A STUDY OF THE CHANGE IN p_H OF THE OFFICIAL ELIXIR FERRIC PYROPHOSPHATE, QUININE AND STRYCHNINE N. F. V.*

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Few official preparations have induced more comment and discussion, among pharmacists, than has **Elixir Ferric Pyrophosphate, Quinine and Strychnine.** It has had the attention of some of our best pharmacists but is a product yet lacking in pharmaceutical elegance and dependability. Despite the fact that this elixir has grown somwhat in disrepute as a galenical, it, or preparations similar to it, continue in use.

This preparation presents three problems to the pharmacist. *First,* it is difficult to make, *second,* it very often precipitates either in the process of making or upon standing and *third,* it almost invariably darkens in color with age especially if exposed to light. The latter two problems are perhaps the most perplexing and discouraging. Among the many causes offered in explanation of these obstacles are, the effect of light, variability of the scale salts of iron, the action of alkalies upon glass bottles and upon sugar in the preparation, the addition of too much or too little ammonium hydroxide for purposes of neutralization, oxidation of the iron salt, concentration, precipitation due to salting-out effects, etc. Many more causes for the deterioration of this elixir could be given. The trouble is not likely due to a single cause but to a combination of causes which complicate the problem.

Preliminary to this study a number of commercial samples of the elixir were exposed to light and, while there were some differences in the degree of color change, they all invariably darkened. In some samples precipitation occurred.

It is not the purpose of this paper to offer a solution to the problems one encounters in making and dispensing this elixir. It is merely a record of the change in p_H, over a period of several months, in various lots of the official preparation. An effort has been made to record the change in color but with no means of measuring color change at hand our observations are crude and approximate at best.

APPARATUS.

An L. and N. student potentiometer was used with normal calomel and quinhydrone electrode. It was set up after the manner prescribed. A saturated potassium chloride solution formed the liquid junction. The reading in millivolts was converted to p_H by means of the chart furnished with the apparatus.

PREPARATION, SAMPLING AND STORAGE OF THE ELIXIR.

The elixir for this study was prepared in amounts of one to four liters. All variations from the official directions for making are noted with each lot. Care was taken to use chemicals and other materials of good quality such as are available to any dispenser.

Each lot of the elixir was allowed to stand at least 24 hours before a p_H was taken. Readings were taken every day for a few days after which the time between readings was extended to every other day, then to every week, every other week and finally to every month or six weeks.

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All lots of the preparation were bottled in clear and amber glass bottles and stored upon open shelves in diffused light at laboratory temperature. These conditions were not greatly unlike those one would find in the average prescription department.

Table I presents the p_H change of three lots of the elixir over a period of about eleven months. These lots were made according to the official directions except that 5 cc. of ammonia water, per liter, were added for purposes of neutralization whereas the directions state that it should be added until the preparation tests neutral to litmus. Half of each lot of the elixir was stored in clear glass, one-ounce stoppered bottles and one-half in amber bottles of the same kind and size. The purpose of storing the elixir in this manner was to permit a p_H reading upon a fresh, undisturbed sample each time. It was thought that this method would minimize any changes that might be caused by taking samples from bottles that had been opened and exposed to the air.

TABLE I.

	Lot I.			Lot II.		Lot III.	
	Clear bottles.	Amber bottles.		Clear bottles.	Amber bottles.	Clear bottles.	Amber bottles.
Age in days	p_H	p_H	Age in days	p_H	p_H	p_H	p_H
1	4.77	4.75	3	5.03	5.03	5.06	5.06
2	4.82	4.74	5	5.08	4.94	5.09	5.10
3	4.94	4.75	11	5.01	4.99	5.11	5.07
4	4.87	4.73	16	5.11	5.05	5.11	5.10
5	4.84	4.76	24	5.20	5.00	5.12	5.04
7	4.84	4.74	28	5.23	5.08	5.24	5.15
9	4.82	4.76	36	5.24	5.02	5.23	5.17
11	4.89	4.73	46	5.18	5.05	5.30	5.16
16	4.97	4.73	51	5.18	5.04	5.30	5.15
37	5.14	4.79	57	5.27	5.12	5.35	5.13
41	5.10	4.85	64	5.34	5.12	5.32	5.17
71	5.23	4.80	69	5.34	5.11	5.30	5.18
92	5.33	4.85	78	5.33	5.15	5.38	5.18
113	5.11	4.85	92	5.36	5.14	5.32	5.21
150	5.03	4.86	115	5.27	5.08	5.33	5.17
208	5.33	4.84	173	5.32	5.13	5.62	5.19
267	5.30	4.90	232	5.38	5.13	5.61	5.23
292	5.46	4.90	257	5.52	5.24	5.57	5.17
352	5.41	4.95	317	5.49	5.33	5.78	5.22
p_H change	0.64	0.20	...	0.46	0.30	0.72	0.16

These p_H readings indicate a much greater change in these samples stored in clear glass than those in the amber glass. This shows the protection that amber glass gives to preparations affected by light. The total change in p_H in the clear glass and amber glass samples was reasonably constant.

The change in color from a bright green for the freshly prepared elixir to a dark amber at the end of our observations was very gradual. While the change in color was observable we had no way of measuring it. Like the p_H change, the color change was much less in these samples stored in amber glass containers.

Table II is a record of the p_H change of three more lots of the official elixir. Each lot was made by a student in the course in manufacturing pharmacy. The finished product was stored, one-half in clear glass bottles and one-half in amber

bottles and placed upon shelves under conditions previously described. The p_H readings were made upon samples poured from the bottles. This disturbed and exposed the preparation each time a reading was taken. It was felt, however, that this procedure closely resembled the treatment that a bottle of the elixir would be subjected to in a prescription department where the bottle is opened and poured from at various intervals.

TABLE II.

	Lot IV.		Lot V.		Lot VI.	
	Clear bottles.	Amber bottles.	Clear bottles.	Amber bottles.	Clear bottles.	Amber bottles.
Age in days	p_H	p_H	p_H	p_H	p_H	p_H
1	4.95	4.95	5.02	5.02	4.83	4.83
14	5.01	4.98	4.99	4.98	4.91	4.91
19	5.01	4.95	5.01	5.02	4.91	4.91
27	5.02	4.94	5.02	4.97	4.94	4.88
37	5.05	5.00	5.19	5.05	5.05	4.93
65	5.00	4.98	5.18	5.05	5.00	4.93
123	5.21	4.98	5.30	...	5.14	4.93
207	5.25	4.98	5.39	5.09	5.35	4.90
267	5.37	4.93	5.23	5.03	5.30	4.86
p_H change	0.42	−0.02	0.21	0.01	0.47	0.03

The p_H change of the three lots in Table II are quite comparable to those of Table I. The protection of amber glass against light effects is again clearly shown. Furthermore it would seem that light is perhaps the chief agent of disturbance upon the product. At least the technique of opening and pouring from the bottles from time to time seems not to have increased the change in p_H or color. It may be further assumed that completely filled bottles are not a necessary factor for the keeping of this preparation.

The change in color for these three lots was, as far as we could tell, about the same as noted for Table I.

Table III is a record of a further study of three lots of the official elixir. Each lot was prepared by a student of the class in manufacturing pharmacy. Care was taken to neutralize each lot with ammonia water as given in the official directions. The finished lots were then stored in clear and amber bottles as described for Lots IV, V and VI.

TABLE III.

	Lot. VII.		Lot VIII.		Lot IX.	
	Clear bottles.	Amber bottles.	Clear bottles.	Amber bottles.	Clear bottles.	Amber bottles.
Age of days	p_H	p_H	p_H	p_H	p_H	p_H
1	5.87	5.87	6.01	6.01	6.67	6.67
14	5.91	5.91	6.05	6.00	6.67	6.72
19	5.85	5.91	6.00	6.00	6.67	6.72
27	6.01	5.93	6.07	6.00	6.72	6.72
37	5.96	5.95	6.07	5.99	6.71	6.65
65	6.00	5.96	6.19	...	6.64	6.65
123	5.96	5.97	6.15	...	6.66	...
207	5.98	5.85	6.10	6.01	6.50	6.49
267	6.08	5.79	6.16	5.99	6.31	6.28
p_H change	0.21	−0.08	0.15	−0.02	−0.36	−0.39

The change in p_H in the lots found in Table III is not significant. However, the observable change in color was much greater than for Lots I to VI, for the samples stored in the amber as well as in the clear glass bottles. A study of this

table suggests two things. *First*, that careful neutralization of the finished elixir with ammonia water seems to stabilize it as to p_H but not as to color. *Second*, that change in p_H is not always an indication of the change in color. Lot IX, Table III, became more acidic upon standing. This is the most significant change in the direction of acidity that we observed.

A study of ten lots of the official elixir is shown in Table IV. These lots were made several months later than those previously described. The purpose of this study was to observe the effects of the addition of stabilizing chemicals to the finished elixir. Lot X was used as a control and no chemical was added to it. It was not even neutralized with ammonia water as the directions suggest.

To Lots XI, XII and XIII were added 3 cc., 6 cc. and 9 cc. of ammonia water per liter, respectively.

To Lots XIV, XV and XVI were added 2, 4 and 6 Gm. of sodium phosphate per liter, respectively.

To Lots XVII, XVIII and XIX were added 2, 4 and 6 Gm. of sodium citrate per liter, respectively.

Each lot was then placed in a clear glass bottle and stored as were the previous lots. Amber glass bottles for storage were omitted in this study.

The p_H was taken upon samples poured from the bottles from time to time.

The color change as observed for these lots was about the same as that of previous lots.

The p_H change of the lots in Table IV was rather regular until the last reading when a few sudden breaks appeared.

TABLE IV.

Lots Age in days	X p_H	XI p_H	XII p_H	XIII p_H	XIV p_H	XV p_H	XVI p_H	XVII p_H	XVIII p_H	XIX p_H
1	4.58	4.99	5.37	5.75	4.75	4.89	5.22	4.67	4.78	4.93
10	4.56	4.99	5.37	5.83	4.76	4.95	5.24	4.67	4.82	4.95
20	4.58	5.03	5.43	5.85	4.83	5.05	5.29	4.74	4.84	4.96
33	4.51	5.01	5.52	5.89	4.89	5.02	5.32	4.81	4.92	5.03
48	4.79	5.01	5.65	5.98	5.11	5.10	5.42	4.90	5.03	5.20
76	4.74	5.23	5.65	6.02	5.20	5.33	5.42	5.10	5.17	5.27
101	4.85	5.35	5.70	6.05	5.32	5.36	5.56	5.21	5.25	5.40
161	5.26	5.50	5.70	6.12	5.38	5.73	5.66	5.41	5.30	5.40
p_H change	0.68	0.51	0.33	0.37	0.63	0.84	0.44	0.74	0.52	0.47

DISCUSSION.

This study suggests the need for a more extended research into what actually happens to the elixir when it changes in color usually from a bright green to a dark amber and sometimes to an inky black liquid. Perhaps the preparation would not change color if completely protected from light but that would hardly be practicable. It has long been known that amber glass protects this preparation from the deteriorating effects of light but our observations indicate that amber does little more than retard the speed of change in p_H and color. It has been claimed that stability of this product is dependent upon its being about neutral. Our readings do not verify such an assumption although that would seem to be true in some cases so far as the p_H was concerned but not so with respect to permanency of color. Lot X, Table IV, maintained a relatively low p_H with about the average change in color. Lot IX, Table III, contained the larger amount of ammonia water and was therefore more nearly neutral and yet it showed a greater darkening than those in the same table which were somewhat more acid. The lots containing sodium citrate showed the formation of a gas to the extent of

blowing out the stoppers, in addition to the general change in color and p_H. According to Burt (1), who studied the effect of sunlight upon citric acid in the presence of ferric salts, the gas formed in such preparations is CO_2.

The most perplexing part of this problem is that of discoloration of the official elixir upon standing. While there may be some relation between p_H change and change in color our observations hardly warrant such an assumption.

Much has been said about this preparation ever since its introduction into medicine. While pharmacists "in the good old days" did not solve this problem, they did, at least, discuss it. In 1894, the *American Druggist* (2) commented editorially upon this preparation, as follows: "We wonder if there is anything which exercises the minds of the pharmacists more than the making of elegant elixirs (and of elixir of triple phosphates in particular). There is certainly no other subject upon which so much good pharmaceutical gray matter has been and is wasted." Edel (3) in 1896, said:

> "Among modern elixirs that of iron, quinine and strychnine easily is the most popular; and I feel warranted in saying that its preparation has proved a stumbling block to many pharmacists."

A few years later Francis (4) said:

> "Formulæ without number have been proposed during the past years and almost every pharmacist has from time to time been thoroughly convinced that he had solved the problem of producing this elixir containing the full measure of genuine soluble ferric phosphate which would not discolor or precipitate with age."

The reasons offered for the deterioriation of this elixir are often contradictory. For instance, Dunn (5) in commenting upon the U. S. P. elixir said:

> "Do not follow the U. S. P. directions and if the solution is acid to litmus paper, neutralize exactly with ammonia water."

In the following year, Fritzinger (6) said that the U. S. P. directions should be followed and there is no objection either pharmaceutically or therapeutically to a slight acidity of the solution. One writer suggested the use of heat to get the iron salt into solution and another one said to avoid its use. Many have criticized the official process for making this elixir and offer better methods for making it. Others say positively that the official directions are all right if correctly followed.

As it seems to us the problem of change in color in this elixir upon standing will never be solved by skirmishing attacks. The composition of the preparation suggests all sorts of possible chemical and physical situations, no one of which could be the sole cause of the trouble. It would at least be interesting and perhaps worth while for some one to work upon this problem giving consideration to every possible factor that might affect the stability of the preparation. Elixir Ferric Pyrophosphate, Quinine and Strychnine has been in the official list for several decades. Since it is official and continues in wide use, as pharmacists we should understand it better than we do.

REFERENCES.

(1) Jour. A. Ph. A., 17 (1928), 651.
(2) *Am. Drug.*, 24 (1894), 136.
(3) *West. Drug.*, 18 (1896), 440.
(4) *Bull. Pharm.*, 19 (1905), 451.
(5) *Merck's Report*, 19 (1910), 197.
(6) *Drug Circ.*, 55 (1911), 685.

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