the next extraction and to combine it with the bulk, thus washing down any residue that may have dried on the inside wall.

3. The greatest losses of alkaloids are apt to occur during the final evaporation. Only water-baths should be used in the evaporation and under no circumstances should *dry alkaloids* be exposed to the heat of the water-bath. A stream of compressed air directed in the beaker while on the water-bath facilitates the evaporation greatly. For volumetric determinations 250-cc. beakers are best. For gravimetric assays usually smaller sizes are to be preferred.

4. It is of utmost importance to keep the beakers in a level position while on the water-bath, and to remove them while still about 3 cc. of the solvent remain. This residual solvent should be blown out with a jet of air. Use as little heat as possible in the manipulation of alkaloids.

The writer wishes to express his thanks and appreciation for valuable suggestions to Mr. E. C. Merrill, Chief Chemist of the United Drug Company, under whose direction the work was carried out.

THE DETERMINATION OF CINCHOPHEN IN TABLETS.*

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Cinchophen was introduced into medicine under the name of atophan. The substance was described in "New and Nonofficial Remedies" under the name of atophan and in the United States Pharmacopœia IX, under the name of phenylcinchoninic acid. During the World War the Federal Trade Commission invented the name "cinchophen" and that designation was adopted by the Council on Pharmacy and Chemistry of the American Medical Association for "New and Nonofficial Remedies." Later the name was included in the United States Pharmacopœia X. In therapy cinchophen finds application in the treatment of gout and certain forms of rheumatism. In pharmacy it is usually marketed in the form of tablets, but occasionally it is found in mixtures with acetylsalicylic acid and perhaps other substances. In the manufacture of tablets various excipients and lubricants are employed, such as starch, starch paste, acacia, talc, lycopodium, calcium carbonate, stearic acid and petrolatum.

The U. S. Pharmacopœia provides an assay for determining the purity of cinchophen, but the literature is singularly bare of references to the determination of the substance in mixtures, such as in tablets or pills. Because of this it was deemed worth while to consider methods for the analysis and examination of cinchophen in preparations. Rabak[1] extracted cinchophen from its mixtures with milk sugar by boiling with absolute alcohol. He filtered and determined the acidity of the filtrate by adding an excess of 0.1 *N* alkali and titrating back with 0.1 *N* acid, using phenolphthalein as indicator. He also tried titrating directly to the color with 0.1 *N* alkali and obtained equally good results. He suggested the use of boiling absolute alcohol as a solvent for the extraction of cinchophen from tablets, but he did not try the method on market tablet material.

* Scientific Section, A. PH. A., Philadelphia meeting, 1926.

[1] *J. Assoc. Official Agr. Chem*, 7, 34 (1923). *Ibid.*, 8 (1924).

As the tests described in the United States Pharmacopœia X, appear to be ample for determining the identity and purity of cinchophen as such, this study was limited primarily to the determination of cinchophen in tablets, although a little work was carried out with the view of estimating the substance in the presence of other medicinals. At the outset it was thought necessary to extract the cinchophen from the tablets by means of solvents before any assay processes or tests for identity or purity could be applied. The literature was searched to ascertain which of the more commonly used solvents would probably best serve the purpose. Very little information could be found. Several years ago the solubilities of the substance in ether, 95 per cent alcohol, 50 per cent alcohol, chloroform, ethyl acetate, and distilled water were determined at 25° in the Chemical Laboratory of the American Medical Association.

TABLE I.—SOLUBILITIES OF CINCHOPHEN AT 25° DETERMINED IN THE CHEMICAL LABORATORY OF THE AMERICAN MEDICAL ASSOCIATION.*

Alcohol 95%.	Alcohol 48%.	Chloroform.	Distilled water.	Ethyl acetate.
119	1143	930	6216	71

* Ann. Repts., *Chem. Lab. Am. Med. Assoc.*, 12, 16 (1919).

The United States Pharmacopœia X also gives the solubilities of cinchophen in each of several solvents. These are given in Table II.

TABLE II.—SOLUBILITIES OF CINCHOPHEN ACCORDING TO THE U. S. P. X.*

Alcohol.	Chloroform.	Ether.	Water.
98	590	72	Almost insoluble

* U. S. P., 10, 110 (1926).

In view of the scarcity of the information concerning the solubilities of cinchophen it was deemed worth while to determine the solubilities of the substance, in an approximate way, in a number of the commonly used solvents. A market specimen of cinchophen was recrystallized once from alcohol. The product was dried in the air at room temperature until sensibly dry and thereafter at 60° in a vacuum.

For the determination of the solubility in the cold solvents the recrystallized material was dissolved in the solvent while hot, the solution was allowed to cool with agitation, the mixture was allowed to stand over night, and the supernatant liquid was decanted through a dry filter, the first portions of the filtrate being rejected. The subsequent portions of the filtrate were collected in a tared glass-stoppered weighing bottle, the solution was weighed, the solvent evaporated, and the residue dried at 100° and weighed. The loss in weight was considered as the solvent taken and the weight of the residue as the material dissolved. The weight of solvent was divided by the weight of the material dissolved; this gave the number of parts of solvent by weight required to dissolve one part of material.

For the determination of the solubility in hot solvents a saturated solution of the material was prepared at the boiling temperature of the solvent. The hot solution was filtered through a dry filter, the first portions of the filtrate being rejected. The subsequent portions of the filtrate were collected in a tared, glass-stoppered weighing bottle, the solution was cooled and weighed, the solvent evaporated, and the residue dried at 100° and weighed.

The findings for the solubility determinations are given in Table III.

TABLE III.—APPROXIMATE SOLUBILITIES OF CINCHOPHEN IN SEVERAL SOLVENTS.

Acetone	cold	....	32.9	38.3	Carbon tetrachloride	cold	28784	....
		30.1	36.3	39.7			26950	....
	hot	15.8	15.8	....		hot	1795	....
		17.4	....	....			1803	....
Alcohol (amylic)	cold	49.3	50.5	....	Chloroform	cold	631.8	627.3
	hot	3.87	3.25	....		hot	305.5	305.7
Alcohol (95% ethylic)	cold	98*	....	....	Ether (ethylic)	cold	72*	....
	hot	16.38	....	....		hot	44.4	47.2
		13.9	....	....				
Amylic acetate	cold	75.3	71.9	....	Toluene	cold	4620	4822
	hot	8.1	10.3	....		hot	44.4	64.9
Benzene	cold	3881	....	....				
		3717	....	....	Xylene	cold	2886	2896
	hot	370	....	....		hot	32.3	37.9
		293	....	....				

* U. S. P., 10, 110 (1926).

The results in Table III show that the solubilities of cinchophen in benzene, carbon tetrachloride,[1] toluene and xylene are so slight as to render each of these solvents impractical for the extraction of cinchophen from tablets. Amylic alcohol is one of the best solvents for cinchophen with amylic acetate a close second. However, the odor of these solvents is so disagreeable to most persons that they were not further considered. The results obtained from the tests with alcohol, acetone and anhydrous ether were so nearly alike as to make a choice of solvent on the factor of solubility alone difficult.

In the hope of being able to choose between these three solvents, four market brands of cinchophen tablets were studied. A number of the tablets from each brand were weighed and the average weight per tablet was calculated. The tablets were pulverized in a mortar and the powder passed through a No. 60 sieve, after which the material was well mixed. Portions of the material were then treated by the following methods.

METHOD I (ALCOHOL).

Weigh a portion of the powder, equivalent to about 0.5 Gm. of cinchophen, into a fat-free extraction thimble and dry the material to approximately constant weight at 80°. Extract the dried material in a Bailey extractor for one hour, or until extraction is complete, with alcohol which has recently been distilled over sodium hydroxide. Recover most of the solvent and evaporate the remainder by rotation of the container on the steam-bath. Add a few cc. of anhydrous ether to the residue and again evaporate. Dry the residue at 80° and weigh. Dissolve the extract in 60 cc. of warm alcohol, which has been neutralized immediately before use with 0.1 *N* sodium hydroxide, using 5 drops of phenolphthalein as indicator, cool the solution, and titrate with 0.1 *N* sodium hydroxide to a reddish color, which persists for at least 15 seconds.

1 cc. of 0.1 *N* NaOH = 0.02492 Gm. of cinchophen.

The findings obtained by this method on four brands of cinchophen tablets are given in Table IV.

[1] Cold carbon tetrachloride might even be suggested for the approximate separation of cinchophen from some other organic substances.

TABLE IV.—EXTRACTION OF CINCHOPHEN TABLETS WITH ALCOHOL.

Brand.	Weight of sample. Grams.	Solids extracted. Gram.	Per cent.	N/10 alkali consumed. Cc.	Equivalent of cinchophen. Gram.	Per cent.
	0.5653	0.4471	79.10	16.17	0.40296	71.10
A	0.6066	0.4816	79.41	17.00	0.42364	69.83
	0.6146	0.5951	80.55	17.54	0.4371	71.11
	0.7884	0.6667	84.43	23.77	0.59235	75.16
B	0.7260	0.6152	84.74	22.02	0.5488	75.58
	0.6354	0.5291	83.26	...	.....	...
C	0.5620	0.4536	80.71	17.97	0.44781	79.68
	0.5008	0.4066	81.19	16.12	0.40171	80.21
	0.7194	0.4738	65.86	17.18	0.4281	59.51
D	1.5470	0.9911	64.07	38.37	0.9562	61.81
	0.5016	0.3179	63.37	12.06	0.3005	59.91

METHOD II (ACETONE).

Weigh a quantity of the finely-powdered material equivalent to about 0.5 Gm. of cinchophen into a fat-free thimble in a Bailey extractor and extract with recently distilled acetone for two hours or until extraction is complete. Evaporate the solution to dryness, dry the residue at 80°, and weigh. Dissolve the residue in 60 cc. of warm alcohol which has been neutralized immediately before use with 0.1 *N* sodium hydroxide, using 5 drops of phenolphthalein test solution as indicator, cool the solution, and titrate with 0.1 *N* sodium hydroxide to a reddish color, which persists for at least 15 seconds.

The findings obtained by this method on the four brands of cinchophen tablets are given in Table V.

TABLE V.—EXTRACTION OF CINCHOPHEN TABLETS WITH ACETONE.

Brand.	Weight of sample. Gram.	Solids extracted. Gram.	Per cent.	N/10 alkali consumed. Cc.	Equivalent of cinchophen. Gram.	Per cent.
	0.6955	0.5306	76.29	19.64	0.4894	70.37
A	0.7074	0.5480	77.46	19.78	0.4929	69.68
	0.5199	0.3962	76.21	14.62	0.3643	70.08
	0.5539	0.4294	77.50	15.71	0.3915	70.67
B	0.5769	0.4705	81.55	17.48	0.4353	75.46
	0.7241	0.5871	81.08	21.79	0.5430	74.99
	0.8980	0.7169	79.83	28.78	0.7176	79.91
C	0.7901	0.6345	80.31	25.43	0.6337	80.21
	0.5744	0.4592	79.95	18.42	0.4590	79.91
	0.7376	0.4551	61.70	17.73	0.4418	59.90
D	0.8580	0.5291	61.66	20.67	0.5151	60.03

By another method the dried material was extracted with anhydrous ether, the solution evaporated, and the residue, dried, weighed and titrated. The details of the method are as follows:

METHOD III (ANHYDROUS ETHER).

Weigh a portion of the powder equivalent to about 0.5 Gm. of cinchophen into a fat-free extraction thimble and dry to approximately constant weight at 80°. Extract the dried material in a Bailey extractor for 4 hours, or until extraction is complete, with anhydrous ether. Recover most of the solvent and evaporate the remainder by rotation of the container on the steam-bath. Add a few cc. of anhydrous ether to the residue and again evaporate. Dry the residue at 80° and weigh. Dissolve the extract in 60 cc. of warm alcohol, which has been neutralized immediately before use with 0.1 *N* sodium hydroxide, using 5 drops of phenolphtha-

lein as indicator, cool the solution, and titrate with 0.1 *N* sodium hydroxide to a reddish color, which persists for at least 15 seconds.

The results obtained on the four brands of cinchophen tablets are given in Table VI.

TABLE VI.—EXTRACTION OF CINCHOPHEN TABLETS WITH ANHYDROUS ETHER.

Brand.	Weight of sample. Gram.	Solids extracted. Gram.	Solids extracted. Per cent.	*N*/10 NaOH consumed. Cc.	Equivalent of cinchophen. Gram.	Equivalent of cinchophen. Per cent.
A	0.6960	0.5302	76.02	19.9	0.49591	71.25
	0.6399	0.4860	75.95	18.35	0.45728	71.46
	0.5805	0.4457	76.78	17.62	0.43910	75.64
B	0.5894	0.4530	76.87	17.92	0.44657	75.76
	0.5723	0.4411	77.07	....	.....	....
	0.6107	0.4672	76.50	18.27	0.4553	74.56
C	0.6779	0.5448	80.36	21.74	0.54176	79.92
	0.6420	0.5161	80.39	20.72	0.51634	80.42
D	0.5744	0.3516	61.21	13.98	0.34838	60.65
	0.4892	0.3006	61.45	11.79	0.2938	60.06

For greater ease in comparing the values found by the several methods, Table VII has been prepared to show the results by weight and by titration for each of the methods so far described.

TABLE VII.—EXTRACTION OF CINCHOPHEN TABLETS BY EACH OF THREE SOLVENTS.

Brand.	Alcohol (recently distilled from NaOH). Weight.	Alcohol (recently distilled from NaOH). Titration.	Acetone. Weight.	Acetone. Titration.	Anhydrous ether. Weight.	Anhydrous ether. Titration.
	79.10	71.10	76.29	70.37	76.05	71.25
A	79.41	69.83	77.46	69.98	75.95	71.46
	80.55	71.11	76.21	70.08	....	....
	....	....	77.50	70.67	....	....
	84.74	75.58	81.55	75.46	77.07	74.56
B	83.26	75.16	81.08	74.99	76.50	75.64
	84.43	....	....	....	....	75.76
	80.71	79.68	79.83	79.91	80.36	79.92
C	81.19	80.21	80.31	80.21	80.39	80.42
	....	....	79.95	79.91	....	....
	65.86	59.51	61.70	59.90	61.61	60.65
D	64.07	61.81	61.66	60.03	61.45	60.06
	63.37	59.91	....	....	....	....

The results show that in general the values found by the gravimetric method are higher than those obtained by titrating the weighed residues. Some of the gravimetric results, particularly with alcohol as a solvent, are considerably higher than those obtained by titration. So far as the results obtained by extraction of these four brands of cinchophen tablets are indicative, it appears probable that dependence cannot be placed on the extraction of cinchophen tablets on the market with organic solvents and weighing the extract after evaporation without titration. Of the three solvents employed, neutral alcohol appeared to be the most rapid extracting medium and anhydrous ether the slowest. The residues from anhydrous ether were the least colored and the titration of these residues gave values which corresponded more closely to the weights of the residues than was the case with the other solvents. On the whole, anhydrous ether would appear to be the most satisfactory solvent for extracting cinchophen from tablets.

Another method tried was the following, which was suggested by Chairman J. P. Snyder, of the Research Committee of the American Drug Manufacturers' Association.

METHOD IV (EXTRACTION WITH ALCOHOL).

Weigh a portion of the powder equivalent to about 0.5 Gm. of cinchophen into a fat-free extraction thimble and extract in a Bailey extractor, until extraction is complete, with 60 cc. of alcohol which has been neutralized with sodium hydroxide immediately before use, using 5 drops of phenolphthalein test solution as indicator. Cool the solution and titrate with 0.1 *N* sodium hydroxide until a reddish color is produced which persists for at least 15 seconds.

The results obtained by this method on several commercial specimens of cinchophen tablets are given in Table VIII.

TABLE VIII.—EXTRACTION OF CINCHOPHEN TABLETS WITH NEUTRAL ALCOHOL.

Brand.	Weight of specimen. Grams.	*N*/10 alkali used. Cc.	Equivalent of cinchophen. Gram.	Per cent.	Percentage of claim.
A	0.7298	20.79	0.5181	70.99	98.4
	0.4986	14.25	0.3551	71.22	98.7
	0.7009	19.46	0.4849	69.19	95.9
	0.6730	19.18	0.4781	71.04	98.5
	0.7128	22.08	0.55023	77.19	100.8
B	0.8773	26.78	0.66734	76.67	99.0
	0.9999	15.57	0.3880	77.60	101.4
	0.7638	11.91	0.2968	77.72	101.7
C	0.7658	11.76	0.2931	76.44	99.9
	0.6374	20.42	0.50887	79.83	98.6
	0.5544	17.80	0.4436	80.01	98.8
D	1.0444	25.12	0.6260	59.94	98.8
	0.7273	17.59	0.43834	60.27	99.3
	0.7755	19.00	0.47348	61.05	100.6
	0.6706	16.26	0.40530	60.43	99.6
E-2	1.0901	30.23	0.7533	69.10	91.5
	0.4539	12.71	0.3168	69.80	92.5
	0.7290	20.02	0.4989	68.44	90.7
	0.7003	19.02	0.4740	67.68	89.7

Another method, which was suggested by Mr. A. G. Murray of the Drug Control Laboratory of the Bureau of Chemistry, consisted in heating the tablet material with neutral alcohol without the use of an extraction apparatus and titrating the solution after cooling. As carried out the method is as follows:

METHOD V (EXTRACTION WITH NEUTRAL ALCOHOL).

Weigh about 0.6 Gm. of the powder into an Erlenmeyer flask of about 200–250-cc. capacity. Add 60 cc. of alcohol, which has been neutralized immediately before use with 0.1 *N* sodium hydroxide, using 5 drops of phenolphthalein test solution as indicator. Heat the mixture to incipient boiling on the steam-bath with occasional shaking, cool the mixture, and titrate the acidity with 0.1 *N* sodium hydroxide to a reddish color, which persists for at least 15 seconds.[1]

[1] This method is suggested for rapid control in manufacturing processes. The analyst should satisfy himself that the extraction by incipient boiling is complete. If untoward results are obtained the sample should be extracted with a neutral solvent, such as anhydrous ether or neutral alcohol, the ether extract should be evaporated, and the residue titrated after solution in neutral alcohol. The alcoholic extract may be titrated without evaporation.

This method was tried on several specimens of cinchophen tablets. The results are given in Table IX.

TABLE IX.—EXTRACTION WITH NEUTRAL ALCOHOL AND TITRATION IN PRESENCE OF EXCIPIENT.

Brand.	Weight taken. Grams.	N/10 KOH consumed. Cc.	Equivalent of cinchophen. Gram.	Per cent.	Percentage of claim.
A-1	0.6752	19.46	0.48494	71.82	99.6
	0.5946	17.09	0.42588	71.62	99.3
A-2	0.4799	13.43	0.3347	69.74	95.4
	0.5066	14.25	0.3551	70.09	95.9
B	0.6989	21.34	0.5318	76.09	99.4
	0.7360	22.29	0.5555	75.47	98.6
	0.5919	18.09	0.4508	76.16	99.5
C	0.5231	16.83	0.42040	80.37	99.2
	0.5669	18.26	0.45504	80.27	99.2
D	1.0577	25.49	0.6352	60.06	99.0
	0.7027	17.13	0.4269	60.75	99.9
	0.7930	19.41	0.48370	60.90	100.3
E-1	0.6420	17.82	0.44407	69.17	....
	0.6907	19.23	0.4792	69.38	....
E-2	0.8356	23.23	0.57889	69.28	91.8
	0.3976	11.11	0.27691	69.64	92.3
	0.6855	19.07	0.47522	69.32	91.9
F	0.6086	16.92	0.42164	69.28	91.8
	0.6203	14.77	0.36807	59.34	97.0
	0.7171	17.17	0.42787	59.67	97.5
G	0.5243	13.81	0.31414	65.64	99.2
	0.6804	17.92	0.44656	65.63	99.2
	0.6427	17.10	0.42613	66.30	100.1
H	0.5686	14.38	0.35835	63.02	82.8
	1.0400	26.33	0.65626	63.10	82.9

The method is much more rapid than the usual extraction processes. It was tried on a larger number of specimens than were the previous methods. So far as the brands were duplicated, the results obtained were favorably comparable with those obtained by the four other extraction methods. It would appear reasonable to suppose that this method might be employed by manufacturers as a control of their output of cinchophen tablets, provided that no acidic substances other than cinchophen were used in the preparation of the tablets. Information collected from the manufacturers of the tablets included in these studies indicates that with one exception no acidic substance had been used as an excipient or lubricant in the preparation of the tablets. The manufacturer of one brand stated that a small amount of stearic acid had been employed.

A specimen of pulverized tablets, which had assayed 60.4 per cent of cinchophen as an average by several methods of analysis, was sent to each of three laboratories and to another chemist in the Bureau of Chemistry with request that it be assayed by Method V. The findings are given in Table X. For comparison, the assays were repeated by the Drug Research Unit.

In a further study of the serviceability of the method in manufacturing control, four manufacturers of cinchophen tablets were asked to try the method. Two of them complied. A digest of their reports is given in Table XI.

TABLE X.—ASSAY OF CINCHOPHEN TABLETS BY SHORT METHOD.

Laboratory.	Weight of samples. Gram.	$N/10$ NaOH. Cc.	Equivalent of cinchophen. Gram.	Per cent.
Chicago Station	0.6000	14.7	0.3663	61.05
	1.000	24.4	0.6080	60.80
Abbott Laboratories	....	...	.....	59.28
	....	...	.....	59.16
Norwich Pharmacal Co.	....	...	.....	61.51*
	....	...	.....	62.22*
	....	...	.....	60.14*
Bureau chemist	0.6008	14.42	0.3593	59.80
	0.6011	14.47	0.3606	59.99
Drug Research Unit	0.6031	14.51	0.36159	59.96
	0.6035	14.55	0.36258	60.08

* The end-point is not sharp.

TABLE XI.—RESULTS OBTAINED IN MANUFACTURING CONTROL OF CINCHOPHEN TABLETS BY THE SHORT METHOD OF ASSAY.

Laboratory.	Weight of sample taken. Gram.	Percentage of cinchophen.	Percentage of theory.	Comment.
Eli Lilly & Co.	....	...	95.76	Gives too low results.
	....	...	90.77	
	....	...	90.33	
	....	...	91.09	
	....	...	92.17	
E. R. Squibb and Sons	0.7153	59.21	96.61	Method satisfactory.
	0.7357	59.57	97.57	
	0.6644	59.67	97.24	
	0.7133	59.71	98.31	
	0.7141	58.64	96.97	

From a comparison of the results obtained by the short method in the hands of various analysts, it was concluded that this method is sufficiently accurate and dependable for use in manufacturing control.

Since medicinal preparations are on the market which contain cinchophen and acetyl salicylic acid in mixture some attempts were made to determine cinchophen in presence of acetyl salicylic acid. It is obvious that direct titration would not be applicable. Saponification of the mixture with an alkali, followed by distillation of the acetic acid from the acidified solution and titration of the distillate, seemed on first thought to be a solution of the problem, but it was found that some salicylic acid came over. A method was desired by which the cinchophen could be determined in the presence of other interfering substances, such, for example, as salicylic acid. Only one method was tried. This consisted in precipitating the cinchophen with silver nitrate and weighing the silver cinchophen compound. Rabak[1] attempted to determine cinchophen by preparing its compounds with barium, calcium, copper, mercury and iodine but the solubilities of these preparations were too great to permit of satisfactory estimations of the cinchophen. The method was carried out as follows on a known weight of recrystallized cinchophen.

Weigh accurately about 0.5 Gm. of cinchophen and dissolve it in 60 cc. of alcohol which has previously been neutralized with 0.1 N sodium hydroxide, using

[1] *J. Assoc. Official Agr. Chem.*, 7, 33 (1923).

5 drops of phenolphthalein test solution as indicator. Warm the mixture if necessary to facilitate solution, cool the solution, and titrate with 0.1 *N* sodium hydroxide until a distinct pink color, which persists for 15 seconds, is obtained. If not clear, filter the neutral, hydro-alcoholic solution of sodium-cinchophen compound and wash the filter with 10 cc. of 50 per cent alcohol. Acidify the filtrate with a few drops of diluted acetic acid and add, with constant shaking from a burette, 0.1 *N* silver nitrate equivalent to the total number of cc. of 0.1 *N* sodium hydroxide used. Shake the mixture thoroughly to insure separation of the silver-cinchophen compound and set the container aside for several hours in a dark closet, preferably in an ice chest. Collect the precipitate in a tared Gooch crucible, wash it well with cold water (slightly acidified with acetic acid), dry it at 100°, and weigh as silver cinchophen ($C_6H_5.C_9H_5N.COOAg$). Multiply the weight of the precipitate by 0.6998 to obtain the equivalent of cinchophen.

The findings from several trials are given in Table XII.

TABLE XII.—ASSAY OF CINCHOPHEN BY SILVER METHOD.

Test.	Weight of sample taken. Gram.	Silver salt. Gram.	Equivalent of cinchophen. Gram.	Recovery. Per cent.
A	0.5016	0.7045	0.49315	98.13
B	0.5008	0.7112	0.49784	99.41
C	0.6260	0.8841	0.6189	98.86
D	0.4383	0.6204	0.4343	99.09

The method was applied to two mixtures. One of these (A) consisted of 50 per cent of cinchophen and 50 per cent of acetyl salicylic acid and the other (B) of 50 per cent of cinchophen and 50 per cent of salicylic acid. The findings are given in Table XIII.

TABLE XIII.—DETERMINATION OF CINCHOPHEN IN MIXTURES.

Weight taken. Gram.	Silver salt. Gram.	Equivalent of cinchophen. Gram.	Equivalent of cinchophen. Per cent.	Percentage of theory.
MIXTURE A:				
0.5038	0.3614	0.25298	50.41	100.82
0.5010	0.3676	0.25732	51.34	102.68
0.5016	0.3574	0.25018	49.87	99.74
0.5006	0.3572	0.25004	49.95	99.90
MIXTURE B:				
0.7010	0.5185	0.36295	51.75	103.5
0.7011	0.5046	0.35322	50.38	100.76
0.7009	0.4986	0.34902	49.77	99.58
0.7010	0.4989	0.34923	49.82	99.64

SUMMARY.

The solubility of cinchophen in several solvents, both hot and cold, has been determined approximately. The solubility in most solvents is too slight to be practically employed in the extraction of cinchophen from tablets. Of the least objectionable solvents found, anhydrous ether appeared to be the most satisfactory from most viewpoints. Several solvents were compared by extracting cinchophen from tablets and titrating the extracted material with or without the removal of the solvent by evaporation and subsequent solution in neutral alcohol.

A short method for the assay of cinchophen tablets, which is believed to be sufficiently dependable for control in manufacturing processes, has been developed.

A method for determining cinchophen in mixtures with some other organic acids has been worked out. The results obtained with it in a limited number of trials are approximately correct.

The writer wishes to acknowledge his appreciation to the several pharmaceutical manufacturers and to others who have aided in this study, either by contributing material or by collaborative work.

NUTRITIONAL VALUE AND STANDARDIZATION OF COD LIVER OIL AND OF ITS NON-SAPONIFIABLE FAT-SOLUBLE VITAMINE CONCENTRATE (OSCODAL).*

BY HARRY E. DUBIN.

The empirical use of cod liver oil for the treatment of such diseases as rheumatism, gout, osteomalacia, tuberculosis, scrofula and rickets is age old. To-day, based upon indisputable experimental evidence demonstrating that the therapeutic value of cod liver oil is due to its fat-soluble antirachitic and antiophthalmic vitamine content, cod liver oil, in one form or another, is employed throughout the world as a specific in the prevention and cure of rickets and as a valuable aid in the management of other diseases and disturbances in nutrition.

Necessarily, the older theories which attributed the medicinal value of cod liver oil to its iodine or phosphorus content or to its peculiar virtues as a fat have been thrown into the discard.

While numerous references have been made to the unpalatability of even the best grades of cod liver oil, there has been no evidence to show that cod liver oil might be detrimental to health. Recently, however, there has been a report from Sweden that cod liver oil, in doses of 0.1 cc. per day, has exhibited a deleterious effect upon young white mice fed on an ordinary basal diet. Such reports as this, if broadcast and left unchallenged, would undoubtedly cause uneasiness in the mind of the layman. The report in question gives no details as to the nature of the diet used nor does it describe exact experimental conditions; consequently, it is not entitled to serious consideration, particularly so in view of the great mass of exact evidence which has accumulated to show the astonishing therapeutic effect of cod liver oil.

Although the publications in this field of research are too numerous to mention in detail, the author cannot resist the temptation to quote the work of Sherman and Campbell (1) who pointed out that a certain proportion of the antiophthalmic vitamine A in the diet would suffice to support normal growth but would not permit of successful reproduction. Eventually, the animals showed a susceptibility to lung disease at an age corresponding to that at which young adults develop pulmonary tuberculosis. Increasing the vitamine content enabled the animals to grow to full size and to reproduce successfully.

Similarly, such representative investigators as Mendel, Park, McCollum, Hess, Steenbock, Drummond, Mellanby and a host of others have conclusively demonstrated the value of cod liver oil in the diet of infants.

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