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A PHARMACEUTICAL STUDY OF SYRUP OF FERROUS IODIDE (1840–1927).

BY CATY J. BRAFORD AND H. A. LANGENHAN.

(*Continued from p. 339.*)

NO. II. FORMULAS AND PROCESSES BOTH ORIGINAL AND IMPROVED.

When Durand,[1] of Philadelphia, first prepared Dr. Jackson's Solution of Iodide of Iron (1833), he used a process which M. M. Baup and Caillot had outlined in a paper on the "Preparation of the Iodides." His formula varied slightly from theirs, however, in that the proportion of the iron filings was changed to avoid, as he said, the production of a "periodide" of iron. He also increased the amount of water used in order to have a solution that was of lesser strength. His revised formula was as follows:

Iodine	10 drachms
Iron filings, perfectly pure and unoxidized	5 drachms
Distilled water	12.5 ounces

The iodine was mixed with one-half of the water and the iron filings were added in small portions. The heat evolved vaporized a small amount of the iodine. When the entire amount of iron had been added, and first an orange and finally a dark red color had been produced, the solution was slowly heated (with continued stirring). An "ioduretted hydriodate of iron" was first produced, which was converted to the "simple hydriodate" by the action of the heat. This reaction caused the solution to become colorless; it was then filtered and the residue and the filter were washed with the remaining half of the water. This process produced twelve and one-half fluidounces of a preparation which contained one drachm of the iodide of iron in each fluidounce.

The following year (1834), Dr. A. T. Thomson[2] of the London University recommended a method in which one part of iron wire was rubbed with three or four parts of iodine. Fifteen parts of water were gradually added and the entire mixture was introduced into a Florence flask with an additional portion of iron wire and of

[1] Durand, *Am. J. Pharm.*, 4, 287 (1833).
[2] Thomson, see Dunglison, "New Rem.," 5th ed., 297 (1846).

distilled water. The solution was boiled until it acquired a pale greenish color and was then filtered. The finished product contained the "hydriodate of the protoxide of iron" and could be used for medicinal purposes, if the amount of iodine had been previously ascertained.

About the same time Beral[1] published a paper discussing several of the iron preparations, among which was Syrup of Iodide of Iron. He offered a formula which directed that the Liquor of Iodide of Iron be added to Simple Syrup. One teaspoonful of the finished product contained one grain of the dry iodide of iron.

Nicot[2] prepared what he called an "Unalterable Solution of the Protoiodide of Iron." His formula is interesting because it directs the use of both sugar and glycerin.

Sugar	4 Gm.
Iron (by hydrogen)	8 Gm.
Distilled water	40 Gm.
Pure glycerin	110 Gm.

"Mix the iodine and sugar in a porcelain mortar, adding the iron by degrees. Heat gently in a capsule, stirring with a glass rod, and filter to separate the excess iron, then add the glycerin. The mixture should weigh one hundred and fifty Gm. The syrup is made to contain six Gm. of ferrous iodide to one hundred cc. of syrup."

Rousillon[3] worked along the same lines and devised a similar preparation. He did not mix the glycerin solution with the simple syrup until the product was to be dispensed.

In 1840, Liquor Ferri Iodidi was introduced into the U. S. Pharmacopœia. The quantities of iron and iodine were in the same proportion as those in Durand's formula. One ounce of iron was used to two ounces of iodine, which, according to the molecular formula for ferrous iodide (FeI_2), leaves an excess of iron. The method of preparation was about the same as that outlined by Durand. When this Liquor was replaced by the Syrupus Ferri Iodidi in the U. S. P. of 1860, a slight change was made in the formula. The new formula directed the use of two Troy ounces or nine hundred and sixty grains of iodine and three hundred grains of iron in the form of cut wire. As will be noted this was a proportionally smaller amount of iron but it was still an excess. The quantities remained the same in the revision of 1870 but in 1880 they were again changed. This time the use of twenty-five parts of iron and eighty-three parts of iodine were prescribed. In the U. S. P., of 1900, the strength of the syrup was changed from 10% to 5% of ferrous iodide so the amount of the iron and iodine was also reduced to one-half. These quantities were also prescribed in the U. S. P. of 1910. The last revision (1920) changed the requirements of the syrup from 5% by volume to 5% by weight which made it necessary to again alter the formula slightly. The new proportions are twenty Gm. of iron to sixty Gm. of iodine, which decreases the excess of iron but still allows enough to combine with all the iodine and yet leave some to be filtered out.

The following table offers a summary of the various changes that have occurred during the sixty years in which Syrup of Ferrous Iodide has been official.

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[1] Beral, *Jour. de Chem. Med.*, from *Jour. Pharm.*, 13, 72 (1842).

[2] Nicot, *Bull. gen. de Pharm.* (July 30, 1888); through *Am. J. Pharm.*, 60, 449 (1888).

[3] Rousillon, *Jour. de Pharm.*, (5) 28, 243; through British Year Book, 31, 201 (1894).

Revision.	Iron.	Iodine.	% of I.	I.	Fe req.	Exc. Fe.	FeI_2.	Sp. Gr. syrup.	Product.
1860	300 grs.	2 tr. oz.	none given		211 grs.	89 grs.	365 grs.		20 fl.oz.
1870	300 grs.	2 tr. oz.	none given		211 grs.	89 grs.	365 grs.		20 fl.oz.
1880	25 parts	82 parts	100	82	18.1 parts	6.0 parts	100.1 parts		1000 parts
1890	25 Gm.	83 Gm.	98.85	82	18.1 Gm.	6.9 Gm.	100.1 Gm.	1.35	1000 Gm.
1900	12.5 Gm.	41.5 Gm.	99	40.6	8.9 Gm.	3.6 Gm.	49.5 Gm.	1.349	1000 Gm.
1910	12.5 Gm.	41.5 Gm.	99.5	41.3	9.1 Gm.	3.4 Gm.	50.4 Gm.	1.35	1000 Gm.
1920	20 Gm.	60 Gm.	99.5	59.7	13.2 Gm.	6.8 Gm.	72.8 Gm.	1.37	1370 Gm.

As will be noted there is no purity rubric given for the iron and it can therefore be supposed that the iron was pure, as stated in the official description. There is, however, a standard given for the iodine with the exception of the 1860 and 1870 revisions. This varies somewhat in the different revisions and partly accounts for the difference in the quantities of iodine prescribed. The fifth column of the table contains the absolute iodine prescribed. Column six indicates the amount or iron necessary to combine with the "absolute" iodine according to the following equation: $Fe + I_2 \longrightarrow FeI_2$.

Column seven is the theoretical amount of iron to be filtered out of the preparation. The next column gives the theoretical amount of ferrous iodide which will be formed. The first three Pharmacopœias gave no specific gravity for the finished syrup and the first two directed that it be made up to a given volume. The U. S. P. of 1880 specified one thousand parts by weight. The next three revisions directed that the finished product weigh one thousand Gm. and also included a requirement as to the specific gravity. The new U. S. P., for 1920, has changed the formula and requires that the syrup be made to measure one thousand cc. It also gives a specific gravity.

The method of preparation has varied somewhat since the Syrup of Ferrous Iodide was first introduced into the U. S. P. in 1860. The following paragraphs offer a brief résumé of seven different methods that have been official.

METHODS OF PREPARATION.

(*a*) *Order of Mixing.*—The revisions of 1860 and 1870 simply directed that the iodine, iron and water be mixed together. The next three revisions specified the addition of the water before the iodine was added. The last two revisions changed the order again and directed that the water be added to the mixture of iron and iodine.

(*b*) *Size and Type of Flask Used.*—Each Pharmacopœia with the exception of the last one (1920) has directed that a "thin glass flask" be used. The size of the flask was not especially considered until in the 1880 edition, when a flask of "suitable capacity" was specified. The remaining revisions definitely stated the size to be five hundred cc. The last U. S. P. made no reference to the kind of glass.

(*c*) *Amount of Water First Used to Facilitate the Reaction.*—The amount of water added in the first two formulas was three fluidounces; in 1880, twenty parts were added; the next three revisions specified one hundred and fifty cc. and the last revision increased that amount to two hundred cc.

(*d*) *Shaking of Flask and Mixture.*—Each of the Pharmacopœias has directed that the flask containing the mixture be shaken occasionally while the iron and

iodine were reacting. The last four have stated that the reaction could be checked, if necessary, by placing the flask in cold water.

(*e*) *Length of Time of Reaction.*—The reaction, in each formula, was allowed to go on until the solution had acquired a green color and lost its odor of iodine.

(*f*) *Filtering of Solution Mixture.*—The Pharmacopœias of 1860 and 1870 directed that the solution be filtered through a small funnel inserted in the neck of a graduated bottle, which contained syrup that had been previously heated to 212° F. In the 1880 revision the solution was filtered at once into the sugar contained in a porcelain capsule. The 1890 directions were more complicated and specified that after the solution had been heated to boiling, it be filtered through a strong double acting filter, the point of which dipped below the surface of six hundred Gm. of syrup contained in a tared dish. The next two revisions added fifty Gm. of sugar to the boiling solution of ferrous iodide and, as soon as it was dissolved, the solution was filtered into the remainder of the sugar contained in a porcelain dish. The last U. S. P. changed the quantity of sugar to be added to the hot solution to one hundred Gm., and directed that the remainder of the sugar be placed in a one thousand-cc. flask, to which the first solution was added.

(*g*) *Rinsing of the Flask and Excess Iron.*—The various revisions since 1880 have all specified that the flask and the excess iron be rinsed with water, with the exception of the revision of 1890. In that revision a mixture of twenty-five cc. of syrup and twenty-five cc. of water, which had been previously heated to "almost boiling," were used.

(*h*) *Solution of the Sugar.*—To insure the solution of the sugar the first two Pharmacopœias directed that the bottle be shaken. The next edition stated that the mixture should be stirred with either a porcelain or a wooden spatula. Such directions were omitted in 1890. In 1900 the procedure was the same as it had been in 1880. The 1900 Pharmacopœia substituted a glass rod for the wooden spatula. The last revision simply specified agitation.

(*i*) *Application of Heat.*—Heat was directed to be applied to complete the solution, only in the revisions of 1880, 1900, 1910 and 1920. And in the last two revisions it was to be applied only if needed.

(*j*) *Completion of Product.*—The last step in the process of the manufacture of the syrup according to the procedures of 1860 and 1870 was to add enough syrup to the cool solution of ferrous iodide to make the whole volume measure twenty fluidounces. After shaking it thoroughly—to mix the finished preparation—it was transferred to two-ounce vials which were then securely stoppered. In the 1880 revision the concentrated syrup was strained through linen into a tared bottle, and distilled water was added to make the finished product weigh one thousand parts; after being shaken, it was likewise transferred to small vials. The 1890 edition added enough simple syrup to make the finished product weigh one thousand Gm. The two following Pharmacopœias directed that the syrup be passed through a clean muslin strainer into a tared bottle and, after the addition of the acid, distilled water was added to make the product weigh one thousand Gm. The directions of the last revision require that the concentrated syrup be cooled to 25° C. and after the addition of the acid, enough distilled water is added to make the finished product measure one thousand cc.; after being well mixed and strained the syrup is ready to be dispensed.

Different workers have presented what they considered to be improved methods of preparation. Chapman,[1] in his report, discussed the formula offered by Squibb, which differed in that the amount of iron used was less than the U. S. P. formula. His method of preparation was slightly different too.

A cold percolation process was worked out by Hunstock.[2] It was essentially the method used for simple syrup prepared by cold percolation, the solution of ferrous iodide being used as the percolating liquid. Klie[3] used a very similar process a few years later.

Tizier,[4] after considerable work, concluded that technique was an important factor. He stated that the faster the reaction the better the syrup would be.

Cloughly[5] introduced a method that was decidedly different, in that the iron wire was first placed in a solution of potassium hydroxide to remove any oxide that might be present and would cause the solution to be darkened.

Toplis[6] substituted reduced iron for iron wire; he gave two reasons for this substitution—the first to prevent oxidation and the second to save time.

Borisch[7] modified the U. S. P. directions by requiring that the iodine be slowly added and the mixture be stirred with a bright iron spatula, which served as a catalytic agent.

Other changes have been suggested from time to time, but as they were generally intended to increase the stability of the preparation, they will be considered under the "Preservation."

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(*To be continued*)

PHARMACEUTICAL EVENTS IN 1776.*

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The Sesqui-Centennial of the Declaration of Independence is duly celebrated this year in Philadelphia. Inasmuch as the A. PH. A. holds its convention this year in that historical city, a paper on a Sesqui-Centennial of Pharmaceutical Events will be in order. This is my excuse for the treatise herewith presented to the Historical Section of the A. PH. A. The arrangement is similar to my previous annual papers on Pharmaceutical Events.

GENERAL.

The Declaration of Independence adopted by The Second Continental Congress. It might be of interest to learn that Dr. Benjamin Rush was one of the signers. Benjamin Franklin sent to France as Commissioner for the United States. A very severe winter in Paris on which Lavoisier wrote a meteorological paper.

[1] Chapman, *Am. J. Pharm.*, 31, 559 (1859).
[2] Hunstock, *Ibid.*, 47, 390 (1873).
[3] Klie, *Ibid.*, 53, 4 (1881).
[4] Tizier, *Ibid.*, 23, 89 (1851).
[5] Cloughly, A. PH. A. YEAR BOOK, 1, 65 (1912); *Proc. Mo. Pharm. Assoc.*, 133 (1912).
[6] Toplis, PROC. A. PH. A., 58, 1258 (1910).
[7] Borisch, A. PH. A. YEAR BOOK, 21, 76 (1913).
* Section on Historical Pharmacy, A. PH. A., Philadelphia, 1926.