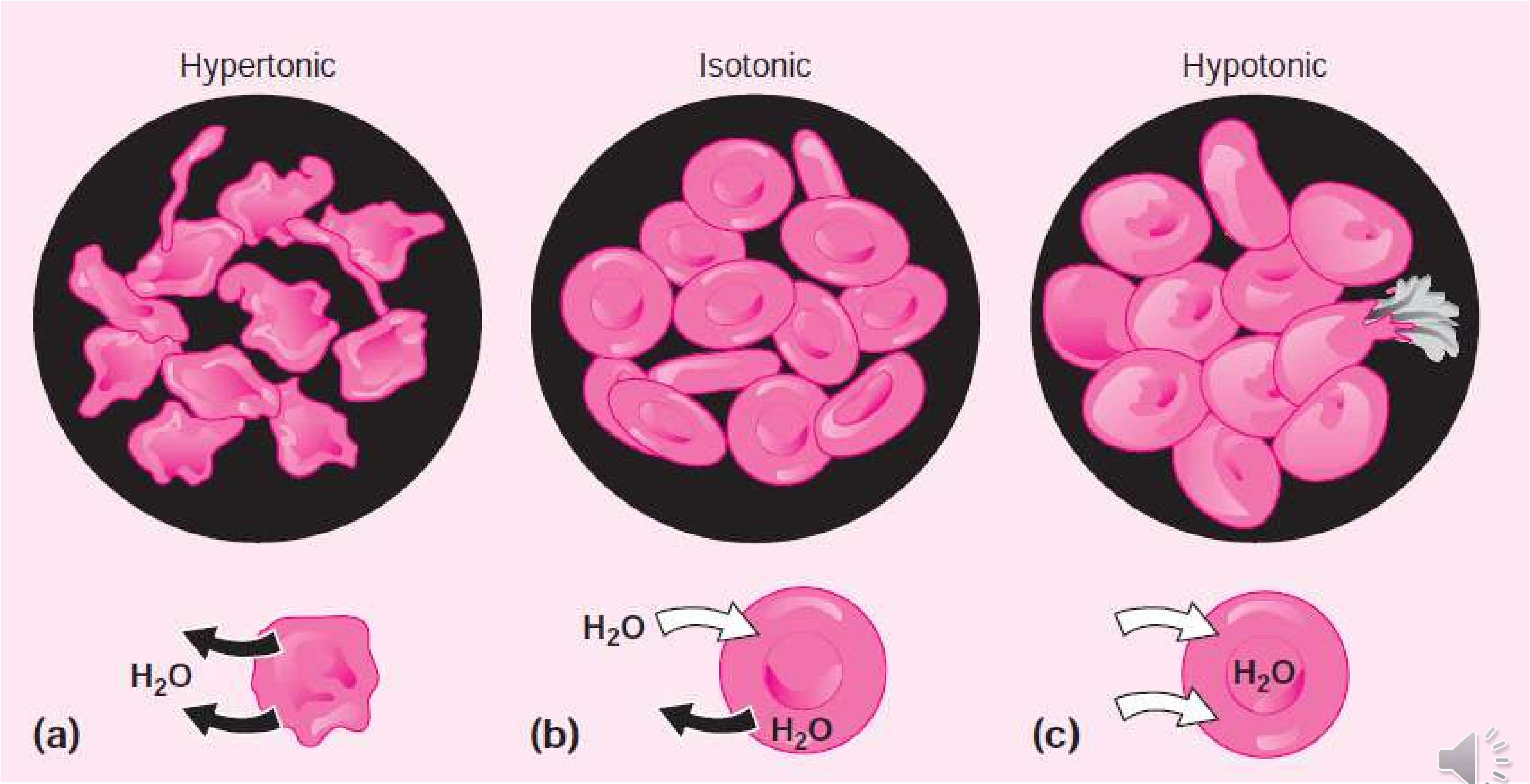
BUFFERED AND ISOTONIC SOLUTIONS

- 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.



Hypertonic
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H_2O
(a)
H_2O
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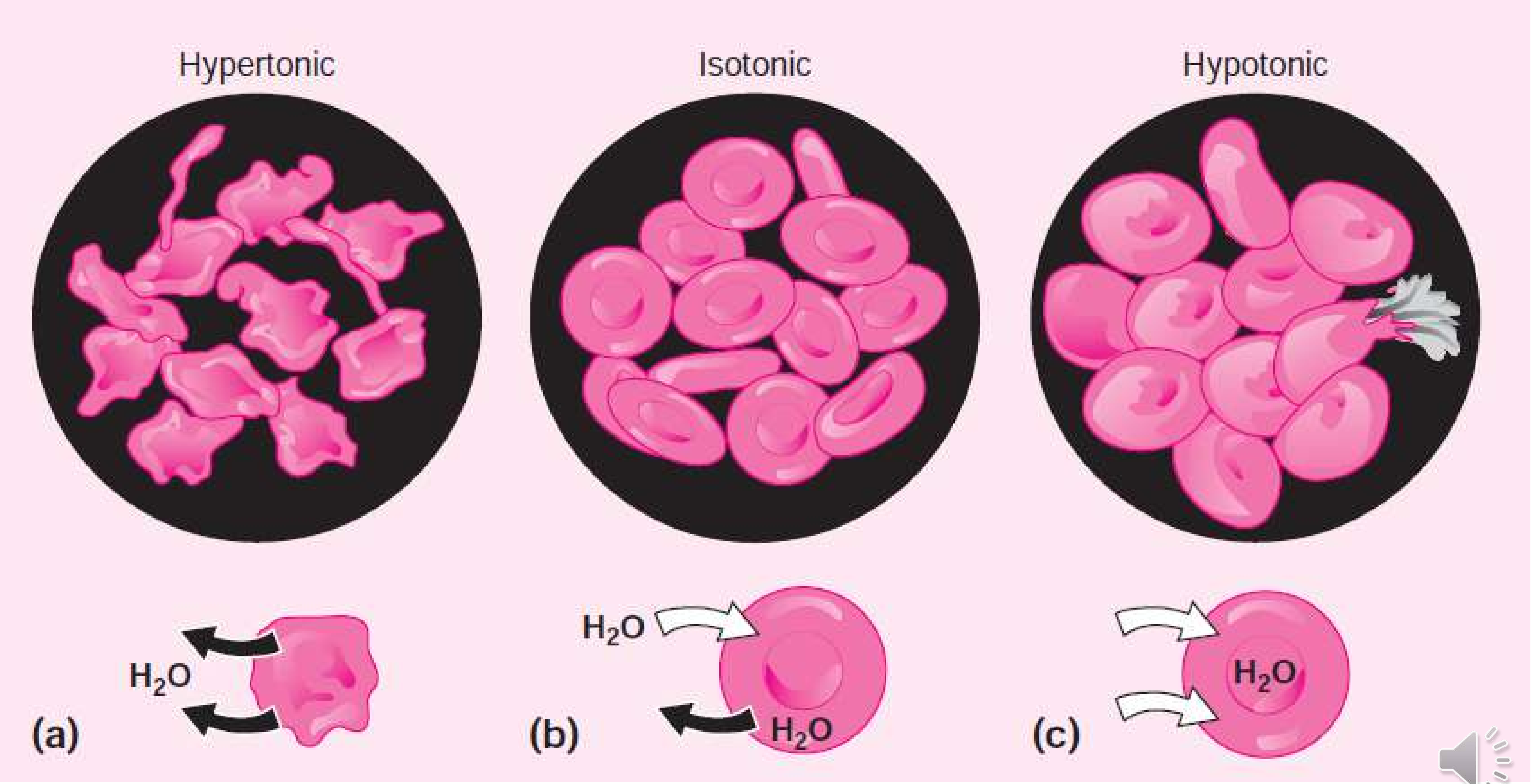
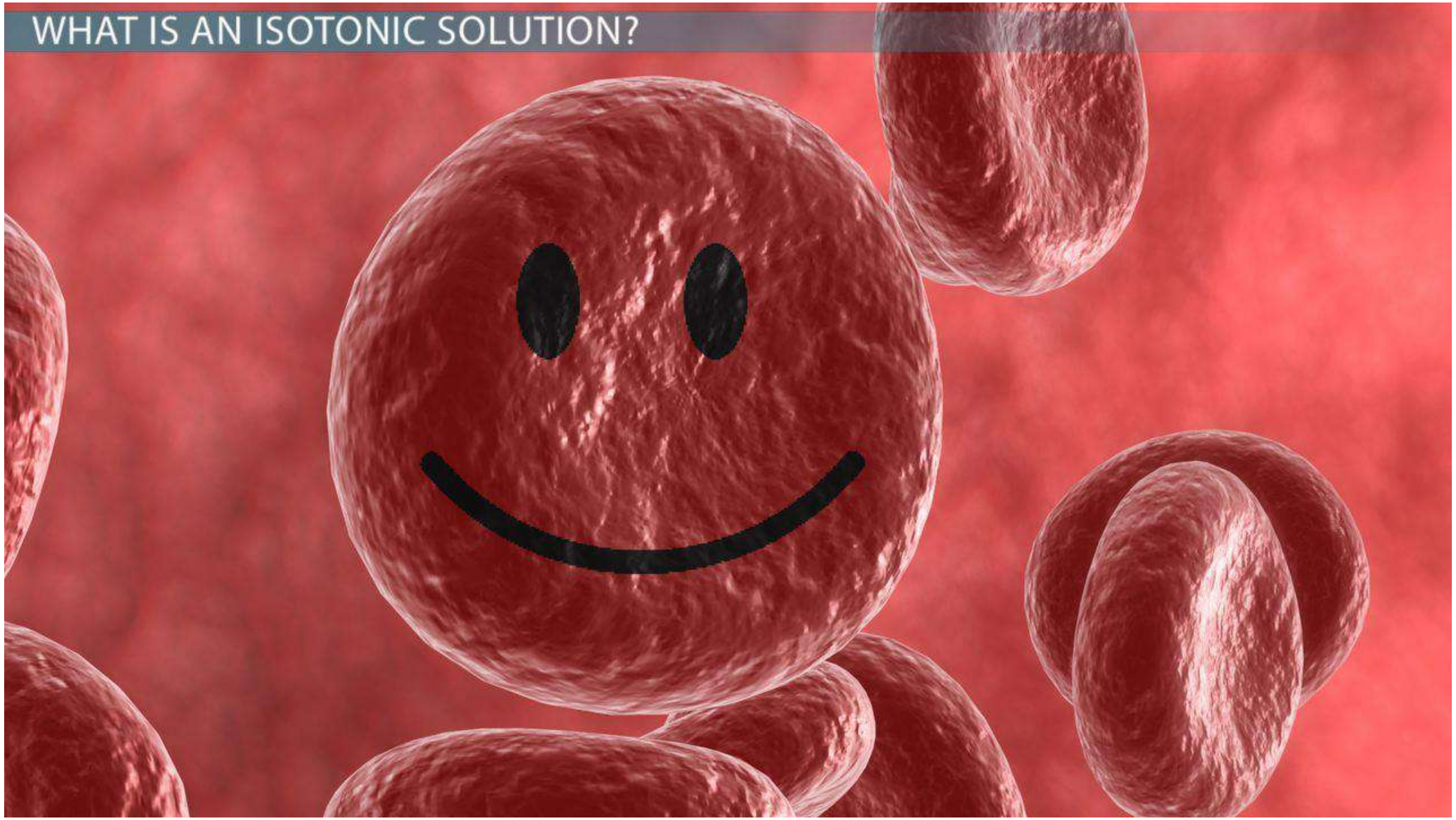

Hypertonic
Isotonic
Hypotonic
H_2O
(a)
H_2O
H_2O
(b)
H_2O
(c)

- **Referance standard isotonic solution**



Measurement of Tonicity

- The tonicity of solutions can be determined by one of two methods:

A. the hemolytic method, the effect of various solutions of the drug is observed on the appearance of red blood cells suspended in the solutions.

B. any of the methods that determine colligative properties: based on a measurement of the slight temperature differences arising from differences in the vapor pressure of thermally insulated samples contained in constant-humidity chambers.

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Calculating Tonicity Using L_{iso} Values

- Because the freezing point depressions for solutions of electrolytes of both the weak and strong types are always greater than those calculated from the equation **$\Delta T_f = K_f . C$**, a new factor, **$L = i.K_f$**, is introduced to overcome this difficulty
- The equation, already discussed is **$\Delta T_f = LC$**
- The L value can be obtained from the freezing point lowering of solutions of representative compounds of a given ionic type at a concentration c that is isotonic with body fluids.
- This specific value of L is written as L_{iso}

- The Liso value for a 0.90% (0.154 M) solution of sodium chloride, which has a freezing point depression of 0.52◦C and is thus isotonic with body fluids, is 3.4: From

$$L_{iso} = \frac{\Delta T_f}{c}$$

$$L_{iso} = \frac{0.52°C}{0.154} = 3.4$$

- The interionic attraction in solutions that are not too concentrated is roughly the same for all uni-univalent electrolytes regardless of the chemical nature of the various compounds of this class, and all have about the same value for *L*iso, namely 3.4.

- As a result of this similarity between compounds of a given ionic type, a table can be arranged listing the L value for each class of electrolytes at a concentration that is isotonic with body fluids.

- The Liso values obtained in this way are given in Table used to obtain the approximate ΔT_f for a solution of a drug if the ionic type can be correctly ascertained.

AVERAGE L_{iso} VALUES FOR VARIOUS IONIC TYPES*

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

- **Example**

- What is the freezing point lowering of a 1% w/v solution of sodium propionate (molecular weight 96 g/mol)?

- Because sodium propionate is a uni-univalent electrolyte, its L_{iso} value is 3.4.
- The molar concentration of a 1% solution of this compound is 0.104.
- $\Delta T_f = L_{iso}.C$
- $\Delta Tf = 3.4 \times 0.104 = 0.35 ^\circ C$

METHODS OF ADJUSTING TONICITY

- One of several methods can be used to calculate the quantity of **sodium chloride, dextrose, and other substances** that may be added to solutions of drugs to render them isotonic.
- **The methods are divided into two classes:**

A- class I methods: sodium chloride or some other substance is added to the solution of the drug to lower the freezing point of the solution to −0.52◦C and thus make it isotonic with body fluids.

Under this class are included:

a) the cryoscopic method
b) the sodium chloride equivalent method.

B- class II methods: water is added to the drug in a sufficient amount to form an isotonic solution. The preparation is then brought to its final volume with an isotonic or a buffered isotonic dilution solution. Included in this class are:

a) the White–Vincent method
b) the Sprowls method.

- *Class I Methods*

1- Cryoscopic Method

- The freezing point depressions of a number of drug solutions, determined experimentally or theoretically, are given in the previos table.
- According to the previous section, the freezing point depressions of drug solutions that have not been determined experimentally can be estimated from theoretical considerations, knowing only the molecular weight of the drug and the L_{iso} value of the ionic class

$$L_{\text{iso}} = \frac{\Delta T_{\text{f}}}{c}$$

ISOTONIC VALUES*,†

MW: molecular weight of the drug

E: sodium chloride equivalent of the drug

V: volume in mL of isotonic solution that can be prepared by adding water to0.3 g of the drug (the weight of drug in 1 fluid ounce of a 1% solution)

$\Delta T_f^{1\%}$: freezing point depression of a 1% solution of the drug

L_{iso}: the molar freezing point depression of the drug at a concentration approximately isotonic with blood and lacrimal fluid.

Substance	MW	E	V	$\Delta T_f^{1\%}$	L_{iso}
Alcohol, dehydrated	46.07	0.70	23.3	0.41	1.9
Aminophylline	456.46	0.17	5.7	0.10	4.6
Amphetamine sulfate	368.49	0.22	7.3	0.13	4.8
Antipyrine	188.22	0.17	5.7	0.10	1.9
Apomorphine hydrochloride	312.79	0.14	4.7	0.08	2.6
Ascorbic acid	176.12	0.18	6.0	0.11	1.9
Atropine sulfate	694.82	0.13	4.3	0.07	5.3
Diphenhydramine hydrochloride	291.81	0.20	6.6	0.34	3.4
Boric acid	61.84	0.50	16.7	0.29	1.8
Caffeine	194.19	0.08	2.7	0.05	0.9
Dextrose · H_2O	198.17	0.16	5.3	0.09	1.9
Ephedrine hydrochloride	201.69	0.30	10.0	0.18	3.6
Ephedrine sulfate	428.54	0.23	7.7	0.14	5.8
Epinephrine hydrochloride	219.66	0.29	9.7	0.17	3.7
Glycerin	92.09	0.34	11.3	0.20	1.8
Lactose	360.31	0.07	2.3	0.04	1.7
Morphine hydrochloride	375.84	0.15	5.0	0.09	3.3
Morphine sulfate	758.82	0.14	4.8	0.08	6.2
Neomycin sulfate	–	0.11	3.7	0.06	–
Penicillin G potassium	372.47	0.18	6.0	0.11	3.9
Penicillin G Procaine	588.71	0.10	3.3	0.06	3.5

- **Example**

How much sodium chloride is required to render 100 mL of a 1% solution of apomorphine hydrochloride isotonic with blood serum?

From Table 8–4 it is found that a 1% solution of the drug has a freezing point lowering of 0.08°C. To make this solution isotonic with blood, sufficient sodium chloride must be added to reduce the freezing point by an additional 0.44°C (0.52°C − 0.08°C). In the freezing point table, it is also observed that a 1% solution of sodium chloride has a freezing point lowering of 0.58°C. By the method of proportion,

$$\frac{1\%}{X} = \frac{0.58^\circ}{0.44^\circ}; X = 0.76\%$$

Thus, 0.76% sodium chloride will lower the freezing point the required 0.44°C and will render the solution isotonic. The solution is prepared by dissolving 1.0 g of apomorphine hydrochloride and 0.76 g of sodium chloride in sufficient water to make 100 mL of solution.

2- Sodium Chloride Equivalent Method

- The *sodium chloride equivalent* or, as referred to by these workers, the "tonicic equivalent" of a drug is the amount of sodium chloride that is equivalent to (i.e., has the same osmotic effect as) 1 g, or other weight unit, of the drug.
- The sodium chloride equivalents E for a number of drugs are listed in Table 8–4.
- When the E value for a new drug is desired for inclusion in Table 8–4, it can be calculated from the Liso value or freezing point depression of the drug

ISOTONIC VALUES*,†

- MW: molecular weight of the drug
- E: sodium chloride equivalent of the drug
- V: volume in mL of isotonic solution that can be prepared by adding water to0.3 g of the drug (the weight of drug in 1 fluid ounce of a 1% solution)
- $\Delta T_f^{1\%}$: freezing point depression of a 1% solution of the drug
- L_{iso}: the molar freezing point depression of the drug at a concentration approximately isotonic with blood and lacrimal fluid.

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Neomycin sulfate	–	0.11	3.7	0.06	–
Penicillin G potassium	372.47	0.18	6.0	0.11	3.9
Penicillin G Procaine	588.71	0.10	3.3	0.06	3.5

- For a solution containing 1 g of drug in 1000 mL of solution, the concentration c expressed in moles/liter can be written as

$$c = \frac{1\ \text{g}}{\text{Molecular weight}}$$

- And since

$$\Delta T_f = L_{iso} \frac{1\ \text{g}}{\text{MW}}$$

- Now, E is the weight of NaCl with the same freezing point depression as 1 g of the drug, and for a NaCl solution containing E grams of drug per 1000 mL,

$$\Delta T_f = 3.4 \frac{E}{58.45}$$

$$\frac{L_{iso}}{\text{MW}} = 3.4 \frac{E}{58.45}$$

$$E \cong 17 \frac{L_{iso}}{\text{MW}}$$

- **Example**

- Calculate the approximate E value for a new amphetamine hydrochloride derivative (molecular weight 187).

- Because this drug is a uni-univalent salt, it has an L_{iso} value of 3.4.

$$E = 17\frac{3.4}{187} = 0.31$$

- **Example**
- 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:
- Ephedrine sulfate: 1.0 g×0.23 = 0.23 g
- 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.

- 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,

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

$$X = 4.2\text{ g of dextrose}$$

- *Class II Methods*

I- White-Vincent Method

- The class II methods of computing tonicity involve the addition of **water** to the drugs to make an isotonic solution, followed by the addition of an isotonic or isotonic-buffered diluting **vehicle** to bring the solution to the final volume.

ISOTONIC VALUES*,†

molecular weight of the drug

sodium chloride equivalent of the drug

volume in mL of isotonic solution that can be prepared by adding water to0.3 g of the drug (the weight of drug in 1 fluid ounce of a 1% solution)

freezing point depression of a 1% solution of the drug

the molar freezing point depression of the drug at a concentration approximately isotonic with blood and lacrimal fluid.

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Example

- Suppose that one wishes to make 30 mL of a 1% solution of procaine hydrochloride isotonic with body fluid.

- First, the weight of the drug, w, is multiplied by the sodium chloride equivalent, E:

$$0.3\ g \times 0.21 = 0.063\ g$$

This is the quantity of sodium chloride osmotically equivalent to 0.3 g of procaine hydrochloride.

Second, it is known that 0.9 g of sodium chloride, when dissolved in enough water to make 100 mL, yields a solution that is isotonic.

$$\frac{0.9\ \text{g}}{100\ \text{mL}} = \frac{0.063\ \text{g}}{V}$$

$$V = 0.063 \times \frac{100}{0.9}$$

$$V = 7.0\ \text{mL}$$

The volume, V, of isotonic solution that can be prepared from 0.063 g of sodium chloride (equivalent to 0.3 g of procaine hydrochloride) is obtained by solving the proportion

$$V = w \times E \times 111.1$$

where V is the volume in milliliters of isotonic solution that may be prepared by mixing the drug with water, w is the weight in grams of the drug given in the problem, and E is the sodium chloride equivalent obtained from Table 8–4.

The constant, 111.1, represents the volume in milliliters of isotonic solution obtained by dissolving 1 g of sodium chloride in water

Example

Make the following solution isotonic with respect to an ideal membrane:

Phenacaine hydrochloride	0.06 g
Boric acid	0.30 g
Sterilized distilled water, enough to make	100.0 mL

$$V = [(0.06 \times 0.20) + (0.3 \times 0.50)] \times 111.1$$

$$V = 18\,\text{mL}$$

The drugs are mixed with water to make 18 mL of an isotonic solution, and the preparation is brought to a volume of 100 mL by adding an isotonic diluting solution.