AROMATIC ELIXIR.*

BY L. D. HAVENHILL AND M. G. SMOLT.

Aromatic Elixir, U. S. P. X is an excellent vehicle and masking agent, one of the best in use to-day. The junior author became interested in the study of this vehicle when large quantities of it were required by the Bell Memorial Hospital in Kansas City, Kansas, and the Watkins Memorial Hospital in Lawrence, Kansas.

The difficulty in preparing this elixir is to secure a clear product. The official process is long and tedious and often disappointing to the busy hospital pharmacist. Several writers, Shiflett (1), Silver (2) and Burlage (3) and others have given the matter of a rapid method of preparing this elixir considerable attention, but their methods in our hands have not been entirely satisfactory.

The volatile oils used in the preparation of the Compound Spirit of Orange from which the Elixir is prepared are shown in Gildemeister and Hoffman (5) to consist, with the exception of Oil of Anise, largely of terpenes which are not readily soluble in a dilute alcohol. These are almost completely precipitated in the preparation of the elixir and are the chief cause of the difficulties encountered.

The oxygenated principles of these oils are the desirable ones. They are also not the ones which cause the cloudiness. The problem resolves itself into the following:

First, to determine a strength of alcohol that can be used in preparing Compound Spirit of Orange that will extract sufficient oxygenated principles from the volatile oils used, but not enough of the terpenes to precipitate on dilution when preparing the aromatic elixir.

Second, to establish the strength of this new spirit as compared with the one now official regarding oxygenated principles.

Third, to ascertain the relative amounts of oxygenated principles present in Aromatic Elixir.

Fourth, to calculate the amount of this "soluble" Spirit necessary to make an Elixir similar in flavoring strength to the one at present official.

A search through the literature yielded very little of value. The articles for the most part were concerned with improving the methods of filtering or with changing the proportions of ingredients used. Krantz and Carr (6) (7), in two articles recorded results using filtering agents other than talc. In actual experience talc has been found to be the most satisfactory filtering medium.

It is reasonable to expect that if a mixture of volatile oils is added to a diluted alcohol, two phases will result. Since the mixture of oils contains oxygenated principles which are also soluble in the diluted alcohol used, an equilibrium will be established in the aldehyde strength of the two immiscible liquids. The amount of oxygenated principles present in the alcoholic phase will depend on both the volume of the solution and the strength of alcohol used. The amount of oxygenated principles remaining in the oil phase is lost in all methods of preparation because this phase is removed through filtration.

Shiflett (1) and Silver (2) claim the products obtained by their methods are identical in strength with Aromatic Elixir, U. S. P. because the same amounts of ingredients have been used, although both processes involve a preliminary pre-

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cipitation of the hydrocarbon principles of the volatile oils, which are filtered out before adding the remainder of the ingredients. This would lead one to think that the "order of mixing" made no difference in the strength of the finished product.

Experiments were carried out which showed that the amount of oxygenated principles removed by the alcoholic liquid varies considerably with the procedure used. It would seem essential, therefore, when suggesting modifications of the official process, that the quantity of oxygenated principles in the finished elixir be comparable to that in the official elixir. This can only be done by assay. Extensive experiments were made in an effort to get a "soluble" Compound Spirit of Orange.

The method used follows:

Varying amounts of Compound Spirit of Orange were introduced into a 50-cc. volumetric flask and diluted to the mark with distilled water. Each portion was then filtered, using talc, and portions of the filtrate used in compounding small amounts of aromatic elixir. It was found that if 32 cc. of Compound Spirit of Orange, U. S. P. be diluted with distilled water to 50 cc., the resulting mixture thoroughly shaken and filtered, using 10 Gm. of talc, portions of the filtrate, could be compounded into Aromatic Elixir giving a clear product of superior fragrance and taste, which does not require a final filtration. The entire operation of compounding, using the "soluble" Compound Spirit of Orange, takes less than 5 minutes.

The next step was to ascertain the strength of the oxygenated principles of the filtrate as compared with the original spirit.

The method of aldehyde assay proposed by Gfeller (4) was rejected because the terpene constituents are determined as well as the oxygenated principles. The method of Klebler (5) with several variations was tried and rejected because of the difficulty in securing a definite end-point in the residual titration. The colorimetric methods of the A. O. A. C. (8) were also tried. The sulphite-fuchsin method was rejected because the alcohol used gave a color varying with the strength of the alcohol. The method using *M*-phenylene-diamine proved to be suitable and the following modification was used throughout in the subsequent determinations.

Freshly prepared alcoholic solutions of *M*-phenylene-diamine hydrochloride produce no color with the minute amount of aldehydes present in ethyl alcohol. (This reagent must be freshly prepared, for in a few hours it becomes badly discolored and is unfit for use.) The method of comparison used was to pipette 10 cc. of the alcoholic solution to be tested into a 25-cc. volumetric flask and dilute to the mark with a one per cent alcoholic solution of *M*-phenylene-diamine hydrochloride. The color developed was compared, using a colorimeter, with a standard solution similarly prepared. To compare the amount of oxygenated principles in the Compound Spirit of Orange used, with that present in the aromatic elixir made from it, the following method was used.

One and two-tenths cc. of Compound Spirit of Orange were diluted to 100 cc. with 95% alcohol. Another portion of 1.2 cc. of Compound Spirit of Orange with enough alcohol added to make 25 cc., was diluted to 100 cc. with water. (Procedure of the U. S. P. X for Aromatic Elixir, minus the syrup which would cause complications with the aldehyde reagent. It is believed that the presence of sugar does not materially affect the solubility of the oxygenated principles of the volatile oils.) Talc was then added and the product filtered. The aldehyde strengths of the two solutions were then compared by the method given. Comparison was also made of the aldehyde strength of the Compound Spirit of Orange of the U. S. P. X and the

Soluble Compound Spirit of Orange. Since the amount of the Soluble Compound Spirit of Orange used in making the elixir is the amount present in the finished product, as none is lost by filtration, the volume of the "soluble" Compound Spirit of Orange required will be that which contains the same amount of oxygenated principles as is found in 1 liter of Aromatic Elixir, U. S. P. X. Careful comparisons showed that the approximately 25% alcohol dilution of the Compound Spirit of Orange, representing Aromatic Elixir, retained but 44% of the aldehyde strength of the Compound Spirit of Orange used, and that the "soluble" Compound Spirit of Orange had an aldehyde content of but 33% of that of the Compound Spirit of Orange. By simple calculation it is evident that approximately 16 cc. per liter of the soluble Compound Spirit of Orange must be used to duplicate the aldehyde strength of the present official aromatic elixir.

The following formulas are offered for preparing a "soluble" Compound Spirit of Orange from the official spirit, for use in making aromatic elixir.

SOLUBLE COMPOUND SPIRIT OF ORANGE.

Compound Spirit of Orange, U. S. P. X	640 cc.
Talc	30 Gm.
Distilled water	365 cc.

Mix the liquids in a large separatory funnel. Shake thoroughly and allow to stand one-half hour. Draw off the cloudy lower liquid, thoroughly mix it with the talc and filter in the approved manner to secure a clear filtrate and to restrict evaporation.

If the use of the oils is preferred to the Compound Spirit of Orange, the following formula is suggested for making the "soluble" Compound Spirit of Orange.

SOLUBLE COMPOUND SPIRIT OF ORANGE.

Oil of Orange	128 cc.
Oil of Lemon	32 cc.
Oil of Coriander	12.8 cc.
Oil of Anise	3.2 cc.
Alcohol	465 cc.
Water	370 cc.
Talc	30 Gm.
To make about	750 cc. of "soluble" Compound Spirit of Orange.

Mix the liquids thoroughly in a separatory funnel of suitable size. Allow to stand for one-half hour. Draw off the cloudy lower liquid, mix it with the talc and filter in the approved manner to secure a clear filtrate and to restrict evaporation.

The chief use of Compound Spirit of Orange is for preparing Aromatic Elixir. In a few instances it is used in prescription compounding for flavoring. It is believed that this "soluble" compound spirit of orange will prove to be an unobjectionable substitute and much more suitable for use in flavoring medicinals which are low in alcoholic strength.

The following formula is offered for an aromatic elixir which meets the U. S. P. X requirements, using the "soluble" Compound Spirit of Orange.

AROMATIC ELIXIR.

Compound Spirit of Orange, soluble	16 cc.
Syrup	375 cc.
Alcohol	250 cc.
Distilled water	380 cc.
To make about	1000 cc.

Mix the soluble compound spirit of orange with the alcohol. Add the syrup in small portions, mixing well after each addition; then in like manner add the distilled water. (The product at this stage is full of minute bubbles, but clears in a few minutes.)

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A STUDY OF VEHICLES FOR MEDICINES.*

BY BERNARD FANTUS, H. A. DYNIEWICZ AND J. M. DYNIEWICZ.

III. ELIXIR OF PHENOBARBITAL.

If the slogan "Every N. F. preparation a pharmaceutic masterpiece" be adopted, it ought to add immeasurably to the prestige and popularity of its formulas with the medical profession. It may take quite some time to rectify the errors of omission in this respect in the old formulas of this Book, many of which, all will agree, could be improved. We should, however, scrutinize all new formulas that seek admission to this publication from that standpoint. Without pretending to crown the formula we are about to propose as "a masterpiece;"—it is not for us to pronounce it as such—we would like to submit it in competition with other formulas for consideration, most especially, from the standpoint of palatability.

The principle underlying the elaboration of this formula is best illustrated by the following experiment:

1. 0.030 Gm. of Phenobarbital dissolved in 15 cc. of alcohol (95%).
2. 0.030 Gm. of Phenobarbital dissolved in 15 cc. of dilute alcohol (50%).
3. 0.030 Gm. of Phenobarbital dissolved in 15 cc. of 25% alcohol.

It will be found that the taste of Solution 3 is much more bitter than that of Solutions 2 and 1. Of course, Solution 1 is unpleasantly strong in alcohol; and, therefore, one does not hesitate in deciding that Solution 2 gives the best result. The reason for the lower degree of bitterness of the stronger alcoholic solution over the weaker, evidently lies in the physical fact that *a substance will not exchange a good solvent for a poor solvent.* Inasmuch as phenobarbital is so much more soluble

* From the Laboratory of Pharmacology of the University of Illinois.