The experiments reported on deterioration show conclusively that the deterioration of the tincture and fluidextract of aconite can be prevented by the addition of 2% acetic acid or 0.1% hydrochloric acid to the menstruum.

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A STUDY OF THE RELATIVE PRESERVATIVE VALUES OF GLYCERIN AND SUGAR SOLUTIONS IN CERTAIN OFFICIAL PREPARATIONS.

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The question of preservation of medicinal salts with glycerin or sugar solutions has been the source of a large amount of investigation and intense study. The rapid deterioration of certain syrups, caused by either oxidation or hydrolysis, and the rapidity with which sucrose is inverted and often caramelized in certain galenicals is a constant source of annoyance to the pharmacist. The decomposition of practically all of the official syrups and solutions containing mineral substances may be divided into two classes: first, oxidation through atmospheric influence, and second, hydrolysis or decomposition caused by the ions of water.

PART I.

A. SYRUP OF FERROUS IODIDE.

As one of the type of preparations which readily decomposes under atmospheric influence, Syrup of Ferrous Iodide may be cited. Accordingly a syrup was prepared by the pharmacopœial process omitting the dilute hypophosphorous acid. At different periods after preparing the amount of invert sugar present was estimated by decomposing a small accurately weighed quantity of the syrup with sodium carbonate solution, removing the precipitated ferrous carbonate by filtration and estimating the invert sugar in the filtrate gravimetrically with Fehling's solution.

5 days showed.................	6.5%	invert sugar
15 days showed.................	7.5%	invert sugar
30 days showed.................	8.8%	invert sugar
75 days showed.................	10.96%	invert sugar

Another syrup was prepared including the dilute hypophosphorous acid and the following results show the inversion of the sucrose:

10 days showed.................	94.2%
20 days showed.................	96.2%

These results indicate that within a period of twenty days practically all of the sugar is inverted, whereas if the acid is omitted the degree of inversion is far less.

This is only what one would expect as it has been found that the rapidity of inversion is a function of the hydrogen ion concentration[1] and by the colorimetric method the official syrup showed a p_H 2.8–3.2, whereas with the acid omitted the p_H value was 5.2. In view of this rapidity of inversion of sucrose in the presence of the diluted hypophosphorous acid and subsequent caramelization caused by the reducing agent, the next step was to supply a preservative medium of equal value with syrup and yet not subject to deterioration. Certain investigators have suggested the use of glucose in this preparation and claim it to be a better preservative for ferrous iodide than sucrose. Accordingly four syrups were prepared with different amounts of chemically pure glucose and their resistance against oxidation was tested in the following manner:

Weigh 10 Gm. of the syrup and add 5 cc solution of hydrogen peroxide 0.3% accurately measured from a burette. Allow to stand for five minutes and titrate the liberated iodine with $N/10$ sodium thiosulphate solution. The following results show the amount of iodine liberated from the different syrups by 5 and 10 cc, respectively, of hydrogen peroxide:

	5 cc	10 cc
Syrup with pure sucrose.........	0.0306 Gm.	0.0679 Gm.
Syrup with 10% dextrose........	0.0308 Gm.	0.0679 Gm.
Syrup with 20% dextrose........	0.0297 Gm.	0.0673 Gm.
Syrup with 30% dextrose........	0.0297 Gm.	0.0667 Gm.
Syrup with 40% dextrose........	0.0297 Gm.	0.0679 Gm.

The foregoing results indicate that the amount of dextrose used has no effect upon the resistance against oxidation of the preparation and that sucrose is equally as good a preservative as dextrose. Experiments carried out in this laboratory, however, showed that commercial dextrose increased the resistance against oxidation, which was due to reducing impurities present.

The next step was to prepare ferrous iodide solutions in other viscous media with the aim of establishing a relationship between viscosity and resistance against oxidation, especially so far as glycerin and sucrose solutions are concerned. A solution was prepared by allowing iron and iodine to react in the presence of 15 cc of distilled water and brought to the boiling point; 5 Gm. of glycerin was added and the solution rapidly filtered, the filter and contents were washed with 15 cc of distilled water and the filtrate was made up to 100 Gm. with pure glycerin. Another solution was prepared in distilled water and by rapid manipulation was made up to weight without the liberation of iodine. A third solution was prepared containing 30 Gm. of pure acacia in 100 Gm. of solution. The resistance against oxidation was tested by the foregoing method and when 10 cc of solution of hydrogen peroxide 0.3% were used the following amounts of iodine were liberated:

Water Solution..............................	0.1234 Gm.
Sucrose Solution............................	0.0679 Gm.
Glycerin Solution...........................	0.0380 Gm.
Acacia Solution.............................	0.0254 Gm.

The relative viscosities of the solutions were determined by the Pharmacopœia method at 20° C.

[1] Fales & Morrel, *Jour. Am. Chem. Soc.*, 44, 2071, 1922.

Water Solution.......	1
Sucrose Solution......	1.8
Glycerin Solution.....	2.5
Acacia Solution.......	20.0

These results indicate that viscosity is a factor in determining the resistance against oxidation and thus the relative preservative power of different media. Generally speaking the greater the viscosity the greater the resistance against oxidation. It should be noticed that viscid glycerin medium although considerably lighter in density than the sucrose solution offers a much higher resistance against oxidation.

Carrying the study of the resistance offered by the glycerin and sucrose solutions further, the following experiment was carried out. Since oxidation may be considered as an increase in positive valence, which may be interpreted to mean the loss of electrons, the glycerin and sucrose solutions were subjected to the oxidizing influence of an anode. Ten cubic centimeters of each solution was placed separately in small porous crucibles and these in turn were immersed in an aqueous solution of ferrous iodide. Platinum anodes were placed in each crucible and after one hour the passage of a current of 2 volts and 0.25 ampere liberated the following amounts of iodine:

Glycerin Solution.....	0.0020 Gm.
Sucrose Solution......	0.0049 Gm.

Turning our attention to the official syrup in order to estimate its resistance against oxidation and formulate a comparison, the following amounts of iodine were liberated when 10 cc of solution of hydrogen peroxide were used:

Pharmacopœial Syrup...	0.0395 Gm.
Glycerin Solution.......	0.0418 Gm.
Sucrose Solution........	0.0617 Gm.

All of the results obtained indicate that glycerin is a better preservative for solutions of ferrous iodide than sugar and when used as a preservative in this preparation the use of diluted hypophosphorous acid is unnecessary. The writer was fortunate enough to obtain a solution of ferrous iodide in 40% glycerin by volume which had remained permanent in a flint glass bottle in diffused light for a period of nine years. The glycerin solution prepared in this laboratory remained unchanged for a period of five months (that is up to the time of writing) stored in a partially filled flint glass bottle in diffused daylight. Let us now consider an explanation for the superior preservative power of glycerin.

The specific gravity of Syrup of Ferrous Iodide is about 1.3 and consequently 1000 Gm., containing 575 Gm. of sugar, occupies a volume of 770 cc. The glycerin solution having a density of about 1.2 occupies a volume of about 833 cc per 1000 Gm. and contains 750 Gm. of glycerin in 1000 Gm. The sucrose solution contains 1.69 moles in 770 cc or 2.18 in a liter, and hence is 2.18 molar in respect to sugar. The glycerin solution contains 8.15 moles in 833 cc or 9.78 in a liter and is therefore 9.78 molar in respect to glycerin. From the colligative properties of solutions, *i. e.*, osmotic pressure, freezing-point depression and boiling-point elevation, it is well known that equal molar concentrations of different non-ionizing solutes produce equal osmotic pressures, freezing-point depressions and boiling-point elevations.

Since these properties are direct functions of the number of molecules present it is assumed that solutions of equal molar concentrations contain in equal volumes, the same number of molecules. From this reasoning we may assume that in this preparation in an equal volume the number of glycerin molecules is 4.48 times as great as the number of sucrose molecules, as this number expresses the ratio of their molar concentrations. The foregoing experiments indicate that the protection offered by these substances is not due to any inherent chemical reactivity of the medium, but likely due to the enclosure of the ferrous iodide molecules in envelopments of molecules of the protecting medium, resembling the protective colloids of acacia and gelatin in their protection of gold sols. It is then obvious that glycerin will exert a far greater protective influence than sucrose as it has 4.48 times as many molecules present to accomplish its purpose of molecular envelopment.

It is generally understood that viscosity is due to molecular friction and it follows then that in any solution having a great viscosity the molecules must be closer together than in one having a lesser viscosity. It seems reasonable to postulate that in a solution where the molecules were literally rubbing each other, the protective envelopment formed by these molecules would render the enclosed molecule far more impervious to atmospheric influences, than a coating of protective molecules which are relatively far apart. Thus glycerin solutions offer better protective coatings than sucrose solutions and consequently show a higher resistance against oxidation.

One other factor in the question of preservation that must be considered is the area of the surface of the preparation exposed to atmospheric influences. It was found that in the same medium the rapidity of oxidation of ferrous iodide was proportional to the area of the surface exposed to the atmosphere. We now have two factors that increase the resistance against oxidation, namely, increasing the number of molecules of the protective substance present, and increasing the viscosity of the medium; the factor accelerating oxidation is the increasing of the amount of surface exposed. Qualitatively this may be expressed by the following mathematical formulæ:

$$R \propto N$$

$$\text{and} \quad R \propto V$$

$$\text{and} \quad R \propto \frac{1}{S}$$

$$\text{then} \quad R \propto NV\frac{1}{S} \text{ or } \frac{NV}{S}$$

where R is resistance against oxidation, V the viscosity, N the number of molecules of protecting medium present, and S the area of the surface exposed.

It is doubtful whether this formula could be used practically to calculate the actual length of time a preparation would remain permanent, as the molarity and viscosity of different media show no constant variation. Nevertheless in a qualitative manner this expression points out the relationship between the permanence of ferrous iodide solutions and the factors controlling it.

CONCLUSIONS.

1. Inversion and caramelization make sucrose solutions quite unsuited for a preservative for ferrous iodide.

2. Glycerin, on account of the opportunity of increasing the molarity, is more efficacious as a preservative and may be used in the preparation without its undergoing any objectional change and the diluted hypophosphorous acid may be deleted from the formula.

3. Resistance against oxidation or keeping qualities increases with the viscosity and molar concentration of the protective medium and varies inversely as the area of the surface exposed.

Let us turn our attention to some other official preparations and test the application of the foregoing principles in other solutions.

B. SYRUP OF HYDRIODIC ACID.

Three solutions of hydriodic acid were prepared in 57.5%, 72.5% and 87.5% by volume of glycerin along with the pharmacopœial syrup. After fifteen days the amount of invert sugar present in the official syrup was estimated in the following manner.

Accurately measure 2.5 cc of the solution and make up to 100 cc in a volumetric flask. Dilute 10 cc of this dilution, representing 0.25 cc of the syrup, with 50 cc of distilled water and estimate the invert sugar gravimetrically with Fehling's solution in the usual manner.

15 days	96.9% invert sugar

This experiment indicates that within a period of two weeks practically all of the sucrose present is inverted.

The resistance against oxidation and viscosity of the four preparations were determined, the former being carried out in the following manner.

In beakers of equal diameter place 10 cc of the solution to be tested. Float carefully over the surface 5 cc of solution of hydrogen peroxide 0.3% and allow diffusion into the viscous media for two hours, then titrate the iodine liberated with $N/10$ sodium thiosulphate solution. The following amounts of iodine were liberated.

Official Syrup	0.0343 Gm.
Glycerin Solution 57.5%	0.0317 Gm.
Glycerin Solution 72.5%	0.0254 Gm.
Glycerin Solution 87.5%	0.0254 Gm.

Relative Viscosities at	20° C.
Solution in Water	1.0° C.
Official Syrup	1.1° C.
Glycerin Solution 57.5%	1.25° C.
Glycerin Solution 72.5%	1.5° C.
Glycerin Solution 87.5%	3.0° C.

Let us now consider the molarity of the sucrose in the official syrup and compare it with the molar concentration of the 72.5% glycerin solution at which concentration the resistance against oxidation seemed to reach a maximum. The pharmacopœial preparation contains 488.75 Gm. of sucrose in a liter, which is 1.42 molar; the glycerin solution contains 906.25 Gm. in a liter, which is 9.85 molar. From the proposed theory we would have anticipated a greater resistance against oxidation power by the glycerin solution than by the official syrup.

CONCLUSION.

1. A glycerite of hydriodic acid containing 72.5% by volume of glycerin yields an excellent preparation which does not readily deteriorate. In this laboratory it has remained permanent for five months (that is, up to the time of writing).

2. The qualitative application of the general expression proposed under syrup ferrous iodide seems applicable to this preparation, *i. e.*,

$$R \propto \frac{NV}{S}$$

C. MASS OF FERROUS CARBONATE.

In the preparation of Mass of Ferrous Carbonate a weak syrup is used to wash the freshly precipitated ferrous carbonate free from sodium sulphate, to prevent the oxidation of the iron salt. Twenty-five per cent. by weight of sugar is added to the ferrous carbonate before evaporation to the required weight is begun. Extending the theory of molecular envelopment and protection against oxidation to this preparation, three masses were carefully prepared by the pharmacopœial process from an uneffloresced sample of ferrous sulphate. Three other samples were prepared using a dilute glycerin solution in place of the syrup and 25% by weight of glycerin in the finished preparation in place of the sugar prescribed by the official formula. Conditions in each series of preparations were made alike as far as possible and the two types of masses compared as for consistency and permanency. The glycerin mass naturally retains its soft consistency indefinitely whereas it is well known that the official mass becomes very hard and dry in a comparatively short time. Immediately after preparation an average of three assays of the Pharmacopœia masses showed 37.61% and those made with glycerin showed an average of 38.58%. After thirty days' exposure to the atmosphere there was practically no greater change in one type of mass than in another.

CONCLUSION.

1. Glycerin again, because of its higher molar concentration, offers a better protection for ferrous carbonate; the glycerin mass also retains its soft consistency for a longer period of time.

D. SYRUP OF AMMONIUM HYPOPHOSPHITE.

Carrying this discussion to the National Formulary preparation of Syrup of Ammonium Hypophosphite some interesting results were obtained. The N. F. syrup contains 10% by volume of glycerin and about 75% of official syrup. Accordingly an N. F. syrup was prepared along with one solution of the salt in 75% syrup, another in 75% glycerin and one in 50% glycerin by volume. The resistance against oxidation of these four products was tested in the following manner.

Place in beakers of equal diameter 10 cc of each of the solutions to be tested. Float carefully over the surface 15 cc solution of hydrogen peroxide solution 3% and allow to stand for forty-eight hours. Add 25 cc of magnesia mixture and warm the solution to 60° C. or until the precipitate of magnesium ammonium phosphate granulates, and set aside for one-half hour. Transfer the precipitate to a Gooch, ignite and weigh as magnesium pyrophosphate. The following results express the amount of magnesium pyrophosphate obtained.

	Det. I.	Det. II.
The National Formulary Syrup...	0.0188 Gm.	0.0193 Gm.
The 75% Syrup Solution.........	0.0263 Gm.	0.0251 Gm.

In neither of the two solutions prepared with glycerin was there any precipitate formed until the solution had been heated considerably with the hydrogen peroxide. This would seem to indicate again that by increasing the molar concentration of the protective medium the diffusion of the oxidizing agent was practically prevented. The molar concentration of the 75% glycerin solution is 5.47 greater than the solution containing 75% syrup and 3.17 greater than that of the official syrup.

At 20° C. the following relative viscosities were found.

Water Solution	1.0
Glycerin Solution 50%	1.1
Syrup Solution 75%	1.2
Glycerin Solution 75%	1.5
N. F. Syrup	1.7

CONCLUSIONS.

1. A seventy-five per cent. solution by volume of glycerin furnishes an excellent medium for ammonium hypophosphite and naturally the disadvantages of inversion and caramelization are obviated.

2. The general relationship of $R \propto \frac{NV}{S}$ shows itself to be approximately true in these oxidations.

PART II.

Let us now consider two types of pharmaceuticals which undergo decomposition by hydrolysis.

A. SOLUTION OF IRON AND AMMONIUM ACETATE.

This solution decomposes due to the formation of basic ferric acetate through hydrolysis. From the standpoint of chemical equilibrium there are two opposing tendencies in operation continuously in this preparation, one the tendency of the hydroxyl ions of water to unite with ferric acetate and form the subsalt, and another the tendency of the hydrogen ions present to form the normal salt and water by union with the basic salt. The force causing the formation of the basic salt may be considered as the frequency of contact of the molecules of the normal salt with the hydroxyl ions of water and the insolubility of the subsalt thus removing it from the field of activity and destroying the opposing tendency.

In 1887 LeValley[1] suggested the use of glycerin in place of syrup in this preparation, because he found it to be a better preservative; later this modification was adopted by the Pharmacopœia. The questions then arise—is there any scientific

[1] *Druggists Circular*, 1887.

reason to propose, accounting for the superior preserving power of glycerin in this preparation, and why do these substances preserve the salt at all?

There is the possibility of combination between the basic iron salt and sugar or glycerin, probably due to the secondary valence of iron, preventing the precipitation of the salt. Then, too, the preservation may be colloidal in nature, these organic molecules peptizing the basic ferric acetate as soon as it is formed and thus keeping it in solution as a colloid.

The writer does not believe that the preservative power is due to any reactivity of the preserving medium, but is entirely due to the protection afforded by the sucrose or glycerin molecules against the attacks of the hydroxyl ions of water. The greater number of molecules of protective substance present the more impervious will be their envelopment of protection against the hydroxyl ions and consequently there is a longer period of time required for the formation of enough basic ferric acetate to exceed its solubility product and thus to precipitate. Applying the assumption of the kinetic theory, that the speed of a chemical reaction is proportional to the number of collisions between the reactive particles of each sort, the length of time of permanency of this preparation is then proportional to the efficiency of the substance used in preventing these collisions of particles. Viscosity,[1] which some have assumed to be a symptom of inertia in the medium, affecting anything happening in it does not affect to any appreciable extent the decomposition of this preparation. It is only natural that this condition would be so, as the rapidity of hydrolysis of methyl acetate by hydrochloric acid is almost as rapid in a gel as it is in water; this eliminates the possibility of a general inertia due to viscosity.

According to the kinetic molecular conception of temperature—one other factor that will increase the decomposition of this salt is an increase in temperature, as this increases the chaotic thermal agitation of molecules affecting more frequent collisions.

With these conceptions in mind, let us now decide why glycerin is found to be more efficient than syrup in the preservation of this solution. Including the sugar present in aromatic elixir 120 cc of syrup in a liter would make the solution 0.41 molar in respect to sugar, whereas an equal volume of glycerin gave a molar concentration of 1.63, practically four times as great. Considering the molecules of glycerin or sugar as retarding the collisions of the reacting substances, the average distance travelled before a collision, or the "mean free path," would be four times greater in the preparation when made with glycerin than if made with syrup. To increase the molar concentration of the sugar to that of the glycerin it is necessary to dissolve 518.25 Gm. of sugar in a liter of the finished preparation. Accordingly five samples of the solution were prepared, one without glycerin or sugar, one of 0.82 molar concentration with glycerin and another the same concentration with sugar (one-half the pharmacopœial strength); two others were prepared with glycerin and sugar in each 1.63 molar concentration or the pharmacopœial strength. These five preparations were placed in direct sunlight at temperatures varying from 25° to 35° C., and the following decompositions recorded.

Sample without glycerin or sugar showed decided precipitation in..............	6 days
Sample with one-half U. S. P. quantity of glycerin showed decided precipitation in	7 days

[1] Scatchard, *Jour. Am. Chem. Soc.*, 45, 1580, 1923.

Sample with one-half U. S. P. quantity of sugar showed decided precipitation in	8 days
Sample with U. S. P. quantity of sugar showed decided precipitation in.........	14 days
Sample with U. S. P. quantity of glycerin showed decided precipitation in.......	15–16 days

From this we can formulate a mathematical expression, calculating the permanency of the solution:

$$T \infty M$$

and $$T \infty \frac{i}{t}$$

therefore $$T \infty \frac{M}{T}$$

and $$T = K\frac{M}{t}$$

where t is constant $$T = K\frac{M}{K} = KM \text{ and } K = \frac{T}{M} = 9.7$$

From Experiment $T = 8 \quad M = 0.82$

then $T = 9.7\ M$

when $M = 1.63 \times 9.7 = T = 15.8$ days

M = molar concentration, T = time, t = temperature.

B. SOLUTION OF MAGNESIUM CITRATE.

The principal decomposition in this solution is the hydrolysis of the acid salt into the less soluble normal salt which subsequently settles out of solution. Sixty cc of glycerin in place of the syrup used will prevent this decomposition for more than a month and in this laboratory when 30 cc of glycerin was used in place of syrup the preparation remained free from turbidity twenty days (that is, up to the time of writing). Preparations made with syrup and kept under the same conditions showed a decided turbidity within four to five days. Glycerin does not, however, prevent the formation of certain fine flocculent material in the preparation which change some writers ascribe to decomposition by microörganisms.

GENERAL CONCLUSIONS.

1. When the question of resistance against oxidation is considered, two factors increase the resistance, namely, viscosity and molar concentration of protective medium.

2. Molar concentration of the protective medium and temperature are the controlling influences in pharmaceuticals where the question of hydrolysis is concerned.

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