→ $\Delta T_f = L_{iso} \times C$ — C → conc. in molarity

$$\Delta T_f = L_{iso} \times \frac{w}{m.w} \times \frac{1000}{v}.$$

Methods of Adjusting Tonicity & pH:

Methods:

Class - I method:
1) Cryoscopic method
ii) Sodium chloride Equivalent method.

Class - II method:
i) White - Vincent method
ii) Sprowls method.

→ 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° and thus make it isotonic with body fluids.

Methods: i) Cryoscopic method
ii) NaCl Eq. method.

→ 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

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buffered isotonic solution.

Methods: i) White - Vincent method

ii) Sprowls method.

Class - I - methods:

i) Cryoscopic method:-

→ The freezing point depression of drug solution is (un-adjusted) compared with freezing point of a 1% w/v solution of the adjusting substance (NaCl).

→ Steps:- 1) freezing point depression of drug soln. (un-adjusted).

2) Temp. at which blood plasma & tears freeze is -0.52°C.

3) Any solution which freeze at -0.52°C is isotonic with blood plasma & tears.

— formula: % w/v of a adjusting substance needed $= \frac{0.52 - a}{b}$.

a — fr. pt. of un-adjusted soln.

b — fr. pt. of 1% w/v soln. of the adjusting substance.

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Ex: How much Nacl is required to render 100 ml of a 1% soln. of apomorphine Hcl isotonic ~ blood Serum?

→ Ft. point depression of apomorphine Hcl (a) = 0.08°

→ To make this soln. isotonic ~ blood, sufficient Nacl must be added to reduce ft. point,

→ 0.52 − 0.08 = 0.44° (Added).

→ 1% (Adjustment) Nacl soln ft. pt depression (b) = 0.58°

$$\text{formula} = \frac{0.52 - a}{b.}$$

$$= \frac{0.52 - 0.44}{0.58} = \frac{0.44}{0.58} = 0.76\%$$

Isotonic soln. prep^{n}:

Dissolve 1.0 gm of apomorphine. Hcl and 0.76 gm of Nacl in suff. water to make 100 ml solution.

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ii) Sodium Chloride Equivalent method:

→ The NaCl equivalent "E" of a drug is the amount of NaCl that is equivalent to (i.e. has the same osmotic effect as) 1gm of the drug.

formula for 'E' value,

$$E = 17 \cdot \frac{L_{i1o}}{M.W.}$$

→ Expl:

$\Delta T_f = L \cdot C.$ (∵ L = L_{i1o}, C = conc

$C = 1gm/m.w$)

$$\Delta T_f = L_{i1o} \cdot \frac{1gm}{m.w.} \rightarrow (1)$$

→ NaCl → E, w. of NaCl same fl. dep. of drug.

m.w. of NaCl = 58.45.

L_{i1o} of NaCl = 3.4.

$$\Delta T_f = 3.4 \cdot \frac{E}{58.45.} - (2).$$

Equating (1). (2)

$$\frac{L_{i1o} \cdot 1gm}{m.w} = \frac{3.4}{58.45} \cdot E.$$

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$$\frac{\text{Liso}}{\text{m.w}} = \frac{1}{17} \cdot E$$

$$E = 17 : \frac{\text{Liso}}{\text{m.w.}}$$

Steps:

1) multiply the drug concn (wt) with drugs E value.

Drug.value = drug wt x E value of drug.

ii) Substracting the drug value from conc. of NaCl, that is isotonic to body fluids (0.9 % NaCl).

Isotonic soln. = 0.9 − drug value

Ex:

A soln. contains 1.0 gm of Ephedrine sulfate in a volume of 100 ml. what qt. of NaCl must be added to make the soln. isotonic? How much dextrose would be required for this purpose?

→ Ephedrine Sulphate = 1.0 gm x 0.23 = 0.23 gm.

→ NaCl added = 0.9 − 0.23 = 0.67 gm

0.67 gm NaCl must be added to make the soln Isotonic.

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→ If dextrose will be used instead of Nacl,

→ The Nacl Equivalent of dextrose is 0.16.

formula:

$$\frac{1 \text{ gm dextrose}}{0.16 \text{ gm Nacl}} = \frac{X}{\text{Nacl must be added}}.$$

$$X = \frac{Y}{E} = \frac{Y \text{ (Additional amt. of nacl for isotonicity)}}{E \text{ (gm of Nacl Eq. to 1 gm of isotonic agent}}.$$

cont:

problem → Amount of dextrose needed,

$$\frac{1 \text{ gm dextrose}}{0.16 \text{ gm Nacl}} = \frac{X}{0.67 \text{ gm Nacl}}.$$

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

→ other agents: mannitol, PG, glycerin.

Formula $\boxed{X = \frac{Y}{E}}$.

X - gm of Isotonic agent required to adjust tonicity.

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TABLE 8–4. *Isotonic Values

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
Ammonium chloride	53.50	1.08	36	0.64	3.4
Amphetamine sulfate (benzedrine sulfate)	368.49	0.22	7.3	0.13	4.8
Antipyrine	188.22	0.17	5.7	0.10	1.9
Antistine hydrochloride (antazoline hydrochloride)	301.81	0.18	6.0	0.11	3.2
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
Aureomycin hydrochloride	544	0.11	3.7	0.06	3.5
Barbital sodium	206.18	0.29	10.0	0.29	3.5
Benadryl hydrochloride (diphenhydramine hydrochloride)	291.81	0.20	6.6	0.34	3.4
Boric acid	61.84	0.50	16.7	0.29	1.8
Butacaine sulfate (butyn sulfate)	710.95	0.20	6.7	0.12	8.4
Caffeine	194.19	0.08	2.7	0.05	0.9
Caffeine and sodium benzoate	—	0.25	8.7	0.28	—
Calcium chloride · $2H_2O$	147.03	0.51	17.0	0.30	4.4
Calcium gluconate	448.39	0.16	5.3	0.09	4.2
Calcium lactate	308.30	0.23	7.7	0.14	4.2
Camphor	152.23	0.20	6.7	0.12	1.8
Chloramphenicol (chloromycetin)	323.14	0.10	3.3	0.06	1.9
Chlorobutanol (chloretone)	177.47	0.24	8.0	0.14	2.5
Cocaine hydrochloride	339.81	0.16	5.3	0.09	3.2
Cupric sulfate · $5H_2O$	249.69	0.18	6.0	0.11	2.6
Dextrose · H_2O	198.17	0.16	5.3	0.09	1.9
Dibucaine hydrochloride (nupercaine hydrochloride)	379.92	0.13	4.3	0.08	2.9
Emetine hydrochloride	553.56	0.10	3.3	0.06	3.3
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 bitartrate	333.29	0.18	6.0	0.11	3.5
Epinephrine hydrochloride	219.66	0.29	9.7	0.17	3.7
Ethylhydrocupreine hydrochloride (optochin)	376.92	0.17	5.7	0.10	3.8
Ethylmorphine hydrochloride (dionin)	385.88	0.16	5.3	0.09	3.6
Eucatropine hydrochloride (euphthalmine hydrochloride)	327.84	0.18	6.0	0.11	3.5
Fluorescein sodium	376	0.31	10.3	0.18	6.9
Glycerin	92.09	0.34	11.3	0.20	1.8
Homatropine hydrobromide	356.26	0.17	5.7	0.10	3.6
Lactose	360.31	0.07	2.3	0.04	1.7
Magnesium sulfate · $7H_2O$	246.50	0.17	5.7	0.10	2.5
Menthol	156.26	0.20	6.7	0.12	1.8
Meperidine hydrochloride (demerol hydrochloride)	283.79	0.22	7.3	0.12	3.7
Mercuric chloride (mercury bichloride)	271.52	0.13	4.3	0.08	2.1
Mercuric cyanide	252.65	0.15	5.0	0.09	2.2
Mercuric succinimide	396.77	0.14	4.8	0.08	3.3
Methacholine chloride (mecholyl chloride)	195.69	0.32	10.7	0.19	3.7
Methamphetamine hydrochloride (desoxyephedrine hydrochloride)	185.69	0.37	12.3	0.22	4.0
Metycaine hydrochloride	292.82	0.20	6.7	0.12	3.4
Mild silver protein	—	0.18	6.0	0.11	—
Morphine hydrochloride	375.84	0.15	5.0	0.09	3.3
Morphine sulfate	758.82	0.14	4.8	0.08	6.2
Naphazoline hydrochloride (privine hydrochloride)	246.73	0.27	7.7	0.16	3.3
Neomycin sulfate	—	0.11	3.7	0.06	—
Neostigmine bromide (prostigmine bromide)	303.20	0.22	6.0	0.11	3.2
Nicotinamide	122.13	0.26	8.7	0.15	1.9
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
Penicillin G sodium	356.38	0.18	6.0	0.11	3.8
Phenacaine hydrochloride (holocaine hydrochloride)	352.85	0.20	5.3	0.11	3.3

TABLE 8–4. ***(continued)***

Substance	*MW*	*E*	*V*	$\Delta T_f^{1\%}$	L_{iso}
Phenobarbital sodium	254.22	0.24	8.0	0.14	3.6
Phenol	94.11	0.35	11.7	0.20	1.9
Phenylephrine hydrochloride (neosynephrine hydrochloride)	203.67	0.32	9.7	0.18	3.5
Physostigmine salicylate	413.46	0.16	5.3	0.09	3.9
Physostigmine sulfate	648.45	0.13	4.3	0.08	5.0
Pilocarpine nitrate	271.27	0.23	7.7	0.14	3.7
Potassium acid phosphate (KH_2PO_4)	136.13	0.43	14.2	0.25	3.4
Potassium chloride	74.55	0.76	25.3	0.45	3.3
Potassium iodide	166.02	0.34	11.3	0.20	3.3
Procaine hydrochloride	272.77	0.21	7.0	0.12	3.4
Quinine hydrochloride	396.91	0.14	4.7	0.08	3.3
Quinine and urea hydrochloride	547.48	0.23	7.7	0.14	7.4
Scopolamine hydrobromide (hyoscine hydrobromide)	438.32	0.12	4.0	0.07	3.1
Silver nitrate	169.89	0.33	11.0	0.19	3.3
Sodium acid phosphate ($NaH_2PO_4 \cdot H_2O$)	138.00	0.40	13.3	0.24	3.2
Sodium benzoate	144.11	0.40	13.3	0.24	3.4
Sodium bicarbonate	84.00	0.65	21.7	0.38	3.2
Sodium bisulfite	104.07	0.61	20.3	0.36	3.7
Sodium borate·$10H_2O$	381.43	0.42	14.0	0.25	9.4
Sodium chloride	58.45	1.00	33.3	0.58	3.4
Sodium iodide	149.92	0.39	13.0	0.23	3.4
Sodium nitrate	85.01	0.68	22.7	0.39	3.4
Sodium phosphate, anhydrous	141.98	0.53	17.7	0.31	4.4
Sodium phosphate·$2H_2O$	178.05	0.42	14.0	0.25	4.4
Sodium phosphate·$7H_2O$	268.08	0.29	9.7	0.17	4.6
Sodium phosphate·$12H_2O$	358.21	0.22	7.3	0.13	4.6
Sodium propionate	96.07	0.61	20.3	0.36	3.4
Sodium sulfite, exsiccated	126.06	0.65	21.7	0.38	4.8
Streptomycin sulfate	1457.44	0.07	2.3	0.04	6.0
Strong silver protein	—	0.08	2.7	0.05	—
Sucrose	342.30	0.08	2.7	0.05	1.6
Sulfacetamide sodium	254.25	0.23	7.7	0.14	3.4
Sulfadiazine sodium	272.27	0.24	8.0	0.14	3.8
Sulfamerazine sodium	286.29	0.23	7.7	0.14	3.9
Sulfanilamide	172.21	0.22	7.3	0.13	2.2
Sulfathiazole sodium	304.33	0.22	7.3	0.13	3.9
Tannic acid	—	0.03	1.0	0.02	—
Tetracaine hydrochloride (pontocaine hydrochloride)	300.82	0.18	6.0	0.11	3.2
Tetracycline hydrochloride	480.92	0.14	4.7	0.08	4.0
Tripelennamine hydrochloride (pyribenzamine hydrochloride)	291.83	0.30	7.3	0.17	3.8
Urea	60.06	0.59	19.7	0.35	2.1
Zinc chloride	139.29	0.62	20.3	0.37	5.1
Zinc phenolsulfonate	555.84	0.18	6.0	0.11	5.9
Zinc sulfate·$7H_2O$	287.56	0.15	5.0	0.09	2.5

*The values in Table 8–4 have been obtained from the data of E. R. Hammarlund