

A STUDY OF VEHICLES FOR MEDICINES.*

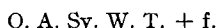
BY BERNARD FANTUS, H. A. DYNIEWICZ AND J. M. DYNIEWICZ.

2. AROMATIC ELIXIRS.

If the question were put to a vote: "Which is the most delicious of all vehicles?" would not the Aromatic Elixir receive first place? That it is popular is evidenced by the fact that, in Prof. E. N. Gathercoal's Prescription Ingredient Survey, it scored a usage of 63.7 per 10,000 prescriptions. We, therefore, started this study with the proposition that the elixir itself is not susceptible to further improvement.

A good deal of dissatisfaction has been expressed about the difficulty and tediousness of clarification of the aromatic elixir, as prepared in accordance with the present formula of the Pharmacopœia. This dissatisfaction is strikingly demonstrated by the number of modifications of the formula that have of late been proposed, all of which deal with the sequence of mixing of the ingredients. To arrive at a rational conclusion regarding these, it seemed necessary to devise a brief method of notation, to make it possible for the eye and mind to contrast the various processes advocated.

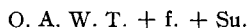
The order of mixing the ingredients of the "Aromatic Elixir of U. S. P. X" is as follows: to the compound spirit of orange (abbreviated O.) add the alcohol (abbr. A.), to this is added the syrup (abbr. Sy.) in several portions and afterward the water (abbr. W.); and the turbid mixture is clarified by filtering (abbr. f.) through talcum (abbr. T.). We propose to represent this sequence by the following formula:



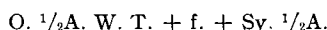
LESSENING OF VISCOSITY TO LESSEN FILTRATION TIME.

One group of suggestions that has been advanced, in order to shorten the filtration time, has been to lessen the viscosity of the fluid to be clarified by using sucrose (abbr. Su.) instead of the syrup; and dissolving it or the syrup in the fluid *after* its clarification.

Thus, Professor Crockett suggests to mix all the ingredients, excepting the sugar, to filter until clear; and then to dissolve the sugar in the filtrate. His sequence might be expressed by the formula:

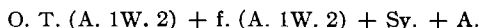


Silver (1) proposes the mixing of the compound spirit of orange with one-half the amount of alcohol and adding the water in several portions, then the talcum and filtering the cloudy fluid through a well-wetted filter, returning the filtrate until clear. Clarification can be accomplished in three-quarters of an hour. We shall call this Chapter I of Silver's process. Chapter II consists in mixing the syrup with the other half of the alcohol. This is then added in divided portions to the clear liquid, shaking after each addition. This process may be expressed by the formula:



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The most complicated modification of the preclarification methods before the addition of the syrup, is that proposed by Schifflet (2). Like Silver, he holds back some alcohol from the original oil mixture and he uses some of this reserved alcohol, in an attempt to wash the talcum free from the absorbed oil; and finally adds another portion of the reserved alcohol to the finished preparation, in order to clarify it of any turbidity that has been produced by the addition of the syrup. His sequence of mixture might be represented in the following manner:



It will be noted that Schifflet's method also consists of two chapters. Chapter I, in which the oil mixture is treated with hydro-alcoholic solvent in the presence of talcum and Chapter II, in which the syrup and the balance of the alcohol are added to the clarified preparation without either of these ever having had the chance to become saturated with the oil mixture.

EVALUATION OF METHODS.

The methods proposed, may be criticized under 3 headings:

1. Unfilterable subdivision of the volatile oils.
2. The use of talcum.
3. Partial use of solvent.

1. The real difficulty in clarifying the aromatic elixir prepared by all the methods in which the oil mixture is dissolved in the alcohol, to which then the aqueous moiety is added in several portions, is the production of an almost colloidal subdivision of the oil particles, a subdivision so fine as to make it incapable of clarification by simple filtration. This is, of course, done with the hope of securing maximum oil saturation of the finished liquid.

2. To remove this almost colloidal turbidity, three per cent of talcum is added which, as Krantz and Carr (3) have pointed out, coagulates the oil particles by neutralizing their negative electric charge by an oppositely charged ion and then absorbs the coagulated particles on the surface of the insoluble filtering medium. It is obvious that, if the subdivision of the oil were not so fine as to have it filter-passing, the use of the talcum and with it the time consumed in filtration could be dispensed with. Indeed, the use of the talcum also affects the hydrogen-ion concentration of the elixirs prepared with it, for we find that the hydrogen-ion concentration of elixirs in which it has been used varies between 6.08 and 6.01, while the hydrogen-ion concentration of the elixirs prepared without talc ranges about a p_H of 5.24.

That the use of the talcum is not only time-consuming, but that it is also wasteful of oil, is suggested by the investigation of Henry Burlage, who compares an elixir made by the official method with one made in the same way, but with the use of twice the quantity of talcum. He finds the percentage of oil content of the latter to be 0.0044+ as compared with the oil content of the official elixir at 0.19-, quite a difference.

3. Silver and Schifflet, by reserving a portion of the solvent (alcohol and syrup), to be added to the clarified oil-alcohol-water mixture (Chapters I and II of their processes) commit the error of not giving *all* the solvent a chance to become

saturated with oil. How grievous this error is, has been beautifully demonstrated by Burlage's investigation which showed that the elixir resulting from Schifflet's procedure contained only 0.003+ and that from Silver's procedure, in which even more alcohol is kept from saturation with the oils, contained only 0.001+ per cent of volatile oil.

THE PRINCIPLES OF ELIXIR MAKING.

We may now be ready to formulate certain principles that might enable us to develop a more satisfactory formula.

1. *Viscosity must be kept low until after clarification.* With this principle most of the students of this question agree.

2. *Filtration through talcum or other absorbent powder must be abandoned,* because it wastes time and oil, and changes the hydrogen-ion concentration of the resulting elixir.

3. To abandon filtration through talcum, and yet be able to add an excess of oil mixture to secure complete oil saturation of the elixir, we must *avoid precipitation of the oils in globules so fine that they pass through filter paper*, which we can do by taking advantage of the law that the fineness of a precipitate is in proportion to the dilution of the reacting solutions. At the same time, the globules must be small enough to remain in suspension: for, to secure the same degree of oil solution from the coarser globules, we must allow a time factor to enter; and, unless some of the oil remains in suspension, frequent agitation would be required to give the solvent adequate opportunity at oil surfaces. No doubt, occasional agitation might be of value in any case, as some of the oil accumulates on the surface. We find that, if we add the compound spirit of orange to the mixed solvents—using an aliquot portion of water instead of the syrup—we secure exactly such subdivision of the oil.

That temperature affects the size of oil globules is shown by the following observations: when we add the compound spirit of orange to the mixed solvents heated to a temperature of 71° C. the resulting liquid is almost clear, but it becomes milky on cooling to room temperature, the degree of its cloudiness being somewhat greater than that of the mixture made at room temperatures. When we agitated the compound spirit of orange with the mixed solvents, previously cooled to a temperature of 10° C., we find that the resulting mixture is still less turbid and that there is a greater quantity of unemulsified oil floating on the surface. The clear filterability of the mixture secured at room temperature, when a hard filter is used, makes the artificial temperature changes merely of interest in showing that variable results might be obtained by variations in temperature.

4. Both Silver and Schifflet have demonstrated that it is a poor policy to retain any of the solvent until after clarification; because, of course, we cannot get a saturated solution unless we give all of the solvent a chance to become saturated.

A RAPID METHOD OF ELIXIR PREPARATION.

It seems, then, that the problem of a more expeditious preparation of the official elixir would be solved were the very *fine* subdivision of the oils prevented: as can be done by adding the compound spirit of orange to *all* the solvent ingredients, previously mixed; permitting this mixture to stand for twenty-four hours

(if time permits), and filtering through a *hard* filter (Whatman 50) to absorb the excess of oil. This process is strictly analogous to the modern method of preparation of aromatic waters, which was introduced into the tenth revision of the Pharmacopœia to take the place of the talcum process, that was objected to, not only because of its adding foreign ions to the solution, but also because the finished water seemed less aromatic.

After all, one cannot force more solute into a liquid than that liquid *can* dissolve; and saturation will occur if one gives the solvent time enough to act upon the solute, even if the latter be not present in the finest possible degree of subdivision. Therefore, it seems to us an error to produce so fine a subdivision of the oil that one has great difficulty in filtering out the excess; and must add an absorbent to the liquid, which wastes not only time but also oil in filtration.

While we hesitate to make the existing confusion still more confounded by proposing another sequence to the many that have been advanced, we do so with the belief that we might thereby clarify the situation and the elixir as well.

ELIXIR AROMATICUM.

Aromatic Elixir.

Elix. Arom.	Simple Elixir
Compound Spirit of Orange.....	12 cc.
Sucrose.....	320 Gm.
Alcohol.....	250 cc.
Distilled Water.....	550 cc.
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To make.....	1000 cc.

Mix the alcohol with the water, add the compound spirit of orange, and agitate vigorously; repeating the agitation from time to time in the course of twenty-four hours. Filter through a hard filter (such as Whatman 50) returning, if necessary, the first portions of the filtrate until it passes through clear. Dissolve the sucrose in the clear filtrate, either by agitation or by percolation, adding enough of water and alcohol, in the proportion of 2 of water to 1 of alcohol, to make the final product measure 1000 cc.

This gives us as the mixing formula:

A. W. O. + f. + Su.,

which may seem almost too simple. Our forefathers said: "*Simplex sigillum veri.*" (The simple is the sign of the truth.)

(*"Iso-Alcoholic Elixirs"* follow in next issue of the JOURNAL.)

STERILITY OF ALCOHOL.

H. Eschenbrenner, *Apoth.-Ztg.*, 47 (1932), 1578. The examination of 34 samples of alcohol of strengths ranging from 70 per cent upward showed that 20 of these were not sterile. In alcohol taken from storage tanks, and especially in the sediment from the tanks, a great variety of spore-forming bacteria were found, chiefly from the groups of hay bacilli, *B. sub-*

tilis and at least five kinds of gram-positive rods. Tetanus spores could not be detected. Although definitely pathogenic bacteria have never been found in alcohol, it is not certain that these other forms are entirely innocuous. It is thus necessary to sterilize alcohol which is to be used for surgical purposes or for the sterilization of instruments, either by distillation or by passing it through a sterilizing filter.