DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 5(2), 93-105 (1979)

DETERMINATIONS OF SODIUM CHLORIDE EQUIVALENTS BY OSMOMETRY

J. Newburger, S. Hays, M. Ruff and J. McGinity
Drug Dynamics Institute
The University of Texas at Austin
College of Pharmacy
Austin, Texas 78712

ABSTRACT

The vapor pressure osmometer was used to calculate the sodium chloride equivalents of several compounds. These values were compared with published values and in some cases, considerable variation was seen. The osmolality was determined for iso-osmotic drug solutions mixed in different ratios with iso-osmotic saline or sorbitol. The drugs investigated included atropine sulfate, tetracycline hydrochloride, homatropine hydrobromide, pilocarpine nitrate, amphetamine sulfate and bromodiphenhydramine hydrochloride. The results of these studies showed that colligative properties of multicomponent aqueous solutions are often non-additive in manner. The changing osmolality suggests that ion-ion or ion-molecule forces are occurring and when osmolality increases, so does the number of particles in solution.

INTRODUCTION

It is generally agreed that solutions designed to be mixed with body fluids or instilled into the eye should be iso-osmotic with the body fluids. Murty et al., (1) explored practical aspects of iso-osmotic problems pertaining to the use of parenteral electrolytes and other large volume parenterals commonly administered intravenously. These researchers demonstrated that differences in actual and theoretical osmolality values do exist in a number of these preparations and urged that available technology (available to manufacturers) be used to provide accurate data to life support professionals.

Murty et al., (1) found that the conversion of osmolality to the more practical osmolarity necessitates the measurement of the solution density. A later report by Streng et al., (2) showed that the conversion to osmolarity requires the use of partial molal volumes of the solutes.

The sodium chloride equivalent method for adjusting the tonicity of pharmaceutical solutions was developed by Mellen and Seltzer (3). The sodium chloride equivalent (E) values are based on the general assumption that non-electrolytes have a dissociation factor symbolized as i, of one, and substances which dissociate into two ions have an i value of 1.8 (4).

The use of E values assumes that when two or more drugs are present in solution their individual colligative properties are additive. This assumption fails to take into consideration that the activity of a solution may be concentration dependent and

that the colligative properties may be influenced by ion-ion or ion-molecule interactions. Most published E values have been calculated from less than accurate ion-ion or ion-molecule interaction data (i values). Daniels and Alberty (5) indicate that there is a difference in the i values for 2 ion compounds and also that the value varies with concentration. For a given solute, i increases as the concentration is decreased and at infinite dilution, i approaches definite limits which are integers.

The true value of i is the very basis for properly comparing the activity of compounds in solution: E, in fact, depends on this activity. Modern methods of osmolality determination using highly reproducible vapor pressure measurements and established mathematical relationships, permit i and subsequently E, to be very precisely described for any known compound.

The purpose of the present communication is to determine the E values of various electrolytes and drug substances using osmolality measurements. In addition, the colligative behavior of isotonic drug solutions was examined in the presence of 0.9% sodium chloride and isotonic sorbitol solutions.

EXPERIMENTAL

Materials - The following substances were used: Sodium chloride[1], zinc sulfate monohydrate[2], sodium carbonate monohydrate[2], boric acid[3], urea[3], atropine sulfate[4], amphetamine sulfate[5], dextrose anhydrous[6], homatropine hydrobromide[7], pilocarpine nitrate[7], bromodiphenhydramine hydrochloride[8], tetracycline hydrochloride[9], and sorbitol[10].

Osmolality Determinations - A vapor pressure osmometer[11] was standardized using solutions supplied by the manufacturer to insure a linear response was obtained over the range of 100-1000 mOsm/kg. Below an osmolality of 100 mOsm/kg, non-linearity increased as the value approached zero. Isotonic solutions of sodium chloride were prepared from recrystallized material and the average osmolality reading for 0.9% (w/v) sodium chloride was found to be 286 mOsm/kg. This value was used as a base line determination for all future comparisons.

Solutions were prepared in de-ionized water using published E values (4), in the range of concentrations which would give osmolality readings from 200-400 mOsm/kg. The plots of osmolality versus concentration were linear over the range investigated. The concentration corresponding to 286 mOsm/kg was extrapolated from the graph and the sodium chloride equivalent value was determined. A solution of the drug substance was then prepared using the experimentally determined sodium chloride equivalent value and tested in the osmometer. In all cases the solution was found to have the same reading (286 ± 2 mOsm/kg) as 0.9% (w/v) sodium chloride. The reported data represent the mean of triplicate measurements.

RESULTS AND DISCUSSION

Using vapor pressure osmolality measurements, the E values for several electrolytes, non-electrolytes and drug substances were experimentally determined. These values are shown in Table 1

Table 1 - Published and Experimentally Determined E Values

Substance	E Values				
	Reference (4)	Reference (8)	Mean Published Value	Experimental	Difference from Mean %
Dextrose Anhy.	0.18	0.18	0.18	0.17	-5.9%
Boric Acid	0.52	0.50	0.51	0.47	-8.5%
Sodium Carbonate·H_2O	0.68	0.60	0.63	0.66	+4.5%
Urea	0.54	0.59	0.565	0.51	-10.8%
Atropine Sulfate·H_2O	0.12	0.13	0.125	0.10	-25%
Pilocarpine Nitrate	0.22	0.23	0.225	0.19	-18.4%
Homatropine Hydrobromide	0.16	0.17	0.165	0.14	-18%
Amphetamine Sulfate	0.23	0.22	0.225	0.21	-7.1%
Zinc Sulfate.$7H_2O$	0.16	0.15	0.155	0.12	-29%

and are compared with published values. As shown in the table, the experimentally determined E varies from the mean literature reported E values from as low as 4.5% for sodium carbonate up to 29% for zinc sulfate.

Murty & Kapoor (6) have previously reported on the linearity of osmotic properties with concentration and suggested the use of the osmometer in the manufacture and control of parenteral products. As mentioned earlier, linearity was also found for each substance over the range of 200-400 mOsm/kg. However, in all cases when iso-osmotic solutions of sodium chloride or sorbitol were mixed with iso-osmotic drug solutions, non-linear relationships of osmolality versus concentration resulted as seen in Figs. 1, 2 and 4.

For tetracycline hydrochloride, the osmolality of the solution when mixed with iso-osmotic saline or sorbitol, increased 28 mOsm/kg and 25 mOsm/kg respectively (see Fig. 1). The maxima occurred when approximately 50% of each solution was present in the mixture.

An increase of 20 to 25 mOsm/kg was also seen with iso-osmotic solutions of atropine sulfate and either sodium chloride or sorbitol solution. These results are seen in Fig. 2. Similar increases in osmolality were also observed with amphetamine sulfate, homatropine hydrobromide and pilocarpine nitrate. When iso-osmotic solutions of saline and sorbitol were mixed in various ratios, a linear relationship was found as seen in Fig. 3.

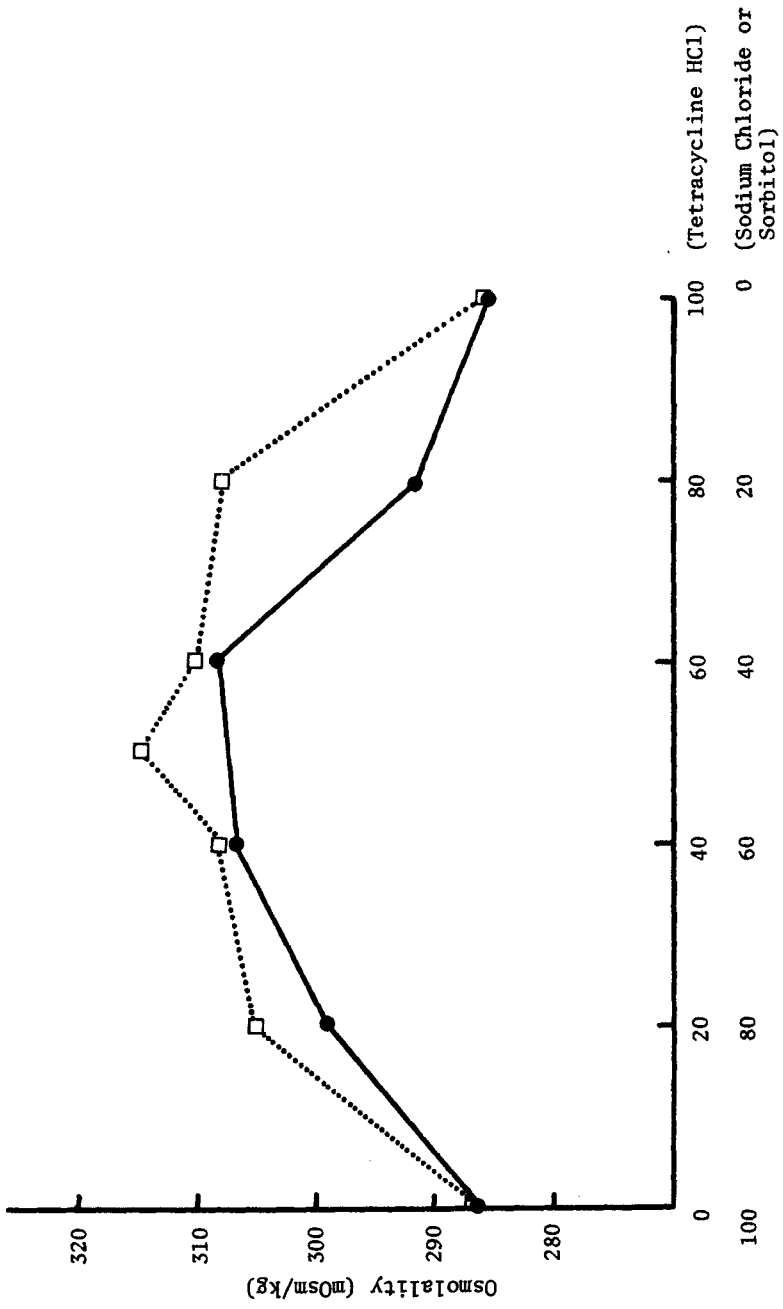

Figure 1: Osmolality of binary solutions of iso-osmotic tetracycline hydrochloride with iso-osmotic sodium chloride (□) and iso-osmotic sorbitol (●).

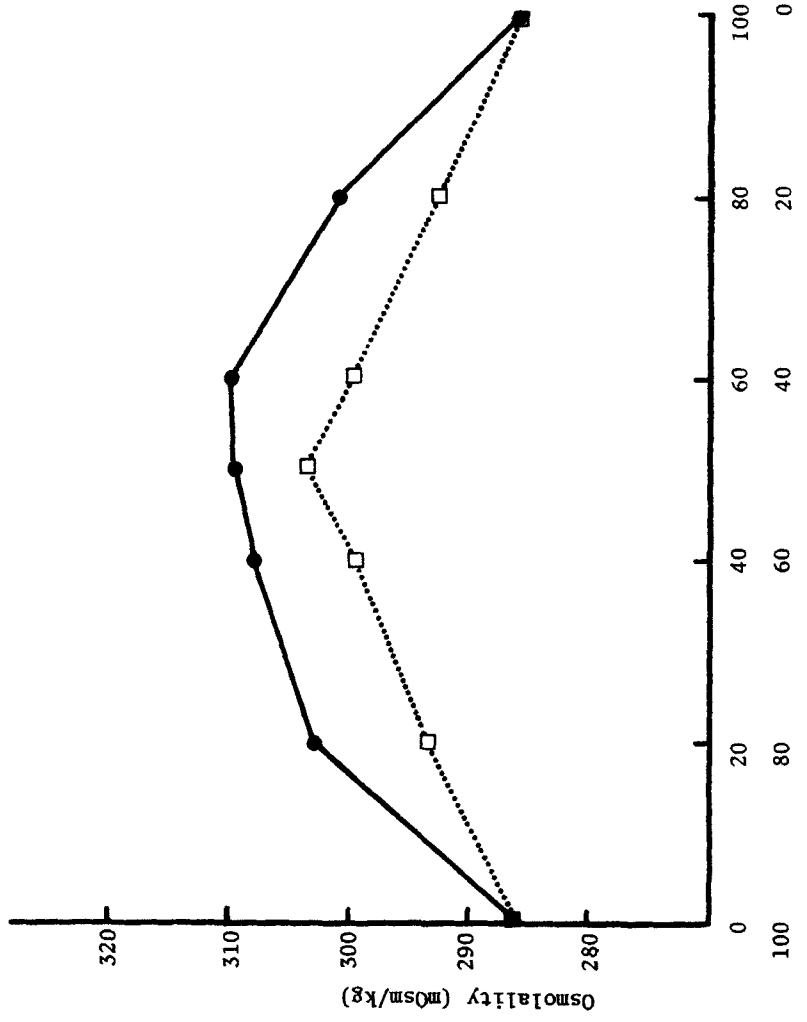

Figure 2: Osmolality of binary solutions of iso-osmotic atropine sulfate with iso-osmotic sodium chloride (□) and iso-osmotic sorbitol (●).

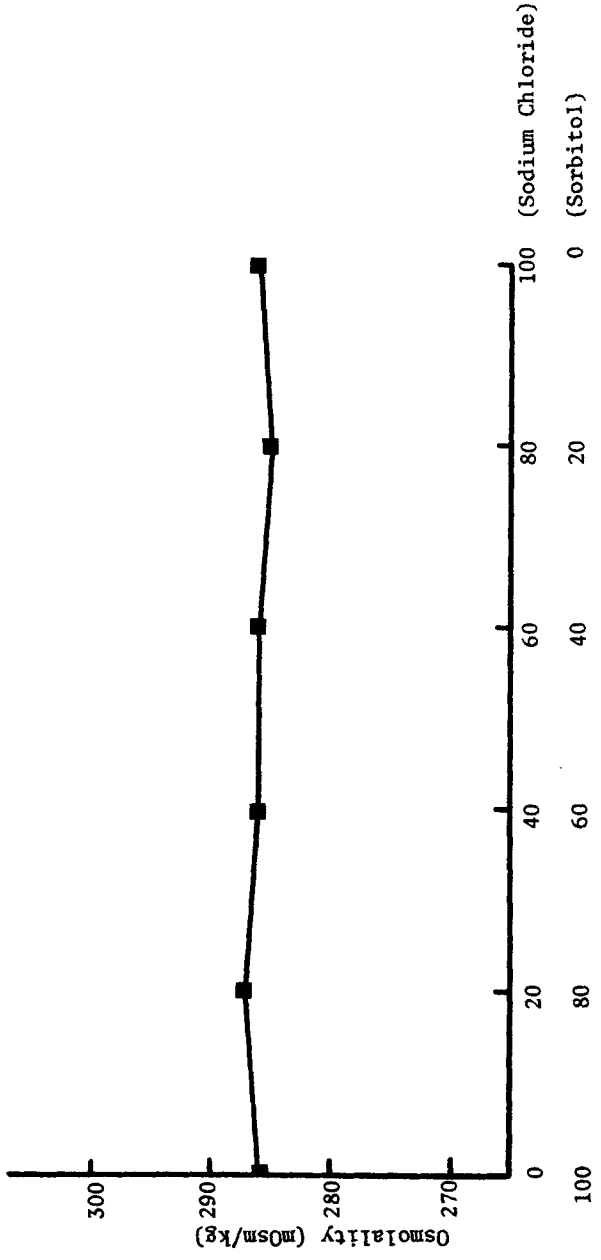

Figure 3: Osmolality of binary solutions of iso-osmotic sodium chloride with iso-osmotic sorbitol.

Of all the drugs studied, the most dramatic effect on osmolality was seen with the antihistamine, bromodiphenhydramine hydrochloride. As shown in Fig. 4, the solution containing 2 parts of iso-osmotic drug solution and 8 parts of sorbitol increases the osmolality reading by 78 mOsm/kg. An increase of approximately 37 mOsm/kg was found when iso-osmotic saline was mixed in various proportions with bromodiphenhydramine hydrochloride.

The changing osmolality with various ratios of drug and electrolyte or non-electrolyte suggests that ion-ion or ion-molecule interactions are occurring and as the osmolality increases, so does the number of particles in solution.

Vapor pressure of solvent water depends, not only on the temperature, but also on the concentration of particles held in solution. By definition, osmolality means the number of dissolved particles, whether molecules, ions, or molecular aggregates, in one kilogram of solvent. Although the calculated osmolality is simply the sum of separately estimated solute concentrations, true osmolality is a property, not of solutes, but of the solvent (7).

It is difficult to speculate at this time on the reasons for the unusual behavior of the iso-osmotic drug solutions in the presence of saline and sorbitol. Similar, but less dramatic results, were seen with dextrose.

The results of this investigation have shown that colligative properties of multicomponent aqueous solutions are often non-additive in a linear fashion. Further investigation is underway in

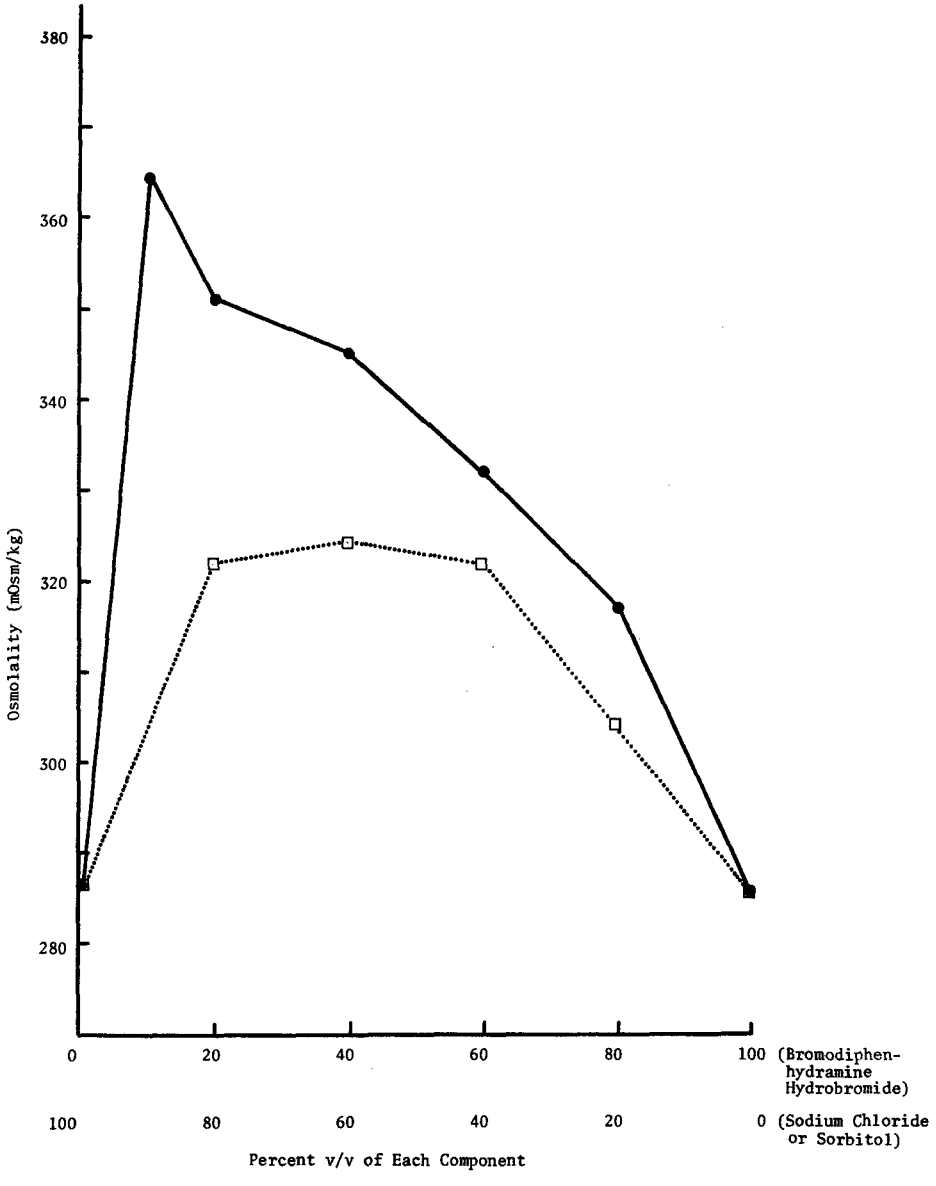

Figure 4: Osmolality of binary solutions of iso-osmotic bromodiphenhydramine hydrochloride with iso-osmotic sodium chloride (□) and iso-osmotic sorbitol (●).

our laboratory to determine the cause of these deviations from ideality.

FOOTNOTES

[1] Fisher Scientific Company, Fair Lawn, NJ

[2] J.T. Baker Chemical Company, Phillipsburg, NJ

[3] Allied Chemical, Morristown, NJ

[4] City Chemical Corporation, New York, NY

[5] Smith Kline and French, Philadelphia, PA

[6] Matheson, Coleman and Bell, Manufacturing Chemists, Norwood, OH.

[7] Merck and Company, Rahway, NJ

[8] Park Davis, Detroit, MI

[9] Reid-Provident Laboratories Inc., Atlanta, GA

[10] Sorbo, ICI Americas Inc., Wilmington, DE

[11] Model 5100B, Wescor Inc., Logan, UT

REFERENCES

1. B.S.R. Murty, J.N. Kapoor and P.P. DeLuca, Am. J. Hosp. Pharm., 33, 546 (1976).

2. W.H. Streng, H.E. Huber and J.T. Carstensen, J. Pharm. Sci., 67, 384 (1978).

3. M. Mellen and L.A. Seltzer, J. Am. Pharm. Assoc., Sci. Ed., 25 759 (1936).

4. M. J. Stoklosa, "Pharmaceutical Calculations," 6th Ed., Lea and Febiger, Philadelphia, Pa. p. 197 (1974).

5. F. Daniels and R.A. Alberty "Physical Chemistry", 1st Ed., John Wiley and Sons Inc., New York p. 231 (1955).

6. B.S.R. Murty and J.N. Kapoor, Pharmaceutical Technology, 1, #2, 37 (1977).

7. T.L. Dormandy, Lancet, 1, 267 (1967).

8. E. Hammarlund and K. Pedersen-Bjergaard, J. Am. Pharm. Assoc. Sci. Ed., 47, 107 (1958).