SOLVENTS IN PHARMACY.*

(Continuation of "Precipitates in Fluid Extracts," 1885.)

(The paper was written in 1885, see Introduction, p. 940, November 1917.)

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PART II.

Solvents Considered. The solvents considered in this series of experiments are (excluding acids and alkalies) those that appeal as being of possible use in plant pharmacy, as solvents or excluders, either alone or mixed. They are numbered herein, successively, and may, for our present purpose, be most rationally classified by group solvent relationships. Three classes, then, result (Table I), as follows:—

TABLE I.

1st,	Glycerin,	
2nd,	Water,	
3rd,	Alcohol (U. S. P. 1880),[1]	*Class 1.*
4th,	Methyl Alcohol.	
5th,	Acetone,	
6th,	Chloroform,	
7th,	Amylic Alcohol,	*Class 2.*
8th,	Acetic Ether,	
9th,	Sulphuric Ether (U. S. P. 1880).[1]	
10th,	Benzol,	
11th,	Carbon Disulphide,	
12th,	Benzin,	*Class 3.*
13th,	Turpentine Oil (rectified),	
14th,	Liquid Petrolatum.	

Class 1—Glycerin, Water, Alcohol and Methyl Alcohol. The members of Class 1 mix[2] with each other in all proportions, regardless of order of mixing them. It is impossible to make any combination that is not transparent. Were it not for the erratic acetone of Class 2, which refuses to mix with glycerin, this substance (acetone) might also be included in Class 1, because acetone mixes freely with the other members of this class. The members of Class 1, when pure, are either odorless or possessed of no very marked odor. Excepting glycerin, they evaporate readily and are easily distilled.

Class 2—Acetone, Chloroform, Amylic Alcohol, Acetic Ether and Sulphuric Ether. The members of Class 2 mix with each other in all proportions. It is impossible to make any combination of any or all of these substances, that is not transparent. The members of this group are all volatile, and excepting amylic alcohol, which boils at about 270° F., may be easily distilled. They are all possessed

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[1] It is essential that liquids in exact accord with those used in the experimentation originally instituted be employed. Hence, neither Alcohol U. S. P. nor Ether U. S. P. 1910 is now admissible. (J. U. L., 1917.)

[2] Where the term *mix* or *miscible* is employed, perfect solution is to be understood. All these liquids may be mechanically mixed by agitation or emulsifying processes.

of marked odors, and these odors, beginning with acetone which is less decided than the others, are successively pleasant, but upon reaching sulphuric ether they become unpleasant, that of amylic alcohol being disagreeable.

Class 3—Benzol, Carbon Disulphide, Benzin, Turpentine Oil and Liquid Petrolatum. The members of Class 3 mix with each other in all proportions. They are, excepting liquid petrolatum, volatile at ordinary temperatures, some of them being very volatile. Excepting benzol and liquid petrolatum, they are all possessed of disagreeable odors.

General Remarks on the Three Classes.

Considering these fourteen liquids in the order given, it is found that between the extremes no solvent affinity whatever exists, but as we progress down or up the series, affiliation increases.

Thus, glycerin, which mixes clear with any member of Class 1, is practically indifferent to all of Class 2, and will not mix freely with any member or combination that may be made of Class 3.

Water is indifferent to all the members of Class 3. Of Class 2 it mixes in all proportions with acetone, takes up of sulphuric ether largely, and is indifferent to the other members.

Alcohol mixes freely with all the members of Classes 1 and 2, and is miscible in varying degrees with all but liquid petrolatum of Class 3.

Methyl alcohol mixes freely with all the members of Class 2, with one member (benzol) of Class 3, and is very friendly towards the other members of the third class. Indeed, the only practically indifferent liquid of the entire list to methyl alcohol is liquid petrolatum.[3]

Thus it is seen that a progressive relationship seems to exist between the members of Class 1, increasingly for certain members of the other classes, as we progress from glycerin to methyl alcohol.

When we step into Class 2, we find that the first member, acetone, is remarkable in that it mixes freely with all the liquids of the entire list excepting the extremes, glycerin and liquid petrolatum. It has no other incompatible.

Next, chloroform is possessed of fully as marked affinities, exclusive of the first two members of Class 1, water and glycerin, with which, however, it very slightly affiliates. Chloroform and amylic alcohol mark the central feature in the list, for from these two as we progress towards the extremes we find increasing antagonisms. Amylic alcohol has practically the solvent relationships of chloroform. It mixes partially with liquid petrolatum, and freely with all the other liquids excepting water and glycerin, in each of which it is sparingly soluble. Begin with amylic alcohol and pass to Class 3. Adding successively the same bulk of each liquid, and shaking after each addition, the liquid remains transparent to, and including, liquid petrolatum. Pass now in the other direction and add to the foregoing mixture each liquid, successively, to the water. Constant transparency results, but the water immediately decomposes the mixture, the line of division being remarkably changed from what might be anticipated. (See Process of Establishing Solubilities.)

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[3] In these experiments equal amounts are shaken together. Liquid petrolatum and methyl alcohol separate, leaving the surface film between them about where it would be in case neither dissolved the other. See "*Process of Establishing Solubilities.*"

Acetic ether will not, in equal amounts, mix with any member of Class 3, and with only two of Class 1, water and glycerin being with it immiscible.

Sulphuric ether, U. S. P. 1880, mixes freely with all members of Class 3 excepting liquid petrolatum.[4]

Passing now to Class 3 we strike first benzol, the most cosmopolitan member of that class. It affiliates[5] with two members of Class 1 (alcohol and methyl alcohol), with all but one member of Class 2 (acetic ether), with which it unites one to two parts. In this respect it is an exception, for any other member of the entire list that freely dissolves sulphuric ether, will also dissolve acetic ether freely. It refuses to unite with water and glycerin in any proportion, thus indicating the relationship that, in our present study, places it in Class 3.

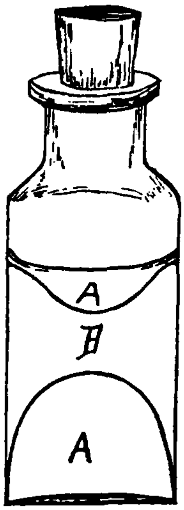

FIG. 4.

A,A—Carbon Disulphide.

B—Glycerin. Position assumed on shaking, Fig. 5. Note meniscus, lower A, reverse of Glycerin (A), Fig. 5.

FIG. 5.

A—Glycerin.

B—Carbon Disulphide. Position assumed when carbon disulphide is poured carefully on the surface of the glycerin, narrow container.

The second member of Class 3, carbon disulphide, mixes freely with all but one member (acetic ether) of Class 2, and mixes with only one (alcohol) of Class 1.[6]

[4] This is important,—indeed, one thought of the writer is the opportunity of establishing standards of purity by behavior of mixed liquids, a very entrancing research. For example, the separation of sulphuric ether (U. S. P. 1880) from liquid petrolatum, is due to the water contained in the U. S. P. ether, 1880. Water-free (Squibb's Anhydrous) ether mixes with all the liquids of Class 3. In order to parallel the experiments (1885) in which sulphuric ether U. S. P. 1880, specific gravity 0.750, was used, ether of the same strength must be employed. This is a very delicate test for water in ether. J. U. L. 1917.

[5] Mixes in equal amounts, by measure.

[6] In this connection, the contact meniscus of three of these,—methyl alcohol, water and glycerin—is fruitful as regards their curvatures, these distinctions being part of my study in connection with capillarity. The mixture of carbon disulphide and glycerin is remarkable because the lighter liquid, glycerin, s. g. 1,250, if the cylinder be small in diameter rests beneath the heavier, Cs_2, s. g. 1.268, when the glycerin is added first (see figures 4 and 5). The cause of this phenomenon, a most interesting study and very fruitful, in its relationships, is studied in another place (not yet published).

Benzin, turpentine and liquid petrolatum stand practically together in their affinities. None will mix with any member of the first class. All mix freely with the three first members of the second class,—acetone, chloroform and amylic alcohol. They all dissolve in acetic and sulphuric ether, but vary somewhat as regards proportion. Liquid petrolatum is separated from the others of this (3rd) class, in that it is odorless, and is not volatile at ordinary temperatures. Thus liquid petrolatum, terminating Class 3, stands isolated as does glycerin in heading Class 1. In all respects these two liquids are so antagonistic that it may be said that from the angle we now consider them, they are the antithesis of each other.

Solutions of Solvents and Mixtures of Neutral Solvents.

We are now led to an unmentioned and yet very well-known phase of the act of solution that confronts us when we consider the separates of the three classes.

Mix any two miscible solvents, *e. g.*, alcohol and water, and, as has been stated, the solvent action of the resultant liquid is different from that of the original. For example, equal parts of water and alcohol, mixed, will not dissolve as much salt and shellac as would either alone (water, the salt,—and alcohol, shellac). Add to a mixture of water and alcohol, successively, other affiliating liquids, and with each addition the solvent power of the product is altered. Change the proportions of the ingredients and, it becomes possible to make a solution of one liquid in another and then, by adding a third liquid, to throw more or less of one or the other constituent (perhaps both) of the first mixture out of solution. In other words, to precipitate it.[7] In like manner other liquids may be added, and thus produce precipitate after precipitate, successively, all perhaps finally redissolving, when the strain is broken by the addition of an affiliating liquid. Each new mixture becomes a new menstruum, each new menstruum is a solvent having distinct affiliating qualities, as is shown by the disappearance or increase of the successive precipitates, and also indicated by the shifting of the line of demarcation as each liquid is added. These qualities present great opportunities in manipulative pharmacy.

Mediators for Uniting Immiscible Solvents.

In mixing neutral solvents we are led to results that occasionally seem to conflict with our theories, if the characters of separated ingredients, as aforenamed are alone taken into account. It is possible to make combinations that will enable liquids of opposite characters to coalesce. We can, for example, by using a mediator, unite some proportion of any member of Class 1 with any member of Class 3.

Thus, if two parts of acetone be mixed with two parts of glycerin, the mixture will at once separate into two layers, about equally divided. Add now one part of methyl alcohol and agitate;—the liquid immediately becomes transparent, forming a single menstruum. The methyl alcohol acts as a mediator, affiliating the three into one, which, however, has a different solvent action from any of its constituents.

Again. Mix two parts of acetic ether with two parts of water, and they will separate. Add now one part of alcohol, and the two layers immediately unite, the

[7] We have in previous articles (*Proc. Am. Pharm. Assoc.*, 1879-1885) endeavored to make it plain that a precipitate, or better, *separate*, may be either a solid or a liquid, and either heavier or lighter than the bulk of the liquid.

three forming a transparent solution. Let us, with this thought, introduce Table II, formulated as follows:—

Begin with the last member (No. 14) of the list, liquid petrolatum, and add successively two parts of each that precedes, agitating after each addition. They will mix transparent until No. 9 is reached (sulphuric ether), when the solution becomes milky, and remains milky after No. 8 (acetic ether) is added, but it again becomes transparent upon the addition of No. 7 (amylic alcohol), remaining transparent therefrom to and including No. 3 (alcohol). It will be seen that an incompatible appears when we add No. 9 (sulphuric ether):—[8]

TABLE II.

Liquid Petrolatum,
Turpentine Oil (rectified),
Benzin,
Carbon Disulphide,
Benzol,
Sulphuric Ether (U. S. P. 1880) (clouds),
Acetic Ether (clouds),
Amylic Alcohol (clears),
Chloroform,
Acetone,
Methyl Alcohol,
Alcohol (U. S. P. 1880),
Water (separates into two sections).

Precipitation or cloudiness may be avoided by merely altering the order of mixing, as follows (Table III), shaking with each addition:[9]

TABLE III.

2 Cc. Liquid Petrolatum,
2 Cc. Turpentine,
2 Cc. Benzin,
2 Cc. Carbon Disulphide,
2 Cc. Benzol,
2 Cc. Amylic Alcohol,
2 Cc. Chloroform,
2 Cc. Acetone,
2 Cc. Methyl Alcohol,
2 Cc. Sulphuric Ether,
2 Cc. Acetic Ether,
2 Cc. Alcohol.

In this case the mixture remains transparent from the beginning to the end. Let us now consider

TABLE IV. (Not necessary to name in detail.)

[8] This is not due to the *ether*, but to the water it contains. This phase of the subject presents a fruitful opportunity that can not now be considered. If pure sulphuric ether be used (U. S. P. 1910) the liquid is clear, to the acetic ether. I infer that acetic ether water free will not cloud (Later Note, 1917). So pronounced is this influence that, if (Table No. III) Sulphuric Ether U. S. P. 1910 be used instead of that of 1880, the meniscus, on the addition of the water, is (1910) about 5, instead of (1880) which is 9.

[9] In these experiments, owing to the convenience of measuring two (2) cubic centimeters in the cylinder employed (see Fig. 3, p. 948; also Figs. 8, 9 and 10) that amount is as a rule taken as the unit. Hence 2 parts, refers to 2 Cc. Any desired unit may be employed.

Begin with methyl alcohol, pass successively (Table I) to (and including) liquid petrolatum, then reverse and add to this mixture the chloroform, passing successively to (not including) water. The liquid is transparent from first to last.

Consider now the natures of these several ingredients (see qualities of the members of Table I). We find that (Table III) we have assimilated a mass of incongruities into a common whole, by dispersing (preventing surface films forming) each mixture as the respective liquid is added. Of the list, only two—chloroform and amylic alcohol—will mix in equal amounts with every member. The others exhibit varying solvent properties, each excluding wholly or in part, when taken separately, nearly half the members included in the list, many being practically insoluble in each other. And yet, the product above-named becomes, at the start, a menstruum of perfect transparency, and remains so to the end.

Breaking the Combination.

Add now to this transparent menstruum (Table III) two parts of water; immediate precipitation results, the upper liquid occupying *nine* (about) parts. (Fig. 6.) Add now two parts of glycerin,—the mixture practically *reverses* itself, the lower layer being about *five* parts (Fig. 7).[10] The original mixture

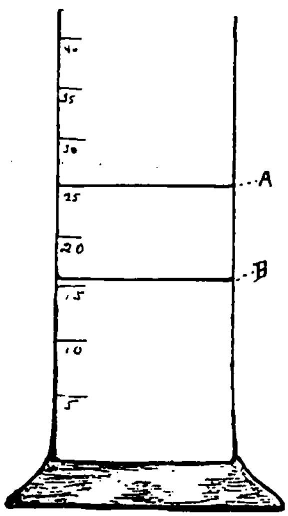

Fig. 6.
A—Air surface.
B—Meniscus between liquids.

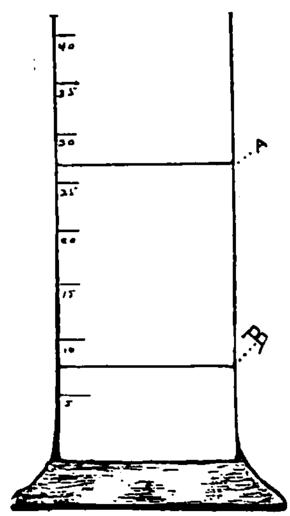

Fig. 7.
A—Air surface.
B—Meniscus between liquids.

is not a solvent for either of these liquids, but each possesses selective affinities for certain members of the group, resulting in the aforenamed remarkable movement of the line of division. Indeed, when we consider the fact that neither glycerin nor water will mix with any member of the third class and that but one member of the third class will mix freely with any member of the first class, and that the members of the second class will in no case mix with all the members of the first and third classes, it is apparently illogical to expect that we could make a mixture

[10] In repeating these experiments, slight deviations in the final line of separation are likely to occur, even to the extent of one division. This is due, not alone to temperature, but to the "shaking" process of admixture. This (shaking action) has been with me subject for a special study, which can not here be intruded. Physical action seems an important factor. Most perplexing discordant results have, in some instances, not as yet been accounted for.

of liquids from the foregoing list that would dissolve liquid petrolatum, glycerin, and water, even in any appreciable amount.

We have to this point considered separates[11] of two layers only.

Three Separates. It is impossible, so far as our experimentation extends, to make a mixture of equal amounts of either the first and second classes, or of the second and third classes, that will separate from each other in three layers. It is possible, however, to select from the central class, and the two extremities, liquids that refuse to unite, forming three layers. Thus a mixture of

2 Cc. Glycerin,
2 Cc. Acetone,
2 Cc. Liquid Petrolatum,

on being shaken together, will separate into three layers, each approximating the amount of the respective original liquid. (Fig. 8.) This equilibrium may be broken by the addition of any solvent that exhibits an attraction for two of the members, in which case one surface film disappears and two layers result. Thus the addition of two parts of water to the aforenamed ingredients will combine the glycerin and acetone (two layers resulting), both (glycerin and acetone) being miscible with water, the liquid petrolatum being excluded, as it is indifferent to all of them. (Fig. 9.) We are again led to the supposition that it must be impossible to unite such opposites (as glycerin and liquid petrolatum) in a single menstruum. To do so, it would appear necessary to construct a solvent (restricted to liquids) such as Paracelsus mentioned and Von Helmont dilated on, under the name Alkahest, or Universal Solvent.

Neutral Solvent Precipitates. It is well known that a solvent capable of holding a solid substance in solution need not necessarily be capable of totally redissolving it after it has been precipitated. It is much easier to produce precipitates than it is to redissolve them in the same solvent. This, too, even though no change to crystalline condition has resulted. Liquid substances, when insoluble in a menstruum, differ from solid precipitates only in being liquid separates. With them, the rule governing re-solution of solids holds good. A precipitated liquid in fine division may be very quickly dissolved in an appropriate menstruum, but, if agglutinated into material drops, or resting in layers, it may dissolve very slowly. Hence it is that the order in which liquids are mixed may become of importance in pharmaceutical manipulation.[12] If a selection of the liquids herein considered be mixed in a certain order so as to avoid drop (agglutinated) separations, the liquid may be transparent from first to last, the ultimate result being a clear liquid having the power of dissolving further amounts of each of its constituents.

If, upon the other hand, the same liquids and the same proportions be maintained, but a different order of admixture employed, the mixture may be continually precipitating (paralleling rain in the air), the final result being a liquid precipitate that refuses to redissolve. This fact is illustrated by first making a mixture, as follows (Table V), shaking after each addition:—

[11] This term is employed to designate the separated layers of liquids. In the study of the "meniscus" as yet unpublished, it is constantly used. See as examples Figs. 4 and 5. Also the different appearances of the meniscus separating the liquids in the other illustrations.

[12] Sometimes, as in making emulsions, the reverse of solution is desired. In these it is desirous that the surface films be not easily broken.

TABLE V.

2 Cc. Liquid Petrolatum,
2 Cc. Turpentine,
2 Cc. Benzin,
2 Cc. Carbon Disulphide,
2 Cc. Benzol,
2 Cc. Amylic Alcohol,
2 Cc. Acetone,
2 Cc. Methyl Alcohol,
2 Cc. Sulphuric Ether,
2 Cc. Acetic Ether,
2 Cc. Glycerin,
2 Cc. Alcohol,
2 Cc. Water.

This mixture is *clear* until the water is added (see also Table IV).

Repeat now the experiment, mixing the same liquids in the following order:—

TABLE VI.

2 Cc. Water,
2 Cc. Liquid Petrolatum,
2 Cc. Glycerin,
2 Cc. Turpentine,
2 Cc. Benzin,
2 Cc. Carbon Disulphide,
2 Cc. Benzol,
2 Cc. Amylic Alcohol,
2 Cc. Acetone,
2 Cc. Methyl Alcohol,
2 Cc. Alcohol,
2 Cc. Sulphuric Ether,
2 Cc. Acetic Ether.

The result will be a mixture that is continuously sectional or emulsified,[13] and yet, excepting the order of arrangement, the liquids are from the beginning in exactly the same proportions employed in the previous experiment. At no point is the mixture possessed of the same solvent power or the same pharmaceutical opportunities as at any other point. And, at no point does one mixture (Table V) parallel the other (Table VI). The study of such phenomena as this is complicated indeed. Pharmaceutical *art* (Plant Pharmacy) depends in its outreaches largely on the application of processes established by the investigation of such problems as these.

Breaking the Surface Film. A Cosmopolitan Solvent.

From a consideration of the *principles* involved in the foregoing line of experiments, regarding surface films and contact curves,[14] it would seem that it might be possible to make a selection of members of the foregoing series in such a manner as to prevent the formation of the surface films, leaving finally several free bonds of attractive associates, thus making a

[13] Each mixture is an emulsion which, if allowed to stand, would separate into sections. The study of emulsions is most important and scientific. Research must yet be applied to this phenomenon. My further researches in contact films, capillarity, mass action and connected phenomena, as yet unpublished, show that pharmacy has herein a great scientific opportunity.

[14] Continuous mention is being made of division lines (surface films and meniscus) between liquids, but no direct attention has been called to them. They, however, have been the subject of my some years' empirical study.

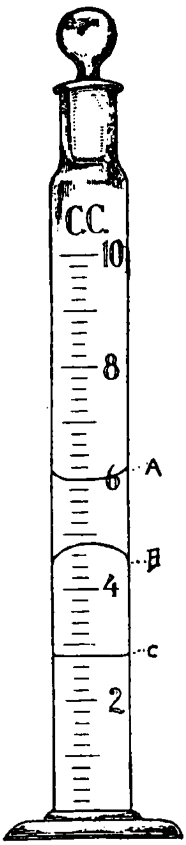

FIG. 8.

A—Air surface.
B—Upper liquid meniscus.
C—Lower liquid meniscus.

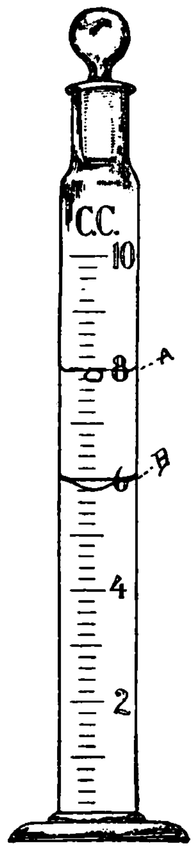

FIG. 9.

A—Air surface.
B—Liquid meniscus. (Note pendant drops).

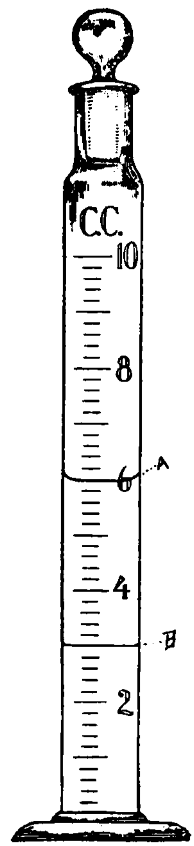

FIG. 10.

A—Air surface.
B—Meniscus between liquids.

solvent that will be capable of breaking other contact films and consequently of dissolving, more or less, liquids that are opposite in character.[15] On the other hand, it might seem that if a mixture be so constituted as to possess an affinity for either extreme, it must be passive to, or repulse the opposite. Thus, if it be composed of a mixture of solvents out of Classes 2 and 3, that, when combined, have free bonds of attraction for, and possess the power of dissolving liquid petrolatum, it would seem natural to expect it to refuse to dissolve water or glycerin. The reverse is also probable, for it appears irrational to expect that a liquid compounded of Classes 1 and 2 can dissolve liquid petrolatum, which separates from each member of these classes. Carrying this thought further, it seems that if it is possible to devise a mixture capable of dissolving the three incongruities, liquid petrolatum, water and glycerin, it will also dissolve more or less of all fats and oils, as well as other substances soluble in any intermediate liquid of this list.

[15] This writer has observed that liquids capable of completely dissolving each other produce no surface films when mixed in any and all proportions. The term "free bonds of attraction," introduced (coined) herewith, seems to apply in directions where an interlaced solvent is unsatisfied in any class direction. Hence, the expression, "free bonds of attractive associates."

In accordance with this line of reasoning the apparently impossible is to be sought, *e. g.*, a solvent capable of dissolving the extremes, glycerin and liquid petrolatum, neither of which dissolves the other, and neither of which vaporizes into the other. A mixture of the following liquids produces a menstruum of these exceptional qualities. At no time is a contact division (meniscus) possible in making this mixture,[16] regardless of the order of mixing (Table VII):—

Table VII.

2 Cc. Benzol,
10 Cc. Sulphuric Ether (U. S. P. 1880),
4 Cc. Acetic Ether,
2 Cc. Amylic Alcohol,
2 Cc. Chloroform,
10 Cc. Acetone,
10 Cc. Methyl Alcohol,
6 Cc. Alcohol (U. S. P. 1880).

Owing to variations in vaporizing points of these ingredients, exposure, even brief, materially alters the solvent reactions of this mixture.

In this menstruum all essential oils tested (those in commercial use and all others attainable), and all members, from 3 to 13 (inclusive) of the three classes of liquids named herein, dissolve in all proportions.[17]

If the mixture is made by adding the material to be dissolved in small portions at a time (drop by drop with liquid petrolatum), shaking after each addition, it will also dissolve:—[18]

$^{2}/_{7}$th its bulk of Water,
[illegible]$/_{7}$th its bulk of Glycerin,
$^{1}/_{16}$ its bulk of Liquid Petrolatum.

Fixed oils, such as Olive Oil, Castor Oil, Linseed Oil, Cotton Seed Oil, Cod Liver Oil and others tested, dissolve freely,—Castor Oil in all proportions. It dissolves every alkaloid tested, even Morphine being very soluble.

Temperature.

Possibly in no other manipulative direction is the influence of temperature more important than in the study of solvents and the meniscus of separation. Temperature, in the preceding investigations, was as near 70° F. as attainable, but there were deviations which should have been recorded.[19] Whether or not such reactions as these can be classed as altogether or in part chemical, is problematical. Nevertheless, "mass attractions" that coalesce seemingly unchanged liquid bodies, are most pronounced, and in these, *temperature* applies as directly as in true chemistry.[20] In other directions,

[16] If absolute alcohol and pure sulphuric ether (free from water) be used, the qualities as a solvent of extremes are enhanced.

[17] The original notes carry experiments with the ordinary fixed oils. These are omitted, not because they are of no value, but because they open up a series of problems that should be discussed if the record is printed.

[18] Statement of 1885 is approximately verified 1917.

[19] The temperature of 32° F. is finally accepted as most easily attainable, and the best standard.

[20] From one view, this word might better be replaced by *liquid*. From another, *liquid* does not fully answer. For example, solid camphor and thymol, triturated together, dissolve each other, a liquid resulting. In like manner, Di-cerberine sulphate triturated with thymol produces a liquid. In these cases solids act as solvents. Indeed, gases may do so. If under a bell glass, a piece of thymol is placed near a piece of camphor, each liquefies the other, by reason of their respective vapors, the thymol first becoming fluid.

as shown in studies of the meniscus between liquids (not yet published) even greater influences are observed than with oils.[21]

The Addition of a Solvent May Over-balance a Perfect Solution and Produce Separation.

It is found that the addition of one solvent to an association of solvents in perfect solution may produce precipitation of one or more of the constituents. Thus, if two parts of alcohol be mixed with two parts of chloroform, and to the clear solution two parts of water be added, separation ensues, the liquids producing two sections about equally divided. The chloroform holds part of the alcohol, and the water the rest of it. However, the hydro-alcoholic layer above the line holds some chloroform in solution and the chloroformic-alcoholic layer below the line holds some water, so that in the equilibrium that is established, all the liquids are partly represented in both sections. This is also exhibited in the separation shown in Tables V and VI, when the water is added to the clear liquid.

Process of Establishing Solubilities.

Where liquids have no solvent affinity whatever, for example liquid petrolatum versus either water or glycerin, a mixture of them in any possible proportion, separates, on standing, each in its full amount. But, if they mutually coalesce, even slightly, the only satisfactory method to determine their solubilities appears to be to add one liquid, drop by drop, to a given bulk of the other, shaking well after each addition, until finally, milkiness follows. To establish reverse solubility, reverse the liquids. This is, in our experiments, accepted as establishing the solvent point of each for the other, the decision being *not from the increase in bulk of the mixture*, but from the amount of the respective liquids added. Here, too, care must be employed to establish the temperature with exactness, if a record of proportions is made.

Change of Location of Line of Demarcation No Criterion of Solubilities.

The change in position of the line of demarcation does not show the proportion dissolved where two liquids are shaken together, and allowed to separate. The division line then locates itself between the *balanced* new liquids. Although each has dissolved much of the other, the meniscus of separation may be on or near the original line.

Example. If 2 Cc. of alcohol, 2 of water and 2 of chloroform be mixed, the line of separation will be at $5^1/_2$, indicating that the chloroform has dissolved $2^1/_2$ parts, which would make it take $^1/_2$ part of water. (Fig. 10.) The fact is, however, that most of the water is in the upper layer. Again, take liquid petrolatum and the mixture of Table VII. The addition of liquid petrolatum, drop by drop, demonstrated the solution of $^1/_{16}$th its bulk. But if we mix equal amounts (5 Cc. each), on separation the liquid petrolatum *rises* $^3/_4$th Cc., which would indicate that it was not at all soluble in the liquid that had previously been shown to dissolve it.

Perhaps a more forcible exhibition of such a disturbance is shown in Table IV and "Breaking the Combination," where, in a transparent compound of 24 Cc.,

[21] The separation of dissolved solids may be very slow when the solution is cooled below their saturation point. Liquids separate almost instantly. Very slight temperature alterations produce immediate sectional disturbances. The temperature change between opalescence and transparency may be too slight to affect the ordinary thermometer.

the addition of 2 Cc. water produced nearly an equal division. Since the water is mainly in the upper layer, it apparently dissolved many times its bulk of the liquid. In reality, it became a disturber, breaking the equilibrium of the complex solution, taking its place as a part of the section with which it chiefly affiliated. Very difficult would it be to establish the exact amount of the integral constituents in either section.

Apply now the foregoing to the series of solvents considered in this paper, beginning with No. 14, liquid petrolatum. It is found that on mixing two parts of each, when the sulphuric ether and acetic ether are successively added, the mixture clouds (see Table V). Then, until the water (No. 2) is reached, the solution is transparent, but on addition of two parts of water, separation ensues, the lower layer consisting of *four* parts instead of two, as might possibly be expected (two parts of water having been used) if division lines were our guide. Continuing the addition of successive portions of water for a reasonable time, it is seen that there is a nearly uniform increase of the lower layer over the two parts of water added, as is shown by the following table:—

2 parts water produce about	4 parts.
4 parts water produce about	6 1/2 parts.
6 parts water produce about	9 parts.
8 parts water produce about	11 1/2 parts.
10 parts water produce about	14 parts.

Finally, if carried far enough, the addition of water results practically in the separation of only the proportion added.

In these examples, the equilibrium established after the water was added, resulted in the formation of two liquids that changed in constitution with each addition of the single substance, water. Simultaneously the solvent power of the sections altered, as is shown by the varying proportions (Movement of Meniscus) that result while the additions were being made. Finally, the members of the third class, especially liquid petrolatum, are nearly separated from the members of the first class, especially glycerin and water, while the intermediate members arrange themselves according to their affinities, in varying proportions in the two layers. After this, the addition of water can not decrease the upper layer, and upon the other hand liquid petrolatum in any amount can not dissociate the lower layer.

An Endless Series of Solvents Produced by Neutral Solvents Combined with Plant Constituents.

Whenever we abstract what is apparently a single substance from a plant, by means of water or alcohol, we form at the same time, as the solution progresses, a series of new solvents, having successive powers of abstracting other plant constituents. Thus are formed a continuously changing line of new liquids, that may be of as many different qualities as it is possible to vary the proportions of the original liquids (resulting from solution of solids), these becoming *new* solvents, in their subsequent action on the soluble plant materials.

Each solid substance that the menstruum dissolves, becomes in turn a part of a new liquid, which is then a thing in itself, and may itself dissolve another substance, insoluble in the original menstruum, thereby forming a menstruum quite different from either of the preceding, and which is capable of dissolving a third substance, a new liquid springing thus into existence with each successive change. No solid body is present at any time after the solution has formed, and yet the *solution of a solid* produces each new solvent.[22] We have a mixture of liquids possessed of individual solvent qualities, as much so as though we had mixed various liquids such as ether and water. Finally, the last liquid formed may not be able to hold in solution a substance that, originally dissolved, constituted a part of the first liquid. This body may then in part be thrown out of solution, resuming the solid form as a precipitate. In so doing, it alters the attributes of the solvent and starts a chain of *backward* reactions and precipitations. Such a "*separate*"[24] may be either liquid or solid. It may rise to the surface, or it may subside. It may be visible (solid), or invisible (liquid). It may be mucilaginous or gelatinous, as transparent as the medium it rests in, but yet not a true liquid or a pronounced solid.[24] As this "backward" reaction follows, chains of alterations and precipitations result, so familiar to persons perplexed by ever-altering plant solutions. Bold must be the man who announces that he comprehends the interchanging rearrangements continuously taking place in a solution of associated plant constituents, seemingly stable and apparently quiescent.

Our three classes of menstrua, with their fourteen numbers (see Table I) thus afford *in themselves*, as various proportions are used, the possibility of an infinite line of combinations. The successive liquids, produced by means of varying abstractions of the constituents of a single plant, may also dovetail into chains of compound solutions in which lines of separation are lost as these substances coalesce, each into the others. In this field, no recorded experiences govern us. The explorer has not attempted even to systematize the various phases of the problem, as applied to the principal constituents of a single known drug, acted upon as a whole by any compound menstruum, indeed, by any simple liquid.

But before we attempt to suggest specific application of these possibilities to plant pharmacy, we need consider an as yet seemingly incidental, but yet all-important and striking feature of this series of experiments, *viz.*, *the plane of separation* (meniscus) between the separated classes of solvents. This study (meniscus) dovetails into and introduces *Capillarity*, one of the most vital influences in the practical application of pharmacy to plant preparations, but as yet totally neglected.

Addenda, 1917—In various directions, necessarily unmentioned, this writer has (since 1885) applied most pleasurable research, the results having been recorded in fragmentary manuscript form during the passing years. He hopes to be permitted to contribute to our Society next year a continuance of these old-time investigations, the same being localized on phenomena connected with capillarity,—the meniscus, surface films, what he denominates as the pendant drop (see the upper A, Fig. 4, and pendent drops A-B, Fig. 9), and "mass action" (term used originally) and physical influences connected with pharmaceutical problems. Let us then pass to the *Meniscus*.

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[22] This phenomenon is not restricted to plants, or plant products. See "Precipitates in Fluid Extracts," *Am. Pharm. Assn. Proceedings*, 1879–1885.

[23] This term may be considered very expressive of this reaction.

[24] In my opinion opportunities will be afforded researchers of the future to *see* the at present *invisible*. I can not but believe, for example, that there are zones, or emulsion surfaces, now *invisible*, but which yet will be *seen* by methods now unknown. This conclusion is furthered by the study of oils. Consider, as an example, the practically invisible globulus of tapioca in some forms of soup, enveloped in oil, water and mucilage.