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COATING BY PHASE SEPARATION

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This invention relates to a process for the coating of liquid and solid hydrophilic material and to the products therefrom, and more particularly to the process of precoating said material by phase separation from non-aqueous media prior to coating by phase separation from aqueous media and to the products thereof.

Coacervation, a particularly useful form of liquid phase separation from aqueous media, is a widely applicable coating procedure capable of providing encapsulated materials having unique characteristics. These unique characteristics include the permissible microscopic size of the capsules, the structure of the coatings, the flexibility in the coating materials used, and the manner in which the coating materials can be modified.

Coating by phase separation from aqueous media, prior to the present invention, was not a satisfactory method for coating either water-soluble material or water-insoluble material of a hydrophilic nature. Obviously, water-soluble material will dissolve in the aqueous media from which the liquid phase separates. Although some of the dissolved molecular units will be encapsulated, this will not occur in sufficient quantity to be practical. Probably due to the hydrophilic surface, water-insoluble hydrophilic material will not be encapsulated by the separating phase.

The present invention comprises the steps of precoating liquid and solid hydrophilic material by the process of phase separation from a non-aqueous medium before encapsulation of said precoated material by the technique of phase separation from aqueous medium.

The material, when coated by the process of the present invention, has a protective coat which comprises two distinct layers, (1) a layer of material (the layer called the precoat) having a lipophilic surface which is deposited by the process of phase separation from non-aqueous medium and (2) a layer of material having a hydrophilic surface deposited by the process of phase separation from aqueous medium. The thickness of the coating is therefore the sum of the thickness of the two layers.

In general, the thickness of the precoat can, within limits, be controlled by the ratio of the amount of material to be coated to the amount of material which separates as a liquid phase. Thus, if a thicker lipophilic layer is desired, more lipophilic material should be used. As is apparent, the smaller the particle size of the material to be coated, the greater the total surface area to weight, a larger amount of lipophilic material is required to achieve the same layer thickness as that required when employing the same weight of material of larger particle size.

Similarly, the thickness of the second layer is variable.

The process of the present invention is particularly

advantageous for the coating of solid and liquid matter which is in an extremely fine state of subdivision, i.e., from about 0.5 to 200 microns in diameter; however, the process can also be used for coating of individual particles that are considerably larger, i.e., the particle can be a tablet which is a centimeter or more in diameter, and, obviously, particles of intermediate size can be coated. The particular particle size is not critical to the process of the invention, but is determined by the use to which the coated particle is to be employed. For example, a micronized powder or finely dispersed liquid (0.5 to 10 micron size) is desirable for vitamins and other food supplements, for substances to be incorporated into cosmetic formulations, and for insecticides; a powdered material (up to 200 micron size) is a desirable size for rodenticides.

Particles, when coated by the process of the present invention, have a coating with unique characteristics. The coating's surface is hydrophilic in nature and is therefore easily wetted and suspended in water, however the coating is not dissolved by water or the usual organic solvents and is not removed or dispersed by surfactants in an aqueous medium. The coating is not melted and the coated particles do not cake together when subjected to warm or humid atmospheric conditions.

The novel encapsulated products of the present invention find applications due to their unique properties in the formulation of compositions for widely diversified fields of use.

In the cosmetic field, products such as soap bars, lotions, and creams can be formulated containing coated water-soluble ingredients which would be unstable or incompatible in uncoated form in the presence of other ingredients of the particular formulation. For example, since certain antibacterials such as the chlorinated phenols and neomycin sulfate are incompatible on prolonged contact with soap, the present invention makes possible the formulation of a soap bar containing both of these ingredients.

In the agricultural field, coated fertilizers, pesticides, food supplements and medicaments can be advantageously formulated. For example, water-soluble fertilizers such as ammonium nitrate, urea and superphosphate can be coated for application to the soil when a slow release or extended action is desirable, e.g., where rapid release would "burn" the vegetation. For the control of pests, coated insecticides such as calcium arsenate and copper acetoarsenite can be deposited on vegetation or in the soil without harm to the vegetation; moreover, the insecticide is not dissolved and washed away by moisture or rain, thereby allowing the insecticide to remain where deposited until ingested by the insect. Anthelmintic agents, such as piperazine phosphate or citrate, and methylrosaniline chloride, when coated can be incorporated into feed material for domestic animals, the coated anthelmintic thereby being tasteless in the feed and also protected from decomposition during storage of the feed. Rodenticides such as calcium cyanide, thallium sulfate and sodium fluoroacetate, which are unstable in the presence of moisture or have an odor or taste repellent to the rodent are advantageously coated. A unique application of the

coated material is the formulation of rodenticides having in the composition a non-coated, water-soluble antidote or emetic agent; the composition furnishing an automatic safeguard in case of accidental ingestion by domestic animals or children. The antidote or emetic can easily be washed away with water by the user or simply be permitted to wash away in actual use by atmospheric moisture or rain.

Vitamins, minerals, amino acids and other food supplements, when coated, can be incorporated in animal feeds and be protected from decomposition during storage periods from such adverse conditions as air, moisture, and incompatible ingredients in the feed composition itself. In a similar manner food supplements can be incorporated in compositions for human use.

The present invention finds application in medicinal treatment of both animals and humans. Medicaments can be coated by the methods of the present invention to give a sustained release upon ingestion with resultant sustained therapeutic action. Coatings which will not dissolve in the stomach can be formulated to overcome the problem of gastric irritation or nausea caused by such medicaments as emetine hydrochloride, quinacrine hydrochloride and para-amino-salicylic acid. Similarly, medicaments such as penicillin and certain glandular extracts which are inactivated by the acid condition or enzymes encountered in the stomach are advantageously coated.

As used in the present specification the term solution means both true solution and colloidal solution.

The term phase separation means the separation of a liquid phase from a liquid phase. Phase separation may be thought of as being a precipitation of a liquid precipitate. The separating liquid phase is of the same qualitative nature as the original single-phase system, hereinafter called mother phase, from which it separates; it is also qualitatively similar to the remaining liquid, hereinafter called equilibrium liquid with which it is in equilibrium. The separating phase differs quantitatively from the mother phase; it is more concentrated in colloid and/or polymer, and less concentrated in solvent.

As used in the present specification the term coating by phase separation means the phenomenon of inducing phase separation in the presence of suspended particles, the separating phase enveloping or encapsulating the suspended particles to form a mantle around each particle.

The liquid phase-forming macromolecular polymers suitable for use in the precoating step of the present invention can be either synthetic polymers or derivatives of naturally occurring polymers.

The derivatives of the naturally occurring polymers can be, for example, ethyl cellulose, cellulose acetate, dinitrocellulose, trinitrocellulose, cellulose acetobutyrate, benzyl cellulose, cellulose acetate phthalate, and amylose acetate phthalate.

Suitable synthetic polymers are macromolecular 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 (e.g., one derived from styrene, an alkyl ring substituted styrene, an ether or ester substituted ethylene), and the other major recurring unit is essentially hydrophilic in character (e.g., 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, i.e., less than either the hydrophilic or lipophilic polymer units. Included among these copolymers are the hydrolyzed styrene-maleic anhydride copolymers, styrene-maleic acid amide copolymer, the sulfonated polystyrenes, polymethacrylic acid, and methyl vinyl ether-maleic acid copolymer.

Among the preferred polymers of this class 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 polymers can be represented by the following formula:

$$\ddagger(R)-(R')\ddagger_n$$

wherein R represents lipophilic polymer units of which more than 70% are styrene residues, the remainder, when present, being residues of other ethylenic monomers such as those 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 1:1 to about 1.2:1, and *n* is an integer from about 90 to 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 modified styrene-maleic anhydride copolymer. 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 it can be 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.

Between pH 1 and 2.5 (the pH found in a 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 more efficaciously utilized when absorbed in the intestines rather than the stomach. Other suitable macromolecular polymers are those of the polybasic type (for example, deacetylated chitin, polyvinyl pyridine, styrene-vinyl pyridine copolymer, polymeric quaternary ammonium salts), and those of the polyamide type (for example, polylysine, polyornithine, poly-p-amino-phenylaniline, and polyacrylamide).

Basically, the precoating step of the present invention comprises preparing a mother solution of a liquid phase-forming macromolecular polymer in a non-aqueous liquid; forming a dispersion of liquid or solid hydrophilic material in the mother solution, adding to the thus prepared dispersion a second liquid which is soluble in the first liquid and is a non-solvent to the macromolecular polymer and to the dispersed liquid or solid particles whereby to induce a liquid-liquid phase separation and encapsulation of the suspended material by the polymer-rich phase. The polymer-rich phase precoat is set to impart rigidity thereto. The precoated particles are separated from the liquids, washed, and dried. Optionally, the precoat can be hardened to impart stability thereto and/or to reduce permeability.

Various systems suitable for the separation of a macro-

molecular polymer-rich liquid phase are, illustratively, the following:

Mother solution comprising—		Phase separation inducing additive—Soluble, Non-solvent Second Liquid
Polymer	First Liquid	
Polyvinyl acetate	Acetone	Water.
Do	Trichloroethylene	Heptane.
Do	Methanol	Butanol Isoamyl alcohol.
Polyvinyl stearate	Benzene	Acetone.
Do	Chloroform	Methyl ethyl ketone.
Do	Kerosene	Mineral oil.
Polyvinyl chloride	Cyclohexane	Glycol.
Dinitrocellulose	Acetone	Water.
Trinitrocellulose	do	Do.
Cellulose acetate	do	Do.
Cellulose acetobutyrate	Methyl ethyl ketone	Isopropyl ether.
Benzylcellulose	Trichloroethylene	Propanol.
Ethyl cellulose	Xylene	Skelly Sol B Heptane, Hexane.
Do	Ethanol	Water.
Do	Benzene	Corn oil, Mineral oil.
Styrene-maleic acid copolymer.	Ethanol, Methanol	Ethyl acetate, Methyl ethyl ketone, Butyl ethyl ketone, Isopropyl ether.

It was quite unexpectedly discovered that phospholipids can also be used to prepare a non-aqueous mother solution capable of producing a liquid-liquid phase separation and encapsulation. For example the lecithins can be dissolved in chloroform and phase separation induced by the addition of ethanol and/or acetone.

In each system incipient liquid-liquid phase separation of the macromolecular polymer is manifested, upon the slow mixing of the second liquid miscible with the first liquid, by the appearance of a cloudy condition. The concentrations of first and second liquids at which the cloudy condition first appears will vary with the concentration of the macromolecular polymer dissolved in the first liquid. Said concentrations can be determined for each particular system independent of the presence of the liquid or solid particle to be coated. When so determined, the appropriate concentrations are thereafter used in the presence of the liquid or solid particles to be coated.

The temperature considerations involve those temperatures at which a solution of a suitable concentration of the polymer can be obtained in the first liquid, and the boiling points of the first and second liquids. The temperature used for the solution, generally, is at least 10 degrees below the boiling point of the lower boiling of the first and second liquids.

The ratio of macromolecular polymer to the liquid or solid particles to be coated is varied with the thickness of the coating desired. Thus, the ratio of the polymer to particle can be varied from about 8 parts by weight of polymer to 1 part by weight of particle, to form about 1 part by weight of polymer to about 8 parts by weight of particle.

Although it is preferred that the liquid and solid particles for coating by phase separation be insoluble in both the first and second liquids, the coating of particles with some or appreciable solubility in either the first or second liquids, or in a mixture thereof, is not outside the concept of the present invention. For example, particles with some solubility in the first liquid can be rendered insoluble, by the addition of the second liquid, prior to the separation of a polymer-rich and a polymer-poor phase.

The setting of the polymer-rich phase after encapsulation to render the phase immobile can be accomplished in various manners. Illustrative, but not limiting, are lowering the temperature; allowing a spontaneous setting by ageing; adding an acid (i.e., a substance capable of accepting a share in a lone electron pair from a base to form a co-ordinate covalent bond) in the case of a polyacidic polymer; adding a base (i.e., a substance capable of donating a share in a lone electron pair to an acid to form a co-ordinate covalent bond) in the case of a polybasic polymer.

The removal of the equilibrium liquid and the separation of the precoated particles thereby is preferably carried out prior to the washing of the precoated particles. Said separation is accomplished by centrifugation or filtration. In the case of washing, in situ, the separation of the precoated particles can be carried out by freeze or spray-drying.

For washing the precoated particles in the centrifuge or during filtration, additional amounts of the non-solvent second liquid are used. Said liquid removes traces of the equilibrium liquid and puts the precoated particles in condition for drying.

The drying of the precoated particles can be carried out by simple evaporation, in vacuo, or by the application of heat, depending on the physical characteristics of the non-solvent second liquid.

The hardening of the precoat, as desired, can be carried out by utilizing various methods. Illustrative thereof are the addition of dicarbonyl compounds, alum, tannic acid, and ferric chloride; the removal of occluded liquid by drying and/or heating; by changes in pH; and by the use of the Van de Graff electron accelerator for irradiation.

After having been precoated and separated, the material is then ready to be coated by phase separation from aqueous medium. The various ways in which coating by phase separation from aqueous medium can be accomplished are conveniently considered with regard to the composition of the coating material or the composition of the mother phase.

In the first method, the mother phase comprises an aqueous solution of a gelable hydrophilic colloid. This method is described in U.S. Patent No. 2,800,458 and classified as a "simple coacervate" by H. G. Bungenberg de Jong and Ong Sian Gwan in Biochemische Zeitschrift 221, 182–205 (1930). By this method an aqueous solution of a gelable hydrophilic colloid, e.g., gelatin, agar-agar, albumin, alginates, casein, pectins, and fibrinogen, is prepared at a temperature above the gelling point of the colloid, the precoated particle is suspended in the system, and phase separation is induced by modifying the system with an additive. Such additives include (1) aqueous solutions of electrolytes such as the salts of sodium, potassium, ammonium and lithium cations and sulfate, citrate, acetate and chloride anions or (2) a water-soluble liquid in which the gelable hydrophilic colloid is less soluble than in water such as methanol, ethanol, propanol, acetone and dioxane. A critical concentration exists for each additive in each particular colloid system below which phase separation will not be induced. This concentration is easily determined by routine testing as shown in U.S. Patent 2,800,458. The colloid-rich phase on separating collects about the surface of the suspended particle, encapsulating the particle with a liquid mantle of the colloid-rich phase. In the absence of the suspended

particle, the colloid-rich phase separates in the form of microscopic droplets which on the addition of the particle will then collect on the particle and encapsulate it. When encapsulation is completed the temperature of the system is lowered below the gelling temperature of the colloid-rich phase thereby changing the colloid mantle from a liquid to a gel. The coated particle can then be removed and/or the coating treated to alter its characteristics.

Another method involves a mother phase comprising an aqueous solution of at least two hydrophilic colloids. This method is described in U.S. Patent 2,800,457 and classified as "complex coacervation" by H. G. Bungenberg de Jong and Ong Sian Gwan in Biochemische Zeitschrift 221, 182–205 (1930). For this method it is essential that at least one of the colloids be gelable and that at least one colloid have an electrophoretic charge opposite from the other(s) in the system. With the preceding requirements in mind, the colloids to be used can be chosen from the various gelable and non-gelable hydrophilic colloids and their derivatives, as, for example, gelatin, agar-agar, albumin, alginates, casein, pectins, fibrinogen, starch acetate phthalate, cellulose acetate phthalate, and the like. The optimal concentration of the colloids can be determined by routine testing as described in U.S. Patent 2,800,457. Phase separation is induced by adjustment of pH and/or addition of water. The proper pH or amount of water to be added is easily determined by testing as described in the cited patent.

The coating of the suspended particles then takes place in a similar manner to that described in the first method.

The following remarks are directed to the coatings produced by both the first and second methods.

The gelation step is significant with respect to the permeability of the coating. With many colloid-rich systems, instantaneous gelling of the colloid-rich phase, as by adding the liquid colloid-rich phase to ice water, produces a gelled coating having high permeability. Prolonged cooling also favors a coating of high permeability. The lowest permeability or highest impermeability is obtained with intermediate cooling rates. Thus a highly impermeable coating is produced in the case of gelatin on cooling the newly-formed coating from 50° C. to about 5° C. in a period of approximately 30 minutes with continuous stirring.

Following gelation of the colloid-rich phase, the gelled coating is hardened, plasticized or otherwise treated to adapt it to the intended use. For example, when the colloid-rich phase contains a protein colloid such as gelatin, fibrinogen or collagen, treating the gelled coating with a 37% aqueous solution of formaldehyde under alkaline conditions produces a hardened shell which can then be dried. For most applications, contact of the coating with the said formaldehyde solution for a period of about 10 mintues is productive of a material having sufficient hardness and resistance to abrasion to withstand the normal usage of packaging or handling. Variations in the hardness of the coating can be obtained by varying the quantity of hardening agent and the period of contact therewith. Hardening likewise has considerable influence on the permeability of the coat, both with respect to the invasion of environmental fluids which would cause disintegration of the coating and to the containment of active ingredients.

Hardening can be accomplished by a drying process. By removing the water occluded within the mantle, the mantle is hardened. The drying can be accomplished by exposure to hot air or other methods such as containment within a closed vessel which contains a desiccant.

Another method of coating by phase separation employs an aqueous solution of a synthetic linear macromolecular polymer whose polymer units comprise both lipophilic and hydrophilic units. Thus, one class of recurring polymer unit is essentially lipophilic in character, e.g., one derived from styrene, an alkyl ring substituted styrene, ether, ester or halogen ring substituted styrene, an ether or ester substituted ethylene; and the other major recurring unit is essentially hydrophilic in character, e.g., derived from maleic acid, maleic acid amide, acrylic acid, crotonic acid, and acrylic acid amide. In combination, these lipophilic and hydrophilic units preferably comprise a majority of the polymeric units present in the polymer. Other polymer units may also be present in the copolymer, so long as they are present in minor amounts, i.e., less than either the hydrophilic or lipophilic polymer units. Included among these polymers are the hydrolyzed styrene-maleic anhydride copolymers, styrene-maleic acid amide polymer, the sulfonated polystyrenes, the carbohydrate acetate phthalates (e.g., starch acetate phthalate, cellulose acetate phthalate and amylose acetate phthalate), polymethacrylic acid, and methyl vinyl ether-maleic acid copolymer.

Preferred among the polymers employed by this method 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, ethyl vinyl ether, methyl vinyl ether, vinyl chloride, vinylidene chloride, etc., and the like.

The solubility of the polymers employed by this method vary considerably in a selected aqueous liquid. For example, completely hydrolyzed styrene-maleic anhydride polymer is about 2% soluble in water but at least 20% soluble in a 50:50 mixture of methanol and water. Thus, solutions of the desired polymer can be prepared in relatively dilute form in water alone. Alternatively, the concentration of the polymer can be increased by the addition of a solubilizing agent, e.g., another hydrophilic liquid such as, for example, methanol or ethanol. Another type of solubilizing agent useful when carboxylic acid polymers are employed are the polysaccharides, e.g. alginates, pectins, methylcellulose, carboxymethylcellulose, etc. Of particular usefulness are the galactose polysaccharides, e.g., carrageen (derived from Irish moss), available as Sea Kem Type No. 1 from Seaplant Chemical Corporation, New Bedford, Massachusetts. For example, the solubility of completely hydrolyzed styrene-maleic anhydride copolymer in water can be raised from about 2% to about 7 to 10% in the presence of relatively small amounts of this polysaccharide, e.g., one part to four parts of the copolymer. Higher concentrations of the acid polymers can also be achieved by passing a solution of an alkali-metal salt thereof through a bed of sulfonic acid ion exchange resin, e.g., Dowex 50.

Phase separation is induced by the addition of a solution of a suitable electrolyte as salts of magnesium, ammonia, potassium and lithium cations and sulfate, phosphate, citrate, acetate, chloride, bromide, thiocyanate and nitrate anions. The salt should be added in amounts sufficient to produce a significant percetage thereof by weight per volume of the resulting mixture, e.g., 1 to 50% and preferably 3 to 20%.

The proper amount of additive for inducing phase separation is readily determined beforehand by the addition of increasing amounts of the selected additive to a previous solution of the polymer, identical with that to be employed in the encapsulation process, until phase separation occurs in an appreciable amount. This is observable as a visible clouding of the solution.

In carrying out the process of this method, the selected polymer is dissolved in the selected aqueous medium, the precoated material is suspended therein, and phase separation is induced by a suitable additive. A polymer-rich liquid phase separates and encapsulates the suspended particle.

In the next step of the process, the pH of the system containing the encapsulated product is adjusted so as to reduce the solubility of the mantle of the thus-produced encapsulated product in the aqueous solvent. If the start-

ing polymer is acidic in character, then the solution is made acidic. Conversely, if the polymer is basic in character, the solution is made basic. In general, it can be said that in this step, the ionizing properties of the mantle are reduced, thus reducing its affinity towards the aqueous solvent. The correct pH can be determined by visual means, either by observing a change in the appearance of the encapsulated product or by observing the particles under a microscope. The mantle or polymer-rich phase as it forms has a somewhat transparent appearance, whereas when it is converted to isolatable form by adjustment of the pH, it becomes more opaque or translucent.

Any strong acid or base can be employed to adjust the pH, e.g., hydrochloric acid, sulfuric acid and sodium or potassium hydroxide.

This method is thus different from methods 1 and 2, both in the material used and the step by which an isolatable encapsulated product is produced. In the first and second methods, the critical step in producing an isolatable product is the step of chilling to below the gelation temperature of the gelable colloid employed. In the instant method, gelability is not a critical characteristic of the polymer employed. Instead, the combination of lipophilic and hydrophilic polymer units in the polymer enable the polymer to encapsulate while at the same time having ionizing properties which can be altered by the adjustment of the pH of the aqueous solvent. Thus when the polymer mantle is formed, it is "fixed" by adjusting the pH of the aqueous solution in which the encapsulated product is suspended, thereby producing a mantle which is rigid enough to separate the encapsulated product from the suspending liquid.

The thus-produced encapsulated product can be isolated by centrifugation of filtration to remove the aqueous liquid and then washing the encapsulated material, e.g., with water, but avoiding such vigorous washing as will redissolve a significant amount of the polymer mantle. Alternatively, the total reaction product can be freeze-dried or dried at from about room temperature to about 60° C., e.g., under vacuum

The mantle of the encapsulated product can be further hardened by exposure to reagents which will chemically alter the surface groups of the polymer mantle, e.g., the polymer can be reacted with a monomer to produce cross-linking or reacted with a salt containing a polyvalent cation, e.g., aluminum sulfate or barium chloride, when the structure of the polymer permits.

Still another method of coating by phase separation employs an aqueous solution of a styrene-maleic acid copolymer capable of having an electrophoretic charge (of the type described in the preceding method) and a gelable hydrophilic colloid which is of opposite charge at the pH at which significant phase separation takes place.

The aqueous solutions which can be employed in the process of this method include water solutions and aqueous solutions which comprise water and a water-soluble hydroxy compound such as a lower alkanol, e.g., methanol and ethanol; a lower alkylene glycol, e.g., ethylene glycol, propylene glycol and trimethylene glycol; a lower alkyl triol, e.g., glycerol; and mixtures thereof.

The glycols and triols as defined above are also useful additives to prevent coalescence of the encapsulated product and to produce a product having superior handling properties. Examples of other anti-coalescing agents are the polyethylene glycols 200 to 600.

Either separately or together with the copolymer, a solution of the selected colloid, e.g., gelatin, agar-agar, albumin, alginates, casein, pectins and chitosans, is prepared. Sometimes, e.g., when it is difficult to stay outside the condition under which phase separation occurs, it is preferred to prepare a solution of the copolymer and a solution of the colloid separately. Ordinarily it is necessary to adjust the pH of one or both of the solutions to prevent phase separation when they are mixed. Alternatively, a mixture of the colloids, copolymer and the selected aqueous solvent can be heated, e.g., to above the gel temperature of the colloid and the pH adjusted until phase separation occurs.

The precoated material is suspended in the mother phase and the phase separation induced by adjusting the pH. The correct pH for inducing phase separation is readily determined by adding acid or base to a clear solution of a mother phase until clouding occurs, similar to the trial procedures in the previous methods.

In the presence of the suspended particles, the separating copolymer-colloid-rich phase coats the particle, forming a mantle thereover, thus producing the encapsulated product.

At this stage, the mantle is ordinarily still quite mobile and not amenable to isolation. However, the mantle is, to a degree, self-hardening and will produce a more stable mantle upon standing, preferably from 30 minutes to several hours or days at a temperature above the gelation temperature of the colloid. Techniques well known in the tanning art for the tanning of hides, can be employed to accelerate this autohardening, e.g., suspending the encapsulated product for 15 minutes in 10% aqueous ferric chloride or 10% tannic acid in isopropyl alcohol, or in 10% aqueous ferric chloride for 15 minutes at room temperature and then in 20% tannic acid in glycerin.

Alternatively, other hardening agent or agents can be added to the total mixture containing the encapsulated product. Preferred are the highly active carbonyl compounds, especially those having from one to 8 carbon atoms, inclusive. Examples of these are formaldehyde glyoxal, phenylglyoxal, malonic acid dialdehyde, pyruvaldehyde, glyceraldehyde, diacetyl and methyl phenyl ketone. Heating will sometimes accelerate the hardening process, but care should be taken not to disrupt the still mobile mantle.

Alternatively, the encapsulated product can be hardened by exposure to reagents which will chemically alter the surface groups of the polymer mantle, e.g., the polymer can be reacted with a monomer to produce cross-linking, when the structure of the polymer permits, or irradiated, e.g., with high velocity electron bombardment, e.g., with a Van de Graff electro generator, to change the molecular structure of the monomer and, desirably to concomitantly sterilize the encapsulated material.

The thus-produced encapsulated product can be isolated by centrifugation or filtration to remove the aqueous liquid and then washing the encapsulated material thoroughly, e.g., with water or dilute acid, e.g., dilute acetic acid, and then dried, e.g., freeze or spray dried.

The following examples are illustrative of the process and products of the present invention and are not to be construed as limiting.

Example 1

15 milliliters of a 0.5%, w./v., aqueous solution of amaranth 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 through the homogenizer to make 150 ml. of emulsion.

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

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

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

A solution of 50 gm. of gelatin in 450 ml. of water is prepared at from about 40° to 50° C. The precoated

amaranth solution is added to this system, with adequate stirring to maintain the particles uniformly suspended. With stirring and with the temperature maintained at from about 40° to 50° C., ethanol (95%) is slowly added to the system. When the concentration of ethanol reaches about 50% v./v., the gelatin-rich phase separates and encapsulates the suspended particles. When the ethanol concentration reaches about 55% v./v., the whole mixture is cooled to from about 2° to 6° C. to gel the gelatin coating. The coated material is separated from the bulk of the residual liquid, advantageously by centrifuging. Thereafter the coated amaranth solution is washed thoroughly by suspending in 2000 ml. of water and then removed by centrifuge and dried.

Example 2

A solution of 10 gm. of benzyl cellulose is prepared at about 40° C. in 300 ml. of trichloroethylene. About 80 gm. of finely divided sodium(2,4-dichlorophenoxy)acetate is suspended in the system with adequate stirring. With stirring and with the temperature maintained at about 40° C., propanol is added. When the concentration of propanol reaches about 51% v./v., a benzyl-cellulose-rich phase separation occurs and the sodium(2,4-dichlorophenoxy)acetate particles are coated by the separating phase. The whole mixture is cooled to room temperature. Thereafter, the precoated material is separated, by centrifuging, thoroughly washed with propanol, and allowed to dry.

A solution of 100 gm. of gelatin in 900 ml. of water is prepared at from about 40° to 50° C. The precoated sodium(2,4-dichlorophenoxy)acetate is added to this system, with adequate stirring to maintain the particles uniformly suspended. With stirring and with the temperature maintained at from about 40° to 50° C., ethanol (95%) is slowly added to the system. When the concentration of ethanol reaches about 50% v./v., the gelatin-rich phase separates and encapsulates the suspended particles. When the ethanol concentration reaches about 55% v./v., the whole mixture is cooled to from about 2° to 6° C. to gel the gelatin coating. The coated material is separated from the bulk of the residual liquid, advantageously by centrifuging. Thereafter the coated sodium(2,4-dichlorophenoxy)acetate is washed thoroughly by suspending in 2000 ml. of water and then removed by centrifuge and dried.

The coated sodium(2,4-dichlorophenoxy)acetate in the form of a dry powder can be placed in commerce for later suspension in water to be usefully applied as a slow release weed control.

Example 3

A solution of 50 gm. of cellulose acetobutyrate is prepared in 1000 ml. of methyl ethyl ketone at about 55° C. About 12.5 gm. of powdered dibasic calcium phosphate is dispersed in the solution with adequate stirring to maintain the phosphate particles uniformly suspended. With stirring and with the temperature maintained at about 50° C., isopropyl ether is added. When the concentration of the ether reaches about 42% v./v., a polymer-rich phase separates and coats the phosphate particles. The system is cooled to room temperature. Thereafter, the precoated phosphate particles are separated, advantageously by centrifuging, washed with isopropyl ether and allowed to dry.

A solution of 50 gm. of pork skin gelatin in 450 ml. of water is prepared at from about 40° to 50° C. The precoated phosphate particles are added to the system, with adequate stirring to maintain the particles uniformly suspended. With stirring and with the temperature maintained at from about 40° to 50° C., ethanol (95%) is slowly added to the system. When the concentration of ethanol reaches about 50% v./v., phase separation is induced and the separating colloid-rich phase encapsulates the dispersed precoated phosphate particles. When the ethanol concentration reaches about 55% v./v., the whole mixture is cooled to below 10° C. to gel the colloid-rich phase. The coated dibasic calcium phosphate is separated from the bulk of the residual liquid, advantageously by centrifuging. Thereafter the coated material is washed thoroughly by suspending in 2000 ml. of water and then removed by centrifuge and dried.

The coated particles of dibasic calcium phosphate are usefully applied to the soil for use as a slow release fertilizer.

Example 4

About 20 gm. of ethyl cellulose are dissolved in a mixture of 400 ml. of xylene and 80 ml. of ethanol. About 5 gm. of microcrystalline ascorbic acid are suspended in the solution and 500 ml. of Skellysolve B (n-hexane) is added dropwise whereby phase separation is induced. The system is spray dried and the precoated ascorbic acid particles collected.

Twenty-five grams of styrene-maleic acid copolymer are dissolved in about 1250 ml. of water and heated to 80° C. The precoated ascorbic acid particles are suspended in the solution. With constant stirring of the suspension, 275 ml. of a 20% sodium sulfate solution, heated to 80° C. are added dropwise (upon addition of the sodium sulfate solution; phase separation is induced and encapsulation of the particles takes place). The suspension is maintained at 80° C. for 20 minutes.

About 250 ml. of glacial acetic acid is mixed with about 2500 ml. of 20% sodium sulfate aqueous solution and cooled to about 5° C. With vigorous stirring, the suspension is slowly added to the cool, acidified sodium sulfate solution.

The coated ascorbic acid particles are removed by centrifugation and washed several times by alternatively suspending in water and separating by centrifugation. As a final step the particles are suspended in 500 ml. of water and freeze dried.

The coated particles of ascorbic acid are usefully administered to animals (including humans) as a therapeutic or prophylactic treatment. The particles can be suspended in aqueous solutions of the water-soluble vitamins, including cyanocobalamin, the protective coating preventing the degradation of cyanocobalamin by ascorbic acid.

Example 5

A solution is prepared with 10 gm. of styrene-maleic acid copolymer and 100 ml. of ethanol. About 80 gm. of powdered pancreatin are dispersed in the solution. With continuous stirring, ethylbutyl ketone is added to the suspension until a concentration of about 60% v./v. is attained. As a result of the addition of ketone, phase separation and encapsulation of the suspended pancreatin occurs. The precoated pancreatin is recovered, washed with butylethyl ketone and dried.

Twenty-seven grams of acacia powder are dissolved in 167 ml. of water heated to 40° C. When the acacia has dissolved, a sufficient amount of a 20% acetic acid solution is added to give a pH of 3.9. The temperature of the solution is maintained at 40° C.

Twenty grams of gelatin are dissolved in 167 ml. of water heated to 40° C. When the gelatin has dissolved, a sufficient amount of a 20% acetic acid solution is added to give a pH of 3.9. The temperature of the solution is maintained at 40° C.

The precoated particles of pancreatin are dispersed in the acacia solution and the gelatin solution is slowly added with stirring. About 415 ml. of water, previously heated to 40° C. is added dropwise to bring about separation of the colloid-rich phase which encapsulates the suspended pancreatin particles. The mixture is maintained at 40° C. for about 20 minutes and then cooled over a period of about 30 minutes to about 4° C. The mixture is maintained below 6° C. for one hour. The pH of the mixture is adjusted to 9.5 by the addition of 10% sodium hy-

droxide solution and about 20 ml. of a 30% glyoxal solution is added dropwise. The solution is maintained below 6° C. for an additional one hour and then allowed to warm to room temperature. The coated particles are removed by centrifugation.

The particles are twice washed by dispersing in 1000 ml. of water and separated by centrifugation. The particles are then redispersed in 1000 ml. of water and spray dried.

The coated pancreatin is thus protected after oral ingestion from the destructive action of the acidic stomach juices.

Example 6

About 40 gm. of micronized methylscopolamine hydrobromide are suspended in 500 ml. of a 5% w./v. solution of cellulose acetate butyrate in methylethyl ketone. The suspension is heated to 55° C. and 350 ml. of isopropyl ether added dropwise to the system with continuous stirring. The system is cooled slowly to room temperature and the precoated methylscopolamine hydrobromide particles separated by centrifugation, washed with isopropyl ether and dried in vacuo.

About 20 gm. of styrene-maleic acid copolymer and about 5 gm. of Sea Kem, Type No. 1 are mixed and dispersed in 100 ml. of propylene glycol. About 500 ml. of water are added to the dispersion and heated to 80° C. to dissolve. The precoated methylscopolamine hydrobromide particles are suspended in the solution and a solution of about 20 gm. of gelation dissolved in 100 ml. of water at 800° C. is added dropwise. The suspension is maintained at 80° C. with stirring for 15 minutes and then cooled to 4° C. over a period of 30 minutes. The suspension is maintained at 4° C. for one hour and then about 20 ml. of 37% aqueous formaldehyde solution is added and the pH adjusted to pH 8.0 with a sufficient amount of 10% aqueous sodium hydroxide solution. The suspension is maintained at 4° C. for one hour and then the encapsulated urea removed by centrifugation. The encapsulated particles are resuspended in 1% hydrochloric acid solution and spray dried.

Example 7

Seventy-five grams of micronized ferrous sulfate, exsiccated, U.S.P. is suspended with constant agitation to 1250 ml. of a 20% (w./v.) solution of lecithin (centrolex H) in chloroform and heated to 50° C. Fifteen hundred milliliters of a 50:50 (v./v.) solution of ethanol and acetone is added slowly and with stirring to the suspension (upon the addition of the ethanol-acetone solution phase separation occurs and encapsulation of the ferrous sulfate particles takes place). The system is cooled to at least −20° C. and filtered. The precoated ferrous sulfate particles are removed from the filter and dispersed in 1000 cc. of acetone at room temperature. The surface of the lecithin precoat is treated by the addition of 1000 cc. of a saturated solution of aluminum chloride in 95% ethanol. The suspension is stirred for 30 minutes and the precoated ferrous sulfate removed by filtration and air dried.

Twenty-seven grams of acacia powder are dissolved in 167 ml. of water heated to 40° C. When the acacia has dissolved, a sufficient amount of a 20% acetic acid solution is added to give a pH of 3.9. The temperature of the solution is maintained at 40° C.

Twenty grams of gelatin are dissolved in 167 ml. of water heated to 40° C. When the gelatin has dissolved, a sufficient amount of a 20% acetic acid solution is added to give a pH of 3.9. The temperature of the solution is maintained at 40° C.

The precoated ferrous sulfate is dispersed in the acacia solution and the gelatin solution is slowly added with stirring. About 415 ml. of water, previously heated to 40° C. is added dropwise to bring about separation of the colloid-rich phase which coats the wax-coated methionine. The mixture is maintained at 40° C. for about 20 minutes and then cooled over a period of about 30 minutes to about 4° C. The mixture is maintained below 6° C. for about one hour. The pH of the mixture is adjusted to 9.5 by the addition of 10% sodium hydroxide solution and about 20 ml. of a 30% glyoxal solution is added dropwise. The solution is maintained below 6° C. for an additional 2 hours and then allowed to warm to room temperature. The coated particles of ferrous sulfate are removed by centrifugation.

The particles are washed twice by dispersing in 1000 ml. of water and separated by centrifugation. The particles are then redispersed in 1000 ml. of water and spray dried.

It is to be understood that this invention is not to be limited to the exact details of operation of 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. A process for the coating en masse of a plurality of individual discrete fluid and solid particles of hydrophilic matter which comprises: (1) preparing a solution of a liquid phase forming macromolecular polymer in a first non-aqueous liquid; (2) dispersing in said solution a plurality of individual discrete particles selected from the group consisting of insoluble fluid hydrophilic particles and insoluble solid hydrophilic particles; (3) adding a second liquid, soluble in the first liquid and non-solvent for said macromolecular polymer and said dispersed particles, whereby phase separation is induced and the separating phase precoats each of the dispersed particles; (4) setting the polymer-rich precoat; (5) separating said precoated particles; (6) suspending the precoated particles in an aqueous solution of a gelable hydrophilic colloid; (7) inducing phase separation, whereby to cause the formation of a colloid-rich phase and the encapsulation of each of the suspended precoated particles, the foregoing steps (6) and (7) being carried out at a temperature above the gelatin point of the colloid material; and (8) gelling the colloid-rich phase by cooling.

2. The process of claim **1** wherein the coated particles are separated and thereafter the coating is dried.

3. The process of claim **1** wherein the coated particles are (1) separated, and (2) the coating material is dried and hardened.

4. A process for the coating en masse of a plurality of individual discrete fluid and solid particles of hydrophilic matter which comprises: (1) preparing a solution of a liquid phase forming macromolecular polymer in a first non-aqueous liquid; (2) dispersing in said solution a plurality of individual discrete particles selected from the group consisting of insoluble fluid hydrophilic particles and insoluble solid hydrophilic particles; (3) adding a second liquid, soluble in the first liquid and non-solvent for said macromolecular polymer and said dispersed particles, whereby phase separation is induced and the separating phase precoats each of the dispersed particles; (4) setting the polymer-rich precoat; (5) separating said precoated particles; (6) suspending the precoated particles in an aqueous solution of at least two colloids, at least one of which is gellable and one of which has the opposite electrophoretic charge from the remaining colloids; (7) inducing phase separation, whereby to cause the formation of a colloid-rich phase and the encapsulation of each of the suspended precoated particles, the foregoing steps (6) and (7) being carried out at a temperature above the gelation point of the gellable colloid; and (8) gelling the colloid-rich phase by cooling.

5. The process of claim **4** wherein the coated particles are separated and thereafter the coating is dried.

6. The process of claim **4** wherein the coated particles are (1) separated, and (2) the coating material is dried and hardened.

7. A process for the coating en masse of a plurality of individual discrete fluid and solid particles of hydro-

philic matter which comprises: (1) preparing a solution of a liquid phase forming macromolecular polymer in a first non-aqueous liquid; (2) dispersing in said solution a plurality of individual discrete particles selected from the group consisting of insoluble fluid hydrophilic particles and insoluble solid hydrophilic particles; (3) adding a second liquid, soluble in the first liquid and non-solvent for said macromolecular polymer and said dispersed particles, whereby phase separation is induced and the separating phase precoats each of the dispersed particles; (4) setting the polymer-rich precoat; (5) separating said precoated particles; (6) suspending the precoated particles in an aqueous solution of a linear macromolecular synthetic polymer, a majority of whose polymer units comprise both lipophilic and hydrophilic units; (7) inducing phase separation, whereby to cause the formation of a polymer-rich phase and the encapsulation of each of the suspended precoated particles; (8) adjusting the pH of the solution whereby to reduce the solubility of the polymer and to rigidify the polymer-rich phase.

8. A process for the coating en masse of a plurality of individual discrete fluid and solid particles of hydrophilic matter which comprises: (1) preparing a solution of a liquid phase forming macromolecular polymer in a first non-aqueous liquid; (2) dispersing in said solution a plurality of individual discrete particles selected from the group consisting of insoluble fluid hydrophilic particles and insoluble solid hydrophilic particles; (3) adding a second liquid, soluble in the first liquid and non-solvent for said macromolecular polymer and said dispersed particles, whereby phase separation is induced and the separating phase precoats each of the dispersed particles; (4) setting the polymer-rich precoat; (5) separating said precoated particles; (6) suspending the precoated particles in an aqueous solution of an electrophoretically chargeable styrene-maleic acid copolymer and an oppositely electrophoretically chargeable gellable colloid at a pH outside the range which induces liquid phase separation; (7) inducing phase separation by the adjustment of a pH whereby to cause the formation of a colloid-copolymer rich phase and the encapsulation of each of the suspended precoated particles, the foregoing steps (6) and (7) being carried out at a temperature above the gelation point of the gellable colloid; (8) rigidifying the colloid-copolymer rich phase, whereby an isolatable encapsulated product is produced, by at least one of the steps of (a) cooling to a temperature of the colloid and (b) adding to the system a highly active carbonyl compound.

9. A process for coating en masse individual discrete particles of water soluble solid material which comprises:

(1) preparing a solution of ethylcellulose in a solvent system comprising a major portion of xylene and a minor portion of ethanol;

(2) suspending in the said solution individual discrete particles of water soluble solid material;

(3) inducing phase separation by means of the addition of n-hexane to the said solution whereby phase separation is induced and the separating phase envelopes individually and precoats individually each of the suspended discrete particles of water soluble solid material;

(4) spray drying the system whereby the individual precoated particles are obtained in a discrete dry condition;

(5) preparing a solution of styrene-maleic acid copolymer and water, said solution being at about 80° C.;

(6) suspending the discrete precoated particles in the aqueous styrene-maleic acid copolymer solution;

(7) inducing phase separation by means of the dropwise addition of an aqueous sodium sulfate solution heated to about 80° C. whereby phase separation is induced and the separating phase envelopes individually and coats individually each of the suspended precoated particles;

(8) maintaining the system at about 80° C. for about 20 minuts;

(9) pouring the system with vigorous stirring into a solution of water, sodium sulfate and glacial acetic acid having a temperature of about 5° C.;

(10) separating out the individually coated discrete particles;

(11) washing the coated particles with water; and

(12) freeze drying the coated particles.

10. A process for coating en masse individual discrete particles of microcrystalline ascorbic acid which comprises:

(1) preparing a solution of ethylcellulose in a solvent system comprising a major portion of xylene and a minor portion of ethanol;

(2) suspending in the said solution individual discrete particles of microcrystalline ascorbic acid;

(3) inducing phase separation by means of the addition of n-hexane to the said solution whereby phase separation is induced and the separating phase envelopes individually and precoats individually each of the suspended discrete particles of ascorbic acid;

(4) spray drying the system whereby the individual precoated particles of ascorbic acid are obtained in a discrete dry condition;

(5) preparing a solution of styrene-maleic acid copolymer and water, said solution being at about 80° C.;

(6) suspending the discrete precoated particles of ascorbic acid in the aqueous styrene-maleic acid copolymer solution;

(7) inducing phase separation by means of the dropwise addition of an aqueous sodium sulfate solution heated to about 80° C. whereby phase separation is induced and the separating phase envelopes individually and coats individually each of the suspended precoated particles of ascorbic acid;

(8) maintaining the system at about 80° C. for about 20 minutes;

(9) pouring the system with vigorous stirring into a solution of water, sodium sulfate and glacial acetic acid having a temperature of about 5° C.;

(10) separating out the individually coated discrete particles of ascorbic acid;

(11) washing the coated particles of ascorbic acid with water; and

(12) freeze drying the coated particles of ascorbic acid.

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