THE PERMANENCE OF TINCTURE OF IODINE, U. S. P.*

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Due to numerous inquiries as to the permanence of Tincture of Iodine, U. S. P., under various conditions, a research was undertaken to determine in an exact manner the stability of this Tincture when subjected to many common conditions of storage and use.

There has undoubtedly been much work done along this line, as every manufacturer of the Tincture would have occasion frequently to check up old lots or returned material. However, I have been unable to find any reports of a systematic study of this nature. That there is some confusion concerning the subject is shown by the number of inquiries received with reference to it.

Several liters of Tincture of Iodine were made up, the ingredients being carefully prepared in order to eliminate the possibility of impurities affecting the product. The iodine was of U. S. P. quality carefully purified by two further sublimations. The potassium iodide was U. S. P. in every respect. The alcohol was the commercial 95% grain alcohol, redistilled in the laboratory. The finished Tincture when assayed by the U. S. P. method contained 4.97 grams of potassium iodide per 100 cc. and 6.99 grams of iodine per 100 cc.

This Tincture was then packaged in thirty bottles of four ounces' capacity each. Amber and flint glass bottles were selected as they are the ones ordinarily met with in commercial use. Cork, rubber and glass stoppers were used in equal proportion. No special care was used in selecting the bottles or stoppers, the ordinary commercial grade of all being used so that the packaging conditions would not differ from those common to manufacturing procedure.

The samples for observation were bottled as follows: amber glass, full and half full of the Tincture and stoppered with cork, rubber and glass stoppers; also flint glass, full and half full, and stoppered as above. The glass stoppers were ground to fit the bottles, but were not greased or sealed in. The cork and rubber stoppers were of the extra long type. The half filled bottles were an elaboration of the original scheme and were employed to study the effect of an air space above the Tincture of Iodine such as is found when oversized bottles are used or when a stock bottle of large size is kept and the smaller dispensing bottles filled from it at intervals.

These thirty sample bottles were then divided into three groups of ten bottles each, each group containing similar bottles representing the different types of glass and stoppers, and each containing corresponding filled and half filled bottles. One group was stored near a window where it was exposed to direct light throughout the day and to sunlight for about two hours daily upon sunny days. Another group was stored in a dark room. Both of these groups were subjected to the usual fluctuations of room temperature. The third group was placed in a refrigerator and shielded from the light. In this way a number of commercial types of packaging and conditions of storage were duplicated as closely as possible on a small scale.

These samples were allowed to stand undisturbed for three months and were then assayed for iodine by the U. S. P. method. They were then stored away again as before and allowed to stand for three months more, at which time they were again assayed and the research discontinued.

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Every effort was made to obtain accurate results upon assay. Standardized glassware was used throughout, the sodium thiosulphate solution was carefully standardized, and all temperatures were uniformly controlled.

These results of the analyses at the end of the first three months were marked by their close agreement in most cases and some rather wide differences in others. Considering first the group of rubber-stoppered bottles, it was found that no change had occurred in any of them. The fact that some bottles were amber and some white glass and that some were full and some half full made no difference. Neither did the conditions of storage such as light and dark and warmth and cold affect the Tinctures.

As stated earlier, the Tincture when bottled contained 6.99 grams of iodine per 100 cc. The assay of the contents of these rubber-stoppered bottles at the end of three months varied from 6.99 grams to 7.02 grams of iodine per 100 cc., a difference of only 0.03 gram which is well within the limits of experimental error. Most of them assayed 6.99 and 7.00 grams per 100 cc. At the end of six months no change had taken place, the results of the assays almost duplicating those obtained at the end of three months.

The results obtained from the Tincture stored in cork-stoppered bottles were very similar to the above. They ranged from 6.98 grams to 7.01 grams of iodine per 100 cc. of Tincture, the variation of 0.03 gram being attributed to experimental error. The Tinctures were all clear and in perfect physical condition. The stoppers were stained but not injured. Here, too, no appreciable changes were found at the end of six months.

The analysis of the Tincture in the glass-stoppered bottles at the end of three months showed some unexpected results. Each bottle showed an increase in iodine strength, the assays ranging from 7.03 grams to 7.31 grams of iodine per 100 cc. The filled bottles gave somewhat higher results, averaging 7.14 grams of iodine per 100 cc., than those which were only half filled and which averaged 7.11 grams of iodine per 100 cc. The results at the end of six months showed still greater changes varying from 7.10 grams to 7.55 grams of iodine per 100 cc. These were the extremes, all of the rest of this group assaying about 7.30 grams of iodine per 100 cc. Upon investigation in an effort to explain these results, it was found that the Tincture of Iodine had exercised its faculty for creeping and had forced its way between the stoppers and the necks of the bottles in spite of the fact that each stopper was ground to fit its individual bottle. There were deposits of crystallized potassium iodide around the stoppers at the top of the bottle necks, and careful manipulation of the stoppers showed a large number of grains of potassium iodide between the stopper and the neck of the bottle. The Tincture of Iodine seemed to have penetrated between the stoppers and the bottle necks and to have lifted the stoppers a slight distance. This is borne out by the fact that the stoppers were all loose, although they were originally placed in the bottles rather firmly. If the ground glass stoppers had been freely greased before being placed in the bottles or had been sealed in place they would undoubtedly have been fully as satisfactory as the cork or rubber stoppers. However, it is not a practice to grease ground-glass stoppers in the commercial bottling of fluids, and as these tests were designed to duplicate practical working conditions, tests using greased ground-glass stoppers in sample bottles were not carried out. When glass stoppers are securely sealed in place by a composition wax, there can be no question as to their efficiency.

Parallel with this investigation of bottling and storage conditions, a similar study was made to determine the stability and permanence of Tincture of Iodine when subjected to the conditions under which it is ordinarily used. Three one-pint bottles, two amber and one flint, were filled with the original Tincture, assaying 6.99 grams of iodine per 100 cc. Two of these pint bottles, one each of amber and white, were closed with rubber stoppers. The other pint bottle, amber with a rather narrow neck, was allowed to remain open. These were stored in a cupboard, at room temperature, which was frequently opened admitting light and air. The intention was to duplicate the condition found in a physician's office or hospital dispensary. To carry out this parallel further the rubber stoppers were removed from the bottles daily, the contents agitated gently and the stoppers allowed to remain out for five minutes. The unstoppered bottle was not agitated as this was intended to represent a stock bottle from which the stopper had been left out accidentally or had blown out as sometimes happens in hot weather.

Samples taken from the Tincture packaged in these three pint bottles were assayed every week, the same precautions for accuracy being taken as were taken for the analysis of the first series. These analyses were continued weekly for twenty-eight weeks. The samples withdrawn each week corresponded to the gradual use of the Tincture under actual conditions of use.

The results obtained indicate clearly that Tincture of Iodine is reasonably permanent under the ordinary conditions of use. The Tincture in the pint amber bottle which was stoppered except for five minutes daily slowly increased in strength from 6.99 grams of iodine per 100 cc. to 7.07 grams per 100 cc. The Tincture packaged in the white glass bottle under the same conditions increased from 6.99 grams to 7.14 grams of iodine per 100 cc. For several weeks at the start the increase in iodine content was very slight, the rapidity of evaporation increasing as the surface of the contents of the bottles became lower and the air space above the liquid increased. Another factor which may have influenced the rate of evaporation was temperature. The tests were started in January and ended in August. The average temperature of the room in which the samples were stored was undoubtedly lower during the winter months than during the summer months, and the more rapid increase in the rate of evaporation with the consequent increase in iodine content of the Tincture became more pronounced as the summer advanced.

The Tincture in the bottle left open all of the time increased rapidly and with almost mathematical precision from 6.99 grams of iodine per 100 cc. to 8.62 grams. It required eight weeks to reach the U. S. P. high limit. A coating of potassium iodide formed upon the neck of the bottle which gradually increased until at the end of the investigation it had made fair progress toward closing the neck of the bottle.

Another short series of tests was carried out to determine the permanence of Tincture of Iodine when a large surface is exposed to the air. Sometimes when considerable of the Tincture is to be used, as in the sterilization of a large skin area prior to an operation, the Tincture is poured into a tray into which the gauze or cotton sponges can be dipped. To duplicate these conditions five hundred cubic centimeters of the Tincture were made up and poured into a circular porcelain dish about seven inches in diameter and an inch deep. This was allowed to stand exposed at room temperature, 80° Fahrenheit, and was assayed every two hours. The original

assay of the Tincture was 6.95 grams of iodine per 100 cc. In two hours evaporation had caused it to increase to 7.43 grams; in four hours to 7.97 grams, in six hours to 8.71 grams, and in eight hours to 9.42 grams. The next morning, twenty-four hours after starting the test, the iodine content had increased to 13.12 grams of iodine per 100 cc.

A rather futile attempt was made to determine the concentration of iodine in Tincture of Iodine necessary to produce a superficial iodine burn when applied in the ordinary manner to the skin. It was found, however, that different people varied so widely in susceptibility that no specific or even general figures can be given. Light-haired and fair-skinned people are the least resistant, in two instances the Tincture of U. S. P. strength being sufficient to cause a distinct burn with peeling of the skin. On the other hand, a certain subject with a skin which was highly resistant was able to stand a concentration of twice that of the U. S. P. without appreciable ill effects.

The conclusions to be drawn from the above investigations are evident:

First—Tincture of Iodine, U. S. P. may be safely stored for six months, and presumably for a much longer time under most of the ordinary conditions of packaging and storage. Either flint or amber glass is satisfactory and good cork or rubber stoppers insure perfect seals. Glass stoppers under the conditions of the test are not satisfactory although they undoubtedly would be satisfactory if coated with vaseline or sealed in place. It is not necessary that the bottles be full, as a small air chamber above the liquid exerts no appreciable effect.

Second—Tincture of Iodine may also be used for a long period of time from a small bottle without any great danger although there will be a gradual increase in iodine strength. It is not advisable to use directly from a large bottle, as the extended time required for its use could easily result in a concentration of iodine too high for safety. It is much better to fill the frequently used small bottle from the larger stock bottle, keeping the large bottle tightly closed as much as possible.

Third—If a bottle of Tincture of Iodine has been left standing open for any length of time, that is, for longer than a few days, it will increase rapidly in iodine concentration and should be assayed and adjusted before use.

Fourth—If Tincture of Iodine is poured into a tray for more convenient use it should not be allowed to stand for longer than two hours at the most as evaporation is rapid and within two hours the percentage of iodine is considerably increased. This is under ordinary conditions of summer temperature, and using a small tray about seven inches in diameter.

Fifth—The susceptibility of a patient to Tincture of Iodine is by no means a measure of the concentration of iodine in the Tincture, as persons vary so greatly in resistance that there is within reasonable limits no parallel between individual susceptibility and the strength of the Tincture.

In general then, it may be stated that under the common conditions of storage and use, Tincture of Iodine U. S. P. is very permanent, and there need be no apprehension as to its use except when through accident or other cause the Tincture has been unduly exposed to the air.

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