A PHARMACEUTICAL STUDY OF IODINE SOLUTIONS FOR ANTISEPSIS.*

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Iodine, since its discovery, has been used externally as a counter-irritant. It was used as such prior to the knowledge of antisepsis. The difficulty with the official preparations lies in the fact that being primarily intended for counter-irritants, they are therapeutically contra-indicated for wound treatment, and when used for antiseptic purposes, their irritating properties prejudice the users against iodine preparations for every-day use for antisepsis.

We do not recommend a change in the present official preparations of iodine, but medicine and pharmacy do need new preparations of iodine which can occupy a place in therapeutics as antiseptic preparations which those now official cannot.

A comprehensive study of various solvents was made to find just which one would be the most suitable for preparing an antiseptic iodine solution. The study included the following: Ethanol, methanol, glycerin, benzene, benzin, normal propanol, isopropanol, ethyl ether, chloroform, ethylene glycol, cellosolve, cellosolve acetate, carbitol, propylene glycol, dioxan, diethylene glycol, butyl cellosolve, ethyl acetate, dichlorethyl ether, ethylene dichloride.

All solvents containing the primary alcohol group (CH_2OH) were found to be decomposed by iodine with the formation of hydrogen iodide and the corresponding aldehyde. *E. g.*, ethanol was found to yield hydrogen iodide and acetaldehyde; no traces of ethyl iodide were found. This test was made by first removing iodine by the use of an excess of sodium thiosulphate, then distilling and testing the distillate for ethyl iodide. Control tests were made in which as small an amount as 0.1% ethyl iodide was added and in every case the added ethyl iodide could be recovered and detected, while the specimens of alcoholic solution of iodine, which had shown marked deterioration with the loss of several per cent in strength expressed as free iodine, showed no ethyl iodide when tested in the same manner.

In consequence of such decomposition, the solvent power for iodine of liquids containing primary alcohol groups could not be accurately determined as the solubility of iodine in such solvents was rapidly increased due to the formation of hydrogen iodide as a result of contact between iodine and the solvent.

After a close and careful examination of various solvents from the standpoints of irritation, penetration and stability, the decision was made that ethanol is the most satisfactory solvent for iodine providing optimum conditions in respect to these factors.

It has long been known that potassium iodide will inhibit the decomposition of solutions of iodine in alcohol; such is its use in preparing the present U. S. P. tincture. It became of interest to establish the optimum concentration of added potassium iodide for the promotion of stability. Varying concentrations of iodine alcohol and potassium iodide were mixed and aged and the free iodine as well as the presence or absence of acidity indicating deterioration were determined. It was found that regardless of the alcoholic concentration, in order to prevent deterioration enough potassium iodide must be added to theoretically form KI_3 with the iodine in solution.

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As a matter of interest, Churchill's Tincture of Iodine which does not contain this requisite amount of iodide, is unstable. However, as its field is chiefly that of a counter-irritant the hydrogen iodide formed would probably act synergistically.

A phenomenon of considerable importance was observed which is additional evidence in favor of the presence of potassium iodide in an antiseptic iodine solution. Iodine was found to pass at a very much increased rate through animal membrane when potassium iodide was added to the iodine solution. These tests were made by using defatted hog's bladder as a diffusion medium, when saturated aqueous solutions of iodine were placed in the diffusing chambers and these were then placed in contact with distilled water containing starch T.S.

Similar experiments were carried on simultaneously with the same iodine solution to which had been added an amount of potassium iodide sufficient to produce the theoretical combination KI_3.

In the presence of this amount of potassium iodide the starch solution would be colored blue within fifteen minutes to a degree of intensity not equalled by the plain iodine solution after an exposure of two hours. Other salts than iodide were added but these were found to be of no value, conclusively showing that the effect was not purely mechanical. The probable explanation of this increase in diffusion rate lies in the combination of iodine with the iodide to form a compound (possibly KI_3) which is more easily permeable to animal membrane. It is known that iodine alone in solution exists in high molecular aggregates. In any case, the addition of a proper proportion of potassium iodide should increase the effectiveness of penetration to both tissue and bacteria.

Steps were next taken to develop a more rational antiseptic iodine preparation for stock and dispensing use. In approaching this problem the current and past pharmaceutical and medical literature was examined in order to learn the opinions of authorities in this field. All were of the same belief, that a seven per cent tincture for antisepsis was excessive in strength.

So that a decision might be made as to what the strength of a preparation should be a preliminary bactericidal study of various strengths of iodine from one to seven per cent was made. It was found that a two per cent solution showed a potency which answered all practical purposes when compared with iodine solutions of both higher and lower strengths, and also when compared with a number of popularly used commercial antiseptics.

A series of experiments was carried out by Dr. George M. Karns of the Iodine Fellowship at the Mellon Institute in order to determine what concentration of ethanol would be most satisfactory as the solvent for a new iodine solution to comply with the requirements previously mentioned. It had been reported previously that an aqueous solution containing 56 per cent by weight of alcohol is devoid of dehydrating properties. It was further found that when using washed blood cells there is a rapid diminution protein coagulation time when the alcohol concentration falls below 50%. From these facts it was decided that Diluted Alcohol U. S. P. (48.4–49.5% by vol.) would provide a concentration, which although possessing a sufficient degree of penetration and evaporation would still not cause dehydration or blood-cell coagulation, and would enable the solvent to evaporate with sufficient rapidity to meet the demand for a popular antiseptic for local application.

In view of the fact that an antiseptic iodine solution would be utilized in many cases as a general antiseptic and consequently subject to dilution it was considered necessary to have present in the solution enough potassium iodide to render the iodine present soluble regardless of the degree of dilution to which it was subjected, a feature not possessed by the present U. S. P. tincture. This figure should at the same time be in excess of the amount of iodide necessary to maintain a solution that would not be subject to deterioration.

It was found that a solution of this type, namely, 2 per cent iodine and 2.4 per cent potassium iodide, would in regard to its saline content be isotonic with human blood serum, a factor which would considerably minimize the pain of application.

The iodine present being undissociated would not appreciably affect the tonicity and due to the much higher molecular weight, 2.4% potassium iodide, the preparation would have the same osmotic pressure as one containing 0.85% sodium chloride.

In a brief summary the salient features of this new preparation are as follows:

1. Germicidal effectiveness (as shown by the paper contributed by Dr. Louis Gershenfeld and Miss Ruth E. Miller).
2. Minimized irritation by low alcoholic content.
3. Approximate isotonicity with blood serum in its saline content.
4. Perfect miscibility with water.

A formula for this preparation is as follows:

ALCOHOLIC IODINE ANTISEPTIC SOLUTION.

Iodine	20 Gm.
Potassium iodide	24 Gm.
Diluted alcohol U. S. P. q. s. to make	1000 cc.

To the iodine and potassium iodide contained in a glass-stoppered bottle add 900 cc. of diluted alcohol. Shake well until dissolved and then add sufficient diluted alcohol to make the finished product measure 1000 cc.

This preparation which would answer all of the requirements for dispensing in a small sized applicator bottle for popular use possesses the dual characteristics of effectiveness, non-irritating qualities and stability.

Still another (and much weaker) antiseptic solution of iodine was produced which is suitable for wound irrigation and which was found to be of surprising effectiveness from the bacteriological standpoint.

The formula for this preparation is as follows:

ANTISEPTIC SOLUTION OF IODINE, WEAK, FOR IRRIGATION PURPOSES.

Iodine, powdered	1 Gm.
Sodium chloride	8.5 Gm.
Distilled water q. s. to make	1000 cc.

To the sodium chloride add 950 cc. of distilled water, agitate until dissolved, then add the powdered iodine and enough distilled water to make 980 cc. Agitate occasionally until the iodine is dissolved. Then filter, determine the iodine content by volumetric assay with $N/100$ sodium thiosulphate solution and adjust to a concentration of 0.02% free iodine. An excess of iodine is purposely used in making this preparation in order to ensure the proper strength of the finished product.

Upon the basis of a few bacteriological tests the germicidal effectiveness of this solution was found to be of marked value. Five cc. of the undiluted solution were

found to kill 1 cc. of a 24-hour culture of *B. Typhosus* and also of *staphylococcus aureus* within two minutes. Five cc. of a 1:10 dilution killed 0.1 cc. of a 24-hour culture of *B. Typhosus* within two minutes.

This solution was found to possess solvent properties similar to Dakin's solution.

This solution has also been found to be excellent for sterilizing maggot eggs used for the production of larvæ for cleaning wounds.

It is superior to the bichloride of mercury solution hitherto employed for this purpose in that, when the iodine solution is used, fewer eggs are killed and complete sterility is obtained.

In presenting the formulas for those two new non-proprietary solutions of iodine to the medical and pharmaceutical professions, it is believed that a contribution has been made which will be appreciated from the combined standpoint of economy and efficiency.

CONTRIBUTED BY THE IODINE SCHOLARSHIP OF THE PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE UNDER THE DIRECTION OF THE IODINE FELLOWSHIP OF THE MELLON INSTITUTE.

NITROSYL CHLORIDE WITH ALCOHOLS AND ALDEHYDES.

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As has been demonstrated (1, 2, 3), aliphatic hydrocarbons react with nitrosyl chloride to form isonitroso compounds. It has also been shown (4) that alkyl ketones undergo similar change and, at the same time, some of them (5) are chlorinated. Similarly, it has been found that certain alcohols (6) are readily converted to the corresponding nitrites. In view of the generic relationship, it seemed of interest to determine the effect upon aldehydes.

In 1903, Bouveault and Wahl (6) showed that nitrosyl chloride will react with certain alcohols in the presence of pyridine to form nitrites. All these alcohols were of fairly high molecular weight, the simplest one being isoamyl alcohol. We have now applied this reaction to other compounds with similar results and find that pyridine is not necessary with those of low molecular weight. It is notable also that this reaction apparently does not take place with glycerin, menthol and benzyl alcohol.

The aldehydes evidently react in a manner analogous to that of isonitrosoketones (5), giving rise to chlorides of the corresponding acids. Benzaldehyde gave benzoyl chloride and benzoic acid; acetaldehyde probably behaves in a similar way to a smaller extent. This ability of nitrosyl chloride to chlorinate is in conformity with previous experiments on ketones (5).

EXPERIMENTAL.

The nitrosyl chloride which was employed was made according to the method as previously described (4).

Ethyl Nitrite.—Absolute ethyl alcohol was placed in a vessel surrounded by a freezing mixture of ice and salt and the gas was run in to the point of saturation, as judged by the appearance of a deep reddish brown color. The product was poured into ice water, and a considerable effervescence and separation of yellow liquid followed. This yellow liquid was removed, washed with a cold solution of sodium