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3,748,277

PROCESS OF FORMING MINUTE CAPSULES

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24 Claims

ABSTRACT OF THE DISCLOSURE

A process for forming minute capsules in a manufacturing vehicle which comprises (a) establishing an agitated system consisting of a liquid vehicle constituting a major portion of said system by volume and forming a continuous liquid first phase, a second phase dispersed in said liquid vehicle consisting of minute, mobile entities of core material, and a third phase dispersed in said liquid vehicle consisting of minute, mobile, non-aqueous, liquid entities of a wall-forming solution of a polymeric material having a viscosity such that said solution of wall-forming polymeric material maintains itself about the core material in the agitated system, the said core material being wettable by said wall-forming solution and the said three phases being mutually incompatible, whereby said wall-forming solution deposits on and around said core entities to form a continuous liquid protective wall, and (b) subsequently hardening the walls so formed.

This application is a continuation-in-part of U.S. patent application Ser. No. 781,918, filed Dec. 22, 1958, by John G. Wagner, and now abandoned.

This invention relates to a process for providing a protective coating or capsule wall for a wide variety of materials and more particularly to a process for providing a protective coating for liquid and solid nucleus or core materials in a liquid manufacturing vehicle through establishment of a three phase system, one phase of which is a coacervate solution of a wall-forming polymer in an organic liquid, and to the coated core material provided thereby. Further, this invention relates to a process of manufacturing minute capsules en masse in an organic liquid manufacturing vehicle and to the capsule product, each capsule comprising a core and a seamless protecting wall surrounding the core. By "minute capsules" are meant capsules from a few microns to several thousand microns and possibly somewhat larger in average size.

In the art of providing protective coatings for various materials and articles, many processes have been utilized. Familiar examples include the following: spray coating, dip coating, pan coating, roll-applicator coating, and brush coating. Essentially, these methods are suitable for coating materials and articles of relatively large surface area per unit. The unit referred to is a single piece or article; for example, an individual nut or bolt, an individual motor, an individual piece of candy, an individual medicinal tablet, an individual sheet of paper or paper board, and the like.

Coacervation is a phenomenon that has been used in the past to effect an encapsulation, en masse, of minute core materials. However, prior to the present invention, processes for the microencapsulation, en masse, of nucleus or core material have been restricted to systems wherein the wall-forming or wrapping about the core material was conducted in an aqueous medium. These prior techniques are described, for example, in United States Reissue Patent No. 24,899, issued to Barrett K. Green on Nov. 29, 1960, and assigned to the assignee herein. Such

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processes do not yield a capsular product wherein the core material is substantially water-soluble.

It is an object, therefore, of the present invention to provide a coating or encapsulation process broadly applicable to the coating of aqueous and water-soluble liquid and solid particles.

Other objects will be apparent to those skilled in the art to which this invention pertains.

The following are related United States patent applications directed to specific process inventions referred to herein, without limitation, as examples of processes employing the broader invention of this application and its above-identified parent application.

(I) Ser. No. 13,725, filed Mar. 9, 1960, by Thomas C. Powell et al., now abandoned.

(II) Ser. No. 192,071, filed May 3, 1962, and now U.S. Pat. No. 3,415,758, as a continuation-in-part of Ser. No. 13,725, now abandoned, by Thomas C. Powell et al.

In a specific form, the present invention comprises preparing a solution of a liquid-phase-forming macromolecular polymer in a first non-aqueous liquid, forming a dispersion of liquid or solid particles in this solution, adding to the thus-prepared dispersion a second non-aqueous liquid miscible with the first liquid and a non-solvent to the macromolecular polymer and to the liquid or solid particles to be coated to cause a liquid-liquid phase separation into a macromolecular polymer-rich, non-aqueous liquid phase (coacervate phase) and a macromolecular, relatively polymer-poor, non-aqueous liquid phase. The macromolecular polymer-rich phase coats the liquid or solid particles. The coating is then set to impart rigidity thereto. The coated particles are separated from the liquids, washed, separated from the wash medium, and dried. Optionally, the coating or capsule wall may be hardened to impart stability thereto, which in some cases also reduces permeability.

In its broadest aspect, the subject invention comprises a capsule-forming process which involves the establishment of a system that is characterized as follows (these terms being defined below):

(1) It is in an agitated state;

(2) It comprises the following three phases, characterized first of all by being mutually incompatible (as defined hereinafter) and further characterized, respectively, as being:

- (a) a continuous liquid phase vehicle that constitutes a major portion by volume of the three phases in total,
- (b) a discontinuous phase of minute, mobile entities of core material, either solid or liquid, dispersed in the vehicle and constituting a minor portion by volume of the three phases in total, and
- (c) a discontinuous coacervate phase of minute, mobile entities of wall-forming material dispersed in the vehicle and constituted by a non-aqueous solution of one or more polymeric substances, the solution being capable of wetting the core material and having a viscosity sufficient to maintain itself about the core material against the shearing or other forces and yet of a viscosity that permits the formation of a seamless wall of polymeric material.

This agitated system results in a deposit of the wall-forming material around the entities of core material. By reason of the viscosity and volume relation of the dispersed phase of wall-forming polymer solution, that phase is capable of deposit around the dispersed entities of core material and is also capable, after deposit, of maintaining itself as a wall against the shearing forces that exist as an incident of the required agitation of the system. The deposits quickly accumulate to a maximum

thickness, which may be varied by varying the amount of the wall material provided and the degree and type of agitation used, and which may vary in accordance with the need for protection of the core material and the protective characteristics of the wall-forming material selected for use.

Depending on the nature of the core material and that of the wall material, the embryonic capsules, prior to hardening, formed in the liquid vehicle by this system are more or less durable. Various supplemental treatments of the capsules so formed may be employed to harden their walls and thereby impart to them greater durability and greater impermeability relative to the core material and the environment, among other properties. Suitable procedures are set forth hereinafter.

A further measure of protection is to cause deposit of an additional surrounding wall of polymeric material by a succeeding encapsulation step in which these initially-formed capsules, with or without hardening treatment, serve as the core entities.

This new process of making capsules en masse in a liquid vehicle by establishing a system as defined above differs from the previously known system of United States Pats. Nos. 2,800,457 and 2,800,458 (Reissue 24,899) in that the present system is non-aqueous, and differs in particulars with respect to the classes of materials that can constitute, and that preferably constitute, the vehicle, the capsule cores, and the capsule wall, respectively. This new process is applicable to the encapsulation of a wide range of core materials, including many that cannot be encapsulated by the processes described in those patents, and uniquely applicable to the encapsulation of water-soluble solids, and also through conjoint use of a further invention of Thomas C. Powell et al. respecting the use of polymeric material having special polar groups (described in United States patent application Ser. No. 192,070, filed May 3, 1962 and now abandoned) is capable of encapsulating water and water-like liquid core materials.

Former specifically-disclosed processes employing a liquid manufacturing vehicle were incapable of usefully encapsulating water-soluble solids and water or water-like liquids. Such known processes of making capsules en masse employed an aqueous vehicle and a three-component system in which a deposit of hydrophilic wall-forming polymeric material around dispersed core entities would occur. This involved an aqueous vehicle and an aqueous solution of hydrophilic wall-forming polymeric material (that is, a coacervate phase having an aqueous liquid as the associated liquid), which precluded the use of water-soluble solids or aqueous core materials. Of course, slightly water-soluble core material could be used with prior systems if the vehicle and the aqueous wall-forming solution were saturated with them and the presence of the water-soluble materials did not adversely affect the protective coating as it would in many instances.

It has been discovered that a non-aqueous coacervate phase may be utilized, such that, if the polymeric material of the capsule wall, the solvent therefor, and the vehicle are selected to meet the foregoing criteria, while satisfying the further criteria set forth herein, not only is it possible to produce a system in which deposit of the dispersed wall-forming entities around the dispersed core entities can be achieved, but also this can be done with core materials that could not before be successfully encapsulated by any en masse process using a liquid manufacturing vehicle.

The further criteria which define the useful classes of materials for the core material, vehicle and wall-forming solution are these: (1) the polymeric material of the wall-forming solution should be capable of dissolving in the particular non-aqueous liquid chosen; (2) the solution of polymeric materials which form the capsule wall must be capable of wetting the core material in order

to deposit around the core entities, and, with regard to wetting properties, the polymeric wall material preferably should have naturally-occurring or artificially supplied wetting groups such as $-\text{COOH}$; $-\text{OH}$; $-\text{COOR}$; $-\text{CN}$; Cl ; and F , the wetting properties of which in certain instances may be enhanced by the liquid in which it is dissolved; (3) the solution of polymeric material should have a viscosity such that it may both deposit itself and also maintain itself deposited around the core entities despite the shearing forces of the agitation needed to maintain the dispersion; (4) the solution of polymeric material should constitute such a percentage of the total three-phase system, by volume, that it can exist as a dispersed phase of mobile entities capable of deposit around the core entities; and (5) the core material, the solution of polymeric material (coacervate phase), and the vehicle must be mutually incompatible.

The wetting action of polymeric materials in solution as regards a particular core material may be measured by standard contact-angle measurements, adsorption measurements, and the like, and suitable selections may be made thereby, all in accordance with existing knowledge of this subject per se. The solvent for the polymeric material may in certain instances be selected to enhance the wetting action of a particular polymeric material solution with respect to a chosen core material. If a solvent is chosen that is too good a solvent for a particular polymer, which inhibits its wetting action with respect to the core material, then a higher molecular weight of the polymer may be used to reduce the solubility of the solvent used, or else a poorer solvent is substituted.

The term "non-aqueous" as used in the specification and claims does not exclude liquids having small amounts of water, provided, however, that the amount of water in the non-aqueous liquid is such that the compatibility or incompatibility of the liquid relative to the other materials in the capsule-forming system is not substantially altered.

The stated criterion that the core material, the coacervate solution of polymeric material, and the vehicle be mutually incompatible is used in the sense that their separate existence in the system must not be impaired by any reactivity or miscibility between them.

Prefabricated incomplete systems for use in carrying out the novel process may be established and stored for future use. Even unskilled operators may complete such systems by the addition of the missing components, with the required agitation, and heat if necessary, together with agents for hardening of the walls, to make capsules at a later time. The missing component(s) may involve any of those three necessary for forming an operative system, and the absence may be total or partial.

The preferred system is one in which the non-aqueous liquid used as the solvent for the wall-forming polymeric material also serves as the major component of the manufacturing vehicle. The vehicle then must contain another material, in solution in it, which is complementary to the wall-forming material in the sense that it creates an incompatibility between the vehicle and the wall-forming polymeric material and induces and/or maintains as a separate liquid phase, a wall-forming solution of the polymeric material. Alternatively, instead of or in conjunction with another complementary material, the entire system may be subjected to a condition which will act to or assist in inducing and or maintaining the incompatibility between the vehicle and the solution of wall-forming polymeric material. In other words, the complementary material or condition completes a liquid system in which the suitably-viscous, wall-forming non-aqueous solution of polymeric material can exist as a separate phase dispersed in the vehicle because of repulsive forces between the polymeric material of the wall-forming non-aqueous solution and the complementary material and/or condition. Without the complementary material and/or

condition, if the vehicle included or consisted of the same liquid that is used as the solvent for the wall-forming polymer, the vehicle would be miscible with and would dilute the polymer solution, which polymer solution then would not exist as a separate phase of proper viscosity.

Viewing the core material as the guide to the selection of the polymeric wall-forming material and its solvent, and also to the selection of the liquid vehicle if that is not to consist of or include as a solvent the same material that is used as the wall-forming polymer solvent, the polymeric material and its solvent must be incompatible with the core material, but capable of wetting and depositing around entities of it; and the polymeric material of the wall-forming non-aqueous solution must be compatible with the liquid that is to form the component of the separated or coacervate phase. When, as preferred, the vehicle is made up chiefly or wholly of the same material as the liquid of the wall-forming polymer solution, the only further choice is with respect to the complementary material and/or condition, which, again, must meet the incompatibility requirement. The complementary material and/or condition must be incompatible with the core material and must act to make it possible for the wall-forming polymeric material solution to exist as a separate phase.

Given these criteria of selection, not known before in total, as the determinants of an operative encapsulation system, the classes of material that are useful in constituting the vehicle and the wall-forming polymer solution of the present system are ascertainable from existing knowledge and means of selection of polymeric materials and solvents in respect of three properties; viz.:

- (1) Solubility of the polymer in various non-aqueous solvents;
- (2) Ability of the polymer solution to wet the given core material, liquid or solid; and
- (3) Ability to exist in separate solution phase in the vehicle liquid.

Materials thus selected are useful in the encapsulation of any incompatible and wettable core material, liquid or solid.

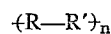
Polymeric material suitable for use in the process of the present invention include synthetic and natural macromolecular polymers such as, for example, polystyrene, cellulose acetate, polyvinyl acetate, polyvinyl alcohol, polyvinyl chloride, dinitrocellulose, trinitrocellulose, cellulose acetobutyrate, benzyl cellulose, and rubber. Additional suitable macromolecular polymers are those of the polybasic type—for example, deacetylated chitin, polyvinyl pyridine, styrene-vinyl pyridine copolymer, and polymeric quaternary ammonium salts—and those of the polyamide type—for example, polylysine, polyornithine, poly-p-amino-phenylaniline, and polyacrylamide.

Another class of suitable polymeric material is made up of macromolecular synthetic polymers having an average molecular weight of at least 20,000 and having a linear, as opposed to a cross-linked, polymeric structure for example, those whose polymer units comprise both lipophilic and hydrophilic units; i.e., one class of recurring polymer unit is essentially lipophilic in character (for example, one derived from styrene, an alkyl ring substitute styrene, an ether or ester substituted ethylene), and the other major recurring unit is essentially hydrophilic in character (for example, derived from maleic acid, maleic acid amide, acrylic acid, crotonic acid, acrylic acid amide). In combination, these lipophilic and hydrophilic units preferably comprise a majority of the polymeric units present in the copolymer. Other polymer units may also be present in the copolymer, so long as they are present in minor amounts; that is, less than either the hydrophilic or the lipophilic polymer units. Included among these polymers are the hydrolyzed styrene-maleic anhydride copolymers, styrene-maleic acid amide copoly-

mers, the sulfonated polystyrenes, polymethacrylic acid, and methyl vinyl ether-maleic acid copolymer.

Additional suitable polymeric materials are the carbohydrate acetate phthalates (e.g., starch acetate phthalate, cellulose acetate phthalate, and amylose acetate phthalate).

Among the preferred synthetic polymers employed in this invention are the hydrolyzed styrene-maleic anhydride copolymers, the anhydride groups of which are preferably at least 50% hydrolyzed. The copolymer can also contain other polymer units in minor amounts; e.g., those derived from acrylonitrile, acrylic acid, methacrylic acid, itaconic acid, vinyl, ethyl vinyl ether, methyl vinyl ether, vinyl chloride, vinylidene chloride, etc., and the like. As used in the present specification, the term "hydrolyzed styrene-maleic anhydride copolymer" is meant to include these modifications as well as other modifications in the structure and method of preparation which do not alter the essential lipophilic and hydrophilic properties of the copolymer. The preferred polymeric material can be represented by the following formula:



wherein R represents lipophilic polymer units of which more than 70% are styrene residues, the remainder, when present, being residues of other ethylenic monomers, for example, of acrylonitrile, acrylic acid, methacrylic acid, itaconic acid, vinyl chloride, vinylidene chloride, and the like; and R' represents hydrophilic polymer units of which more than 50% are maleic acid residues, preferably more than 70% with the ratio of R to R' being from 1:1 to about 4:1, preferably from about 1:1 to about 1.2:1, and n is an integer from about 90 to about 1000. The average molecular weight of the copolymer ranges preferably from about 20,000 to about 200,000. Styrene-maleic anhydride copolymer, which is readily hydrolyzable to styrene-maleic acid copolymer, is a commercially available styrene-maleic anhydride copolymer which may be modified or unmodified. This copolymer can be hydrolyzed to obtain a styrene-maleic acid copolymer which is useful in the present invention. The hydrolysis can be partial or complete and involves a conversion of the acid anhydride linkages to α -dicarboxylic acid units. It is preferred that the hydrolysis be substantially complete; i.e., more than about 50% complete.

Garrett and Guile (J. Am. Chem. Soc., 73, 4533 (1951)) have shown that, in the polymerization of styrene and maleic anhydride, for a 1:1 molar reactant ratio (styrene (R):maleic anhydride (R')), the molar ratio of monomeric units in the polymer (R:R') was 1.124; for a 3:1 molar reactant ratio (R:R') the molar ratio of monomeric units in the polymer (R:R') was 1.183; for a 1:3 molar reactant ratio (R:R'), the molar ratio of monomeric units in the polymer (R:R') was 1.026.

Between pH 1 and 2.5 (the pH found in the normal stomach), a styrene-maleic acid copolymer as defined herein is only 0 to 1% ionized and thus is insoluble at this pH, making this copolymer a useful enteric coating for oral pharmaceutical products whose active ingredient is most efficaciously utilized when absorbed in the intestines rather than the stomach.

While the invention has been discussed and exemplified in terms of a single polymeric material as the principal component of the coacervate phase, the invention is not so restricted and it is within the intended scope of this invention to include mixtures of polymers in the coacervate phase, or in the vehicle, so long as the criteria set forth herein are maintained.

Non-aqueous liquid systems suitable for the separation of a macromolecular polymer-rich liquid phase are, illustratively, the following:

D—V—M
D—II—K
D—II—M

H—VI—L
J—VII—L

Phase forming polymer	First liquid	Miscible, non-solvent liquid
Polyvinyl chloride.....	Cyclohexane.....	Glycol.
Cellulose acetobutyrate.....	Methyl ethyl ketone.....	Isopropyl ether.
Benzyl cellulose.....	Trichloroethylene.....	Propanol.
Polyethylene.....	Xylene.....	Amyl chloride.
Styrene-maleic acid copolymer.	Ethanol, methanol.....	Ethyl acetate, methyl ethyl ketone, butyl ethyl ketone isopropyl ether.
Rubber.....	Benzene.....	Methanol, propanol, glycol, glycerol.
Polyvinyl acetate.....	Chloroform.....	Ethanol.
Do.....	Methanol.....	Butanol.
Ethyl cellulose.....	Xylene methanol.....	n-Hexane.

ADDITIONAL WALL-FORMING POLYMERIC MATERIALS

(A) Ethyl cellulose (preferably one having an ethoxyl content of about 47.5 by weight and a viscosity of 22 centipoises in a 5% concentration, by weight, in an 80/20 toluene-ethanol bath at 25 degrees centigrade).

(B) Cellulose nitrate (preferably of 11.8% to 12.2% nitrogen content).

(C) Cellulose acetate phthalate (preferably of 30% to 40% esterified phthaloyl and of 17% to 22% esterified acetyl content).

(D) Polymethyl methacrylate (about 100,000 to 150,000 molecular weight by viscometric measurement).

(E) Acrylonitrile-styrene copolymer (about 15/85 by weight).

(F) Polystyrene (about 80,000 to 100,000 molecular weight by viscometric measurement).

(G) Vinylidene chloride-acrylonitrile copolymer (a)—78.8%/21.2% or (b)—90.2%/9.8%.

(H) Epoxy resin (viscosity of 100–160 poises at 25 degrees centigrade, epoxide equivalent 175–218).

(J) Polyvinyl-formal (preferred 30,000 molecular weight, hydroxyl content expressed as percent, polyvinyl alcohol 5–7; and acetate content expressed as 25% polyvinyl acetate).

SOLVENTS

- (I) Toluene-ethanol
(II) Methyl ethyl ketone
(III) Toluene-ethanol-ethyl acetate
(IV) Acetone
(V) Benzene
(VI) Toluene
(VII) Nitropropane
(VIII) Dioxane
(IX) Tetrahydro-naphthalene

COMPLEMENTARY SUBSTANCES FOR INDUCING PHASE SEPARATION

(K) Petroleum distillate, boiling point 35 to 70 degrees centigrade.

(L) Polybutadiene, 8,000 to 10,000 molecular weight as determined by the osmotic pressure method.

(M) Polydimethyl-siloxane, 500 centistokes viscosity.

(N) Ethanol.

(O) Phenol-methyl siloxane, 475 to 525 centistokes viscosity.

(P) Methacrylic polymer, viscosity 325 centistokes in low-viscosity petroleum distillate.

THREE-PHASE SYSTEMS

(Symbols as above)

A—I—K
A—I—L
A—II—L
A—II—M
B—III—N
C—IV—K
C—V—K
D—V—K
D—V—M
E—II—L
E—II—M
F—V—M
B—II—L
B—VII—P
G(a)—II—L
G(b)—II—L

CORE MATERIALS

- Sodium amobarbitol
Penicillin acid
20 Ascorbic acid
Polyvinyl pyrrolidone
Acetyl p-amino phenol
Bacillus thuringiensis
Lead
25 Titanium dioxide
Zirconium hydride
Iron
Zinc
Calcium hydride
Tetracyclines
30 Sodium chloride
Phthalic anhydride
Magnesium hydride
Ammonium dichromate
35 Sodium bicarbonate
Stannous fluoride
Sodium acid pyrophosphate
Quinine sulfate
Aspirin
40 Methylene blue
Vanillin
Quinidine gluconate
Dichlorocyanuric acid
Trichlorocyanuric acid
45 Potassium penicillin
d-propoxyphene hydrochloride
d-desoxyephedrine hydrochloride
Sulfamerazine
Crystal violet
50 Pepsin enzyme
Riboflavin
Thiamine chloride
Quinidine sulfate
Albumin
55 Pancreatin
Bacitracin
Aluminum aspirin
Calcium salicylate
Gelatin
60 Gum arabic
Methyl cellulose
Carboxymethyl cellulose
Cellulose acetate phthalate
Starches
65 Sucrose
Mannitol
Potassium chloride
Potassium iodide
Citric acid
70 In its broader aspect, the invention is not in the discovery of particular polymers or solvents or vehicles but rests on and applies the discovery that liquid and solid nucleus materials, including materials compatible with water, can be encapsulated in a system wherein the liquid associated with the wall-forming polymer in the wall-

forming polymer solution is non-aqueous and which comprises the combination of three separate phases of the respective kinds here defined. It is the combination of the three rather than the particular substances used in any one that is the basic invention.

In a narrower aspect, the invention includes a particular procedure for establishing the defined system. This particular procedure involves the formation of a system comprising a wall-forming polymeric material and at least two liquids, said liquids being miscible with each other and at least one of the liquids being incompatible with the wall-forming polymeric material; the polymeric material being the intended wall former, and a separation of this system into two separate solution phases, one being the polymeric wall-forming material and associated liquid (coacervate phase) and the other being the equilibrium liquid. The polymeric material and the liquids may be assembled in any order to effect the phase separation, but it is preferable first to form a dilute solution of the polymeric material that is intended to be in the wall-forming phase, and then to induce phase separation by the addition of a second liquid miscible with the first liquid but incompatible with the wall-forming polymer, the role of the secondary liquid being to induce and maintain the phase separation. The addition of the secondary complementary liquid to an initial dilute solution of the wall-forming polymeric material permits easier control of the phase separation to yield a wall-forming solution phase of suitable viscosity and volume, especially in an initial operation before the procedure is standardized quantitatively for any particular polymeric material and liquids. In such an initial operation, and by any technique of establishing the three phases as described herein, the attainment of the desired viscosity in the wall-forming solution phase may be ascertained by microscopic observation of an agitated sample of the system containing dispersed core material, the criterion being that, when a useful wall-forming solution is present, it is seen that the discrete entities with liquid walls are formed. A confirmation and basis for quantitative statement can be had by allowing the two separated solution phases to stratify and then measuring the viscosity and relative volume of the phase containing the intended wall-forming polymeric material. If the viscosity is too low, addition of more of the complementary material will cause additional concentration of the wall-forming phase to occur, with a consequent increase of viscosity of that phase, until the desired viscosity is attained.

The proper volume relation of the wall-forming phase (of proper viscosity) can be predetermined to a close enough approximation by calculation from readily-ascertained data on the relation of viscosity to concentration for a solution of the intended wall-forming polymer in the chosen solvent.

The order of addition can be reversed, or the polymeric material and the liquids can be brought together at one time, once the proper quantitative relations are established for the particular materials being used. However, experience has shown that in the case where the complementary material is a non-solvent for the wall-forming polymer that the non-solvent should be added gradually for the best results.

The core material, always a minor component of the total volume of the system, can be added either before, during or after the formation of the wall-forming solution of polymeric material. Similarly, the agitation of the system can be begun before, during, or after either of these steps. It is preferred, however, to agitate before, during, and after the phase separation.

The intensity of the agitation is made such as to reduce the core material to the desired entity size, if such is necessary, and, in any event, to assure thorough dispersion of it in the vehicle. The core entity size is pre-selected to give the desired capsule size after allowance for encapsulating wall thickness. With solid core materials, the

entity size can be predetermined and obtained by suitable grinding or milling, or other means known in the art.

An alternative way of establishing a three-phase system, consisting of a continuous vehicle, a dispersed nucleus phase, and a dispersed wall-forming solution phase, involves forming a system comprising two different polymeric materials and a common solvent, one polymeric material being the intended wall former, and a separation of this system into two separate solution phases, one containing chiefly the other polymeric material, by a phenomenon of phase separation known in itself from the work of Dobry and Boyer-Kawenski, published in the "Journal of Polymer Science," volume 2, No. 1, pages 90 to 100 (1947), but not before known to be useful in a system of encapsulation. The two polymeric materials and the solvent may be assembled in any order to effect the phase separation, but it is preferable first to form a dilute solution of the polymeric material that is intended to be in the wall-forming phase, and then to induce the phase separation by addition of the second, or complementary, polymeric material, the role of which is to induce and maintain the phase separation.

The second polymeric material in that case is one that has either no affinity or a lesser affinity for the core material, so that the solution of the first polymeric material (the intended wall former) will be the one that preferentially deposits around the dispersed core entities. This second polymeric material is referred to as a "complementary polymeric material."

The addition of the complementary polymeric material to an initial dilute solution of the wall-forming polymeric material permits easier control of the phase separation to yield a wall-forming solution phase of the proper viscosity and relative volume, especially in an initial operation before the procedure is standardized quantitatively for any particular polymeric materials and common solvent.

The order of addition can be reversed, or the two polymeric materials and the solvent can be brought together at one time, once the proper quantitative relations are established for the particular materials being used, since the resulting volume and viscosity (concentration) of the two separate phases are independent of the order of assembly.

By reason of the discovery of Thomas C. Powell et al. described in U.S. patent application Ser. No. 192,070, filed May 3, 1962, and now abandoned, that polymeric materials having one or more groups from the class consisting of hydroxyl, carboxyl, the ester COOR (where R is an alkyl of up to four carbon atoms), cyano, chlorine, or fluorine groups are capable, when in solution, of wetting water and water-like core materials, and of depositing around them to form capsules by the basic process of the present invention, such polymeric materials are within the class of wall forming materials useful in the present invention. When such polymeric materials are used, the conditions in other respects are those created by the present invention, and this discovery of a sub-class of polymeric materials which can wet and encapsulate aqueous liquid core material therefore satisfies that condition of the process of this invention with respect to the polymer material of the wall-forming solution and makes its use a specific instance of use of the present invention.

Polymeric solutions which meet the requirement of incompatibility with the vehicle are known from the study of Dobry et al., cited above, concerning the incompatibility of different polymers when in solution in a common solvent, whereby separation into two solution phases occurs when it is impeded by excessive viscosity of the system. That impeding viscosity does not exist under the conditions here defined with respect to the viscosity and volumetric proportion of the wall-forming polymer solution as a component of the present three-phase system.

Thus, where another polymeric material is used as the complementary incompatibilizing material in a system in which the same liquid is used as the solvent for the wall-forming polymeric material and as the major liquid component of the vehicle, the polymeric material used in the wall-forming solution may be any polymer that has a greater affinity for the core material than does the polymer serving as the complementary material, so that the wall-forming polymeric material will deposit preferentially around the core entities.

When the three-phase capsule-forming system is established by the presence of a complementary polymeric material, the continuous or vehicle phase consists of a more dilute and less viscous solution containing the greater part of the complementary polymeric material; and that polymeric material is the material which imparts the necessary incompatibility between the vehicle and the wall-forming solution phase and permits the latter to exist as a separate dispersed phase. The small amount of complementary polymeric material that may pass into the separated wall-forming solution phase by entrainment or otherwise is not objectionable.

Another alternative procedure is to pre-form a solution of wall-forming polymeric material having the desired viscosity, and then to disperse it in a vehicle which is a liquid that is immiscible with this polymeric material solution and with the core material. This avoids any phase separation step such as is necessary when the wall-forming polymeric material is initially present in dilute solution and has to be driven out in a more concentrated solution as a separate phase having the desired viscosity, whether by reason of a complementary other polymeric material or by reason of a complementary non-solvent for the wall-forming polymer, or other means.

The temperature of the system is dictated by the nature of the components. In the instance where the wall-forming polymeric material sets on cooling, the mass should be maintained above the setting temperature during the wrapping step. Moreover, the upper temperature limit is determined by the stability of the components at elevated temperatures and further by the respective boiling points. It is preferred to conduct the wrapping and subsequent steps at a temperature below the boiling point of any of the components.

The ratio of macromolecular polymer to the liquid or solid core material to be coated is varied with the thickness of the coating desired.

In order to obtain a desired coat thickness, the ratio of the amount of macromolecular polymer to the amount of the core material to be coated varies with the total surface area of the core material. Thus, for larger surface areas, controlled by the degree of dispersion in the case of liquid core material, and by a prior reduction in size in the case of solid core material, the amount of macromolecular polymer is increased.

Although it is preferred that the liquid and solid core material for coating by phase separation be insoluble, the coating of core material with some or appreciable solubility is not outside the concept of the present invention. For example, core material with some solubility in the first liquid can be rendered insoluble, by the addition of the second liquid, prior to the formation of the coacervate or wall-forming phase.

The setting of the liquid phase about the core material to render the liquid phase immobile can be accomplished in various manners. Illustrative, but not limiting, are cooling in the case of a gelable polymeric material, raising the pH in the case of a polybasic polymer, reducing the pH in the case of an acidic polymer, reacting acidic groups with a divalent or multivalent ion—for example, Ca^{++} , Mg^{++} , Fe^{++} , Fe^{+++} , or Al^{+++} —modification of the coat by the addition of a monomer and modification by the utilization of an additional non-solvent.

The further setting or hardening of the coat to prevent reversibility of the phase separation, as desired, can be carried out by utilizing various methods. Illustrative there-

of are the addition of dicarbonyl compounds, alum, tannic acid, and tannic acid and ferric chloride, the removal of occluded liquid by drying and/or heating; changes in pH; and the use of the Van de Graaff sterilizer for irradiation; it being within the skill of the art, after having the benefit of this disclosure, to adapt specific techniques to the nature of the wall-forming polymeric material.

The removal of the vehicle liquid and the separation of the coated core material thereby are preferably carried out prior to the washing of the coated particles. Said separation is preferably accomplished by centrifugation; however, filtration and decantation can be employed. In the case of washing, in situ, the separation of the coated core material can be carried out by spray-drying.

For washing the coated core material, at the centrifuge or during filtration, a non-solvent for the wall-forming polymer may be used and in the case where a non-solvent was employed to effect the formation of the wall-forming polymer solution additional amounts of the non-solvent second liquid may be used. The liquid wash removes traces of the vehicle liquid and puts the coated core material in condition for drying.

The drying of the coated core material may be carried out by simple evaporation, in vacuo, or by the application of heat, depending on the nature of the mass.

The process of the present invention possesses utility in providing coatings that (1) protect the coated liquid or solid core material from oxidative degeneration, (2) prevent contact between incompatible substances in a mixture of ingredients, (3) mask undesirable odors and tastes, (4) provide a barrier to release of the coated liquid or solid core material until the desired pressure is applied to rupture the coat, (5) provide controlled release of the coated material in various media such as the stomach and the intestine, (6) provide increased stability of the coated material, and (7) provide a coating permitting the handling of corrosive and/or irritating materials.

The following examples are for the purpose of illustration and to set forth the best mode contemplated by the application of carrying out his invention. They are not to be construed as limiting.

EXAMPLE 1

A solution of 5 grams of cellulose acetobutyrate is prepared in 100 milliliters of methylethyl ketone at about 65 degrees centigrade. 1.25 grams of dibasic calcium phosphate is dispersed in this solution with adequate stirring to maintain the phosphate compound uniformly mixed. With stirring and with the temperature maintained at 50 degrees centigrade, isopropyl ether is added. When the concentration of the ether reaches about 42%, v./v., a cellulose acetobutyrate-rich liquid phase (coacervate phase) separates and coats the phosphate compound. The whole mixture is cooled to room temperature. Thereafter, the coated particles are separated, advantageously by centrifuging, thoroughly washed with isopropyl ether, and allowed to dry. A capsule having a powdery phosphate compound as the core material is thereby obtained which is suitable for use as a slow-release fertilizer.

EXAMPLE 2

A solution of 10 grams of benzyl cellulose is prepared at about 40 degrees centigrade in 300 milliliters of trichloroethylene. 80 grams of sodium (2,4-dichlorophenoxy) acetate is added to this system with adequate stirring. With stirring and with the temperature maintained at about 40 degrees centigrade, propanol is added. When the concentration of propanol reaches about 51%, v./v., a benzyl cellulose-rich liquid phase separation occurs, and the sodium (2,4-dichlorophenoxy) acetate is coated by the separating phase. The whole mixture is cooled to room temperature. Thereafter, the coated material is separated, by centrifuging, thoroughly washed with propanol, and allowed to dry. A capsule comprising a benzyl cellulose-coated as the wall material and powdery

acetate as the interior material is obtained which is suitable for use in slow-release weed control.

EXAMPLE 3

A macromolecular solution is prepared with 25 grams of styrene-maleic acid copolymer and 25 milliliters of ethanol at about 50 degrees centigrade. 25 grams of morphine monohydrate is dispersed therein. Ethyl acetate is slowly added to the whole mixture with adequate stirring. When the concentration of ethyl acetate reaches about 74%, v./v., a copolymer-rich liquid phase separation occurs, which coats the dispersed morphine monohydrate. Thereafter, the coated morphine compound is recovered, washed with ethyl acetate, and alloyed to dry. The so-obtained coated morphine compound is suitable for use in aqueous suspensions.

EXAMPLE 4

A macromolecular solution is prepared with 6 grams of styrene-maleic acid copolymer and 100 milliliters of ethanol at about 50 degrees centigrade. 30 grams of sodium (2,4-dichlorophenoxy) acetate is dispersed therein. Isopropyl ether is added to the whole mixture with adequate stirring. At a relative concentration of 46% isopropyl ether, v./v., a copolymer-rich liquid phase separation occurs, which coats the acetate compound. Thereafter, the coated acetate compound is recovered, washed with isopropyl ether, and allowed to dry. The thus-obtained coated compound is suitable for use in slow-release weed control application.

EXAMPLE 5

A macromolecular solution is prepared with 100 grams of styrene-maleic acid copolymer and 100 milliliters of methanol. 800 grams of pancreatin is dispersed therein. Butylethyl ketone is added to the whole mixture with adequate stirring. At a relative concentration of 60% of the ketone, v./v., a copolymer-rich liquid phase separation occurs, which coats the pancreatin. Thereafter, the coated pancreatin is recovered, washed with more of the ketone, and dried. The so-coated pancreatin is protected from the destructive acidic action of the stomach juices after oral ingestion.

EXAMPLE 6

A macromolecular solution is prepared from 70 grams of styrene-maleic acid copolymer in 700 milliliters of ethanol at 50 degrees centigrade. 17 grams of tribasic sodium phosphate is dispersed therein. With constant stirring, butylethyl ketone is slowly added to a concentration of 60%, v./v., to cause separation of a liquid copolymer-rich liquid phase. The so-separated phase coats the phosphate compound, which is thereafter recovered, washed with butylethyl ketone, and allowed to dry. The coated phosphate compound can be handled without the corrosive and irritating action of the uncoated compound and is suitable, for example, as a drain cleaner.

EXAMPLE 7

A macromolecular solution is prepared from 100 grams of styrene-maleic acid copolymer in 1000 milliliters of methanol. 25 grams of methylsilicone oil is dispersed therein at about 50 degrees centigrade. With constant stirring, isopropyl ether is slowly added until the ether concentration reaches 47%, v./v. A liquid copolymer-rich liquid phase separates and coats the dispersed oil. Thereafter, the coated oil is recovered, washed with isopropyl ether, and allowed to dry. The thus-coated oil is useful as a lubricating grease.

EXAMPLE 8

An ethylcellulose-coated water-soluble dye is prepared and coated in the following manner:

5 grams of ethylcellulose is dissolved in a mixture of 100 milliliters of xylene and 20 milliliters of ethanol. One-half gram of alizarine cyanine dye is dispersed in the solution. 125 milliliters of n-hexane (Skellysolve B) is

added drop by drop to separate an ethylcellulose-rich liquid phase, which coats the green dye. The coated dye particles are separated by filtration, washed with n-hexane, and vacuum dried.

A solution of 5 grams of cellulose acetobutyrate is prepared in 100 milliliters of methylethyl ketone. The above-coated dye particles are dispersed in this solution at about 40 degrees centigrade. With constant stirring, isopropyl ether is added to a concentration of 42%, causing the separation of a cellulose acetobutyrate-rich liquid phase. Said liquid phase forms an additional coat on the ethylcellulose pre-coated dye particles. The double-coated particles are recovered by centrifugation, washed with isopropyl ether, and dried at about 30 degrees centigrade.

EXAMPLE 9

A solution of 100 grams of gelatin in 900 milliliters of water is prepared at 45 degrees centigrade. Eight grams of oil of rose is dispersed in this solution, with adequate stirring to maintain the oil thoroughly and uniformly mixed. With stirring and with the temperature maintained at 45 degrees centigrade, ethyl alcohol is added to the dispersion. It is preferred to use a denatured alcohol; for example, one of the commercial denatured ethyl alcohols containing a minor amount of methanol. The methyl alcohol is added slowly with stirring. When the concentration of ethanol reaches about 50%, v./v., a gelatin-rich liquid phase separates and coats the dispersed oil. When the ethanol concentration reaches about 55%, v./v., the whole mixture is cooled to about 5 degrees centigrade to set the coating. The coated oil is separated from the bulk of the residual liquid by centrifugation. Thereafter, the coated oil is washed thoroughly with ethanol and allowed to dry in vacuo at 25 degrees centigrade.

2.5 grams of the gelatin-coated particles are dispersed at 50 degrees centigrade in a solution of 10 grams of styrene-maleic acid copolymer in 100 milliliters of ethanol. With adequate stirring, butylethyl ketone is added to a concentration of 60%. A copolymer liquid phase separates and superimposes a second coat on the gelatin-coated oil of rose. The pH of the whole mixture is lowered to pH 1.0 to set the copolymer coat. Thereafter, the double-coated oil of rose particles are recovered by centrifugation, washed with butylethyl ketone, and dried at room temperature.

EXAMPLE 10

15 milliliters of a 0.5% w./v. aqueous solution of amaranth (F.D. & C. No. 2) is added with vigorous agitation to 90 milliliters of a 5.0%, w./v., solution of cellulose acetate butyrate in methylethyl ketone. This mixture is then passed through a hand homogenizer three times. Enough additional butyrate solution is added to the homogenizer to make 150 milliliters of emulsion.

The emulsion is then heated to 55 degrees centigrade on a steam bath while being stirred rapidly. An additional 15 milliliters of amaranth solution is added at this time.

To the emulsion system, isopropyl ether, previously heated to 50 degrees centigrade, is added in small portions with agitation. An increased cloudiness is noted when 100 milliliters had been added. The presence of liquid phase-coated water droplets can be confirmed by microscopic examination.

Thereafter an additional 10 milliliters of isopropyl ether is added with stirring to produce further separation of liquid phase. The mixture is allowed to cool slowly without agitation. The coated particles are separated by centrifugation, washed with isopropyl ether, and dried in vacuo.

EXAMPLE 11

In this example, there will be considered the encapsulation of ammonium nitrate particles in ethyl cellulose, the whole process being carried on in a 200-milliliter beaker at 25 to 50 degrees centigrade, with the materials being agitated constantly. There is introduced into the beaker 50 grams of a 2%, by weight, solution of ethyl

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cellulose in an 80/20 toluene-ethanol solvent, the particular ethyl cellulose having a viscosity grade of 22 centipoises, and an ethoxyl content of 47.5%, by weight, the viscosity being determined when the ethyl cellulose is dispersed dry in a 5% concentration, by weight, in an 80/20 toluene-ethanol bath at 25 degrees centigrade. Into the ethyl cellulose is introduced 40 grams of ammonium nitrate particles which have a 200-micron average dimension, followed by the introduction of 25 grams of polybutadiene having a molecular weight of 8000 to 10,000 as determined by the osmotic pressure method, said butadiene being a liquid and introduced over a period of fifteen to thirty minutes, during which time a coacervate phase comprising a solution of ethyl cellulose separates from the rest of the system as small liquid entities which deposit on and surround each ammonium nitrate particle individually, such being brought about mechanically by the agitation and chemically by the wetting substituent groups of the ethyl cellulose. The phase separation of the ethyl cellulose as a liquid includes the carrying with it of a part of its original solvent, and in this particular example such mostly consists of the ethanol component and a small part of the toluene component. The liquid deposits are hardened by introducing into the system, after the liquid walls have been formed, 15 grams of toluene diisocyanate over a period of a minute or two, the toluene diisocyanate seemingly combining with the ethanol of the deposited wall material, forming plasticized self-supporting firm ethyl cellulose walls which are substantially water-impermeable.

Water-sensitivity of the core material is not a requirement necessary for the practice of the invention, as materials not sensitive to water may be encapsulated thereby.

The finished capsules may be recovered from their liquid environment and dried for their end use, one of such uses being to act as core entities to receive a second wall of the same material or another material applied by the method of this invention or by any other en masse method, or by coating, spraying, or rolling.

EXAMPLE 12

To 196 grams of toluene add 4 grams of ethyl cellulose, as specified in Example 11, and stir at 25 degrees centigrade until a clear solution is formed. Disperse therein 16 grams of the desired core material reduced to any desired particle size between 40 and 5,000 microns, and, with agitation, slowly add, over a period of fifteen minutes, 40 grams of polybutadiene of 8,000 to 10,000 molecular weight, as obtained by the osmotic pressure method, which addition induces phase separation of the ethyl cellulose in solution of proper viscosity and the encapsulation of the core particles with it. The capsule walls may be hardened by the addition to the agitated system of 0.2 gram of tetrabutyl titanate.

EXAMPLE 13

To 196 grams of carbon tetrachloride add 4 grams of ethyl cellulose, as specified in Example 11, and stir until there is a clear solution at 25 degrees centigrade, thereafter dispersing in the solution 16 grams of the selected core material (for example, aspirin) divided into the desired particle entity size. Add 120 grams of mineral spirits having a boiling point of 130 degrees to 190 degrees centigrade, to cause phase separation of the viscous ethyl cellulose solution and its deposit on the core entities. The walls of the resulting embryonic capsules then may be hardened with tetrabutyl titanate, as has been described in Example 12.

EXAMPLE 14

Prepare a solution of 4 grams of ethyl cellulose, as specified in Example 11, in 196 grams of cyclohexane, stirring at 80 degrees centigrade. Add 16 grams of particles of intended core material (iron powder, for example), and, with continued agitation, add, over a period of five minutes, 20 grams of polybutadiene, as specified

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in Example 12, during which the system is allowed to cool to 50 degrees centigrade. The further cooling to room temperature, with stirring, results in a hardening of the capsule walls.

EXAMPLE 15

Stir 4 grams of cellulose nitrate (11.8% to 12.2% nitrogen content) into 196 grams of methyl ethyl ketone at 25 degrees centigrade until a clear solution is formed, and then add 4 grams of the particulate intended core material (for example, titanium dioxide). To the still-being-stirred solution add 50 grams of the polybutadiene specified in Example 14 to form liquid-walled embryonic capsules. The capsule walls are hardened by stirring in 0.2 gram of tetrabutyl titanate.

EXAMPLE 16

Make a solution of 10 grams of vinylidene chloride-acrylonitrile copolymer, having a component ratio of 78.8/21.2, in 196 grams of tetrahydrofuran at 25 degrees centigrade until a clear solution is formed. Stir in 16 grams of the selected core material particles, and, with agitation, add 30 grams of polybutadiene of 8,000 to 10,000 molecular weight specified in Example 12, to cause a polymer phase separation and the deposit of it on the core particles. The capsule walls may be hardened by the addition of tetrabutyl titanate in an amount of 0.4 gram with stirring.

EXAMPLE 17

Add 10 grams of cellulose acetate phthalate (preferably of 30% to 40% esterified phthaloyl and 17% to 22% acetyl content) to 190 grams of dioxane at 25 degrees centigrade to form a clear solution. To this is added, as exemplary coloring material, 20 grams of ammonium dichromate having a particle size of 250 to 800 microns. With agitation, add 72 grams of polybutadiene of 8,000 to 10,000 molecular weight as determined by the osmotic pressure method, which addition, with continued agitation, forms capsules with liquid walls which may be hardened by extraction of the solvent with petroleum distillate.

EXAMPLE 18

In this example, water-sensitive materials are encapsulated in ethyl cellulose by forming a three-phase system of a liquid vehicle, the capsule wall-forming ethyl cellulose in solution, and particles of intended core material, the separate phase of the ethyl cellulose being brought about by introduction, into the vehicle in which it was dissolved, of a non-polymeric liquid which is preferentially soluble in the vehicle. More specifically, a room-temperature solution of 36 grams of toluene, 9 grams of ethanol, and 5 grams of the ethyl cellulose specified in Example 11 is formed, and with agitation, 5 grams of finely-divided ammonium dichromate is dispersed therein. The temperature of the system is raised to 70 degrees centigrade, and, still with agitation, 40 grams of petroleum distillate (boiling point slightly above 70 degrees centigrade) is added slowly, as by pipette, over a period of ten to fifteen minutes. This causes separation of a dense ethyl cellulose solution of the required wall-forming viscosity, the solvent being mostly of the ethanol part of the vehicle, as a dispersed liquid phase which deposits on the ammonium dichromate particles. This deposited material is robbed of its solvent by the addition of more petroleum distillate (about 100 grams) after the system has been reduced to room temperature. The walls of the capsules then are firm, and the capsules may be recovered from the liquid vehicle and dried to a free-flowing powder.

EXAMPLE 19

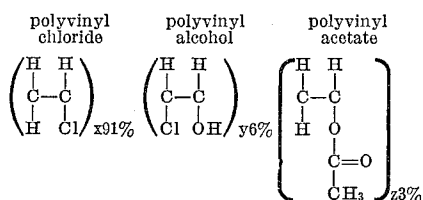
This is the same process as Example 18 except that polymethyl methacrylate (of about 100,000 molecular weight by viscometric measurement) may be used in place of ethyl cellulose, and methyl ethyl ketone or benzene may be used as the solvent in place of the toluene-

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ethanol solvent, the same proportions of materials being used. Either petroleum distillate or hexane may be used as the phase-separation-inducing material.

EXAMPLE 20

This process, particularly adapted to the encapsulation of aqueous solutions, is begun by introducing into a 500-milliliter beaker, at room temperature, 100 grams of a 5%, by weight, solution of a specially-modified copolymeric material having the general structure



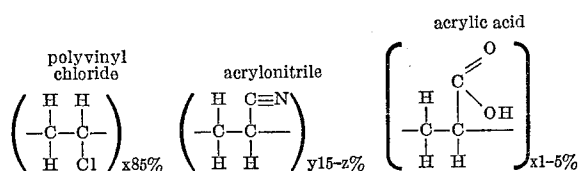
dissolved in ethylene chloride. Next, 10 grams of a 10%, by weight, solution of sodium ferrocyanide in water is introduced, with agitation to reduce it to the desired drop size, to furnish the capsule core material ingredient. This preferred core material is exemplary of a colorless water solution of a color reactant. To the agitated mixture (which may be termed a water-in-oil emulsion) is added slowly, as a phase-separation-inducing polymeric material, 15 grams of polydimethyl siloxane, of for instance, 500 centistoke viscosity, the addition preferably being made drop by drop over a period of three or four minutes to prevent agglomeration of the modified polyvinyl chloride wall-forming material as it separates out, thus permitting it to break up into small entities which deposit evenly over the droplets of nucleus material.

With continued agitation, the so-formed liquid-walled embryonic capsules are treated by the addition to the agitated system of 0.2 gram of tetrabutyl titanate, drop by drop, which results in the cross-linking of the polymeric material content of the deposited liquid wall material, to a dense self-supporting condition, within a matter of a few minutes. If the drop size of the core material is of an average diameter of 100 microns, the capsules will have walls of 1 to 5 microns in thickness, such thickness being governed largely by the ratio of wall material to nucleus material that is used in a given vehicle system.

Other core materials, of a watery or aqueous nature, that can be encapsulated in place of the solution of sodium ferrocyanide in water are similar solutions of solids in either water, or ethylene glycol, and glycerine or their solutions with water or other materials, or solids which are not soluble in the liquid system, and all of the various materials heretofore mentioned as core materials.

EXAMPLE 21

This example is the same as Example 20 except that the polymeric material intended for the capsule walls is a copolymer of vinyl chloride and acrylonitrile with acrylic acid groups, and having the empirical formula:



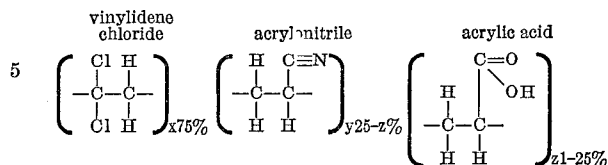
Typical solvents to be used with the above wall-forming material are cyclohexane or methylisobutyl ketone, in the same amounts and in place of ethylene dichloride. The materials are used in the same ratio as in Example 20.

EXAMPLE 22

Example 21 is followed, except that the wall-forming polymeric material is a copolymer of vinylidene chloride

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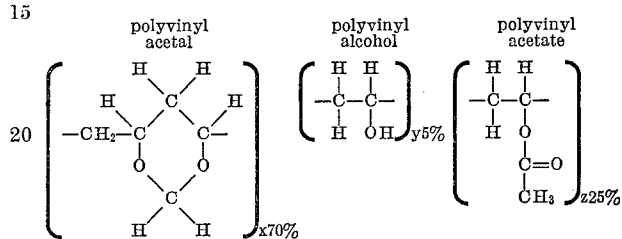
and acrylonitrile with acrylic acid groups having the empirical formula:



used in the same amount.

EXAMPLE 23

Example 21 is followed, except that the wall-forming polymeric material is of the empirical formula:



and used in the same amount.

Examples 20, 21, 22, and 23, exhibit the use of polymeric wall-forming material that have special water-wetting groups thereon to facilitate the encapsulation of watery nuclei, but such property does not exclude them from use in the encapsulation of non-watery materials according to the broad aspects of the invention. However, the use of these special materials is claimed in the Powell et al. application Ser. No. 192,070, filed May 3, 1962, and now abandoned.

It is to be understood that the invention is not to be limited to the exact details of operation or exact compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the scope of the appended claims.

What is claimed is:

1. The process of forming minute capsules en masse which comprises

(a) establishing an agitated system consisting of a liquid vehicle constituting a major portion of said system by volume and forming a continuous liquid first phase, a second phase dispersed in said liquid vehicle consisting of minute, mobile entities of core material, and a third phase dispersed in said liquid vehicle consisting of minute, mobile, non-aqueous, liquid entities of a wall-forming solution of a polymeric material having a viscosity such that said solution of wall-forming polymeric material maintains itself about the core material in the agitated system, the said core material being wettable by said wall-forming solution and the said three phases being mutually incompatible, whereby said wall-forming solution deposits on and around said core entities to form a continuous liquid protective wall, and

(b) subsequently hardening the walls so formed.

2. The process of claim 1 in which the first phase is a non-aqueous organic liquid.

3. The process of claim 1 in which the core material is a liquid.

4. The process of claim 1 in which the core material is a solid.

5. The process of claim 1 in which the core material is partly liquid and partly solid.

6. The process of claim 1 in which the core material is water-soluble.

7. The process of forming minute capsules en masse in accordance with claim 1 and further wherein there is curing of the deposited wall-forming solution of polymeric material by reaction with a cross-linking agent for it.

8. The process of forming minute capsules en masse in accordance with the process of claim 1 and further comprising the hardening of the walls so formed by displacing the solvent of said wall-forming solution, after deposit, with a solvent of greater volatility and thereafter removing a substantial part of said displacing solvent by evaporation.

9. The process of forming minute capsules en masse in accordance with the process of claim 1 and further comprising the step of isolating the hardened capsules from other liquids encountered during their manufacture.

10. The process of forming minute capsules en masse, comprising

(a) establishing an agitated system consisting of a liquid vehicle comprising a non-aqueous solvent for a wall-forming polymer and a liquid miscible with said non-aqueous solvent and non-miscible with other phases of the system, constituting a major portion by volume of the system and forming a continuous liquid first phase, a second phase dispersed in said liquid vehicle consisting of minute, mobile entities of core material, and a third phase dispersed in said liquid vehicle consisting of minute, mobile, non-aqueous liquid entities of a wall-forming solution of a polymeric material, the said core material being wettable by said wall-forming solution and the three phases being mutually incompatible, whereby said wall-forming solution deposits on and around said core entities to form a protective wall, and

(b) subsequently hardening the walls so formed.

11. The process of claim 10 in which the first phase is a non-aqueous organic liquid.

12. The process of claim 10 in which the core material is a liquid.

13. The process of claim 10 in which the core material is a solid.

14. The process of claim 10 in which the core material is partly liquid and partly solid.

15. The process of claim 10 in which the core material is water-soluble.

16. The process of forming minute capsules en masse in accordance with the process of claim 10 and further comprising the step of isolating the hardened capsules from other liquids encountered during their manufacture.

17. The encapsulation process which comprises preparing a solution of a synthetic linear polymer in an organic solvent therefor, mixing in the solution hydrophilic solid core materials to form a dispersion containing uniformly dispersed core material, forming a polymer-rich liquid phase coating about said uniformly dispersed core materials by mixing into the dispersion a liquid which is miscible with the organic solvent and a non-solvent for said polymer, and said added liquid being inert with respect to the core material and polymer; setting the coating and separating the coated core materials.

18. The process of claim 17 wherein solid core materials, pre-coated with a hydrophilic coat, are used.

19. The encapsulation process which comprises: preparing a solution of a polymer in a liquid non-aqueous solvent therefor; mixing in the solution hydrophilic solid core material to form a dispersion containing uniformly dispersed core material; forming a liquid polymer-rich phase coating about said uniformly dispersed core material by mixing uniformly into the dispersion a liquid non-aqueous nonsolvent for said polymer and said particles and miscible with said solvent; and separating the coated particles.

20. The encapsulation process which comprises: preparing a solution of a polymer in a liquid non-aqueous solvent therefor; mixing in the solution hydrophilic liquid core material to form a dispersion containing uniformly dispersed particles; forming a liquid polymer-rich phase coating about said uniformly dispersed particles by mixing uniformly into the dispersion a liquid non-aqueous nonsolvent for said polymer and said core material and

miscible with said solvent; and separating the coated core material.

21. The encapsulation process which comprises: dispersing hydrophilic liquid core material in a non-aqueous liquid, adding a polymer to said non-aqueous liquid to form a solution of said polymer in the non-aqueous liquid, separating a polymer-rich liquid phase to coat said core material by adding a liquid which is soluble in the non-aqueous liquid and a non-solvent for said polymer and said core material; and separating the coated core material.

22. The encapsulation process which comprises: dispersing hydrophilic solid core material in a non-aqueous liquid, adding a polymer to the non-aqueous liquid to form a solution of said polymer in the non-aqueous liquid, separating a polymer-rich liquid phase to coat said core material by adding a liquid which is soluble in the non-aqueous liquid and a non-solvent for said polymer and said core material; and separating the coated core material.

23. The encapsulation process which comprises: preparing a solution of a synthetic linear polymer in an organic solvent therefor, adding to the solution hydrophilic liquid core material to form a dispersion, with agitation, containing uniformly dispersed core material, forming a polymer-rich liquid phase coating about said core materials by adding into said dispersion a liquid which is miscible with the organic solvent and is a non-solvent for said polymer, said liquid being inert with respect to the core material and polymer; hardening the coating and separating the coated core material.

24. The process of making microcapsules comprising the steps of: forming a dispersion of colloidal droplets of an aqueous solution in a continuous phase of a non-aqueous organic liquid substantially immiscible with said aqueous solution, said non-aqueous organic liquid having dissolved therein an encapsulating polymeric material, and adding a non-polar organic non-solvent liquid for said encapsulating polymeric material to said continuous phase at a rate such that the polymeric material is caused to precipitate around said colloidal droplets and thereby form microcapsules, said non-polar organic non-solvent liquid being substantially miscible with said continuous phase and substantially immiscible with said colloidal droplets.

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RICHARD D. LOVERING, Primary Examiner

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8—79; 71—64 F, 117, DIG 1; 106—308 C, 308 M; 117—62.2, 100 A, 100 B, 100 M; 252—10, 135; 264—4; 424—33, 35, 94, 230, 260