THE DETERIORATION OF DIGITALIS LEAVES.*[1]

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The U. S. P. XI, in order to prevent as far as possible the appearance of substandard digitalis on the market, adopted the requirement that the drug must be preserved in water-tight and air-tight containers under all conditions of storage and transportation, and also the requirement that the drug must not contain more than 8 per cent of moisture. The necessity of these requirements was immediately questioned. Since the amount of factual data concerning the stability of the drug available in the literature is limited, the work herein reported was undertaken in order to determine the keeping qualities of digitalis leaves containing varying amounts of moisture in both air-tight and open containers at various controlled temperatures.

Hale (1), Sharp and Lancaster (2), Hatcher and Eggleston (3), Gold and De Graff (4), Haag and Hatcher (5, 6) and Rowe and Pfeifle (7) have investigated the stability of digitalis, and all have reported data indicating that digitalis leaves do not deteriorate on standing for periods of several years even when the drug is stored with no special precautions. On the other hand, Focke (8), Gronberg (9) and Wastensen (10) have also investigated the problem, and their published data indicate strongly that digitalis leaves are most unstable. Focke, Gronberg and Wastensen have all recommended most emphatically that the moisture content of the drug should not exceed 1.5 per cent and that the drug should be stored in air-tight containers.

EXPERIMENTAL.

Two twenty-five pound lots of digitalis leaves were obtained, one lot from each of two reputable dealers in crude drugs. These two lots were examined for moisture content by the oven method of the U. S. P. XI and were assayed for potency by the official one-hour frog method.

From each commercial lot 100-Gm. representative samples were taken and stored in both open and air-tight containers at room temperature and also in ovens having thermostatically controlled temperatures of 70° F., 80° F., 90° F. and 100° F. for a 100-day storage period. The closed containers used were glass jars with metal caps, rendered air-tight by means of a rubber seal. The open containers were glass jars with a pledget of cotton placed lightly in the mouth of the jar in such a manner as to allow a free access of air.

Additional representative quantities of the two commercial lots were adjusted to the moisture contents indicated in the accompanying table and 100-Gm. samples were sealed in glass jars and stored at the same thermostatically controlled temperatures for a storage period of one hundred days.

In adjusting the moisture content of the various samples, the quantity of drug to be adjusted was spread out in a thin layer in a drying oven in which the temperature was 40° C. ± 1° C. After drying, the drug was immediately sealed in air-tight containers and the moisture content determined.

At regular intervals of one week during the storage period, each sample was examined by means of a magnifying lens in order to ascertain whether any physical changes would occur. At the end of the storage period all samples of each moisture content stored at each temperature were reassayed pharmacologically in order to determine whether any deterioration in potency had oc-

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curred. Also, since it has been suggested that the moisture content of the drug may increase when stored in air-tight containers at high temperatures, the moisture content of a representative number of the samples so stored was redetermined at the end of the storage period.

TABLE OF RESULTS.

Sample from Lot No.	Moisture Content, Per Cent.	Storage Temp., Degrees F.	Type of Container.	Potency after Storage, Per Cent.	* Deterioration, Per Cent.
1	4.8	70	Air-tight	67	38
2	4.8	70	Air-tight	80	40
1	4.8	80	Air-tight	67	38
2	4.8	80	Air-tight	100	25
1	4.8	90	Air-tight	67	38
2	4.8	90	Air-tight	100	25
1	4.8	100	Air-tight	80	25
2	4.8	100	Air-tight	100	25
1	6.3	70	Air-tight	80	25
2	6.8	70	Air-tight	100	25
1	6.3	80	Air-tight	80	25
2	6.8	80	Air-tight	80	40
1	6.3	90	Air-tight	80	25
2	6.8	90	Air-tight	80	40
1	6.3	100	Air-tight	80	25
2	6.8	100	Air-tight	100	25
1	8.8	70	Air-tight	67	38
2	8.3	70	Air-tight	80	40
1	8.8	80	Air-tight	80	25
2	8.3	80	Air-tight	80	40
1	8.8	90	Air-tight	80	25
2	8.3	90	Air-tight	100	25
1	8.8	100	Air-tight	67	38
2	8.3	100	Air-tight	100	25
1	11.4	70	Air-tight	80	25
2	11.9	70	Air-tight	100	25
1	11.4	80	Air-tight	80	25
2	11.9	80	Air-tight	100	25
1	11.4	90	Air-tight	80	25
2	11.9	90	Air-tight	100	25
1	11.4	100	Air-tight	80	25
2	11.9	100	Air-tight	100	25
1	11.4	Room	Air-tight	67	38
2	11.9	Room	Air-tight	80	40
1	11.4	70	Open	67	38
2	11.9	70	Open	80	40
1	11.4	80	Open	80	25
2	11.9	80	Open	80	40
1	11.4	90	Open	80	25
2	11.9	90	Open	100	25
1	11.4	100	Open	67	38
2	11.9	100	Open	80	40
1	11.4	Room	Open	67	38
2	11.9	Room	Open	80	40

* Original potency of Lot 1—107 per cent.
Original potency of Lot 2—134 per cent.

DISCUSSION OF RESULTS.

In evaluating the results obtained in carrying out the potency determinations it must be remembered that although the method of physiological assay employed in this investigation has been adopted by the U. S. P. XI as the most accurate available, the method permits a 40 per cent range of experimental error. The assay results, therefore, may be considered to represent accurately the true potency of the drug only to within ±20 per cent. Therefore, in drawing any conclusions from the results obtained, the inherent limitations of the assay have been borne in mind.

After determining the potency of each sample at the end of the storage period, the percentage of deterioration was calculated by taking the original potency as 100 per cent. The deterioration figures arrived at by this means may be observed in the accompanying table.

It was hoped that some correlation might be found between the degree of deterioration, the moisture content and the temperature of storage. However, as a study of the results obtained indicates, no such relationship was observed.

Every sample exhibited some deterioration at the end of the storage period. Without exception, the amount of deterioration was either 25, 38 or 40 per cent. Since the greatest difference between any two of these figures is only 15 per cent, it is impossible to conclude that any moisture content between 4.8 per cent and 11.9 per cent possesses any advantage over any other so far as it affects the keeping qualities of the drug during a 100-day storage period. Likewise, no evidence was obtained which would indicate that digitalis deteriorates to any greater degree at any particular temperature within a range of 70° to 100° F. during the course of 100 days.

In considering the results obtained from the comparison of the deterioration of samples stored in air-tight and open containers, no evidence was noted which would appear to indicate that storage in air-tight containers enhances the keeping qualities of the drug during a 100-day storage period. Disregarding storage temperatures, the average deterioration of samples stored in open containers was only 7 per cent greater than the average for the samples stored in air-tight containers. Considering the accuracy of the assay employed, such a small difference probably has no significance.

During the storage period each sample was examined at regular intervals in order to ascertain whether or not there was any evidence of physical deterioration, such as the development of mold, which could be noted without opening the container. In no case was any development of mold observed in samples stored in either open or air-tight containers. At the higher moisture contents and temperatures, however, samples stored in air-tight containers exhibited a color change. The original green color of the leaves changed first to a grayish green color, which later changed to a brownish green color. This change was proportional to both the moisture content and the temperature at which the samples were stored. No such change was observed in the samples stored in containers which allowed a free access of air.

Finally, the moisture contents of eight samples which had been stored in air-tight containers at temperatures of from 80° F. to 100° F. were redetermined. In each case the moisture content was unchanged.

CONCLUSIONS.

1. From the results obtained, it would appear that digitalis leaves containing from 4.8 per cent to 11.9 per cent moisture deteriorate on standing.

2. The percentage of deterioration which occurs during a storage period of 100 days does not appear to bear any relation to the moisture content within a range of 4.8 per cent to 11.9 per cent or to the temperature of storage within a range of 70° F. to 100° F.

3. No evidence was obtained which would appear to indicate that storage in air-tight containers enhances the keeping qualities of the drug during a 100-day storage period.

4. Further investigation should be carried out employing a longer storage period and moisture contents lower than 4.5 per cent.

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FURTHER EVIDENCE OF THE STRONG AND VARIABLE ACTION OF THE U. S. P. XI DIGITALIS STANDARD.*

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In a previous report (1) a considerable amount of experimental data was presented showing that the U. S. P. XI standard for Tr. Digitalis is 50% stronger than the U. S. P. X standard and nearly 25% stronger than the International Standard.

Since that time the 150% figure has been confirmed by Munch and his Committee (2) and by Thompson (3). This seems to point to the fact that the present official standard is definitely higher in potency than it was intended to be by its sponsors (4), since the International Standard was never reported to be 50% stronger than the U. S. P. X standard for Tr. Digitalis.

During the past year further work with official extracts of this U. S. P. XI digitalis standard powder No. 915,921, by the official one-hour frog method, has given additional evidence of its variable action which may be attributed either to the unsuitability of the method itself or of the standard digitalis powder or both.

EXPERIMENTAL DATA.

Last year it was noted that the minimum systolic dose of the corrected standard digitalis tincture was running consistently from 0.0050 cc. to 0.0070 cc. per Gm. which seemed quite low. This was with regular 1 to 3 and 1 to 4 dilutions of the standard which are permissible since the

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