(4) Of all the Commercial Psyllium seeds examined, those yielded by *Plantago ovata* rank highest in mucilage content and therefore in demulcent qualities with the seeds of *Plantago Psyllium* ranking second. *Lallemantia royeleana* fruits yield more mucilage than Psyllium seeds but must not be regarded as even a variety of Psyllium.

(5) The mucilage yielded by the seeds of *Plantago Psyllium* and *Plantago ovata* is of superior quality to that yielded by the seeds of *Plantago lanceolata.*

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THE EFFECT OF VARIOUS CONDITIONS OF STORAGE ON THE POTENCY OF TINCTURE OF DIGITALIS.*

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I. DEFINITION.

One of the most important preparations appearing in the United States Pharmacopœia is tincture of digitalis. When this drug is prescribed a definite action upon the heart is expected. Often this characteristic digitalis action—slowing of the rate, decrease in conductivity, increase in irritability, lengthening in diastole and more effective systole, is not obtained, or is only weakly exhibited by old preparations. Although such tinctures at the time of manufacture assay full strength, at the end of the period of storage biological tests show that they have undergone a loss of all or part of their potency.

This work represents a study of the influence of several factors upon the keeping qualities of the tincture during storage. The factors concerned were temperature, hydrogen-ion concentration of the extracting menstruums, exclusion of air by sealing and displacement of air in container with carbon dioxide.

II. INTRODUCTION.

Numerous investigations considering the effect of changes in the hydrogen-ion concentration upon the potency of the tincture as well as the infusion of digitalis have been performed. Pittenger (1), as well as Wokes (2), found that a normal tincture lost 30% of its potency during a sixteen months' period. Wokes also observed that a variation in p_H value of the tincture over a range of 5.47 to 5.93 decreased its potency, and when a tincture was made distinctly alkaline (p_H 8) an increase in the rate of deterioration occurred. Contrary to the findings of Wokes,

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Joachimoglu and Bose (3) stated that tincture of digitalis can be rendered more stable by the addition of tartaric acid until a p_H of about 5.2 is obtained. Of interest is the work of Krantz, Jr. (4), who contributed information concerning the neutralizing properties of tincture of digitalis.

Hintzelmann and Joachimoglu (5) found that an alkaline infusion of digitalis (p_H 8) deteriorated much more rapidly than a similar infusion at p_H 6.7. By the addition of 0.1 per cent of hydrochloric acid to an infusion of digitalis, Takahashi (6) observed an increase in the stability of the preparation.

III. METHODS AND PROCEDURES.

The various tinctures of digitalis were manufactured according to the United States Pharmacopœia X specifications with one exception, the changing of the hydrogen-ion concentration of the menstruum. In making the normal tincture the official method was followed throughout. Selected leaves donated by the Upsher Smith Company and Parke, Davis and Company were used.

The menstruum for each tincture was made separately. Part of the distilled water was replaced by the necessary quantity of an aqueous solution of the chemical required to obtain the desired p_H value. This procedure guarded against any change in the alcoholic strength of the finished product which was 70%. The colorimetric method was used to determine the hydrogen-ion concentration. The results were checked by the use of a Leeds and Northrup quinhydrone p_H apparatus.

The following table shows the chemicals used, as well as the respective p_H values of the menstruum employed in the making of the tincture.

Chemical.	p_H of Menstruum.									
Normal					5.8					
HCl	4.1	4.5	5.2	5.6						
NaH_2PO_4		5.2	5.4	5.7						
$HC_2H_3O_2$		5.1	5.4	5.6						
KOH					6.4	7.0	7.6	8.1		
NaOH					6.5	7.1	7.7	8.2	8.5	
Na_2CO_3					6.2	6.8	7.5			

The tinctures were made by the official method. After obtaining the finished preparations each one was assayed by the one-hour frog method.

Four samples of each individual tincture were stored in two-ounce amber, glass-stoppered bottles. The tinctures were kept under the following conditions for one year.

Group I. Well filled, not sealed, room temperature.

Group II. Well filled, sealed with paraffin, room temperature.

Group III. Carbon dioxide replacing air of partially filled bottles, sealed with paraffin, room temperature.

Group IV. Well filled, not sealed, refrigerator.

Amber bottles were used in order to avoid any action that light may have upon the preparation. Group I represents the condition in which most tinctures of digitalis appear on the market. In Group II the paraffin excludes the air other than that which was present in the bottle. Through the use of carbon dioxide in Group III we replace the air with a non-oxidizing gas. Low temperature was considered in Group IV.

After the expiration of a year the tinctures were again assayed by the official method and the results compared with those obtained from the freshly made products.

IV. EXPERIMENTS AND TABLES.

CHART A.

				Room Temperature.				Refrigerator.		
Chemical.	p_H.	Original.	Sealed.	% Loss.	Unsealed.	% Loss.	CO_2.	% Loss.	Unsealed.	% Loss.
Normal	5.8	0.006	0.011	83.3	0.011	83.3	0.010	66.7	0.011	83.3
HCl	4.1	0.008	0.012	50.0	0.012	50.0	0.011	37.5	0.011	37.5
HCl	4.5	0.009	0.010	11.2	0.011	22.3	0.010	11.2	0.012	33.4
HCl	5.2	0.009	0.010	11.2	0.011	22.3	0.011	22.3	0.011	22.3
HCl	5.6	0.008	0.010	25.0	0.011	37.5	0.011	37.5	0.011	37.5
NaH_2PO_4	5.2	0.008	0.011	37.5	0.011	37.5	0.011	37.5	0.011	37.5
NaH_2PO_4	5.4	0.008	0.011	37.5	0.011	37.5	0.011	37.5	0.010	25.0
NaH_2PO_4	5.7	0.008	0.011	37.5	0.011	37.5	0.011	37.5	0.011	37.5
$HC_2H_3O_2$	5.1	0.009	0.012	33.3	0.012	33.3	0.011	22.3	0.011	22.3
$HC_2H_3O_2$	5.4	0.008	0.012	50.0	0.012	50.0	0.010	25.0	0.011	37.5
$HC_2H_3O_2$	5.6	0.008	0.011	37.5	0.011	37.5	0.011	37.5	0.011	37.5

CHART B.

				Room Temperature.				Refrigerator.		
Chemical.	p_H.	Original.	Sealed.	% Loss.	Unsealed.	% Loss.	CO_2.	% Loss.	Unsealed.	% Loss.
KOH	6.4	0.009	0.013	44.4	0.013	44.4	0.013	44.4	0.012	33.3
KOH	7.0	0.010	0.013	30.0	0.013	30.0	0.013	30.0	0.012	20.0
KOH	7.6	0.010	0.013	30.0	0.013	30.0	0.013	30.0	0.012	20.0
KOH	8.1	0.011	0.014	27.3	0.014	27.3	0.013	18.2	0.012	9.1
NaOH	6.5	0.009	0.013	44.4	0.013	44.4	0.013	44.4	0.013	44.4
NaOH	7.1	0.009	0.013	44.4	0.013	44.4	0.013	44.4	0.013	44.4
NaOH	7.7	0.010	0.014	40.0	0.014	40.0	0.014	40.0	0.013	30.0
NaOH	8.2	0.010	0.014	40.0	0.014	40.0	0.014	40.0	0.014	40.0
NaOH	8.5	0.010	0.014	40.0	0.015	50.0	0.014	40.0	0.014	40.0
Na_2CO_3	6.2	0.009	0.014	55.6	0.014	55.6	0.014	55.6	0.014	55.6
Na_2CO_3	6.8	0.010	0.015	50.0	0.015	50.0	0.015	50.0	0.014	40.0
Na_2CO_3	7.5	0.010	0.014	40.0	0.015	50.0	0.014	40.0	0.014	40.0

Charts A and B present results of 708 experiments in which the various tinctures were assayed. The first column of figures from the left designates the type of chemical used to change the hydrogen-ion concentration of the menstruum, while the second gives the result in p_H values. In the third is listed the fraction of a cc. of the tincture necessary to stop the frog's heart in systole at the end of one hour when assayed immediately after manufacture. The remaining columns state the conditions of storage, the assay dosage, as well as the percentage loss in potency, after an elapse of one year. It is to be noted that the acid p_H value following the use of alkalies is due to the fact that the tincture is normally acid.

V. RESULTS OBTAINED.

From the results as tabulated in Charts A and B it is evident that changing the p_H value of the extracting menstruum, within the limits of these experiments, produces tinctures of substandard strengths. This is independent of the type of acid or alkali used.

By the addition of HCl various p_H ranges from 5.6 to 4.1 were obtained. The tincture showed a decrease in potency from 30% to 50% in comparison to a normal tincture. The tincture, after one year of storage displayed a further decrease of from 12% to 50%. Nevertheless those preparations having the greatest

decrease after manufacture now show the smallest drop, while those with the lower percentage decrease originally, now show a greater substandard condition. Due to this counter-balancing the product at the end of the time period showed about the same potency, a decrease of 65% to 100% from the normal tincture, regardless of the condition of storage.

The series containing sodium acid phosphate possessing p_H values of 5.7 to 5.2 all showed a comparative decrease of 33% and an additional loss of 37.5% during storage. This in terms of the normal tincture would mean a lowering of the potency 83.3%.

In those preparations containing the largest quantity of acetic acid (p_H 5.1) the decrease was found to be 50% while those with p_H values of 5.4 and 5.6 lost 33.3%. After the second assay the tinctures kept at a low temperature and those possessing CO_2 were slightly more stable, the potency decreasing from the first assay 37.5% and from the normal tincture 83.3%. The two tinctures having the p_H values of 5.1 and 5.4 and kept in sealed and unsealed bottles at room temperature showed at the end of one year a decrease of 33.3% and 50%, respectively, or a 100% when compared with the normal.

On the alkali side of the scale the potency is lowered more than when acids are added. In the original assay the decrease was proportional to the alkalinity. With a p_H of 6.4 there is a fall of 50%; and with a p_H of 8.1, a loss of 83.3% when compared with the normal. At the end of the year a second assay showed further decrease of 27.3% to 44.4% for those kept at room temperature. The ultimate potency of all these tinctures was approximately the same. Nevertheless compared with the normal all the KOH tinctures displayed a decrease of 116.7%. Those kept in the refrigerator had a loss of 9.1% to 33.3% from the original value. When compared with the normal tincture, the decrease was 100%.

When NaOH was used we obtained p_H values of 6.5 to 8.5 with a resulting change similar to that effected by KOH. The initial decrease ranged from 50% to 66.7%, while at the end of the year an additional loss of 40% to 44% was noticed. Comparison with the normal was 116.7% to 133.3%.

With the last chemical used, Na_2CO_3, p_H values of 6.2, 6.8 and 7.5 were acquired. The same initial decrease was found with the other two alkalies. Nevertheless at the end of the year of storage the greatest of all losses in potency was shown; a decrease of 40% to 55.6% from the original being equal to a 133.3% to 150% from the normal, regardless of the method of storage.

VI. DISCUSSION.

It is evident from the results obtained that a change in the hydrogen-ion concentration is not indicated for tincture of digitalis, a product showing at least a 30% decrease in potency is obtained when the p_H is changed. Results from the various experiments show that alkalies are more detrimental to the active constituents of digitalis than are acids. This being in agreement with the findings of Wokes (2). By comparison it was found that acids cause a decrease in potency of 33.3% to 50% while the alkalies a lowering of 50% to 66.7%. When either acid or alkali menstruums are used the decrease in potency is proportional to the change in the hydrogen-ion concentration.

The question of storage is still a great problem. Low temperatures seem to

have only a very slight advantage over higher temperatures. Thus the refrigerator is of very little use as a means of storage. The replacing of the oxygen with a non-oxidizing gas, carbon dioxide, inhibits deterioration to a slight degree.

Sealing with paraffin to have the container air tight, proved useless since the results show some loss of potency whether the container was sealed or unsealed.

It is to be noted that the assay of all the tinctures at the end of a year of storage shows them to be of approximate equality, regardless of the original activity. It would seem that after a period of time an equilibrium is reached when no further destruction of glucosides occurs, disregarding the method of manufacture and the conditions of storage. This may be due to an inactivation of the added alkali or acid, or may be due to the fact that some of the glucosides are stable and not destroyed while others are labile and readily broken up in an acid or alkali medium. This process probably occurs in the normal tincture also, since there is comparable loss in activity.

The exact mechanism involved in this process of deterioration is at present not known but is the subject of further investigation.

VII. CONCLUSIONS.

1. Increasing or decreasing the p_H of the menstruum in making tincture of digitalis produces an inferior product.

2. Storage at room temperature, or 6° C., has no differential effect on the keeping qualities of this preparation.

3. Tincture of digitalis stored in sealed or unsealed containers deteriorates to the same degree.

4. Displacing the air in a container with carbon dioxide has but a slight inhibitory action on the deterioration.

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STUDIES ON THE PREPARATION, TOXICITY AND ABSORPTION OF BISMUTH COMPOUNDS. I. BISMUTH SALTS OF FATTY ACIDS.*

BY W. M. LAUTER, A. E. JURIST AND W. G. CHRISTIANSEN.

While a great many clinical reports have been made describing the results obtained with bismuth salts of fatty acids in the treatment of syphilis, very little has been published concerning the results obtained in carefully controlled experimental studies on animals. Most of the results so far published are concerned chiefly with the excretion of bismuth giving very little accurate data concerning the relative toxicity and absorption of these compounds. The purpose of these studies is to compare these substances with a number of other types of bismuth

* Scientific Section, A. PH. A., Toronto meeting, 1932.