Description

This invention relates to a process for preparing free-flowing ethylcellulose microcapsules.

It is known that in preparing microcapsules by taking advantage of the phase-separation of ethylcellulose in cyclohexane, butyl rubber having a Mooney viscosity (ML-8/100°C) of 60 to 75, polybutadiene having a molecular weight of 8,000 to 10,000, polyethylene having a molecular weight of 7,000 or polyisobutylene having a molecular weight of 8,700 to 135,000 are used as the phase-separation-inducing agent [Japanese Patent Publication (examined) Nos. 528/1967 and 30136/1970, U.S. Patent No. 3,341,416].

However, for industrial production of microcapsules these known methods are still unsatisfactory in that it is difficult to recover free-flowing discrete microcapsules in a high yield because microcapsules formed in the microencapsulation step is liable to agglomerate together into a large lump each containing a myriad of individual capsules and also stick to apparatuses for production of microcapsules. Additionally, when butyl rubber, polybutadiene or polyisobutylene having a molecular weight of not less than 7,000 is used as the phase-separation-inducing agent, the removal of said agent from the microcapsules obtained can be effected only by washing the microcapsules with the large excess (e.g., 50 ml/g) of cyclohexane for a long time because of their high adhesiveness and slow velocity of dissolution in the solvent. Further, in making such microcapsules, as long as 4 to 10 hours are required to dissolve only one gram of the above-mentioned agent (i.e., butyl rubber, polybutadiene or polyisobutylene having a molecular weight of not less than 7,000) in 30 ml of cyclohexane at 80°C. This inevitably impairs the operational efficiency in making the microcapsules. On the other hand, when polyethylene having a molecular weight of not less than 7,000 is used as the phase-separation-inducing agent, said polyethylene is separated as minute particles during cooling the dispersion and deposited on and in the wall of the microcapsules. Since such minute particles of polyethylene can not be washed out completely with a poor solvent such as cyclohexane and can not be separated from the microcapsules by passing through a sieve, therefore, such polyethylene is not suitable for use as the phase-separation-inducing agent in making microcapsules having a particle size less than 100 µm.

As an alternative to the above-mentioned methods, U.S. Patent 4,218,333 discloses a method of making microcapsules by using a mixture of polyisobutylene having a molecular weight of 8,000 to 12,000 and polyisobutylene having a molecular weight of 60,000 to 140,000 as the phase-separation-inducing agent. In this method, however, it is still difficult to completely remove the polyisobutylene from the formed microcapsules by washing them with a solvent such as cyclohexane or n-hexane because of its poor solubility in the solvent. It is also difficult to control the thickness of the ethylcellulose walls and obtain microcapsules having complete and compact walls. In U.S. Patent 3 626 056 an aqueous penicillin suspension comprising coated particles of certain penicillins is disclosed. The coating comprises ethylcellulose together with a pharmaceutical acceptable wax.

As a result of various investigations for seeking a method free from the foregoing disadvantages of the known methods, we have now found that free-flowing ethylcellulose microcapsules having compact and complete walls can be readily obtained by carrying out the liquid-liquid phase separation of ethylcellulose in cyclohexane in the presence of a hydrocarbon compound which is soluble in cyclohexane and has a molecular weight of 150 to 3,000 and a solubility parameter (δ, at 25°C) of 7 to 10 $(cal/cm^3)^{1/2}$. Namely, when said hydrocarbon compound is used as the phase-separation-inducing agent instead of those known in the art, no substantial adhesion or agglomeration of each microcapsules takes place in the microencapsulation step.

According to the present invention, free-flowing microcapsules can be prepared by the steps of:

(i) dispersing particles of a core material in a cyclohexane solution containing ethylcellulose and a hydrocarbon compound, said hydrocarbon compound being soluble in cyclohexane and having a molecular weight of 150 to 3,000 and a solubility parameter (δ, at 25°C) of 7 to 10 $(cal/cm^3)^{1/2}$,

(ii) cooling the dispersion until the ethylcellulose separates out from the dispersion to form coating walls on and around the particles of said core material, and then

(iii) recovering the thus-formed microcapsules therefrom.

A wide variety of hydrocarbon compounds which are soluble in cyclohexane and have a molecular weight of 150 to 3,000, especially 150 to 1,000, more specially 160 to 600 and a solubility parameter of 7 to 10 $(cal/cm^3)^{1/2}$, especially 7.5 to 9.5 $(cal/cm^3)^{1/2}$, more especially 8.0 to 9.2 $(cal/cm^3)^{1/2}$, can be used as the phase-separation-inducing agent in the present invention. As shown in J. Appl. Chem., Vol. 3, pp. 71—80 (1953), the solubility parameter (δ, at 25°C) is given by the following formula:

$$\delta = \frac{\Sigma F}{V} = \left(\frac{E}{V}\right)^{1/2}$$

wherein F is Small's molar-attraction constant at 25°C, V is molar volume and E is molar cohesive energy. Examples of the hydrocarbon compounds to be used as the phase-separation-inducing agent in the present invention include, for example, liquid paraffin, vaseline, ceresin, paraffin, microcrystalline wax, squalane, squalene, pristane, polubutadiene (Molecular weight: 500 to 3,000), polybutene (Molecular weight: 200 to

3,000), polyisoprene (Molecular weight: 1,000 to 3,000) and butadiene-styrene copolymer (Molecular weight: 1,500 to 3,000). Among these hydrocarbon compounds, a preferred subgenus is liquid paraffin, paraffin and polybutene (Molecular weight: 200 to 2,500). The most preferred subgenus is liquid paraffin. It is preferred to use 0.1 to 20 g, especially 1 to 10 g, more especially 1 to 3 g, of the hydrocarbon compound per 100 ml of cyclohexane.

On the other hand, ethylcellulose having an ethoxy content of 46.5 to 55 w/w % is preferably used as the wall-forming material of the present 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 0.003 to 0.5 Pa · s, especially 0.04 to 0.12 Pa · s. It is also preferred that said ethylcellulose is used in an amount of 0.03 to 5 grams, especially 0.05 to 0.5 gram, per gram of the core material used.

Any one of 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 either 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 about 5 to about 1000 µm, especially 50 to 500 µm. Eligible for microencapsulation as solids are particles of material such as, for example, vitamines (e.g., ascorbic acid), amino acids (e.g., potassium aspartate, magnesium aspartate), minerals (e.g., potassium chloride), anti-microbial agents (e.g., benzylpenicillin potassium salt, sulfomethiazole), anti-tumor agents (e.g., 5-fluorouracil, bleomyin hydrochloride), metabolic agents (e.g., glutathione), cardiovascular agents (e.g., diltiazem hydrochloride), analgesics (e.g., acetylsalicylic acid), anti-histaminics (e.g., diphenhydramine hydrochloride), neurosychotropin agents (e.g., calcium N - (γ,γ - dihydroxy - β,β - dimethylbutyryl) - γ - aminobutyrate), agents affecting digestive organs (e.g., methylmethionine sulfonium chloride, timepidium bromide, precipitated calcium carbonate, 2 - dimethylamino - 2 - phenylbutyl 3,4,5-trimethoxybenzoate hydrogen maleate), agents affecting respiratory organs (e.g., trimethoquinol hydrochloride, 1 - methyl - 5 - methoxy - 3 - (dithien - 2 - ylmethylene)piperidine hydrobromide) and so forth. Also eligible for microencapsulation as semi-solids are, for example, slurrys such as a slurry composed of 30 w/w % of sodium polyacrylate, 40 w/w % of water and 30 w/w % of 5-fluorouracil. And pharmaceutically active compounds in the form of "gel" which can be microencapsulated include, for example, dextran gel having a medicament (e.g., methylmethionine sufonium chloride) adsorbed therein, formalin-treated gelatin gel having dispersed a medicament (e.g., sulfamethomidine) therein, and so forth.

In making the microcapsules in accordance with the present invention, particles of a core material are first dispersed in cyclohexane containing ethylcellulose and the hydrocarbon compound. This dispersing step is preferably carried out by adding ethylcellulose, the hydrocarbon compound and particles of a core material to cyclohexane under stirring and then heating the mixture to 75° to 80°C. Said dispersing step is also carried out by dissolving ethylcellulose and the hydrocarbon compound in cyclohexane at 75° to 80°C and then dispersing particles of a core material in the solution under stirring. It is preferred to use the ethylcellulose so that the concentration of said ethylcellulose in cyclohexane becomes 0.5 to 10 w/v %, especially 1 to 5 w/v %. When the thus-prepared dispersion is then cooled gradually (e.g., at a rate of 0.05° to 4°C, especially 0.5° to 2°C, per minute) under continuous stirring at 100 to 400 rpm, ethylcellulose in the form of "gel" separates out from the dispersion at about 70° to 55°C mainly by coacervation thereof thereby depositing on or wrapping the particles of the core material, and the ethylcellulose gel thus deposited forms seamless walls. When the temperature is further lowered to a temperature not higher than 40°C (e.g., 40° to 20°C), the thus-formed embryonic microcapsules are shrunken and become solid by solvent loss from the capsule walls, thus giving stable microcapsules. Once stable microcapsules are formed, a poor solvent such as cyclohexane, petroleum-ether or n-hexane may be, if necessary, added to the dispersion to further stabilize the microcapsules.

In the above-mentioned method of the present invention, the hydrocarbon compound to be used as the phase-separation-inducing agent may be used in combination with a hydrocarbon polymer (e.g., polyethylene, butyl rubber, polybutadiene, polyisobutylene) having a molecular weight of 4,000 to 2,000,000 and/or an organopolysiloxane (e.g., dimethyl polysiloxane, diphenyl polysiloxane, polystyrene-polydimethyl-siloxane block copolymer). The organopolysiloxane to be used in the present invention may be a mixture of 99 to 50 w/w % of the above-mentioned organopolysiloxane and 1 to 50 w/w % of additives such as silicon dioxide, titanium oxide, calcium stearate or talc. It is preferred to add said hydrocarbon polymer and/or organopolysiloxane to cyclohexane at the state of addition of ethylcellulose and the hydrocarbon compound. Suitable amount of the hydrocarbon polymer to be added is 0.1 to 10 grams, especially 1 to 3 grams, per 100 ml of cyclohexane. On the other hand, the organopolysiloxane is preferably used in an amount of 0.01 to 10 grams, especially 0.1 to 3 grams, per 100 ml of cyclohexane.

The microcapsules thus obtained may be recovered by conventional manners such as, for example, decantation, filtration, centrifugation and so forth. In addition, free-flowing discrete microcapsules which are substantially free from the hydrocarbon compound, the hydrocarbon polymer and the organopolysiloxane can be readily obtained by washing the thus-obtained microcapsules with cyclohexane, petroleum-ether, n-hexane and so forth, i.e., with an organic solvent which dissolves the hydrocarbon compound, the hydrocarbon polymer and the organopolysiloxane but does not dissolve both of ethylcellulose and the core material used.

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According to the above-mentioned method of the present invention, the hydrocarbon compound which is used as the phase-separation-inducing agent binds to molecules of ethylcellulose through the interaction thereof such as van der Waals force to deposit on and around the core material. The deposited hydrocarbon compound induces coacervation of ethylcellulose without causing flocculation of ethylcellulose and at the same time prevents the formed microcapsules from adhering and agglomerating together. Further, according to the present invention, free-flowing discrete microcapsules having complete and compact walls can be obtained in such a high yield as over 90% and the operational efficiency in making microcapsules is remarkably improved because the formed microcapsules neither agglomerate together nor stick to apparatuses for production thereof. After the microencapsulation step of the present invention, the hydrocarbon compound used can be readily removed from microcapsules by washing them with a solvent such as n-hexane because of high solubility of said compound in the solvent.

Experiment

Microcapsules containing timepidium bromide (Chemical name: 1,1-dimethyl-5-methoxy-3-(dithien-2-ylmethylene)piperidinium bromide) were prepared in accordance with the following method. The thus-obtained microcapsules (i.e., microcapsules which met the requirements of "Fine Granules" specified in The Pharmacopoeia of Japan 10th-Edition) were examined with respect to the yield of said microcapsules and the content of active ingredient (i.e., timepidium bromide) contained in said microcapsules.

(Method)

(1) Core material

7 parts by weight of an aqueous 45 v/v % ethanol solution were added to a powder mixture of 10 parts by weight of timepidium bromide, 84 parts by weight of lactose and 6 parts by weight of white dextrin, and the mixture was kneaded and granulated in conventional manners. The granules were dried. The granules having a particle size of 105 to 350 µm were used as the core material.

(2) Preparation of microcapsules

24 g of a phase-separation-inducing agent shown in the following Table 1, 20 g of ethylcellulose ethoxy content: 48 w/w %, viscosity (measured at 25°C with respect to a toluene-ethanol (4:1) solution containing 5 w/w % of said ethylcellulose):0.1 Pa · s] and 140 g of the core material prepared in paragraph (1) were added to 800 ml of cyclohexane. The mixture was stirred at 80°C to give a dispersion of the core material. The dispersion was cooled to room temperature under stirring at 300 rpm. The microcapsules thus formed were recovered by filtration, washed with n-hexane and dried. Said microcapsules were passed through the nest of JIS (Japanese Industrial Standard) standard sieve (500 µm aperture) and then the nest of JIS standard sieve (105 µm aperture). The microcapsules which passed through the former sieve but did not pass through the latter sieve were collected, whereby timepidium bromide-containing microcapsules which met the requirements of "Fine Granules" specified in The Pharmacopoeia of Japan 10th-Edition were obtained).

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(Results)

The results are shown in the following Table 1.

TABLE 1

Nos.	Phase-separation-inducing agents	Solubility parameter δ $(cal/cm^3)^{1/2}$	Yield of micro-capsules (g)	Amount of active ingredient contained in micro-capsules (%)
1.	liquid paraffin	8.3—9.1	157	8.76
2.	vaseline	8.0—8.7	155	8.75
3.	ceresin	8.8—8.9	151	8.77
4.	paraffin	9.0—9.3	149	8.77
5.	microcrystalline wax	8.7—8.0	151	8.75
6.	squalane	8.9	157	8.75
7.	squalene	9.2	153	8.79
8.	pristane	7.6	153	8.77
9.	polybutadiene (M.W.=700)	8.1	155	8.81
10.	polybutadiene (M.W.=2,000)	8.1	151	8.95
11.	polybutene (M.W.=270)	8.8	157	8.74
12.	polybutene (M.W.=900)	8.4	151	8.97
13.	polybutene (M.W.=2,350)	8.4	149	8.76
14.	cis-1,4-polyisoprene (M.W.=2,000)	8.1	147	8.78
(Positive control)	polyisobutylene (M.W.=10,000)	7.9	45	8.75

Note: M.W. stands for molecular weight.

Example 1

16.8 g of liquid paraffin (δ=8.3—9.1 $(cal/cm^3)^{1/2}$), 7.2 g of polyisobutylene (molecular weight: 4,000), 20 g of ethylcellulose [ethoxy content: 48 w/w %, viscosity (measured at 25°C with respect to a toluene-ethanol (4:1) solution containing 5 w/w % of said ethylcellulose):0.1 Pa · s] and 140 g of trimebutine maleate (Chemical name: 2 - dimethylamino - 2 - phenylbutyl, 3,4,5-trimethoxybenzoate hydrogen maleate) having a particle size of 105—177 μm were added to 800 ml of cyclohexane. The mixture was stirred at 80°C to give a dispersion of the core material (i.e., trimebutine maleate). The dispersion was cooled to room temperature (about 25°C) under stirring at 400 rpm. The microcapsules thus formed were recovered by filtration, washed with n-hexane and dried. Then, said microcapsules were passed through the nest of JIS standard sieve (350 μm aperture), whereby 156 g of trimebutine maleate-containing

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microcapsules which met the requirements of "Pulvers" specified in The Pharmacopoeia of Japan 10th-Edition were obtained.

For comparison, microcapsules were prepared in the same manner as described above except that 24 g of polyisobutylene (molecular weight: 4,000) were used in stead of 16.8 g of liquid paraffin and 7.2 g of polyisobutylene, whereby only 39 g of trimebutine maleate-containing microcapsules which met the requirements of "Pulvers" specified above were obtained.

Example 2

Microcapsules were prepared in the same manner as described in Example 1 except that 12 g of liquid paraffin (δ=8.3—9.1 $(cal/cm^3)^{1/2}$) and 12 g of polyisobutylene (molecualr weight: 10,000) were used instead of 16.8 g of liquid paraffin and 7.2 g of polyisobutylene (molecular weight: 4,000). 154 g of trimebutine maleate-containing microcapsules which met the requirements of "Pulvers" specified above were obtained.

Example 3

Microcapsules were prepared in the same manner as described in Example 1 except that 24 g of polybutene (molecular weight: 1,000, δ=8.4 $(cal/cm^3)^{1/2}$) were used instead of 16.8 g of liquid paraffin and 7.2 g of polyisobutylene. 156 g of trimebutine maleate-containing microcapsules which met the requirements of "Pulvers" specified above were obtained.

Example 4

Microcapsules were prepared in the same manner as described in Example 1 except that 7.2 g of dimethyl polysiloxane (Viscosity measured at 25°C: $100\times10^{-4}m^2\cdot s^{-1}$) were used instead of polyisobutylene. 156 g of trimebutine maleate-containing microcapsules which met the requirements of "Pulvers" specified above were obtained.

Example 5

16.8 g of liquid paraffin (δ=8.3—9.1 $(cal/cm^3)^{1/2}$), 7.2 g of silicone resin which met the requirements specified in 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 dimethyl polysiloxane (viscosity measured at 25°: 1×10^{-4} to $11\times10^{-4}m^2\cdot s^1$)], 20 g of ethylcellulose (the ethoxy content and viscosity are the same as defined in Example 1) and 240 g of vitamin C having a particle size of 105—250 µm were added to 800 ml of cyclohexane. The mixture was stirred at 80°C to give a dispersion of the core material (i.e., vitamin C). The dispersion was cooled to room temperature (about 25°C) under stirring at 300 rpm. The microcapsules thus formed were recovered by filtration, washed with n-hexane and dried. Then, said microcapsules were passed through the nest of JIS standard sieve (350 µm aperture), whereby 254 g of vitamin C-containing microcapsules which met the requirements of "Pulvers" specified above were obtained.

Example 6

24 g of polybutene (molecular weight: 1,000; δ=8.4 $(cal/cm^3)^{1/2}$), 20 g of ethylcellulose (the ethoxy content and viscosity are the same as defined in Example 1) and 200 g of diltiazem hydrochloride (chemical name: d - 3 - acetoxy - cis - 2,3 - dihydro - 5 - [2 - (dimethylamino)ethyl] - 2 - (p - methoxyphenyl) - 1,5 - benzothiazepin - 4(5H) - one hydrochloride) having a particle size of 105—210 µm were added to 800 ml of cyclohexane. The mixture was stirred at 80°C to give a dispersion of the core material (i.e., diltiazem hydrochloride). The dispersion was cooled to a room temperature (about 25°C) under stirring at 300 rpm. The microcapsules thus formed were recovered by filtration, washed with n-hexane and dried. Then, said microcapsules were passed through the nest of JIS standard sieve (350 µm aperture), whereby 216 g of diltiazem hydrochloride-containing microcapsules which met the requirements of "Pulvers" specified above were obtained.

Example 7

16.8 g of liquid paraffin (δ=8.3—9.1 $(cal/cm^3)^{1/2}$), 7.2 g of silicone resin (said silicone resin being the same as that of Example 5), 20 g of ethylcellulose (the ethoxy content and viscosity are the same as defined in Example 1) and 140 g of 1 - methyl - 5 - methoxy - 3 - (dithien - 2 - ylmethylene)piperidine hydrobromide (core material) having a particle size of 105—350 µm were added to 800 ml of cyclohexane. The mixture was stirred at 80°C to give a dispersion of the core material. The dispersion was cooled to room temperature (about 25°C) under stirring at 300 rpm. The microcapsules thus formed were recovered by filtration, washed with n-hexane and dried. Said microcapsules were passed through the nest of JIS standard sieve (500 µm aperture) and then the nest of JIS standard sieve (105 µm aperture). The microcapsules which passed thorugh the former sieve but did not pass through the latter sieve were collected, whereby 152 g of 1 - methyl - 5 - methoxy - 3 - (dithien - 2 - ylmethylene)piperidine hydrobromide-containing microcapsules which met the requirements of "Fine Granules" specified in The Pharmacopoeia of Japan 10th-Edition were obtained.

For comparison, microcapsules were prepared in the same manner as described above except that 24 g of silicone resin were used instead of 16.8 g of liquid paraffin and 7.2 g of silicone resin, whereby only 27

g of 1 - methyl - 5 - methoxy - 3 - (diethien - 2 - ylmethylene)piperidine hydrobromide-containing microcapsules which met the requirements of "Fine Granules" specified above were obtained.

Claims

1. A method of preparing free-flowing microcapsules which comprises the steps of:
(i) dispersing particles of a core material in a cyclohexane solution containing ethylcellulose and a hydrocarbon compound, said hydrocarbon compound being soluble in cyclohexane and having a molecular weight of 150 to 3,000 and a solubility parameter (δ, at 25°C) of 7 to 10 $(cal/cm^3)^{1/2}$,
(ii) cooling the dispersion until the ethylcellulose spearates out from the dispersion to form coating walls on and around the particles of said core material, and then
(iii) recovering the thus-formed microcapsules therefrom.

2. The method according to Claim 1, wherein said hydrocarbon compound has a solubility parameter of 7.5 to 9.5 $(cal/cm^3)^{1/2}$.

3. The method according to Claim 1, wherein said hydrocarbon compound has a solubility parameter of 8.0 to 9.2 $(cal/cm^3)^{1/2}$.

4. The method according to Claim 1, wherein said hydrocarbon compound is a member selected from the group consisting of liquid paraffin, vaseline, ceresin, paraffin, microcrystalline wax, squalane, squalene, pristane, polybutadiene (Molecular weight: 500 to 3,000), polybutene (Molecular weight: 200 to 3,000), polyisoprene (Molecular weight: 1,000 to 3,000), and butadiene-styrene copolymer (Molecular weight: 1,500 to 3,000).

5. The method according to Claim 1, wherein said hydrocarbon compound is a member selected from the group consisting of liquid paraffin, paraffin and polybutene (Molecular weight: 200 to 2,500).

6. The method according to Claim 1, wherein the hydrocarbon compound is used in an amount of 0.1 to 20 g per 100 ml of cyclohexane.

7. The method according to Claim 1, wherein the hydrocarbon compound is used in an amount of 1 to 10 g per 100 ml of cyclohexane.

8. The method according to Claim 1, wherein the hydrocarbon compound is used in an amount of 1 to 3 g per 100 ml of cyclohexane.

9. The method according to Claim 6, wherein ethylcellulose having an ethoxy content of 46.5 to 55 w/w % is used.

10. The method according to Claim 6, wherein 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 0.003 to 0.5 Pa · s is used.

11. The method according to Claim 9, wherein ethylcellulose is used in an amount of 0.03 to 5 grams per gram of the core material.

12. The method according to Claim 11, wherein the hydrocarbon compound is liquid paraffin.

13. The method according to Claim 4, wherein the dispersing step (i) is carried out by adding ethylcellulose, the hydrocarbon compound and the core material to cyclohexane and then heating the mixture to 75° to 80°C.

14. The method according to Claim 4, wherein the dispersing step (i) is carried out by dissolving ethylcellulose and the hydrocarbon compound in cyclohexane at 75° to 80°C and then dispersing the core material in the solution under stirring.

15. The method according to Claim 4, wherein the hydrocarbon compound is used in combination with a hydrocarbon polymer selected from the group consisting of butyl rubber, polybutadiene, polyethylene and polyisobutylene, said hydrocarbon polymer having a molecular weight of 4,000 to 2,000,000.

16. The method according to Claim 4, wherein the hydrocarbon compound is used in combination with an organopolysiloxane selected from the group consisting of dimethyl polysiloxane, methylphenyl polysiloxane, diphenyl polysiloxane and polystyrene-polydimethylsiloxane block copolymer.

17. The method according to Claim 15, wherein the hydrocarbon compound is used in an amount of 0.1 to 20 g per 100 ml of cyclohexane, and the hydrocarbon polymer is used in an amount of 0.1 to 10 grams per 100 ml of cyclohexane.

18. The method according to Claim 16, wherein the hydrocarbon compound is used in an amount of 0.1 to 20 g per 100 ml of cyclohexane, and the organopolysiloxane is used in an amount of 0.01 to 10 grams per 100 ml of cyclohexane.

Patentansprüche

1. Verfahren zur Herstellung von freifliessenden Mikrokapseln, gekennzeichnet, durch folgende Stufen:
(i) Dispergieren von Teilchen eines Kernmaterials in einer Cyclohexanlösung, enthaltend Ethylcellulose und eine Kohenwasserstoffverbindung, wobei die Kohlenwasserstoffverbindung in Cyclohexan löslich ist und ein Molekulargewicht von 150 bis 3.000 und ein Löslichkeitsparameter (δ, bei 25°C) von 7 bis 10 $(cal/cm^3)^{1/2}$ aufweist,
(ii) Dispergieren der Dispersion, bis die Ethylcellulose sich in Form von Überzugswandungen auf und um die Teilchen des Kernmaterials abscheidet und dann

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g of 1 - methyl - 5 - methoxy - 3 - (diethien - 2 - ylmethylene)piperidine hydrobromide-containing microcapsules which met the requirements of "Fine Granules" specified above were obtained.

Claims

1. A method of preparing free-flowing microcapsules which comprises the steps of:
(i) dispersing particles of a core material in a cyclohexane solution containing ethylcellulose and a hydrocarbon compound, said hydrocarbon compound being soluble in cyclohexane and having a molecular weight of 150 to 3,000 and a solubility parameter (δ, at 25°C) of 7 to 10 $(cal/cm^3)^{1/2}$,
(ii) cooling the dispersion until the ethylcellulose spearates out from the dispersion to form coating walls on and around the particles of said core material, and then
(iii) recovering the thus-formed microcapsules therefrom.

2. The method according to Claim 1, wherein said hydrocarbon compound has a solubility parameter of 7.5 to 9.5 $(cal/cm^3)^{1/2}$.

3. The method according to Claim 1, wherein said hydrocarbon compound has a solubility parameter of 8.0 to 9.2 $(cal/cm^3)^{1/2}$.

4. The method according to Claim 1, wherein said hydrocarbon compound is a member selected from the group consisting of liquid paraffin, vaseline, ceresin, paraffin, microcrystalline wax, squalane, squalene, pristane, polybutadiene (Molecular weight: 500 to 3,000), polybutene (Molecular weight: 200 to 3,000), polyisoprene (Molecular weight: 1,000 to 3,000), and butadiene-styrene copolymer (Molecular weight: 1,500 to 3,000).

5. The method according to Claim 1, wherein said hydrocarbon compound is a member selected from the group consisting of liquid paraffin, paraffin and polybutene (Molecular weight: 200 to 2,500).

6. The method according to Claim 1, wherein the hydrocarbon compound is used in an amount of 0.1 to 20 g per 100 ml of cyclohexane.

7. The method according to Claim 1, wherein the hydrocarbon compound is used in an amount of 1 to 10 g per 100 ml of cyclohexane.

8. The method according to Glaim 1, wherein the hydrocarbon compound is used in an amount of 1 to 3 g per 100 ml of cyclohexane.

9. The method according to Claim 6, wherein ethylcellulose having an ethoxy content of 46.5 to 55 w/w % is used.

10. The method according to Claim 6, wherein 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 0.003 to 0.5 Pa · s is used.

11. The method according to Claim 9, wherein ethylcellulose is used in an amount of 0.03 to 5 grams per gram of the core material.

12. The method according to Claim 11, wherein the hydrocarbon compound is liquid paraffin.

13. The method according to Claim 4, wherein the dispersing step (i) is carried out by adding ethylcellulose, the hydrocarbon compound and the core material to cyclohexane and then heating the mixture to 75° to 80°C.

14. The method according to Claim 4, wherein the dispersing step (i) is carried out by dissolving ethylcellulose and the hydrocarbon compound in cyclohexane at 75° to 80°C and then dispersing the core material in the solution under stirring.

15. The method according to Claim 4, wherein the hydrocarbon compound is used in combination with a hydrocarbon polymer selected from the group consisting of butyl rubber, polybutadiene, polyethylene and polyisobutylene, said hydrocarbon polymer having a molecular weight of 4,000 to 2,000,000.

16. The method according to Claim 4, wherein the hydrocarbon compound is used in combination with an organopolysiloxane selected from the group consisting of dimethyl polysiloxane, methylphenyl polysiloxane, diphenyl polysiloxane and polystyrene-polydimethylsiloxane block copolymer.

17. The method according to Claim 15, wherein the hydrocarbon compound is used in an amount of 0.1 to 20 g per 100 ml of cyclohexane, and the hydrocarbon polymer is used in an amount of 0.1 to 10 grams per 100 ml of cyclohexane.

18. The method according to Claim 16, wherein the hydrocarbon compound is used in an amount of 0.1 to 20 g per 100 ml of cyclohexane, and the organopolysiloxane is used in an amount of 0.01 to 10 grams per 100 ml of cyclohexane.

Patentansprüche

1. Verfahren zur Herstellung von freifliessenden Mikrokapseln, gekennzeichnet, durch folgende Stufen:
(i) Dispergieren von Teilchen eines Kernmaterials in einer Cyclohexanlösung, enthaltend Ethylcellulose und eine Kohenwasserstoffverbindung, wobei die Kohlenwasserstoffverbindung in Cyclohexan löslich ist und ein Molekulargewicht von 150 bis 3.000 und ein Löslichkeitsparameter (δ, bei 25°C) von 7 bis 10 $(cal/cm^3)^{1/2}$ aufweist,
(ii) Dispergieren der Dispersion, bis die Ethylcellulose sich in Form von Überzugswandungen auf und um die Teilchen des Kernmaterials abscheidet und dann

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(iii) Gewinnen der so gebildeten Mikrokapseln.

2. Verfahren gemäss Anspruch 1, worin die Kohlenwasserstoffverbindung ein Löslichkeitsparameter von 7,5 bis 9,5 $(cal/cm^3)^{1/2}$ hat.

3. Verfahren gemäss Anspruch 1, worin die Kohlenwasserstoffverbindung ein Löslichkeitsparameter von 8,0 bis 9,2 $(cal/cm^3)^{1/2}$ hat.

4. Verfahren gemäss Anspruch 1, worin die Kohlenwasserstoffverbindung ein Glied, ausgewählt aus der Gruppe, bestehend aus flüssigem Paraffin, Vasiline, Ceresin, Paraffin, mikrokristallines Wachs, Squalan, Squalen, Pristan, Polybutadien (Molekulargewicht 500 bis 3.000). Polybuten (Molekulargewicht 200 bis 3.000), Polyisopren (Molekulargewicht 1.000 bis 3.000) und Butadien-Styrol-Copolymer (Molekulargewicht 1.500 bis 3.000) ist.

5. Verfahren gemäss Anspruch 1, worin die Kohlenwasserstoffverbindung ein Glied, ausgewählt aus der Gruppe, bestehend aus flüssigem Paraffin, Paraffin und Polybuten (Molekulargewicht 200 bis 2.500) ist.

6. Verfahren gemäss Anspruch 1, worin die Kohlenwasserstoffverbindung in einer Menge von 0,1 bis 20 g pro 100 ml Cyclohexan verwendet wird.

7. Verfahren gemäss Anspruch 1, worin die Kohlenwasserstoffverbindung in einer Menge von 1 bis 10 g pro 100 ml Cyclohexan verwendet wird.

8. Verfahren gemäss Anspruch 1, worin die Kohlenwasserstoffverbindung in einer Menge von 1 bis 3 g pro 100 ml Cyclohexan verwendet wird.

9. Verfahren gemäss Anspruch 6, worin ein Ethylcellulose mit einem Ethoxygehalt von 46,5 bis 55 W/W-% verwedent wird.

10. Verfahren gemäss Anspruch 6, worin eine Ethylcellulose mit einem Ethoxygehalt von 46,5 bis 55 W/W-% und einer Viskosität (gemessen bei 25°C an einer 5 W/W-%-igen Lösung in Toluol-Ethanol (4:1)) von 0,003 bis 0,5 Pa . s verwendet wird.

11. Verfahren gemäss Anspruch 9, worin Ethylcellulose in einer Menge von 0,03 bis 5 g pro Gramm des Kernmaterials verwendet wird.

12. Verfahren gemäss Anspruch 11, worin die Kohlenwasserstoffverbindung ein flüssiges Paraffin ist.

13. Verfahren gemäss Anspruch 4, worin die Dispergierungsstufe (i) durchgeführt wird, indem man Ethylcellulose, die Kohlenwasserstoffverbindung und das Kernmaterial zu Cyclohexan gibt und dann das Gemisch auf 75 bis 80°C erhitzt.

14. Verfahren gemäss Anspruch 4, worin die Dispergierungsstufe (i) durchgeführt wird, indem man Ethylcellulose und die Kohlenwasserstoffverbindung in Cyclohexan bei 75 bis 80°C löst und dann das Kernmaterial in der Lösung unter Rühren dispergiert.

15. Verfahren gemäss Anspruch 4, worin die Kohlenwasserstoffverbindung in Kombination mit einem Kohlenwasserstoffpolymer, ausgewählt aus der Gruppe, bestehend aus Butylkautschuk, Polybutadien, Polyethylen und Polyisobutylen, wobei das Kohlenwasserstoffpolymer ein Molekulargewicht von 4.000 bis 2.000.000 aufweist, verwendet wird.

16. Verfahren gemäss Anspruch 4, worin die Kohlenwasserstoffverbindung in Kombination mit einem Organopolysiloxan, ausgewählt aus der Gruppe, bestehend aus Dimethylpolysiloxan, Methylphenylpolysiloxan, Diphenylpolysiloxan und Polystyrol-Polydimethylsiloxan-Blockcopolymer, verwendet wird.

17. Verfahren gemäss Anspruch 15, worin die Kohlenwasserstoffverbindung in einer Menge von 0,1 bis 20 g pro 100 ml Cyclohexan verwendet wird und das Kohlenwasserstoffpolymer in einer Menge von 0,1 bis 10 g pro 100 ml Cyclohexan verwendet wird.

18. Verfahren gemäss Anspruch 16, worin die Kohlenwasserstoffverbindung in einer Menge von 0,1 bis 20 g pro 100 ml Cyclohexan verwendet wird und das Organopolysiloxan in einer Menge von 0,01 bis 10 g pro 100 ml Cyclohexan verwendet wird.

Revendications

1. Méthode de préparation de microcapsules coulant librement, comprenant les étapes de:

(I) dispersion des particules d'un matériau formant noyau dans une solution de cyclohexane contenant de l'éthyl-cellulose et un composé hydrocarboné, ledit composé hydrocarboné étant soluble dans le cyclohexane et ayant un poids moléculaire de 150 à 3000 et un paramètre de solubilité (δ, à 25°C) de 7 à 10 $(cal/cm^3)^{1/2}$;

(II) refroidissement de la dispersion jusqu'à ce que l'éthyl-cellulose se sépare de la dispersion pour former des parois de revêtement sur et autour des particules dudit matériau formant noyau;

(III) puis, récupération des microcapsules ainsi formées.

2. Méthode selon la revendication 1, dans laquelle ledit composé hydrocarboné a un paramètre de solubilité de 7,5 à 9,5 $(cal/cm^3)^{1/2}$.

3. Méthode selon la revendication 1, dans laquelle ledit composé hydrocarboné a un paramètre de solubilité de 8,0 à 9,2 $(cal/cm^3)^{1/2}$.

4. Méthode selon la revendication 1, dans laquelle le composé hydrocarboné est un élément choisi parmi le groupe constitué par la paraffine liquide, la vaseline, la cérésine, la paraffine, la cire microcristalline, le squalane, le squalène, le pristane, le polybutadiène (poids moléculaire: 500 à 3000), le polybutène (poids moléculaire: 200 à 3000), le polyisoprène (poids moléculaire: 1000 à 3000) et le copolymère butadiène-styrène (poids moléculaire: 1500 à 3000).

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5. Méthode selon la revendication 1, dans laquelle ledit composé hydrocarboné est un membre choisi parmi le groupe constitué de la paraffine liquide, la paraffine, et le polybutène (poids moléculaire: 200 à 2500).

6. Méthode selon la revendication 1, dans laquelle le composé hydrocarboné est employé à raison de 0,1 à 20 g pour 100 ml de cyclohexane.

7. Méthode selon la revendication 1, dans laquelle le composé hydrocarboné est employé à raison de 1 à 10 g pour 100 ml de cyclohexane.

8. Méthode selon la revendication 1, dans laquelle le composé hydrocarboné est employé à raison de 1 à 3 g pour 100 ml de cyclohexane.

9. Méthode selon la revendication 6, dans laquelle on utilise de l'éthyl-cellulose ayant une teneur en éthoxy de 46,5 à 55% en poids.

10. Méthode selon la revendication 6, dans laquelle on utilise de l'éthyl-cellulose ayant une teneur en éthoxy de 46,5 à 55% en poids et une viscosité (mesurée à 25°C en solution à 5% en poids dans un mélange toluène-éthanol (4:1)) de 0,003 à 0,5 Pa . s.

11. Méthode selon la revendication 9, dans laquelle l'éthyl-cellulose est employée à raison de 0,03 à 5 g par gramme du matériau formant noyau.

12. Méthode selon la revendication 11, dans laquelle le composé hydrocarboné est de la paraffine liquide.

13. Méthode selon la revendication 4, dans laquelle on effectue l'étape de dispersion (I) en ajoutant de l'éthyl-cellulose, le composé hydrocarboné, et le matériau formant noyau, au cyclohexane, et en chauffant ensuite le mélange à 75—80°C.

14. Méthode selon la revendication 4, dans laquelle on effectue l'étape de dispersion (I) en dissolvant l'éthyl-cellulose et le composé hydrocarboné dans le cyclohexane à 75—80°C, et en dispersant ensuite le matériau formant noyau dans la solution sous agitation.

15. Méthode selon la revendication 4, dans laquelle on utilise le composé hydrocarboné en combinaison avec un polymère hydrocarboné choisi parmi le groupe constitué de la gomme butylique, du polybutadiène, du polyéthylène, et du polyisobutylène, ledit polymère hydrocarboné ayant un poids moléculaire de 4000 à 2.000.000.

16. Méthode selon la revendication 4, dans laquelle le composé hydrocarboné est utilisé en combinaison avec un organopolysiloxane choisi parmi le groupe constitué du diméthylpolysiloxane, du méthylphénylpolysiloxane, du diphénylpolysiloxane, et du copolymère en blocs polystyrène-polydiméthylsiloxane.

17. Méthode selon la revendication 15, dans laquelle le composé hydrocarboné est employé à raison de 0,1 à 20 g pour 100 ml de cyclohexane, et le polymère hydrocarboné est utilisé à raison de 0,1 à 10 g pour 100 ml de cyclohexane.

18. Méthode selon la revendication 16, dans laquelle le composé hydrocarboné est utilisé à raison de 0,1 à 20 g pour 100 ml de cyclohexane, et l'organopolysiloxane est utilisé à raison de 0,01 à 10 g pour 100 ml de cyclohexane.

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