Two grams granulated talc	24 hours	0.0757 Gm.
Three grams granulated talc	24 hours	0.0757 Gm.
One gram powdered talc	24 hours	0.0755 Gm.
One gram granulated talc	Immediately	0.0757 Gm.
One gram powdered talc	Immediately	0.07725 Gm.

A standard Elixir of Cinchona Alkaloids was prepared, which contained in 20 cc the prescribed amount of alkaloidal salts, corresponding to 0.0619 Gm. of free anhydrous alkaloids. The following method was used to determine the amount of alkaloids present after the various methods of filtration, as described above:

Transfer 20 cc of the elixir, accurately measured, to a separator, dilute with 20 cc of distilled water and make the mixture decidedly alkaline to litmus with ammonium hydroxide. Extract the alkaloids with three portions of chloroform (15, 10, 10 cc) and evaporate the combined chloroform extractions to dryness. Dry the residue to a constant weight at 110° C. and weigh as anhydrous alkaloids.

The following results are the average of two or more determinations for each sample:

Filtering agent used for 50 cc.	Length of time before using.	Grams of alkaloid found.
Not filtered		0.0654 Gm.
One gram silica gel	24 hours	0.0640 Gm.
One gram granulated talc	24 hours	0.0601 Gm.
Two grams granulated talc	24 hours	0.0623 Gm.
Three grams granulated talc	24 hours	0.0653 Gm.
One gram powdered talc	24 hours	0.0613 Gm.
One gram granulated talc	Immediately	0.0660 Gm.
One gram powdered talc	Immediately	0.0648 Gm.

CONCLUSIONS.

1. The results indicate that neither silica gel nor talc adsorb alkaloidal salts from these elixirs.

2. In carrying out these experiments it was noticed that the inclusion of any filtering agent in either formula is quite unnecessary, as these elixirs filter brilliantly clear through paper with one filtration.

UNIVERSITY OF MARYLAND.

THE PREPARATION OF ISOTONIC SOLUTIONS.*

BY WILBUR L. SCOVILLE.

Items appear occasionally in pharmaceutical literature which advocate the making of collyria, as well as of hypodermic solutions, isotonic with the body fluids. Occasionally a formula appears which is stated to give an isotonic solution, but the formula applies only to the particular combination quoted and has a very limited interest to the pharmacist. And since the formula or the method proposed is empirical or of limited value, the subject receives but little attention.

There is, however, a growing demand for isotonic solutions and for the application of isotonic principles in collyria as well as in injection solutions. Just recently a letter was referred to me inquiring if the preparation of such solutions were practicable or upon what principles they could be made so.

* Section on Practical Pharmacy and Dispensing, A. Ph. A., Asheville meeting, 1923.

At present, the demand is very limited because physicians do not know that such adjustments can be made at the prescription counter, and consequently they do not ask for them. Indeed, until quite recently a simple working formula of sufficient accuracy has been lacking. A few months ago Dr. F. S. Nicola of Italy published a simple formula whereby any weak (hypotonic) solution can be made isotonic by the addition of any desired salt or chemical substance.

A general practice of such adjustments of collyria will add much to the comfort of both patients and nurses. This is particularly true with children, who resent, sometimes sharply, even a momentary smarting. In the treatment of measles and the eye inflammation of children both the doctor and the parents would appreciate the making of collyria more comforting in use, which will not only avoid objections to treatment by the little sufferers but add to its efficacy. It remains for the pharmacist to inform the prescribers that the adjustment of collyria to an isotonic condition is now entirely practicable to create a general demand for it.

First, a brief consideration of the principles involved. Blood serum is composed of about 8.8 Gm. of inorganic salts, largely sodium chloride, and about 83 Gm. of organic matter, chiefly colloidal in character, per liter. It freezes at -0.55 to $-0.56°$ C. The lachrymal secretion is thinner and contains less colloidal organic matter, but more salt. It freezes at about $-0.80°$ C. corresponding to 1.4 Gm. of sodium chloride per liter. Now since tonicity refers to the tension of the tissues, and that is a matter, in this case, of osmotic pressure, it is plain that a solution which contains less than 8 Gm. of sodium chloride in 1000 cc will, if injected under the skin, cause osmosis of salt from the serum and if the difference is great enough it will cause pain until an equilibrium is reached. (Since the composition of blood serum will vary slightly the standards of salt strength are considered as 7.5 to 9.5 Gm. of sodium chloride per 1000 cc.) And since the lachrymal (tear) secretion is stronger in salt than blood serum, a collyrium should contain close to 1.4 Gm. of sodium chloride, or its osmotic equivalent, in 1000 cc to avoid temporary smarting.

The osmotic pressure comes from the diffusion of the inorganic salts, the organic colloidal substances only acting as hindrances to rapid diffusion. So the main emphasis in isotony is placed upon the salt content, though similar results can be obtained by adding colloidal bodies.

This is all aside from the special action of the medicinal substance. An irritant will be irritating even if isotonic, but such are not commonly prescribed. Also the acidity of the solution is a factor. But very slight amounts of acid or of alkali (not caustic) are not irritating in themselves. Yet solutions for this purpose should be made as nearly neutral as is consistent with stability and activity. It is well also to bear in mind that slightly acid solutions are better borne if a little hypotonic (weak), while alkaline solutions are better if slightly hypertonic (strong). Most alkaloidal solutions for injection, or for sterilization, must be made slightly acid to prevent decomposition.

Whether a solution is isotonic—*i. e.*, has the same effect or tonicity upon the tissues of the body—therefore depends (1) upon the amount or proportion of dissolved substance which it contains, and (2) upon the character of those substances. Both of these are shown by the freezing point of the solution, for all substances in solution lower the freezing point in proportion to the amount present, but in different degree. The greater the dissociation of the salt, the more it affects the freezing point of its solution.

Formulas have been offered by which the amount of any salt needed to produce an isotonic solution can be calculated from the freezing point. But these formulas have not proved entirely satisfactory.

Lumiere and Chevrotiere (*Bull. sci. pharmacol.*, through *Chem. Abst.*, 1914, 2196) have given the following list of freezing points of weak solutions which are convenient for use in collyria and hypodermic solutions.

1.7% Boric acid	−0.56° C.	1.0% Morphine Hydrochloride	−0.099° C.
0.5% Alum	−0.05° C.	0.9% Sodium Chloride	−0.56° C.
1.0% Alum	−0.10° C.	1.0% Sodium Chloride	−0.58° C.
0.3% Formaldehyde	−0.15° C.	1.4% Sodium Chloride	−0.80° C.
1.0% Formaldehyde	−0.30° C.	1.0% Sodium Nitrate	−0.40° C.
10.0% Protargol	−0.18° C.	1.4% Sodium Nitrate	−0.56° C.
1.0% Borax	−0.22° C.	2.0% Sodium Nitrate	−0.80° C.
1.0% Cocaine Hydrochloride	−0.12° C.	1.0% Sodium Bicarbonate	−0.40° C.
3.0% Cocaine Hydrochloride	−0.35° C.	1.4% Sodium Bicarbonate	−0.56° C.
1.0% Atropine Sulphate	−0.075° C.	2.0% Sodium Bicarbonate	−0.80° C.
3.0% Atropine Sulphate	−0.25° C.	Tear secretions	−0.80° C.

Solutions of silver nitrate and of potassium permanganate 1 in 1000 are too weak to show any freezing-point depression.

The above list contains most of the substances which would be used to make isotonic collyria, and a little judgment will suffice to gauge the amount to be used in any particular case. Allowance must be made, of course, for the influence of the active ingredient on osmosis.

A more accurate method is that given by Dr. F. Nicola (*Giorn. farm. chim.*, through *Chem. Abst.*, 1921, 3120) who calculates first the tonicity of the active ingredient, then the amount of other salt or substance needed to produce an isotonic solution. Dr. Nicola uses three factors in the calculations, namely, (1) the percentage strength of solution expressed as weight-volume, (2) the molecular weights of the salts or compounds used, and (3) the approximate dissociation constants of the ingredients. From these he establishes an isotonic factor which is constant for each type of solution.

The isotonic factor for hypodermic solutions is obtained as follows, based on the strength of the U. S. P. Physiological Salt Solution:

$$\frac{0.85 \text{ (Gm. NaCl in 100 cc)}}{58.5 \text{ (mol. wt. NaCl)}} = 0.01453$$

then 0.01453×1.86 (diss. const.) $= 0.027026$.

All solutions intended for injection into the blood stream are to be based on this serum-isotonic factor, 0.027026.

The collyrium factor is similarly calculated:

$$\frac{1.4 \text{ (Gm. NaCl in 100 cc)}}{5.85 \text{ (mol. wt. NaCl)}} = 0.02393$$

then 0.02393×1.80 (diss. const.) $= 0.04307$.

All solutions intended for application to the eyes are to be based on this tear-isotonic factor, 0.04307.

The dissociation constants will vary with different salts and also with different dilutions, but for practical purposes the following constants can be used. Sodium chloride being more generally used than any other salt is calculated on the tone constant for the dilution used, namely, 1.86 for injections and 1.80 for collyria. Other salts are approximated as follows:

For non-electrolytes and weak electrolytes, such as sugars, gums, gelatin, tannin, boric acid, borax, alkali phosphates, citrates, acetates and bicarbonates, the constant is 1.0; for salts which dissociate into two ions, such as alkali chlorides, iodides and bromides, silver nitrate, zinc sulphate, etc., the constant is 1.5; for salts which dissociate into three ions, such as the chlorides, bromides and iodides of calcium, zinc, or copper, sodium sulphate, alum, etc., the constant is 2.0; and for salts which dissociate into four factors, such as ferric chloride, aluminum chloride, etc., the constant is 2.5.

The following examples will illustrate the method of calculation, employing these factors:

A 1% solution of cocaine hydrochloride made isotonic for hypodermic injection.

$$\frac{1\ (\%)}{339.5\ (\text{mol. wt.})} \times 1.5\ (\text{diss. const.}) = 0.00442$$

$0.027026 - 0.00442 = 0.022606$

$0.022606 \times 58.5 = 1.32245 \div 1.86 = 0.7$

Then 0.71 Gm. of sodium chloride must be added to each 100 cc of a 1% solution of cocaine hydrochloride to render it isotonic with blood serum.

A 1% solution of cocaine hydrochloride made into an isotonic collyrium.

$$\frac{1}{339.5} \times 1.5 = 0.00442$$

$0.04307 - 0.00442 = 0.03865$

$0.03865 \times 58.5 = 2.255175 \div 1.8 = 1.25$

Then 1.25 Gm. of sodium chloride is to be added to each 100 cc of 1% solution of cocaine hydrochloride to make it isotonic with the lachrymal secretion.

A 1% solution of cocaine hydrochloride made isotonic with boric acid for a collyrium.

$$\frac{1}{339.5} \times 1.5 = 0.00442$$

$0.04307 - 0.00442 = 0.03865$

$0.03865 \times 62 = 2.39 \div 1 = 2.39$ Gm. of boric acid to be added to each 100 cc.

A 0.1% solution of silver nitrate made isotonic with sodium nitrate for a collyrium.

A solution as weak as 0.1% (1 in 1000) may be considered as having no tonicity factor. Then:

0.04307×85 (mol. wt. sod. nit.) $= 3.6609$

$3.6609 \div 1.5$ (diss. const.) $= 2.44$ Gm. of sodium nitrate to be added to 100 cc.

A 0.5% solution of zinc sulphate made isotonic with sugar for a collyrium.

$$\frac{0.5}{287.5} = 0.001739 \times 1.5 = 0.0026$$

$0.04307 - 0.0026 = 0.04047$

$0.04047 \times 342 \div 1 = 13.84$ Gm. of sugar per 100 cc.

LABORATORY OF PARKE, DAVIS & CO.,
DETROIT, MICH.