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# Pharmaceutical Sciences

UNIVERSITY of NORTH CAROLINA

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## Chapter **79** Tonicity, Osmoticity, Osmolality, and Osmolarity

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It is generally accepted that osmotic effects have a major place in the maintenance of homeostasis (the state of equilibrium in the living body with respect to various functions and to the chemical composition of the fluids and tissues, e.g., temperature, heart rate, blood pressure, water content, blood sugar, etc.). To a great extent these effects occur within or between cells and tissues where they cannot be measured. One of the most troublesome problems in clinical medicine is the maintenance of adequate body fluids and proper balance between extracellular and intracellular fluid volumes in seriously ill patients. It should be kept in mind, however, that fluid and electrolyte abnormalities are not diseases, but are the manifestations of disease.

The physiologic mechanisms which control water intake and output appear to respond primarily to serum osmoticity. Renal regulation of output is influenced by variation in rate of release of pituitary antidiuretic hormone (ADH) and other factors in response to changes in serum osmoticity. Osmotic changes also serve as a stimulus to moderate thirst. This mechanism is sufficiently sensitive to limit variations in osmoticity in the normal individual to less than about 1%. Body fluid continually oscillates within this narrow range. An increase of plasma osmoticity of 1% will stimulate ADH release, result in reduction of urine flow, and at the same time stimulate thirst that results in increased water intake. Both the increased renal reabsorption of water (without solute) stimulated by circulating ADH and the increased water intake tend to lower serum osmoticity.

The transfer of water through the cell membrane occurs so rapidly that any lack of osmotic equilibrium between the two fluid compartments in any given tissue is usually corrected within a few seconds, and at most within a minute or so. However, this rapid transfer of water does not mean that complete equilibration occurs between the extracellular and intracellular compartments throughout the whole body within this same short period of time. The reason for this is that fluid usually enters the body through the gut and must then be transported by the circulatory system to all tissues before complete equilibration can occur. In the normal person it may require 30-60 minutes to achieve reasonably good equilibration throughout the body after drinking water. Osmoticity is the property that largely determines the physiologic acceptability of a variety of solutions used for therapeutic and nutritional purposes.

Pharmaceutical and therapeutic consideration of osmotic effects has been to a great extent directed toward the side effects of ophthalmic and parenteral medicinals due to abnormal osmoticity, and to either formulating to avoid the side

The author gratefully acknowledges suggestions received from Dr. Frederick P. Siegel Professor of Pharmacy, and from Dr. John K. Siepler, osmotic effects definitions osmolarity computation abnormal osmoticity effects osmometry and the clinical laboratory osmoticity and enteral hyperalimentation osmolality determination freezing-point calculations

effects or finding methods of administration to minimize them. More recently this consideration has been extended to total (central) parenteral nutrition, to enteral hyperalimentation ("tube" feeding), and to concentrated-fluid infant formulas.<sup>1</sup> Also, in recent years the importance of osmometry of serum and urine in the diagnosis of many pathological conditions has been recognized.

There are also instances of the direct therapeutic effect of osmotic action, such as the intravenous use of mannitol as a diuretic, which is filtered at the glomeruli and thus increases the osmoticity of tubular urine. Water must therefore be reabsorbed against a higher osmotic gradient than otherwise, so reabsorption is slower and a diuretic effect is observed. The same principle applies, for example, to cathartics such as magnesium sulfate, to plasma substitutes such as polyvinylpyrrolidone, to 5% sodium chloride solution used topically for corneal edema, and to the new drug-delivery system called an "Elementary Osmotic Pump."<sup>2</sup>

Osmometry may be used also in such studies as determining the extent of binding of drugs to macromolecules, and in following the course of chemical reactions in which a net change in the number of particles occurs.

Many medicinal agents affect serum and urine osmoticity. They act either by increasing ADH release, or by inhibiting physiological responses induced by ADH. For example, release of ADH is stimulated by barbiturates, carbamazepine, chlorpropamide, clofibrate, cyclophosphamide, vincristine, and by various tricyclic antidepressants.<sup>3</sup>

If a solution is placed in contact with a membrane that is permeable to molecules of the solvent, but not to molecules of the solute, the movement of solvent through the membrane is called osmosis. Such a membrane is often called *semipermeable*. As the several types of membranes of the body vary in their permeability, it is well to note that they are *selectively* permeable. Most normal living-cell membranes maintain various solute concentration gradients. A selectively permeable membrane may be defined either as one that does not permit free, unhampered diffusion of all the solutes present, or as one that maintains at least one solute concentration gradient across itself. Osmosis then is the diffusion of water through a membrane that maintains at least one solute concentration gradient across itself.

Assume a solution A on one side of the membrane, and a solution B of the same solute but of a higher concentration on the other side; the solvent will tend to pass into the more concentrated solution until equilibrium has been established. The pressure required to prevent this movement is the osmotic pressure. It is defined as the excess pressure, or pressure greater than that above the pure solvent, which must be applied to solution B to prevent passage of solvent through

pressure is related to the number of particles (un-ionized molecules, ions, macromolecules, aggregates) of solute(s) in solution and thus is affected by the degree of ionization or aggregation of the solute. The osmotic pressure, as well as other colligative properties, is determined by the number of particles because they have, on the average, equal kinetic energy, regardless of size. As the effect does not depend on mass, concentration in this case should not be stated in terms of mass.

Body fluids, including blood and lacrimal fluid, normally have an osmotic pressure which is often described as corresponding to that of a 0.9% solution of sodium chloride. The body also attempts to keep the osmotic pressure of the contents of the gastrointestinal tract at about this level, but there the normal range is much wider than that of most body fluids. The 0.9% sodium chloride solution is said to be isoosmotic with physiologic fluids. The term isotonic, meaning equal tone, is in medical usage commonly used interchangeably with isoosmotic. However, terms such as isotonic and tonicity should be used only with reference to a physiologic fluid. Isoosmotic is actually a physical term which compares the osmotic pressure (or another colligative property, such as freezing point depression) of two liquids, neither of which may be a physiologic fluid, or which may be a physiologic fluid only under certain circumstances. For example, a solution of boric acid that is isoosmotic with both blood and lacrimal fluid is isotonic only with the lacrimal fluid. This solution causes hemolysis of red blood cells because molecules of boric acid pass freely through the erythrocyte membrane regardless of concentration. As another example, a "chemically defined elemental diet" or enteral nutritional fluid can be isoosmotic with the contents of the gastrointestinal tract, but would not be considered a physiologic fluid, or suitable for parenteral use.

A solution is isotonic with a living cell if there is no net gain or loss of water by the cell, or other change in the cell when it is in contact with that solution. Physiologic solutions with an osmotic pressure lower than that of body fluids, or of 0.9% sodium chloride solution, are commonly referred to as being hypotonic. Physiologic solutions having a greater osmotic pressure are termed hypertonic.

Such qualitative terms are of limited value, and it has become necessary to state osmotic properties in quantitative terms. To do so a term must be used that will represent all particles that may be present in a given system. The term used is osmol. An osmol is defined as the weight in grams of a solute, existing in a solution as molecules (and/or ions, macromolecules, aggregates, etc.), that is osmotically equivalent to the gram-molecular-weight of an ideally behaving nonelectrolyte. Thus the osmol-weight of a nonelectrolyte, in a dilute solution, is generally equal to its gram-molecularweight. A milliosmol, abbreviated mOsm, is the weight stated in milligrams.

For a solute such as sodium chloride, which is completely ionized, the osmol weight in dilute solution will be about half its gram-molecular-weight. However, as concentration is increased, other factors enter. With strong electrolytes, interionic attraction causes a decrease in their effect on colligative properties. In addition, and in opposition, for all solutes, including nonelectrolytes, solvation and possibly other factors operate to intensify their colligative effect. Therefore it is very difficult and often impossible to predict accurately the osmoticity of a solution. It may be possible to do so for a dilute solution of a single, pure and well-characterized solute, but not for most parenteral and enteral medicinal and/or nutritional fluids: experimental determined in the solution of the so

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## Osmoticity, Osmolality, Osmolarity

It is, moreover, necessary to use three additional terms to define the osmotic situation of solutions: osmoticity, osmolality, and osmolarity. They are all needed. Many professional people, including authors of textbooks, who use the terms do not have a clear understanding of their meaning. This applies especially to the terms osmolality and osmolarity, as the term osmoticity has been in less frequent use. The terms osmolality and osmolarity are often used interchangeably. This is no doubt due, at least in part, to the circumstance that until recent years most of the systems involved were body fluids, where the difference between the numerical values of the two quantities is small, perhaps 1%, and probably similar in magnitude to the error involved in their determination. The confusion seems to have done no real harm up to this time. However, it can be a problem, in some cases a dangerous one, with certain fluids. This seems most likely to occur with the more concentrated solutions used in Total Parenteral Nutrition, Enteral Hyperalimentation, and oral nutritional fluids for infants.

The reasons that all three terms are needed deserve a fairly lengthy explanation but can be summarized as follows:

Osmolarity, which expresses a wt/vol relationship, is simpler to visualize, understand and use than osmolality, but is more difficult to determine with satisfactory accuracy. It is not measured experimentally, the values being approximated by computation from values of osmolality or from ingredient concentration. Osmolarity is affected by temperature changes; osmolality is not.

Osmolality, which expresses a wt/wt relationship, is, compared to osmolarity, more difficult to use in extemporaneous preparation of enteral nutritional fluids (oral or "tube"), and even more difficult to use in extemporaneous preparation of sterile intravenous medicinal and nutritional fluids. However, it can be determined quite readily experimentally. It generally cannot be calculated. Examples of some approximate methods of calculation for serum are given in a later section.

Osmoticity is a more general term. It is useful when one wishes to refer to an osmotic state without stipulating whether one refers to osmolality or osmolarity. Much current confusion could be avoided if this term is used, except in the instances when one specifically means osmolality or osmolarity, as defined in the following section.

As these concepts are coming with increasing frequency to the attention of physicians, nurses, dietitians, the clinical laboratory staff, and to some individuals of the general public, the pharmacist should be able to explain them when necessary.

The unit of osmolality is "that mass of solute which, when dissolved in a kilogram of water, will exert an osmotic pressure equal to that exerted by a gram-molecular-weight of an ideal un-ionized substance dissolved in a kilogram of water," while the unit of osmolarity is "that mass of solute which, when dissolved in sufficient solvent to produce a liter of solution, will exert an osmotic pressure equal to that exerted by a gram molecular weight of an ideal un-ionized substance dissolved in a liter of solution."<sup>4</sup>

In brief, osmolality represents the number of osmols of the solute in a kg of *solvent*, and osmolarity represents the number of osmols in a liter of *solution*. For example, if one assumes the case of the kilogram of solvent measuring 1 liter, and assumes using the same weight of a given solute in the same solvent in both cases, the concentrations (in terms of wt/vol) would be slightly different because in the first case the total volume would be more than 1 liter due to the volume contribution of the solute. Therefore a one-molal solution

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