# SECTIONS

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## THE CHEMISTRY AND PHARMACOLOGY OF THE SOLUBLE CONSTITUENTS OF AMPUL GLASS.*[1]

BY R. K. SNYDER.[2]

### INTRODUCTION.

It is a well-known fact that the glass of ampuls and vials used for parenteral solutions should be of a resistance grade; otherwise finely adjusted pharmaceutical and chemical preparations may be seriously altered in their character. In an earlier paper (15) the author gave a brief review of the literature on the history and composition of ampul glass, the nature of the attack of water on glass and discussed various methods for determining the alkalinity imparted to water by glass and the results obtained by applying these tests to samples of glass.

The Kimble titration method and the Colorimetric $p_H$ method were shown to be the most effective and standards were provided for glass to be used in ampuls of 100 cc. capacity or less. It was evident, however, that the latter method was inferior to the Kimble method because there was no way of providing for the decrease in concentration of solute as the ratio of area of glass exposed to unit volume of water decreased.

In view of the fact that intravenous solutions are put up in containers of larger capacity than 100 cc. as well as in small ampuls and that the concentration of the solution of glass decreases as the size of the container increases, it was considered desirable to continue the investigation. A study of the chemical characteristics of the water soluble components of glass and the pharmacological significance of the minute quantities present in ampul solutions would tend to clarify the situation.

### THE PHYSICAL CHEMISTRY OF THE SOLUTE.

Soft glass was crushed to a fine powder and then refluxed with water for a week. The suspension was then carefully filtered and the filtrate evaporated to dryness. This residue upon analysis and allowing for loss on ignition and absorbed $CO_2$, yielded 55.6% $SiO_2$, a trace of $R_2O_3$, 0.3% CaO, a trace of MgO, 5.6% $K_2O$ and 38.3% $Na_2O$. Harman (5) has found that $Na_2O:SiO_2$ in 1:1 ratio is an excellent conductor and that in 0.01 *N* solutions both hydrolytic and ionic dissociation takes place. For this ratio he found the Transport Numbers to be as follows: N Na = 0.37, N silicate = 0.16, N OH = 0.47. Since the ratio of $Na_2O$ to $SiO_2$ as found in the above analysis is close to 1:1, these values would be similar for a solution obtained from glass. In solutions as dilute as those obtained by heating water in glass containers for 30 minutes, the solute would be well dissociated. Accordingly the conductance of such a solution would vary approximately with the concentration of solute (12).

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[2] A. PH. A. Laboratory, Washington, D. C.

To confirm this statement the following experiment was performed. Five grams of soft glass crushed to a No. 40 to No. 60 powder was placed in a hard glass ampul, 50 cc. of conductivity water added, the ampul sealed, autoclaved for 30 minutes at 15 pounds pressure and allowed to stand until all solid material had settled. This was considered as containing 100% solute. Dilutions were made with conductivity water in such proportions that the dilutions contained 75%, 50%, 25% and 10% of the original solution. Zero % represents the conductivity water. The conductance of these solutions was then measured and the values obtained are shown in the following table.

TABLE I.—RELATION OF CONCENTRATION AND CONDUCTANCE.

| Concentration of Solute. | Conductance. |
|---|---|
| 100% | $203.4 \times 10^{-6}$ |
| 75 | 157.8 |
| 50 | 113.8 |
| 25 | 64.5 |
| 10 | 27.6 |
| 0 | 3.6 |

When these figures are graphed it can be seen that the curve is almost linear. Therefore, it can be assumed that in the low concentrations obtained in the case of ampuls, vials and bottles, changes in the conductance approximately represent proportional changes in the concentration of the solute.

As mentioned earlier the ratio of the area of glass exposed to the volume of water is quite important when testing a whole container. If this ratio is doubled the concentration is doubled and therefore any test based on a whole container must take this fact into consideration. To provide experimental evidence for this, the following procedure was carried out. A series of ampuls prepared from soft glass test-tubes were made of such dimensions that these ratios increased progressively in steps. They were filled with conductivity water and sealed, care being taken to protect the tips from burnt burner gases in the sealing. They were autoclaved for 30 minutes at 15 pounds, cooled and the conductance measured. The following table shows that it is necessary to take this ratio into consideration.

TABLE II.—RELATION OF CONDUCTANCE TO THE AREA-CAPACITY RATIO.

| Size of Ampul. | Area: Capacity. | Change in Conductance. | Calculated Change in Conductance. |
|---|---|---|---|
| 48.0 cc. | 1.79 | $25.5 \times 10^{-6}$ | ..... |
| 24.0 | 2.16 | 29.0 | $28.8 \times 10^{-6}$ |
| 12.0 | 2.51 | 35.4 | 36.4 |
| 10.0 | 3.04 | 45.7 | 41.6 |
| 6.0 | 3.16 | 47.4 | 47.5 |
| 3.0 | 3.82 | 53.9 | 57.3 |
| 1.5 | 4.76 | 70.3 | 65.8 |

METHODS FOR TESTING LARGE CONTAINERS.

There are two types of bottles commercially used for intravenous solutions at the present time. These are pyrex or other resistance glass containers, and soft glass with treated interior surfaces. The following methods were used to test a series of these bottles.

*Kimble Titration Method.*—This method has been described earlier, however, a slight modification has been introduced here. The glass after crushing was washed with alcohol to remove fine dust and then dried.

*Electroconductivity Method (12).*—Cleanse the bottles thoroughly with hot water and then rinse with distilled water. Fill them with conductivity water the conductance value of which has been determined at 25° C., cover the neck with a small pyrex beaker and autoclave for 30 minutes at 15 pounds pressure. Allow to stand one hour in the autoclave after the pressure has been released and then cool as rapidly as possible. Immediately determine the conductance value at 25° C.

*Residue Method.*—The procedure is the same as above except that samples of the conductivity water and autoclaved water are evaporated to dryness and the residue weighed.

The following table indicates that the Kimble method distinguishes only between resistance and soft glass containers; treated surfaces are not indicated. The electroconductivity and residue methods distinguish between treated and untreated bottles, but not satisfactorily between treated soft glass and resistance glass bottles.

TABLE III.

| Bottle or Flask Liter Size. | Area per Cc. | Conductance $\times 10^{-6}$. | Residue P. P. M. | Titration Method. |
|---|---|---|---|---|
| No. 1 | 0.50 | 0.05 | 0.2 | 0.03 |
| No. 1 after 20 hrs'. autoclaving | 0.50 | 0.04 | 0.1 | .. |
| No. 2 | 0.45 | 0.06 | 0.2 | 0.03 |
| No. 2 after 20 hrs.' autoclaving | 0.45 | 0.06 | 0.0 | .. |
| No. 3 | 0.45 | 0.06 | 0.1 | 0.08 |
| No. 3 after 20 hrs.' autoclaving | 0.45 | 0.06 | 0.2 | .. |
| No. 4 | 0.50 | 0.97 | 1.4 | 0.60 |
| No. 4 after 20 hrs.' autoclaving | 0.50 | 2.50 | 1.0 | .. |
| No. 5 | 0.50 | 13.23 | 13.6 | 6.84 |
| No. 5*a* | 0.50 | 0.10 | 0.6 | 6.86 |
| No. 5*a* after 2nd autoclaving | 0.50 | 0.05 | 0.6 | .. |
| No. 5*a* after 20 hrs.' autoclaving | 0.50 | 4.66 | 5.0 | .. |
| No. 6 | 0.66 | 21.20 | 18.2 | 6.70 |
| No. 6*a* | 0.66 | 1.41 | 3.6 | 6.68 |
| No. 6*a* after 2nd autoclaving | 0.66 | 0.50 | 0.9 | .. |
| No. 6*a* after 20 hrs.' autoclaving | 0.66 | 3.00 | 4.5 | .. |

No. 1 Borosilicate Glass A
No. 2 Borosilicate Glass B
No. 3 Borosilicate Glass C
No. 4 Borosilicate Glass D
No. 5 Soda-Lime Glass (untreated)
No. 5*a* Soda-Lime Glass (treated by heating at 1000° F. in acid gas)
No. 6. Soda-Lime Glass (untreated)
No. 6*a* Soda-Lime Glass (treated by autoclaving)

PHARMACOLOGICAL PROPERTIES OF THE SOLUBLE CONSTITUENTS OF GLASS.

The chemical effect of the soluble constituents of glass upon parenteral solutions is due to alkalinity and is largely individual, that is the action must be determined for each product. However, the pharmacological effect, if any, would be general.

The solution obtained by heating water in glass containers is a dilute solution of sodium and potassium silicates, with the sodium salt predominating. Both salts behave the same chemically. As mentioned earlier, sodium silicate hydrolyzes to give sodium, silicate and hydroxyl ions as well as colloidal silica. The size of the colloidal silica particles depends upon the time and temperature when formed and on the time of standing when aging. Any physiological effects from this solution would probably be more largely from the colloidal silica than from the silicate ions or alkalinity.

Kohganic (10) Kagenyama and Murata (7) Nieuwenhuyzen (13) Hefferman and Green (6) Gardner and Cummings (4) all find that silica in a very fine state of subdivision is toxic and causes injury to the tissues when injected. The tendency is to explain these harmful effects of colloidal silica by its potentialities in disturbing the colloidal system of protoplasmic proteins in the cells. Starkenstein (16) Doerr and Moldovan (2) find that colloidal silica produces shock. The latter authors believe the symptoms are probably due to alterations in the proteins of the blood which affect its coaguability and that the cause of shock from injected silica is closely related to that which causes anaphylaxis.

The question appears likely to be one of concentration and particle size. Will the very dilute solutions of colloidal silica obtained from glass containers produce effects similar to those obtained by the above authors who worked with more concentrated solutions?

### EXPERIMENTS ON YEAST, DAPHNIA MAGNA AND GOLDFISH.

It was demonstrated that yeast in the presence of sodium silicate did not ferment dextrose with the production of $CO_2$. However, $Na_2CO_3$ in sufficient quantities to produce approximately equal hydroxyl-ion concentration and titratable alkalinity also stopped fermentation. The action on yeast then is largely due to its alkalinity.

Daphnia Magna reacted similarly when sodium silicate and sodium carbonate were added to their medium. Concentrations of either salt of 1 in 500 produced death in two hours. As the concentrations decreased, the actions were similar, therefore the effect was due mainly to alkalinity.

Goldfish reacted similarly to the Daphnia except that they required a concentration of 1 in 250 to produce death in four hours.

### EXPERIMENTAL WORK ON RATS AND RABBITS.

Twenty-four young rats were divided into three groups of eight and fed special diets for a period of twelve weeks. One group served as a control, the second and third had the same food but containing 0.5% and 1.0% of sodium silicate, respectively.

All groups increase in weight and developed during the twelve weeks practically the same; however, the weight increase was slightly better in the control group. At the end of the twelve weeks the rats were killed and their livers analyzed for silica. The livers of the controls contained 0.4 mg. per liver, the second group 0.5 mg. per liver and the third 0.8 mg. per liver.

Twelve young rabbits were divided into four groups of three. The first served as a control, the second received doses of 0.5 cc., 1.0 cc., 2.0 cc. of 0.5% solution of sodium silicate twice a week for six weeks, the third the same size doses of 1% and the fourth similar doses of 5%.

The doses of the 5% solution were fatal to the rabbits, however the controls and other two groups increased in weight and developed during the six weeks with little difference. At the end of the six weeks the liver, kidneys, spleen and a piece of striated muscle were removed from a control rabbit and from the rabbit receiving the 2 cc. of 1% solution which was the largest dose any living rabbit had received. These were examined histologically and also assayed for silica (11). The liver of the rabbit receiving the 1% solution was the only organ of either animal which showed any possible changes in structure and these were doubtful. Also this liver showed by analysis that it contained 3.3 mg. of $SiO_2$ which is about five times as much as was found in any organ examined in either animal.

It, therefore, can be assumed that very little injury had been done to the animal. 2 cc. of a 1% solution of sodium silicate contains approximately the same amount of the chemical as does a liter of water sterlized in an untreated soft glass bottle.

### EXPERIMENTAL WORK ON DOGS.

The dogs were anesthetized with sodium pentobarbital, 35 mg. per kilo given intraperitoneally, and set up to record blood pressure and respiration. Solutions of sodium silicate of 0.5%, 1.0% and 5.0% were injected intravenously. The 0.5% solution had little effect even in large quantities (700 cc.). The 1% solution required 20 cc. per kilo to produce death, while the 5% required 2.5 cc. The blood pressure fell steadily, the rate depending on the concentration of the solution and the speed of the injection. Respiration showed little change but failed before the circulation did. Temperature showed no change. Solutions of equal hydroxyl-ion concentration and titratable alkalinity in large quantities (1000 cc.) had little if any effect. The toxicity must therefore lie in the silicate ions and colloidal silica.

### CLINICAL WORK.

Although there have been many intravenous injections of saline, sterilized and stored in soft glass containers, which have produced no deleterious results, there probably have been no closely controlled experiments.

Isotonic saline was prepared with freshly redistilled water (1) and analytical reagent sodium chloride. It was immediately sterilized in untreated soft glass bottles which had been previously cleaned and sterilized. This saline was then free from any material which might produce shock (14) except sodium silicate which was present 18 mg. per 1000 cc. This was the largest amount to be liberated from any bottle tested in this work and probably represents the maximum that would be found in practice.

A liter was injected into each of eleven patients. The injection time was 45 to 60 minutes. The temperature, pulse and respiration were taken hourly the day before each injection and again on the day of the injection, which was given in the morning. In none of the cases was there any appreciable difference in the recorded data before and after the injection.

SUMMARY.

1. The Kimble titration method is capable of distinguishing between resistance and soft glass containers regardless of capacity, but not between untreated and surface treated soft glass containers.

2. Either the electroconductivity or the residue method, in the case of new unused containers, is capable of distinguishing between treated and untreated soft glass and between untreated soft glass and resistance glass. The values obtained with treated soft glass and resistance glass are too close to make either method entirely satisfactory.

Either method is likely to be unsatisfactory when testing used containers.

If a standard is set for either method, allowance must be made for the variation in concentration in different sized containers due to the difference in the ratio of the area of glass exposed to the volume of water.

3. The water-soluble constituents of glass, of which sodium silicate predominates, have apparently no pharmacological significance in the concentration in which they exist in sterilized parenteral solutions in glass containers. However, these results are based on single injections and do not represent the effect of a series of injections into an individual.

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