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MICROENCAPSULATION

I. PHASE SEPARATION OR COACERVATION

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ABSTRACT

Phase separation or coacervation is one of the oldest and perhaps the most widely used method of microencapsulation. This paper discusses phase separation or coacervation as a technique of preparing microcapsules. The basic differences between simple and complex coacervation are described and the various factors which influence simple and complex coacervation are discussed. Schematic ternary phase diagrams involved in the phase separation or coacervation processes are included and the basic schemes describing the process of microencapsulation are outlined.

INTRODUCTION

Microencapsulation is not a new process. The concept of microencapsulation has been known for many years, but it has received increasing attention only in recent years.

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TABLE I

INDUSTRIAL APPLICATIONS OF PHASE SEPARATION (COACERVATION) TECHNIQUES

COMPANY	PROCESS
American Agriculture Co.	Aqueous Phase Separation
Fabergelene	Aqueous Phase Separation
IBM	Organic Phase Separation
Moore Business Forms	Spray Drying
National Cash Register	Coacervation
National Cash Register	Meltable Dispersion
National Cash Register	Organic Phase Separation
National Starch and Chemicals	Spray Drying
North American Phillips Co.	Fluidized Bed Spray Drying
Polaroid	Aqueous Phase Separation
U.S. Plywood-Champion Paper Inc.	Organic Phase Separation

Although the concept of encapsulation has been considered and practiced to some degree by several industries for many years, the literature on microencapsulation is not extensive. This is because most of it comes from company brochures or U.S. patents.

Microencapsulation is a process which involves the enclosure of a solid, liquid, or gas in a shell or a membrane. The shell or the membrane is usually of an inert nature and the re-

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sulting product is known as microcapsules. Although most microcapsules range in diameter between 5 and 500 microns, it is possible to prepare microcapsules which may be less than one micron in diameter or may be as large as 0.5 mm in diameter.

The technique of microencapsulation has gained popularity primarily because of its potential applicability in a wide variety of situations. In the pharmaceutical industry, microencapsulation is used for:

(i) sustained or prolonged release of drugs, e.g., aspirin

(ii) taste-masking of bitter drugs, e.g., acetyl-p-aminophenol

(iii) masking of unpleasant odors

(iv) elimination of incompatabilities, e.g., eutectic substances

(v) stabilization of drugs sensitive to oxygen, light, moisture, etc., e.g., vitamins A and K

(vi) preparation of free-flowing powders

(vii) prevention of vaporization of volatile drugs

(viii) modifying the physical properties of chemical entities, e.g., oils may be encapsulated to produce free-flowing powders

(ix) facilitating the dispersion of one substance in another, e.g., to stabilize emulsions

(x) altering the rate of solubility of chemical reactants, e.g., to slow down the rate of a chemical reaction

(xi) reducing the toxicity, e.g., the handling of fumigants, insecticides, herbicides, and pesticides

(xii) as an aid to formulation in general

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METHODS OF PREPARATION:

Microcapsules may be prepared by a number of methods. Due to the diverse nature of the techniques involved, it is not possible to classify the methods in a rigid fashion. The methods of preparation and/or the techniques employed in these methods exhibit a large degree of overlap. One convenient classification which appears to show the minimum overlap and at the same time seems to categorize the various methods is: coacervation or phase separation, interfacial reactions, and miscellaneous mechanical methods.

COACERVATION OR PHASE SEPARATION

Coacervation is a colloidal phenomenon. In Latin acervus means heap, coacervation then means literally "heaping together" or "coming together in a heap." Chemists have used the term coacervation to describe the phenomenon of salting out or phase separation of lyophilic colloids into liquid droplets rather than solid aggregates. The term was first introduced into colloidal chemistry by Kruyt and Bungenberg de Jong to describe the flocculation or separation of liquids from solutions when at least one of the liquids contained a macromolecular or colloidal solute.

Coacervation may be distinguished from crystallization or flocculation as follows:

If one starts from a solution of a colloid in an appropriate solvent, then according to the nature of the colloid,

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TABLE II

COMPARISON OF COACERVATION WITH OTHER SIMILAR PROCESSES

PROCESS	STATE OF DISPERSION OF THE COLLOID-RICH PHASE	SYSTEM OBTAINED
Crystallization	low dispersion	Colloid crystals + dilute sol
Coacervation	low dispersion	Coacervate + dilute sol
Flocculation	higher dispersion	Floccules + dilute sol
Lyophobic sols	high dispersion	Apparent single colloid system (liquid)
Gelation	high dispersion	Apparent single colloid system (solid)
Gelation	very high dispersion	Gels

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various changes (e.g., temperature, pH, addition of certain substances) can bring about a reduction of the solubility of the colloid. As a result of the reduction of the solubility of the colloid, a large part of the colloid will separate out in a new phase. Thus, the original one-phase system divides into two phases: one rich and the other poor in colloid concentration.

The separated colloid-rich phase can appear in one of two states: in a low dispersed state or in a higher dispersed state. In the first case macroscopic or microscopic investigation allows one to distinguish between crystallization and coacervation-crystallization, when obviously crystalline individuals are formed, and coacervation, when amorphous liquid droplets are formed. The amorphous liquid droplets are called coacervate droplets which, on standing, coalesce into one clear homogeneous colloid-rich liquid layer, known as the coacervate layer.

In the case of flocculation, the separated colloid-rich phase is present in a higher dispersed state. Flocculation frequently causes a great deal of trouble and in most cases microscopic examination of the floccules may make it impossible to determine exactly the category to which the separated phase belongs.

Coacervation can be brought about in a number of different ways. For example, a change in temperature, a change of

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pH, addition of a micromolecular substance, or addition of a second macromolecular substance.

Coacervation has been classified by Bungenberg de Jong into two broad groups: simple coacervation and complex coa-

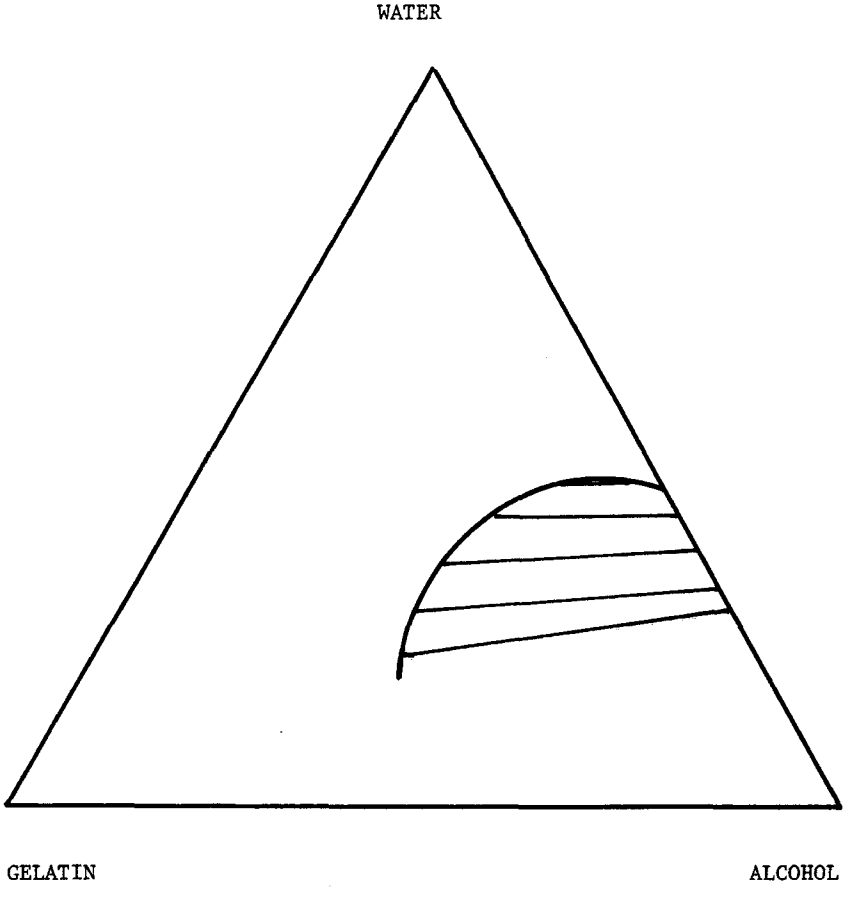

FIGURE I

SCHEMATIC TERNARY DIAGRAM FOR THE SYSTEM:

GELATIN-WATER-ALCOHOL

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cervation. The classification is based upon whether or not the ionized groups of the macromolecule play an active part in the coacervation process. Simple coacervation is concerned with the non-ionized groups in the macromolecule. It can

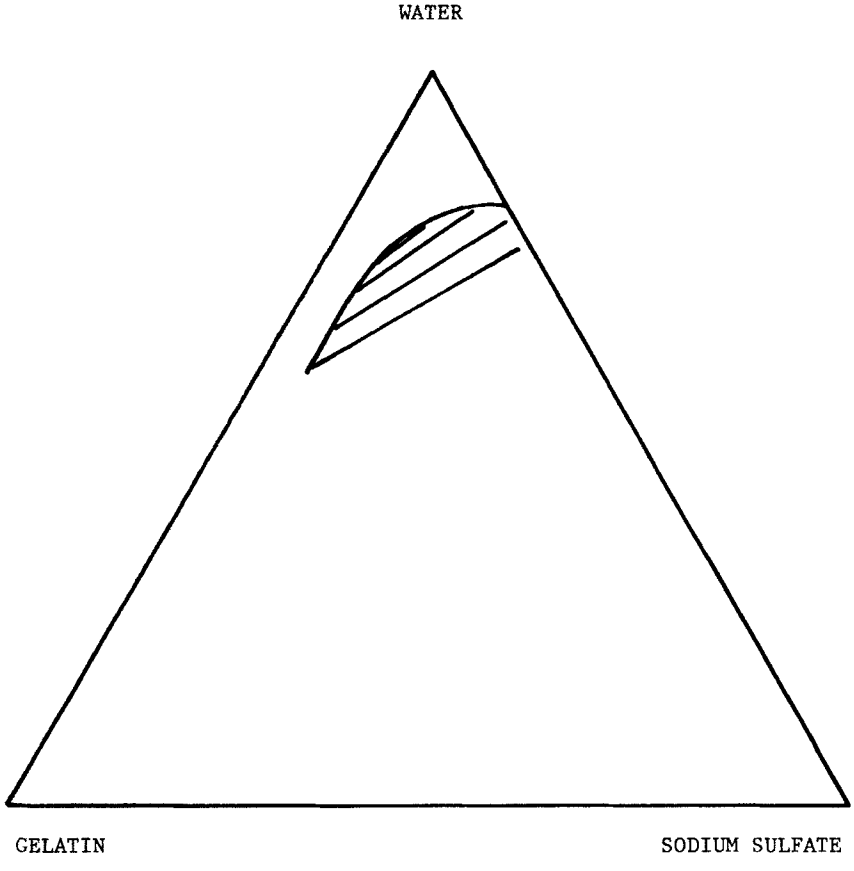

FIGURE 2

SCHEMATIC TERNARY DIAGRAM FOR THE SYSTEM:

GELATIN-WATER-SODIUM SULFATE

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be brought about by a reduction in the solubility of the macromolecule and the associations deriving from it. Complex coacervation is concerned with the charges and consequently with the formation of salt bonds associated with the macromolecules. In general, simple coacervation usually deals

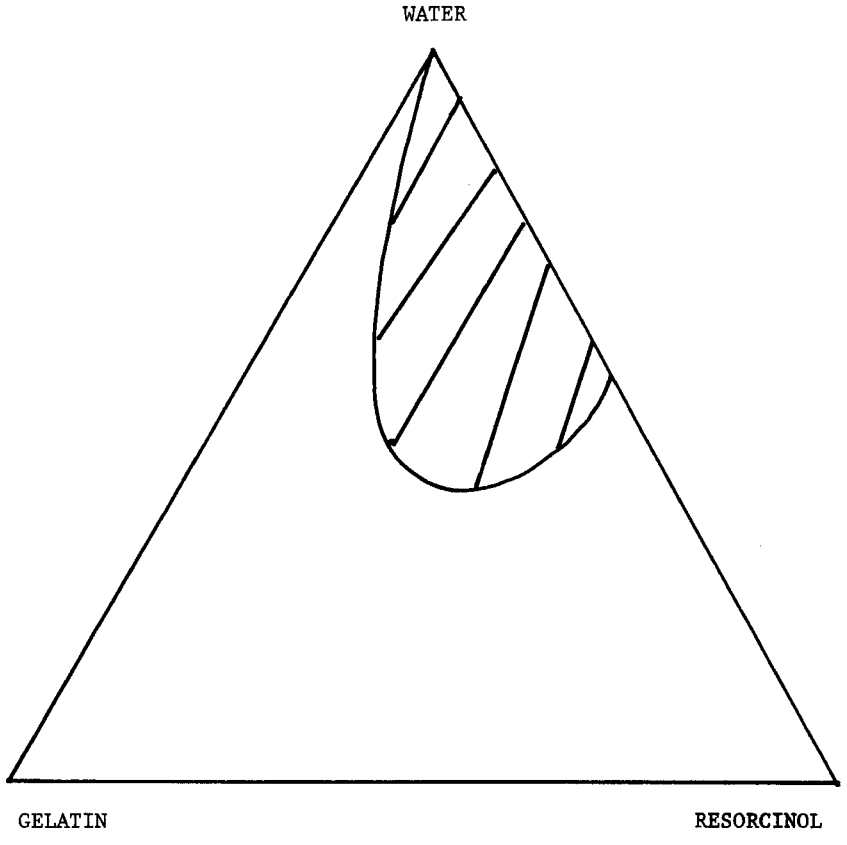

FIGURE 3

SCHEMATIC TERNARY DIAGRAM FOR THE SYSTEM:

GELATIN-WATER-RESORCINOL

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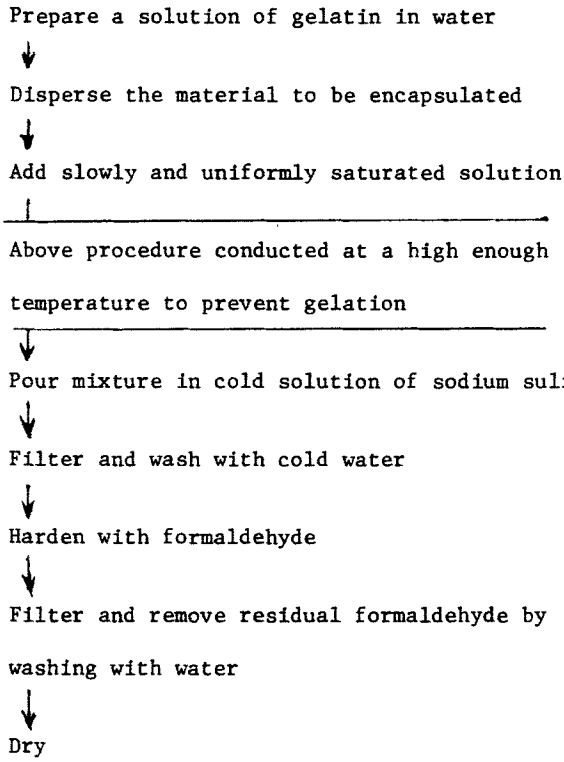

SCHEME I: MICROENCAPSULATION BY COACERVATION - SALT COACERVATION PROCESS

with systems containing only one colloidal solute and complex coacervation almost always deals with systems containing more than one colloid.

SIMPLE COACERVATION

Simple coacervation can be effected either by mixing two colloidal dispersions, each of which contains a colloid in a concentration from approximately 20 to 40 per cent and one of

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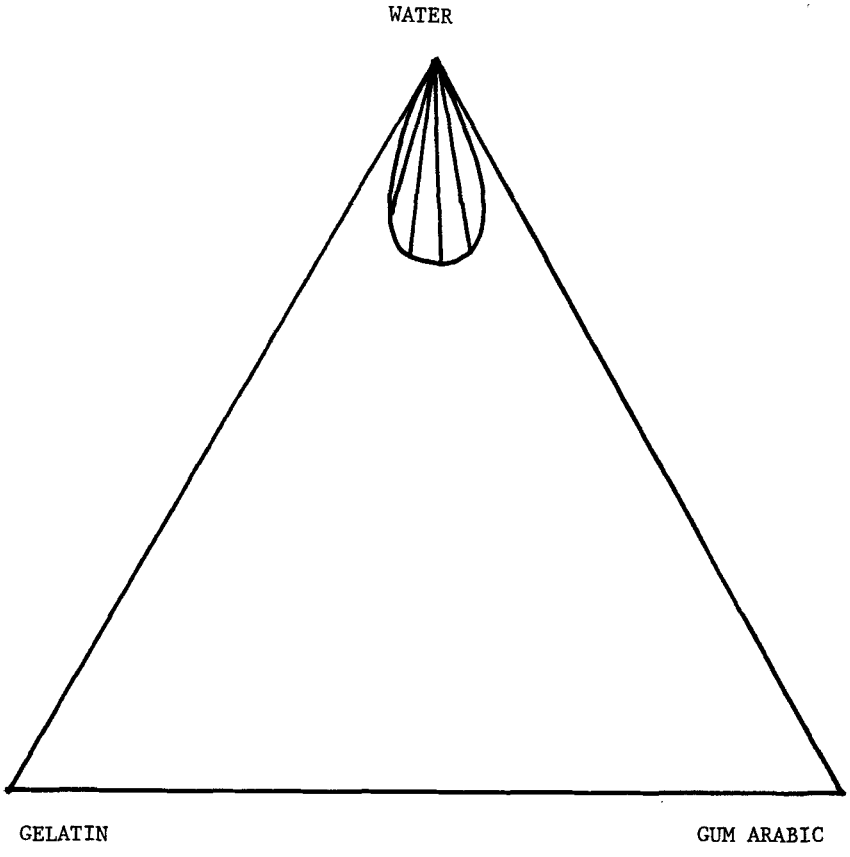

FIGURE 4

SCHEMATIC TERNARY DIAGRAM FOR THE SYSTEM:

GELATIN-WATER-GUM ARABIC

which has a high affinity for water; or it can be induced in a dispersion of a less concentrated single colloid by the addition of a strongly hydrophilic substance such as alcohol or sodium sulfate. The addition of a hydrophilic substance causes

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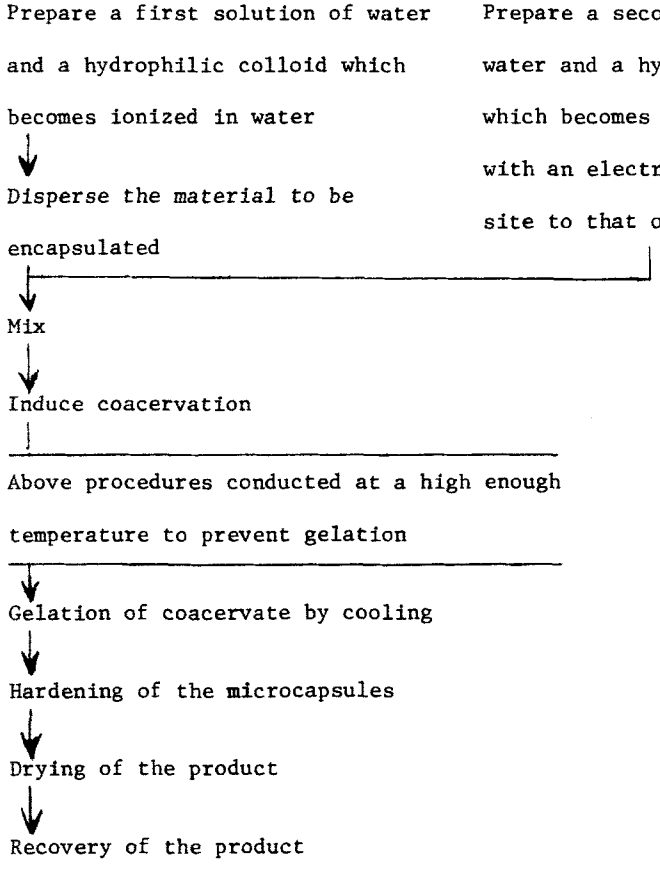

SCHEME II: COMPLEX COACERVATION - GENERAL OUTLINE

two phases to be formed, one rich and the other poor in colloidal materials. Simple coacervation depends primarily on the degree of hydration produced and it is possible to redisperse the aggregated colloidal droplets by addition of water. The principle requirement here is the creation of an insufficiency of water in a part of the total system since neither the isoelectric

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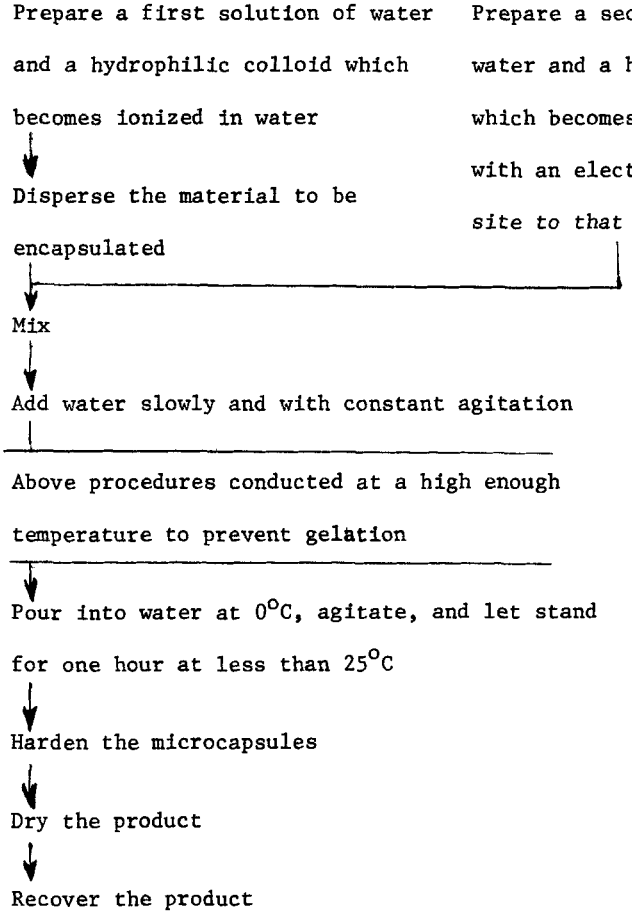

SCHEME III: MICROENCAPSULATION BY COACERVATION - DILUTION WITH WATER

point of the colloids nor the presence of indifferent salts appear to be of any significance to the process.

The most commonly employed simple coacervation procedures utilize gelatin as the wall-forming material. In a system consisting of gelatin and water, coacervation is brought about

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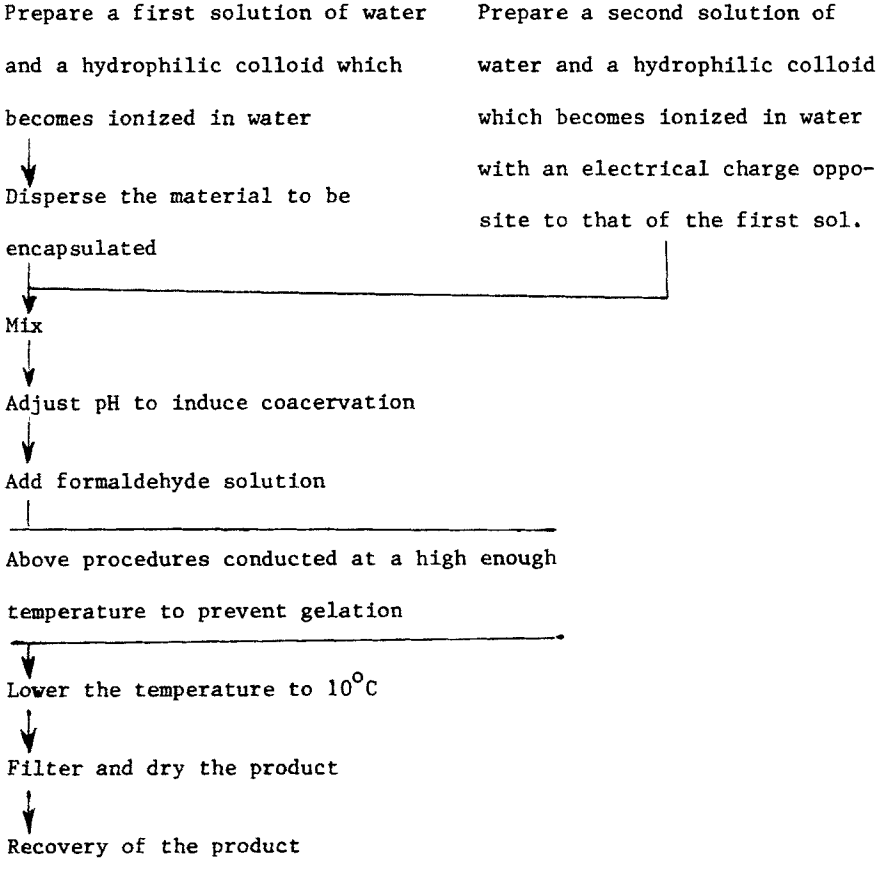

SCHEME IV: MICROENCAPSULATION BY COACERVATION - pH CONTROL

by the addition of a third component which may be any one of the following:

(a) alcohol: unpublished data from this laboratory indicate that a variety of alcohols, e.g., methanol, ethanol, propanol, isopropanol etc., may be used

(b) sodium sulfate

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(c) ammonium sulfate

(d) macromolecules, e.g., starch

(e) phenol

(f) diphenols, e.g., catechol, resorcinol, hydroquinone

(g) triphenols, e.g., pyrogallol, phloroglucinol

(h) digalloyl glucose

(i) chebulic acid

(j) tannic acid

COMPLEX COACERVATION:

Complex coacervation has a number of characteristic features, but depends primarily on pH. It can be induced in systems having two dispersed hydrophilic colloids of opposite electrical charges. Bungenberg de Jong studied phase separation in colloids by mixing aqueous solutions of gum arabic and gelatin. Phase separation was produced at pH values below the isoelectric point of gelatin, but not above this pH. Phase separation also occurred in other systems containing two dispersed colloids, one of which was ampholytic. In either case, one phase contained most of the two polymers combined with a small amount of solvent, and the other phase was often a very dilute solution of one or both the polymers.

The process of complex coacervation using gelatin and acacia has been explained by Bungenberg de Jong. He states that with gum arabic, a carbohydrate carrying carboxyl group, and gelatin, a protein carrying both carboxyl and amino groups, complex coacervation is possible only at pH values below the

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isoelectric point of gelatin since it is at those pH's that gelatin becomes positively charged, while gum arabic continues to be negatively charged. The optimum pH for complex coacervation was that pH at which equivalents of oppositely charged molecules were present, since at that point the greatest possible number of salt bonds were formed and the highest degree of coacervation occurred. In such a system, therefore, the pH is adjusted so that the gelatin particles are positive, while the gum arabic particles remain negative. Lowering the pH beyond this can suppress the dissociation of the carboxyl groups of gum arabic.

The tendency towards coacervation was found to be decreased in the presence of electrolytes, since the charged groups on the colloids are screened by the formation of dense ionic atmosphere around each charge, thereby diminishing the interactions and hence the attractions between the charged groups. This effect is more pronounced in the presence of electrolytes or ions of higher valency. It is obvious that this effect will be dependent upon the valency of the added ions. The suppresive action is seen to increase with the valency of the added ions and the suppression of coacervation by salts therefore should follow a Schulze-Hardy rule both with respect to the cations and to the anions.

$4-1 > 3-1 > 2-1 > 1-1$: valency rule of the cations, and

$1-4 > 1-3 > 1-2 > 1-1$: valency rule of the anions.

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MECHANISM OF MICROCAPSULE FORMATION:

Three mechanisms have been suggested for the formation of microcapsules by the method of coacervation: (a) individual coacervate droplets may be drawn to and coalesce about particles immiscible in the system, or (b) a single coacervate droplet may encompass one or a group of immiscible nuclei, or (c) the microcapsule wall may be formed as a result of a molecular interaction between the colloidal marco-molecule particles.

Encapsulation processes using coacervation can therefore be summarazied as taking place in a series of four steps: (a) establishment of a system, with liquid vehicle containing the coating materials as a continuous phase, and material to be coated as dispersed phase; (b) changing the solvent characteristics of the polymer solution such as to cause phase separation of the wall material, (c) deposition of the liquid wall material as a continuous coating about the dispersed material to be coated; (d) hardening of the polymeric coating material. For microencapsulation to occur, adsorption of the wall material on the material to be coated is an essential prerequisite. Solidification of the wall material can be accomplished in a variety of ways including addition of non-solvent or phase-inducing polymer, further change in pH, reduction in temperature, or by chemical reactions involving cross linking, chelation, etc.

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TABLE III
NON-AQUEOUS PHASE SEPARATION

WALL-FORMING POLYMER	SOLVENT (S)	COMPLEMENTARY SUBSTANCE FOR INDUCING PHASE SEPARATION
Acrylonitrile-styrene copolymer	Methyl ethyl ketone	Polybutadiene
Acrylonitrile-styrene copolymer	Methyl ethyl ketone	Polydimethyl-siloxane
Cellulose nitrate	Methyl ethyl ketone	Polybutadiene
Cellulose nitrate	Nitropropane	Metlacrylic polymer
Epoxy resin	Toluene	Polybutadiene
Ethylcellulose	Toluene-ethanol	Polybutadiene
Ethylcellulose	Methyl ethyl ketone	Polybutadiene
Ethylcellulose	Methyl ethyl ketone	Polydimethyl-siloxane
Polymethyl methacrylate	Methyl ethyl ketone	Polydimethyl-siloxane
Polymethyl methacrylate	Benzene	Polydimethyl-siloxane
Polystyrene	Benzene	Polydimethyl-siloxane
Polyvinyl-formal	Nitropropane	Polybutadiene
Vinylidene chloride-acrylonitrile copolymer	Methyl ethyl ketone	Polybutadiene

NON-AQUEOUS PHASE SEPARATION:

The foregoing discussion has been restricted to the coacervation process involving microencapsulation of water-insoluble substances. This has been referred to as "Aqueous Phase Separation." When the substance to be encapsulated is water-soluble, the technique of "Non-Aqueous Phase Separation" is employed. In this technique the continuous wall-containing phase is organic or hydrophobic in nature and a suitable combination of organic solvents or polymers are used to induce phase separation.

In order to effect non-aqueous phase separation, an emulsion consisting of the aqueous dispersed phase containing the material to be encapsulated is prepared in the organic continuous phase containing the organic polymeric wall material. Microencapsulation of the aqueous phase is achieved by inducing phase separation from the organic phase. This may be achieved by the addition of a suitable second organic solvent which must be miscible with the first organic solvent but must be a non-solvent for the polymer. Thus, due to the decreased solubility of the polymeric wall material in the new solvent system, the wall material is forced to phase out and forms a film around the aqueous droplets.

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