ingly, the kinetic current is expected to be greater for *N*-nitrosoephedrine than that for *N*-nitrosopseudoephedrine. The experimental results confirm this view. In addition, these results suggest that intramolecular hydrogen bonding occurs in both diastereoisomers in dilute aqueous solution, and that the NNO, OH gauche conformation is important in both compounds.

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Coating Pharmaceuticals by Coacervation

By RUSSELL E. PHARES, JR., and G. J. SPERANDIO*

The objectives of this study were to investigate the phenomenon of coacervation as a new means of coating pharmaceuticals and to develop procedures of operation for coating some commonly used drugs. Factors affecting coacervate drop size, some methods of regulating coating thickness, and techniques of controlling the volume of the coacervate produced were determined. Using sodium sulfate solutions and gelatin solutions as the coacervating liquids, five solids and two liquids were coated and processed to produce dry powders.

THE OBJECTIVES of this project were to investigate the phenomenon of coacervation as it is related to the coating of pharmaceuticals and to originate and develop procedures for coating pharmaceuticals by coacervation.

Coacervation is a phenomenon associated with colloidal solutions. A colloidal system is commonly defined as a two-phase system in which one phase is a continuous liquid, while the other phase is a solid which is highly dispersed throughout the liquid as particles ranging in size from 0.001 to 0.5 μ. This definition has been extended to include any (micro) homogeneous system containing colloidal particles or structures derived from them, so that systems containing kinetic units smaller than 0.001 μ may still be considered colloids (1).

In a true solution of macromolecules, that is, a system containing kinetic units smaller than 0.5 μ, certain changes—such as changes of temperature or pH or the addition of substances—can produce a reduction in solubility that will cause a large part of the macromolecules to separate into a new phase. This colloid-rich phase may exist either in a high or low state of dispersion. When a system contains a colloid-rich phase in a low state of dispersion, it is possible to distinguish microscopically and macroscopically between crystallization and coacervation, which is the formation of amorphous liquid drops. These liquid drops constitute the coacervate and under favorable conditions will coalesce in a matter of hours into one clear, homogeneous liquid layer known as a coacervate layer (1).

Coacervates will, in general, accept and surround drops of organic liquids which are immiscible with water, as well as insoluble solid particles, when they are offered in the equilibrium liquid (1). It is this ability of coacervates to coat insoluble materials present in the equilibrium liquid that makes it a method of microencapsulation. "Simple" coacervation as a coating method has been shown to be economically feasible by the National Cash Register Co., Dayton, Ohio,

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which produces oil-containing capsules for use in making "carbonless carbon paper" (2–4).

EXPERIMENTAL

Since references to previous pharmaceutical investigations of coacervation as a coating method could not be found, it was often impossible to plan entirely all phases of this work in advance. Many facts which are related to one phase of the work were discovered while working on another aspect of the problem. In this report all experiments and their results have been arranged for the convenience of the reader and therefore are not necessarily presented in the order in which the work was actually done.

In all the experimental investigations, gelatin (Type *A*) solutions were used as the solution of macromolecules. In the first set of experiments the gelatin solutions were coacervated with alcohol. The effects produced by varying the amount of gelatin in a coacervated system while keeping the ratio of water to alcohol constant were first determined. Ten grams, 5 Gm., and 2.5 Gm. of gelatin were each dissolved in 50-ml. portions of distilled water at 50°, and each solution was then coacervated by adding a mixture of 50 ml. of distilled water and 100 ml. of alcohol. After the coacervated systems lwhich were stored at 50°) had separated into two ayers, the only noticeable differences between them were the volumes of their coacervate layers. These volumes varied directly with the amount of gelatin used in the preparation of the original systems.

Experiments in which a constant ratio of gelatin to distilled water was maintained while the amount of alcohol was varied were performed next. The noticeable differences between the systems were again the volumes of the coacervate layers, which in this experiment varied inversely with the volume of ethanol used. A variation in the viscosities of the coacervate layers was also noticed. This variation was directly proportional to the volume of alcohol used in the original systems.

The conditions in the above experiments can be represented on Kruyt's (5) phase diagram for the system gelatin, water, and alcohol (Fig. 1). Line *AE* on the diagram represents all systems having a ratio of ethanol to water of 1:1, and line *DB* represents all systems having a ratio of gelatin to water of 1:19. The farther a point such as *V* is from side *c* of the curve, the smaller will be the proportion of coacervate phase produced in the system that the point represents. Since point *V* lies farther from curve *c* than does point *W*, the system represented by *V* should have less coacervate phase than does the system represented by *W;* and since point *V* represents a system containing a smaller amount of gelatin than does point *W*, the theoretical and experimental results are in agreement. Similarly, it can be seen that the theoretical and actual results for the second experiment are in agreement.

In another series of experiments, factors influencing the size of coacervate drops were studied. The diameters of the coacervate drops were measured using a microscope with a calibrated eyepiece. As soon as a system had been coacervated, it was cooled in an ice bath until it was below 25°. The capsules were thus gelled to prevent the coacervate drops from coalescing on the microscope slide before their size could be measured.

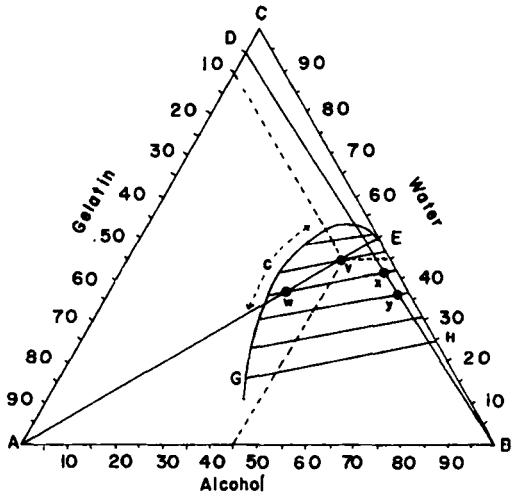

Fig. 1.—Phase diagram of gelatin, water, and alcohol (5).

The proportion of ingredients in a coacervate system had little if any effect on the size of coacervate drops, but the material added to cause gelatin solutions to coacervate could have an effect. When alcohol was added to a gelatin solution, coacervate drops which had a modal diameter of 30–35 μ were formed. Ethanol containing as little as 1% dissolved aspirin produced drops having a modal diameter of 2–3 μ. Solutions of sodium sulfate also produced coacervate drops having a modal diameter of 2–3 μ. Other salt solutions gave the same results as the sodium sulfate solutions. When coacervate drops that had been permitted to coalesce into a single layer were reformed by gentle shaking, they had the same modal diameter as those in a freshly coacervated system. The temperature at which gelatin solutions were coacervated also had an effect on the size of the resulting coacervate drops. As the temperature was raised above 50°, the coacervate droplets became smaller; as the temperature was lowered below 50°, the droplets increased in size.

It is felt that the size of coacervate drops is dependent upon the interaction of many complex physical properties of the entire coacervate system and therefore cannot be attributed to a single controllable factor. The interfacial tension of a coacervated system appeared to have an important effect on the size of coacervate drops; by controlling this property, one may be able to regulate the size of the drops.

Experiments showed that when insoluble drugs were present in a coacervated system, the coacervate drops would surround the suspended particles. When the coacervate drops were gelled by cooling, encapsulation of the drug was complete.

Recovery of the gelled capsules offered considerable problems. Many different filter media were tried, using both gravity and suction filtration; but the gelatin capsules always clogged the pores of the filters. The only successful method of recovering the capsules was to allow them to settle from the surrounding liquid for several hours in a closed container. After the capsules had settled, the upper phase could be decanted.

When the recovered capsules were allowed to air

dry, a very hard, solid mass resulted. Many samples of capsules were washed with cold water, alcohol, formaldehyde, and various proportions and combinations of these materials, but with only occasional—and not necessarily reproducible—success. Treatment with a combination of formaldehyde and alcohol produced a desirable product. The best procedure was to add 1 ml. of formaldehyde to each milliliter of capsules and stir the mixture for 5 minutes. Two milliliters of ethanol were then added for each milliliter of formaldehyde which had been used, and the entire system was stirred for 5 more minutes. The large white floccules which had occurred upon the addition of the alcohol were next removed by gravity filtration through filter paper. Upon drying, the filter cake could be easily crumbled into a fine powder which was washed in a large volume of cold water and again filtered and dried.

The final phase of this study was concerned with actually coating pharmaceuticals and obtaining them as dry powders. The procedure consisted of preparing a solution containing 11 Gm. of sodium sulfate and 45 ml. of distilled water at 37° and another solution containing 4 Gm. of gelatin and 40 ml. of distilled water at 37°. The material to be coated was then thoroughly suspended or dispersed in the warm gelatin solution. Coacervation was effected by the addition of the sodium sulfate solution with stirring. After the coacervated system had been thoroughly mixed, it was cooled by immersion in an ice bath at 10° and stirring steadily until the temperature of the mixture was below 30°. The system was covered with aluminum foil, and the capsules were permitted to separate from the equilibrium phase by gravity. The gelled capsules were then recovered as a dry powder by the method previously described.

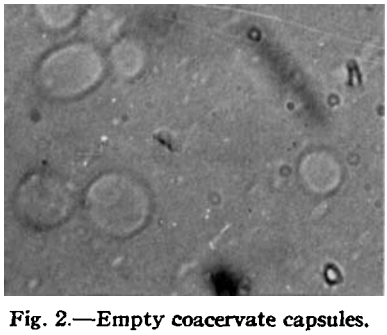

Fig. 2.—Empty coacervate capsules.

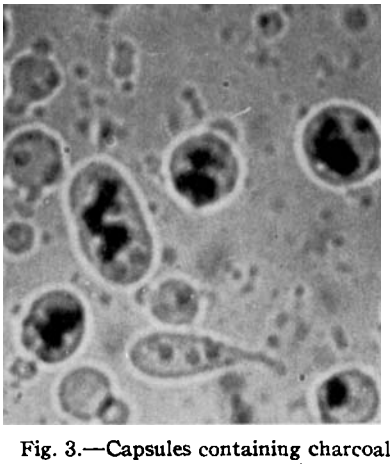

Fig. 3.—Capsules containing charcoal.

The following pharmaceuticals were coated and recovered as fine powders: riboflavin, cod liver oil, procaine penicillin G, carbon tetrachloride, charcoal, micro-ion-exchange resin, and castor oil. Aspirin and acetanilid could not be coated by this method because they were both incompatible with the system being used.

Aspirin was successfully coated and recovered as a fine powder, however, by using a modification of the above system. Two and five-tenths grams of aspirin were suspended in a solution containing 1 Gm. of gelatin and 50 ml. of distilled water at 37°. This system was then coacervated by the addition of 28.5 ml. of distilled water which contained 13 Gm. of sodium sulfate. The aspirin-containing coacervate drops which were produced were gelled and recovered as a powder by the method previously described.

Acetanilid was coated by suspending 1.5 Gm. in a solution containing 1 Gm. of gelatin and 25 ml. of distilled water at 37°. This system was then coacervated by adding 10 Gm. of sodium sulfate dissolved in 50 ml. of distilled water at 37°. The resulting coacervate drops, containing acetanilid, were gelled and recovered as previously described.

During the coating experiments it was noticed that the size of the encapsulated materials had an effect on the diameter of the gelled coacervate drops. By comparing Fig. 2 (which is a photomicrograph of empty coacervate capsules) with Fig. 3 (which shows coacervate capsules containing charcoal) and with Fig. 4 (which shows coacervate capsules containing riboflavin), the effect of "particle" size can be seen. Small coacervate drops like those in Fig. 2 are able to coalesce and form larger drops which will encapsulate large particles or cohering small particles. This phenomenon can be seen in Figs. 3 and 4. Whenever particles smaller than the coacervate drops are present, they are coated singly or as groups without any increase in coacervate drop size. This can be seen in the case of some charcoal particles in Fig. 3.

SUMMARY AND CONCLUSIONS

1. The objectives of the work were to investigate the phenomenon of coacervation as it is related to the coating of pharmaceuticals and to originate and develop procedures to be employed when coating pharmaceuticals by coacervation.

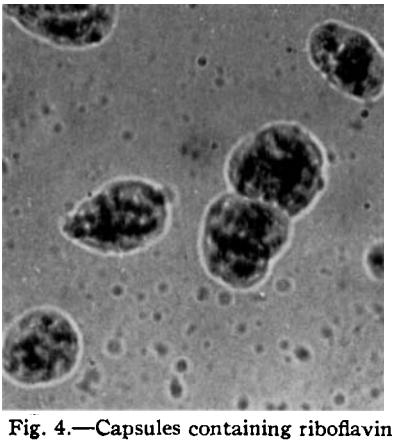

Fig. 4.—Capsules containing riboflavin.

2. A preliminary investigation revealed that many different compounds could be used to coacervate gelatin solutions.

3. By varying the proportion of the components of a coacervate system, the amount of a coacervate phase and/or the composition of a coacervate could be controlled.

4. Almost any insoluble particle can be coated with coacervate drops.

5. Of all the variables investigated, it appeared that only those that affected interfacial tension had an effect on coacervate drop size.

6. Pharmaceuticals can be coated by coacervation, but they may intensify the degree of coacervation.

7. A process was originated for obtaining coacervate-coated pharmaceuticals as fine, dry powders.

8. The following pharmaceuticals were coated and recovered as fine, dry powders: riboflavin, cod liver oil, procaine penicillin G, carbon tetrachloride, charcoal, a micronized ion-exchange resin, castor oil, aspirin, and acetanilid.

9. Coacervation not only seems to be an effective method of coating pharmaceuticals but also a superior method of coating many drugs.

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Preparation of a Phase Diagram for Coacervation

By RUSSELL E. PHARES, JR., and G. J. SPERANDIO*

The objective of this study was to develop a method of preparing a phase diagram of coacervated systems using physical measurements instead of chemical analyses. The per cent weight-in-weight concentration of three-component solutions of micro and macromolecules was related to the refractive indexes and specific gravities of the solutions by an algebraic equation. The composition of both phases of several different coacervated systems was determined by using the derived equations. By making accurate quantitative dilutions, it was also possible to determine the composition of solutions the specific gravity of which did not remain linear because of a high concentration of electrolyte. This study indicates that the points needed for plotting a phase diagram (including tie lines) of three-component systems can quickly and accurately be determined by using measurements of specific gravities and refractive indexes.

Most of the quantitative assay procedures currently available cannot be universally adapted to three-component systems without separating the components. The procedure of Leach and Lithgoe, as corrected by Williams (1, 2), for the determination of the percentage composition of a solution of water plus methanol plus ethanol could be very useful if it were not for the need of preparing extensive tables. If this technique, which uses specific gravity and refractive index, could be improved to eliminate the need of tables, it would be useful not only for the analysis of alcohol but also for obtaining the data necessary for plotting three-component phase diagrams. The role of phase diagrams in pharmacy will become increasingly important as coacervation, which was recently introduced as a pharmaceutical operation (3), is used as a means of obtaining many improved pharmaceuticals.

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The purpose of this work was to develop a simple method of preparing a three-component phase diagram which would eliminate the need for complicated chemical assays of the ingredients. It was felt that the per cent weight-in-weight concentration of a solution of three components could be calculated directly from the experimentally determined specific gravity and refractive index of the solution without using tables.

THEORY

The weight-in-weight composition of an ideal three-component solution in which there is no interaction may be represented by

$$m + n + p = 1 \qquad \text{(Eq. 1)}$$

where m, n, and p represent the grams of solvent, ingredients 1 and 2, respectively, per gram of solution. Therefore

$$m = 1 - n - p \qquad \text{(Eq. 2)}$$

The refractive index of the solution can be written

$$\text{R.I. of solution} = \text{R.I. of solvent} + Cn + Dp$$

or

$$p = (\Delta\text{R.I.} - Cn)/D \qquad \text{(Eq. 3)}$$