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(54) **Ethylcellulose microcapsules**

(57) Pharmaceutically active compound-containing microcapsules the coating walls of which consist essentially of ethylcellulose and a water-insoluble, acid-soluble polymer material, and a method of preparing them which comprises:–

(1) dissolving ethylcellulose in a solvent,

(ii) dispersing particles of a pharmaceutically active compound (core material) in the solution,

(iii) cooling the dispersion in the presence of a water-insoluble, acid-soluble polymer material until the ethylcellulose separates out from the dispersion to form coating walls on and around the particles of the pharmaceutically active compound, and

(iv) recovering the microcapsules therefrom.

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SPECIFICATION

Ethylcellulose microcapsules and process for preparing same

This invention relates to novel ethylcellucose microcapsules and to a process for preparing same.

It is known that ethylcellulose microcapsules are prepared by taking advantage of the liquid-liquid phase separation of ethylcellulose in cyclohexane. For example, Japanese Patent Publications (examined) Nos. 528/1967, 11399/1969 and 30136/1975 disclose that said microcapsules are obtained by preparing a hot solution in cyclohexane of ethylcellulose and a phase-separation-inducing agent (e.g., butyl rubber, polybutadiene, polyethylene or polyisobutylene), dispersing particles of a core material in the solution, cooling the dispersion until the ethylcellulose separates out from the dispersion to form a liquid phase depositing on and around the particles of the core material, and then recovering the so formed microcapsules therefrom. Further, U.S. Patent No. 3,531,418 discloses a method of preparing ethylcellulose microcapsules without using a phase-separation-inducing agent, i.e., direct flocculation of ethylcellulose by change of temperature. According to the known methods, however, it is difficult to obtain microcapsules which show rapid release of a pharmaceutically active compound in the stomach because the compact wall structure of ethylcellulose retards the release of the pharmaceutically active compound.

The present invention provides pharmaceutically active compound-containing ethylcellulose microcapsules which show more rapid release of said pharmaceutically active compound in stomach or gastric juice than known microcapsules. The present invention also provides pharmaceutically active compound-containing microcapsules the coating walls of which consist essentially of ethylcellulose and a water-insoluble, acid-soluble polymer material. The present invention further provides a method for preparing such ethylcellulose microcapsules.

According to the present invention pharmaceutically active compound-containing microcapsules are provided with coating walls of which consist essentially of ethylcellulose and a water-insoluble, acid-soluble polymer material.

The microcapsules of the invention can be prepared by the steps of:

(i) dissolving ethylcellulose in a solvent,

(ii) dispersing particles of a pharmaceutically active compound (core material) in the solution thus obtained,

(iii) cooling the dispersion in the presence of a water-insoluble, acid-soluble polymer material until the ethylcellulose separates out from the dispersion to form coating walls on and around the particles of said core material, and then,

(iv) recovering the thus-formed microcapsules therefrom.

A wide variety of polymer materials soluble in water at a pH of not higher than 5 can be used as the water-insoluble, acid-soluble polymer material of the present invention. Examples of such polymer material are dialkylaminoalkyl-cellulose (e,g., diethylaminomethylcellulose), benzylaminoalkyl-cellulose (e.g., benzylaminomethylcellulose), carboxyalkyl-(benzylamino) cellulose (e.g., carboxymethyl(benzylamino)-cellulose), dialkylaminoacetate.cellulose.acetate (e,g., diethylaminoacetate.cellulose.acetate), cellulose.acetate.dialkylamino.hydroxyalkyl ether (e.g., cellulose.acetate.N,N,-di-n-butylamino.hydroxypropyl ether), piperidyl.alkyl.hydroxyalkylcellulose (e.g., piperidyl.ethyl.hydroxypropylcellulose, piperidyl.ethyl.hydroxyethylcellulose), carboxyalkyl.piperidyl.-starch (e.g., carboxymethyl.piperidyl.starch), poly-dialkylaminoalkylstyrene (e.g., poly-diethylaminomethylstyrene), polyvinylacetacetal.dialkylaminoacetate (e.g., poly-vinylacetal.dimethylaminoacetate, poly-vinylacetacetal.diethylaminoacetate), 2-(p-vinylphenyl) glycine.vinyl acetate copolymer, N-vinylglycine.styrene copolymer, a copolymer of (A) dialkylaminoalkyl methacrylate and (B) one or two alkyl methacrylates (e.g., dimethylaminoethyl methacrylate.methyl methacrylate copolymer, butyl methacrylate.2-dimethylaminoethyl methacrylate.methyl methacrylate copolymer), a copolymer of (C) 2-alkyl-5-vinylpyridine, (D) alkyl acrylate or acrylonitrile and (E) methacrylic acid (e.g., 2-methyl-5-vinylpyridine.methyl acrylate.methacrylic acid copolymer, 2-methyl-5-vinylpyridine.acrylonnitrile.methacrylic acid copolymer), a copolymer of 2-vinyl-5-alkylpyridine and styrene (e.g., 2-vinyl-5-ethylpyridine.styrene copolymer), and a copolymer of 2-vinylpyridine and alkyl methacrylate (e.g., 2-vinylpyridine.methyl methacrylate copolymer). Preferred examples of such polymer material are diethylaminonmethylcellulose, benzylaminomethylcellulose, carboxymethyl(benzylamino)cellulose, diethylaminoacetate.cellulose.acetate, cellulose.acetate.N,N-di-n-butylamino.hydroxypropyl ether, piperidyl.ethyl.hydroxyoropylcellulose, piperidyl.ethyl.hydroxyethylcelluose, carboxymethyl.piperidyl.starch, poly-diethylaminomethylstyrene, poly-vinylacetacetal.diethylaminoacetate, 2-(p-vinylphenyl) glycine.vinyl acetate copolymer, N-vinylglycine.styrene copolymer, dimethylaminoethyl methacrylate.methyl methacrylate copolymer, butyl methacrylate.2-dimethyl-aminoethyl methacrylate-methyl methacrylate copolymer, 2-methyl-5-vinylpyridine.methyl acrylate.methacrylic acid copolymer, 2-methyl-5-vinylpyridine.acrylonitrile.methacrylic acid copolymer, 2-vinyl-5-ethylpyridine.styrene copolymer and 2-vinylpyridine.methyl methacrylate copolymer. More preferred examples of the polymer material

are 2-methyl-5-vinylpyridine.methyl acrylate.methacrylic acid copolymer, poly-vinyl-acetacetal.diethylaminoacetate, dimethylaminoethyl methacrylate.methyl acrylate copolymer and cellulose.-acetate.N,N-di-n-butylamino.hydroxypropyl ether.

In making the microcapsules of the present invention it is preferred that these polymer materials have a particle diameter of not more than one-tenth that of the the core material especially a particle size of not more than 50μ, more especially of not more than 20μ. It is also preferred that these polymer materials are used in an amount of 0.1 to 20 grams, especially 0.5 to 10 grams, per gram of ethylcellulose used.

On the other hand,ethylcellulose having an ethoxy content of 47 to 55 W/W % is preferably used as the wall-forming material of the present invention. It is 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 3 to 500 cP, especially 20 to 200 cP. It is also preferred that said ethylcellulose is used in an amount of 0.05 to 5 grams, especially 0.1 to 1 gram, per gram of the core material used.

Any solvent which dissolves ethylcellulose a temperature of 70° to 80°C and which does not dissolve the core material and the water-insoluble, acid-soluble polymer material can be used as the solvent of the invention. Examples of such solvent are cyclohexane, a mixture of cyclohexane and n-hexane, and the like. Especially, it is preferred to use cylohexane as the solvent.

Any pharmaceutically active compounds (or medicaments) can be used as the core material to be microencapsulated in the present invention. Such pharmaceutically active compound or medicament to be microencapsulated may be solid, gel or semi-solid. In order to prepare a homogeneous dispersion at the microencapsulation step, it is preferred that said pharmaceutically active compound or medicament has a particle size of 30 to 1000 μ, especially 50 to 500 μ. Eligible for microencapsulation as solids are particles of materials such as, for example, vitamins (e.g., ascorbic acid), amino acids (e.g., potassium asparate, magnesium asparate), minerals (e.g., potassium chloride), anti-microbial agents (e.g., benzylpenicillin potassium salt, sulfomethizole), anti-tumor agents (e.g., 5-fluorouracil, bleomycin hydrochloride), metabolic agents (e.g., glutahion), cardiovascular agents (e.g., dilthiazem hydrochloride), analgesics (e.g., acetylsalicyclic acid), anti-histaminics (e.g., diphenhydramine hydrochloride), neuro-psychotropic agents (e.g., calcium N-(γ,γ-dihydroxy-β,β-dimethylbutyryl-γ-aminobutyrate), agents affecting digestive organs (e.g., methylmethionine sulfonium chloride, 1, 1-dimethyl-5-methoxy-3-(dithien-2-yl-methylene)-piperidinium bromide, precipitated calcium carbonate, 1-(3,4,5-trimethoxybenzoyloxy)-2-dimethylamino-2-phenylbutane maleate), agents affecting respiratory organs (e.g., trimethoquinol hydrochloride), and so forth. Also eligible for microencapsulation as semi-solids are, for example, slurrys such as slurry composed of 30 W/W % of sodium polyacrylate, 40 W/W % of water and 30 W/W % of 5-fluorouracil. Pharmaceutically active compounds in the form of "gel" which can be microencapsulated are, for example, dextran gel having a medicament (e.g., methylmethionine sulfonium chloride) adsorbed thereon, formalin-treated gelatin gel having a medicament (e.g., sulfamethomidine) dispersed therein, and so forth.

Futher, the core material to be microencapsulated may contain a water-soluble organic acid. The organic acid serves to accelerate the release of the pharmaceutically active compound from microcapsules. Examples of such organic acid are hydroxy-lower alkane-dicarboxylic acid (e.g., malic acid, tartaric acid), hydroxy-lower alkaline-tricarboxylic acid (e.g., citric acid), lower alkane-dicarboxylic acid (e.g., malonic acid, succininc acid and lower alkenedicarboxylic acid (e.g., maleic acid). It is preferred that the acid has a particle size of not more than 30 μ. It is also preferred that the amount of the acid in the core material is within the range of one to 90 W/W %, especially 10 to 80 W/W %. The organic acid-containing core material may be prepared for example by granulating a mixture of the core material and the organic acid in a conventional manner (e.g., wet-granulation method, dry-granulation method), and the particle size of the organic acid-containing core material should be preferably within a range of 30 to 1,000μ.

In making the microcapsules of a pharmaceutically active compound according to the present invention, it is preferred to dissolve ethylcellulose in a solvent such as for example those mentioned above, and then disperse the particles of a pharmaceutically active compound (core material) in the solution under stirring. In this case, it is preferred to dissolve ethylcellulose at a temperature of 70° to 80°C. Further, it is also preferred to dissolve ethylcellulose at a concentration of 0.5 to 10 W/W %, especially one to 5 W/W %.

When the above-mentioned dispersion is cooled in the presence of the water-insoluble, acid-soluble polymer material, ethycellulose separates out in the form of "gel" from the dispersion by flocculation thereof to form coating walls on and around particles of the core material and at the same time the water-insoluble, acid-soluble polymer material is incorporated into the coating walls of the embryonic microcapsules. It is preferred to cool the dispersion at a rate of 0.05 to 4°C, especially 0.1 to 2°C, per minute.

The water-insoluble, acid-soluble polymer material may be added to the dispersion either before cooling the dispersion or during the cooling step. Especially, it is preferred that the polymer material 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 pharmaceutically active compound (core material) and the thus-formed coating walls have a viscosity of 0.1 to 50 P, especially 1 to 10 P. More specifically, since the coating wall having a viscosity of the above-mentioned range is formed on and around the core material by cooling the dispersion to 55° to 75° C, especially 60° to 70°C, it is preferred that the polymer material is added to the dispersion when cooled to said temperature. When the dispersion is further cooled to a temperature not higher than 40°C (e.g., 30° to 20°C), the thus-formed embryonic microcapsules shrink and become solid by solvent loss from the coating walls, thus giving stable ethylcellulose microcapsules.

The microcapsules thus obtained may be recovered for example in a conventional manner e.g. decantation, centrifugation, filtration and so forth. Further, if required, the ethylcellulose microcapsules may be washed with a suitable solvent (e.g., cyclohexane, petroleum-ether or n-hexane) and then dried in a conventional manner (e.g., hot-air drying method).

Further, in carrying out the phase-separation of ethylcellulose, a phase-separation-inducing agent, an organopolysiloxane and a surfactant may be used in combination with ethylcellulose. Suitable examples of the phase-separation-inducing agent are polyethylene, butyl rubber, polyisobutylene and polybutadiene. Dimethylpolysiloxane and methylphenylpolysiloxane are examples of the organopolysiloxane. Examples of the surfactants which can be used in the present invention are an ester of C_{12-18} fatty acid with sorbitan (e.g., sorbitan monolaurate, sorbitan sesquilaurate, sorbitan trilaurate, sorbitan monooleate), an ester of C_{6-18} fatty acid with glycerin (e.g., glycerin monocaprylate, glycerin monolaurate, glycerin monooleate), a phospholipid (e.g., soybean phospholipid) and calcium stearoyl-2-lactylate. It is preferred that the phase-separation-inducing agent, organopolysiloxane and surfactant are added to the ethylcellulose solution prior to dispersing the core material in the solution. The concentrations of the phase-separation-inducing agent, the organopolysiloxane and the surfactant in the ethylcellulose solution may be, for example, 0.1 to 10 W/V %, 0.01 to 10 W/V % and 0.003 to 10 M/W %, respectively.

Pharmaceutically active compound-containing microcapsules the capsule walls of which are composed of ethylcellulose and a water-insoluble, acid-soluble polymer material may be obtained by any one of the above-mentioned operations. A preferred amount of the polymer material which is contained or incorporated in the coating walls of ethylcellulose is 0.1 to 20 grams, especially 0.5 to 10 grams, per gram of ethylcellulose.

The pharmaceutically active compound-containing microcapsules of the present invention thus obtained show more rapid release of the pharmaceutically active compound (core material in the stomach or other gastric organs then known microcapsules because the water-insoluble, acid-soluble polymer material incorporated or contained in the coating walls of ethylcellulose dissolves swiftly in the presence of hydronium ion, for example, in an acidic solution such as gastric juice. The coating walls of the microcapsules of the invention when contacted with hydronium ion become porous and permeable to water, and water thus permeated or penetrated into the microcapsules serves to dissolve the core material and release it more rapidly from the microcapsules than from known microcapsules. Moreover, when an organic acid-containing core material is used in the invention, the acid further accelerates the release of a pharmaceutically active compound from the microcapsules because the hydronium ion which the organic acid releases in water induces the dissolution of the polymer material from the interior side of the coating walls and serves to increase the porosity of the coating walls. In the microcapsules of the present invention the release velocity of a pharmaceutically active compound can be controlled by suitable choice of the amount of the polymer material and/or organic acid used. Further, as mentioned above, hydronium ion which the organic acid releases in water makes the coating walls porous enough to release the pharmaceutically active compound in the stomach from the microcapsules and, therefore, the microcapsules which are obtained by using an organic acid-containing core material show no substantial retardation in release of a pharmaceutically active compound in the stomach even when administered orally to patients suffering from hypoacidity or anacidity.

Practical and presently-preferred embodiments of the present invention are illustratively shown in the following lines. Throughout the specification and claims, the terms "alkyl", "lower alkane" and "lower alkene" should be interpreted as referring to alkyl of one to 4 carbon atoms, lower alkane of one to 4 carbon atoms and lower alkene of 2 to 4 carbon atoms, respectively.

Experiment A

Microcapsules containing trimebutine maleate (chemical name: 1-(3,4,5-trimethoxybenzoyloxy)-2-dimethylamino-2-phenyl-butane maleate) wer prepared according to the following method. Then, the yield of microcapsules thus obtained, the amount of the active ingredient contained in the microcapsules and the 50 % release time (i.e., a period of time which was necessary to release 50 % of the active ingredient from the microcapsules) were examined,

respectively.
(Method)
(1) Core material:
20 parts (by weight) of an aqueous 15 W/V % methylcellulose solution were added to a mixture of 23 parts (by weight) of trimebutine maleate and 74 parts (by weight) of lactone, and the mixture was granulated and dried in a conventional manner. The granules (particle size: 105–210 μ) thus obtained were used as the core material.
(ii) Preparation of microcapsules.
27 g of silcicone resin which met the requirements specified JAPANESE STANDARDS OF FOOD ADDITIVE 4th-Edition [said silicone resin being prepared by dispersing silicon dioxide at a concentration of 3–15 W/W % in dimethylpolysiloxane viscosity: 100–1,100 cST at 25°C)] and 20 g of ethyl cellulose (ethoxy content; 48.5 W/W %, viscosity: 100 cP) were dissolved at 80°C in 700 ml of cyclohexane under stirring. 100 g of the core material were dispersed in the solution, and the dispersion was cooled to about 70°C under stirring at 400 r.p.m. . Then, a suspension of 2-methyl-5-vinylpyridine.methyl acrylate.methacrylic acid copolymer (molar ratio = 2.4 : 1.9 : 1; average particle size: 7μ) in 200 ml of cyclohexane containing soybean phospholipid (0.8 g/ 200 ml) was added to the dispersion, and the dispersion was cooled to room temperature. The microcapsules thus obtained were recovered by filtration, washed with n-hexane and then dried. The microcapsules were passed through JIS standard sieve (350 μ aperture). Trimebutine maleate-containing microcapsules which met the requirements of "Pulvers" specified in THE PHARMACOPOEIA OF JAPAN 9th-Edition were obtained. were added to water or a simulated gastric fluid specified in THE PHARMACOPOEIA OF JAPAN 9th-Edition, and the mixture was stirred at 37°C. The amount of the active ingredient released from the microcapsules was examined with the lapse of time, and the 50 % release time of the active ingredient was estimated therefrom.
(Results)
The results are shown in the following Table 1

Table 1

Experiment Nos.	Amount of copolymer used (g)	Yield of microcapsules (g)	Amount of active ingredient contained in microcapsules (%)	50% release time (minutes) water	50% release time (minutes) simulated gastric fluid
(The methods of the present invention)					
1.	30	144	15.5	80	17
2.	100	209	10.7	87	8
3.	150	265	8.5	76	5
(Control)					
4.	0	114	19.3	78	37

Experiment B
Microcapsules containing timepidium bromide (chemical name: 1,1-dimethyl-5-methoxy-3-(diethien-2-ylmethylene)-piperidinium bromide) and citric acid were prepared according to the following method. Then, the yield of microcapsules thus obtained, the amount of the active ingredient contained in the microcapsules and the 50 % release time (i.e., a period of time which was necessary to release 50 % of the active ingredient from the microcapsules) were examined, respectively.
(Method)
(i) Core material:
28 parts (by weight) of a 25 W/V % solution of poly-vinyl acetate in ethanol were added to a mixture of 23 parts (by weight) of timepidium bromide, 37 parts (by weight) of citric acid and 33 parts (by weight) of lactose, and the mixture was granulated and dried in a conventional manner. The granules (particle size: 105–210 μ) thus obtained were used as the core material.
(ii) Preparation of microcapsules;
22.5 g of dimethylpolysiloxane (viscosity: 10,000 cSt at 25°C) and 25 g of ethylcellulose (ethoxy content: 48.5 W/W % viscosity: 100 cP) were dissolved at 80°C in 700 ml of cyclohexane under stirring. 100 g of the core material were dispersed in the solution, and the dispersion was cooled to about 75°C under stirring at 400 r.p.m. To the dispersion was added a suspension of 2-methyl-5-vinylpyridine.methyl acrylate.methacrylic acid copolymer (molar ratio

= 2.4 : 1.9 : 1) in 150 ml of cyclohexane containing soybean phospholipid (0.085 g/150 ml). Then, the dispersion was treated in the same manner as described in Experiment A. Timepidium bromide-containing microcapsules which met the requirements of "Pulvers" specified in THE PHARMACOPOEIA OF JAPAN 9th-Edition were there obtained as shown in the following Table 2.

Table 2

Experiment Nos.	Amount of copolyer used (g)	Yield of micro-capsules (g)	Amount of active ingredient contained in micro-capsules (%)
(The method of the present invention)			
5.	125	243	9.3
(Control)			
6.	0	122	18.2

(iii) Estimation of release time:

The microcapsules obtained in paragraph (ii) were added to water, and the mixture was stirred at 37°C. The amount (%) of the active ingredient released from the microcapsules was examined with the lapse of time, and the 50 % release time of the active ingredient were estimated therefrom.

(Results)

The results are shown in the following Table 3.

Table 3

Period of time (minutes)	The amount (%) of the active ingredient released from the microcapsules	
	Microcapsules of the present invention (the amount of copolymer: 125 (g)	Control (the amount of copolymer: 0 g)
10	15	2
15	28	3
20	41	7
30	60	12
45	76	20
60	86	28
90	94	43
120	98	56
50 % release time	24 minutes	106 minutes

Example 1

30 g of polyethylene (molecular weight: 7,000) and 25 g of ethylcellulose (ethoxy content: 48.0 W/W %; viscosity: 45 cP) were dissolved at 80°C in 850 ml of cyclohexane, and 100 g of glutathion having a particle size of 105–210 μ were dispersed in the solution. The dispersion was cooled to about 65°C under stirring at 350 r.p.m. . 150 g of polyvinylacetal diethylaminoacetate (nitrogen content: 2.0 W/W %; average particle size: 10 μ9 were added gradually to the dispersion, and the dispersion was cooled to room temperature. The microcapsules thus obtained were recovered by filtration, washed with n-hexane, and then dried. Then, the microcapsules were passed through JIS standard sieve (350 μ aperture). 265 g of glutathion-containing microcapsules which met the requirements of "Pulvers" specified in THE JAPANESE PHARAMACOPOEIA OF JAPAN 9th-Edition were obtained.

Amount of glutathion contained in the microcapsules;	36.4 W/W %
50% release time of glutathion in water (estimated in the same manner as described in Experiment A)	106 minutes
50% release time of glutathion in a simulated gastric fluid (estimated in the same manner as described in Experiment A)	17 minutes

Example 2

Microcapsules were prepared in the same manner as described in Example 1 except that 30 g of polyisobutylene (molecular weight: 700,000) (and 150 g of dimethylaminoethyl methacrylate.methyl methacrylate copolymer (molar ratio = 1 : 1) (average particle size: 9.6 μ) were used instead of polyethylene and polyvinylacetal.diethylaminoacetate. 268g of glutathion-containing microcapsules which met the requirements of "Pulvers" specified above were obtained.

Amount of glutathion contained in, the microcapsules;	36.3 W/W %
50 % release time of glutathion in water (estimated in the same manner as described in Experiment A):	98 minutes
50 % release time of glutathion in a simulated gastric fluid (estimated in the same manner as described in Experiment A):	20 minutes

Example 3

30 g of polyethylene (molecular weight: 7,000) and 25 g of ethylcellulose (ethoxy content: 48.0 W/W %; viscosity: 45 cP) were dissolved at 80°C in 850 ml of cyclohexane, and 100 g of trimethoquinol hydrochloride (chemical name: l-1-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride monohydrate) having a particle size of 149–297 μ were dispersed in the solution. The dispersion was cooled to about 65°C under stirring at 350 r.p.m. . 150 g of 2-vinyl-5-ethylpyridine.styrene copolymer (molar ratio = 1 : 1) (average article size: 13 μ) were added gradually to the dispersion, and said dispersion was cooled to room temperature. The microcapsules thus obtained are treated in the same manner as described in Example 1, whereby 265 g of trimethoquinol hydrochloride-containing microcapsules which met the requirements of "Pulvers" specified above were obtained.

Amount of trimethoquinol hydrochloride contained in the microcapsules:	36.3 W/W %
50 % release time of trimethoquinol hydrochloride in water (estimated in the same manner as described in Experiment A):	158 minutes
50 % release time of trimethoquinol hydrochloride in a simulated gastric fluid (estimated in the same manner as described in Experiment A):	21 minutes

Examples 4–17

Microcapsules were prepared in the same manner as described in Experiment A except that 100 g of a polymer shown in the following Table 4 were used instead of 2-methyl-5-vinylpyridine.methyl acrylate.methacrylic acid copolymer. Timebutine maleate-containing microcapsules which met the requirements of "Pulvers" specified above were thereby obtained as shown in Table 4.

Table 4

Example Nos.	Polymers	Yield of microcapsules (g)	(%)*1
4.	diethylaminomethyl-cellulose	213	97
5.	benzylaminomethyl-cellulose	202	92
6.	carboxymethyl (benzyl-amino)cellulose	209	95
7.	diethylaminoacetate. cellulose.acetate	205	93
8.	cellulose.acetate.N,N-di-n-butylamino.hydroxy-propyl ether	200	91
9.	piperidyl.ethyl. hydroxypropylcellulose	202	92
10.	piperidyl.ethyl.hydroxyethyl-cellulose	205	93
11.	carboxymethyl.piperidyl-starch	216	98
12.	poly-diethylaminomethyl-styrene	207	94
13.	2-methyl-5-vinylpyridine. acrylonitrile.methacrylic acid copolymer	194	88
14.	2-vinylpyridine.methyl methacrylate copolymer	200	91
15.	2-(p-vinylphenyl)glycine. vinyl acetate copolymer	209	95
16.	N-vinylglycine.styrene copolymer	202	92
17.	butyl methacrylate.2-dimethyl-aminoethyl methacrylate.methyl methacrylate copolymer	203	92

Note: *1) : The yield (%) of microcapsules was calculated to the following formula:

$$Y = \frac{a}{b} \times Yobs$$

a : amount (%) of active ingredient contained in microcapsules
b : amount (grams) of active ingredient used
Yobs : yield (grams) of microcapsules which met the requirements of ''Pulvers'' specified in PHARMACOPEIA OF JAPAN 9th-Edition.

CLAIMS

1. Pharmaceutically active compound-containing microcapsules the coating walls of which consist essentially of ethylcellulose and a water-insoluble, acid-soluble polymer material.

2. Microcapsules according to claim 1 wherein the water-insoluble, acid-soluble polymer material is diakylaminoalkylcellulose, benzylaminoalkylcellulose, carboxyalkyl (benzylamino) cellulose, dialkylaminoacetate.cellulose.acetate, cellulose.acetate.dialkylamino.hydroxyalkyl ether, piperidyl.alkyl.hydroxyalkylcellulose, carboxyalkyl.piperidyl.starch, poly-dialkylaminoalkylstyrene, poly-vinylacetacetal.dialkylaminoacetate, 2- (p-vinylphenyl) glycine.vinyl acetate copolymer, N-vinylglycine.styrene copolymer, a copolymer of (A) dialkylaminoalkyl methacrylate and (B) one or two alkyl methacrylates, a copolymer of (A) 2-alkyl-5-vinylpyridine, (B) alkyl acrylate or acrylonitrile and (C) methacrylic acid, a copolymer of 2-vinyl-5-alkylpyridine and styrene, or a copolymer of 2-vinylpyridine and alkyl methacrylate.

3. Microcapsules according to claim 1 wherein the water-insoluble, acid-soluble polymer material is diethyl-aminomethylcellulose, benzylaminomethylcellulose, carboxymethyl-(benzylamino)cellulose, diethylaminoacetate.cellulose.acetate, cellulose.acetate. N,N-di-n-butylamino.hy-

droxypropyl ether, piperidyl.ethyl.hydroxypropylcellulose, piperidyl.ethyl.hydroxyethylcellulose, carboxymethyl.piperidyl.starch, polydiethylaminomethylstyrene, poly-vinylacetacetal.diethyl-aminoacetate, 2-(p-vinylphenyl) glycine.vinyl acetate copolymer N-vinylglycine.styrene copolymer, dimethylaminoethyl.methacrylate.methyl methacrylate copolymer, butyl methacrylate.2-dimethylaminoethyl methacrylate.methyl methacrylate copolymer, 2-methyl-5-vinylpyridine.methyl acrylate.methacrylic acid copolymer, 2-methyl-5-vinylpyridine.acrylonitrile.methacrylic acid copolymer, 2-vinyl-5-ethylpyridine.styrene copolymer or 2-vinylpyridine.methyl methacrylate copolymer.

4. Microcapsules according to claim 1 wherein the water-insoluble, acid-soluble polymer material is 2-methyl-5-vinylpyridine.methyl acrylate.methacrylic acid copolymer, poly-vinylacetacetal.diethylaminoacetate, dimethylaminoethyl methacrylate.methyl acrylate copolymer or cellulose.acetate.N,N-di-n-butylamino-hydroxypropyl ether.

5. Microcapsules according to any of claims 1 to 4 wherein the water-insoluble, acid soluble polymer material is contained in the coating walls of ethylcellulose in an amount of 0.1 to 20 grams per gram of ethyl cellulose.

6. Microcapsules according to any of claims 1 to 5 wherein the ethylcellulose has an ethoxy content of 47 to 55 W/W %.

7. Microcapsules according to any of claims 1 to 6 wherein the ethylcellulose has 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 cP.

8. Microcapsules according to any of claims 1 to 7 wherein particles of the pharmaceutically active compound (core material contain a hydroxyl-lower alkane-dicarboxylic acid, hydroxy-lower alkanetricarboxylic acid, lower alkane-dicarboxylic acid or lower alkene-dicarboxylic acid.

9. Microcapsules according to any of claims 1 to 7 wherein particles of the pharmaceutically active compound (core material) contain malic acid, tartaric acid, citric acid, malonic acid, succinic acid, maleic acid or fumaric acid.

10. Microcapsules according to claims 8 or 9 wherein the acid is contained in the core material at a concentration of one to 90 W/W %.

11. Microcapsules according to claim 10 wherein the acid is contained in the core material at a concentration of 10 to 80 W/W %.

12. Pharmaceutically active-compound containing microcapsules substantially as herein described with reference to and as illustrated in any of Examples 1 to 17.

13. A method of preparing ethylcellulose microcapsules which comprises the steps of:

(i) dissolving ethylcellulose in a solvent,

(ii) dispersing particles of a pharmaceutically active compound (core material) in the solution thus obtained,

(iii) cooling the dispersion in the presence of a water-insoluble, acid-soluble polymer material until the ethylcellulose separates out from the dispersion to form coating walls on and around the particles of the pharmaceutically active compound, and then

(iv) recovering the thus-formed microcapsules therefrom.

14. A method according to claim 13 wherein the water-insoluble, acid-soluble polymer material is dialkylamino-alkylcellulose, benzylaminoalkylcellulose, carboxyalkyl-(benzylamino) cellulose, dialkylaminoacetate.cellulose.acetate, cellulose.acetate.dialkylamino.hydroxyalkyl ether, piperidyl.alkyl.hydroxyalkylcellulose, carboxyalkyl.piperidy.starch, poly-dialkylaminnoalkyl-styrene, poly-vinylacetacetal.dialkylaminoacetate, 2-(p-vinylphenyl) glycine.vinyl acetate copolymer, N-vinylglycine.styrene copolymer, a copolymer, a copolymer of (A) dialkylaminoalkyl methacrylate and [B) one or two alkyl methacrylates, a copolymer of (A) 2-alkyl-5-vinylpyridine, (B) alkyl acrylate or acrylonitrile and (C) methacrylic acid, a copolymer of 2-vinyl-5-alkylpyridine and styrene, or a copolymer of 2-vinylpyridine and alkyl methacrylate.

15. A method according to claim 13 wherein the water-insoluble, acid-soluble polymer material is diethylamino-methylcellulose, benzylaminomethylcellulose, carboxymethyl(benzylamino) cellulose, diethylaminoacetate.cellulose.acetate, cellulose.acetate.N,N-di-n-butylamino.hydroxypropyl ether, piperidyl.ethyl.hydroxypropyl ether, piperidyl.ethyl.hydroxypropylcellulose, piperidyl.ethyl.hydroxyethylcellulose, carboxymethyl.piperidyl.starch, polydiethylaminomethylstyrene, poly-vinylacetacetal.diethylaminoacetate, 2-(p-vinylphenyl)glycine.vinyl acetate copolymer, N-vinylglycine.styrene copolymer, dimethylaminoethyl methacrylate.methyl methacrylate copolymer, butyl methacrylate.2-dimethlaminoethyl methacrylate. methyl methacrylate copolymer, 2-methyl-5-vinylpyridine.methyl acrylate.methacrylic acid copolymer, 2-methyl-5-vinylpyridine.acrylonitrile.methacrylic acid copolymer, 2-vinyl-5-ethylpyridine.styrene copolymer or 2-vinylpyridine.methyl methacrylate copolymer.

16. A method according to claim 13 wherein the water-insoluble, acid-soluble polymer material is 2-methyl-5-vinylpyridine.methyl acrylate.methacrylic acid copolymer, poly-vinylacetacetal.diethylaminoacetate, dimethylaminoethyl methacrylate.methyl acrylate copolymer or cellulose.acetate.N,N-di-n-butylamino.hydroxypropyl ether.

17. A method according to any of claims 13 to 16 wherein ethylcellulose having an ethoxy

content of 47 to 55 W/W % is used.

18. A method according to any of claims 13 to 17 wherein ethylcellulose having 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 cP is used.

19 A method according to claim 18 wherein the viscosity of the ethylcellulose is 20 to 200 cP.

20. A method according to any of claims 13 to 19 wherein the ethylcellulose is used in an amount of 0.05 to 5 grams per gram of core material.

21. A method according to claim 20 wherein the ethylcellulose is used in an amount of 0.1 to 1 gram per gram of core material.

22. A method according to any of claims 13 to 21 wherein the polymer material has a particle diameter of not more than one-tenth that of the core material.

23. A method according to claim 22 wherein the polymer material has a particle size of not more than 50 μ.

24. A method according to claim 23 wherein the polymer material has a particle size of not more than 20 μ.

25. A method according to any of claims 13 to 24 wherein the solvent is cyclohexane.

26. A method according to any of claims 13 to 25 wherein particles of the pharmaceutically active compound having a particle size of 30–1000 μ are disprsed in the solution of alkylcellulose and the water-insoluble, acid-soluble polymer material is added to the dispersion before cooling.

27. A method according to any of claims 13 to 25 wherein particles of the pharmaceutically active compound having a particle size of 30–1000 μ are dispersed in the solution of alkylcellulose, the dispersion is cooled until coating walls having a viscosity of 0.1 to 50 P are formed on and around the particles of the pharmaceutically active compound, the water-insoluble, acid-soluble polymer material is added to the dispersion, and the dispersion containing the polymer material is further cooled until the resultant embryonic microcapsules shrink and become solid by solvent loss from the coating walls.

28. A method according to claim 26 or 27 wherein the size of the particles of the pharmaceutically active compound is 50 to 500 μ.

29. A method according to any of claims 13 to 28 wherein the water-insoluble, acid-soluble polymer material is used in an amount of 0.1 to 20 grams per gram of ethylcellulose.

30. A method according to claim 29 wherein the water-insoluble, acid-soluble polymer material is used in an amount of 0.5 to 10 grams per gram of ethylcellulose.

31. A method according to any of claims 13 to 30 wherein the particles of the pharmaceutically active compound contain a hydroxy-lower alkane-dicarbolic acid, hydroxy-lower alkane tricarboxylic acid, lower alkane-dicarboxylic acid or lower alkenedicarboxylic acid.

32. A method according to claim 31 wherein the acid is malic acid, tartaric acid, citric acid, malonic acid, succinic acid, maleic acid or furmaric acid.

33. A method according to claim 31 or 32 wherein the particle size of the acid is not more than 30 μ.

34. A method according to any of claims 13 to 33 wherein a phase-separation -inducing agent is added to the solution of ethylcellulose, and the phase-separation-inducing agent is polyethylene, butyl rubber, polyisobutylene or polybutadiene.

35. A method according to any of claims 13 to 34 wherein dimethylpolysiloxane or methylphenylpolysilane is added to the solution of ethycellulose.

36. A method according to any of claims 13 to 35 wherein a surfactant is added to the solution of ethylcellulose, and the surfactant is an ester of C_{12-18} fatty acid with sorbitan, an ester of C_{6-18} fatty acid with glycerin, phospholipids or calcium stearoyl-2-lactylate.

37. A method according to any of claims 13 to 36 wherein the ethylcellulose is dissolved at a temperature of 70°C to 80°C.

38. A method according to any of claims 13 to 37 wherein the ethylcellulose is dissolved at a concentration of 0.5 to 10 W/W %.

39. A method according to claim 38 wherein the ethylcellulose is dissolved at a concentration of 1 to 5 W/W %.

40. A method according to any of claims 13 to 39 wherein the dispersion is cooled at a rate of 0.05 to 4°C per minute.

41. A method according to claim 40 wherein the dispersion is cooled at a rate of 0.1 to 2°C per minute.

42. A method according to any of claims 13 to 41 wherein the polymer material is added to the dispersion at the stage when the coating walls have a viscosity of 0.1 to 50 P.

43. A method according to claim 42 wherein the polymer material is added to the dispersion when the coating walls have a viscosity of 1 to 10 P.

44. A method of preparing ethylcellulose microcapsules substantially as herein described with reference to and as illustrated in any of Examples 1 to 17.

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