TINCTURES*.

WILBUR L. SCOVILLE.

The following paper presents a comparison of tinctures made by percolation of drugs and by diluting fluidextracts. A purpose of the work undertaken was to determine the relative stability of the two classes of tinctures.—[EDITOR].

In the fall of 1912 a series of tinctures was made in order to ascertain what differences, if any, could be observed between a tincture prepared by the official process from the drug and one made by diluting the corresponding fluidextract with the proper menstruum.

Forty-six of the Pharmacopoeial tinctures were made by the official process, in lots of 500 cc. to 2000 cc. each, according to the quantities which would be needed in making subsequent tests. The drugs were taken from stock and were all of good quality, though no special selection was made in any case, and the official process was carefully followed in making the tinctures. At the same time a line of the same tinctures was made by diluting the corresponding fluidextracts according to directions on the labels, the fluidextracts also being taken from stock without special selection in any case.

It is at once apparent that since different lots of drug of the same kind vary in strength, in soluble extractive, and to some extent in color, that the two corresponding tinctures would not be absolutely comparable because the fluidextract used was made from a different lot of drug than the official tincture. But the purpose of the investigation was not to see how closely the tinctures cold be made to compare by the two methods, but to note such differences as might be found under ordinary commercial conditions.

When the tinctures were finished each was tested for specific gravity, alcohol strength, dry extractive and the standardized tinctures were assayed for alkaloidal strength. A comparison of the color and brilliancy of each pair of tinctures was also made.

The tinctures were stored in amber glass bottles in a diffused light, and under the ordinary temperature changes of a working laboratory. The bottles were all full at first, but as tests were made some of each was taken out and the bottle re-stoppered, leaving increasingly voluminous air-spaces above the liquids. At the end of the two years from half to seven-eights of each tincture had been removed.

The extractive-estimations and alkaloidal assays were repeated at the end of the first year, and all the tests at the end of the second year. The results are shown in the following table:

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Drug	Tinct.	Spec. Grav. 1912	Spec. Grav. 1914	Alcohol % 1912	Alcohol % 1914	Dry Extractive 1912	Dry Extractive 1913	Dry Extractive 1914	Alkaloid Str. 1912	Alkaloid Str. 1913	Alkaloid Str. 1914	Colors	Physical Appear.
Aconite	U. S. P.	.8980	.8970	65.3	66.2	1.76	1.68	1.70	.045	.045	.045	Same	vy. sl. ppt.
	Fld.	.8970	.8969	68.0	67.4	2.80	2.77	2.80	.045	.045	.045		Clear.
Aloes	U. S. P.	.9810	.9810	42.9	43.3	13.6	13.6	13.4				Same	ppt. heav. than fld.
	Fld.	.9768	.9760	39.2	41.8	10.9	10.8	10.8					Mod. ppt.
Aloes and Myrrh.	U. S. P.	.9200	.9224	65.1	66.1	17.9	12.1	12.0				Same	Much ppt.
	Fld.	.9290	.9309	63.9	62.8	17.8	12.2	12.5					Much ppt.
Arnica Flors	U. S. P.	.9354	.9337	45.0	45.8	4.58	4.60	4.56				Sl. darker	Sl. ppt.
	Fld.	.9272	.9267	46.6	46.5	3.26	3.20	3.22					Sl. ppt.
Asafoetida	U. S. P.	.8350	.8350	89.9	89.3	6.70	6.55	6.50				Lighter	Sl. ppt.
	Fld.	.8486	.8482	85.1	85.7	8.95	8.92	8.94					Sl. ppt.
Belladonna Leaf.	U. S. P.	.9464	.9457	48.1	46.5	3.03	2.88	2.88	.034	.0345	.035	Dk. brown	Cons. ppt.
	Fld.	.8846	.8847	71.9	71.6	1.35	1.31	1.32	.030	.031	.029	Dp. Green	Sl. ppt.
Benzoin	U. S. P.	.8724	.8732	81.6	80.1	17.8	17.7	17.8				Same	Clear.
	Fld.	.8600	.8592	83.4	82.7	10.5	10.5	10.5					Vy. sl. ppt.
Benzoin Comp.	U. S. P.	.8840	.8848	77.9	76.3	20.0	19.4	18.8				Same	Sl. ppt.
	Fld.	.8842	.8846	77.4	75.9	18.8	18.8	18.9					Sl. ppt.
Calendula	U. S. P.	.8264	.8260	91.6	90.8	4.40	4.50	4.40				Darker	Clear.
	Fld.	.8234	.8227	93.0	92.0	2.20	2.20	2.20					Vy. sl. ppt.
Calumba	U. S. P.	.9268	.9295	56.1	55.3	3.1	3.1	3.1				Sl. lighter	Sl. ppt.
	Fld.	.9134	.9133	60.8	60.3	2.5	2.5	2.5					Sl. ppt.
Cannabis Ind.	U. S. P.	.8178	.8182	93.3	92.3	1.46	1.40	1.42				Red-brown	Vy. sl. ppt.
	Fld.	.8144	.8140	94.1	93.3	1.36	1.37	1.36				Dp. green	Clear.
Capsicum	U. S. P.	.8332	.8330	88.0	87.4	2.8	2.8	2.8				Sl. darker	Vy. sl. ppt.
	Fld.	.8290	.8288	89.7	89.6	1.7	1.7	1.7					Clear.
Cimicifuga	U. S. P.	.8204	.8200	91.3	91.8	1.30	1.26	1.32				Yel.-br.	Clear.
	Fld.	.8254	.8247	91.7	90.6	1.32	1.34	1.32				Lt. Brown	Mod. ppt.
Cinchona	U. S. P.	.9272	.9260	61.8	62.7	10.9	10.8	10.4	.528	.509	.485	Same	Much ppt.
	Fld.	.9318	.9272	62.0	61.4	13.9	13.7	13.7	.850	.750	.720		Much ppt.
Cinchona Comp.	U. S. P.	.9394	.9392	60.1	60.7	14.4	14.2	12.8	1.06	1.038	1.037	Same	Much ppt.
	Fld.	.9104	.9082	71.3	70.8	12.8	12.5	11.2	0.476	0.473	0.450		Much ppt.
Cinnamon	U. S. P.	.9246	.9247	61.9	61.7	10.1	9.8	9.8				Darker	Sl. ppt.
	Fld.	.9180	.9185	62.5	62.8	8.9	8.7	8.7					Clear
Colchicum Sd	U. S. P.	.9176	.9187	57.0	56.5	1.21	1.22	1.22	.040	.040	.040	Same.	Vy. sl. ppt.
	Fld.	.9200	.9208	54.8	54.2	0.63	0.62	0.63	.040	.040	.040		Clear.
Gambir Comp.	U. S. P.	.9546	.9548	44.5	44.4	4.55	4.6	4.6				Same	Clear.
	Fld.	.9524	.9524	46.1	45.8	5.55	4.5	4.5					Clear.
Gelsemium	U. S. P.	.9100	.9093	61.7	61.0	1.85	1.80	1.88	.047	.047	.043	Sl. darker	Sl. ppt.
	Fld.	.9132	.9128	60.0	59.4	1.47	1.45	1.44	.045	.047	.042		Vy. sl. ppt.
Gentian Comp.	U. S. P.	.9306	.9308	56.2	54.8	4.37	4.44	4.42				Sl. lighter	Sl. ppt.
	Fld.	.9300	.9295	55.1	55.6	4.33	4.35	4.38					Sl. ppt.
Ginger	U. S. P.	.8174	.8180	93.3	93.0	0.82	0.82	0.90				Sl. lighter	Clear.
	Fld.	.8178	.8175	92.0	91.7	0.84	0.85	0.90					Clear.
Guaiac	U. S. P.	.8880	.8898	81.8	80.1	22.1	21.2	21.1				Dk. brown	Mod. ppt.
	Fld.	.8780	.8806	81.6	79.7	18.5	18.2	18 2				Red-brown	Vy. sl. ppt.
Ammon Guaiac	U. S. P.	.9648	.9650	54.8	54.0	24.2	23.6	22.4				Same	Heavy ppt.
	Fld.	.9390	.9456	60.4	59.2	18.8	18.7	18.75					Less ppt.
Hydrastis	U. S. P.	.9235	.9223	60.3	60.2	5.1	5.2	5.0	0.47	0.39	0.29	Same	Mod. ppt.
	Fld.	.9272	.9265	58.5	58.8	5.3	5.3	5.4	0.38	0.37	0.36		Sl. ppt.
Hyoscyamus	U. S. P.	.9456	.9457	47.0	46.8	2.82	2.83	2.90	.0070	.0071	.0072	Red-brown	Mod. ppt.
	Fld.	.9356	.9377	48.6	49.1	1.65	1.60	1.64	.0055	.0055	.0056	Dp. green	Sl. ppt.
Krameria	U. S. P.	.9524	.9554	44.4	44.3	4.47	4.40	4.50				Same	Mod. ppt.
	Fld.	.9560	.9584	43.6	43.6	5.2	5.3	5.3					
Lavender Comp.	U. S. P.	.8834	.8920	71.4	69.2	0.90	0.90	0.92				Lighter	Clear.
	Fld.	.8830	.8830	71.7	71.3	0.65	0.66	0.67					Clear.
Lobelia	U. S. P.	.9460	.9462	46.7	45.3	2.28	2.32	2.32				Sl. lighter	Mod. ppt.
	Fld.	.9468	.9465	46.8	45.8	2.88	2.88	2.90					Sl. ppt.
Myrrh	U. S. P.	.8380	.8410	87.0	86.8	7.6	7.5	7.4				Cons. light.	Clear.
	Fld.	.8310	.8310	90.0	90.2	5.7	5.8	5.8					Clear.
Nux Vomica	U. S. P.	.8850	.8840	72.0	71.6	1.5	1.4	1.4	.098	.097	.079	Sl. lighter	Sl. ppt.
	Fld.	.8842	.8845	72.9	70.8	1.2	1.1	1.1	.100	.099	.090		Clear .
Opium	U. S. P.	.9618	.9615	44.8	43.0	7.9	6.9	6.9	1.21	1.20	1.21	Same	Mod. ppt.
	Fld.	.9554	.9552	44.5	43.6	4.5	4.5	4.5	1.25	1.25	1.25		Mod. ppt.
Camphorated Opium.	U. S. P.	.9492	.9490	43.5	44.0	4.5	4.4	4.5				Same	Clear.
	Fld.	.9445	.9443	47.0	46.8	4.5	4.5	4.5					Clear.
Orange, Bitter.	U. S. P.	.9390	.9412	55.5	56.4	6.48	6.44	6.47				Same	Sl. ppt.
	Fld.	.9316	.9320	54.5	55.1	4.96	4.98	4.90					Less ppt.
Physostigma	U. S. P.	.8142	.8148	94.7	93.7	0.32	0.29	0.30	.0143	.0106	.0077	Reddish	Vy. sl. ppt.
	Fld.	.8134	.8135	94.8	94.2	0.20	0.19	0.20	.0146	.0140	.0125	Greenish	Clear.
Pyrethrum	U. S. P.	.8188	.8185	92.8	92.1	1.16	1.20	1.10				Sl. lighter	Clear.
	Fld.	.8216	.8215	91.9	92.1	1.48	1.50	1.40					Mod. ppt.
Quillaja	U. S. P.	.9806	.9810	28.5	30.0	5.01	4.99	5.00				Darker	Heavy ppt.
	Fld.	.9750	.9748	30.7	29.9	4.24	4.16	4.18					Mod. ppt.
Rhubarb	U. S. P.	.9960	.9964	44.0	44.1	20.2	19.9	20.2				Same	Cons. ppt.
	Fld.	.9860	.9863	43.7	43.1	17.3	17.3	17.4					Sl. ppt.
Arom, Rhubarb.	U. S. P.	1.003	1.014	42.3	42.1	21.5	21.1	21.1				Same	Sl. ppt.
	Fld.	1.015	1.004	42.3	41.8	21.4	21.6	21.4					Cons, ppt.
Sanguinaria	U. S. P.	.9314	.9322	54.3	57.4	3.37	3.36	3.35				Darker	Cons. ppt.
	Fld.	.9174	.9192	53.4	56.0	1.57	1.55	1.56					Cons. ppt.
Serpentaria	U. S. P.	.9112	.8972	61.7	60.4	2.40	2.52	2.50				Same	Sl. ppt.
	Fld.	.9110	.8960	60.1	60.7	1.32	1.41	1.36					Clear.
Squill	U. S. P.	.9040	.9041	70.2	69.1	6.6	6.2	6.2				Same	Sl. ppt.
	Fld.	.8900	.8922	68.7	68.5	2.4	2.3	2.35					Clear.
Stramonium Lf.	U. S. P.	.9246	.9362	47.1	46.9	2.48	2.45	2.50	.025	.025	.024	Red-brown	Cons. ppt.
	Fld.	.9262	.9365	48.2	48.2	1.56	1.53	1.50	.0245	.0245	.0238	Dk green	Mod. ppt.
Tolu	U. S. P.	.8790	.8795	79.2	79.2	18.0	17.8	17.8				Sl. lighter	Clear.
	Fld.	.8880	.8890	76.8	76.0	17.9	16.9	16.9					Vy. sl. ppt.
Valerian	U. S. P.	.8844	.8850	70.8	70.9	1.67	1.67	1.68				Sl. lighter	Clear.
	Fld.	.8882	.8878	72.1	71.6	2.40	2.42	2.42					Clear.
Ammon. Valerian.	U. S. P.	.9066	.9056	65.8	65.7	4.20	4.20	4.26				Same	Mod. ppt.
	Fld.	.9026	.9012	65.4	65.0	2.70	2.70	2.71					Mod. ppt.
Veratrum	U. S. P.	.8190	.8186	94.1	92.9	1.32	1.34	1.34	.063	.063	.063	Same	Clear.
	Fld.	.8154	.8153	94.1	92.9	0.75	0.76	0.75	.063	.072	.071		Clear.

The specific gravities were taken the first time with a 50 cc. pycnometer on an ordinary prescription balance, and the second time a 100 cc. pyconometer was used on the same balance. The gravities are thus approximate only.

Alcohol estimations were made by diluting one part of the tincture with two parts of water and distilling two parts. The alcohol was then calculated from the specific gravity of the distillate. When volatile oils or other volatile substances are present in a tincture, these will come over in varying quantities, depending upon the rate of distillation and the amount distilled. This affects the specific gravity and consequently the results, and a variation of one percent on different estimations is within the ordinary limits of error. Hence it is not considered that any actual change in alcohol strength occurred in the two years unless the difference is decided.

In the greater number of instances the second estimation shows results slightly lower than the first, which may indicate a tendency to loss in alcohol strength, but in no instance is the difference great enough to draw positive conclusions, and there are numerous instances of reverse results.

When marked precipitation has occurred the second results are often higher than the first, as might be expected, but here again the differences are too small to be important.

The only instance of marked difference between the two tinctures of a pair is in the case of Tincture of Belladonna. The official tincture is made with a menstruum of diluted alcohol while the fluidextract is made with a menstruum of about 75 percent alcohol. In making the tincture, the fluidextract was diluted with this stronger menstruum since it causes less precipitation than would diluted alcohol. In the other cases the difference between the menstruum for the fluidextract and that for the tincture is less marked, and clear tinctures are obtained by the use of the official tincture-menstruum for diluting.

Dry extractives were obtained by evaporating 5 cc. of the tincture in a small copper evaporating dish, having a capacity of about 10 cc. Evaporation was conducted on a sand-bath heated by a normal-pressure steam coil, and was continued over night, or 15 to 16 hours. Different pipettes were used each time, and the variations in these probably will account for the slight discrepancies which may be noted in the results.

It will be observed that changes in extractive usually correspond to precipitation, but not always. It is probable that in some instances oxidation occurs to an appreciable extent.

In the case of the standardized (alkaloidal) tinctures, and also with tinctures of cannabis indica, and squill, which were made from physiologically standardized fluidextracts, the extractives indicate only the physical condition of the tinctures at the beginning and end of the tests.

As a standard of the strength or value of a tincture the amount of extractive is only partially satisfactory, since the ratio of extractive to activity is not constant in any case. For those tinctures which cannot be assayed for active principle it affords the only test we have, in many instances. That it may be deceitful, however, is shown in the fact that of the two tinctures of capsicum, the one containing the less extractive is decidedly the more pungent, hence presumably the more active.

Of the 30 tinctures for which no better method of comparison was found, seventeen show the U. S. P. tincture to contain the larger proportion of extractive at the end of two years, six contain a smaller proportion, and seven are practically equal.

There is no suggestion in these results that certain classes of tinctures tend to run above or below normal when made from fluidextracts. For instance, of the resinous tinctures, Benzoin, Guaiac, Ammoniated Guaiac, Myrrh and Tolu are higher in the U. S. P. tinctures, while Benzoin Compound and Ginger are about equal and Asafoetida and Aloes and Myrrh are below. Of the cathartic tinctures the U. S. P. Aloes and Rhubarb are higher while Aloes and Myrrh is lower and Aromatic Rhubarb is about equal.

It will also be noticed that the U. S. P. tinctures tend to precipitate more than the others, and that at the end of a year the two tinctures are more nearly equal than when freshly made.

The alkaloidal tinctures disclose two unexpected changes, namely the loss in strength of the tinctures of Nux Vomica and of Hydrastis. The fluidextracts of these two drugs have been shown to be permanent, but the loss in strength of the tinctures is unmistakable. In each instance the U. S. P. tincture has lost more than the tincture made from the fluidextract, and the loss is greater during the second year, but each tincture has lost. The assays were repeated in each instance, so that these cannot be questioned. The U. S. P. tinctures have precipitated, but the others are so nearly clear that the loss in strength does not appear to be due to this cause.

The tinctures of Physostigma have also deteriorated, but this was more to be expected since the stability of Physostigma preparations has previously been questioned.

The U. S. P. tincture has lost half of its original strength and has precipitated some, while the other tincture has lost much less and remains clear.

The Cinchona tinctures have all lost in strength, and have also precipitated badly. It has previously been shown that precipitation in galenical preparations of Cinchona carries down some of the alkaloids, so this result was anticipated.

The other alkaloidal tinctures show no material loss in strength in two years.

With regard to color, tinctures made by the different methods in most instances show no more differences in color than would be expected from different lots of drugs. Where a difference is noted in the table, the difference is usually slight and would not be observed except by comparison. There are, however, five notable exceptions:—the tinctures of Belladonna, Hyoscyamus, Stramonium, Cannabis Indica and Physostigma can be easily distinguished as to source by color alone. In the first four, the U. S. P. preparations all have a brownish color with little or no tint of green, while the tinctures made from the fluidextracts are all bright green in color with no trace of red or brown. This cannot be accounted for by differences in menstruum, (unless possibly in the case of Belladonna) and it is not easy to understand. The U. S. P. tinctures when first made had a decidedly greenish color, but lost it on standing. Why the others did not change also is not understood

Much less difference is observed in the two tinctures of Physostigma, yet even here there is a marked difference in tint.

In the other cases any difference observable is one of shade rather than of tint. The differences in the tinctures of Asafoetida, Calendula, Myrrh, Quillaja and (perhaps) Guaiac is marked enough so that they might be noticed by a patient, but in the rest of the cases a comparison is necessary.

As might be expected, precipitation most often occurs in the U. S. P. tinctures, and so far as could be judged by the eye, most of it occurred during the first year. However, the table shows that tinctures will often precipitate when the corresponding fluidextracts do not. This is in accordance with the general observation that concentrated solutions are usually more stable than dilute.

Conclusions: On the whole the tinctures made from fluidextracts compare very favorably with those made direct from the drugs. In the case of the standardized tinctures, the strength is necessarily the same, and the stability is fully as good, if not better.

The non-standardized tinctures leave more to the judgment because we have no definite standards for comparison, but it is probable that there is no more difference between those made by the two methods than there would be between different tinctures made by the same method with different lots of drugs.

One of the main purposes of this investigation was to ascertain if tinctures from fluidextracts are as stable as those made direct from the drugs. This question is answered satisfactorily. The results show a greater rather than a less stability.

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ABSTRACT OF DISCUSSION.

Dr. Asher: I would like to ask Professor Scoville whether in diluting these tinctures the same menstrumm was used, or if a menstruum was used equivalent to U. S. P. strength. What was the alcoholic strength of the menstruum employed?

Prof. Scoville: In the case of belladonna it was diluted with the same menstruum as the fluidextract. I cannot say definitely in every case, but in most cases the dilution was made with the menstruum for the tincture, but as a rule there is very little difference. The difference in menstrua of tinctures and fluidextracts is very much less than it used to be. They are getting to be more and more uniform. The next Pharmacopoeia will make them still more uniform.

Mr. Lackenbach: The dispensing pharmacist, particularly in the smaller communities, has always been timid about making tinctures from fluidextracts. He would do it almost invariably, but in an underhanded way, thinking it was not right to do so. In some cases it has been carried to extremes, for instance in the preparation of tincture of digitalis from the fluidextract. But according to Mr. Scoville's paper it would seem that the dispensing pharmacist is justified in using the fluidextracts, especially the standardized fluidextracts. I think that would be a great relief to the pharmacists, especially in the smaller communities, who do not have occasion to make large batches of tinctures, and the fluidextracts sent out by the large pharmaceutical houses are very convenient.

Dr. Turner: It may be stated that in the case of tinctures prepared from fluidextracts which contain alkaloids there should not be any difference. In making the fluidextracts the drug is exhausted, so it no longer contains any alkaloid. Tinctures prepared from these must be just as active as the ones which are prepared by percolation directly from the drug. It is interesting to note that Professor Hatcher in his paper read recently before the New York Branch of this Association, gave illustrations of tinctures made from drugs as well as fluidextracts wherein he showed that there was no variation in the products.

Mr. Lackenbach: I think there must be an exception in the case of digitalis because the alcoholic menstruum will remove the principles that are not desired in the diuretic effect of

the drug. It seems to me rather reprehensible to use fluidextract of digitalis in preparing a tincture.

Dr. Arny: Ten years ago if we had heard Professor Scoville make that statement in regard to tinctures, I would have been ready to fight him. Dr. Hatcher in his little book on Materia Medica, published ten years ago, stated that the infusion of digitalis from the fluidextract was scarcely short of criminal, and he got up at the meeting of the New York Branch and stated that the physiological tests now showed that the two were identical. That being the case, I think we must revise our Pharmacopoeia as well as our Materia Medica.

Dr. Wulling: This discussion merely emphasizes the fact that we are not sufficiently qualified to determine the value of the drug unless we test it in more than one way, and the physiological test of drugs has compelled many of us to change our views.

THE ESTIMATION OF MORPHINE IN PILLS AND TABLETS.

H. W. JONES.

The author reviews various methods proposed for extracting morphine with immiscible solvents. The method of estimation described depends on the conversion of morphine into diacetyl morphine and elimination of the diluents employed in making pills and tablets.

The assay of pills and tablets containing morphine or its salts presents certain difficulties because of the comparatively slight solubility of the alkaloid in any of the immiscible solvents ordinarily used. Of the simple solvents, amyl alcohol is the only one which dissolves morphine to any extent and this to so small a degree as to preclude its use where accurate results are desired. In case the morphine is present as a salt, it is always possible to estimate the acid radical but in the case of the sulphate at least, it has been the writer's experience that this procedure leads to high results.

Various compound solvents have been suggested, among which may be mentioned phenylethyl alcohol-benzol, methyl alchohol-benzol, methyl alchohol-chloroform, ethyl alcohol-chloroform and isobutyl alcohol-chloroform, all of which have been used with varying degrees of success. It is not the purpose of this paper to discuss the merits of these different solvents further than to mention that a mixture of one part alcohol and two parts chloroform by volume, as suggested by Williams[1], has been used in this laboratory for the extraction of morphine with excellent results. We have modified slightly the method as described by Williams, using sodium bicarbonate instead of ammonia to liberate the alkaloid. By introducing this modification we have been able to obtain more concordant results, verifying the findings of Puckner..[2]

The object of this paper is to describe a method devised by me and which in my hands has given very good results. The principle of this method is the conversion of the morphine into an acetyl derivative, extraction with chloroform, and subsequent titration with standard acid. As morphine is most commonly used as the sulphate, this salt was used in the investigation. It was

* Presented in Scientific Section A. Ph. A., San Francisco meeting.

[1] A paper presented at the meeting of the American Chemical Society, Washington, D. C., December, 1911. See American Journal Pharmacy, 86, 308.

[2] Journal American Chemical Society, 23 (1901), 470.