Osmolality of Parenteral Solutions

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Abstract □ Osmolality–concentration profiles for individual and mixed solute systems are presented. Linear relationships between osmolality and concentration held true in all systems examined at concentrations below 0.2 molal levels. At higher concentrations, linearity existed only in select systems. Deviations from linearity can be greater or less than extrapolated values. In view of the need to determine an osmolarity conversion factor for each parenteral formulation and the many errors possible in the use of these values, adoption of osmolality values for labeling parenteral products rather than osmolarity, as stipulated in USP XIX–NF XIV third supplement, is strongly recommended.

Keyphrases □ Osmolality—parenteral solutions, compared to osmolarity, calculations □ Osmolarity—parenteral solutions, compared to osmolality, calculations □ Parenteral solutions—osmolality and osmolarity compared, calculations

Use of the terms osmolality and osmolarity was once confined largely to clinical laboratories and hospital pharmacies; however, the terms are now being applied to parenteral solutions. The third supplement of USP XIX–NF XIV (1) requires that pharmacopeial solutions providing intravenous replenishment of fluid, nutrients, or electrolytes, as well as the osmotic diuretic mannitol injection, state the osmolar concentration.

These terms are not familiar to many; and with the compendial requirements for labeling, it seems appropriate to discuss them at length. The purposes of this manuscript are to review the important theoretical considerations of osmolality and osmolarity and to present a few experimentally obtained osmolality–concentration profiles to illustrate the interrelation of some representative solutes utilized in parenteral formulas. This information serves as a basis for a recommendation on parenteral labeling.

BACKGROUND

Labeling—In 1975, USP XIX required sodium chloride injection labeling to state the total osmolarity of the solution, expressed in milliosmoles per liter. Since label components of a quantitative nature usually require some analytical method to demonstrate the label claim within limits, it was considered reasonable to determine what production experience would show in lot-to-lot variation.

As some investigators discovered, instrumentation measures the osmolality of a solution, milliosmoles per kilogram of solvent, not the osmolarity, milliosmoles per liter of solution. To be precise for labeling purposes, a search was undertaken for a mathematical expression to relate these two entities. Little was found in the literature or textbooks to equate these two terms. The problems in this area were recognized previously and reviewed at length (2). Previous investigators also attempted to equate the two expressions to resolve the problem and pointed out that solution measurements can be carried out only in terms of osmolality. In the physical chemistry discipline, osmolality is used and is well defined in terms of basic concepts. In pharmaceutical practice, a definition of osmolarity has been developed, but a derivation of the basic relationship between osmolality and osmolarity was not found.

Streng *et al.* (3) carried out this mathematical exercise and determined that osmolarity was not measurable as a defined parameter. The conversion of osmolality measurements to osmolarity requires determination of the partial molal volume of the solute(s) at infinite dilution and the density of the pure solvent. In simple one-solute aqueous systems, this determination is not difficult, and a single conversion factor can be de-

termined for all concentrations. For more complex systems such as hyperalimentation fluids, conversion factor determination becomes more complex and questionable.

The alternative to such a dilemma would be to label the products in osmolality terms, directly measurable by instrumentation, provided the concentrations are within the 100–2000-milliosmoles/kg range usually measurable with commercially available osmometers.

Osmolarity Calculations—Pharmacists over the years have used gravimetric measurements for solids and volumetric measurements for liquids. The preparation of solutions by weighing the liquid occurs primarily in industry. This practice of bringing solutions to volume rather than using a specific solvent weight has led to the term osmolarity.

Although one cannot measure osmolarity (osmoles or milliosmoles per liter of solution), it is commonly assumed the numerical values do not differ significantly from those of osmolality (milliosmoles per kilogram of solvent) and that the two can be used interchangeably. This assumption may be reasonable in some cases. However, these terms must be fully understood so that they can be used correctly and, perhaps, interchangeably where the error is negligible or insignificant.

Calculations in the pharmaceutical literature that utilize osmolality or osmolarity values assume that the values change in direct proportion to the change in solute(s) concentration. The literature also teaches that the osmolality/osmolarity values for individual solute systems can be used
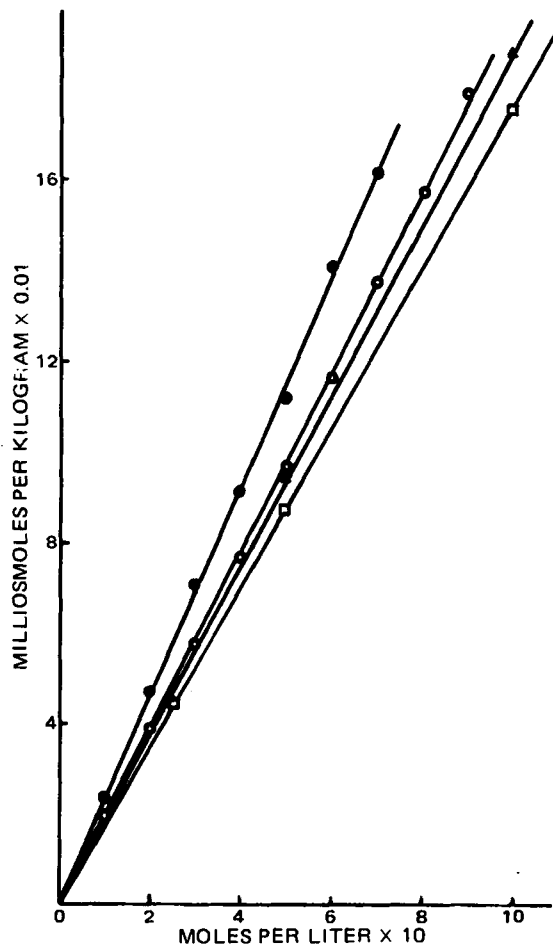

Figure 1—*Osmolality–molar concentration profiles of sodium chloride (△), potassium chloride (□), sodium acetate (O), and sodium tartrate (●) aqueous solutions.*

Table I—Osmotic Coefficients for Sodium Chloride and Calcium Chloride Aqueous Solutions at 25°

| Molal Concentration (m) | Molar Concentration (M^a) | | Osmotic Coefficient at 25° (φ^{25}) | | Osmolality, mOs/kg | |
	Sodium Chloride	Calcium Chloride	Sodium Chloride	Calcium Chloride	Sodium Chloride	Calcium Chloride
0.100	0.098	0.098	0.9324	0.854	186.5	256.2
0.200	0.196	0.197	0.9245	0.862	369.8	517.2
0.300	0.294	0.296	0.9215	0.876	552.9	788.4
0.400	0.391	0.394	0.9203	0.894	736.2	1072
0.500	0.488	0.494	0.9209	0.917	920	1375
0.600	0.587	0.592	0.9230	0.940	1109	1692
0.700	0.685	0.690	0.9257	0.963	1295	2022
0.800	0.783	0.786	0.9288	0.988	1486	2371
0.900	0.881	0.880	0.9320	1.017	1677	2745
1.000	0.978	0.974	0.9355	1.046	1871	3138

[a] Calculated from m = 1000 × M/C_w. The C_w values were obtained from Ref. 6.

additively to calculate the value for a solution containing two or more solutes.

In reality, few solutions exhibit a linear relationship between osmolality and concentration except in dilute solutions, and the linear concentration range varies from one substance to another. The assumption of an additive property was tested and found to hold for all solutions tested at less than 0.2 molal concentrations. The results constitute the following experimental section.

Basic Principles—Before proceeding further, a review of basic principles should be extended to clarify the terminology. A solution can be characterized by what is referred to in physical chemistry as its colligative properties: (a) freezing point, (b) boiling point, (c) vapor pressure, and (d) osmotic pressure. All of these measurable parameters are related to the same physical property: the ratio of solute "particles" to molecules of water or mole fraction of water.

Osmolality is defined as that mass of solute which, when dissolved in 1 kg of water, will exert an osmotic pressure equal to that exerted by a gram-molecular weight of an ideal unionized substance dissolved in 1 kg of water. Osmolarity is defined as that mass of solute which, when dissolved in 1 liter of solution, will exert an osmotic pressure equal to that exerted by a gram-molecular weight of an ideal unionized substance dissolved in 1 liter of solution.

From the derivations of Streng et al. (3), osmolality can be described by:

$$\xi_m = vm\varphi\frac{\bar{v}_1^0}{\bar{v}_1} \qquad \text{(Eq. 1)}$$

where:

ξ_m = osmolality
v = number of ions into which the solute theoretically dissociates
m = molality of the solution
φ = osmotic coefficient
$\dfrac{\bar{v}_1^0}{\bar{v}_1}$ = ratio of the partial molal volumes for the solvent at infinite dilution and in the solution
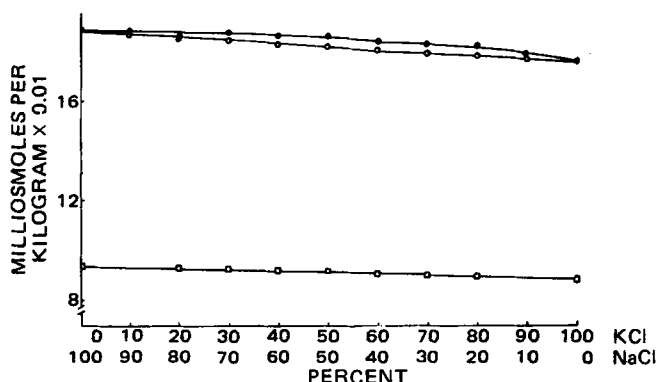
Figure 2—*Osmolality-molar concentration profile of mixtures of sodium chloride and potassium chloride in aqueous solutions. Key: ●, measured osmolality values for aqueous solutions containing a mixture of sodium chloride and potassium chloride totaling 1.0 M concentrations; ○, calculated osmolality values determined by summing values for each component at its respective concentration; and □, measured osmolality and calculated osmolality values for solutions containing mixtures of sodium chloride and potassium chloride at 0.5 M total concentration.*

For the concentration ranges normally considered, the ratio $(\bar{v}_1^0/\bar{v}_1)$ has a value close to one[1].

Osmolarity is described by:

$$\xi_c = vm\varphi[d_1^0(1 - 0.001\bar{v}_2^0)] \qquad \text{(Eq. 2)}$$

where:

ξ_c = osmolarity
d_1^0 = density of the pure solvent
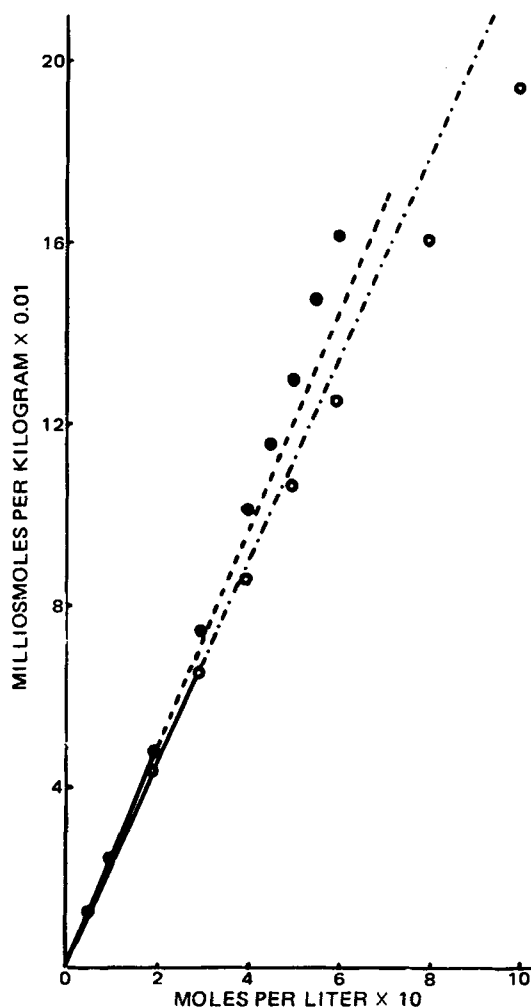$\bar{v}_2^0$ = partial molal volume of the solute

Figure 3—*Osmolality-molar concentration profile for aqueous solutions of calcium chloride (●) and sodium sulfate (○).*

[1] The ratio $(\bar{v}_1^0/\bar{v}_1)$ is dependent upon the solute system. There is, however, little difference in this ratio between simple salt solutions. Sodium chloride solution has a value of 1.001 for a 1 molal concentration.
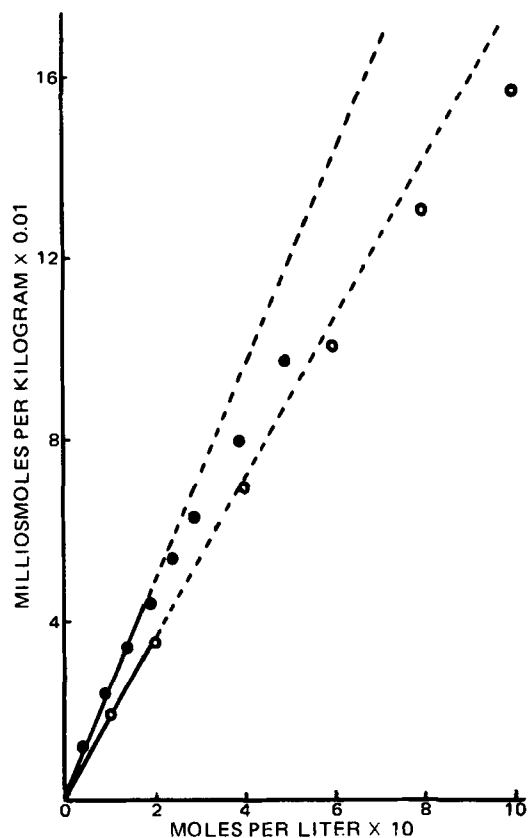
Figure 4—*Osmolality-molar concentration profile for aqueous solutions of dibasic sodium phosphate (●) and monobasic sodium phosphate (○).*

Thus, osmolarity can be calculated from osmolality measurements by:

$$\xi_c = \xi_m[d_1^0(1 - 0.001\bar{v}_2^0)] \qquad \text{(Eq. 3)}$$

The conversion factor $[d_1^0(1 - 0.001\bar{v}_2^0)]$ for sodium chloride solutions is 0.98049; for potassium chloride solutions, it is 0.97041(3).

Partial molal volumes are available in the literature for some solutes; however, for most pharmaceutical compounds, it is necessary to determine these values experimentally.

Table I shows the osmotic coefficients and osmolality values for sodium chloride and calcium chloride solutions taken from the literature (4).
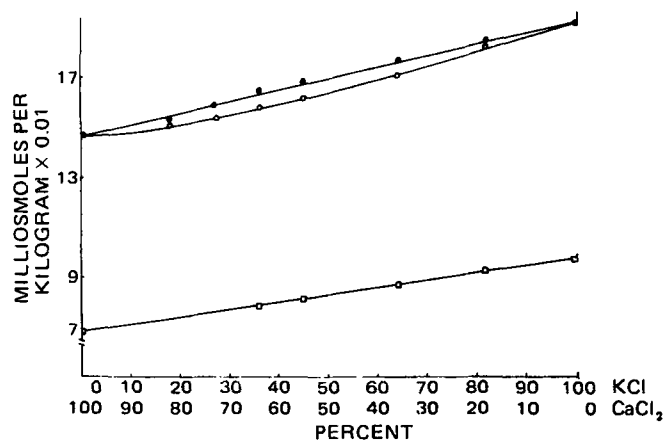

Figure 5—*Osmolality-molar concentration profile of aqueous solutions containing mixtures of calcium chloride and potassium chloride. Key: ○, measured osmolality values for mixtures of calcium chloride and potassium chloride totaling 1.1 M chloride concentration; ●, calculated osmolality values determined by summing values for each component at its respective concentration; and □, measured osmolality and calculated osmolality values for mixtures of calcium chloride and potassium chloride at 0.55 total chloride concentration.*
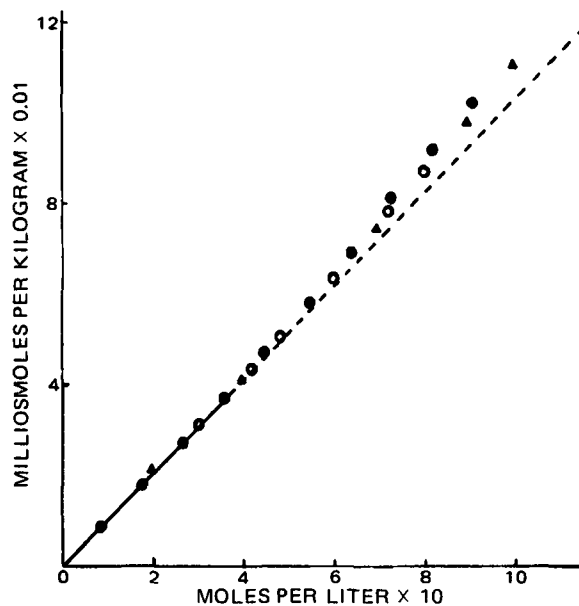

Figure 6—*Osmolality-molar concentration profiles for aqueous solutions of dextrose (●), mannitol (○), and sorbitol (△).*

Osmotic coefficients can be found in these tables for many electrolytes and for a few nonelectrolytes. However, coefficients for most pharmaceutical compounds need to be determined. Examination of Table I shows that deviation from linearity is small for sodium chloride in terms of milliosmoles per kilogram up to a 1.0 molal concentration. For calcium chloride solutions, the deviation becomes much greater. In the case of a twofold dilution of a 0.8 molal solution, the value is about 100 mOs/kg less than expected. For the same dilution with sodium chloride solution, the value is only 7 mOs/kg less than expected. A 0.9% sodium chloride solution is ~0.15 molal.

EXPERIMENTAL

Experiments were carried out to determine the extent of change in the osmolality as a function of concentration for various solutes and for mixtures of these solutes in aqueous solutions.

Solutions were prepared, in the usual manner, on a molar rather than molal basis; a concentration–osmolality profile was obtained for each solute as well as for solute combinations in aqueous solution. Any concentration representation could have been used, such as milligrams per milliliter or molality. All molar concentrations were calculated on an anhydrous basis.

A vapor pressure osmometer[2] was used to measure the osmolality (milliosmoles per kilogram) of each solution. Prior to use, the instrument was calibrated with the appropriate sodium chloride reference standard[3]. A minimum of three readings was taken for each solution, and the standard deviations fell well within the areas of the open or solid geometric forms used in the graphs.

Profiles of the experimental solutions for sodium chloride, potassium chloride, sodium acetate, calcium chloride, sodium sulfate, dibasic sodium phosphate, and monobasic sodium phosphate were checked against calculated profiles obtained by using the osmotic coefficients reported in the literature (4) for the solutes in solutions at 25° ($\xi_m = \nu m\varphi^{25}$). In all cases except calcium chloride, the experimental osmolality values did not differ significantly from the calculated values. For calcium chloride, the values were slightly less than expected, indicating that the material contained water and was not completely anhydrous. Due to the hygroscopic nature of anhydrous calcium chloride, this finding was not surprising.

Profiles for dextrose, mannitol, and sorbitol sugars were also determined. These compounds are used in parenterals and are representative of nonionizing substances. Similar profiles for some of these components were reported previously (2).
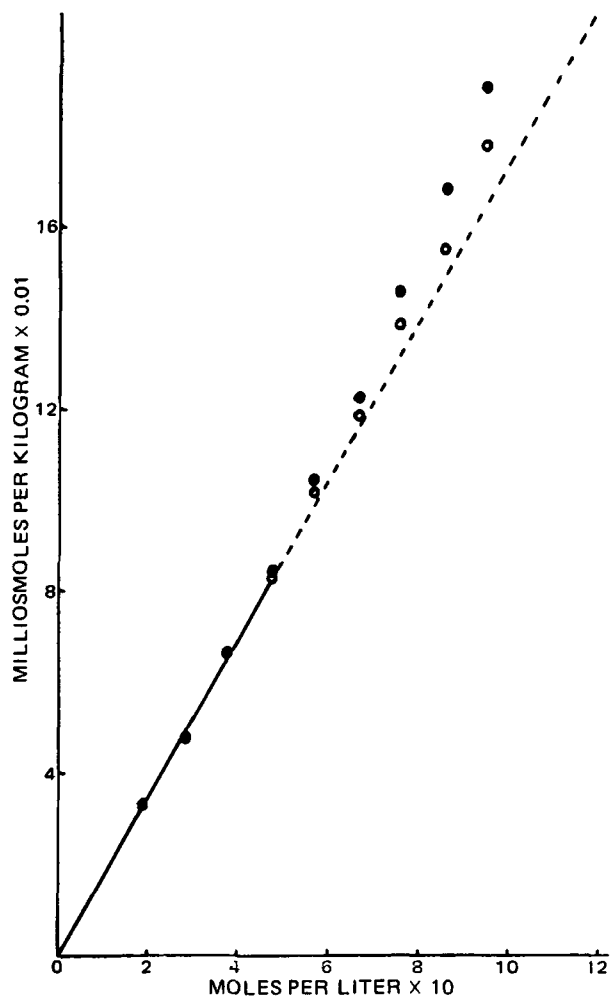
Figure 7—*Osmolality-molar concentration profile for aqueous solutions containing equal molar amounts of calcium chloride and dextrose. Key:* ●, *measured osmolality values for mixtures of calcium chloride and dextrose; and* O, *calculated osmolality values determined by summing values for each component at its respective concentration.*

To determine the resulting osmolality values for combinations of these components, solutions with various compositions and concentrations were measured as a function of concentration. The values obtained were then compared to calculated values, assuming additive relationships for each component, as is common practice.

RESULTS

Monovalent Solutes—Figure 1 shows the approximately linear response between osmolality and concentration, up to 1.0 M, for sodium chloride, potassium chloride, sodium acetate, and sodium tartrate. Figure 2 shows the measured osmolality values for sodium chloride–potassium chloride mixtures made in different ratios at 1 M and diluted to 0.5 M total concentrations. The measured osmolality value for each mixture differed or agreed with the sum of the experimentally obtained values for each compound as shown. For the mixed salts at 1 M concentration, the values differed by as much as 50 mOs/kg in the region where ratios between 40:60 and 60:40 were used. Upon dilution to 0.5 M, these same solutions gave measured results identical to calculated values.

Polyvalent Solutes—Figure 3 shows the values obtained for calcium chloride and sodium sulfate. With calcium chloride, the osmotic coefficient values increased as the concentration increased from 0.1 to 1.0 molal; with sodium sulfate, the coefficient decreased over this same range. The result is a positive deviation (higher values) with increased concentration for calcium chloride solutions but negative deviation (lower values) with increased concentration for sodium sulfate solutions.

Figure 4 illustrates a negative deviation for the phosphate salt (dibasic sodium phosphate and monobasic sodium phosphate) solutions. Although
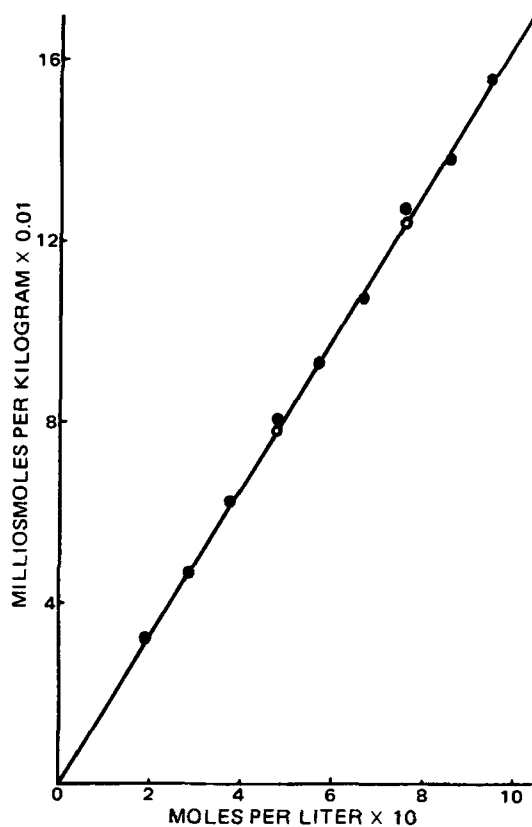

Figure 8—*Osmolality-molar concentration profile for aqueous solutions containing equal molar amounts of sodium sulfate and dextrose. Key:* ●, *measured osmolality values for mixtures of sodium sulfate and dextrose; and* O, *calculated osmolality values determined by summing values for each component at its respective concentration.*

not as obvious as in a plot using molal concentrations *versus* osmolality, the greater negative deviation from linearity of dibasic sodium phosphate solutions over monobasic sodium phosphate solutions is apparent since the number of ions, ν, for dibasic sodium phosphate is three and that for monobasic sodium phosphate is two.

Solutions containing mixtures of potassium chloride and calcium chloride in varying ratios to give 1.1 M chloride concentrations were studied in the same manner as potassium chloride and sodium chloride. The difference between the calculated and measured values for 1.1 M solutions can be seen in Fig. 5. Again, dilution to 0.55 M concentration gave the same calculated values as observed values.

Nonionic Sugar Solutes—Figure 6 shows the relationships obtained for the nonionizing sugars dextrose, mannitol, and sorbitol. All three showed a positive deviation from linearity above 0.4 M concentrations, and the osmolality values agreed very closely with each other for the same molar concentrations. For a point of comparison, a 5% dextrose solution is ~0.3 M and a 20% solution is ~1 M.

Solutions of Ionic and Nonionic Solutes—Finally, solutions prepared with an ionic salt and nonionic dextrose gave the results shown in Figs. 7–9. In the first experiment, calcium chloride and dextrose, both positive deviating solutes, were combined in solution to give the results shown in Fig. 7. A positive deviation greater than that calculated for the contribution of each solute was found for total concentrations above ~0.4 M.

Combination of the negatively deviating solute sodium sulfate with dextrose, a positively deviating solute, gave the results shown in Fig. 8. The calculated sum of the values from each single solute system was in close agreement with the measured values. In addition, combination of these two solutes in equal amounts resulted in a linear profile up to 1.0 M total concentration.

A combination of equal molar concentrations of sodium chloride and dextrose gave a linear response in total concentrations up to 0.9 M and a positive deviation at concentrations above 1 M (Fig. 9). For this combination, summation of the osmolality values obtained for each component was on the low side, and the error appeared to increase as the total concentration progressed above 1 M.
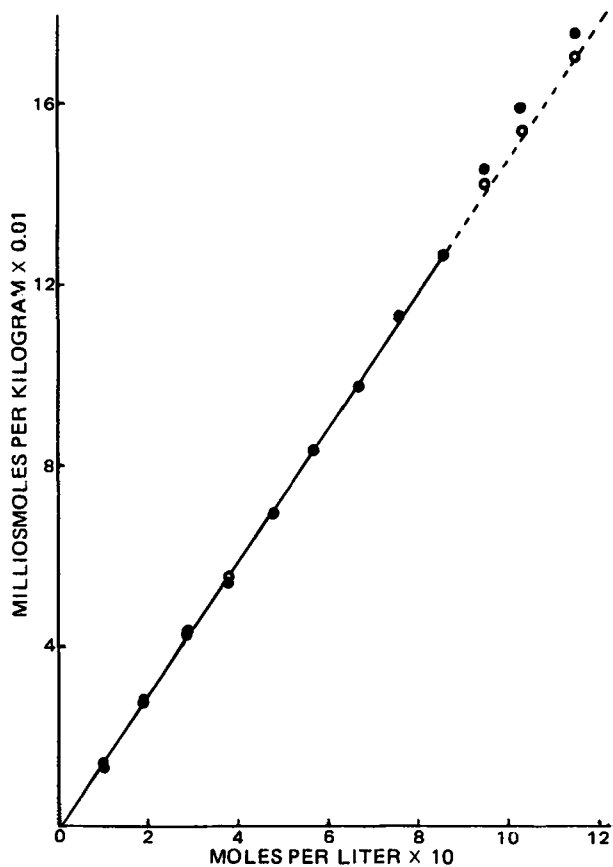
Figure 9—*Osmolality-molar concentration profile for aqueous solutions containing equal molar amounts of sodium chloride and dextrose. Key:* ●, *measured osmolality values for mixtures of sodium chloride and dextrose; and* ○, *calculated osmolality values determined by summing values for each component at its respective concentration.*

DISCUSSION

These studies demonstrated that the measured osmolality values for solute mixtures above 0.2–0.4 M concentrations differed from calculated values by amounts that were dependent on the total solute concentration and the specific combination of solutes. In general terms, if the osmolality of the solution exceeded 500–800 mOs/kg, a difference between measured and calculated values could be expected. The deviations also could be greater or less than calculated values, depending on the solutes.

Although these experiments were carried out with volumetrically formulated solutions, it would have been well to have used molal concentrations and weighed the solvent as well as the solutes. Recalculation of the molar solutions to molal equivalents in order to compare experimental results with literature values was tedious and not possible in some cases.

Measurement of solution colligative properties is based on the molal relationship; use of molar concentrations makes calculations more difficult or, possibly, incorrect if the molar concentration is assumed to be the same as a molal concentration. Although it may be more convenient to formulate by volumetric measurement, for accuracy and meaningful data interpretation, this practice should be abandoned when carrying out research in this area. There is also the added advantage of avoiding the errors introduced when incorrectly calibrated volumetric equipment is used or when the solution temperature is not controlled.

Based on these considerations, it is recommended that osmolality values be used in labeling parenteral products and that the term osmolarity be avoided. This practice would eliminate the need to determine a conversion factor for each parenteral system. In some cases, it may be impossible to calculate a conversion factor and only osmolality values can be obtained.

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