SCIENTIFIC SECTION

THE CAUSES OF PRECIPITATION IN TINCTURES AND FLUIDEXTRACTS.*

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Much work has been done on the problem of preventing precipitation in tinctures and fluidextracts through modifications of the menstrua, the use of qualifying agents in the menstrua, such as acids, alkalis or glycerin, and more recently through a closer study of the reaction by adjustment of the p_H value. Such studies have resulted in many and marked improvements in official preparations, but have not disclosed much information regarding the reasons for change in these preparations.

The present study is designed to throw some light on the causes of precipitation in order that further studies may follow more intelligently on the means of preventing this change. It is recognized that the causes are probably complex, and that serious deterioration in these preparations is not always shown by precipitation; but that precipitation is an indication of chemical change which may influence the therapeutic value of the product, is generally accepted, and any information on the causes of precipitation will lead to further methods of improving and stabilizing these preparations. It is therefore necessary that we have more definite information concerning the influences which produce precipitates in an initially clear liquid, in order that deterioration may be prevented.

The present study aims solely at the causes, and the experiments that have been carried out have not been designed to find a possible means of improvement.

There are two ways of approaching the problem. One could make an analytical study of the precipitates that are formed, and by comparing these with the natural soluble constituents of the drug ascertain what change has occurred whereby the soluble has become insoluble. This is a direct method, and if accurately and scientifically carried out would definitely settle the problem. But the complexity of drug extracts, the difficulty of finding methods of analysis which would be adequate as well as accurate, and the very limited and uncertain amount of material on which one could work offers a discouraging prospect for this line of attack.

The indirect method, of noting what conditions or agents, when applied in rather excessive amounts, may either hinder or hasten precipitation was the method adopted.

Four classes of drugs were selected for study, the individual drugs in each class being those which are prone to form precipitates in the respective tinctures or fluidextracts: Alkaloidal drugs, astringent drugs, cathartic drugs and a rather miscellaneous collection of drugs containing neutral principles were chosen. These are designated in the tables and discussion which follow.

The method pursued is as follows:

Five hundred Gm. of the drug was percolated with the official menstruum in the usual manner, and 1000 cc. of tincture was collected and well mixed. This gave a fairly concentrated tincture, representing approximately 50 Gm. of drug in

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100 cc. in which the soluble constituents have not been subjected to heat or undue exposure. The tinctures are strong enough to produce a material amount of precipitate on aging, and such precipitation will be due solely to conditions within the tincture itself. The question of the relation of drug to tincture will not be definite, but is not important for this work. The avoidance of heat or of undue exposure is important and was the main factor in choosing this type of preparations.

The respective tinctures were divided into eight portions of 125 cc. each, which well filled the four-ounce bottles used. One sample was placed in a flint-glass bottle, and a second in an amber-colored bottle for comparison. The other six samples were placed in amber-colored bottles, and treated as follows: To one was added 2 cc. of concentrated hydrochloric acid (or in the alkaloidal preparations 3 to 6 cc. of this acid) or 2 Gm. of sodium chloride. The object in view was first to learn the influence of an excess of acid on the drug extracts, or second to get some indication of the effect of a strongly ionizing agent upon the colloidal conditions of the extractive. Sodium chloride was used in only a few of the samples, in which it was thought desirable to avoid an excessive acidity.

To another sample was added 5 cc. of 50 per cent hypophosphorous acid for the purpose of learning the influence of a strong reducing agent.

To another sample was added 2 cc. of a 3 per cent solution of hydrogen peroxide to ascertain the action of an oxidizing agent.

Another sample was saturated with carbon dioxide by passing the gas into it at a moderately rapid rate for fifteen minutes, after which the bottles were tightly stoppered while the gas still filled the bottles. The stoppers of these samples have not been withdrawn except in the cases where extractive was taken.

Another sample was rendered slightly alkaline to litmus paper by the cautious addition of sufficient stronger water of ammonia.

To another sample was added as much sodium acetate as would practically saturate its water content, as calculated from the menstruum used. The object here was to learn the effect of a saline buffer, and also to get a dehydrating action. Sodium acetate was chosen because of its solubility in alcoholic liquids. Its alkaline character is objectionable for this purpose, but the citrates were ruled out because of their insolubility in alcoholic liquids.

The samples were all stored in a case having glass doors, the case being directly beside an east window but at right angles to it, and setting parallel to a north wall. The specimens were thus exposed to a fairly strong light but not to direct sunlight. The samples in flint-glass bottles were placed in the front rows in order to get the full effect of the light, and have stood in this position for four years.

The aim of the experiments was to learn the effect of (1) light, (2) of acidity, (3) of alkalinity, (4) of oxidation, (5) of reduction, (6) of strongly ionizing agents, (7) of saline buffers and (8) of dehydrating agents upon the liquids.

All experiments were kept under close observation until the first precipitates appeared, or for three months where precipitation was slow. Then they were examined at intervals during the first year. Since the first year little attention has been paid to them until at about the end of the four-year period. It will be noted, however, that in most instances no material change is noticeable since the end of the first year.

TABLE I.—ALKALOIDAL DRUGS.

Table of menstrua and strengths.

	Menst. alcohol.	Alkaloid assay.	Extractive assay.
Red Cinchona	77%	0.31%	13.40%
Cinchona calisaya	77%	0.82%	5.50%
Kola	64%	0.75%	4.56%
Lobelia	49%	0.195%	9.40%
Sanguinaria	58%	2.55%	17.90%

Table of precipitation results.

	Clear bottle.	Amber bottle.	HCl.	HPH_2O_2.	H_2O_2.	CO_2.	NH_3.	Sod. acet. Amt.	Sod. acet. Ppt.
Red Cinchona									
Time 1st ppt.	21 d.	1 mo.	2 1/2 mo.	2 mo.	3 d.	1 mo.	30 m.	12 G.	14 d.
Amt. in 1 y.	s.	s.	s.	1/32 in.	1/16 in.	s.	1/2 in.		1/4 in.
Amt. in 4 y.	s.	s.	3/8 in.	3/8 in.	1/16 in.	s.	1/2 in.		1/4 in.
C. Calisaya									
Time 1st ppt.	1 mo.	1 mo.	14 d.	21 d.	21 d.	2 1/2 mo.	1 m.	12 G.	21 d.
Amt. in 1 y.	s.	s.	1/16 in.	1/16 in.	1/8 in.	1/32 in.	1 in.		1/4 in.
Amt. in 4 y.	s.	s.	1/16 in.	3/4 in.	1/8 in.	1/32 in.	1 in.		1/4 in.
Kola									
Time 1st ppt.	12 w.	2 mo.	7 w.	4 w.	7 w.	7 w.	12 h.	16 G.	4 w.
Amt. in 1 y.	s.	s.	s.	s.	s.	s.	3/8 in.		1/4 in.
Amt. in 4 y.	s.	s.	s.	s.	s.	s.	1/8 in.		1/4 in.
Lobelia									
Time 1st ppt.	2 mo.	2 mo.	6 w.	4 w.	3 w.	2 mo.	2 w.	24 G.	4 in.
Time in 1 y.	s.	s.	s.	s.	s.	s.	1/2 in.		s.
Amt. in 4 y.	s.	s.	s.	s.	s.	s.	1/2 in.		s.
Sanguinaria									
Time 1st ppt.	2 w.	2 w.	2 w.	2 w.	2 w.	2 w.	1 w.	28 G.	2 w.
Amt. in 1 y.	st.	st.	1/4 in.	1/8 in.	st.	st.	st.		st.
Amt. in 4 y.	st.	st.	3/8 in.	1/2 in.	st.	st.	st.		st.

Abbreviations: ppt., precipitate; m., minute; d., day; mo., month; w., week; h., hour; y., year; st., sticky; s., slight and slightly; c., considerable; in., inch; gel., gelatinized; G., gram; the abbreviations apply to plurals as well as singular.—These abbreviations apply to all of the tables and explanation is only made here.

Table I discloses the following:

Light does not show any action on any of these tinctures. Precipitation began at about the same time in the amber bottles as in the clear glass in three of the five drugs, a little earlier in red cinchona and later in kola. But at the end of four years there is no appreciable difference in any of the pairs.

Hydrochloric Acid.—The amount of this acid was varied in the different samples. To the Red Cinchona was added 6 cc. of acid, making the tincture to contain about 2.5 per cent of absolute acid; to the Calisaya was added 4 cc. of acid, making the tincture to contain about 1.5 per cent; to Lobelia and Kola was added 3 cc. each of acid, making the tinctures to contain about 1 per cent; and to Sanguinaria was added 5 cc. of acid, making the tincture to contain about 2 per cent. This acid shows no influence on precipitation in the cases of Kola, Lobelia and Sanguinaria, except that it aids in flocculating the last. It first retarded, then increased precipitation in Red Cinchona and had the opposite effect in Calisaya. The final result in all cases except Red Cinchona is practically the same. (It may be noted that the effect of hydrochloric acid when added to the tincture is very different from that obtained when this acid is used in the menstruum.)

Oxidation and Reduction.—Hypophosphorus acid apparently hastened and also increased precipitation in all except Red Cinchona, where its action is similar to hydrochloric acid. Hydrogen peroxide produced a more prompt precipitation, in the Cinchonas and Lobelia, but did not cause any marked increase in the final amount of precipitate. Neither of these reagents shows any marked influence.

Carbon dioxide shows a slight retarding effect in all cases except Calisaya, but the influence is not marked.

Alkali in the form of ammonia shows a marked influence in all cases. Precipitation occurred much more quickly and the amount was increased, in each case. This precipitate would not be entirely alkaloidal because more than enough alcohol is present in each case to hold the free alkaloids in solution. The effect of rendering the tinctures alkaline is sufficiently marked to leave its influence without any doubt.

Sodium acetate.—Precipitation is increased on the Cinchonas and on Kola, but its influence on Lobelia and Sanguinaria is not plain. To ascertain whether the reaction was sufficiently changed to account, in part perhaps, for the increased precipitation the p_H value was kindly ascertained for me by Mr. Sultzaberger on the untreated and treated Kola samples, at the end of the four-year period. He found that the untreated tincture which had been kept in an amber bottle showed a p_H value of 5.2—which is decidedly acid, while that containing sodium acetate showed a value of 7.1 which is slightly alkaline. This alone may possibly account for the increased precipitation in these cases, when considered in the light of the other experiments.

The precipitation in the Cinchonas and in Sanguinaria adhered to the sides of the bottles, and made comparisons difficult. In the case of Sanguinaria a comparison of the amounts was impracticable, and extractives were taken at the end of the first year. These showed as follows: Original extractive 17.92 per cent (w. v.). After one year—clear-glass bottle, 14.0 per cent; amber-glass bottle, 13.8 per cent; hydrochloric acid sample, 12.86 per cent; hypophosphorous acid sample, 16.24 per cent; hydrogen peroxide sample, 12.26 per cent; carbon dioxide sample, 13.86 per cent; alkaline sample, 13.84 per cent. This shows a stabilizing influence on the part of the hypophosphorous acid, and a precipitating influence on the part of hydrochloric acid and hydrogen peroxide.

TABLE II.—CATHARTIC DRUGS.

Table of menstrua and strengths.

	Menst. alcohol.	Extractive.
Aloe	49%	47.3%
Frangula	Water	9.6%
Juglans	49%	12.3%
Rhubarb	49%	19.7%
Senna, Alex.	33%	11.9%
Senna, Tinnev.	33%	15.4%

Table of precipitation results.

	Clear glass.	Amber glass.	HCl.	HPH_2O_2.	H_2O_2.	CO_2.	NH_3.	Sod. acet. Amt.	Sod. acet. Ppt.
Aloe									
Time 1st ppt.	3 d.	2 w.	1 mo.	2 w.	3 d.	10 d.	3 w.	24 G.	1 y.
Amt. in 1 y.	s.	s.	s.	s.	1/16 in.	s.	1/16 in.		...
Amt. in 4 y.	1/8 in.	1/8 in.	1/8 in.	1/8 in.	3/8 in.	3/8 in.	3/8 in.		1/8 in.
Frangula									
Time 1st ppt.	3 d.	3 d.	3 d.	3 d.	3 d.	3 d.	14 d.	36 G.	14 d.
Amt. in 1 y.	1/16 in.	1/16 in.	1/8 in.	3/16 in.	1/4 in.	1/8 in.	1/2 in.		s.
Amt. in 4 y.	1/8 in.	1/8 in.	1/4 in.	3/8 in.	3/8 in.	1/4 in.	1/2 in.		s.
Juglans									
Time 1st ppt.	8 d.	8 d.	2 d.	2 d.	2 d.	8 d.	8 d.	24 G.	8 d.
Amt. in 1 y.	1/8 in.	1/8 in.	5/8 in.	1/4 in.	1/16 in.	1/4 in.	1 1/4 in.		1/2 in.
Amt. in 4 y.	1/8 in.	1/8 in.	3/4 in.	5/8 in.	1/2 in.	1/4 in.	1/2 in.		3/4 in.
Rhubarb									
Time 1st ppt.	12 d.	12 d.	20 d.	30 d.	25 d.	10 d.	1 d.	24 G.	6 w.
Amt. in 1 y.	1/16 in.	1/16 in.	1/4 in.	5/8 in.	1/8 in.	1/16 in.	1/16 in.		1/2 in.
Amt. in 4 y.	1/8 in.	1/8 in.	3/8 in.	5/8 in.	1/8 in.	1/8 in.	1/8 in.		1/2 in.
Senna, Alex.									
Time 1st ppt.	2 w.	2 w.	3 d.	3 d.	17 d.	2 w.	2 w.	32 G.	8 w.
Amt. in 1 y.	c.	c.	s.	s.	s.	s.	1 in.		s.
Amt. in 4 y.	c.	c.	3/8 in.	3/8 in.	1/8 in.	1/8 in.	3/4 in.		1/16 in.

	Clear glass.	Amber glass.	HCl.	HPH_2O_2.	H_2O_2.	CO_2.	NH_3.	Sod. Acet. Amt.	Ppt.
Senna, Tinnev.									
Time 1st ppt.	24 h.	24 h.	3 d.	24 h.	3 d.	3 d.	10 d.	32 G.	12 d.
Amt. in 1 y.	c.	s.	s.	1/4 in.	s.	s.	gel.		1/16 in.
Amt. in 4 y.	1/4 in.	1/2 in.	3/8 in.	1/2 in.	1/4 in.	1/8 in.	1 in.		1/8 in.

Table II shows that light has no appreciable effect on precipitation except in the case of Aloe. Hydrochloric acid increased precipitation in all, but sodium chloride (2 Gm. in 125 cc.) was used in Aloe to avoid the strongly acid reaction. Hypophosphorous acid increased precipitation in all, while hydrogen peroxide increased it in Aloe, Frangula and Juglans and reduced it in Rhubarb and Sennas. Carbon dioxide shows no very marked effects, but shows a slightly increased precipitation in most. Ammonia also shows an increased precipitation, but its action was, in general, slower and less marked than on other drugs. Sodium acetate shows a stabilizing influence, except in Juglans and Rhubarb.

Precipitation in the Senna tinctures was adhesive and did not settle satisfactory. Extractives were taken on these at the end of about one year, and showed the following results.

Alexandrian Senna.—Original 11.9 per cent; after one year in clear-glass bottle 11.4 per cent; in amber bottle 11.26 per cent; with hydrochloric acid 11.9 per cent; with hypophosphorous acid 13.1 per cent; with hydrogen peroxide 11.0 per cent; with carbon dioxide 11.26 per cent; with ammonia 11.26 per cent. In none of these is the change in extractive very great.

Tinnevelly Senna.—Original 15.4 per cent. After one year, in clear-glass bottles 14.1 per cent; in amber bottles 14.2 per cent; with hydrochloric acid 14.1 per cent; with hypophosphorous acid 16.0 per cent; with hydrogen peroxide 13.3 per cent; with carbon dioxide 14.4 per cent; with ammonia 14.4 per cent. In this series, hydrogen peroxide shows the greatest change.

TABLE III.—ASTRINGENT DRUGS.

Table of menstrua and strengths.

	Menst. alcohol.	Extractive.
Castanea	Water	8.54%
Gambir	49%	36.4%
Geranium	58%	15.9%
Hamamelis	33%	8.9%
Krameria	49%	11.2%
Rhus Glabra (bark)	49%	15.1%
Rhus Glabra (berries)	49%	5.4%
Rosa	49%	22.4%
Prunus Virginiana	24%	8.48%
Quercus	49%	6.96%

Table of precipitation results.

	Clear bottle.	Amber bottle.	HCl.	HPH_2O_2.	H_2O_2.	CO_2.	NH_3.	Sod. acet. Amt.	Ppt.
Castanea									
Time 1st ppt.	7 d.	3 w.	5 w.	5 w.	1 y.	3 w.	1 m.	36 G.	1 m.
Amt. in 1 y.	1/16 in.	1/16 in.	s.	1/16 in.	1/32 in.	1/32 in.	1 1/2 in.		1/2 in.
Amt. in 4 y.	1/16 in.	1/16 in.	1/16 in.	1/8 in.	1/8 in.	1/8 in.	1 1/2 in.		5/8 in.
Gambir									
Time 1st ppt.	2 w.	4 w.	4 w.	2 w.	10 w.	4 w.	2 d.	24 G.	2 d.
Amt. in 1 y.	s.	s.	s.	s.	s.	s.	1/8 in.		s.
Amt. in 4 y.	s.	s.	s.	s.	s.	s.	1/8		s.
Geranium									
Time 1st ppt.	4 w.	4 w.	6 w.	2 w.	7 w.	4 w.	1 m.	19 G.	5 w.
Amt. in 1 y.	s.	s.	1/16 in.	3/32 in.	3/32 in.	1/16 in.	7/8 in.		3/32 in.
Amt. in 4 y.	1/8 in.	1/8 in.	1/8 in.	1/8 in.	1/4 in.	1/8 in.	7/8 in.		1/8 in.
Hamamelis									
Time 1st ppt.	6 w.	6 w.	6 w.	6 w.	6 w.	6 w.	1 m.	32 G.	12 d.
Amt. in 1 y.	s.	s.	s.	s.	s.	s.	1 in.		7/8 in.
Amt. in 4 y.	s.	s.	s.	s.	1/8 in.	1/8 in.	1 in.		7/8 in.

	Clear bottle.	Amber bottle.	HCl.	HPH_2O_2.	H_2O_2.	CO_2.	NH_3.	Sod. Acet. Amt.	Sod. Acet. Ppt.
Krameria									
Time 1st ppt.	1 d.	1 d.	1 d.	1 d.	1 d.	12 d.	...	24 G.	...
Amt. in 1 y.	s.	s.	1/32 in.	s.	s.	s.	...		...
Amt. in 4 y.	s.	s.	1/8 in.	1/4 in.	1/8 in.	s.	s.		...
Rhus Glabra (Bark)									
Time 1st ppt.	6 w.	6 w.	10 d.	10 d.	10 d.	6 w.	1 d.	24 G.	10 d.
Amt. in 1 y.	s.	s.	s.	s.	s.	s.	1/8 in.		s.
Amt. in 4 y.	s.	s.	1/16 in.	1/16 in.	s.	s.	1/4		3/8 in.
Rhus Glabra (Berries)									
Time 1st ppt.	...	...	3 d.	3 d.	5 w.	...	...	24 G.	...
Amt. in 1 y.	s.	s.	s.	s.	s.	s.	s.		s.
Amt. in 4 y.	s.	s.	s.	s.	s.	s.	s.		s.
Rosa									
Time 1st ppt.	1 d.	1 d.	2 mo.	...	1 d.	4 d.	1 m.	24 G.	1 d.
Amt. in 1 y.	1/8 in.	1/8 in.	s.	s.	1/8 in.	1/16 in.	1/4 in.		1/2 in.
Amt. in 4 y.	1/8 in.	3/16 in.	s.	1/4 in.	1/4 in.	1/8 in.	1/4 in.		1/2 in.
Prunus Virg.									
Time 1st ppt.	3 d.	3 d.	15 h.	15 h.	3 d.	3 d.	10 m.	36 G.	3 d.
Amt. in 1 y.	1/8 in.	1/8 in.	3/16 in.	gel.	1/8 in.	1/8 in.	1/2 in.		1/8 in.
Amt. in 4 y.	1/4 in.	1/4 in.	1/4 in.	gel.	1/4 in.	1/4 in.	1/2 in.		3/8 in.
Quercus									
Time 1st ppt.	...	...	2 1/2 mo.	...	...	...	5 d.	24 G.	5 d.
Amt. in 1 y.	...	...	s.	s.	s.	s.	1/4 in.		1/4 in.
Amt. in 4 y.	...	...	1/4 in.	1/2 in.	s.	s.	1/2 in.		3/4 in.

In this series light shows a little accelerating action in Castanea and Gambir, but none in the others. Hydrochloric acid hastened precipitation in the Sumacs, Quercus and Wild Cherry, retarded it in Castanea, Geranium and Rose, but showed no material difference in the amounts at the end of four years, and had no appreciable influence on the rest. Hypophosphorous acid retarded precipitation in Castanea, Rose and Quercus, hastened it in Gambir, Geranium, the Sumacs and Wild Cherry, and had no appreciable action in the rest. Hydrogen peroxide retarded precipitation in Castanea, Gambir and Geranium, hastened it in the Sumacs, and shows no influence on the others. Carbon dioxide had a marked retarding influence on Krameria and Sumac but no appreciable action on the rest. Sodium acetate promoted precipitation in Castanea, Gambir, Hamamelis, Sumac bark, Rose and Quercus, and shows little effect on the rest.

The p_H value of Hamamelis taken at the end of four years, showed 4.26 in the untreated tincture, and 7.6 in that containing sodium acetate, showing a marked change from acid to alkali.

Ammonia shows a marked effect on all except Krameria, hastening precipitation in all cases.

TABLE IV.—MISCELLANEOUS DRUGS.

Table of menstrua and strengths.

	Menst. alcohol.	Extractive.
Cinnamon, Cassia	64%	18.3%
Cinnamon, Ceylon	64%	11.2%
Cinnamon, Saigon	64%	10.8%
Chionanthus	73%	23.6%
Glycyrrhiza	Water	12.8%
Iris Versicolor	95%	8.3%
Salix nigra	49%	8.4%
Senega	64%	17.7%
Stillingia	49%	5.1%
Uva ursi	32%	19.8%

Table of precipitation results.

	Clear bottle.	Amber bottle.	HCl.	HPH_2O_2.	H_2O_2.	CO_2.	NH_3.	Sod. acet. Amt.	Sod. acet. Ppt.
Cinnamon, Cassia									
Time 1st ppt.	2 mo.	2 mo.	6 w.	1 d.	?	?	1 d.	16 G.	14 d.
Amt. in 1 y.	gel.	gel.	gel.	gel.	gel.	gel.	gel.		gel.
Amt. in 4 y.	gel.	gel.	gel.	gel.	gel.	gel.	gel.		gel.
Cinnamon, Ceylon									
Time 1st ppt.	18 d.	5 w.	5 w.	1 w.	1 w.	6 w.	1 h.	16 G.	3 w.
Amt. in 1 y.	s.	s.	s.	gel.	gel.	s.	gel.		gel.
Amt. in 4 y.	1/16 in.	1/16 in.	1/16 in.	gel.	gel.	s.	gel.		gel.
Cinnamon, Saigon									
Time 1st ppt.	1 w.	1 w.	1 w.	1 w.	5 w.	1 d.	1 w.	16 G.	3 w.
Amt. in 1 y.	gel.	gel.	gel.	gel.	1/4 in.	gel.	gel.		gel.
Amt. in 4 y.	gel.	gel.	gel.	gel.	1/4 in.	gel.	gel.		gel.
Chionanthus									
Time 1st ppt.	1 d.	1 d.	5 d.	3 w.	1 d.	1 d.	1 d.	12 G.	...
Amt. in 1 y.	1/16 in.	1/16 in.	s.	s.	1/16 in.	1/32 in.	1/8 in.		...
Amt. in 4 y.	1/16 in.	1/16 in.	s.	s.	1/16 in.	1/16 in.	1/8 in.		sl.
Glycyrrhiza									
Time 1st ppt.	2 w.	2 w.	2 w.	3 w.	4 w.	2 w.	1 d.	36 G.	...
Amt. in 1 y.	s.	s.	1/32 in.	1/32 in.	s.	s.	1/8 in.		s.
Amt. in 4 y.	s.	s.	1/32 in.	1/4 in.	s.	s.	1/4 in.		s.
Iris Versicolor									
Time 1st ppt.	...	...	...	1 mo.	2 mo.	...	1 d.	...	...
Amt. in 1 y.	...	...	s.	s.	s.	...	1/8 in.	...	...
Amt. in 4 y.	...	...	s.	s.	s.	...	1/8 in.	...	...
Salix Nigra									
Time 1st ppt.	3 w.	5 w.	3 d.	3 d.	5 w.	5 w.	2 w.	24 G.	...
Amt. in 1 y.	s.	s.	s.	s.	s.	s.	1/2 in.		...
Amt. in 4 y.	s.	s.	1/16 in.	1/16 in.	s.	1/16 in.	1/2 in.		...
Senega									
Time 1st ppt.	3 w.	4 w.	10 d.	10 d.	3 w.	2 mo.	1 d.	16 G.	...
Amt. in 1 y.	s.	s.	s.	s.	s.	s.	1/4 in.		...
Amt. in 4 y.	s.	s.	s.	s.	s.	s.	1/4 in.		...
Stillingia									
Time 1st ppt.	5 w.	5 w.	1 y.	3 d.	5 w.	5 w.	1 m.	24 G.	3 mo.
Amt. in 1 y.	1/4 in.	3/16 in.	1/16 in.	1/10 in.	1/16 in.	1/16 in.	1 in.		1 1/2 in.
Amt. in 4 y.	1/4 in.	3/16 in.	3/4 in.	1/16 in.	1/16 in.	1/16 in.	1 in.		2 in.
Uva Ursi									
Time 1st ppt.	10 d.	10 d.	10 d.	10 d.	17 d.	10 d.	1 m.	32 G.	17 d.
Amt. in 1 y.	3/16 in.	1/8 in.	1/8 in.	1/8 in.	1/8 in.	1/8 in.	1 1/2 in.		s.
Amt. in 4 y.	3/16 in.	1/8 in.	1/8 in.	1/8 in.	1/8 in.	1/8 in.	1 1/2 in.		1/8 in.

Light shows some action on Ceylon Cinnamon and perhaps on Senega, but not on any of the others. Hydrochloric acid shows little effect on any, except Stillingia, in which it seems first to have retarded precipitation, then greatly increased it. Hypophosphorous acid hastened precipitation in half the cases and had little effect on the others. Hydrogen peroxide and carbon dioxide show no marked effects. Ammonia hastened and in most cases increased precipitation, even in Glycyrrhiza and Senega, which drugs have been considered as needing alkali for solubility. Sodium acetate hastened gelatinization in two of the Cinnamons and reduced it in the third. It prevented precipitation in Chionanthus, Glycyrrhiza, Salix Nigra and Senega, and first hindered, then increased precipitation in Stillingia, as did hydrochloric acid.

In a paper entitled "The Permanence of Some Astringent Preparations," published in the Journal of the American Pharmaceutical Association in 1912, the writer showed that the tannin in each of the eighteen preparations examined undergoes a rapid change by hydrolysis, which was not always shown by precipitation. This suggested that hydrolysis may be an important factor in the precipitation of other galenical preparations. To get some indication of this, another series of preparations was made from thirteen of the drugs used in the preceding tests.

A.—Fifty per cent tinctures were made as before, using 94% alcohol as the menstruum. The fact that strong alcohol extracts a different proportion of principles from that of weaker alcohol was not overlooked, and the two series are not wholly comparable. The object in this second series was to learn whether the corresponding preparations, containing but little water, would show any marked differences in stability from those containing considerable water.

B.—A modification of this strongly alcoholic series was made by taking 125 cc. of the tincture and evaporating it under an air blast at a very low temperature to such volume that on the addition of glycerin to restore the original volume of 125 cc. the tincture would contain about the same proportion of alcohol as the official preparations—the water thus being replaced by glycerin.

C.—A third series was also made by percolating the drug with a menstruum composed of alcohol and glycerin in the same proportions as alcohol and water used in the official menstrua. In other words, glycerin replaced water in the menstrua or in the preparation. These preparations were stored in 4-ounce amber-colored bottles in the same case as the others.

In the following report, line *A* refers to the sample made with strong alcohol, and containing no glycerin, line *B* to that which had been adjusted with glycerin to contain the same proportion of alcohol as the official preparations, and line *C* to that made by percolation with the menstruum of alcohol and glycerin.

Cassia Cinnamon.

A—clear after 1 year, gelatinized in 4 years.
B—slight ppt. in 1 year, ditto in 4 years.
C—clear after 4 years.

Ceylon Cinnamon.

A, *B* and *C* all clear after 4 years.

Saigon Cinnamon.

A—clear during 1 year, $^1/_8$ in. ppt. in 4 years.
B—slight ppt. in 1 year, ditto in 4 years.
C—slight ppt. in 1 year, ditto in 4 years.

Gambir.

A—$^1/_4$ in. ppt. in 1 year, ditto in 4 years. Tannin No. 1:500,000.
B—clear after 4 years. Tannin No. 1:400,000.
C—slight ppt. in 1 year, $^1/_8$ in. ppt. in 4 years. Tannin No. 1:250,000.

Geranium.

A—very slight ppt. in 1 year, ditto in 4 years. Tannin No. 1:50,000.
B—same as *A*. Tannin No. 1:50,000.
C—same as *A*. Tannin No. 1:60,000.

Hamamelis.

A—very slight ppt. in 1 year, ditto in 4 years. Tannin no. 1:50,000.
B—same as *A*. Tannin No. 1:30,000.
C—same as *A*. Tannin No. 1:50,000.

Krameria.

A—very slight, ppt. in 1 year, ditto in 4 years.
B—same as *A*.
C—same as *A*.

Nutgall.

A—slight ppt. in 1 year, ditto in 4 years.
B—$^1/_{16}$ in. ppt. in 1 year, $^1/_8$ in. in 4 years.
C—$^1/_{16}$ in. ppt. in 1 year, $^1/_8$ in. in 4 years.

Rhubarb.

A—slight ppt. in 1 year, ditto in 4 years.
B—slight ppt. in 1 year, ditto in 4 years.
C—$^1/_8$ in. ppt. in 1 year, 1 in. ppt. in 4 years.

Rose.

A—slight ppt. in 1 year, $^1/_{16}$ in. ppt. in 4 years.
B—very slight ppt. in 1 year, ditto in 4 years.
C—slight ppt. in 1 year, $^1/_8$ in. ppt. in 4 years.

Sanguinaria.

A—slight ppt. in 1 year, ditto in 4 years. Extractive 5.54%.
B—clear after 4 years.
C—slight ppt. in 1 year, $^1/_8$ in. ppt. in 4 years.

Sumac Berries.

A—slight ppt. in 1 year, ditto in 4 years.
B—clear after 4 years.
C—clear after 4 years.
C much darker than *A* and *B*.

Uva Ursi.

A—$^1/_{16}$ in. ppt. in 1 year, ditto in 4 years.
B—clear in 1 year, slight ppt. and thickened in 4 years.
C—clear in 1 year, slight ppt. and thickened in 4 years.

In this series all samples showed less precipitation than the series made with hydro-alcoholic menstrua. In half of them the amount of precipitate formed in four years was so slight as to be practically immeasurable, and only one—Cassia—acted in any degree like the hydro-alcoholic preparations. While some principles, such as gums and proteins are wholly insoluble in strong alcohol, most drug principles are soluble in some degree, and tannoids, which are particularly troublesome factors in precipitation, are quite soluble in both water and alcohol. Thus the main ingredients of the drugs are probably present in both kinds of percolate. This is shown in the gelatinizing of the cassia tincture in both instances, though the percolate with strong alcohol remained clear and limpid for a number of months whereas the hydro-alcoholic percolate gelatinized in a few weeks.

CONCLUSIONS.

While the results of this work are more negative than positive, there is some value in the elimination of certain questions regarding the causes of precipitation.

Light is evidently not a serious factor. At least such light as will pass through clear glass. It may be that the dark color of the liquids themselves acts as repellant of the actinic rays and so prevents action. Of the thirty-one samples only five show any increased precipitation in the light bottles, and two of these are doubtful. On the other hand in some cases there seems to be slightly less precipitation in the light than in the amber glass, though the difference is not marked enough to report positively.

Acidity is undoubtedly an important factor but the manner of its addition is also important. In Cinchona, for instance, when the menstruum is acidulated the product is decidedly more stable than when a neutral menstruum is employed, but the addition of an equivalent amount of acid to a percolate made with a neutral menstruum does not show the same result.

Hydrochloric acid or sodium chloride added to the percolate, aided materially in preventing precipitation in only one case, showed no effect in eighteen, and increased precipitation in twelve—ten of the latter belonging to the cathartic and astringent groups, in which hydrochloric acid is known to form insoluble compounds. The influence upon colloidal conditions does not appear to be of importance.

On the other hand, rendering the percolates alkaline to litmus with ammonia caused precipitation in every case—and in most cases at once. This was true even with Licorice, and Senega, and Rhubarb, which have been considered as needing an alkali to hold the constituents in solution. This is one line of experimentation which gave positive and uniform results, but in this, as with acid, there is evidently a different action when the alkali is added to the percolate than when it is used in the menstruum.

Oxidation is also a minor factor in producing precipitation. Hydrogen peroxide increased precipitation in only five samples, decreased it in five, and showed no effect in twenty-one. Saturating the liquid and the atmosphere in the bottle with carbon dioxide—a neutral gas—showed a slight beneficial effect in five samples and no effect in twenty-four. Hypophosphorous acid—a strong reducing agent—showed a beneficial effect on three (astringent) samples, increased precipitation in twenty, and showed no effect in eight. This acid was used in quite liberal proportions, and the results may be due in part to the change in the alcoholic strengths by the water added with the acid. The fact that it caused increased precipitation in two-thirds of the samples cannot be ascribed to its reducing action, but may be due to its dilution of the alcoholic strength, as shown by the fact that its action was impartial on all four types of drugs. Thus neither the addition of an oxidizing agent, nor of a reducing agent, nor the exclusion of an oxidizing or reducing action by means of a neutral gas, shows any marked results.

The conclusions to be drawn from the use of sodium acetate are complicated by its alkaline character. It is noted that as with ammonia, precipitation usually appeared quickly, but in less than half the cases—or fourteen in all—was there an increased precipitation though ammonia increased it in all thirty-one. The acetate showed a beneficial action in eight, had no effect in ten, and increased precipitation in twelve, as compared to untreated samples. But it shows much less precipitation than was caused by ammonia in nineteen cases, and more than ammonia in only six.

If the action of sodium acetate is both alkaline and dehydrolyzing, then the latter action is beneficial in at least eighteen of the thirty samples—a larger proportion than with any other agent.

The results obtained with the series of tinctures made with 94 per cent alcohol or with alcohol-glycerin menstrua also support the theory that the leading factor in precipitation is a hydrolytic action, and this is again upheld by the results obtained in the study of astringent drugs made in 1912 and above referred to.

The most troublesome drugs in forming precipitate in their percolates are largely those that contain tannoids, and we know that certain types of tannins easily hydrolyze and form insoluble compounds.

The fact that hydrolysis is usually favored, in organic reactions, by alkalis and hindered by acids, also points to the hydrolytic theory in the above study.

Furthermore the very general use of glycerin as a means of preventing precipitation in galenical preparations, and the observance that sugars act in a similar and very effective way, is best explained on the ground of their dehydrolyzing action in the menstrua.

Thus not simply the experiments conducted for the purposes of this paper, but much of the evidence of experience and established pharmaceutical practice point to a hydrolyzing action as the main factor in precipitation in galenicals.

European pharmacists have long favored stronger alcohol for tinctures and fluidextracts than has been used in America, and it would look as though they are nearer to right in this. In Europe a diluted alcohol is not equal volumes of alcohol and water but is usually a mixture containing 68 to 70 per cent by volume of absolute alcohol. This strength of alcohol is often used as a menstruum in preparations which correspond to those made with our 49% alcohol. Thus many of the European preparations are approximately 1.4 times as strong in alcohol as the corresponding American preparations.

The stronger alcohols tend to prevent hydrolysis and thus to preserve drug principles in their original condition. Change by hydrolysis is not always evidenced by precipitation, as we have learned from the deterioration of Aconite, Digitalis and other potent preparations, as well as some astringent tinctures, but the value of the preparation depends upon its activity, and hydrolysis usually destroys this. The tendency of recent years to reduce the alcoholic content of pharmaceutical preparations to a minimum may easily result in inferior preparations for therapeutic use through the ignoring or forgetting the stabilizing effect of stronger alcohols. Therapeutic power and dependability should be the first consideration in all such cases.

The most prominent development in pharmacy during the past generation has been that of standardization of medicines. We are now facing the logical sequence of this—the development of conditions or methods that make for stability in standardized medicinals. Standards in many cases need to be made more trustworthy by stabilizing the preparations. This is one of the most important problems of the immediate future.

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PHARMACEUTICAL PRODUCTS FROM MUCIC ACID.

BY F. F. BLICKE AND J. L. POWERS.

About 1780 Scheele, the celebrated Swedish apothecary, published the results of an investigation entitled "Milk and Its Acids."[1] During this investigation milk sugar was treated with nitric acid; a white powder was obtained thereby which resembled saccharic acid. An aqueous solution of the material tasted sour, turned blue-litmus red and reacted with calcium carbonate with the evolution of carbon

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[1] Carl Wilhelm Scheele, "Sämtliche Physische und Chemische Werke," edited by Hermbstadt (Berlin, 1793), Vol. II, p. 261.