GENERAL PHARMACOPOEIA MONOGRAPH

Osmolarity   **GPM**.1.2.1.0003.15

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Osmolarity is a characteristic of a solution that demonstrates its osmotic pressure by showing the total concentration of kinetically active particles per solution volume unit (mOsm/L).

Instead of osmolarity, the currently available instrumental methods permit determination of osmolality, i. e. the concentration of kinetically active particles per kilogramme of the solvent (mOsm/kg).

Kinetically active particles include molecules, ions, or ion complexes of one or several dissolved substances that are freely distributed throughout the solvent volume and exhibit an ability to move chaotically inside the solution.

Osmolarity and osmolality characterize the osmotic pressure created by solutions.

Osmolarity is one of the most important characteristics of infusion solutions. The theoretical osmolarity value should be specified on the label of an infusion solution. In the event when the theoretical osmolarity cannot be calculated, the average experimental osmolarity value for the respective medicinal product should be specified.

Theoretical osmolarity can be calculated according to the following equation:

$$C_{осм} = \frac{m}{M} \cdot n \cdot 1000 \qquad\qquad (1)$$

where: $C_{осм.}$ is the osmolarity of the solution expressed in milliosmols per litre (mOsm/L);

  m is the content of the substance in the solution (g/L);

  M is the molar weight of the substance (g);

  n is the total number of ions produced from the same molecule of a dissolved substance as a result of dissociation ($n = 1$ for non-dissociating substances; $n = 2, 3$ for substances producing the respective number of ions when dissolving).

In practical terms, the number of particles (n) is somewhat lower than the theoretically calculated amount, and can be approximately described with the following equation:

$$n = n_o \cdot \varphi \qquad\qquad (2),$$

where: n is the actual number of particles produced upon dissolution of the respective substance;

  n_0 is the theoretically calculated number of particles ($n = 1, 2, 3...$);

  φ is the molar osmotic coefficient reflecting the interaction between the particles in the solution and depending only on the amount of dissolved substance.

The φ coefficient is determined in the experimental way.

Solutions with an osmolarity equal to that of 0.9 % sodium chloride solution are called isotonic. For isotonic solutions, theoretically calculated osmolarity values lie within the range of 239 - 376 mOsm/L.

The osmolarity of a solution consisting of several components can be defined as the total osmolarity of all its components.

Concentration of an infusion solution is conventionally expressed as a weight – volume characteristic (in *g/L),* and therefore it appears convenient that the content of kinetically active particles should be calculated in *milliosmols per litre* (osmolarity) rather than per *kilogramme* (osmolality) of the solution.

Differences between the osmolarity and osmolality values of solutions with an osmolarity close to or less than the osmolarity of 0.7 – 1.1 % sodium chloride solution can be ignored (the theoretical osmotic pressure of 0.9 % sodium chloride solution is 308 mOsm/L; the experimental value is 286 mOsm/L); for more concentrated solutions (for instance, 10 % sodium chloride solution), osmolarity can be described by the following formula:

2

$$C(mOsm/L) = C(mOsm/kg) \cdot \rho \qquad (3)$$

where: ρ is the density of the solution (kg/L).

Notes. 1. The theoretical osmolarity limits are calculated in the following manner: *the minimal value* is the osmolarity of a solution containing the minimal acceptable ingredient quantities; *the maximal value* is the osmolarity of a solution containing the maximal acceptable ingredient quantities.

2. If a high-molecular-weight substance is present in the solution, the average molecular weight of the fraction is considered to be its molar weight.

3. In osmolarity calculations, hydrogen carbonates are regarded as salts of a monobasic acid.

OSMOLALITY DETERMINATIONS FOR AQUEOUS SOLUTIONS

Three methods may be used for osmolality determinations: cryoscopy, membrane and vapour pressure osmometry.

The cryoscopy method

This method is based on the decrease in the freezing point of a solution, as compared with the freezing point of the pure solvent.

1 osmol per kilogramme of water decreases the freezing point by 1.86 °C. Measurement of these changes underlies the cryoscopy method.

This relationship can be described by the following equation:

$$C_{ocm} = \frac{(T_2 - T_1)}{K} \cdot 1000 \quad (mOsm/kg\ H_2O) \quad (4)$$

where: C_{ocm} is the osmolality of the solution (mOsm/kg);
T_2 is the freezing point of the pure solvent (in degrees Celsius);
T_1 is the freezing point of the tested solution (in degrees Celsius);
K is the cryometric constant of the solvent (for water: 1.86).

At present, osmolality of solutions is determined using automatic cryoscopic osmometers.

The required amount of the tested solution is transferred into the device cell. After that, the measurement is performed in accordance with the Instructions for Use of the instrument. If necessary, the device is calibrated using standard sodium or potassium chloride solutions, which should overlap the investigated osmolarity range (Table 1).

Table 1 – Standard freezing point reduction and osmotic concentration efficacy reference values for aqueous solutions of sodium chloride and potassium chloride

Analytical concentration of the salt, p, g/kg H_2O	Freezing point reduction, $\Delta T_{зам.}$, K	Effective (osmotic) concentration, $m_{эф}$, mmol/kg H_2O
Sodium chloride solutions		
5.649	0.3348	180
6.290	0.3720	200
9.188	0.5394	290
9.511	0.5580	300
11.13	0.6510	350
12.75	0.7440	400
16.00	0.9300	500
Potassium chloride solutions		
7.253	0.3348	180
8.081	0.3720	200
11.83	0.5394	290
12.25	0.5580	300
14.78	0.6696	360
20.71	0.9300	500

The membrane osmometry method

This method is based on the use of the potential of semi-permeable membranes to selectively transmit molecules of substances.

The driving force of this process is osmosis. The solvent moves inside the tested solution until equilibration is achieved; the additional hydrostatic pressure thus occurring is approximately equal to the osmotic pressure, and can be calculated according to the following equation:

$$\pi_{осм} \approx P_{гидр.} = \rho \cdot g \cdot \Delta h \qquad (5)$$

where: $\pi_{осм}$ is the osmotic pressure (Pa);
$P_{гидр.}$ is the hydrostatic pressure (Pa);
ρ is the density of the liquid (kg/m^3);
g is the acceleration of free fall (N/kg);
Δh is the height of the liquid column (m).

Osmolality can be calculated according to the following equation:

$$C_{осм} = \pi_{осм} / R \cdot T \qquad\qquad (6)$$

where: R is the universal gas constant (8.314 J/molK);
            T is the absolute temperature on the Kelvin scale.

Note. This method is only applicable for solutions of high-molecular-weight substances (10^{-4} - 10^6 g/mol). When analyzing solutions containing electrolytes and other low-molecular-weight substances, only osmotic pressure created by high-molecular-weight components of the solution will be determined.

The osmolality of the tested solution is determined using a membrane osmometer. Preliminary calibration of the device and measurements are carried out in accordance with the Instructions for Use of the device.

The vapour pressure osmometry method

1 osmol per kilogramme of water decreases vapour pressure by 0.3 mm Hg at 25 °C. Measurement of these changes underlies the vapour pressure osmometry method.

This method is based on measurement of the temperature difference occurring on thermistors that have been placed in a measuring cell saturated with vapour of the solvent after a drop of the pure solvent is applied to one of the thermistors and a drop of the tested solution is applied to the other. The temperature difference occurs as a result of condensation of the solvent vapour on the drop of the solution, because the pressure of the solvent vapour over this surface is lower. The temperature of the drop of the solution increases because of the exothermic process of condensation until the vapour pressure over the solvent drop becomes the same as the pressure of the pure solvent in the cell. The temperature difference is zero when the pure solvent is applied to both thermistors. The temperature difference is practically proportional to the molal concentration of the solution.

The osmolality of the tested solution is determined using a vapour osmometer. Preliminary calibration of the device and measurements are carried out in accordance with the Instructions for Use of the device.