

A METHOD OF ENCAPSULATING WATER-SOLUBLE ACTIVE COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to a method of encapsulating water-soluble active
5 compounds. In particular, the invention relates to a method of encapsulating water-
soluble active compounds using octenyl succinic anhydride (OSA)-modified starch and
selected cross-linkers.

BACKGROUND

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There are several challenges that one may encounter when a multi-component mixture
of ingredients of different physical and chemical properties is being developed. Firstly,
the selected active ingredients may be incompatible with each other, that is, they are
potentially capable of interacting with each other by means of complexation or a
15 chemical reaction that may result in loss of their original activity. Secondly, the active
ingredients may degrade during processing and/or during storage. Lastly, the most
common and effective stabilizing additives (stabilizers) may not be permissible in all
such formulations. The problems are of particular significance to pharmaceutical and
food industry, and in other applications as well where the composition of the formulations
20 must meet very strict safety criteria and the exact dose of the active ingredients needs
to be known and well-controlled.

A process of encapsulation provides solution to some of the problems arising from
mixing potentially incompatible actives in a single formulation. Moreover, the
25 encapsulation allows targeted delivery of actives as well as their controlled release
under specific conditions. Many methods have been developed to encapsulate oil-
soluble and water-soluble actives. However, majority of these methods involve the use
of organic solvents and/or toxic and harmful additives, such as stabilizers and cross-
linkers, rendering the final products unacceptable for human consumption. Whereas the
30 encapsulation of oil-soluble actives is relatively straightforward, the reliable
encapsulation of water-soluble actives with high encapsulation efficiency remains a
challenge.

It is therefore desirable to provide a method that seeks to address a problem of encapsulating water-soluble actives under mild conditions using ingredients approved for human consumption, with high efficiency.

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SUMMARY OF INVENTION

In accordance with a first aspect of this invention, there is provided a method of encapsulating a water-soluble active compound. The method comprises mixing an aqueous solution comprising a water-soluble active compound with an oil in the presence of a surfactant under high shear condition to form a water-in-oil emulsion; adding an aqueous solution of octenyl succinic anhydride (OSA)-modified starch to the water-in-oil emulsion and homogenizing further to obtain a water-in-oil-in-water double emulsion; and mixing an aqueous solution comprising a cross-linker selected from the group consisting of adipic acid dihydrazide and methylglyoxal with the thus formed double emulsion for cross-linking the OSA-modified starch, thereby forming starch microcapsules with the water-soluble active compound encapsulated within the starch microcapsules.

In some embodiments, the water-soluble active compound is selected from the group consisting of amaranth dye and L-ascorbic acid.

In one embodiment, the method further comprises purifying the starch microcapsules by means of dialysis.

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In one embodiment, the method further comprises freeze-drying the starch microcapsules to obtain the encapsulated water-soluble active compounds in granular or powdered form.

BRIEF DESCRIPTION OF THE DRAWINGS

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The above advantages and features of a method in accordance with this invention are described in the following detailed description and are shown in the drawings:

Figure 1 is a schematic representation of formation of the capsule wall. The cross-linking reaction, facilitated by adipic acid dihydrazide or methylglyoxal, takes place at slightly acidic pH, and involves predominantly hydroxide groups of octenyl succinic anhydride (OSA)-modified starch.

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Figure 2 shows the distribution of the apparent ζ -potential of starch microcapsules containing L-ascorbic acid and cross-linked with methylglyoxal. Each curve refers to a separate measurement.

10 Figure 3 shows the distribution of the apparent ζ -potential of starch microcapsules containing L-ascorbic acid and cross-linked with methylglyoxal after dialysis against deionised water. Each curve refers to a separate measurement.

Figure 4 shows the distribution of the apparent ζ -potential of starch microcapsules
15 containing L-ascorbic acid and cross-linked with adipic acid dihydrazide. Each curve refers to a separate measurement.

Figure 5 shows the distribution of the apparent ζ -potential of starch microcapsules containing amaranth dye and cross-linked with methylglyoxal. Each curve refers to a
20 separate measurement.

Figure 6 shows the distribution of the apparent ζ -potential of starch microcapsules containing amaranth dye and cross-linked with methylglyoxal after dialysis against deionised water. Each curve refers to a separate measurement.

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Figure 7 shows the distribution of the apparent ζ -potential of starch microcapsules containing amaranth dye and cross-linked with adipic acid dihydrazide. Each curve refers to a separate measurement.

30 Figure 8 shows the size distribution of starch microcapsules containing amaranth dye and cross-linked with methylglyoxal. Each curve refers to a separate measurement.

Figure 9 shows the size distribution of starch microcapsules containing amaranth dye and cross-linked with methylglyoxal, after dialysis against deionised water. Each curve
35 refers to a separate measurement.

Figure 10 shows the size distribution of starch microcapsules containing amaranth dye and cross-linked with adipic acid dihydrazide. Each curve refers to a separate measurement.

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Figure 11 shows the size distribution of starch microcapsules containing L-ascorbic acid and cross-linked with methylglyoxal. Each curve refers to a separate measurement.

Figure 12 shows the size distribution of starch microcapsules containing L-ascorbic acid and cross-linked with methylglyoxal, after dialysis against deionised water. Each curve refers to a separate measurement.

Figure 13 shows the size distribution of starch microcapsules containing L-ascorbic acid and cross-linked with adipic acid dihydrazide. Each curve refers to a separate measurement.

Figures 14(a) to (d) are SEM images of selected capsules. Figure 14(a) shows the SEM image of amaranth encapsulated in N-Creamer® OSA-modified starch, cross-linked with methylglyoxal and hydrochloric acid (emulsification time: 10 + 7 min). Figure 14(b) shows the SEM image of dialysed amaranth encapsulated in N-Creamer® OSA-modified starch, cross-linked with methylglyoxal and hydrochloric acid (emulsification time: 10 + 7 min). Figure 14(c) shows the SEM image of L-ascorbic acid encapsulated in N-Creamer® OSA-modified starch, cross-linked with methylglyoxal and hydrochloric acid (emulsification time: 15 + 7 min). Figure 14(d) shows the SEM image of dialysed L-ascorbic acid encapsulated in N-Creamer® OSA-modified starch, cross-linked with methylglyoxal and hydrochloric acid (emulsification time: 10 + 7 min). For imaging, a small drop of capsules suspension was placed on smooth silicon wafer and left to dry. Subsequently, the thus dried samples were coated with gold.

30 DETAILED DESCRIPTION

The present invention utilizes the concept of encapsulation to address the above outlined challenges. The encapsulation technology employed in the present invention requires a step of forming a double emulsion, in particular, a water-in-oil-in-water (W₁/O/W₂) emulsion under high shear condition, followed by a step of forming starch

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microcapsules with water-soluble active compound encapsulated within the starch microcapsules.

5 In one embodiment, the method of encapsulating a water-soluble active compound comprises (i) mixing an aqueous solution comprising a water-soluble active compound with an oil in the presence of a surfactant under high shear condition to form a water-in-oil emulsion; (ii) adding an aqueous solution of octenyl succinic anhydride (OSA)-modified starch to the water-in-oil emulsion and homogenizing further to obtain a water-in-oil-in-water double emulsion; and (iii) adding an aqueous solution comprising a cross-
10 linker selected from the group consisting of adipic acid dihydrazide and methylglyoxal to the thus formed double emulsion for cross-linking the OSA-modified starch, thereby forming starch microcapsules with the water-soluble active compound encapsulated within the starch microcapsules.

15 In one embodiment, the mixing in steps (i) and (ii) are a continuous process. The mixing continues from step (i) while aqueous solution of OSA-modified starch is added to the water-in-oil emulsion.

20 "High shear condition" as used herein refers to a condition whereby the solutions or a mixture comprising several components are mixed using suitable homogenizer including, but not limited to, high speed homogenizer, high pressure homogenizer, membrane homogenizer, etc., and including microchannel droplets generators. In various embodiments, the mixing is carried out at a speed of 20k to 24k rpm. In one embodiment, the mixing in step (i) is carried out under a higher shear rate than step (ii). Preferably,
25 the mixing in step (i) is carried out at a rate of 20k to 24k rpm and in step (ii), at a rate of less than 6k rpm. The duration of mixing may vary, depending on the type of water-soluble active compound to be encapsulated, and the type of oil used.

30 In general, a "microcapsule" is an encompassing structure or a spherical particle that comprises a core material surrounded by a wall, shell or coating, with dimensions in micrometres range. In the present invention, the core material of the microcapsule consists of a water-soluble active compound that is surrounded by a wall or shell formed by the cross-linked OSA-modified starch. The capsule wall or shell of the microcapsule consists of a single component which is the OSA-modified starch cross-linked for
35 improved stability.

The method of the present invention can be employed to encapsulate any suitable water-soluble active compounds. Examples of such water-soluble active compounds include, but are not limited to, L-ascorbic acid, amaranth dye, and other water-soluble molecules. Amaranth dye and L-ascorbic acid are used as exemplary embodiments as described in the Examples hereinbelow to demonstrate the encapsulation technology employed in the present invention and it is not meant to be limited as such.

The amount of the water-soluble active compound encapsulated within the microcapsule can be any amount ranging from 1% to 90% w/w or 1% to 75% w/w of the microcapsule, depending on the molecular weight of the water-soluble active compound that is encapsulated.

In step (i), the aqueous solution comprising the water-soluble active compound is mixed with an oil in the presence of a surfactant. The type of oil to be used is dependent on the type of water-soluble active compound being used for the encapsulation. Suitable types of oil include, but are not limited to, any light edible oils such as sunflower oil, canola oil, olive oil or the like that are suitable for use in food, beverages and pharmaceutical products.

Extensive use of surfactants may lead to environmental pollution and food safety problems. The method of the present invention requires minimal use of surfactant to form the water-in-oil emulsion. This is because the OSA-modified starch which is added to form the second emulsion (the double emulsion) acts as an emulsifier as well as an encapsulating material. The only surfactant used in the method is in step (i). Suitable surfactant includes sorbitan monooleate (Span-80), low-HLB (hydrophilic lipophilic balance) sorbitans and surfactants with low HLB value.

The aqueous solution of OSA-modified starch is prepared by dissolving OSA-modified starch in water. In various embodiments, the OSA-modified starch solution comprises 4.5 to 6% w/v of OSA-modified starch in water.

The starch microcapsules are formed upon the addition of the aqueous solution of OSA-modified starch to the water-in-oil emulsion, followed by cross-linking the OSA-modified starch with a cross-linker. The type of cross-linker to be used is dependent upon the final application of the microcapsules and the cross-linker toxicity which will determine if

the cross-linker is suitable for use in producing a pharmaceutical product, a food grade or non-food grade encapsulated product. It also depends on whether a hydrophilic or hydrophobic encapsulated product is to be obtained. In the present invention, the inventors have found that cross-linkers such as adipic acid dihydrazide and methylglyoxal are exceptionally suitable for use in cross-linking OSA-modified starch for encapsulating water-soluble active compound. These cross-linkers are selected as they are considered safe within concentration limits. Moreover, methyl glyoxal is naturally derived from Manuka honey and responsible for its anti-microbial properties.

10 The cross-linking reaction results in the formation of cross-linked wall on each of the starch microcapsules. The starch microcapsules are covalently cross-linked for enhanced stability.

Figure 1 represents schematically the formation of a microcapsule wall (101) of the starch microcapsule loaded with a water-soluble active compound (102). The cross-linking reaction, facilitated by the cross-linker (103a or 103b), takes place at a slightly acidic pH and involves predominantly the hydroxide groups (-OH) of the OSA-modified starch (104). In one embodiment, the cross-linking reaction takes place at a pH of less than 4.

20 The method of the present invention may further include purifying the starch microcapsules by means of dialysis, freeze drying for storage, and reconstituting the starch microcapsules into an aqueous suspension by mixing with aqueous solution.

25 In one embodiment, the process of dialysis involves transferring suspension of microcapsules into a dialysis tube, being a membrane, which is closed at both ends and immersed in a large volume of deionized water. The suspension of microcapsules in the dialysis tube is then left for several days under gentle agitation. The deionized water surrounding the dialysis tube is replaced every few hours. The membrane allows molecules of specific size (or molecular weight) to pass through. The transportation of such molecules is driven by a concentration difference (gradient) on both sides of the membrane, i.e., from a higher concentration of unreacted cross-linker and acid in the suspension of capsules into the deionized water. Thus, the unreacted cross-linker and acid from the capsules suspension are removed from the suspension into the deionised water. By keeping the concentration gradient high (i.e., concentration in deionized water

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low, by replacing the water), the process can continue until the concentrations of unreacted cross-linker and the acid in the suspension of microcapsules become very low. This applies to any molecule smaller than the membrane cut-off. In the case of the present invention, it is between 3.5k and 7k Daltons.

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The starch microcapsules may be freeze dried and process into granular or powdered form. The starch microcapsules in this form can be reconstituted into an aqueous suspension by mixing the granules or powders in aqueous solution. The stability of such suspension can be enhanced by the addition of common additives to the aqueous solution. The starch microcapsules can be incorporated into water-based or oil-based formulations.

The size of a microcapsule in granular or powdered form is typically one having a diameter in the range from 1 to 100 micrometres. The size is tunable and depends on, among other factors, the parameters of the emulsification process, etc. The size of the microcapsules can be adjusted within a certain range to cater to a user's intended application. The size can be adjusted before encapsulation takes place, for example, by adjusting the size of the droplets during the emulsification process or by adjusting the pressure applied during the emulsification process. For the former, it can be done by using any suitable method including, but not limited to, application of stronger shear, use of membrane to generate droplets of desired size, etc. The type of surfactant used can also influence the size and size distribution of the microcapsules. The surface of the starch microcapsules can be further modified with respect to its surface charge, wettability, etc.

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The method of the present invention has several advantages. One advantage is that the method is simple and effective in encapsulating water-soluble active compounds in food-grade materials, at high encapsulation efficiency and yields, and making them fully miscible with water, at high concentrations. The microcapsules are covalently cross-linked at mild conditions, at variable degree of cross-linking for enhanced stability. The method can be applied to various water-soluble active compounds that are suitable to be encapsulated. The encapsulation of the water-soluble active compounds protects the encapsulated active compounds from oxidation and degradation due to exposure to heat and light. The encapsulation promotes stability and flavour-masking and also helps to retain the active compounds' nutritional properties. The method does not require the use

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of any organic solvents. Moreover, starch is digestible by specific enzymes at specific location and hence the starch capsules can be used for targeted delivery.

5 The encapsulation technology employed in the present invention (i) allows effective separation of active compounds in single formulation from each other by providing each one with its own protective shell; (ii) allows the surface properties of the microcapsules to be modified in order to mitigate their interactions in suspension; and (iii) able to control the capsule size and the capsule size distribution to facilitate administration of the formulation by designed mode. The method also allows the water-soluble active
10 compound to be released from the microcapsules only after the microcapsules is administered and it prevents the active compound from releasing from the microcapsules during storage. The choice of the material used for encapsulation is crucial in achieving these results. The inventors have found that carbohydrates-based encapsulation materials are able to achieve the purpose. Human body produces
15 amylase that digests starch and complex carbohydrates. It is present in saliva (alpha-amylase) and small intestine (pancreatic amylase). The surfaces of thus formed starch microcapsules can be further modified to form stable suspensions in aqueous solutions.

20 The encapsulation technology employed in the present invention is a versatile and adaptable technology. The method can be employed for use in pharmaceutical applications. It can be used for producing formulations that require incorporation of sensitive or unstable molecules soluble in aqueous solvents which may potentially interact with each other when simply dissolved in a solution.

25 The method can be used for producing food products, for example, in fortification of food with water-soluble active compounds that may require stabilization, protection from degradation or flavour masking. It can also be easily adapted for use in any consumer care, such as cosmetics, supplements, etc. applications. It can also be used for encapsulating water-soluble active compounds that are sensitive to environmental
30 conditions, for example, oxidation for enhanced stability and extended shelf life.

To facilitate a better understanding of the present invention, the following examples of specific embodiments are given. In no way should the following examples be read to limit or define the entire scope of the invention. One skilled in the art will recognize that

the examples set out below are not an exhaustive list of the embodiments of this invention.

EXAMPLES

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Example 1

Materials

In the examples that follow, the following materials were used.

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Octenyl succinate (OSA) - modified starch (N-Creamer 3334®); amaranth dye (A1016-50G), L-ascorbic acid, adipic acid dihydrazide (A0638-25G), methylglyoxal (67028-100ML), Span-80 (S6760-250ML), and hydrochloric acid; sunflower oil (Naturel® brand). Dialysis membranes (SnakeSkin® dialysis tubing) with cut-off molecular weight of 3.5

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Preparation of starch stock solution

An amount of 4 to 5g of OSA-modified starch was dissolved in 100 ml of hot, but not boiling, water, under gentle agitation, to form 4 to 5% w/v solution. The solution was cooled to room temperature for use within 2 days.

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Preparation of amaranth stock solution

210.7 mg of amaranth dye powder was dissolved in 100 ml of deionized water. This solution was stored in an amber bottle, in dark cabinet at room temperature for further use.

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Preparation of L-ascorbic acid stock solution

6.0914 g of solid L-ascorbic acid was dissolved in 20 ml of deionized water to prepare 304.57 g/l solution. This solution was stored in dark cabinet at room temperature for use within two days.

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Preparation of adipic acid dihydrazide stock solution

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10 g/l of adipic acid dihydrazide in deionized water was prepared and stored for further use.

5 Preparation of methylglyoxal stock solution

10 ml of 40% methylglyoxal was mixed with 10 ml of 3.7% HCl and stored for further use.

10 Formation of microcapsules

The process of encapsulation of the present invention requires the formation of a double water-in-oil-in-water ($W_1/O/W_2$) emulsion, followed by the formation of starch microcapsules.

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To avoid overheating, the samples were placed in an ice-water bath during homogenization. 1 ml of amaranth dye (or L-ascorbic acid) stock solution was mixed with 4 ml of sunflower oil and 0.5 ml of Span-80 in a high pressure homogenizer (Ultra-Turrax, IKAO T18 basic) for about 10 min at setting #6 of high pressure homogenizer to form a water-in-oil (W_1/O) emulsion. This is followed by the addition of 20 ml of OSA-modified starch stock solution and the mixture was mixed for an additional 7 min at setting #3 of the high pressure homogenizer to form the water-in-oil-in-water ($W_1/O/W_2$) double emulsion. The mixing was carried out without stopping for the addition of the OSA-modified starch stock solution. Subsequently, the thus formed microcapsules were left to rest for approximately 1 minute, followed by the addition of 2 ml of cross-linking stock solution. The cross-linking stock solution that was used in this example includes adipic acid dihydrazide and methylglyoxal. The thus prepared samples, with each cross-linked with either adipic acid dihydrazide or methylglyoxal were placed on shaker at 150 rpm for 1 to 4 hours. Subsequently, the samples were dialyzed against deionised water for 48 to 72 hours, with deionised water being replaced every 24 hours, to remove unreacted cross-linker. The capsules were left in aqueous suspension. Alternatively, the capsules may be freeze dried.

35 Characterization of microcapsules

The microcapsules were characterized by means of surface potential measurements, particle size and particle size distribution (Zetasizer, Malvern Instruments). Sample for each measurement was prepared by dilution of the suspension of microcapsules, prepared by first mixing 0.100 ml of capsules suspension with 2.900 ml of deionised water directly prior to the measurement. There was no pH adjustment after the dilution.

Samples for Scanning Electron Microscopy (SEM, JEOL JSM6700F) were prepared by deposition of small droplet of the original microcapsule suspension, prepared as described in hereinabove, on smooth surface of clean silicon wafer and left to dry. Subsequently, the thus prepared sample was coated with a layer of gold by ion sputtering directly before the imaging.

Results

Aqueous suspensions of starch microcapsules, loaded with the water-soluble active compounds, amaranth dye and L-ascorbic acid, respectively, were characterized using Zetasizer to characterize their surface potential and particle size, as well as using SEM to assess their morphology. The results are shown in Figures 2 to 14.

The results shown in Figures 2 to 13 indicate that regardless of the compound being encapsulated, the apparent surface potential of the final microcapsule depends on the cross-linker used, and is close to zero (average: -0.93 [mV] and -1.62 [mV] for microcapsules loaded with amaranth dye and L-ascorbic acid, respectively) for methylglyoxal, and negative (average: -43.8 [mV] and -4.50 [mV] for microcapsules loaded with amaranth dye and L-ascorbic acid, respectively), for adipic acid dihydrazide as measured for undialysed samples. The decrease of surface charge (average: -8.59 [mV] and -11.04 [mV] for capsules loaded with amaranth dye and L-ascorbic acid, respectively) as well as increased surface charge distribution was measured for samples after dialysis against pure water, as shown in Figure 3 and Figure 6. We note that the pH of the samples was not adjusted at any point.

As shown in Figures 8-14, the microcapsules have relatively broad size distribution, with majority being smaller than 1µm in diameter. As expected, the results do not show any effect of the cross-linker molecule or the dialysis against deionised water on capsules size or on capsules size distribution. The capsules size and capsules size distribution

are determined by the process conditions, in particular, by the emulsification process, and the size of the water-in-oil emulsion droplets. This parameter can be adjusted within a certain range and thus, the capsules size and capsules size distribution could be further refined.

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Figure 14 shows the SEM images of each of the water-soluble active compounds, amaranth dye and L-ascorbic acid and the dialysed amaranth dye and L-ascorbic acid, encapsulated in OSA-modified starch, cross-linked with methylglyoxal and hydrochloric acid.

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Table 1 below shows the theoretical estimations of the loading capacity of the OSA-modified starch microcapsules cross-linked with methylglyoxal, containing amaranth dye or L-ascorbic acid. Calculations are based on the assumptions that the internal aqueous phase (W_1) is fully encapsulated during emulsification-based process. The loading is determined by initial concentrations of loaded molecules.

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Table 1

Load	Estimated loading: dye solution [% w/w] in dry capsules	Estimated loading: dissolved solid [mg/ml] in dry capsules	Concentration of dye stock solution (W_1) [mg/ml] (<i>solubility limit</i>)
Amaranth dye (4% starch)	15.01	0.38	2.107 (10 mg/ml)
Amaranth dye (5% starch)	14.57	0.38	2.107 (10 mg/ml)
L-ascorbic acid (5% starch)	13.32	55.38	304.57 (330 mg/ml)

Conclusions

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A successful and effective method to encapsulate water-soluble active compounds in starch microcapsules has been developed and tested in the present invention. The method requires minimal amount of additional surfactants to form the primary water-in-oil (W_1/O) emulsion and is carried out without addition of organic solvents. The microcapsules are covalently cross-linked for enhanced stability, with tunable degree of the cross-linking. The surface charge of the obtained microcapsules can be adjusted to be close to neutral by choice of the suitable cross-linker. The majority of the microcapsules is of sub-micron size. The capsules size and capsules size distribution can be further optimized by optimizing the parameters of the emulsification process. Such parameters include the shear rate, the type of homogenizer or mixer used, the

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different geometries of mixing blades of the mixer or running a more costly membrane process that generates droplets of uniform size. The final products can be formulated into granules or powders by means of freeze-drying, or liquid formulations, following purification by dialysis against required aqueous solvent(s). The technology is adaptable
5 for use in encapsulating various water-soluble active compounds.

Although an embodiment of the present invention has been shown and described, the present invention is not limited to the described embodiments. Instead, it would be appreciated by those skilled in the art that changes may be made to the embodiments
10 without departing from the scope of the invention, the scope of which is set forth in the following claims.

CLAIMS

1. A method of encapsulating a water-soluble active compound, the method comprising:
 - mixing an aqueous solution comprising a water-soluble active compound with an oil in the presence of a surfactant under high shear condition to form a water-in-oil emulsion;
 - adding an aqueous solution of octenyl succinic anhydride (OSA)-modified starch to the water-in-oil emulsion and homogenizing further to obtain a water-in-oil-in-water double emulsion; and
 - mixing an aqueous solution comprising a cross-linker selected from the group consisting of adipic acid dihydrazide and methylglyoxal with the thus formed double emulsion for cross-linking the OSA-modified starch, thereby forming starch microcapsules with the water-soluble active compound encapsulated within the starch microcapsules,
 - wherein the water-soluble active compound is selected from the group consisting of amaranth dye and L-ascorbic acid.
2. The method according to claim 1, wherein the surfactant is selected from the group consisting of sorbitan monooleate, low-HLB sorbitans and surfactants with low HLB value.
3. The method according to claim 1, wherein the oil is selected from the group consisting of light edible oils including sunflower oil, canola oil and olive oil.
4. The method according to any one of claims 1 to 3, further comprising purifying the starch microcapsules by means of dialysis.
5. The method according to any one of claims 1 to 3, further comprising freeze-drying the starch microcapsules to obtain the encapsulated water-soluble active compounds in granular or powdered form.