(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 September 2020 (17.09.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/182792 A1

(51) International Patent Classification:
A61K 9/16 (2006.01) *A61K 9/50* (2006.01)

(21) International Application Number:
PCT/EP2020/056306

(22) International Filing Date:
10 March 2020 (10.03.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
19162276.0 12 March 2019 (12.03.2019) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,

(54) Title: COATED COACERVATE CAPSULES

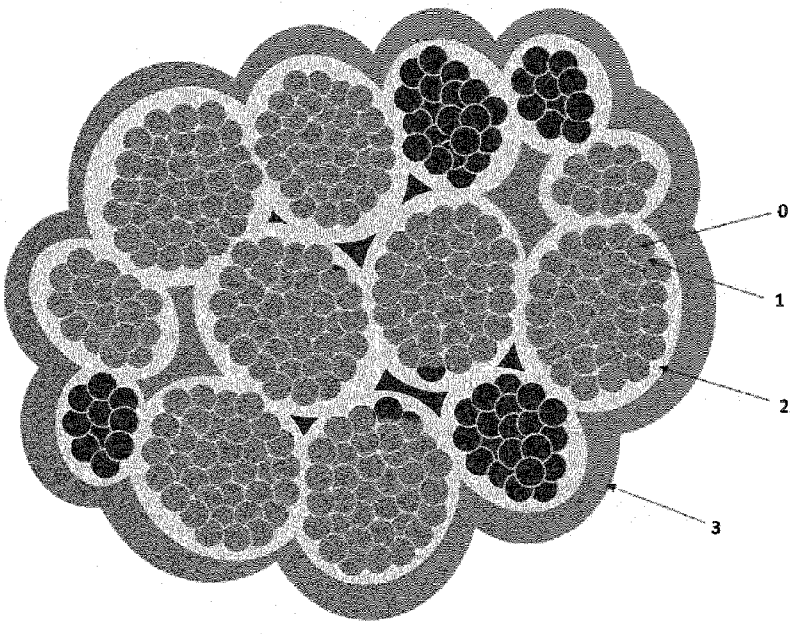


Figure 2

(57) Abstract: The present invention relates to coated coacervate capsules and to a process of manufacturing such capsules. The process of manufacturing coated coacervate capsules comprises the steps: (a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient; and (b) spray-drying the suspension provided in step a). Preferably, the at least one concomitant ingredient is an active pharmaceutical ingredient (API), a vitamin, a micronutrient, a probiotic, an enzyme, a physiologically active ingredient, a colorant or a taste masking agent.

WO 2020/182792 A1

[Continued on next page]

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

Coated coacervate capsules

Technical field

The present invention relates to solid formulations which are suitable for co-administration.

Background of the invention

The giving of two or more compounds at the same time is referred to as co-administration. Whereas it is possible to simultaneously administer two separate formulations, it is preferred to combine the compounds into one single formulation.

Merging several compounds into one single solid formulation is particularly challenging if one or more of the following conditions apply:

- the compounds to be merged have different solubility (e.g. one compound is lipophilic whereas the other is hydrophilic)
- the formulation needs to be water-dispersible despite of comprising lipophilic compounds
- one of the compounds is sensitive to light and/or oxygen
- one of the compounds requires taste-masking

WO 2018/198102 discloses a bilayer tablet comprising two layers, wherein each of the layers comprises a selected active pharmaceutical ingredient. Such bilayer tablets are sometimes referred to as fixed-dose combination (FDC).

Whereas bilayer tablets are well-established in the pharmaceutical area, there is a need for a more versatile formulation which can also be used in the food industry.

The problem to be solved by the present invention is the provision of a versatile formulation platform suitable for co-administration. The formulation

platform should be a solid formulation. The formulation platform should be suitable for co-administering a lipophilic and a hydrophilic compound. The formulation platform should also be suitable for co-administering two lipophilic compounds. The formulation platform should be suitable for co-administering a lipophilic compound which is sensitive to oxygen and/or light and which might require taste-masking. The formulation platform should suitable for pharmaceutical drugs, but it should not be limited to the use in the pharmaceutical area. Finally, the formulation platform should be water-dispersible even if it contains lipophilic compounds.

WO 2018/169960 discloses a drug delivery platform for treating bladder associated diseases. In one embodiment, the platform is a formulation where a therapeutic agent is encapsulated within a polymeric nanoparticle. A preferred polymer is poly-L-aspartic acid (PAA).

Yan Ma et al. published in Molecular Pharmaceutics an article about how to co-deliver hydrophilic and hydrophobic anticancer drugs (Combinational delivery of hydrophobic and hydrophilic anticancer drugs in single nanoemulsions to treat MDR in cancer, Molecular Pharmaceutics, 4 August 2014, 11(8):2623-2630).

Summary of the invention

The problems underlying the present invention are solved by spray-drying a suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient. Preferably, the at least one concomitant ingredient is an active pharmaceutical ingredient, a vitamin, a micronutrient, a probiotic, an enzyme, a physiologically active ingredient, a colorant or a taste-masking agent.

In a preferred embodiment of the invention, the suspension to be spray-dried comprises sugar, wherein said sugar comprising at most 70 weight-%, preferably at most 60 weight-% and most preferably at most 50 weight-% of monosaccharides and/or disaccharides, based on the total weight of the

sugar. An example of such sugar is maltodextrin. Preferred disaccharides are trehalose, maltose and mixtures thereof.

If high levels of sugar are involved, spray-drying is notoriously challenging. This is mostly due to the stickiness of sugar. The present invention solves this problem by a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;
b) spray-drying the suspension provided in step a),

wherein step b) is preferably done by spraying the suspension provided in step a) onto at least one belt, and wherein said at least one belt has preferably an air permeability which enables air to pass through the belt, and wherein said at least one belt is most preferably a wire mesh belt or a wire cloth belt.

Thus, the present invention also relates to the use of a spray dryer apparatus for manufacturing coated coacervate capsules, wherein said spray dryer apparatus comprises at least one belt. The thus manufactured product is a powder comprising or consisting of coated coacervate capsules.

Typically, the powder obtained by the process of the invention comprises or consists of coated coacervate capsules having a specific surface area of less than 0.2 m^2/g or even less than of less than 0.1 m^2/g when measuring BET specific surface area by gas physisorption using krypton gas. The powder obtained by the process of the invention has very minor or even no off-flavor, even it contains fish oil as a source of polyunsaturated fatty acids (PUFAs).

Sugar is the generic name for sweet-tasting, water-soluble carbohydrates. In the pharmaceutical area, lactose is frequently used despite of many patients suffering from lactose intolerance. Sugar as used in the context of the present invention is sweet-tasting, water-soluble and preferably comprises or consist of trehalose. According to a recently published study, “Trehalose inhibits solute carrier 2A (SLC2A) proteins to induce autophagy and prevent hepatic steatosis” (DeBosch et al., Science Signaling, Vol 9, Issue 416, ra21, February 2016).

In one embodiment of the invention, the at least one concomitant ingredient is a colorant. In this embodiment, the coated coacervate capsules can be used for preparing a colored liquid composition. Thereby, the suspension of step a) comprises preferably at least one emulsified lipophilic concomitant ingredient (e.g. at least one emulsified lipophilic colorant). To emulsify the least one lipophilic concomitant ingredient, a hydrocolloid is preferably used.

In another embodiment of the invention, the coated coacervate capsules encapsulate at least one lipophilic active pharmaceutical ingredient and/or the at least one concomitant ingredient is an active pharmaceutical ingredient. In this embodiment, the coated coacervate capsules can be used as medicament, e.g. to co-deliver hydrophilic and hydrophobic drugs.

Detailed description of the invention

The present invention relates to a versatile formulation platform useful for co-delivering more than one compound. Thereby, at least one of the compounds is encapsulated in coated coacervate capsules whereas at least one compound is comprised in the coating of the coated coacervate capsules. The coating comprises water-soluble sugar. Thus, when dispersing the coated coacervate capsules in water, the at least one compound in the coating of the coacervate capsules is released whereas the compound encapsulated in coated coacervate capsules remains encapsulated.

In the context of the present invention, the at least one compound in the coating of the coated coacervate capsules is referred to as the “at least one concomitant ingredient”. Preferably, the at least one concomitant ingredient is an active pharmaceutical ingredient, a vitamin, a micronutrient, a probiotic, an enzyme, a physiologically active ingredient, a colorant and/or a taste masking agent. The envisaged use of the coated coacervate capsules determines the choice of the at least one concomitant ingredient or the mixture of concomitant ingredients. The at least one concomitant ingredient of the invention is not an excipient, unless the excipient is mulitfunctional.

Typically, the at least one compound being encapsulated in the coated coacervate capsules of the invention is a lipophilic compound. A typically lipophilic compound is an oil (e.g. fish oil or algae oil) or can be dissolved in an edible oil. Thus, in one embodiment, the coated coacervate capsules of the invention encapsulate at least one an oil, vitamin E or a mixture thereof. In case a solid lipophilic compound is the be co-delivered together with the at least one concomitant ingredient, the solid lipophilic compound may be dissolved in an edible or pharmaceutical acceptable carrier oil before being encapsulated in coacervate capsules.

In one embodiment of the invention, the at least one concomitant ingredient is a hydrophilic compound or a water dispersible compound whereas the at least one of compound being encapsulated in coated coacervate capsules is a lipophilic compound. A typical hydrophilic compound can be dissolved in water, but not in oil. In one embodiment, the at least one concomitant ingredient of the invention is a solid hydrophilic compound.

In case the at least one compound being encapsulated in the coated coacervate capsules has a bad taste, the at least one concomitant ingredient may be a taste masking agent.

In case a hydrophilic drug and a hydrophobic drug are to be co-administered, the hydrophobic drug is preferably encapsulated in the coated coacervate capsules, whereas the hydrophilic drug is preferably the at least one concomitant ingredient of the invention.

In an also preferred embodiment, the coated coacervate capsules of the invention are used for preparing a colored liquid composition. In this embodiment, the at least one concomitant ingredient of the invention is a colorant or a mixture of colorants. Blending colorants is one way to achieve a desired shade or hue. Preferably, the liquid composition of the invention is a liquid pharmaceutical composition, liquid food or a beverage, or even more preferably enteral nutrition, parenteral nutrition or a liquid oral nutritional supplement. Most preferably, the colored liquid composition of the invention is a colored beverage or a colored liquid oral nutritional supplement.

Typically, the coated coacervate capsules of the invention are meant for human consumption, for addition to feed, or for oral administration. Therefore, colorants which are not suitable for human consumption, for addition to feed, or for oral administration are preferably excluded. Preferred colorants are edible colorants such as carotenoids. In a preferred embodiment, the at least one concomitant ingredient of the invention is beta-carotene, lutein, zeaxanthin, or even more preferably a mixture thereof.

In case the at least one concomitant ingredient is lipophilic, it is preferred to emulsify the at least one lipophilic concomitant ingredient before enclosing it in the coating of coated coacervate capsules of the invention. This can be done by providing an emulsion which comprises the at least one lipophilic concomitant ingredient and at least one emulsifier. Preferred emulsifiers are proteins and hydrocolloids such as modified starch. The preferred modified starch is octenyl succinate starch. Emulsifiers which are not suitable for human consumption, for addition to feed, or for oral administration are preferably excluded.

The present invention also relates to a powder comprising or consisting of coated coacervate capsules. Such powder is obtainable by the process of the invention.

The process of the invention is a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar, at least one concomitant ingredient and optionally at least one antioxidant;
b) spray-drying the suspension provided in step a).

In the context of the present invention, the optional at least one antioxidant is preferably a water-soluble antioxidant. Preferred antioxidants are ascorbic acid, edible salts of ascorbic acid (such as sodium ascorbate), citric acid, edible salts of citric acid (such as sodium citrate), chelating agents (such as EDTA) and plant extracts (such as green tea extract or rosemary extract). The most preferred antioxidant is sodium ascorbate.

When applying the process of the present invention, coated coacervate capsules are being produced. Based on the number of polymer types used, coacervate capsules may be simple coacervate capsules (i.e. one polymer type only) or complex coacervate capsules (i.e. more than one polymer type).

Preferably, the coacervate capsules of present invention are complex coacervate capsules. Complex coacervation is a phenomenon in which cationic and anionic water-soluble polymers interact in water to form complex coacervates.

Optimum coacervation depends on the pH. At the isoelectric point, a polymer such as gelatin has an equal number of anionic and cationic charges. To become a cationic polymer, the pH of the system is to be adjusted accordingly. In complex coacervation, the cationic polymer is typically chosen from animal proteins (such as pig or fish gelatin), albumin, vegetable proteins (derived, for example, from soya, from potato or from wheat), chitosan and its derivatives, synthetic polymers resulting from the combining of amino acids such as polylysine, or else polymers of vegetable origin (such as guar gum and its derivatives). The anionic polymer is typically chosen from natural polymers, such as gum arabic, alginates, carrageenan, cellulose derivatives such as carboxymethylcellulose, starch derivatives such as carboxymethyl starch, or synthetic polymers (such as acrylic, methacrylic, polylactic or polyglycolic polymers, or combinations thereof).

A preferred embodiment of the invention relates to a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;
b) spray-drying the suspension provided in step a),

wherein said coacervate capsules comprise:

- at least one cationic polymer, being preferably gelatine; and
- at least one anionic polymer, being preferably sodium polyphosphate.

In order to increase the strength of the shell of a coacervate capsule, the polymers in the complex coacervate capsules' shells can be crosslinked. Various crosslinking agents, such as glutaraldehyde, are known. In the context of the present invention, enzymes and in particular transglutaminase is preferably used to crosslink the polymers in the complex coacervate capsules' shells at least partially.

Thus, a preferred embodiment of the invention relates to a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;
b) spray-drying the suspension provided in step a),

wherein said coacervate capsules are complex coacervate capsules, and wherein the shells of said coacervate capsules preferably comprise at least one cationic polymer being preferably gelatine and at least one anionic polymer being preferably sodium polyphosphate, and

wherein said polymers are preferably at least partially crosslinked.

In a preferred embodiment, the coacervate capsules to be coated comprise at least one agglomeration of primary coacervate capsules, each individual primary coacervate capsules having a primary shell and the at least one agglomeration being encapsulated by an outer shell. Such coacervate capsules are described in WO 03/086104, the entire disclosure of which is hereby incorporated by reference.

Thus, in a preferred embodiment of the invention, the coated coacervate capsule comprises a multitude of agglomerations of primary coacervate capsules, and wherein said multitude of agglomerations of primary coacervate capsules is coated. In the context of the present invention, "multitude of" means more than 1 and preferably at least 3 or at least 5.

In Figure 2, a coated coacervate capsule comprising thirteen agglomerations of primary coacervate capsules is shown, wherein each individual primary coacervate capsule has a primary shell (1), and wherein each of said

agglomeration is encapsulated by an outer shell (2), and wherein said multitude of agglomerations of primary coacervate capsules has a coating (3) which comprises sugar. The primary shell (1) comprises preferably at least one cationic polymer and at least one anionic polymer which are preferably crosslinked. The outer shell (2) comprises preferably also at least one cationic polymer and at least one anionic polymer. However, in contrast to the primary shell (1), the polymers of outer shell (2) are preferably not crosslinked. Primary shell (1) and outer shell (2) comprise preferably the same type of polymers.

The size of particles can be measured e.g. by laser granulometry (see, for example, Renliang Xu, "Light scattering: A review of particle characterization applications", Particuology 18 (2015)). In the context of the present invention, a Malvern Mastersizer 3000 is preferably used for measuring the size of the coacervate capsules which are present in the herein described suspension. Preferably, the same Malvern Mastersizer 3000 is also used for measuring the size of the coated coacervate capsules of the invention.

The average particle size D (v,0.5) of the coated coacervate capsules of the present invention ranges preferably between 50 µm and 500 µm, more preferably between 50 µm and 300 µm and even more preferably between 50 µm and 200 µm, measured by Laser Diffraction; Malvern Mastersizer 3000, MIE volume distribution.

Coacervation (and in particular complex coacervation) can be used to encapsulate lipophilic compounds.

Preferably, the coacervate capsules of the invention encapsulate at least one oil. Said oil may be a carrier oil that comprises a lipophilic pharmaceutical active ingredient (API) or the oil as such may have a health benefit. Examples of oil have a health benefit are fish oil and algae oil, both comprising polyunsaturated fatty acids (PUFAs).

Thus, a preferred embodiment of the invention relates to a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;
b) spray-drying the suspension provided in step a),

wherein said coacervate capsules encapsulate at least one lipophilic compound, and wherein said at least one lipophilic compound is preferably an oil, and wherein said oil comprises preferably polyunsaturated fatty acids, and wherein said oil is most preferably fish oil and/or algae oil comprising omega-3 polyunsaturated fatty acids.

Preferred PUFAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These preferred PUFAs have a beneficial effect on the intestinal microbiota of a person. Therefore, one embodiment of the invention relates to a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;
b) spray-drying the suspension provided in step a),

wherein said coacervate capsules encapsulate at least one oil which comprises eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA).

According to the invention, any kind of water-soluble sugar can be used. Good results are achieved if the suspension of step a) comprises maltodextrin.

Thus, a preferred embodiment of the invention relates to a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, maltodextrin and at least one concomitant ingredient;
b) spray-drying the suspension provided in step a),

wherein said coacervate capsules encapsulate at least one oil which comprises polyunsaturated fatty acids.

Maltodextrin is produced from starch by partial hydrolysis. It comprises or consists of glucose units connected in chains of variable length. An example of a short glucose chain is the disaccharide maltose. Preferably, maltodextrin having a dextrose equivalent from 2 to 10 or maltodextrin having a dextrose equivalent from 40 to 60 is used in the context of the present invention. Most preferably, maltodextrin having a dextrose equivalent of 6 (noted as maltodextrin DE6) is used in the context of the present invention. When using maltodextrin DE6, caking can be prevented even under humid conditions. Particularly good results are achieved if maltodextrin DE6 only is used as illustrated in Example 10a. The person skilled in the art is familiar with the concept of dextrose equivalent (DE). By way of example, if one hundred grams of dry solid from a glucose syrup has a DE of 42 it means that the solids act (in reducing terms) as if they were 42 grams of dextrose. Preferably, the DE of maltose is determined as explained in the publication "Determination of Dextrose Equivalent Value and Number Average Molecular Weight of Maltodextrin by Osmometry" (Rong, Y.; Sillick, M.; Gregson, C.M., Journal of Food Science, January 2009, 74(1):C33-C40). In an also preferred embodiment of the invention, a mixture of two kinds of maltodextrin is used, wherein one kind of maltodextrin has a lower dextrose equivalent than the other kind of maltodextrin.

Thus, one embodiment of the invention relates to a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, maltodextrin having a dextrose equivalent from 2 to 10, maltodextrin having a dextrose equivalent from 40 to 60, and at least one concomitant ingredient;
b) spray-drying the suspension provided in step a),

wherein said coacervate capsules encapsulate at least one oil which comprises polyunsaturated fatty acids.

An also sweet disaccharide is trehalose. Using trehalose for coating coacervate capsules is particularly beneficial because trehalose may help to prevent fatty liver disease.

An also preferred embodiment of the invention relates to a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;

b) spray-drying the suspension provided in step a),

wherein said coacervate capsules encapsulate at least one oil which comprises polyunsaturated fatty acids, and

wherein the suspension of step a) comprises at least 5 weight-%, preferably at least 10 weight-% and most preferably at least 15 weight-% of at least one disaccharide, based on the total weight of the suspension, and wherein said at least one disaccharide is preferably trehalose, maltose or a mixture thereof.

An even more preferred embodiment of the invention relates to a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;

b) spray-drying the suspension provided in step a),

wherein said coacervate capsules encapsulate at least one oil which comprises eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA), and

wherein the suspension of step a) comprises at least 5 weight-%, preferably at least 10 weight-% and most preferably at least 15 weight-% of sugar, based on the total weight of the suspension, and

wherein the suspension of step a) comprises preferably at least 5 weight-% of trehalose, based on the total weight of the suspension.

Suspensions having a high sugar content are sticky and therefore difficult to spray-dry. Surprisingly, spray-drying is successful despite of a high sugar content when a spray dryer apparatus as herein described is used.

Therefore, the present invention also relates to the use of a spray dryer apparatus for manufacturing coated coacervate capsules, wherein said spray dryer apparatus comprises at least one belt, and wherein said at least one belt has preferably an air permeability which enables air to pass through the belt, and wherein said at least one belt is more preferably a wire mesh belt or a wire cloth belt. Such spray dryer apparatus is commercially available under the tradename Filtermat®.

Accordingly, a preferred embodiment of the invention relates to a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;
b) spray-drying the suspension provided in step a),

wherein said coacervate capsules encapsulate at least one lipophilic compound, and wherein said at least one lipophilic compound is preferably an oil, and wherein said oil comprises preferably polyunsaturated fatty acids, and wherein said oil is most preferably fish oil comprising omega-3 polyunsaturated fatty acids and/or algae oil comprising omega-3 polyunsaturated fatty acids, and

wherein the suspension of step a) comprises at least 5 weight-%, preferably at least 10 weight-% and most preferably at least 15 weight-% of at least one disaccharide, based on the total weight of the suspension, and

wherein step b) is done by spraying the suspension provided in step a) onto at least one belt, and wherein said at least one belt has preferably air permeability which enables air to pass through the belt, and wherein said at least one belt is more preferably a wire mesh belt or a wire cloth belt.

An even more preferred embodiment of the invention relates to a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;

b) spray-drying the suspension provided in step a),

wherein said coacervate capsules encapsulate eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA), and

wherein the suspension of step a) comprises at least 5 weight-%, preferably at least 10 weight-% and most preferably at least 15 weight-% of at least one disaccharide, based on the total weight of the suspension, and

wherein step b) is done by spraying the suspension provided in step a) onto at least one belt, and wherein said at least one belt has preferably air permeability which enables air to pass through the belt, and wherein said at least one belt is more preferably a wire mesh belt or a wire cloth belt.

In a preferred embodiment, an air flow is provided in step b), said air flow directing the sprayed particles downwards onto the herein described belt.

Thus, an even more preferred embodiment of the invention relates to a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;

b) spray-drying the suspension provided in step a),

wherein said coacervate capsules encapsulate eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA), and

wherein the suspension of step a) comprises at least 5 weight-%, preferably at least 10 weight-% and most preferably at least 15 weight-% of at least one disaccharide, based on the total weight of the suspension, and

wherein step b) is done by spraying the suspension provided in step a) onto at least one belt, wherein said at least one belt has air permeability which enables air to pass through the belt, and wherein an air flow is provided in step b) which directs the sprayed particles downwards onto said belt.

The most preferred embodiment of the invention relates to a process of manufacturing coated coacervate capsules, said process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;

b) spray-drying the suspension provided in step a),

wherein said coacervate capsules encapsulate eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA), and

wherein said coacervate capsules comprise:

- at least one cationic polymer, being preferably gelatine; and
- at least one anionic polymer, being preferably sodium polyphosphate, and

wherein the suspension of step a) comprises at least 5 weight-%, preferably at least 10 weight-% and most preferably at least 15 weight-% of at least one disaccharide, based on the total weight of the suspension, and

wherein step b) is done by spraying the suspension provided in step a) onto at least one belt, wherein said at least one belt has air permeability which enables air to pass through the belt, and wherein an air flow is preferably provided in step b) which directs the sprayed particles downwards onto said belt.

When applying the process of the invention, a preferably flowable powder is obtained. Said powder may comprises a significant amount of water-soluble sugar.

When applying the process of the invention, coated coacervate capsules having a very smooth sugar coating are obtained. The powder of the invention preferably comprises or consists of coated coacervate capsules having a specific surface area of less than 0.2 m^2/g, preferably of less than 0.1 m^2/g and most preferably of less than 0.05 m^2/g, when measuring BET specific surface area by gas physisorption using krypton gas. The person skilled in the art is familiar with BET specific surface area analysis by gas physisorption. In such analysis, surface area is calculated based on the BET model (static volumetric method) normalized by the sample mass. As the amount of gas adsorbed onto the sample surface is critical to the analysis, moisture and other impurities must be removed from the sample surface prior to analysis (degassing).

The coated coacervate capsules as herein described have a specific surface area of preferably less than 0.2 m^2/g, more preferably of less than 0.1 m^2/g and most preferably of less than 0.05 m^2/g, when measuring BET specific surface area by gas physisorption using krypton gas. Such coated coacervate capsule is shown in Figure 1.

Coacervate capsules as used in the context of the invention are preferably complex coacervate capsules, wherein the shells of said coacervate capsules preferably comprise at least one cationic polymer and at least one anionic polymer, and wherein said polymers are preferably at least partially crosslinked. In the context of the present invention, any suitable cationic polymer, anionic polymer and crosslinker can be used. Preferred cationic polymer are gelatine, soy protein isolate, pea protein isolate and canola protein. Preferred anionic polymer are sodium polyphosphate and gum arabic. Preferred crosslinkers are non-toxic crosslinker, in particular enzymes such as transglutaminase.

Thus, the powder of the invention preferably comprises or consists of coated coacervate capsules. Preferably, said coated coacervate capsules are complex coacervate capsules, wherein the shell of said coacervate capsules preferably comprise at least one cationic polymer and at least one anionic polymer, and wherein said polymers are preferably at least partially crosslinked.

Preferably, the coated coacervate capsules of the invention have a specific surface area of less than 0.1 m^2/g, when measuring BET specific surface area by gas physisorption using krypton gas, and comprise:

- at least one cationic polymer, being preferably gelatine;
- at least one anionic polymer, being preferably sodium polyphosphate;
- a mixture of monosaccharides and preferably water-soluble oligosaccharides;
- oil, said oil being preferably fish oil and/or algae oil comprising omega-3 polyunsaturated fatty acids;
- at least one concomitant ingredient, and

- optionally at least one emulsifier being preferably a hydrocolloid.

More preferably, the coated coacervate capsules of the invention have a specific surface area of less than 0.1 m^2/g, when measuring BET specific surface area by gas physisorption using krypton gas, and comprise or consist of:

- 5-90 weight-%, preferably 5-70 weight-%, more preferably 5-60 weight-% and most preferably 5-50 weight-% of sugar, based on the total weight of the coated coacervate capsules;
- 1-70 weight-%, preferably 1-50 weight-%, more preferably 1-45 weight-% and most preferably 1-40 weight-% of at least one lipophilic compound, based on the total weight of the coated coacervate capsules;
- 1-45 weight-%, preferably 1-40 weight-%, more preferably 1-30 weight-% and most preferably 1-25 weight-% of at least one concomitant ingredient, based on the total weight of the coated coacervate capsules;
- at least one cationic polymer; and
- at least one anionic polymer; and
- optionally at least one emulsifier; and
- optionally at least one auxiliary compound; and
- optionally residual water,

The person skilled in the art understands that embodiments, wherein the sum of all percentages is greater than 100%, are excluded.

Also preferably, the coated coacervate capsules of the invention comprise or consist of:

- 5-90 weight-%, preferably 5-70 weight-%, more preferably 5-60 weight-% and most preferably 5-50 weight-% of sugar, based on the total weight of the coated coacervate capsules;
- 1-70 weight-%, preferably 1-50 weight-%, more preferably 1-45 weight-% and most preferably 1-40 weight-% of at least one lipophilic compound, based on the total weight of the coated coacervate capsules;

- 1-45 weight-%, preferably 1-40 weight-%, more preferably 1-30 weight-% and most preferably 1-25 weight-% of at least one concomitant ingredient, based on the total weight of the coated coacervate capsules;
- at least one cationic polymer; and
- at least one anionic polymer; and
- optionally at least one emulsifier; and
- optionally at least one auxiliary compound; and
- optionally residual water

wherein said coated coacervate capsule has a specific surface area of less than 0.2 m^2/g, preferably of less than 0.1 m^2/g and most preferably of less than 0.05 m^2/g, when measuring BET specific surface area by gas physisorption using krypton gas. The person skilled in the art understands that embodiments, wherein the sum of all percentages is greater than 100%, are excluded.

Also preferably, the coated coacervate capsules of the invention comprise or consist of:

- 5-90 weight-%, preferably 5-70 weight-%, more preferably 5-60 weight-% and most preferably 5-50 weight-% of sugar, based on the total weight of the coated coacervate capsules;
- 1-70 weight-%, preferably 1-50 weight-%, more preferably 1-45 weight-% and most preferably 1-40 weight-% of at least one lipophilic compound, based on the total weight of the coated coacervate capsules;
- 1-45 weight-%, preferably 1-40 weight-%, more preferably 1-30 weight-% and most preferably 1-25 weight-% of at least one concomitant ingredient, based on the total weight of the coated coacervate capsules;
- at least one cationic polymer; and
- at least one anionic polymer; and
- optionally at least one emulsifier; and
- optionally at least one auxiliary compound; and
- optionally residual water

wherein each of said coated coacervate capsules comprises at least one agglomeration of primary coacervate capsules, each individual primary coacervate capsules having a primary shell and the at least one agglomeration being encapsulated by an outer shell, and/or wherein the average particle size D (v,0.5) size of said coated coacervate capsules ranges preferably between 50 µm and 500 µm, more preferably between 50 µm and 300 µm and even more preferably between 50 µm and 200 µm, measured by Laser Diffraction; Malvern Mastersizer 3000, MIE volume distribution. The person skilled in the art understands that embodiments, wherein the sum of all percentages is greater than 100%, are excluded.

The present invention also relates to the use of the coated coacervate capsules of the invention as a medicament. Thus, the present invention also relates to method of treating a disease, wherein the coated coacervate capsules of the invention is administered to a patient.

A preferred embodiment of the invention relates to a method of treating of treating or protecting against inflammation in a biological system, preferably in a mammal or in a bird, wherein the coated coacervate capsules of the invention is administered to the subject to be treated. In this preferred embodiment, the coated coacervate capsule is obtainable by a process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;

b) spray-drying the suspension provided in step a).

wherein the suspension of step a) comprises coacervate capsules which encapsulate at least one lipophilic compound, and wherein said at least one lipophilic compound is preferably an oil, and wherein said oil comprises preferably polyunsaturated fatty acids and/or vitamin E, and wherein vitamin E is preferably selected form the group consisting of (R,R,R)-alpha- tocopherol, (R,R,R)-beta-tocopherol, (R,R,R)-gamma-tocopherol, (R,R,R)-delta-tocopherol, (R,E,E)-alpha-tocotrienol, (R,E,E)-beta-tocotrienol, (R,E,E)-gamma-tocotrienol, and (R,E,E)-delta-tocotrienol.

In this preferred embodiment, the at least one concomitant ingredient is preferably the compound disclosed in claim 1 of WO 2018/191732, and more preferably any one of the compounds disclosed in claim 27 of WO 2018/191732.

In an alternative embodiment, the compound disclosed in claim 1 of WO 2018/191732 or any one of the compounds disclosed in claim 27 of WO 2018/191732 is dissolved in a pharmaceutically acceptable carrier oil. The thus obtained solution or dispersion is then encapsulated in the coated coacervate capsule of the invention. Preferably, said pharmaceutically acceptable carrier oil comprises polyunsaturated fatty acids such as DHA. Thus, an also preferred embodiment of the invention relates to coated coacervate capsule obtainable by a process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;

b) spray-drying the suspension provided in step a).

wherein the suspension of step a) comprises coacervate capsules which encapsulate at least one lipophilic compound, and wherein said at least one lipophilic compound is an oil, and wherein said oil comprises polyunsaturated fatty acids and any one of the compounds disclosed in claim 1 of WO 2018/191732, wherein said oil comprises preferably docosahexaenoic acid and any one of the compounds disclosed in claim 27 of WO 2018/191732.

An also preferred embodiment of the invention relates to coated coacervate capsule obtainable by a process comprising the steps:

a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;

b) spray-drying the suspension provided in step a).

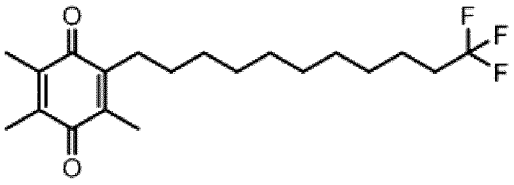
wherein said at least one lipophilic compound is an oil, and wherein said oil comprises vitamin E and any one of the compounds disclosed in claim 1 of WO 2018/191732, and wherein said oil comprises preferably vitamin E and any one of the compounds disclosed in claim 27 of WO 2018/191732, and wherein vitamin E is preferably selected form the group consisting of (R,R,R)-

alpha-tocopherol, (R,R,R)-beta-tocopherol, (R,R,R)-gamma-tocopherol, (R,R,R)-delta-tocopherol, (R,E,E)-alpha-tocotrienol, (R,E,E)-beta-tocotrienol, (R,E,E)-gamma-tocotrienol, and (R,E,E)-delta-tocotrienol.

The content of WO 2018/191732 is hereby incorporated by reference.

5

Claim 27 of WO 2018/191732 discloses the following compounds: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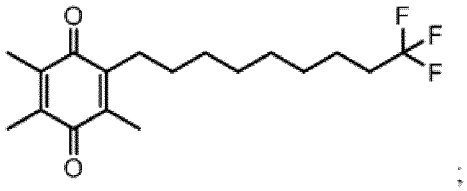
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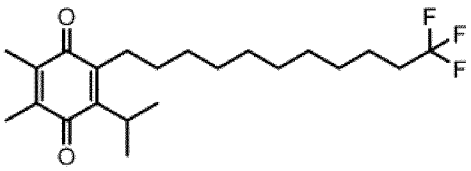
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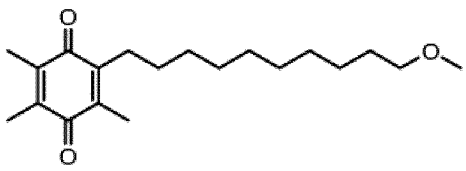
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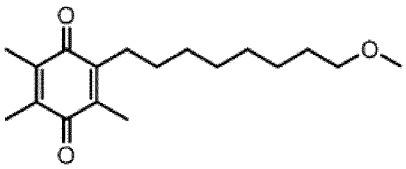
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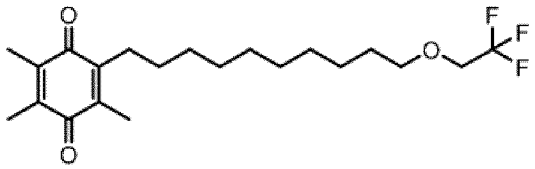
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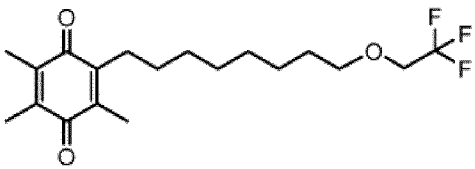
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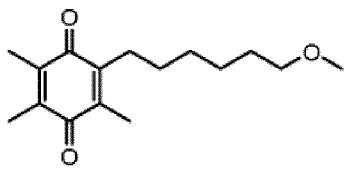
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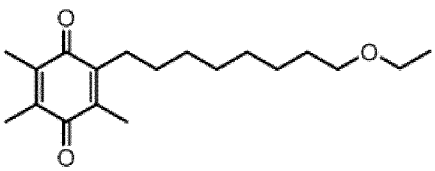
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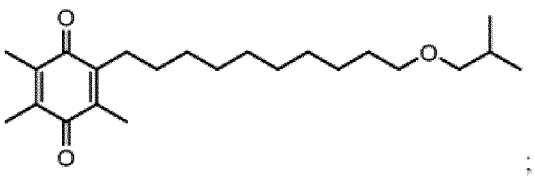
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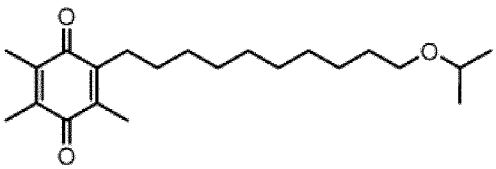
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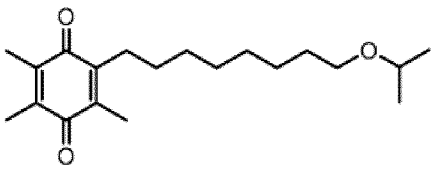
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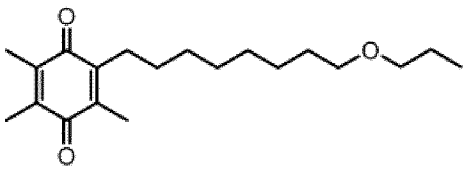
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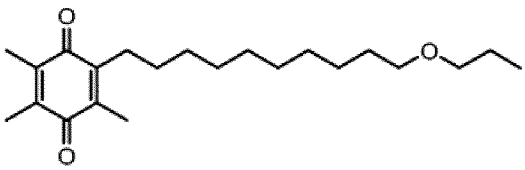
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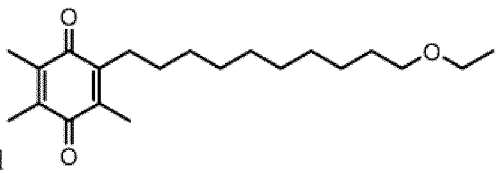
and

; and the hydroquinones thereof.

Figures

FIGURE 1 shows a SEM picture of a coated coacervate capsule according to a preferred embodiment of the invention. A Hitachi S-4700 Field Emission Scanning Electron Microscope (SEM) with transmitted electron detector was used for taking the picture. The scale bar in Figure 1 shows the magnification.

The coated coacervate capsule shown in Figure 1 has a structure similar as depicted in FIGURE 2. Each of the primary coacervate capsules shown in Figure 2 comprises a lipophilic core (0) surrounded by a primary shell (1). Said primary shells (1) comprise cationic and anionic polymers which are preferably crosslinked. Each agglomeration of primary coacervate capsules is then surrounded by outer shell (2). The outer shell (2) is preferably made of the same polymers as the primary shells (1) but the polymers are preferably not crosslinked. The third shell (3) is the coating of the coated coacervate capsule. Said coating comprises sugar and the at least one concomitant ingredient.

Due to the agglomerations of primary coacervate capsules within the coated coacervate capsule, the surface of the particle shown in Figure 1 and depicted in Figure 2 looks like the surface of a raspberry or of a blackberry. Nonetheless, due to the sugar coating, the BET surface of the particles shown in Figure 1 and depicted in Figure 2 is very small.

Examples

Example 1

Step a)

A stock solution of gelatine (solution A) was prepared by mixing 4500 g of warm deionised water and 550 g of gelatine (bovine gelatin, 270 Bloom, supplied by Gelita) and stirring in a vessel until it was completely dissolved; the solution was maintained at 45°C. 80 g of sodium ascorbate dry powder (DSM® Nutritional Products) was added to the vessel and completely dissolved.

A stock solution of sodium polyphosphate (solution B) was prepared by mixing 500 g of room temperature deionised water and 55 g sodium polyphosphate (Vitrafos, Innophos) in a beaker until it was completely dissolved.

Solution B was then added to solution A (yielding solution C).

1000 g of PUFA oil (available under the tradename Meg-3™ at DSM® Nutritional Products) was added to solution C and mixed via a high shear mixer (Silverson L4RT-A, model L4R) at >7000 rpm to produce oil droplets being < 2 µm in average diameter. 10 kg of deionised water was added to the shear mixed solution; the coacervation process was then initiated by adjusting the pH to ~4.5 with a 20% w/w aqueous phosphoric acid solution until a final particle size of 30-50 µm was obtained. In this manner, a slurry with a solid concentration of 10 weight-%, based on the total weight of the slurry, was obtained.

The coacervate slurry was cooled to 6°C, and then 30 g transglutaminase enzyme (Activa®, Ajinomoto Food Ingredients) was added to induce crosslinking of gelatin. Coacervate slurry pH was adjusted to 6.0 with a 20% sodium hydroxide solution, and the slurry temperature was adjusted to 25°C and held for 11 hours to ensure complete crosslinking of gelatin. The slurry was subsequently centrifuged, and water was removed to achieve a solid concentration of 15 weight-%, based on the total weight of the slurry. Said slurry contains gelatin-based microencapsulated oil droplet clusters, hereinafter referred to as “Coacervate Solids”.

1180 g of trehalose powder (supplied by Hayashibara®) and 510 g of GLUCIDEX® Maltodextrin 2 (maltodextrin DE2 powder, supplied by Roquette®) were then added to the coacervate slurry and stirred until the sugar (i.e. trehalose powder and maltodextrin powder) are completely dissolved. The thus obtained product is a suspension which is ready for spray-drying

Step b)

To obtain a flowable dry powder, the suspension provided in step a) was then sprayed via a Filtermat® spray drier (GEA) at the following parameters: 0.032" nozzle diameter (number 67, Spray Systems Co.), 400 psi pump speed, 70-80°C outlet temperature (measured right before the machine's cyclone).

Example 2

Example 1 was repeated. In example 2, however, maltodextrin DE2 was replaced by maltodextrin DE47. Maltodextrins are classified by DE (dextrose equivalent). The higher the DE value, the shorter the glucose chains and the higher the sweetness.

Example 3

Example 1 was repeated. In example 3, however, Maltodextrin DE2 was replaced with 1:1 mixture of DE2 and DE47.

The composition of powders obtained in Example 1-3 is shown in below TABLE 1. Indicated are weight-%, based on the total weight of the dried powder:

		Example 1	**Example 2**	**Example 3**
Coacervate Solids		50 wt.-%	50 wt.-%	50 wt.-%
sugar	Trehalose	35 wt.-%	35 wt.-%	35 wt.-%
	Maltodextrin DE2	15 wt.-%	-	7.5 wt.-%
	Maltodextrin DE47	-	15 wt.-%	7.5 wt.-%
Total		**100 wt.-%**	**100 wt.-%**	**100 wt.-%**

Table 1

Comparative example 4

Example 1 was repeated. In example 4, however, no sugar was added before spray-drying. Thus, the slurry containing "Coacervate Solids" was spray dried without having added maltodextrin, trehalose or any other kind of sugar. Thus, the obtained comparative powder does not contain any coated coacervate capsules.

The composition of powders obtained in comparative Example 4 is shown in below TABLE 2. Indicated are weight-% based on the total weight of the dried powder:

		Comparative Example 4
Coacervate Solids		100 wt.-%
sugar	Trehalose	-
	Maltodextrin DE2	-
	Maltodextrin DE47	-
Total		**100 wt.-%**

Table 2

Example 5

In Example 5, a sensory test was done. The participants of the sensory test were trained and had previously attended at least 50 sensory panels. The participants were asked to rate the "painty" aroma (i.e. the smell/taste of fresh paint) intensity on a scale of 1 to 15. A score of 15 means a very strong, unpleasant and therefor unacceptable aroma.

After two months storage time, the powder of Example 3 scored 0.3 whereas the powder of comparative Example 4 scored 3.8.

A score of 3.8 is unacceptable. Thus, if the product of comparative Example 4 (i.e. uncoated "Coacervate Solids") was used to provide an edible product, such product could not be commercialized as the consumer would immediately notify the unpleasant painty aroma. Most likely, the consumer would discharge the seemingly spoilt product.

A score below 2 means that food can be successfully prepared by adding the coated coacervate capsules.

The result of the sensory testing is shown in below TABLE 3:

Example	*Time Point*	*Painty*
Example 1	initial	1.2
	2 months	1.0
Example 2	initial	1.2
	2 months	0.6
Example 3	initial	1.3
	2 months	0.3
comparative Example 4	**initial**	**1.2**
	2 months	**3.8**

Table 3

Example 6

The BET specific surface area of the particles of the powders obtained in example 3 and comparative example 4, respectively, was measured on a Micromeritics TriStar II 3020 (static pressure gas adsorption/Volumetric). Below TABLE 4 shows the results:

Sample	BET Specific Surface Area[1)] (m^2/g)	adsorbate Gas
Example 3	0.04	Krypton
comparative Example 4	0.13	Krypton

[1)] surface area calculated based on the BET model normalized by the sample mass

Table 4

The powder of Example 3 has a sugar content of 50 weight-%, based on the total weight of the dry powder. The powder consists of sugar-coated coacervate capsules. Due to the sugar-coating, the BET surface is particularly low.

The powder of comparative Example 4 consists of uncoated coacervate capsules. Due to the lack of the sugar-coating, the BET surface is higher, which probably explains the more pronounced painty off-flavor.

Example 7

In Example 7, Example 3 was repeated in modified manner:

First, the emulsion shown in below TABLE 5 was first prepared.

emulsion comprising three lipophilic concomitant ingredients		
octenyl succinate starch		25 g
lipophilic concomitant ingredients	lutein	10.4 g
	zeaxanthin	2.4 g
	beta-carotene	1 g
auxiliary compounds (sucrose, antioxidant)		6.4 g
water		54.7 g
Total		**26 g**

Table 5

To this emulsion, sugar (trehalose, maltodextrin DE2 and maltodextrin DE47) and the two types of coacervates (Type A and Type B) were added. To obtain a flowable dry powder, the thus obtained suspension was then sprayed via a Filtermat® spray drier (GEA brand) at the following parameters: 0.032" nozzle diameter (number 67, Spray Systems Co.), 400 psi pump speed, 70-80°C outlet temperature (measured right before the machine's cyclone).

Comparative Example 8

Coacervate capsules which encapsulate lutein (supplied by Kemin), zeaxanthin (supplied by Kemin) and beta-carotene were prepared as described in WO 06/085227 A2. The coacervate capsules of comparative Example 8 were not coated and thus, they did not comprise a concomitant ingredient as herein described.

Example 9

In Example 9, the coated coacervate capsules of Example 7 and the *un*coated coacervate capsules of comparative Example 8 were dispersed in water.

The result of this dispersion test in shown in below TABLE 6.

Test	**dispersed coacervates**	**visual appearance of obtained dispersion**
#1	as provided in Example 7	beverage with intense orange color
#2	as provided in comparative Example 8	water with red particles

Table 6

Example 9 shows that the coated coacervate capsules of the invention can be used to provide a colored beverage.

The coating of the coated coacervate capsules of the invention comprises sugar which dissolves in water. Upon dissolution of the sugar, the concomitant ingredient is released from the coating. In case the concomitant ingredient is a colorant (or a mixture of colorants), a colored liquid is obtained.

The coating of the coated coacervate capsules of Example 7 comprised several lipophilic colorants. To obtain an even color in the aqueous beverage, the lipophilic colorants had been emulsified with octenyl succinate starch. Such emulsified lipophilic concomitant ingredients are water-dispersible.

The comparative coacervate capsules of Example 8 also comprised colorants. However, when dispersed in water, these colorants remained within the coacervate capsules. It was therefore not possible to obtain an even color.

Example 10

In Example 10, different DE grades of maltodextrin were used to prepare powders as described in Examples 1 to 4. The thus prepared powders were stored in open jars at 25°C /60% RH. After two weeks storage time, caking was observed when using trehalose in combination with maltodextrin DE1, DE2, DE47 or with mixtures of these maltodextrin grades. The maltodextrin grade that performed well in this test was maltodextrin DE6.

		Example 10a	**Example 10b**
Coacervate Solids		80 wt.-%	60 wt.-%
sugar	Sucrose	-	20 wt.-%
	Maltodextrin DE6	20 wt.-%	20 wt.-%
Total		**100 wt.-%**	**100 wt.-%**

Table 7

When striving for a long term shelf storage at low humidity condition, a mixture of sucrose maltodextrin DE6 is preferred, as illustrated by the composition of Example 10b.

In dry blend beverages which are used in hot and humid climate, the composition of Example 10a is preferred. After 2 months storage at 40°C and 75% relative humidity, the powder of Example 10a did not show any caking or clumping. Therefore, a preferred embodiment of the present invention relates to a powder that comprises or consists of sugar-coated coacervate capsules, wherein said sugar-coated coacervate capsules comprise 5-90 weight-%, preferably 5-70 weight-%, more preferably 5-60 weight-% and most preferably 5-50 weight-% of maltodextrin DE6, based on the total weight of the sugar-coated coacervate capsules.

Claims

1. Process of manufacturing coated coacervate capsules, said process comprising the steps:
    a) providing a suspension, said suspension comprising water, coacervate capsules, sugar and at least one concomitant ingredient;
    b) spray-drying the suspension provided in step a).

2. Process according to claim 1, wherein the suspension of step a) comprises coacervate capsules which encapsulate at least one lipophilic compound, and

    wherein said at least one lipophilic compound is preferably an oil, and wherein said oil comprises preferably polyunsaturated fatty acids and/or vitamin E.

3. Process according to claim 1 or 2, wherein said at least one concomitant ingredient is an active pharmaceutical ingredient, a vitamin, a micronutrient, a probiotic, an enzyme, a colorant or a taste-masking agent, and

    wherein said at least one concomitant ingredient is preferably an edible colorant, said edible colorant being preferably beta-carotene, lutein or zeaxanthin.

4. Process according to any one of claims 1 to 3, wherein the suspension of step a) comprises at least one emulsified lipophilic concomitant ingredient, and

    wherein preferably a hydrocolloid or a protein has been used to emulsify the least one lipophilic concomitant ingredient, and wherein said hydrocolloid is preferably modified starch, and wherein said modified starch is preferably octenyl succinate starch.

5. Process according to any one of claims 1 to 4, wherein step b) is done by spraying the suspension provided in step a) onto at least one belt, and wherein said at least one belt has preferably air permeability which enables air to pass through the belt, and wherein said at least one belt is more preferably a wire mesh belt or a wire cloth belt.

6. Coated coacervate capsules, obtainable by the process according to any one of the preceding claims.

7. Coated coacervate capsules according to claim 6, wherein said coated coacervate capsules have a specific surface area of less than 0.2 m^2/g, preferably of less than 0.1 m^2/g and most preferably of less than 0.05 m^2/g, when measuring BET specific surface area by gas physisorption using krypton gas.

8. Coated coacervate capsules according to claim 6 or 7, wherein said coated coacervate capsules comprise:
   - 5-90 weight-%, preferably 5-70 weight-%, more preferably 5-60 weight-% and most preferably 5-50 weight-% of sugar, based on the total weight of the coated coacervate capsules, wherein said sugar is preferably maltodextrin DE1, maltodextrin DE2 or maltodextrin DE6 and wherein said sugar is most preferably maltodextrin DE6;
   - 1-70 weight-%, preferably 1-50 weight-%, more preferably 1-45 weight-% and most preferably 1-40 weight-% of at least one lipophilic compound, based on the total weight of the coated coacervate capsules;
   - 1-45 weight-%, preferably 1-40 weight-%, more preferably 1-30 weight-% and most preferably 1-25 weight-% of at least one concomitant ingredient, based on the total weight of the coated coacervate capsules;
   - at least one cationic polymer; and
   - at least one anionic polymer; and
   - optionally at least one emulsifier; and

- optionally at least one auxiliary compound; and
- optionally residual water

9. Coated coacervate capsules according to any one of claims 6 to 8, wherein said sugar comprises at most 70 weight-%, preferably at most 60 weight-% and most preferably at most 50 weight-% of monosaccharides and/or disaccharides, based on the total weight of the sugar, and wherein said at least one lipophilic compound is preferably an oil, and wherein said least one concomitant ingredient is preferably a colorant.

10. Use of coated coacervate capsules according to any one of claims 6 to 9 for preparing a liquid composition.

11. Use according to claim 10, wherein said liquid composition is a liquid pharmaceutical composition, liquid food or a beverage, and wherein said liquid composition is preferably enteral nutrition, parenteral nutrition or a liquid oral nutritional supplement.

12. Use according to claim 10 or 11, wherein the least one concomitant ingredient is a colorant and wherein the coated coacervate capsules are used for preparing a colored liquid composition, said colored liquid composition being preferably a colored beverage or a colored liquid oral nutritional supplement.

13. Coated coacervate capsules according to any one of claims 6 to 9 for use as a medicament, wherein said coated coacervate capsules comprise at least one active pharmaceutical ingredient.

14. Coated coacervate capsules according to claim 13, wherein said coated coacervate capsules encapsulate at least one lipophilic active pharmaceutical ingredient and/or wherein the at least one concomitant ingredient is an active pharmaceutical ingredient.

15. Pharmaceutical dosage form, food, feed or a cosmetic product, comprising coated coacervate capsules according to any one of claims 6 to 9.

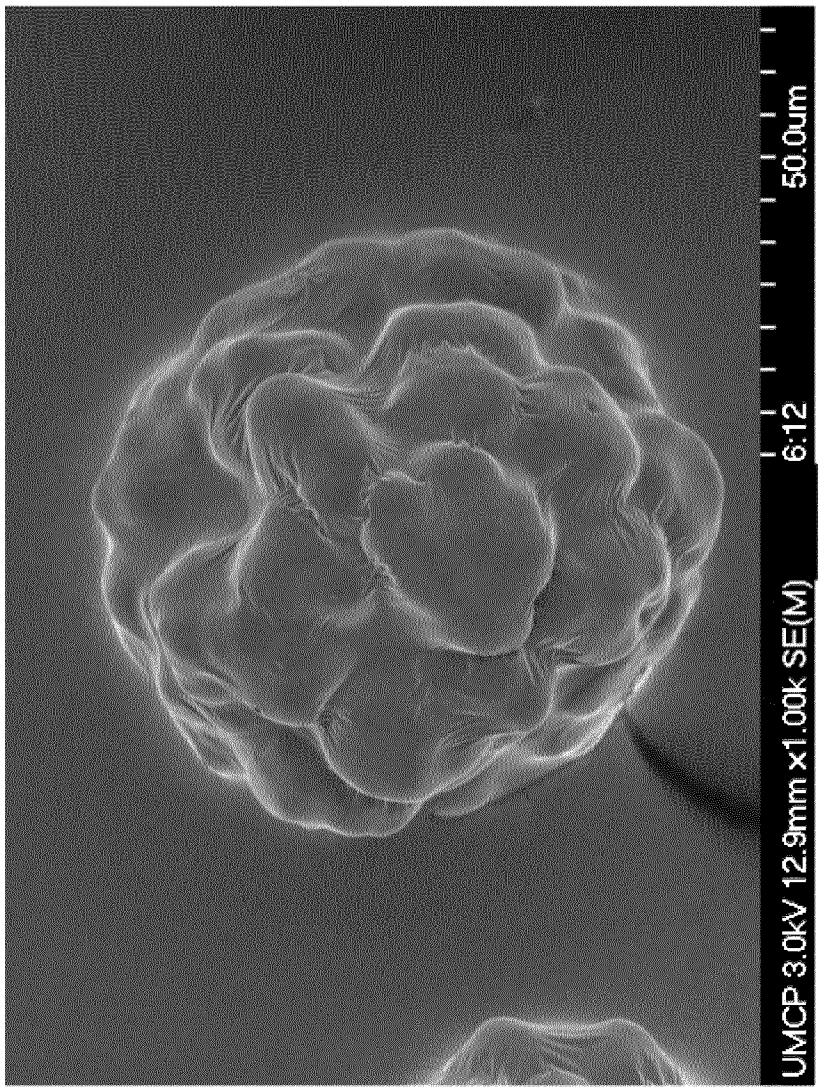

Figure 1

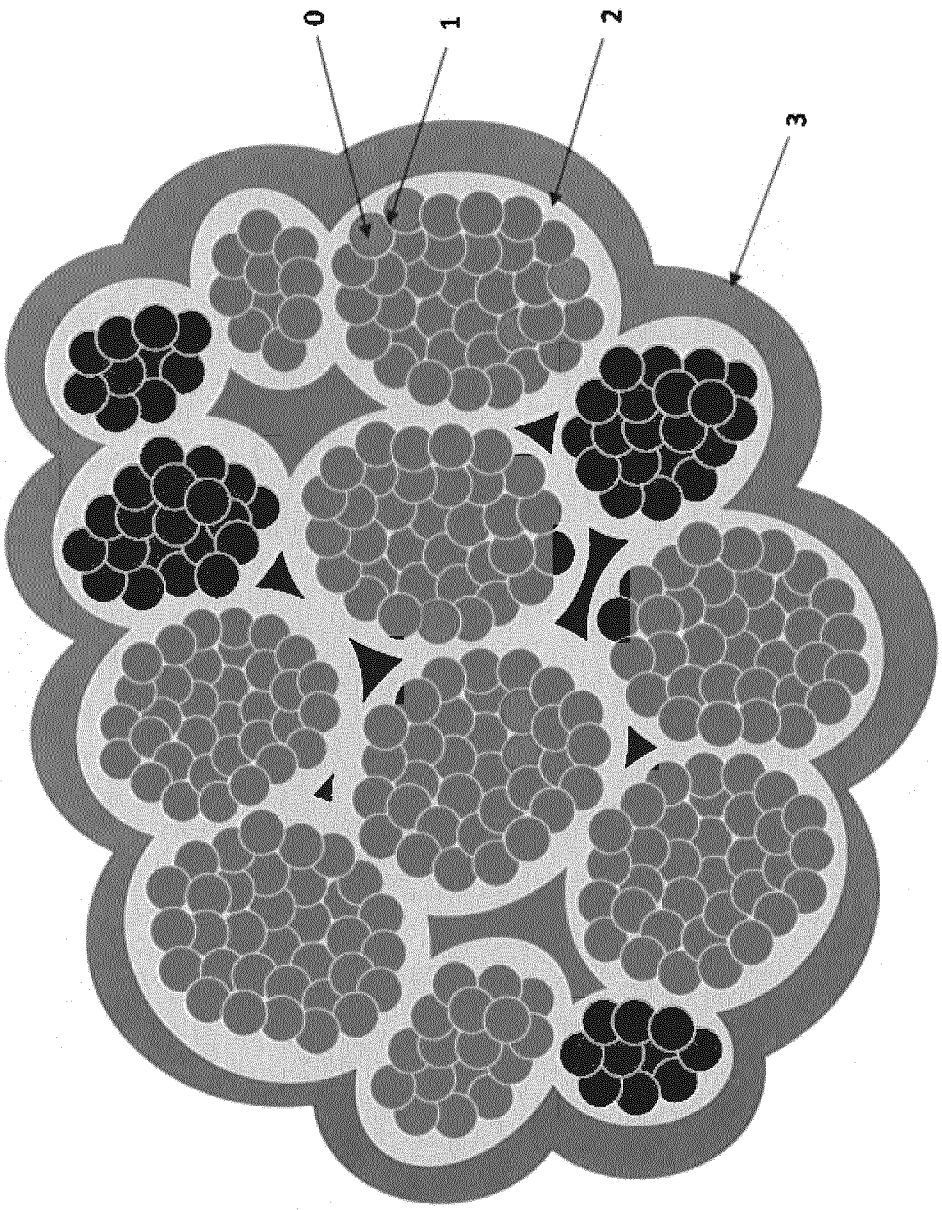

Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/056306

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/50
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/026307 A2 (FIRMENICH & CIE [CH]; BOUQUERAND PIERRE-ETIENNE [FR] ET AL.) 8 March 2007 (2007-03-08) the whole document claims 1-16; examples 1-7 examples 1-2,5-6	1-15
X	WO 97/13416 A1 (PORZIO MICHAEL A [US]; MADSEN MICHAEL G [US]) 17 April 1997 (1997-04-17) the whole document claims 1-19; examples 1-7	1-15
Y	WO 2008/017962 A2 (OCEAN NUTRITION CANADA LTD [CA]; YULAI JIN [CA] ET AL.) 14 February 2008 (2008-02-14) the whole document claims 1-383	1-15

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent 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 when the document is taken alone

"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

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2020	12/05/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Felder, Christian

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/056306

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93/19622 A2 (TASTEMAKER [US]) 14 October 1993 (1993-10-14) the whole document claims 1-29 -----	1-15

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2020/056306

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