Description

This invention relates to novel microcapsules and a method of preparing the same.

The release control of a core material from microcapsules have been so far accomplished by increasing the thickness of the coating walls of said microcapsules or by forming compact coating walls on and around the core material thereof so as to decrease the permeability thereof. However, since ethylcellulose have been usually used as a wall-forming material for microcapsules of a medicament in order to mask unpleasant odor or taste thereof, such ethylcellulose microcapsules do not release the active ingredient in stomach.

US—A—3 247 066 describes colloid beads in the size range of 590 to 840 µm contained in coating walls of ethylcellulose and including a water-swellable colloid material such as starch or agar. These beads are used for a controlled release dosage form for internal administration.

As a result of various investigations, we have now found that ethylcellulose microcapsules which enable to protect the core material effectively and, when administered orally, release the core material rapidly in digestive organs such as stomach can be readily obtained by incorporating a swellable polymer material, i.e., a polymer material swellable in water, into the ethylcellulose coating walls and optionally into the core materials of said microcapsules.

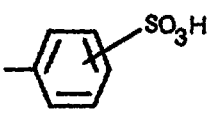
The new ethylcellulose microcapsules comprise (i) particles of a core material and (ii) ethylcellulose coating walls deposited on and around said particles of the core material, wherein a polymer material which shows at least 1.2 times increase in weight by immersing it in water at 37°C is incorporated into the ethylcellulose coating walls and optionally into the core material of the microcapsules.

Such novel microcapsules can be prepared by the steps of:

i) dissolving ethylcellulose in cyclohexane,
ii) dispersing particles of a core material in said solution (said core material optionally containing a polymer material which shows at least 1.2 times increase in weight by immersing it in water at 37°C),
iii) cooling the dispersion in the presence of a polymer material (said polymer material being the one which shows at least 1.2 times increase in weight by immersing it in water at 37°C) until ethylcellulose separates out from the dispersion to form coating walls on and around the particles of the core material, and
iv) recovering the resultant microcapsules therefrom.

Any pharmaceutically active compounds or medicaments which are insoluble or incompatible in cyclohexane or a mixture of cyclohexane and other solvent (e.g., n-hexane) can be used as the core material to be microencapsulated in the present invention. Such pharmaceutically active compounds or medicaments to be microencapsulated may be either solid, gel or semi-solid. In order to prepare a homogeneous dispersion at the microencapsulation step it is preferred that said pharmaceutically active compounds or medicaments have a particle size of about 30 to about 1000 µm, especially about 50 to about 500 µm. On the other hand, ethylcellulose having an ethoxy content of about 46.5 to about 55 w/w% is preferably used as the wall-forming material of the invention. It is also preferred that the viscosity of said ethylcellulose when measured at 25°C with respect to a 5 w/w% solution of it in toluene-ethanol (4:1) is within the range of about 3 to about 500 mPa . s, especially 40 to 200 mPa . s. Suitable amount of said ethylcellulose to be used is about 0.01 to 10 grams, especially about 0.05 to about 2 grams, per gram of the core material used. If required, the solvent cyclohexane may be used in admixture with other solvent such as n-hexane.

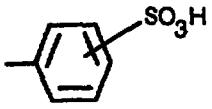
A wide variety of polymer materials which show at least 1.2 times increase in weight by immersing them in water at 37°C can be used as the "polymer material swellable in water" of the present invention. Representative examples of such polymer material include starch; crystalline cellulose; agar; alginic acid or its alkali earth metal salt; hydroxy-lower alkyl-polysaccharide, carboxy-lower alkyl-polysaccharide or alkali earth metal (e.g., calcium) salt thereof; a graft copolymer of polysaccharide, polyvinylalcohol or gelatin with a monomer of the formula (I): $CH_2=C(R^1)—Y$, wherein R^1 is hydrogen or methyl, and Y is carboxy, nitrile, lower alkoxycarbonyl or 2-pyrrolidon-1-yl; a cross-linked polysaccharide, a cross-linked polyvinylalcohol, a cross-linked gelatin, a cross-linked polyacrylic acid or an alkali metal salt of said cross-linked polyacrylic acid; and a copolymer of divinylbenzene with a monomer of the formula: $CH_2=C(R^2)—X$, wherein R^2 is hydrogen or methyl, and X is carboxy, lower alkoxycarbonyl, lower alkanoyloxy,



or 2-pyrrolidon-1-yl. Either one of potato starch, corn starch and wheat starch can be used as the polymer material swellable in water of the invention. On the other hand, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylstarch, carboxymethylcellulose or its alkali earth metal salt (e.g., calcium salt) and carboxymethylstarch or its alkali earth metal salt (e.g., calcium salt) and carboxymethylstarch or its alkali earth metal salt (e.g., calcium salt) are suitable as the above-mentioned hydroxy-lower alkyl-poly-

saccharide or carboxy-lower alkyl-polysaccharide. The polysaccharide which can be used to form the graft copolymers thereof with the monomer of the formula (I) may be either starch, cellulose, carboxymethylcellulose or agar. Acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, acrylonitrile and vinylpyrrolidone are suitable as the monomer of the formula (I). Preferred examples of the graft copolymer of said polysaccharide, polyvinylalcohol or gelatin with the monomer of the formula (I) include starch acrylic acid graft copolymer or its alkali metal salt (e.g., sodium, potassium salt), starch · acrylonitrile graft copolymer, starch · methacrylic acid graft copolymer or its alkali metal salt (e.g., sodium, potassium salt), cellulose · acrylic acid graft copolymer or its alkali metal salt (e.g., sodium, potassium salt), cellulose · methacrylic acid graft copolymer or its alkali metal salt (e.g., sodium, potassium salt), cellulose · acrylonitrile graft copolymer, carboxymethylcellulose · methyl acrylate graft copolymer, agar · vinylpyrrolidone graft copolymer, polyvinylalcohol · ethyl acrylate graft copolymer, polyvinylalcohol · acrylic acid graft copolymer or its alkali metal salt (e.g., sodium, potassium salt), and the like. Moreover, starch, cellulose, dextrin, dextran, alkali metal alginate, gum arabic, hydroxy-lower alkyl-starch (e.g., carboxymethylstarch), hydroxy-lower alkyl-cellulose (e.g., hydroxyethylcellulose, hydroxypropylcellulose), lower alkyl-cellulose (e.g., methylcellulose), polyvinylalcohol, gelatin, polyacrylic acid or its alkali metal salt (e.g., sodium or potassium salt) and the like may be used to form the cross-linked compound with a cross-linking agent such as epichlorohydrin, formaldehyde, glutaraldehyde or acrylic acid. Suitable examples of such cross-linked compound include epichlorohydrin cross-linked carboxymethylcellulose, epichlorohydrin cross-linked carboxymethylstarch or its sodium salt, epichlorohydrin cross-linked hydroxyethylcellulose, epichlorohydrin cross-linked hydroxypropylcellulose, epichlorohydrin cross-linked methylcellulose, epichlorohydrin cross-linked alginic acid, self cross-linked polyacrylic acid or its potassium salt, epichlorohydrin cross-linked dextrin, epichlorohydrin cross-linked dextran, epichlorohydrin cross-linked gum arabic and formaldehyde cross-linked gelatin. Further, acrylic acid, methacrylic acid, methyl acrylate, styrenesulfonic acid, vinyl acetate and vinylpyrrolidone can be suitably used as the monomer of the formula (II).

Preferred examples of the copolymer of divinylbenzene with the monomer of the formula (II) are divinylbenzene · acrylic acid copolymer or its alkali metal salt (e.g., sodium, potassium salt), divinylbenzene · methacrylic acid copolymer or its alkali metal salt (e.g., sodium, potassium salt), divinylbenzene · styrenesulfonic acid copolymer or its alkali metal salt (e.g., sodium, potassium salt), divinylbenzene · vinylacetate copolymer, divinylbenzene · methyl acrylate copolymer, divinylbenzene · vinylpyrrolidone copolymer and the like. Among the above-mentioned various polymers, a preferred subgenus of the polymer material swellable in water of the present invention includes starch, crystalline cellulose, agaralginic acid, or alkali earth metal salts of alginic acid; hydroxy-lower alkyl-cellulose, hydroxy-lower alkyl-starch, carboxy-lower alkyl-cellulose, carboxy-lower alkyl-starch or an alkali earth metal salt thereof; a graft copolymer of starch, cellulose or polyvinylalcohol with a monomer of the formula: $CH_2=C(R^1)—Y'$, wherein R^1 is the same as defined above and Y' is carboxy or nitrile; a cross-linked dextrin, a cross-linked dextran, a cross-linked arabic gum, a cross-linked alginic acid, a cross-linked gelatin or a cross-linked polyacrylic acid: and a copolymer of divinylbenzene and a monomer of the formula: $CH_2=C(R^2)—X'$ wherein R^2 is hydrogen or methyl and X' is carboxy or



More preferred subgenus of said polymer material swellable in water of the invention includes, for example, starch, crystalline cellulose, agar, alginic acid or its alkali earth metal salt, hydroxypropylstarch (hydroxypropyl content: 2—7 w/w%), hydroxy-propylcellulose (hydroxypropyl content: 2—7 w/w%), carboxymethyl-cellulose or its alkali earth metal salt (e.g., calcium salt), starch · acrylic acid graft copolymer or its alkali metal salt (e.g., sodium, potassium salt), starch · acrylonitrile graft copolymer, cellulose · acrylic acid graft copolymer or its alkali metal salt (e.g., sodium, potassium salt), cellulose · acrylonitrile graft copolymer, polyvinylalcohol · acrylic acid graft copolymer or its alkali metal salt (e.g., sodium, potassium salt), epichlorohydrin cross-linked dextrin, epichlorohydrin cross-linked arabic gum, epichlorohydrin cross-linked dextran, epichlorohydrin cross-linked alginic acid, epichlorohydrin cross-linked polyvinylalcohol, formaldehyde cross-linked gelatin, self cross-linked polyacrylic acid, divinylbenzene · acrylic acid copolymer or its alkali metal salt (e.g., sodium, potassium salt), divinylbenzene · methacrylic acid copolymer or its alkali metal salt (e.g., sodium, potassium salt), divinylbenzene · styrenesulfonic acid copolymer or its alkali metal salt (e.g., sodium, potassium salt) and the like. It is preferred to use such swellable polymer material in the form of fine powder, especially in the form of fine particles having a particle size of about 0.1 to about 300 µm. Suitable amount of said polymer material to be incorporated into the core material is about 99 to 3 w/w%, especially about 90 to about 5 w/w%, and more especially about 10 to about 50 w/w%. For incorporation of said polymer material swellable in water into the coating walls of the microcapsules, it is preferred to use said swellable polymer material in an amount of not less than about 0.01 gram, especially about 0.01 to 20 grams, more especially about 0.1 to about 10 grams, per gram of the wall-forming material. When the polymer material swellable

in water is incorporated into both of the coating walls and core material of the microcapsules, the amount of said polymer material to be used should also be within the ranges mentioned above.

In making the ethylcellulose microcapsules of the core material, it is preferred to dissolve ethylcellulose in cyclohexane at about 80°C, and then dispersing the core material therein. Alternatively, when the ethylcellulose microcapsules are prepared by the use of the swellable polymer material-containing core material, it is preferred that a mixture of the core material and the swellable polymer material is granulated into particles having a particle size of about 30 to about 1000 µm, especially about 50 to about 500 µm in a conventional manner, and the swellable polymer material-containing core material thus obtained is then dispersed in the ethylcellulose solution at about 80°. In these cases, it is also preferred that ethylcellulose is dissolved in cyclohexane at a concentration of about 0.5 to about 10 w/v%, especially about one to about 5 w/v%. Moreover, particles of the swellable polymer material-containing core material may be made by treating a mixture of the core material and the swellable polymer material according to either conventional wet-granulation or dry-granulation methods as described in Remington's "Pharmaceutical Science" 13-th Edition pages 568 to 572 (1965).

When the above-mentioned dispersion is then cooled gradually (e.g., at a rate of 0.05 to 4°C, especially about 0.4°C, per minute), ethylcellulose in the form of "gel" separates out from the dispersion at about 75°C thereby depositing on or wrapping the particles of the core material, and the ethylcellulose gel thus deposited forms seamless and complete walls at about 50°C. It is preferred to carry out said phase separation of ethylcellulose under continuous stirring at about 100 to about 600 r.p.m. . When the dispersion is then further cooled to a temperature not higher than 40°C (e.g., 30° to 20°C), the thus-formed embryonic microcapsules are shrunken and become solid by solvent loss from the coating walls, thus giving stable ethylcellulose microcapsules. Moreover, said phase-separation of ethylcellulose in cyclohexane may be conducted either in the presence or absence of a phase-separation-inducing agent, i.e., either by coacervation or flocculation of ethylcellulose. If required, in carrying out said phase-separation of ethylcellulose, an organosilicon polymer and/or a surfactant may be used in combination with ethylcellulose. Suitable examples of the phase-separation-inducing agent include polyethylene, butyl rubber, polyisobutylene and polybutadiene. Dimethylpolysiloxane and methylphenylpolysiloxane are suitable as the organosilicon polymer. Further, the surfactants which can be used in the present invention include, for example, an ester of C_{12-18} fatty acid with sorbitan (e.g., sorbitan monolaurate, sorbitan sesquilaurate, sorbitan trilaurate, sorbitan monooleate), an ester of C_{8-18} fatty acid with glycerin (e.g., glycerin monocaprylate, glycerin monolaurate, glycerin monooleate), a phospholipid (e.g., soybean phospholipids, egg-yolk phospholipids), calcium stearoyl-2-lactate, an ester of C_{8-18} fatty acid with propylene glycol (e.g., propylene glycol monocaprylate, propylene glycol monostearate) and an ester of C_{12-18} fatty acid with sucrose (e.g., sucrose mono-, di or tri-stearate). It is preferred that said phase-separation-inducing agent, organosilicon polymer and surfactant are added to the ethylcellulose solution prior to dispersing the core material in said solution. Suitable concentration of the phase-separation-inducing agent, the organosilicon polymer and the surfactant in the ethylcellulose solution is about 0.1 to about 10 w/v%, about 0.01 to about 10 w/v% and about 0.001 to about 10 w/v%, respectively.

Further, for incorporating the swellable polymer material into the coating walls of the ethylcellulose microcapsules, said swellable polymer material is added to the dispersion either before cooling the dispersion or during the cooling step. Especially, it is preferred that the polymer material swellable in water is added to the dispersion at the stage where coating walls of ethylcellulose in the form of "gel" is formed on and around the particles of the core material and the coating walls of the thus-obtained embryonic microcapsules have a viscosity of about 0.01 Pa . s to about 5.0 Pa . s, especially 0,1 to 1 Pa . s. More specifically, since the coating walls having a viscosity of the above-mentioned range is formed by cooling the dispersion to about 55° to 75°C, especially about 60° to about 70°C, it is preferred that the swellable polymer material is added to the dispersion when cooled to said temperature. By adding the swellable polymer material in the manner as mentioned above, said polymer material is incorporated or dispersed into the coating walls of the microcapsules. When the dispersion is then further cooled to a temperature not higher than 40°C (e.g., 30° to 20°C), the thus-formed embryonic microcapsules are shrunken and become solid by solvent loss from the coating walls, thus giving stable ethylcellulose microcapsules.

The microcapsules thus obtained may be recovered by conventional manners such as, for example, decantation, filtration, centrifugation and so forth. In accordance with any one of the methods of the present invention, the ethylcellulose microcapsules can be obtained without being agglomerated together into large lumps each consisting of a myriad of individual capsules. Moreover, if required, the ethylcellulose microcapsules may be washed with cyclohexane, petroleum ether or n-hexane and then dried by conventional manners (e.g., hot-air drying method).

Further, the above-mentioned methods of the present invention can be used for microencapsulation of a wide variety of pharmaceutically active compounds or medicaments. Such pharmaceutically active compounds or medicaments which can be used in the present invention include, for example, vitamines, amino acids, peptides, chemotherapeutic agents, antibiotics, agents affecting respiratory organs, antitussive expectorants, antitumor agents, autonomic drugs, neuropsychotropic agents, local anesthetics, muscule relaxants, agents affecting digestive organs, antihistaminic agents, sedatives, anticonvulsants, analgesics, antipyrretic anticoagulants, hepatics, blood sugar-lowering agents and so forth. The

medicament to be microencapsulated may also be a composition containing said pharmaceutically active compound together with an inert excipient or vehicle.

The pharmaceutically active compound-containing ethylcellulose microcapsules of the present invention thus obtained show no substantial retardation in release of said pharmaceutically active compound (core material) in stomach or other digestive organs because the polymer material swellable in water incorporated into the coating walls and optionally core material of the microcapsules can effectively accelerate the release of the active ingredient from the microcapsules. Namely, when the ethylcellulose microcapsules of the invention is contacted with an aqueous solution such as gastric juice, the polymer material swellable in water which is incorporated into the coating walls and optionally core material is swollen rapidly by absorbing water penetrated into the microcapsules and serves to break the ethylcellulose coating walls or to accelerate the dissolution of the core material in water so as to release rapidly the active ingredient from the core material. Moreover, in the microcapsules of the present invention, the release velosity of a pharmaceutically active compound can be controlled not only by suitable choice of the water-swellable polymer material and the amount thereof, but also by incorporating said swellable polymer material into both of the coating walls and core material of the microcapsules.

By incorporating the polymer material swellable in water into the coating walls, said ethylcellulose coating walls of the microcapsules when contacted with gastric juice lose their compact network structure and become permeable to water due to increase in volume of said polymer material, and water thus penetrated into the microcapsules serves to dissolve the core material gradually. Moreover, when said polymer material swellable in water is incorporated into both of the coating walls and core material of the microcapsules, the active ingredient can be released swiftly in stomach because gastric juice first serves to break the ethylcellulose coating walls, and water when contacted with the core material also serves to accelerate the dissolution of the core material in water. Further, the ethylcellulose microcapsules of the invention which are made by incorporating the swellable polymer material into the coating walls thereof are advantageous in that said swellable polymer material serves to improve the wall characteristics of ethylcellulose film deposited on particles of the core material, and such ethylcellulose microcapsules show excellent free-flowing characteristics. Thus, pharmaceutical preparations such as tablets can be made therefrom without deterioration in the quality of such pharmaceutical preparations such as sticking or capping in compressed tablets.

Practical and presently preferred embodiments of the present invention are illustratively shown in the following Examples. Throughout the specification and claims, the terms " lower alkyl", "lower alkoxy" and "lower alkanoyl" should be interpreted as referring to those having one to 4 carbon atoms.

Experiment I

Pyridoxal phosphate-containing microcapsules (a polymer material swellable in water being incorporated into the core material thereof) were prepared according to the following methods. Then, the yield of the microcapsules obtained, the amount of the active ingredient contained in the microcapsules and the t_{50}-values thereof (i.e., a period of time which was required to release 50% of the active ingredient from the microcapsules) in water (37°C) were examined, respectively.

(i) Core materials:

33 parts (by weight) of water were added to a mixture of 80 parts (by weight) of fine powder of pyridoxal phosphate and 20 parts (by weight) of a swellable polymer material shown in the following Table 1, and the mixture was granulated and dried in a conventional manner. The thus-obtained granules having particle size of 105—210 µm were used as the core materials in Experiment Nos. 1—16. On the other hand, the core materials (particle size: 105—210 µm) in Experiment Nos. 17—20 were prepared from a mixture of 79 parts (by weight) of fine powder of pyridixal phosphate, one part (by weight) of methylcellulose, 20 parts (by weight) of a water-swellable polymer material and 10 parts (by weight) of water in the same manner as described above.

(ii) Preparation of microcapsules:

14 g of ethylcellulose (ethoxy content: 48 w/w%, viscosity: 0,1 Pa . s (100 cP) and 21 g of silicone resin (prepared by dispersing 3—15 w/w% of silicon dioxide in 97—95 w/w% of dimethylpolysiloxane having a viscosity of (1—11)$\times 10^{-4}$ $m^2 \cdot s^{-1}$ (100—1100 cSt) at 25°C) were dissolved in 700 ml of cyclohexane at 80°C under stirring. 56 g of the core material were dispersed to the solution, and the mixture was cooled gradually to room temperature (about 25°C) under stirring at 400 r.p.m.. The microcapsules thus formed were recovered by filtration, washed with n-hexane and dried. Then, said microcapsules were passed through JIS (Japanese Industrial Standard) standard sieve (350 µm aperture). Pyridoxal phosphate-containing microcapsules which met the requirements of "Pulvers" specified in The Pharmacopoeia of Japan 10th-Edition were obtained.

On the other hand, pyridoxal-containing microcapsules of a control group were prepared in the same manner as described above except that 56 g of pyridoxal phosphate having particle size of 105—210 µm were used as the core material.

The results are shown in the following Table 1.

TABLE 1

Experiment Nos.	Polymer materials swellable in water: Polymer materials	Degree of swelling*	Yield (g) of micro-capsules	Active ingredient contained in micro-capsules (%)	t_{50}-** values (hrs)
1	Starch · acrylic acid graft copolymer (sodium salt)	400	61	64.8	0.4
2	Polyvinylalcohol · acrylic acid graft copolymer (sodium salt)	200	67	64.2	0.6
3	Cellulose · acrylic acid graft copolymer (sodium salt)	700	67	64.8	0.6
4	Starch · acrylonitrile graft copolymer alkali hydrolysate	400	64	64.5	0.8
5	Cellulose · acrylonitrile graft copolymer alkali hydrolysate	600	61	64.5	0.8
6	Epichlorohydrin cross-linked dextrin	50	67	64.3	3.2
7	Epichlorohydrin cross-linked arabic gum	100	65	64.3	2.8
8	Epichlorohydrin cross-linked polyvinylalcohol	60	63	64.6	1.2
9	Formaldehyde cross-linked gelatin	20	65	64.4	7.5
10	Divinylbenzene · acrylic acid copolymer (sodium salt)	1000	62	64.9	2.1
11	Divinylbenzene · methacrylic acid copolymer (sodium salt)	240	64	64.7	1.2
12	Potato starch	1.4	63	64.9	16.5
13	Epichlorohydrin cross-linked dextran	35	63	64.5	1.6
14	Self cross-linked poly-acrylic acid (sodium salt)	400	64	64.0	0.4
15	Self cross-lined poly-acrylic acid (sodium salt)	900	61	64.1	0.6

TABLE 1-(continued)

Experiment Nos.	Polymer materials swellable in water: Polymer materials	Degree of swelling*	Yield (g) of micro-capsules	Active ingredient contained in micro-capsules (%)	t_{50}-** values (hrs)
16	Carboxymethylcellulose (calcium salt)	1.9	65	64.1	6.0
17	Carboxymethylcellulose	2.3	63	64.3	5.7
18	Sulfonated styrene divinylbenzene copolymer (sodium salt)	1.5	61	63.7	3.5
19	Methacrylic acid divinyl-benzene copolymer (sodium salt)	1.8	64	63.5	2.9
20	Crystalline cellulose	1.2	63	64.5	23.5
(Control) 21	—	—	62	86.5	only 5% of the active ingredient was released after 24 hrs of the experiment.

Note: *:"Degree of swelling" means the weight (grams) of the water-swellable polymer material which was swollen by immersing one grm of said polymer material in water (37°C).
**:Period of time required to release 50% of the active ingredient from the microcapsules

Experiment II

Trimebutine maleate (Chemical name: 2-dimethylamino-2-phenylbutyl-3,4,5-trimethoxybenzoate hydrogen maleate)-containing microcapsules (a polymer material swellable in water being incorporated into the coating wall thereof) were prepared according to the following methods. Then, the yield of the microcapsules obtained, the amount of the active ingredient (trimebutine maleate) contained in the microcapsules and the t_{50}-values thereof (i.e., a period of time which was required to release 50% of the active ingredient from the microcapsules) in water (37°) were examined, respectively.

(i) Core materials:

A solution of 3 parts (by weight) of methylcellulose in 15 parts (by weight) of water was added to a mixture of 23.3 parts (by weight) of trimebutine maleate and 73.7 parts (by weight) of lactose, and the mixture was granulated and dried in a conventional manner. The thus-obtained granules having particle size of 105—350 µm were used as the core materials.

(ii) Preparation of microcapsules:

0.8 g of soybean phospholipids and 24 g of silicon resin (prepared by dispersing 3—15 w/w% of silicon dioxide in 97—85 w/w% of dimethylpolysiloxane having a viscosity of $(1—11)\times10^{-4}$ $m^2 \cdot s^{-1}$ (100—1100 cSt) at 25°C) were dissolved in 800 ml of cyclohexane, and 20 g of ethylcellulose (ethoxy content: 48 w/w%, viscosity: 0,1 Pa . s (100 cP) were further dissolved therein at 80°C. 100 g of the core material were dispersed in the solution, and the mixture was cooled gradually under stirring at about 400 r.p.m.. When the mixture was cooled to about 65°C, 100 g of fine powder of a polymer material swellable in water was added thereto. Then, the mixture was further cooled to room temperature under the same conditions as above. The microcapsules thus formed were recovered by filtration, washed with n-hexane and dried. The microcapsules were passed through JIS standard sieve (500 µm aperture) and then JIS standard sieve (105 µm). The microcapsules which passed through the former sieve but did not pass through the latter sieve were collected. Trimebutine maleate-containing microcapsules which met the requirements of "Fine Granules" specified in The Pharmacopoeia of Japan 10th-Edition were obtained.

Trimebutine maleate-containing microcapsules of a control group were prepared in the same manner as described above but without using said swellable polymer material.

The results are shown in the following Table 2.

TABLE 2

Experiment Nos.	Polymer materials swellable in water: Polymer materials	Degree of swelling*	Yield (g) of micro-capsules	Active ingredient contained in micro-capsules (%)	t_{50}-values (hrs)
1	Carboxymethylcellulose (calcium salt)	1.9	208	10.8	8
2	Carboxymethylcellulose	2.3	203	10.9	7
3	Corn starch	1.3	204	11.2	24
4	Potato starch	1.4	204	10.6	20
5	Hydroxypropyl starch	1.3	206	10.7	26
6	Epichlorohydrin cross-linked dextran	35	205	10.5	5
7	Epichlorohydrin cross-linked polyvinylalcohol	60	209	11.1	4
8	Hydroxypropyl cellulose	20	207	10.7	11
9	Agar	4.4	209	11.0	9
(Control) 10	—	—	101	19.9	78

Note: *: same as defined in the footnote of Table 1.

Experiment III

Pyridoxal phosphate-containing microcapsules (a polymer material swellable in water being incorporated into both of the core material and coating wall thereof) were prepared according to the following methods. Then, the yield of the microcapsules obtained, the amount of the active ingredient contained in the microcapsules and the t_{50}-values thereof (i.e., a period of time which was required to release 50% of the active ingredient from the microcapsules) in water (37°C) were examined, respectively.

(i) Core materials:

25 parts (by weight) of water were added to a mixture of 90 parts (by weight) of fine powder of pyridoxal phosphate and 10 parts (by weight) of self cross-linked polyacrylic acid (Degree of Swelling: 400), and the mixture was granulated and dried in a conventional manner. The thus-obtained granules having particle size of 105—210 were used as the core materials.

(ii) Preparation of microcapsules:

24 g of a phase separation-inducing agent shown in the following Table 3 were dissolved in 800 ml of cyclohexane, and 16 g of ethylcellulose (ethoxy content: 49 w/w%, viscosity: 90 mPa . s) were further dissolved therein at 80°C. 64 g of the core material were dispersed in the solution, and the mixture was cooled gradually under stirring at 400 r.p.m.. When the mixture was cooled to about 65°C, 80 g of carboxymethylcellulose (calcium salt) (degree of swelling: 1.9) were added thereto. Then, the mixture was cooled to room temperature under the same conditions as above. The microcapsules thus formed were recovered by filtration, washed with n-hexane and dried. The microcapsules were passed through JIS standard sieve (350 µm aperture). Pyridoxal phosphate-containing microcapsules which met the requirements of "Pulvers" specified in The Pharmacopoeia of Japan 10th-Edition were obtained.

The results are shown in the following Table 3.

TABLE 3

Experiment Nos.	Phase separation-inducing agents	Yield (g) of micro-capsules	Active ingredient contained in micro-capsules (%)	t_{50}-values (minutes)
1	Polyisobutyrene (molecular weight: 800,000)	156	36.3	57
2	Polyethylene (molecular weight: 7,000)	152	36.9	33
3	Silicon resin*	153	36.5	65
4	Butyl rubber (viscosity of 67 "Mooney" 8 minutes reading at 100°C)	155	36.7	41
5	Dimethyl polysiloxane (viscosity at 25°C: 500,000 mPa . s)	157	36.7	69

Note: *: same as used in Experiment I.

Example 1

0.4 g of soybean phospholipids and 24 g of silicon resin (same one as used in Experiment II) were dissolved in 800 ml of cyclohexane, and 20 g of ethylcellulose (same one as used in Experiment I) were dissolved therein at 80°C. 60 g of timepidium bromide (Chemical name: di-(2-thienyl)-(N-methyl-5-methoxy-3-piperidilidene)methane methyl bromide) having particle size of 88—210 µm were dispersed in the solution, and the mixture was cooled gradually under stirring at 400 r.p.m.. When the mixture was cooled to 65°C, 100 g of carboxymethylcellulose were added thereto. Then, the mixture was cooled to room temperature under the same conditions as above. The microcapsules thus formed were recovered by filtration, washed with n-hexane and dried. Then, the microcapsules were passed through JIS standard sieve (350 µm aperture). 176 g of timepidium bromide-containing microcapsules which met the requirements of "Pulvers" specified in The Pharmacopoeia of Japan 10th-Edition were obtained.

Example 2

232 g of timepidium bromide-containing microcapsules were obtained in the same manner as described in Example 1 except that 160 g of wheat starch were used instead of carboxymethylcellulose (calcium salt).

Example 3

(1) 7 parts (by weight) of aqueous 45 v/v% ethanol were added to a mixture of 13.3 parts (by weight) of diltiazem hydrochloride, 41.7 parts (by weight) of corn starch, 40 parts (by weight) of lactose and 5 parts (by weight) of dextrin, and the mixture was granulated and dried in a conventional manner. The thus-obtained granules having particle size of 105—250 µm were used as the core material.

(2) 0.4 g of calcium stearyl-lactate (Chemical name: calcium stearoyl-2-lactate) and 24 g of silicon resin (same one as used in Experiment I) were dissolved in 800 ml of cyclohexane, and 16 g of ethylcellulose (same one as used in Experiment I) were dissolved therein at 80°C. 80 g of the core material were dispersed in the solution, and the mixture was cooled gradually under stirring at about 400 r.p.m.. When the mixture was cooled to about 65°C, 80 g of carboxymethylcellulose and 80 g of corn starch were added thereto. Then, the mixture was cooled to room temperature under the same conditions as above. The microcapsules thus formed were recovered by filtration, washed with n-hexane and dried. The microcapsules were passed through JIS standard sieve (350 µm aperture). 250 g of diltiazem hydrochloride-containing microcapsules which met the requirements of "Pulvers" specified in The Pharmacopoeia of Japan 10th-Edition were obtained.

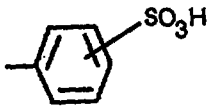
Example 4

249 g of diltiazem hydrochloride-containing microcapsules were obtained in the same manner as described in Example 3 except that 80 g of agar and 80 g of hydroxypropyl-starch were used instead of carboxy methylcellulose and corn starch.

Claims

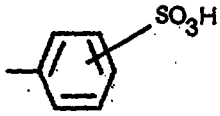
1. Ethylcellulose microcapsules comprising (i) particles of a core material and (ii) ethylcellulose coating walls deposited on and around said particles of the core material, wherein a polymer material which shows at least 1.2 times increase in weight by immersing it in water at 37°C is incorporated into the ethylcellulose coating walls and optionally into the core material of the microcapsules.

2. The ethylcellulose microcapsules of Claim 1, in which said polymer material is selected from the class consisting of starch, crystalline cellulose, agar, alginic acid or its alkali earth metal salt, hydroxy-C_{1-4}alkyl-polysaccharide, carboxy-C_{1-4}alkyl-polysaccharide or its alkali earth metal salt, a graft copolymer of polysaccharide, polyvinylalcohol or gelatin with a monomer of the formula: $CH_2=C(R^1)—Y$ (wherein R^1 is hydrogen or methyl, and Y is carboxy, nitrile, C_{1-4}-alkoxycarbonyl or 2-pyrrolidon-1-yl), a cross-linked polysaccharide, a cross-linked polyvinylalcohol, a cross-linked gelatin, a cross-linked polyacrylic acid or its alkali metal salt, and copolymer of divinylbenzene with a monomer of the formula: $CH_2=C(R^2)—X$ (wherein R^2 is hydrogen or methyl, and X is carboxy, C_{1-4}alkoxycarbonyl, C_{1-4}alkanoyloxy,



or 2-pyrrolidon-1-yl).

3. The ethylcellulose microcapsules of Claim 1, in which said polymer material is selected from the class consisting of starch, crystalline cellulose, alginic acid or its alkali earth metal salt, agar, hydroxy-C_{1-4}-alkyl-cellulose, hydroxy-C_{1-4}-alkyl-starch, carboxy-C_{1-4}-alkyl-cellulose, carboxy-C_{1-4}-alkyl-starch or its alkali earth metal salt, a graft copolymer of starch, cellulose or polyvinylalcohol with a monomer of the formula: $CH_2=C(R^1)—Y'$ (wherein R^1 is hydrogen or methyl and Y' is carboxy or nitrile), a cross-linked dextrin, a cross-linked dextran, a cross-linked gum arabic, a cross-linked gelatin, a cross-linked alginic acid, a cross-linked polyacrylic acid and a copolymer of divinylbenzene with a monomer of the formula: $CH_2=C(R^2)—X'$ (wherein R^2 is hydrogen or methyl and X' is carboxy or



).

4. The ethylcellulose microcapsules of Claim 1, in which said polymer material is selected from the class consisting of starch, crystalline cellulose, agar, alginic acid or its alkali earth metal salt, hydroxypropylstarch (hydroxypropyl content: 2—7 w/w%), hydroxypropylcellulose (hydroxypropyl content: 2—7 w/w%), carboxymethylcellulose or its alkali earth metal salt, starch · acrylic acid graft copolymer or its alkali metal salt, starch · acrylonitrile graft copolymer, cellulose · acrylic acid graft copolymer or its alkali metal salt, cellulose · acrylonitrile graft copolymer, polyvinylalcohol · acrylic acid graft copolymer or its alkali metal salt, epichlorohydrin cross-linked dextran, epichlorohydrin cross-linked alginic acid, epichlorohydrin cross-linked polyvinylalcohol, formaldehyde cross-linked gelatin, acrylic acid cross-linked polyacrylic acid, divinylbenzene · acrylic acid copolymer or its alkali metal salt, divinylbenzene · methacrylic acid copolymer or its alkali metal salt and divinylbenzene · styrene-sulfonic acid copolymer or its alkali metal salt.

5. The ethylcellulose microcapsules of Claim 1, 2, 3 or 4, in which said polymer material is incorporated into the ethylcellulose coating walls in an amount of not less than 0.01 gram per gram of ethylcellulose and/or into the core material in an amount of 3 to 99 w/w%.

6. The ethylcellulose microcapsules of Claim 1, 2, 3 or 4, in which said polymer material is incorporated into the ethylcellulose coating walls in an amount of 0.01 to 20 grams per gram of ethylcellulose and/or into the core material in an amount of 3 to 90 w/w%.

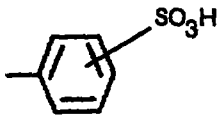
7. The ethylcellulose microcapsules of Claim 1, 2, 3, 4, 5 or 6, in which the core material is a pharmaceutically active compound having a particle size of 30—1000 µm, ethylcellulose having an ethoxy content of 46.5—55 w/w% and a viscosity (measured at 25°C with respect to a 5 w/w% solution of it in toluene-ethanol (4:1)) of 3 to 500 mPa . s is used, and the swellable polymer material having a particle size of 0.1 to 300 µm is used.

8. A process for preparing the ethylcellulose microcapsules of Claim 1, which comprises the steps of:

i) dissolving ethylcellulose in cyclohexane,
ii) dispersing particles of a core material in said solution (said core material optionally containing a polymer material which shows at least 1.2 times increase in weight by immersing it in water at 37°C),
iii) cooling the dispersion in the presence of a polymer material (said polymer material being one which shows at least 1.2 times increase in weight by immersing it in water at 37°C) until ethylcellulose separates out from the dispersion to form coating walls on and around the particles of the core material, and
iv) recovering the resultant microcapsules therefrom.

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9. The process according to Claim 8, wherein said polymer material is selected from the class consisting of starch, crystalline cellulose, agar, hydroxy-C_{1-4}alkylcellulose, hydroxy-C_{1-4}alkyl starch, carboxy-C_{1-4}alkylcellulose, carboxy-C_{1-4}alkylstarch or its alkali starch metal salt, a graft copolymer of starch, cellulose or polyvinylalcohol with a monomer of the formula: $CH_2=C(R^1)—Y'$ (wherein R^1 is hydrogen or methyl and Y' is carboxy or nitrile), a cross-linked dextrin, a cross-linked dextran, a cross-linked gum arabic, a cross-linked gelatin, a cross-linked polyacrylic acid and a copolymer of divinylbenzene with a monomer of the formula: $CH_2=C(R^2)—X'$ (wherein R^2 is hydrogen or methyl and X' is carboxy or



).

10. The process according to Claim 8, wherein said polymer material is selected from the class consisting of starch, crystalline cellulose, agar, hydroxy-propylstarch (hydroxypropyl content: 2—7 w/w%), hydroxypropyl-cellulose (hydroxypropyl content: 2—7 w/w%), carboxymethylcellulose or its alkali earth metal salt, starch · acrylic acid graft copolymer or its alkali metal salt, starch · acrylonitrile graft copolymer, cellulose · acrylic acid graft copolymer or its alkali metal salt, cellulose · acrylonitrile graft copolymer, polyvinylalcohol · acrylic acid graft copolymer or its alkali metal salt, epichlorohydrin cross-linked dextrin, epichlorohydrin cross-linked gum arabic, epichlorohydrin cross-linked dextran, epichlorohydrin cross-linked polyvinylalcohol, formaldehyde cross-linked gelatin, acrylic acid cross-linked polyacrylic acid, divinylbenzene · acrylic acid copolymer or its alkali metal salt, divinylbenzene · methacrylic acid copolymer or its alkali metal salt and divinylbenzene · styrenesulfonic acid copolymer or its alkali metal salt.

11. The process according to Claim 8, wherein ethylcellulose having an ethoxy content of 46.5 to 55 w/w% is used in an amount of 0.01 to 10 grams per gram of the core material, and the dispersion is cooled in the presence of not less than 0.01 gram (per gram of ethylcellulose) of the polymer material.

12. The process according to Claim 11, wherein the dispersion is cooled in the presence of 0.01 to 20 grams of the polymer material per gram of ethylcellulose.

13. The process according to Claim 8, 11 or 12, wherein the core material contains 3—99 w/w% of the polymer material.

14. The process according to Claim 13, wherein the core material contains 3—90 w/w% of the polymer material.

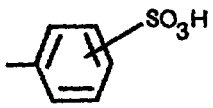
15. The process according to Claim 8, 9 or 10, wherein the core material is a pharmaceutically active compound having a particle size of 30—1000 µm, ethylcellulose having an ethoxy content of 46.5 to 55 w/w% and a viscosity (measured at 25°C with respect to a 5 w/w% solution of it in toluene-ethanol (4:1)) of 3 to 500 mPa . s is used in an amount of 0.01 to 10 grams per gram of the core material, and the dispersion is cooled in the presence of 0.01 to 20 grams (per gram of ethylcellulose) of the polymer material having a particle size of 0.1 to 300 µm.

16. The process according to Claim 8, 9, 10 or 15 wherein at least one member selected from a phase-separation-inducing agent, an organosilicon polymer and a surfactant is further added to the solution of ethylcellulose.

Patentansprüche

1. Ethylcellulose-Mikrokapseln aus (i) Teilchen eines Kernmaterials und (ii) Ethylcellulose-Überzugswandungen, die auf und um die Teilchen des Kernmaterials abgeschieden sind, worin ein Polymermaterial, welches eine wenigstens 1,2-fache Gewichtserhöhung beim Eintauchen in Wasser bei 37°C zeigt, in die Ethylcellulose-Überzugswandung und gewünschtenfalls in das Kernmaterial der Mikrokapseln inkorporiert ist.

2. Ethylcellulose-Mikrokapseln gemäss Anspruch 1, bei welchen das Polymermaterial ausgewählt ist aus der Klasse, bestehend aus Stärke, kristalliner Cellulose oder deren Erdalkalisalz, Hydroxy-C_{1-4}-alkyl-polysaccharid, Carboxy-C_{1-4}-alkyl-polysaccharid oder deren Erdalkalisalzen, einem Pfropfcopolymer von Polysaccharid, Polyvinylalkohol oder Gelatine mit einem Monomer der Formel $CH_2=C(R^1)—Y$ (worin R^1 Wasserstoff oder Methyl und Y Carboxy, Nitril, C_{1-4}-Alkoxycarbonyl oder 2-Pyrrolidon-1-yl bedeuten), einem vernetzten Polysaccharid, einem vernetzten Polyvinylalkohol, einer vernetzten Gelatine, einer vernetzten Polyacrylsäure oder deren Alkalisalz, und einem Copolymer aus Divinylbenzol mit einem Monomer der Formel $CH_2=C(R^2)—X$ (worin R^2 Wasserstoff oder Methyl und X Carboxy, C_{1-4}-Alkoxycarbonyl, C_{1-4}-Alkanoyloxy

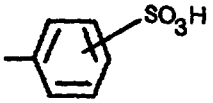


oder 2-Pyrrolidon-1-yl bedeuten).

3. Ethylcellulose-Mikrokapseln gemäss Anspruch 1, worin das Polymermaterial ausgewählt ist aus der Klasse, bestehend aus Stärke, kristalliner Cellulose, Alginsäure oder deren Erdalkalisalz, Agar,

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Hydroxy-C_{1-4}-alkyl-cellulose, Hydroxy-C_{1-4}-alkyl-stärke, Carboxy-C_{1-4}-alkyl-cellulose, Carboxy-C_{1-4}-alkyl-stärke oder deren Erdalkalisalz, einem Pfropfcopolymer von Stärke, Cellulose oder Polyvinylalkohol mit einem Monomer der Formel $CH_2=C(R^1)—Y'$ (worin R^1 Wasserstoff oder Methyl und Y' Carboxy oder Nitril bedeuten), einem vernetzten Dextrin, einem vernetzten Dextran, einem vernetzten Gummiarabikum, einer vernetzten Gelatine, einer vernetzten Alginsäure, einer vernetzten Polyacrylsäure und einem Copolymer aus Divinylbenzol mit einem Monomer der Formel $CH_2=C(R^2)—X'$ (worin R^2 Wasserstoff oder Methyl und X' Carboxy oder



bedeuten).

4. Ethylcellulose-Mikrokapseln gemäss Anspruch 1, worin das Polymermaterial ausgewählt ist aus der Klasse, bestehend aus Stärke, kristalliner Cellulose, Agar, Alginsäure oder deren Erdalkalisalz, Hydroxypropylstärke (Hydroxypropylgehalt: 2 bis 7 w/w-%), Hydroxypropylcellulose (Hydroxypropylgehalt: 2 bis 7 w/w-%), Carboxymethylcellulose oder deren Erdalkalisalz, Stärke-Acrylsäure-Pfropfcopolymer oder dessen Alkalisalz, Stärke-Acrylnitril-Pfropfcopolymer, Cellulose-Acrylsäure-Pfropfcopolymer oder dessen Alkalisalz, Cellulose-Acrylnitril-Pfropfcopolymer, Polyvinylalkohol-Acrylsäure-Pfropfcopolymer oder dessen Alkalisalz, Epichlorhydrin-vernetztes Dextran, Epichlorhydrin-vernetzte Alginsäure, Epichlorhydrin-vernetzter Polyvinylalkohol, Formaldehyd-vernetzte Gelatine, Acrylsäure-vernetzte Polyacrylsäure, Divinylbenzol-Acrylsäure-Copolymer oder dessen Alkalisalz, Divinylbenzol-Methacrylsäure-Copolymer oder dessen Alkalisalz und Divinylbenzol-Styrolsulfonsäure-Copolymer oder dessen Alkalisalz.

5. Ethylcellulose-Mikrokapseln gemäss Anspruch 1, 2, 3 oder 4, worin das Polymermaterial in die Ethylcellulose-Überzugswandung in einer Menge von nicht weniger als 0,01 g/g Ethylcellulose und/oder in das Kernmaterial in einer Menge von 3 bis 99 w/w-% inkorporiert ist.

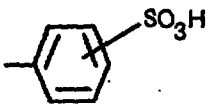
6. Ethylcellulose-Mikrokapseln gemäss Anspruch 1, 2, 3 oder 4, worin das Polymermaterial in die Ethylcellulose-Überzugswandung in einer Menge von 0,01 bis 20 g/g Ethylcellulose und/oder in das Kernmaterial in einer Menge von 90 w/w-% inkorporiert ist.

7. Ethylcellulose-Mikrokapseln gemäss Anspruch 1, 2, 3, 4, 5 oder 6, worin das Kernmaterial eine pharmazeutisch aktive Verbindung mit einer Teilchengrösse von 30 bis 1.000 µm ist, Ethylcellulose mit einem Ethoxygehalt von 46,5 bis 55 w/w-% und einer Viskosität (gemessen bei 25°C bei einer 5 w/w-%-igen Lösung in Toluol-Ethanol; 4:1) von 3 bis 500 mPa . s verwendet wird und das quellbare Polymermaterial mit einer Teilchengrösse von 0,1 bis 300 µm verwendet wird.

8. Verfahren zur Herstellung von Ethylcellulose-Mikrokapsen gemäss Anspruch 1, gekennzeichnet durch die Stufen

(i) Auflösen von Ethylcellulose in Cyclohexan;
(ii) Dispergieren von Teilchen eines Kernmaterials in der Lösung (wobei das Kernmaterial gewünschtenfalls ein Polymermaterial enthält, welches beim Eintaucher in Wasser bei 37°C eine wenigstens 1,2-fache Gewichtszunahme aufweist);
(iii) Kühlen der Dispersion in Gegenwart eines Polymermaterials (wobei das Polymermaterial ein solches ist, welches beim Eintauchen in Wasser bei 37°C eine wenigstens 1,2-fache Gewichtszunahme aufweist), bis Ethylcellulose sich aus der Dispersion unter Ausbildung von Überzugswandungen an und um die Teilchen des Kernmaterials abscheidet; und
(iv) Gewinnen der gebildeten Mikrokapseln.

9. Verfahren gemäss Anspruch 8, worin das Polymermaterial ausgewählt ist aus der Klasse, bestehend aus Stärke, kristalliner Cellulose, Agar, Hydroxy-C_{1-4}-alkylcellulose, Hydroxy-C_{1-4}-alkylstärke, Carboxy-C_{1-4}-alkylcellulose, Carboxy-C_{1-4}-alkylstärke oder deren Erdalkalisalz, einem Pfropfcopolymer von Stärke, Cellulose oder Polyvinylalkohol mit einem Monomer der Formel $CH_2=C(R^1)—Y'$ (worin R^1 Wasserstoff oder Methyl und Y' Carboxy oder Nitril bedeuten), einem vernetzten Dextrin, einem vernetzten Dextran, einem vernetzten Gummiarabikum, einer vernetzten Gelatine, einer vernetzten Polyacrylsäure und einem Copolymer aus Divinylbenzol mit einem Monomer der Formel $CH_2=C(R^2)—X'$ (worin R^2 Wasserstoff oder Methyl und X' Carboxy oder



bedeuten).

10. Verfahren gemäss Anspruch 8, worin das Polymermaterial ausgewählt ist aus der Klasse bestehend aus Stärke, kristalliner Cellulose, Agar, Hydroxypropylstärke (Hydroxypropylgehalt: 2 bis 7 w/w-%), Hydroxypropylcellulose (Hydroxypropylgehalt: 2 bis 7 w/w-%), Carboxymethylcellulose oder deren Erdalkalisalz, Stärke-Acrylsäure-Pfropfcopolymer oder dessen Erdalkalisalz, Stärke-Acrylnitril-Pfropfcopolymer, Cellulose-Acrylsäure-Pfropfcopolymer oder dessen Alkalisalz, Cellulose-Acrylnitril-Pfropf-

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copolymer, Polyvinylalkohol-Acrylsäure-Pfropfcopolymer oder dessen Alkalisalz, Epichlorhydrin-vernetztes Dextrin, Epichlorhydrin-vernetztes Gummiarabikum, Epichlorhydrin-vernetztes Dextran, Epichlorhydrin-vernetzter Polyvinylalkohol, Foramdehyd-vernetzte Gelatine, Acrylsäure-vernetzte Polyacrylsäure, Divinylbenzol-Acrylsäure-Copolymer oder dessen Alkalisalz, Divinylbenzol-Methacrylsäure-Copolymer oder dessen Alkalisalz und Divinylbenzol-Styrolsulfonsäure-Copolymer oder dessen Alkalisalz.

11. Verfahren gemäss Anspruch 8, worin Ethylcellulose mit einem Ethoxygehalt von 46,5 bis 55 w/w-% in einer Menge von 0,01 bis 10 g/g des Kernmaterials verwendet wird und die Dispersion in Gegenwart von nicht weniger als 0,01 g (pro g Ethylcellulose) des Polymermaterials gekühlt wird.

12. Verfahren gemäss Anspruch 11, worin die Dispersion in Gegenwart von 0,01 bis 20 g des Polymermaterials pro g Ethylcellulose gekühlt wird.

13. Verfahren gemäss Anspruch 8, 11 oder 12, worin das Kernmaterial 3 bis 99 w/w-% des Polymermaterials enthält.

14. Verfahren gemäss Anspruch 13, worin das Kernmaterial 3 bis 90 w/w-% des Polymermaterials enthält.

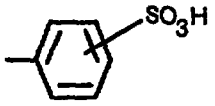
15. Verfahren gemäss Anspruch 8, 9 oder 10, worin das Kernmaterial eine pharmazeutisch aktive Verbindung mit einer Teilchengrösse von 30 bis 1.000 µm ist, Ethylcellulose mit einem Ethoxygehalt von 46,5 bis 55 w/w-% und mit einer Viskosität (gemessen bei 25°C bei einer 5 w/w-%-igen Lösung in Toluol-Ethanol; 4:1) von 3 bis 500 mPa . s in einer Menge von 0,01 bis 10 g/g des Kernmaterials verwendet wird und die Dispersion in Gegenwart von 0,01 bis 20 g (pro g Ethylcellulose) des Polymermaterials mit einer Teilchengrösse von 0,1 bis 300 µm gekühlt wird.

16. Verfahren gemäss Anspruch 8, 9, 10 oder 15, worin wenigstens ein Glied, ausgewählt aus einem Phasentrennungs-Einleitungsmittel, einem Organosiliciumpolymer und einem oberflächenaktiven Mittel zusätzlich zu der Lösung der Ethylcellulose gegeben wird.

Revendications

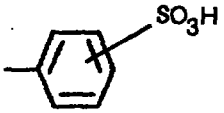
1. Microcapsules en éthylcellulose comprenant (i) des particules d'une matière de noyau et (ii) des parois d'enrobage en éthylcellulose déposées sur et autour desdites particules de la matière de noyau, dans lesquelles une matière polymère, qui fait apparaître une augmentation de poids d'au moins 1,2 fois en l'immergeant dans l'eau à 37°C est incorporée dans les parois d'enrobage en éthylcellulose et, facultativement, dans la matière de noyau des microcapsules.

2. Microcapsules en éthylcellulose selon la revendication 1, dans lesquelles ladite matière polymère est choisie dans le groupe comprenant l'amidon, la cellulose cristalline, l'agar-agar, l'acide alginique ou son sel de métal alcalino-terreux, l'hydroxyalkyl (C_{1-4})polysaccharide, le carboxyalkyl(C_{1-4})polysaccharide ou son sel de métal alcalino-terreux, un copolymère greffé de polysaccharide, d'alcool polyvinylique ou de gélatine avec un monomère de formule $CH_2=C(R^1)—Y$ (dans laquelle R^1 est un atome d'hydrogène ou le radical méthyle, et Y est un groupe carboxyle, nitrile alcoxy(C_{1-4})carbonyle ou 2-pyrrolidon-1-yle), un polysaccharide réticulé, un alcool polyvinylique réticulé, une gélatine réticulée, un acide polyacrylique ou son sel de métal alcalin réticules, et un copolymère de divinylbenzène avec un monomère de formule $CH_2=C(R^2)—X$ (dans laquelle R^2 est un atome d'hydrogène ou le radical méthyle, et X est un groupe carboxyle, alcoxy(C_{-4})carbonyle, alcanoyloxy en C_{1-4},



ou 2-pyrrolidon-1-yle).

3. Microcapsules en éthylcellulose selon la revendication 1, dans lesquelles ladite matière polymère est choisie parmi l'amidon, la cellulose cristalline, l'acide alginique ou son sel de métal alcalino-terreux, l'agar-agar, l'hydroxyalkyl(C_{1-4})cellulose, l'hydroxyalkyl(C_{1-4})amidon, la carboxyalkyl(C_{1-4})cellulose, le carboxyalkyl(C_{1-4})amidon ou son sel de métal alcalino-terreux, un copolymère greffé d'amidon, de cellulose ou d'alcool polyvinylique avec un monomère de formule $CH_2=C(R^1)—Y'$ (dans laquelle R^1 est un atome d'hydrogène ou un radical méthyle et Y' est le radical carboxy ou nitrile), une dextrine réticulée, un dextranne réticulé, une gomme arabique réticulée, une gélatin réticulée, l'acide alginique réticulé, l'acide polyacrylique réticulé et un copolymère de divinylbenzène et d'un monomère de formule $CH_2=C(R^2)—X'$ (dans laquelle R^2 est un atome d'hydrogène ou un radical méthyle, et X' est un radical carboxyle ou



).

4. Microcapsules en éthylcellulose selon la revendication 1, dans lesquelles ladite matière polymère est choisie parmi l'amidon, la cellulose cristalline, l'agar-agar, l'acide alginique ou son sel d'un métal alcalino-terreux, l'hydroxypropylamidon (teneur en hydroxypropyle: 2 à 7% p/p), l'hydroxypropylcellulose (teneur en hydroxypropyle: 2 à 7% en poids), la carboxyméthylcellulose ou son sel d'un métal

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alcalino-terreux, un copolymère greffé amidon/acide acrylique ou son sel d'un métal alcalin, un copolymère greffé amidon/acrylonitrile, un copolymère greffé cellulose/acide acrylique ou son sel d'un métal alcalin, un copolymère greffé cellulose/acrylonitrile, un copolymère greffé alcool poly-vinylique/acide acrylique ou son sel d'un métal alcalin, le dextranne réticulé, à l'épichlorhydrine, l'acide alginique réticulé à l'épichlorhydrine, l'alcool polyvinylique réticulé à l'épichlorhydrine, la gélatine réticulée au formaldéhyde, l'acide polyacrylique autoréticulé, un copolymère divinylbenzène/acide acrylique ou son sel de métal alcalin, un copolymère divinylbenzène/acide styrènesulfonique ou son sel de métal alcalin.

5. Microcapsules en éthylcellulose selon la revendication 1, 2, 3 ou 4, dans lesquelles ladite matière polymère est incorporée dans les parois d'enrobage d'éthylcellulose en une proportion qui n'est pas inférieure à 0,01 g par gramme d'éthylcellulose et/ou dans la matière du noyau à raison de 3 à 99% p/p.

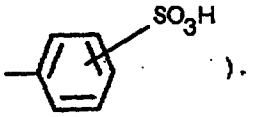
6. Microcapsules en éthylcellulose selon la revendication 1, 2, 3 ou 4, dans lesquelles on incorpore ladite matière polymère dans les parois d'enrobage en éthylcellulose à raison de 0,01 à 20 g par gramme d'éthylcellulose et/ou dans la matière de noyau à raison de 3 à 90% p/p.

7. Microcapsules en éthylcellulose selon la revendication 1, 2, 3, 4, 5 ou 6, dans lesquelles la matière de noyau est un composé pharmaceutiquement actif ayant une grosseur de particules de 30 à 1000 micromètres, une éthylcellulose ayant une teneur en groupe éthoxy de 46,5 à 55% p/p et une viscosité (mesurée à 25°C sur une solution à 5% p/p dans un mélange de toluène et d'éthanol 4:1) de 3 à 500 mPa . s et on utilise une matière polymère gonflable ayant une taille de particule de 0,1 à 300 micromètres.

8. Procédé de préparation de microcapsules en éthylcellulose selon la revendication 1, qui comporte les stades consistant:

(i) à dissoudre l'éthylcellulose dans le cyclohexane,
(ii) à disperser des particules d'une matière de noyau dans ladite solution (ladite matière de noyau contenant facultativement une matière polymère qui fait preuve d'une augmentation de poids d'au moins 1,2 fois en l'immergeant dans de l'eau à 37°C),
(iii) à refroidir la dispersion en présence d'une matière polymère (ladite matière polymère étant celle qui fait preuve d'une augmentation de poids d'au moins 1,2 fois en l'immergeant dans de l'eau à 37°C), jusqu'à ce que l'éthylcellulose se sépare de la dispersion pour former des parois d'enrobage sur et autour des particules de la matière de noyau, et
(iv) à récupérer les microcapsules résultantes à partir de cette dispersion.

9. Procédé selon la revendication 8, dans lequel on choisit ladite matière polymère dans le groupe comprenant l'amidon, la cellulose cristalline, l'agar-agar, l'hydroxyalkyl(C_{1-4})cellulose, l'hydroxyalkyl(C_{1-4})amidon, la carboxyalkyl(C_{1-4})cellulose, le carboxyalkyl(C_{1-4})amidon ou son sel de métal alcalino-terreux, un copolymère greffé d'amidon, de cellulose ou d'alcool polyvinylique avec un monomère de formule $CH_2=C(R^1)—Y'$ (dans laquelle R' est un atome d'hydrogène ou le radical méthyle, et Y' est un groupe carboxyle ou nitrile), une dextrine réticulée, un dextranne réticulé, une gomme arabique réticulée, et un copolymère de divinylbenzène avec un monomère de formule $CH_2=C(R^2)—X'$ (dans laquelle R^2 est un atome d'hydrogène ou le radical méthyle, et X' est un groupe carboxyle ou



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10. Procédé selon la revendication 8, dans lequel ladite matière polymère est choisie parmi l'amidon, la cellulose cristalline, l'agar-agar, l'hydroxypropylamidon (teneur en hydroxypropyle: 2 à 7% p/p), l'hydroxypropylcellulose (teneur en hydroxypropyl: 2 à 7% p/p), la carboxyméthylcellulose ou son sel d'un métal alcalino-terreux, un copolymère greffé amidon/acide acrylique ou son sel d'un métal alcalin, un copolymère greffé amidon/acrylonitrile, un copolymère greffé cellulose/acide acrylique ou son sel d'un métal alcalin, un copolymère greffé cellulose/acrylonitrile, un copolymère greffé alcool polyvinylique/acide acrylique ou son sel d'un métal alcalin, la dextrine réticulée à l'épichlorhydrine, la gomme arabique réticulée à l'épichlorhydrine, le dextranne réticulé à l'épichlorhydrine, l'alcool polyvinylique réticulé à l'épichlorhydrine, la gélatine réticulée au formaldéhyde, l'acide polyacrylique auto-réticulé, un copolymère divinylbenzène/acide acrylique ou son sel de métal alcalin, un copolymère divinylbenzène/acide méthacrylique ou son sel de métal alcalin, et un copolymère divinylbenzène/acide styrènesonfonique ou son sel de métal alcalin.

11. Procédé selon la revendication 8, dans lequel on utilise l'éthylcellulose ayant une teneur en éthoxy de 46,5 à 55% p/p à raison de 0,01 à 10 g par gramme de la matière de noyau et on refroidit la dispersion en présence d'un minimum de 0,01 g (par gramme d'éthylcellulose) de la matière polymèr.

12. Procédé sealon la revendication 11, dans lequel on refroidit la dispersion en présence de 0,01 à 20 g de matière polymère par gramme d'éthylcellulose.

13. Procédé selon la revendication 8, 11 ou 12, dans lequel la matière de noyau contient 3 à 99% p/p de matière polymère.

14. Procédé selon la revendication 13, dans lequel la matière de noyau contient 3 à 90% p/p de matière polymère.

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15. Procédé selon la revendication 8, 9 ou 10, dans lequel la matière de noyau est un composé pharmaceutiquement actif ayant une taille de particule de 30 à 1000 micromètres, une éthylcellulose ayant une teneur en éthoxy de 46,5 à 55% p/p et une viscosité (mesurée à 25°C sur une solution à 5% p/p dans un mélange 4:1 de toluène et d'éthanol) de 3 à 500 mPa . s, qu'on utilise à raison de 0,01 à 10 g par gramme de la matière de noyau, et on refroidit la dispersion en présence de 0,01 à 20 g (par gramme d'éthylcellulose) de la matière polymère ayant une taille de particule de 0,1 à 300 micromètres.

16. Procédé selon la revendication 8, 9, 10 ou 15, dans lequel on ajoute à la solution de l'éthylcellulose au moins un élément choisi parmi un agent amorçant la séparation de phases, en polymère d'organosilicium et un tension-actif.

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