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SPRUSON & FERGUSON

Commonwealth of Australia

Patents Act 1990

PATENT REQUEST: STANDARD PATENT

We, the Applicants/Nominated Persons specified below, request we be granted a patent for the invention disclosed in the accompanying standard complete specification.

[70,71] Applicants/Nominated Persons:

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[54] Invention Title:

Encapsulation of Active Substances in Starch

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Fluntera AG, Ivan Tomka

Registered Patent Attorney

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NOTICE OF ENTITLEMENT

I, Matthys Gschwind, Director, of Fluntera AG

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being authorised by one of the Applicants/Nominated Persons in respect of Application No 70531/91
and
I, Ivan Tomka of Chalet Breitfeld, CH-1722 Bourguillon, Switzerland being one the Applicants/Nominated Persons in respect of Application No.70531/91

both state the following:

The Applicants/Nominated Persons have entitlement from the actual inventors as follows:-

Ivan Tomka made the basic application as assignee of his co-inventor, Robert Sala and assigned a part interest in the invention to F.Hoffmann-La Roche AG and Fluntera AG. F.Hoffmann-La Roche AG have assigned their rights in the invention insofar as Australia is concerned to Ivan Tomka and Fluntera AG

The Applicants/Nominated Persons are entitled to rely on the application listed in the Declaration under Article 8 of the PCT as follows:

Ivan Tomka made the basic application as assignee of his co-inventor, Robert Sala and assigned a part interest in the invention to F.Hoffmann-La Roche AG and Fluntera AG. F.Hoffmann-La Roche AG have assigned their rights in the invention insofar as Australia is concerned to Ivan Tomka and Fluntera AG

The basic application listed on the Declaration under Article 8 of the PCT is the application first made in a Convention country in respect of the invention.

DATED this 29th day of January 1992

.....
(Signature)

Matthys Gschwind, Director
(Name & Title)

DATED this 29th day of January 1992

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(57) Claim

1. Method for encapsulating or for coating one or more active compounds in a or with a carrier substance, characterised in that the encapsulating or coating carrier substance used is a mixture of essentially native starch and at least one agent at least partially swelling the starch and which, for encapsulation or for coating, is mixed together with the active compound and at least one emulsifier.

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(54) Title: ENCAPSULATION OF ACTIVE SUBSTANCES IN STARCH

(54) Bezeichnung: EINKAPSELUNG VON WIRKSTOFFEN MITTELS STÄRKE

(57) Abstract

In order to encapsulate or coat one or more active substances with a material, a mixture is used as the encapsulating or coating material which consists of substantially natural starch and at least one agent which at least partly swells the starch and which, for the encapsulation or coating, is mixed with the active ingredient and at least one emulsifier. Preferably also added to the swollen starch plus active ingredient during mixing is at least one oily substance which substantially cannot form a homogeneous mixture or with which substantially no phase intermixing takes place bwteen the oil and the swollen starch. Mixing the swelling agent, emulsifier, oily substance and natural starch with the active ingredient is preferably carried out at elevated temperature in a mixing device such as a mixer, kneader or extruder.

(57) Zusammenfassung

Für das Einkapseln oder Beschichten eines oder mehrerer Wirkstoffe in einer oder mit einer Trägersubstanz wird als einkapselnde oder beschichtende Trägersubstanz ein Gemisch aus im wesentlichen nativer Stärke und mindestens einem die Stärke mindestens teilweise quellenden Mittel verwendet, das für die Einkapselung oder für das Beschichten zusammen mit dem Wirkstoff und mindestens einem Emulgator gemischt wird. Beim Mischen wird der gequollenen Stärke mit dem Wirkstoff weiter vorzugsweise mindestens ein ölartiger Stoff zugesetzt, der mit der Stärke im wesentlichen kein homogenes Gemisch bilden kann resp. wobei keine Phasendurchmischung zwischen dem Öl und der gequollenen Stärke stattfindet. Die Mischung des Quellmittels, des Emulgators, des ölartigen Stoffes, der nativen Stärke mit dem Wirkstoff erfolgt vorzugsweise bei erhöhter Temperatur in einem Mischaggregat, wie Mischer, Kneter oder Extruder.

PCT/CH 91/00020

Encapsulation of Active Substances with Starch

The present invention relates to a method for encapsulating or coating one or more active compounds in a or with a carrier substance, to an encapsulated or coated active compound which is coated by a carrier substance and to uses of the methods according to the invention.

The presence of active compounds, such as, for example, pharmaceuticals, adhesives, fragrances, detergent additives, dyes, concrete additives, pesticides etc., in a reprocessible, reusable, transportable, marketable etc. form has been a central problem for a long time. In particular, active compounds must be protected from environmental influences, such as moisture, UV radiation, mechanical stress etc., and at the same time should be easy to meter and practical to handle.

A large number of processes, methods and techniques is known to present active compounds in a handleable form, as is necessary in accordance with the abovementioned statement of the problem.

For example, the production of tablets, where essentially solid active compounds are compressed into tablet form by a consolidating means, is known. This form of handling is unsuitable, in particular, for moisture- sensitive active compounds or for fine metering.

Packing in small bags, for example composed of plastic, has the disadvantage that the packaging, i.e. the bag, must first be opened when using the active compounds, which, in particular with small bags, is very impracticable. Moreover waste results if the bag is not additionally usable.

Of particular interest is the coating or encapsulation of active compounds, for which purpose in the latter case capsules or microcapsules are prepared which are filled with the active

compound. The methods customary for the production of these capsules or for their filling, however, are very complicated and expensive, so that in particular with relatively inexpensive active compounds they are hardly viable or not viable at all. The principle of this encapsulation has until now been essentially restricted to pharmaceutical active compounds, as these active compounds are relatively expensive and the costs of the encapsulation process are not so crucial. This technique has previously been described in many different ways, for which purpose, for example, reference is made to the following specifications.

In EP-A-0,092,908, EP-PS-0,090,600, EP-A-0,118,240 and EP-A-0,304,401 the production of capsules by injection moulding or deep drawing is described, hydrophilic polymers, such as gelatin or starch, being proposed for the production of the capsules, which can be brought at least partially into thermoplastically processible form for the processing and production of the capsules by means of suitable processes. What is concerned here is exclusively the production of capsules of the larger type, which are only filled with active compounds or sealed after their production.

In the Encyclopedia of Polymer Science and Engineering, Vol. 9, John Wiley & Sons, pp. 724 ff., various methods and applications and a large number of literature citations about production methods for the production of microcapsules are described. In these methods, an active compound, such as, for example, an active agent, a core material, a filler, a nuclide etc., is encapsulated by a carrier material, a coating or a membrane etc. The size of these microcapsules is between 1 and 1000 µm. The most important areas of application are in the production of carbon-free copying papers and in the microencapsulation of pharmaceutical active compounds.

In particular, the use of the methods used until now for microencapsulation is described in detail in the Encyclopedia of Chemical Technology by Kirk-Othmer, 3rd Edition, Vol. 15, on pp. 487 ff. In this literature citation, reference may in particular be made to the literature index on pp. 492 and 493.

As the production of microcapsules per se has been described adequately in the two literature citations mentioned and the various production methods are varied and extensive, a detailed description of the latter is dispensed with, the contents of these two literature citations herewith being considered all-embracing as a part of the present introduction.

All the methods or techniques proposed above for producing capsules or microcapsules have the important disadvantage that they are very expensive and thus are only worth considering at all in connection with expensive active compounds, such as, for example, pharmaceutical products. This statement is further corroborated in the literature citation of Kirk-Othmer on p. 491 in the last section in that it is mentioned here that so-called "large scale" industrial use of the production of microcapsules is limited as a result of high costs and thus only has future prospects in the pharmaceutical area, medicine and some special markets.

It is therefore an object of the present invention to develop a method according to which active compounds and active substances can be encapsulated or coated in a simple and inexpensive manner, the carrier substance used for the encapsulation or coating preferably including a material which can be additionally used in the reuse of the active substance or the active compound, such that waste products are not formed nor is the further use of the active substance negatively influenced by the carrier substance.

This object is achieved by a method, preferably according to at least one of the claims, such as in particular according to one of Claims 1 or 18.

A method for encapsulating or for coating one or more active compounds in a or with a carrier substance is proposed in which a mixture of essentially native starch and at least one agent at least partially swelling the starch is used as the encapsulating or coating carrier substance and is mixed together with the active compound and at least one emulsifier for encapsulation or for coating.

Thus according to a broad form of this invention there is provided a method for encapsulating or for coating one or more active compounds in a or with a carrier substance, characterised in that the encapsulating or coating carrier substance used is a mixture of essentially native starch and at least one agent at least partially swelling the starch and which, for encapsulation or for coating, is mixed together with the active compound and at least one emulsifier.

Generally, the swelling agent includes at least one substance whose solubility parameter is greater than 15 [cal 1/2cm $^{-3/2}$] and which on mixing with the starch reduces its melting point in such a way that the melting temperature of the starch together with the substance is below the decomposition temperature of the starch.

Typically, the swelling agent in the mixture together with the starch has a vapour pressure of less than 1 bar at temperatures in the range closely below the melting point of the mixture.

Advantageously, the swelling agent is essentially formed from at least one aminoalcohol of the following formula:

$$[NH_XR_{3-X}]Y$$

$$X=O,\ 1 \text{ or } 2$$

where:

at least one R = R_1OH, R_2OH and/or R_3OH,

where R_1, R_2 or R_3 is aliphatic or cycloaliphatic, but not aromatic, and where Y = 1, 2, 3 ... 100 with a molar mass <2000.

The agent which initiates swelling or which swells the starch is preferably chosen in such a way that the active substance to be encapsulated is poorly or sparingly soluble in the swelling agent.

Correspondingly, in the case of active substances highly soluble in water, it is further proposed that on mixing the essentially native starch with the agent swelling the starch moisture is at least partially removed from the starch.

It may be preferable here that the at least partially swollen starch contains less than 12% by weight of water during the encapsulation or coating of the active compound, it being possible for this to lead in a further preferred embodiment of the method according to the invention to the most extensive freedom from water of the swollen starch.

In addition, it is also possible that the active compound itself is at least partially the agent swelling the starch or else is soluble in the swelling agent.

Suitable swelling agents or agents which initiate the dissolution of the starch which have in particular emerged are glycerol and aminoalcohols, as are claimed in the characterising part of Claim 5. In the case of the aminoalcohols, monomers and also oligomers of the aminoalcohols mentioned can come into consideration here. Triethanolamine, for example, has proved particularly suitable.

As is proposed according to the invention, an emulsifier is additionally added to the mixture of native starch and the swelling agent. Owing to the boundary surface activity, this emulsifier concentrates on the surface of the swollen starch and influences the wetting between the active compound and the swollen starch. The complete wetting of the swollen starch is assisted by the emulsifier, as a result of which the absorption of the active substance by the starch

or the coating of the active substance is favoured. Preferably, it is proposed that up to about 4% by weight, relative to the total mixture, of the emulsifier be used.

In order further to ensure that the swelling agent/starch phase does not form a coherent homogeneous material, it is further proposed that on mixing the swollen starch with the active substance at least one oily substance is additionally added, which is essentially unable to form a homogeneous mixture with the starch, or in which the oil and the swollen starch form two separate phases and the swollen starch grains are coated with a film of oil or dispersed in the oil.

Preferably, it is proposed that on mixing the swollen starch with the active compound up to 10% by weight, preferably 5 to 10% by weight, relative to the total mixture, of an oily substance is admixed, which does not allow homogeneous mixing with the swollen starch. It is essential here that the active compound, on the one hand, is not soluble in this oily phase, and moreover it must be more wettable by the swelling agent/starch phase than by the oil phase, as a result of which it is ensured that the starch/swelling agent phase encloses the active compound.

Likewise, in order to prevent the formation of a coherent homogeneous material, it is further proposed that the native starch is at least partially swollen and mixed with the swelling agent in such a way that a grain structure is essentially retained. This means, for example, that the temperature chosen is not so high that the grains are melted and form a homogeneous amorphous starch phase. On the other hand, the mechanical stress on the grains (shearing, kneading, mixing) may only be so large that the active compound is incorporated into the grains, but the grains are not destroyed. The structural viscosity of the starch grains must not fall below a lower limit which, for example, is about 20 Pa/sec at a shear rate of 100 sec^{-1}. The swollen starch grains in this case can already exhibit increased amorphous structure, but the individual grains still do not coagulate, i.e. a homogeneous melt is still not formed. The so-called particulate phase of the swollen starch must be retained.

Thus, for example, the temperature must not be above 170°C on mixing the individual components when using 40% glycerol as the swelling agent.

It is further proposed in the process according to the invention that up to 60% by weight, preferably 30 to 50% by weight, of the swelling agent is added. It is ensured by this that the formerly hard native grains of the starch are adequately swollen up and thus form elastic grains into which the various active compounds can be easily kneaded. The choice of the amount of added swelling agent added here is strongly dependent on the swelling agent chosen, by which of course active substances can also be effectively encapsulated with less than 30% of added swelling agent, such as, for example, of water. However, if more than 60% of a swelling agent is added, the grains become too soft, so that they burst even under slight mechanical stress and the granular, pulverulent material can agglutinate to give a compact mass.

Depending on the required properties of the final product, and also owing to possible toxic properties of the swelling agent, it may possibly be advantageous to at least partially remove the swelling agent again after encapsulation or coating.

In particular when using up to 10% by weight addition of an oily substance, the added amount of the emulsifier used is preferably 1 to 2% by weight, relative to the total mixture.

The method according to the invention for encapsulating or for coating one or more active compounds in a or with a carrier substance in particular includes mixing a mixture of 20 to 60% by weight of a swelling agent to start to swell the native starch, preferably 30 to 50% by weight, 0.1 to 4% by weight of an emulsifier, 0 to 10% by weight of an oily substance, and the remainder of native starch in a mixing apparatus, such as a mixer, kneader or extruder, the mixing taking place together with the active compound, preferably at elevated temperature, in order to produce an essentially homogeneous powder which contains the encapsulated or coated active compound.

The mechanical agitation in the mixer, kneader or extruder is carried out at elevated temperature because the wetting and sorption process of the swollen starch by the active substance takes place only very slowly without these additional measures as a result of the high viscosity of the starch/swelling agent phase. The swelling process can also be carried out at room temperature, the following problems emerging:

- Depending on the content of swelling agent, it takes up to 24 hours for all the swelling agent to be absorbed.
- Because of poor mixing, the homogeneity of the product is not ensured (variously sized grains).

In this case, the mixture is first heated to a temperature which is below the melting temperature of the starch/swelling agent mixture. The starch is then at least partially swollen by means of the swelling agent, whereupon under the action of the mechanical agitation the swollen starch coats the active compound or takes this up by sorption, the emulsifier and possibly the oil causing an essentially homogeneous powder to be formed instead of a coherent material.

The following substances inter alia, for example, have proved suitable as emulsifiers:

- lecithin,
- a polyoxyethylene derivative of a sorbitan ester, such as, for example, Tween from the company ICI,
- an ethylene oxide derivative of a sugar or sugar ester, sugar alcohol and/or sugar alcohol ester.

A triglyceride can be used, for example, as the oily substance.

The metering of the carrier substance with the active compound(s) is carried out by the choice of the mean particle size of the native starch used and/or the degree of swelling of the starch or the ratio of starch content to swelling agent. If, for example, the starting material used is a native starch grain from maize whose mean particle size is in the range of about 14 µm, a starch grain of this type can be essentially more poorly "filled" with an active substance than,

for example, a native starch grain of the potato, whose mean particle size is in the range of about 35 µm. As a generalisation, it can be said that the larger the mean particle size of the native starch which is used as a starting material, the more active compound can be coated with the same protective action. However, it has to be considered here that larger grains probably have greater protective action, but the total mixture of the encapsulated active substances is less homogeneous.

As the active substances once encapsulated cannot be ground, it is therefore also important to control the particle size of the finally encapsulated active compound via the particle size of the native starch which is used as a starting material.

By means of the process according to the invention described above, an encapsulated or coated active compound is prepared which is covered by a carrier substance, the carrier substance for the encapsulation or coating being essentially composed of at least partially swollen starch.

The encapsulated or coated active compound is distinguished in particular by the fact that a mixture of essentially native starch and at least one agent at least partially swelling the starch is used as an encapsulating or coating carrier substance for its preparation and, for encapsulation or coating, is mixed together with the active compound and at least one emulsifier.

The methods according to the invention described above are in particular suitable for encapsulating or coating pharmaceutical active compounds and/or for the production of medicaments or medicinal indications.

The method according to the invention is moreover of particular interest for encapsulating water-soluble or water-miscible substances, in particular water-soluble vitamins and citric acid.

The methods are additionally suitable for the encapsulation or coating of adhesives, flavourings, fragrances, detergents, pesticides,

herbicides, dyes, synthetic resin additives, building material additives, concrete additives and/or reactants for the coating of carbon-free copying papers.

As representative of these areas of application, specific reference may be made to the use of the method according to the invention for the encapsulation of concrete additives, such as wetting agents, hardening regulators, synthetic resin additives etc., whose use is difficult as a result of their existence as highly viscous or viscous liquids. They cannot be added, or cannot be added in metered form, to the dry cement, and on adding to the wet cement their reaction is immediately started.

In contrast, the dry, pulverulent starch/active compound mixture can easily be admixed with the dry cement, both metering and also subsequent storage of the cement during a relatively long period of time being unproblematic. The additives become in each case active on adding water.

At this point reference may be made to the literature citations with respect to the production and use of microcapsules which have been mentioned as prior art in the introduction and in which extensive applications of microcapsules are mentioned. In this connection, reference may additionally be made to Ullmann's Encyclopedia of Industrial Chemistry, 5th Edition, Vol. A 5, where on pp. 518 ff. reference is made in detail to possible additives for the preparation of concrete, for whose encapsulation the methods according to the invention mentioned above are also suitable.

The invention described above will now be illustrated in greater detail with reference to the appended 5 examples of the encapsulation of vitamin C.

Encapsulation of vitamin C:

Example 1:

4 kg of native potato starch are extruded with 2.5 kg of a mixture composed of the following components:

- 77.6% of glycerol,
- 15.5% of triglycerol (Miglyol 812),
- 6.9% of emulsifier (Tween 80 from ICI),

using a kneading extruder (Buss, Pratteln, Switzerland) during the course of one hour. The water content of the starch in this case was about 12%. The following process conditions were chosen in the kneading extruder:

- Spindle temperature 110°C,
- Heating zone 1: 113°C,
- Heating zone 2: 116°C,
- Heating zone 3: 122°C,
- Speed: 140 revolutions/min.,
- Power consumption: 0.6 kw.

A flaky white powder was formed as the product, individual grains, which are swollen with glycerol, being clearly detectable under the microscope.

A mean particle size of about 100 µm is achieved by homogenising in the kneader. Due to the oil used, aglommeration of the starch polymer spheres is prevented. Other starches can of course also be used as the polymer, which in the present example is potato starch.

20% of vitamin C was added to the powder obtained in the above manner and kneaded in with the same parameters during a second passage through the kneader. The result can likewise be clearly seen under the microscope. The largest part of the vitamin C crystals is embedded in the elastic bodies. If, for example, the grains are pressed flat, the embedded vitamin C crystals can be detected therein under the polarising microscope.

Other active compounds can also be incorporated into these elastic grains. The only condition is that a certain affinity of the active compound for the polar glycerol starch must be present, i.e. the active compound must be wettable by the glycerol starch mass.

Example 2:

The same composition as under 1), but allowed to stand overnight (not extruded). 12 hours later, a swollen powder is likewise obtained, into which vitamin C is kneaded. This experiment shows that the increase in the temperature only accelerates swelling, but is not a condition that swelling takes place. The vitamin C is incorporated as in the first example using the Buss kneader.

Example 3:

40 g of starch (water content: 12%) and 25 g of the mixture from Example 1) are kneaded for about 2 minutes in a Brabender laboratory kneader (70 g batches) and 16 g (20%) of vitamin C are then added and the mixture is kneaded for a further 2 minutes. The vitamin C is kneaded into the starch grains to more than 90%. Further experiments with 30% or 40% of vitamin C also give positive results, and the percentage of non- encapsulated vitamin C only rises slowly.

Example 4:

16 kg of native potato starch (water content: 5%) are swollen with 10.8 kg of the same mixture as above in a synchronised double spindle extruder at 150°C. 20% of vitamin C is added to this powder in a tumbler mixer and the mixture is then extruded again at 140°C in order to knead in the vitamin C.

Example 5:

The same conditions as under Example 4), only carried out in one step. The screw configuration of the extruder is modified in such a way that during entry starch and emulsion are mixed and swollen to give powder and vitamin C is added directly to the centre of the

extruder. At the end, a fine powder of encapsulated vitamin C is obtained which does not additionally have to be subsequently treated (grinding, sieving, etc.).

The abovementioned examples of the encapsulation of vitamin C by glycerol/starch are only used to explain the method according to the invention, which of course can be modified in all sorts of ways, as disclosed in detail in the description.

Thus, the method is also suitable for encapsulating other vitamins, pharmaceutical or cosmetic active compounds, of particular interest being encapsulation or coating of or with water-soluble or with water-miscible substances, such as, in particular, water- soluble vitamins and, inter alia, with citric acid. As representatives, some active substances have been processed according to the method according to the invention in the following Example 6, it being possible, of course, to extend the list of possible active substances in the most varied manner.

Example 6:

As mentioned above, various active compounds were incorporated into swollen or thermoplastically processible starch, comprising about 27% to 30% of glycerol. The practical procedure was carried out at 140°C in a so-called Brabender kneader, 70 g batches being employed analogously to the examples described above.

Riboflavine (vitamin B_2), pyridoxine (vitamin B_6), nicotinic acid, methionine, citric acid, thiamine NO_3 (nitrate) and lysine HCl were used as active compounds.

Basically, the active compounds described can be incorporated into the swollen starch analogously to vitamin C, as described in Example 5, in order to form a fine powder of encapsulated active compound.

As the active compounds mentioned behave like fillers in industrial polymers, extrusion of these active compounds into a

swollen starch melt is also possible, the corresponding melt, the fluidity of the melt and the subsequent cuttability being investigated or listed in Table I which follows.

Table I

Substance	% by wt. of active comp.	Melt	Decompo-sition	Tacki-ness	Extrusion
Riboflavine(B_2)	20%	++,yellow	none	d,h,b	++
Pyridoxine(B_6)	30%	++	possible	gummy	+
Nicotinic acid	20%	++,viscous	none	d,++	++
Methionine	20%	++,brown	possible	d,++	+
Citric acid	20%	++	none	d,++	++
Thiamine NO_3	20%	++,yellow	possible	d,++	+
Lysine HCl	20%	rubber	none	t,+	+

Key:

+	good
++	very good
d	dry
h	hard
b	brittle
t	tacky

The results presented in Table I have only restricted validity in this respect, as when using additional additives in the melt the statements can appear completely different.

As already mentioned above in the description, the method according to the invention is not only suitable for the coating of medicinal, cosmetic or pharmaceutical active compounds, but also for the encapsulation and coating of dye additives, foodstuff additives, concrete additives, detergent additives etc.

As representatives of this almost unrestricted group of possible additives, the invention will be explained in greater detail in the following, for example, with reference to a foodstuff additive and concrete additives.

Example 7: Lemon flavour

Up to 40% by weight of lemon flavour are kneaded in cold form with dry starch. The lemon flavour emulsion contains very volatile components, which would evaporate on increasing the temperature. The emulsion is absorbed into the starch within 2 min., and a yellow powder is formed which smells less intensively of lemon than the emulsion itself. If the powder is heated, it immediately begins to adhere and forms pearl grey lumps.

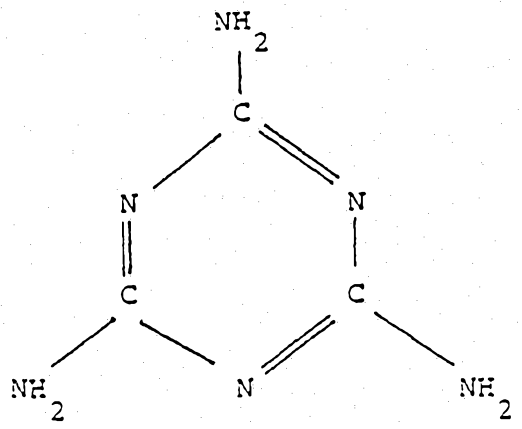
The advantage of the powder prepared in this way compared to the emulsion itself is that the powder can be very simply reprocessed and in particular can be very easily metered. The emulsion used hitherto, on the other hand, is not stable and it must be stirred again and again. Moreover, the emulsion dries out rapidly and loses the flavour if it is allowed to stand in the open. In contrast, the powder hardly loses the lemon flavour.

Example 8: Concrete additives

The concrete additives are usually highly viscous or viscous substances which can be metered only poorly and in particular cannot be admixed homogeneously to the dry cement. If the concrete additives are only added to the already made-up aqueous cement, their activity is immediately initiated and the cement must be processed immediately.

The concrete additives investigated in connection with the method according to the invention are

- Rheobuild 1000, a naphthalene sulphonate (Na salt), SO_4-Na,
- Rheobuild 2000, a melamine derivative of the following formula:



where 1 or 2 -NH_2 can be replaced by -Cl or -OH or alkyl,

- Rheobuild SV 87056, a polycarboxyl compound based on polyacrylic acid Na salt or a copolymer of acrylic acid esters and free acrylic acids and their Na salt,
- Beckopox EH 623, an amine epoxide hardener, and
- Rütapox EH 4000, an epoxy resin.

All the concrete additive active compounds mentioned are commercial products and can be obtained from Masterbuilders Technologies Europe AG, Ifangstrasse 11 in 8952 Schlieren/ Switzerland.

These liquid concrete additives can be easily kneaded with dry starch without additional swelling agent, such as glycerol or aminoethanol. Glycerol in addition could not be used because of its incompatibility with concrete. Obviously, in the present cases the active compound itself also still forms the swelling agent for the swelling of the starch. After at most 2 min. with heating if necessary, the liquids are absorbed in the starch, this occasionally taking place with evolution of heat.

If aminopropanol or ethanol is additionally employed as the swelling agent, the swelling should be started in the cold in order that the starch does not form a paste, or else an emulsifying oil must be added as in the examples described above with respect, for example, to vitamin C.

The active compounds according to Examples 7 and 8 are represented in tabular form in the followingTable II, in which their behaviour on swelling or absorption into the starch has likewise been more closely investigated.

Table II

Type	Swelling agent for starch	Soluble in amino-ethanol	Mixing ratio	Process Description
Lemon flavour	yes, only cold (20°C)		30-40%	only cold kneaded
Rheobuild 1000	no	yes	max.30%	hot kneaded
Rheobuild 2000	yes, but cold		max.30%	hot kneaded
Rheobuild SV 87056	yes, heat (140°C)	yes	max.30%	hot kneaded
Beckopox EH 623	yes, good	yes	20%	hot kneaded
Rütapox EH 4000	yes	yes	20%	hot kneaded

The active compounds described in Examples 1 to 8 are representative of a nearly unlimited list of possible active compounds and substances which can be encapsulated or coated by the method according to the invention. The encapsulation and coating method itself can also be changed or modified in any desired ways.

It is essential for the method according to the invention to use native starch, a swelling agent at least partially swelling the native starch and, under certain circumstances, an emulsifier, where the active substance must be wettable by the swelling agent/starch phase. It is thoroughly possible here that the active compound itself serves as the swelling agent. An oily substance is preferably additionally used

Patent Claims

1. Method for encapsulating or for coating one or more active compounds in a or with a carrier substance, characterised in that the encapsulating or coating carrier substance used is a mixture of essentially native starch and at least one agent at least partially swelling the starch and which, for encapsulation or for coating, is mixed together with the active compound and at least one emulsifier.

2. Process, preferably according to at least one of the claims, such as according to Claim 1, characterised in that the swelling agent includes at least one substance whose solubility parameter is greater than 15 [cal 1/2cm $^{-3/2}$] and which on mixing with the starch reduces its melting point in such a way that the melting temperature of the starch together with the substance is below the decomposition temperature of the starch.

3. Method, preferably according to at least one of the claims, such as according to one of Claims 1 or 2, characterised in that the swelling agent in the mixture together with the starch has a vapour pressure of less than 1 bar at temperatures in the range closely below the melting point of the mixture.

4. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 3, characterised in that the swelling agent is essentially formed from glycerol.

5. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 3, characterised in that the swelling agent is essentially formed from at least one aminoalcohol of the following formula:

$$[NH_XR_{3-X}]_Y$$

where: $X = 0, 1$ or 2

at least one R = R_1OH, R_2OH and/or R_3OH,

where R_1, R_2 or R_3 is aliphatic or cycloaliphatic, but not aromatic, and where $Y = 1, 2, 3 \ldots 100$ with a molar mass <2000.

6. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 5, characterised in that on mixing the essentially native starch with the agent swelling the starch moisture is at least partially removed from the starch.

7. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 6, characterised in that the at least partially swollen starch contains less than 12% by weight of water during the encapsulation or coating of the active compound.

8. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 7, characterised in that the at least partially swollen starch is essentially anhydrous.

9. Method, preferably according to at least one of the claims, such as according to one of Claims 1, 2, 6 or 7, characterised in that the swelling agent is essentially water.

10. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 9, characterised in that the active compound(s) at least partially forms or form the agent swelling the starch.

11. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 10, characterised in that up to about 4% by weight, relative to the total mixture, of the emulsifier is used.

12. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 11, characterised in that on mixing the swollen starch with the active compound additionally at least one oily substance is added, which is essentially unable to form a homogeneous mixture with the starch, or in which the oil and the swollen starch form two separate phases and the swollen starch particles are covered individually with at least one oil film or are dispersed in the oil phase.

13. Process, preferably according to at least one of the claims, such as according to one of Claims 1 to 12, characterised in that on mixing the swollen starch with the active compound up to 10% by weight, preferably 5 to 10% by weight, relative to the total mixture, of an oily substance is admixed, which does not allow itself to be homogeneously mixed with the swollen starch.

14. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 13, characterised in that the native starch is at least partially swollen and mixed with the swelling agent in such a way that a grain structure is essentially retained.

15. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 14, characterised in that up to 60% by weight, preferably 30 to 50% by weight, of the swelling agent is added.

16. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 15, characterised in that the swelling agent is removed at least partially again after encapsulation or coating.

17. Method, preferably according to at least one of the claims, such as according to one of Claims 11 to 16, characterised in that 1 to 2% by weight, relative to the total mixture, of the emulsifier is used.

18. Method for encapsulating or for coating one or more active compounds in a or with a carrier substance, preferably according to at least one of the claims, characterised in that a mixture of:

- 20 to 60% by weight of a swelling agent for initiating the swelling of the native starch, preferably 30 to 50% by weight,
- 0.1 to 4% by weight of an emulsifier,
- 0 to 10% by weight of an oily substance and
- the remainder of native starch

is mixed in a mixing apparatus, such as a mixer, kneader or extruder, together with the active compound, preferably at elevated temperature, in order to produce an essentially homogeneous powder which contains the encapsulated or coated active compound.

19. Method, preferably according to at least one of the claims, such as according to Claim 18, characterised in that the mixture is first heated to a temperature which is below the melting temperature of the starch/ swelling agent mixture, then the starch is swollen at least partially by the swelling agent, whereupon under the action of the mechanical agitation the swollen starch coats the active compound or takes this up by sorption, the emulsifier and possibly the oil causing an essentially homogeneous powder to be formed instead of a coherent material.

20. Method, preferably according to at least one of the claims, such as according to one of Claims 11 to 19, characterised in that the emulsifier chosen is at least one of the following substances:

- lecithin,
- a polyoxyethylene derivative of a sorbitan ester (Tween = ® from ICI),
- an ethylene oxide derivative of a sugar or sugar ester, sugar alcohol and/or sugar alcohol ester.

21. Method, preferably according to at least one of the claims, such as according to one of Claims 12 to 20, characterised in that essentially at least one triglyceride is used as the oily substance.

22. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 21, characterised in that the metering of the carrier substance with the active compound(s) is adjusted by the choice of the mean particle size of the native starch used and/or the degree of swelling of the starch or the ratio of starch contents to swelling agent in the mixture.

23. Method, preferably according to at least one of the claims, such as according to one of Claims 1 to 22, characterised in that the mean particle size of the encapsulated active compounds is adjusted by the choice of the mean particle size of the native starch used.

24. Encapsulated or coated active compound, which is covered by means of a carrier substance, characterised in that the carrier

substance for the encapsulation or coating is essentially composed of at least partially swollen starch.

25. Encapsulated or coated active compound, preferably according to at least one of the claims, such as according to Claim 24, characterised in that the encapsulating or coating carrier substance used for its preparation is a mixture of essentially native starch and at least one agent at least partially swelling the starch and which, for encapsulation or for coating, is mixed together with the active compound and at least one emulsifier.

26. Encapsulated or coated active compound, preferably according to at least one of the claims, such as according to one of Claims 24 or 25, characterised in that the active compound is a water-soluble or water- miscible substance, such as, in particular, a water- soluble vitamin or citric acid.

27. Use of the method according to one of Claims 1 to 23 for encapsulation or coating of pharmaceutical or cosmetic active compounds and/or for the production of medicaments or medicinal indications.

28. Use of the method according to one of Claims 1 to 23 for the encapsulation or coating of water-soluble or water-miscible substances, such as, in particular, water- soluble vitamins and/or citric acid.

29. Use of the method according to one of Claims 1 to 23 for the encapsulation or coating of adhesives, flavourings, fragrances, detergents, pesticides, herbicides, dyes, synthetic resin additives, building material additives, concrete additives and/or reactants for the coating of carbon-free copying papers.

30. Use of the method according to one of Claims 1 to 23 for the encapsulation or coating of viscous and highly viscous liquids and/or emulsions, such as flavourings, dye additives, synthetic resin additives, building material additives, concrete additives etc., in particular for improving their processibility or meterability.

31. A method for encapsulating or for coating one or more active compounds in a or with a carrier substance, substantially as herein described with reference to any one of the Examples.

32. An encapsulated or coated active compound, which is covered by means of a carrier substance, substantially as herein described with reference to any one of the Examples.

DATED THIS TWENTY SIXTH DAY OF NOVEMBER 1992
FLUNTERA AG
IVAN TOMKA

SPRUSON & FERGUSON
Patent Attorneys for the Applicant

INTERNATIONAL SEARCH REPORT

International Application No PCT/CH 91/00020

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.[5] A 61 K 9/50, A 61 K 47/36

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl.[5]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	DE, A, 2708513 (BOEHRINGER) 31 August 1978 see claims	1,4,9,24, 27,29
A	EP, A, 0281513 (ZYMA) 7 September 1988 see claims 1-8,11,16	1,9,24,27
A	GB, A, 2021948 (SPEYWOOD) 12 December 1979 see claims 1-3,7; page 1, lines 52-54	1,9,24,27, 29
A	US, A, 4755397 (J. EDEN) 5 July 1988 see claims 1,2; column 2, lines 13-18	1,9,24,27 29,30

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12 April 1991 (12.04.91)	23 May 1991 (23.05.91)
International Searching Authority	**Signature of Authorized Officer**
European Patent Office	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. CH 9100020 SA 43605

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 29/04/91 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A- 2708513	31-08-78	None	
EP-A- 0281513	07-09-88	AU-A- 1119488	04-08-88
		JP-A- 63196511	15-08-88
		US-A- 4882169	21-11-89
		ZA-A- 8800726	03-08-88
GB-A- 2021948	12-12-79	None	
US-A- 4755397	05-07-88	None	

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen PCT/CH 91/00020

I. KLASSIFIKATION DES ANMELDUNGSGEGENSTANDS (bei mehreren Klassifikationssymbolen sind alle anzugeben)[6]

Nach der Internationalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC

Int.Cl.[5] A 61 K 9/50, A 61 K 47/36

II. RECHERCHIERTE SACHGEBIETE

Recherchierter Mindestprüfstoff[7]

Klassifikationssystem	Klassifikationssymbole
Int.Cl.[5]	A 61 K

Recherchierte nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Sachgebiete fallen[8]

III. EINSCHLÄGIGE VERÖFFENTLICHUNGEN[9]

Art*	Kennzeichnung der Veröffentlichung[11], soweit erforderlich unter Angabe der maßgeblichen Teile[12]	Betr. Anspruch Nr.[13]
A	DE, A, 2708513 (BOEHRINGER) 31. August 1978 siehe Ansprüche	1,4,9,24, 27,29
A	EP, A, 0281513 (ZYMA) 7. September 1988 siehe Ansprüche 1-8,11,16	1,9,24,27
A	GB, A, 2021948 (SPEYWOOD) 12. Dezember 1979 siehe Ansprüche 1-3,7; Seite 1, Zeilen 52-54	1,9,24,27, 29
A	US, A, 4755397 (J.EDEN) 5. Juli 1988 siehe Ansprüche 1,2; Spalte 2, Zeilen 13-18	1,9,24,27, 29,30

* Besondere Kategorien von angegebenen Veröffentlichungen[10]:

"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist

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"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden

"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

IV. BESCHEINIGUNG

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
12. April 1991	23 MAY 1991
Internationale Recherchenbehörde	Unterschrift des bevollmächtigten Bediensteten
Europäisches Patentamt	MISS T. TAZELAAR

ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR.

CH 9100020
SA 43605

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 29/04/91
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
DE-A- 2708513	31-08-78	Keine	
EP-A- 0281513	07-09-88	AU-A- 1119488	04-08-88
		JP-A- 63196511	15-08-88
		US-A- 4882169	21-11-89
		ZA-A- 8800726	03-08-88
GB-A- 2021948	12-12-79	Keine	
US-A- 4755397	05-07-88	Keine	

EPO FORM P0473

Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr.12/82