

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

(19) World Intellectual Property

Organization

International Bureau



(10) International Publication Number

WO 2018/189584 A1

(43) International Publication Date

18 October 2018 (18.10.2018)

(51) International Patent Classification:

A61K 9/48 (2006.01)

(21) International Application Number:

PCT/IB2018/000448

(22) International Filing Date:

10 April 2018 (10.04.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/485,854 14 April 2017 (14.04.2017) US

(71) Applicant: CAPSUGEL BELGIUM NV [BE/BE]; Rijksweg 11, Bornem, B-2880 (BE).

(72) Inventors: TARDY, Claire Genevieve, Odile; C/o Capsugel Belgium Nv, Rijksweg 11, B-2880 Bornem (BE). TAKUBO, Takahisa; C/o Capsugel Belgium Nv, Rijksweg 11, B-2880 Bornem (BE).

(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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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, 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).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

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

WO 2018/189584 A1

(54) Title: PULLULAN CAPSULES

(57) Abstract: The instant disclosure provides a capsule composition comprising pullulan, a setting system and a surfactant system that is a sucroglyceride or a sugar fatty acid ester, and methods for making such capsules.

## PULLULAN CAPSULES

### **CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of U.S. Provisional Application No. 62/485,854, filed April 14, 2017, which is herein incorporated by reference in its entirety.

### FIELD

[0002] The present application relates to capsules comprising pullulan, to film forming compositions comprising pullulan, and to methods for making capsules.

### SUMMARY

[0003] Hard and soft capsules comprising pullulan are known. Pullulan provides a number of advantages over other conventional capsule film forming polymers such as gelatin or hydroxypropyl methyl cellulose. Pullulan is a natural product of non-animal origin made without the need for chemical modification. High product quality consistency can be obtained by controlling the fermentation process. The resulting films formed with pullulan have excellent homogeneity and transparency. In addition, such films have very low oxygen permeability. Accordingly, capsules made from pullulan are particularly useful for the filling of oxygen sensitive products such as fish and vegetable oils. Such films and resulting capsules made from pullulan also have relatively low water content, and exhibit high stability over storage, such as with respect to mechanical and dissolution properties.

[0004] The natural origin of pullulan and its superior properties as a film forming material has made pullulan a desired polymer for the manufacture of capsules having ingredients of all natural origin. This would enable capsules made with pullulan to meet the requirements for "organic" labeling. Notwithstanding the commercial need for a capsule meeting the organic labeling requirements, no satisfactory pullulan capsules have to date been developed that meet the organic labeling requirements.

[0005] In one embodiment, a capsule comprises: pullulan in an amount of at least 70wt% of the capsule; a setting system in an amount of at least 0.01wt% of the capsule; and a surfactant comprising a sucroglyceride or a sugar fatty acid ester or mixture thereof. In one embodiment, the surfactant is present in an amount of at least 0.2wt% of the capsule. The wt% amounts are exclusive of water present in the capsule.

[0006] In another embodiment, a capsule consists essentially of: pullulan in an amount of at least 70wt% of the capsule; a setting system in an amount of at least 0.01wt% of the capsule; and a surfactant selected from the group consisting of sucroglycerides, sugar fatty acid sugar esters, and mixtures thereof in an amount of at least 0.2wt% of the capsule. The wt% amounts are exclusive of water present in the capsule.

[0007] In another embodiment, the pullulan used to manufacture the capsule is manufactured using an organic fermentation process.

[0008] In another embodiment, the sugar fatty acid ester comprises a sugar head group selected from the group consisting of glucose, fructose, galactose, sucrose, maltose, trehalose, lactose, and raffinose.

[0009] In another embodiment, the sucroglyceride or the sugar fatty acid ester comprises a lipophilic group derived from the fatty acid esters of a vegetable oil selected from the group consisting of coconut oil, palm oil, palmist oil, soy oil, rapeseed oil, sunflower oil, cottonseed oil, peanut oil, olive oil, canola oil, castor oil, corn oil, flaxseed oil, safflower oil, and sesame oil.

[0010] In another embodiment, the surfactant is a sucrose fatty acid ester.

[0011] In another embodiment, the surfactant is a sucroglyceride.

[0012] In another embodiment, the surfactant is derived from the fatty acids of coconut oil.

[0013] In another embodiment, the surfactant is sucrose cocoate.

[0014] In another embodiment, the surfactant is present in an amount of from 0.2wt% to 2wt% of the capsule composition, or from 0.4wt% to 1.5wt% of the capsule composition, or from 0.5wt% to 1wt% of the capsule composition (exclusive of water).

[0015] In another embodiment, the setting system comprises carrageenan, gellan or agar. In one embodiment, the setting system comprises carrageenan and cations. In another embodiment, the setting system comprises agar and cations.

[0016] In one embodiment, the capsules have a Ca<sup>2+</sup> content of at least 200mg/kg, or at least 300mg/kg, or even at least 500 mg/kg.

[0017] In one embodiment, the capsules have a Mg<sup>2+</sup> content of at least 30mg/kg, or at least 40 mg/kg, or even at least 50mg/kg.

[0018] In one embodiment, the capsules have a ratio of K<sup>+</sup>/(Mg<sup>2+</sup> + Ca<sup>2+</sup>) that is less than 50, or less than 40, or less than 30, or even less than 20. In another embodiment, the capsule further comprises at least one sequestering agent.

[0019] In another embodiment, the capsule further comprising plasticizers or/and flavoring agents.

[0020] In another embodiment, the capsule further comprises coloring agents in a range from about 0% to 10% based upon the weight of the composition.

[0021] In another embodiment, the capsule comprises a coating.

[0022] In another embodiment, a caplet is encapsulated in the capsule.

[0023] In another embodiment, a method for manufacturing the capsule of claim 1 or 2, comprises:

[0024] a) providing an aqueous dipping composition comprising pullulan, the setting system, and the surfactant;

[0025] b) dipping mold pins in the aqueous dipping composition;

[0026] c) extracting the mold pins from the aqueous dipping composition such that a film is formed over each of the mold pins;

[0027] d) drying the film to form a solid coating on the mold pins;

[0028] e) removing the solid coating from the mold pins to provide capsule shells.

[0029] In another embodiment, the mold pins are lubricated with a mixture of lecithin and a vegetable oil.

[0030] In another embodiment, the solid coating is lubricated with a mixture of lecithin and a vegetable oil.

[0031] In another embodiment, the mold pins are lubricated with a sucroglyceride or sugar fatty acid ester. In another embodiment, the mold pins are lubricated with a mixture of a sucroglyceride and lecithin.

[0032] In another embodiment, the lecithin is selected from the group consisting of soybean lecithin, peanut lecithin, cottonseed lecithin, sunflower lecithin, rapeseed lecithin, corn lecithin, and groundnut lecithin. In a preferred embodiment, the lecithin is sunflower lecithin.

[0033] In another embodiment, the vegetable oil is selected from the group consisting of coconut oil, palm oil, palmist oil, soy oil, rapeseed oil, sunflower oil, cottonseed oil, peanut oil, olive oil, canola oil, castor oil, corn oil, flaxseed oil, safflower oil, and sesame oil.

[0034] In another embodiment, the lubricant comprises a mixture of coconut oil and sunflower lecithin.

[0035] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the claimed subject matter.

### **DETAILED DESCRIPTION**

[0036] **Definitions**

[0037] As used herein, reference to an element by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present, unless the context clearly requires that there is one and only one of the elements. The indefinite article "a" or "an" thus usually means "at least one." The disclosure of numerical ranges should be understood as referring to each discrete point within the range, inclusive of endpoints, unless otherwise noted. The term "about" as used in the disclosure of numerical ranges indicates that deviation from the stated value is acceptable to the extent that the deviation is the result of measurement variability and/or yields a product of the same or similar properties.

[0038] As used herein, "w/w %" and "wt%" means by weight as a percentage of the total weight.

[0039] In one aspect, a composition comprises pullulan, a setting system, water and a surfactant system. For example, a composition can contain from 75% to 95% by weight of pullulan, from 0.1% to 15% by weight of the setting system, and from 0.2wt% to 3wt% of the surfactant. For capsule compositions, wt% is based on total weight of contents of the capsule exclusive of any water present in the composition.

[0040] **Pullulan**

[0041] Pullulan (CAS number 9057-02-7; chemical synonyms 1,4-1,6- $\alpha$ -D-Glucan, 1,6- $\alpha$ -linked maltotriose) is a polysaccharide polymer consisting of maltotriose units. Three glucose units in maltotriose are connected by an  $\alpha$ -1,4 glycosidic bond, whereas consecutive maltotriose units are connected to each other by an  $\alpha$ -1,6 glycosidic bond. Maltotetraose units consisting of four 1,4-linked glucose molecules also occur, probably randomly, but are generally rare (about 6%). There is also evidence for a rare occurrence of branching points where poly-maltotriosyl side-chains are attached to the main chain by a 1,3-glycosidic bond.

[0042] Pullulan is generally produced from starch by the fungus *Aureobasidium pullulans*. Pullulan has good film forming properties and a particularly low oxygen permeability. Its existence was reported for the first time in 1938. Hayashibara Company started the commercial production in 1976.

[0043] In one embodiment, the pullulan has low amounts of mono-, di-, and oligosaccharides. Pullulan can be made free of mono-, di-, and oligosaccharides either through a post-manufacturing process

step (e.g. precipitation of the mono-, di-, and oligosaccharides from a sample of a commercial pullulan grade in ethanol) or from its very production, by choosing appropriate fermentation conditions.

[0044] In one embodiment, the pullulan has an average molecular weight comprised between about 10 kDa to 1,000,000 kDa, preferably between 100 KDa and 750 KDa, more preferably between 200 KDa and 500 KDa. A 10 wt% aqueous solution of pullulan may have a viscosity of from 100mm<sup>2</sup>/s to 180mm<sup>2</sup>/s at 30 °C.

[0045] In one embodiment, pullulan is manufactured using an organic fermentation process. In one such process the fermentation media contains calcium phosphate and magnesium chloride. This results in a capsule containing an excess of calcium and magnesium relative to monovalent cations such as potassium. In one embodiment, the capsules have a Ca<sup>2+</sup> content of at least 200mg/kg, or at least 300mg/kg, or even at least 500 mg/kg. In another embodiment, the capsules have a Mg<sup>2+</sup> content of at least 30mg/kg, or at least 40 mg/kg, or even at least 50mg/kg. In one embodiment, the ratio of K<sup>+</sup>/(Mg<sup>2+</sup> + Ca<sup>2+</sup>) is less than 50, or less than 40, or less than 30, or even less than 20. A process for making pullulan using an organic manufacturing process is disclosed more fully in US provisional patent application no. 62/485,855 filed April 14, 2017, and filed as PCT/US2018/026663, on April 9, 2018, both incorporated in their entireties by reference.

[0046] Setting System

[0047] The addition of a setting system, preferably based on polysaccharides, to pullulan solutions enables the adaptation of specific and desired gelling properties for the production of hard pullulan capsules by a conventional dipping process. In the dip molding process, the aqueous film forming pullulan solution from which the capsules are made remains on the mold pins after dipping, and does not flow down the pins. Otherwise the obtained film will not have the desired uniform thickness.

[0048] In one embodiment the setting system comprises a hydrocolloid or mixtures of hydrocolloids. Suitable hydrocolloids or mixtures thereof may be selected from natural seaweeds, natural seed gums, natural plant exudates, natural fruit extracts, biosynthetic gums, gelatines, and polysaccharides such as starch or cellulose derivatives.

[0049] In one embodiment, the polysaccharides are selected from the group comprising alginates, agar gum, guar gum, locust bean gum (carob), carrageenan, tara gum, gum arabic, ghatti gum, Khaya grandifolia gum, tragacanth gum, karaya gum, pectin, arabian (araban), xanthan, gellan, starch, Konjac mannan, galactomannan, funoran, and other exocellular polysaccharides. Preferred are exocellular polysaccharides.

[0050] Preferred exocellular polysaccharides for use in the present invention are selected from the group comprising xanthan, acetan, gellan, welan, rhamsan, furcelleran, succinoglycan, scleroglycan, schizophyllan, tamarind gum, curdlan, and dextran.

[0051] In a further preferred embodiment of the present invention the hydrocolloids of the setting system are kappa-carrageenan or gellan gum or combinations like xanthan with locust bean gum or xanthan with konjac mannan.

[0052] In one embodiment, the setting system is kappa-carrageenan with cations. In another embodiment, the setting system is gellan gum with cations. In another embodiment the setting system is agar with cations. These setting systems produce high gel strength at low concentrations and have good compatibility with pullulan.

[0053] As mentioned above, the setting system may contain a cation containing salt. The cation containing salt in the setting system serves to enhance the setting ability of the gelling agents. Preferably, the salt comprises cations such as K<sup>+</sup>, Li<sup>+</sup>, Na<sup>+</sup>, NH<sub>4</sub><sup>+</sup>, Ca<sup>2+</sup>, or Mg<sup>2+</sup>, etc. The amount of cations in the capsule is from 0.01 to 1wt%, preferably less than 3wt%.

[0054] Surfactant

[0055] The pullulan containing compositions further comprise a surfactant that is selected from the group consisting of sucroglycerides, sugar fatty acid esters, and mixtures thereof.

[0056] Sucroglycerides are obtained by reacting sucrose with an edible fat or oil with or without the presence of a solvent. They consist of a mixture of mono- and di-esters of sucrose and fatty acids together with mono-, di- and triglycerides from the fat or oil. Exemplary fats and oils include lard oil, tallow, coconut, palm oil, and palmist oil. In one embodiment, the sucroglyceride is selected from the group consisting of coconut oil sucroglyceride, palm oil sucroglyceride, palmist oil sucroglyceride, soy oil sucroglyceride, rapeseed oil sucroglyceride, sunflower oil sucroglyceride, cottonseed oil sucroglyceride, palmist oil sucroglyceride, peanut oil sucroglyceride, olive oil sucroglyceride, canola oil sucroglyceride, castor oil sucroglyceride, corn oil sucroglyceride, flaxseed oil sucroglyceride, safflower oil sucroglyceride, and sesame oil sucroglyceride.

[0057] A preferred sucroglyceride is coconut oil sucroglyceride, or sucrose cocoate. Sucrose cocoate is a thick liquid that is pale yellow in color and derived from the fatty acids in coconut oil.

[0058] Sugar fatty acid esters are nonionic surfactants consisting of a sugar as the hydrophilic group and a fatty acid as lipophilic group. They are also referred to as sugar esters. In one embodiment, the only surfactants present in the composition are sugar fatty acid esters. Sugar ester fatty acids may be prepared from sugar and methyl and ethyl esters of food fatty acids by esterification in the presence of a catalyst or by extraction from the appropriate glyceride, such as from sucroglycerides.

[0059] Exemplary sugars that may be used as the head group include monosaccharides such as glucose, fructose, and galactose, disaccharides such as sucrose, maltose, trehalose and lactose, and trisaccharides such as raffinose.

[0060] Exemplary fatty acids that may be used as the lipophilic group include fatty acids having from 6 to 18 carbon atoms, including caprylic acid (C8), decanoic acid (C10), lauric acid (C12), myristic acid (C14), palmitic acid (C16) and oleic acid (C18). The lipophilic group may be derived from the fatty acid esters from vegetable oils, such as those selected from the group consisting of coconut oil, palm oil, palmist oil, soy oil, rapeseed oil, sunflower oil, cottonseed oil, peanut oil, olive oil, canola oil, castor oil, corn oil, flaxseed oil, safflower oil, and sesame oil.

[0061] In a preferred embodiment, the vegetable oil is coconut oil.

[0062] In one embodiment, the sugar fatty acid ester is a sucrose fatty acid ester. Such sucrose esters may be formed from combining sucrose with particular fatty acids, and include sucrose laurate, sucrose stearate, sucrose erucate, sucrose oleate, sucrose palmitate, sucrose myristate, sucrose behenate, and sucrose ricenoleate. It is to be understood that such sucrose esters include the mono-, di-, tri- and poly-esters.

[0063] In one embodiment, the surfactant may also contain lecithin. The lecithin may be selected from any naturally occurring plant based source. In one embodiment, the lecithin is selected from the group

consisting of soybean lecithin, peanut lecithin, cottonseed lecithin, sunflower lecithin, rapeseed lecithin, corn lecithin, and groundnut lecithin. In a preferred embodiment, the lecithin is sunflower lecithin.

[0064] The surfactant is present in an amount sufficient to aid in film formation on the mold pins during manufacturing. In one embodiment, the surfactant is present in an amount of at least 0.2wt% of the capsule composition (exclusive of water content). In one embodiment, the amount of surfactant is present in an amount of from 0.2wt% to 2wt% of the capsule composition, or from 0.4wt% to 1.5wt% of the capsule composition, or from 0.5wt% to 1wt% of the capsule composition (exclusive of water).

[0065] Water

[0066] The capsules also generally comprise between 2wt% and 20wt%, preferably between about 5wt% and 15wt% of moisture or water over the total weight of the capsule. Unless otherwise indicated, when discussing capsule compositions, moisture and water are terms that can be used interchangeably. The amount of water present in the capsule compositions depends on both the materials present in the capsule, as well as the relative humidity of the environment in which the capsules are stored. (Accordingly, relative amounts of materials in the capsule compositions is determined relative to compositions not including water, since the amount of water is variable depending on the relative humidity of the environment.)

[0067] Typically, a capsule of the invention is dried to water content between about 10wt% and 15wt%. However, water content can be brought to lower % by e.g. further drying, capsule shell storage at low relative humidity or filling the capsule with hygroscopic substances.

[0068] Optional Materials

[0069] In addition to the pullulan, setting system, surfactant and water, the capsule compositions may contain a variety of other materials and processing aids, including those typically used in the manufacture of capsules.

[0070] Optionally, the capsule composition may further comprise at least one sequestering agent. Sequestering agents may be selected from the group consisting of ethylenediaminetetraacetic acid, acetic acid, boric acid, citric acid, edetic acid, gluconic acid, lactic acid, phosphoric acid, tartaric acid, or salts thereof, methaphosphates, dihydroxyethylglycine, lecithin or beta cyclodextrin and combinations thereof. Especially preferred is ethylenediaminetetraacetic acid or salts thereof or citric acid or salts thereof.

[0071] In the case that gellan is used as gelling agent, the compositions preferably contain a sequestering agent to improve the capsule solubility. The preferred sequestering agents are ethylenediaminetetraacetic acid or salts thereof and citric acid and salts thereof. The amount is preferably less than xwt% in the capsule compositions.

[0072] In another embodiment the capsule composition may additionally comprise pharmaceutically or food acceptable coloring agents in the range of from 0.01wt% to 10wt%. The coloring agents may be selected from the group consisting of azo-, guinophthalone-, triphenylmethane-, xanthene- or indigoid dyes, iron oxides or hydroxides, titanium dioxide or natural dyes or mixtures thereof. Examples are patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D+C red 33, D+C red 22, D+C red 26, D+C red 28, D+C yellow 10, yellow 2 G, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, brilliant black BN, carbon black, iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, anthocyanines, turmeric, cochineal extract, chlorophyllin, canthaxanthin, caramel, or betanin.

[0073] In addition, the capsule compositions may optionally further include other minor components such as titanium dioxide and/or colorants such as mineral colorants, natural colorants, and tar colorants, anti-oxidants and the like.

[0074] In one embodiment, the pullulan composition optionally comprises one or more pharmaceutically or food acceptable plasticisers. In one embodiment, the one or more plasticizers are selected in the group of plasticizers typically used in the manufacture of hard capsule shells and in particular in the group consisting of: phthalic esters (e.g. dimethyl-, diethyl-, dibutyl-, diisopropyl- and diethyl-phtalate); citric esters (e.g. triethyl-, tributyl-, acetyltriethyl- and acetyltributyl-citrate); phosphoric esters (e.g. triethyl-, tricresyl, triphenyl-phosphate); oils (e.g. purified mineral oils, ricin oil, corn oil, cotton oil); butyl stearate; dibutyl sebacate; dibutyl tartrate; diisobutyl adipate, glycerol monostearate; glycerol triacetate; tributyrin; oleic acid; stearic acid; cetyllic acid; myristic acid; propylene glycol; glycerol; PEG 4000, PEG 6000, and mixtures thereof.

[0075] In one embodiment, the aqueous composition of the invention contains one or more pharmaceutically or food acceptable sweeteners and/or flavoring agents. Such sweeteners and flavoring agents are typically present in amounts from 0.01wt% to 1wt% of the pullulan composition.

[0076] Method for Making Capsules

[0077] In one aspect the capsules are manufactured by a conventional dip molding process as normally used in the production of conventional pullulan capsules. Consequently the use of a surfactant system comprising a sucroglyceride or sugar fatty acid ester enables hard pullulan capsules to be produced with the same equipment used for the production of conventional hard pullulan capsules in the same range of process conditions. Furthermore capsules produced from compositions of the present invention have the same dimensional specifications and allow the use of the existing filling machinery and do not require specific and new equipment for the filling process.

[0078] Capsules according to the present disclosure are typically made via a dip-molding process. Dip-molding processes for making acid-resistant two-piece hard capsules comprise the steps of:

[0079] a) providing an aqueous dipping composition comprising pullulan, a setting system, and a surfactant that is a sucroglyceride, a sugar fatty acid ester or mixture thereof;

[0080] b) dipping mold pins in the aqueous dipping composition;

[0081] c) extracting the mold pins from the dipping composition such that a film is formed over each of the mold pins;

[0082] d) drying the film to form a solid coating on the mold pins;

[0083] e) optionally applying an external lubricant to the solid coating on the mold pins;

[0084] f) removing the solid coating from the mold pins to provide capsule shells.

[0085] Steps (a) to (f) are typically to be performed in the order they are presented.

[0086] As described herein, "finished capsule shells" are those capsule shells for which step (f) has been completed.

[0087] In step (a) the aqueous dipping composition is prepared by combining water, pullulan, the setting system, and the sugar fatty acid ester. In one embodiment, the aqueous composition of the invention has a total amount of solids typically comprised between about 10% and 55% by weight, preferably between about 15% and 40%, more preferably between 20% and 30% by weight over the total weight of the

composition. For amounts of materials in the aqueous dipping composition, wt% is given based on the total weight of the aqueous dipping composition including water.

[0088] In one embodiment, the aqueous composition of the invention has a total amount of solids so that the viscosity of the aqueous dipping composition at a temperature comprised between about 50° C and 70° C is between about 500 cPs and 5000 cPs, preferably between about 1000 to 3000 cps.

[0089] In one embodiment, the concentration of pullulan in the aqueous dipping composition is in a range of 10 to 60wt%, preferably 10 to 50wt%, more preferably 15 to 40wt%, and most preferably 10 to 40wt%.

[0090] The amount of the setting system is preferably in the range of 0.01 to 5% by weight and especially preferred 0.03 to 1.0% in the aqueous dipping composition. The preferred salt concentration in the aqueous dipping concentration is less than 2wt%.

[0091] In another embodiment of the present invention, the amount of the optional sequestering agent is less than 5% by weight, preferably less than 3%, more preferably 0.01% to 3% by weight, even more preferably 0.5% to 2% by weight especially 0.01 to 1% by weight of the aqueous dipping composition.

[0092] In addition, the aqueous dipping compositions may optionally further include other minor components such as titanium dioxide and/or colorants such as mineral colorants, natural colorants, and tar colorants, anti-oxidants and the like. In one embodiment, the coloring agents, or mixtures thereof are present in an amount ranging from about 0 to about 5% by weight, e.g., from about 0 to about 2.5% by weight, and from about 0 to about 1.5% by weight over the total weight of the aqueous dipping composition.

[0093] In step (b) mold pins are dipped in the aqueous dipping composition. The relative temperatures of the aqueous dipping composition and mold pins are chosen to result in film formation on the mold pins once the mold pins are dipped into the aqueous composition. In this embodiment the aqueous composition at the time the mold pins are dipped is kept at a temperature of from 45° C to 65° C, preferably from 50° C to 65° C. The temperature range of the pins is 25-35° C, meaning that this is the mold pin temperature when mold pins are dipped.

[0094] In step (c), the mold pins are extracted from the aqueous dipping composition such that a film is formed over each of the mold pins. After being withdrawn from the aqueous dipping composition, the mold pins can be turned from a "top- down" dipping position to a "top-up" drying position according to conventional capsule dip molding processes. In this step the pins are rotated about a horizontal axis of about 180° with respect to the dipping position of step (c).

[0095] In step (d), the film on the mold pins is dried. The purpose of the drying step (d) is to reduce the water content (also referred to herein as "moisture") in the capsule shells on the mold pins. In one embodiment, drying occurs at a temperature above the gelling temperature of the aqueous dipping composition so as to obtain molded capsule shells on the pins. The drying step is preferably carried out at a temperature of less than 65° C, preferably less than 60° C, even more preferably from 25° C to 45° C. Step (d) is typically carried out for a period of time from 30 to 60 minutes, preferably not exceeding the above identified temperatures. Generally, the water content in the molded capsule shells is reduced from around 80% to around 10 to 15% by weight, based on the total weight of the molded capsule shells (measured at room conditions).

[0096] In step (f) the solid coating is removed from the mold pins to provide capsule shells. The solid coating may be removed using any conventional manufacturing technique.

[0097] The solid coating in step (e) and the mold pins may be lubricated. In the case of the solid coating, the lubricant enhances gliding of the capsule shells to facilitate filling and closing. With respect to the mold pins, the lubricant facilitates removal of the capsule shells. In yet another aspect of the invention, the lubricant used for the external application to the solid coatings and/or to the mold pins is selected from a mixture of lecithin and a vegetable oil. The lecithin may be selected from any naturally occurring plant based source. In one embodiment, the lecithin is selected from the group consisting of soybean lecithin, peanut lecithin, cottonseed lecithin, sunflower lecithin, rapeseed lecithin, corn lecithin, and groundnut lecithin. In a preferred embodiment, the lecithin is sunflower lecithin.

[0098] The vegetable oil may be selected from any naturally occurring vegetable oil. In one embodiment, the vegetable oil is selected from the group consisting of coconut oil, palm oil, palmist oil, soy oil, rapeseed oil, sunflower oil, cottonseed oil, peanut oil, olive oil, canola oil, castor oil, corn oil, flaxseed oil, safflower oil, and sesame oil. In a preferred embodiment, the vegetable oil is coconut oil.

[0099] The relative amount of lecithin to vegetable oil ranges from 90/10 lecithin/vegetable oil to 50/50 lecithin/vegetable oil.

[0100] In one embodiment, the lubricant comprises a mixture of coconut oil and sunflower lecithin. The mixture of sunflower lecithin and coconut oil is at a ratio of between 90/10 to 50/50 sunflower lecithin/coconut oil, more preferably between 80/20 and 60/40 sunflower lecithin/coconut oil.

[0101] In another embodiment, the lubricant comprises a sucroglyceride or sugar fatty acid ester. In one embodiment, the lubricant is a sucroglyceride, preferably sucrose cocoate. In another embodiment, the lubricant comprises a sugar fatty acid ester derived from coconut oil. The lubricant may also optionally comprise lecithin in addition to the sucroglyceride or sugar fatty acid ester in a ratio of from 1/99 to 50/50 lecithin/sucrose glyceride or lecithin/sugar fatty acid ester.

[0102] In one embodiment, the lubricant comprises a mixture of sucrose cocoate and sunflower lecithin in a ratio of from 1/99 to 50/50 sunflower lecithin/sucrose cocoate. In one embodiment, the lubricant consists essentially of a mixture of sucrose cocoate and sunflower lecithin in a ratio of from 1/99 to 50/50 sunflower lecithin/sucrose cocoate.

[0103] The molded capsule shells mentioned to above, generally refer to both bodies and caps, depending on the shape of the mold pin. Thus, after step (e) the dried capsule shells on the dipping pins can be processed according to conventional steps. This means that in general after step (e), the capsule shells (bodies and caps) are stripped from the pins. This step can be followed by cutting the stripped shells to a desired length.

[0104] Methods of Use

[0105] The capsule compositions are suitable for use in pharmaceutical, veterinary, food, cosmetic or other products.

[0106] Drugs (i.e. medicaments) suitable for use in the capsules described herein may take any form and be for any treatment of a human or animal subject. This includes not only pharmaceutical compounds but also dietary supplements such as vitamins, minerals and the like. The drug may be in a state selected from solid or liquid, preferably solid, at room temperature and atmospheric pressure, and comprises one or more active compounds. The medicament may be solid and in the form of spray dried dispersions, pellets, granules and the like.

[0107] Suitable compounds (and generally encompassed by the term "medicament" as used herein) for delivery according to the disclosure include, but are not limited to, particulate, powder, waxy, liquid, and/or pellet forms of the following:

[0108] a) pharmaceuticals (also called pharmaceutical actives) such as betamethasone, thioctic acid, sotalol, salbutamol, norfenefrine, silymahn, dihydroergotamine, buflomedil, etofibrate, indomethacin, oxazepam, acetyl-digitoxins, piroxicam, haloperidol, isosorbide mononitrate, amithptyline, diclofenac, nifedipine, verapamil, pyritinol, nitrendipine, doxy-cycline, bromhexine, methylprednisolone, clonidine, fenofibrate, allopurinol, pirenzepine, levothyroxine, tamoxifen, metildigoxin, o-(B-hydroxyethyl)-rutoside, propicillin, aciclovir- mononitrate, paracetamol, naftidrofuryl, pentoxifylline, propafenone, acebutolol, 1-thyroxin, tramadol, bromocriptine, loperamide, ketofinen, fenoterol, cadobesilate, propranolol, minocycline, nicergoline, ambroxol, metoprolol, B-sitosterin, enalaprilhydrogenmaleate, bezafibrate, isosorbide dinitrate, gallopamil, xantinolnicotinate, digitoxin, flunitrazepam, bencyclane, depanthenol, pindolol, lorazepam, diltiazem, piracetam, phenoxymethylpenicillin, furosemide, bromazepam, flunarizine, erythromycin, metoclopramide, acemetacin, ranitidine, biperiden, metamizol, doxepin, dipotassiumchlorazepat, tetrazepam, estramustinephosphate, terbutaline, captopril, maprotiline, prazosin, atenolol, glibenclamid, cefaclor, etilefrin, cimetidine, theophylline, hydromorphone, ibuprofen, primidone, clobazam, oxaceprol, medroxyprogesterone, flecainide, Mg pyhdoxal-5-phosphateglutamate, hymechromone, etofyllineclofibrate, vincamine, cinnarizine, diazepam, ketoprofen, flupentixol, molsidomine, glibornuhde, dimethindene, melperone, soquinolol, dihydrocodeine, clomethiazole, clemastine, glisoxepid, kallidino-genase, oxyfedhne, baclofen, carboxymethylcystsin, thiorodoxin, betahistine, 1-tryptophan, myrtol, bromelain, prenylamine, salazosulfapyridine, astemizole, sulpiride, benzerazid, dibenzepin, acetylsalicylic acid, miconazole, nystatin, ketoconazole, sodium picosulfate, colestyramate, gemfibrozil, rifampin, fluocortolone, mexiletine, amoxicillin, terfenadine, mucopolysaccharidpolysulfuric acid, triazolam, mianserin, tiaprofensaure, ameziniummethylsulfate, mefloquine, probucol, quinidine, carbamazepine, Mg-1- aspartate, penbutolol, piretanide, amitriptyline, caproteron, sodium valproinate, mebeverine, bisacodyl, 5-amino-salicylic acid, dihydralazine, magaldrate, phenprocoumon, amantadine, naproxen, carteolol, famotidine, methyldopa, auranofine, estriol, nadolol, levomepromazine, doxorubicin, medofenoxt, azathioprine, flutamide, norfloxacin, fendiline, prajmaliumbitartrate, aescin acromycin, anipamil, benzocaine, [beta]-carotene, cloramphenicol, chlorodiazepoxid, chlormadinoneacetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, dicumarol, digoxin, drotaverine, gramicidine, griseofulvin, hexobarbital hydrochlorothiazide, hydrocortisone, hydroflumethiazide, ketoprofen, Ionetil, medazepam, mefruside, methandrostenolone, sulfaperine, nalidixic acid, nitrazepam, nitrofurantoin, estradiol, papaverine, phenacetin, phenobarbital, phenylbutazone, phenytoin, prednisone, reserpine, spironolactine, streptomycin, sulfamethizole, sulfamethazine, sulfamethoxoazole, sulfamethoxydiazinon, sulfathiazole, sulfisoxazole, testosterone, tolazamide, tolbutamide, trimethoprim, tyrothricin, antacids, reflux suppressants, antiflatulents, antidopaminergics, proton pump inhibitors, H2- receptor antagonists, cytoprotectants, prostaglandin analogues, laxatives, antispasmodics, antidiarrhoeals, bile acid sequestrants, opioids, beta-receptor blockers, calcium channel blockers, diuretics, cardiac glycosides, antiarrhythmics, nitrates, antianginals, vasoconstrictors, vasodilators, ACE inhibitors, angiotensin receptor blockers, alpha blockers, anticoagulants, heparin, antiplatelet drugs, fibrinolytic, anti-hemophilic factor, haemostatic drugs, hypolipidaemic agents, statins, hypnotics, anaesthetics, antipsychotics, antidepressants (including tricyclic antidepressants,

monoamine oxidase inhibitors, lithium salts, selective serotonin reuptake inhibitors), anti-emetics, anticonvulsants, antiepileptics, anxiolytics, barbiturates, movement disorder drugs, stimulants (including amphetamines), benzodiazepine, cyclopyrrolone, dopamine antagonists, antihistamines, cholinergics, anticholinergics, emetics, cannabinoids, 5-HT antagonists, analgesics, muscle relaxants, antibiotics, sulfa drugs, aminoglycosides, fluoroquinolones, bronchodilators, NSAIDs, anti-allergy drugs, antitussives, mucolytics, decongestants, corticosteroids, beta-receptor antagonists, anticholinergics, steroids, androgens, antidiabetics, gonadotropin, corticosteroids, growth hormones, insulin, antidiabetic drugs (including sulfonylurea, biguanide/metformin, and thiazolidinedione), thyroid hormones, antithyroid drugs, calcitonin, diphosphonate, vasopressin analogs, contraceptives, follicle stimulating hormone, luteinising hormone, gonadotropin release inhibitor, progestogen, dopamine agonists, oestrogen, prostaglandin, gonadorelin, clomiphene, tamoxifen, diethylstilbestrol, antimalarials, anthelmintics, amoebicides, antivirals, antiprotozoals, vaccines, immunoglobulin, immunosuppressants, interferon, monoclonal antibodies, and mixtures thereof;

[0109] b) vitamins, e.g., fat-soluble vitamins such as vitamins A, D, E, and K, and water soluble vitamins such as vitamin C, biotin, folate, niacin, pantothenic acid, riboflavin, thiamin, vitamin B6, vitamin B12, and mixtures thereof;

[0110] c) minerals, such as calcium, chromium, copper, fluoride, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium, sodium (including sodium chloride), zinc, and mixtures thereof;

[0111] d) dietary supplements such as herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites, as well as concentrates, metabolites, constituents, extracts of dietary ingredients, oils such as krill oil and mixtures thereof;

[0112] e) homoeopathic ingredients such as those listed in the Homeopathic Pharmacopoeia of the United States Revision Service (HPRS), and mixtures thereof. It must be recognized, of course, that the HPRS is periodically updated and that the present invention includes homeopathic ingredients that may be added to the HPRS;

[0113] f) probiotics and yeast, such as bacteria selected from the group consisting of Lactobacillus (Döderlein's bacilli) such as Lactobacillus crispatus, Lactobacillus jensinii, Lactobacillus johnsonii, Lactobacillus gasseri, Enterococcus faecium, or fungi selected from the group of Saccharomycetales such as *Saccharomyces boulardii*.

[0114] g) hormones, such as estrogen (i.e. a natural estrogen or a synthetic compound that mimics the physiological effect of natural estrogens) including, without limitation, estradiol (17-estradiol), estradiol acetate, estradiol benzoate, estradiol cypionate, estradiol decanoate, estradiol diacetate, estradiol heptanoate, estradiol valerate, 17a-estradiol, estriol, estriol succinate, estrone, estrone acetate, estrone sulfate, estropipate (piperazine estrone sulfate), ethynodiol (17a-ethynodiol, ethynodiol, ethynodiol, ethynodiol, ethynodiol), ethynodiol 3-acetate, ethynodiol 3-benzoate, mestranol, quinestrol, nitrated estrogen derivatives or combinations thereof; or progestin (i.e. natural or synthetic compounds that possesses progestational activity including, without limitation, nortestosterone, ethynodiol, deacetylorgestrel, hydroxyprogesterone, 19-norprogesterone, 3P-hydroxydesogestrel, 3-ketodesogestrel (etonogestrel), acetoxyprogrenolone, algestone acetophenide, allylestrenol, amgestone, anagestone acetate, chlormadinone, chlormadinone acetate, cyproterone,

ciproterone acetate, demegestone, desogestrel, dienogest, dihydrogesterone, dimethisterone, drospirenone, dydrogesterone, ethisterone (pregnenolone, 17a-ethynyltestosterone), ethynodiol diacetate, fluorogestone acetate, gastrinone, gestadene, gestodene, gestonorone, gestrinone, hydroxymethylprogesterone, hydroxymethylprogesterone acetate, hydroxyprogesterone, hydroxyprogesterone acetate, hydroxyprogesterone caproate, levonorgestrel (1-norgestrel), lynestrenol (lynoestrenol), mecirogestone, medrogestone, medroxyprogesterone, medroxyprogesterone acetate, megestrol, megestrol acetate, melengestrol, melengestrol acetate, nestorone, nomegestrol, norelgestromin, norethindrone (norethisterone) (19-nor-17a-ethynyltestosterone), norethindrone acetate (norethisterone acetate), norethynodrel, norgestimate, norgestrel (d-norgestrel and dl-norgestrel), norgestriene, normethisterone, progesterone, promegestone, quingestanol, tanaproget, tibolone, trimegestone, or combinations thereof.

[0115] Once filled, the capsules can be made tamper-proof by using any conventional technique in the field of hard capsules to make the joint permanent. Banding or sealing are suitable techniques. Sealing is a technique well known in the field of hard shell capsules. Various alternative techniques are currently used for this purpose. A suitable procedure is disclosed for example in US 4,539,060 and US 4,656,066.

[0116] In yet another embodiment of the invention, the compositions comprising pullulan, a setting system, water and a sucroglyceride or sugar fatty acid ester may be used to form films. Such films may be used for a variety of other purposes, such as for wrapping food, or for forming aspics or jellies.

[0117] It should be understood that the embodiments described herein are not limited thereto. Other embodiments of the present disclosure will be apparent to those skilled in the art from consideration of the specification and practice of the disclosed embodiments. The following examples should be considered as exemplary only, with a true scope and spirit of the present disclosure being indicated by the following claims.

**[0118] Example 1**

[0119] Capsules were made as follows. An aqueous dipping solution was prepared by first adding 443 liters of an aqueous solution of pullulan (22wt% pullulan) to a melt tank and heating the solution to 65 °C. 1.65 kg potassium chloride was mixed in 3 liters of 65 °C water, and the resulting solution was added to the melt tank and stirred. 460.5g of kappa carrageenan (available from CP Kelco, Denmark), was added to the melt tank as follows. An aliquot of 115.13g of carrageenan was mixed with 3 liters of cold water and then added to the melt tank and stirred. Three additional aliquots of 115.13g of carrageenan were similarly prepared and added to the melt tank. The solution was then mixed at 50 RPM for 60 minutes, and then placed under vacuum and mixed for an additional 60 minutes. The solution was then mixed for 60 minutes at 33 RPM under vacuum. 160 liters of the solution in the melt tank were then dispensed into a transfer tank. 1600g of a 12.5wt% aqueous solution of sucrose cocoate (ESAC 80 available from Tensac, Argentina) was then added to the transfer tank and stirred to form the dipping composition. Water was then added to achieve a viscosity of 800 cps.

[0120] Capsules were prepared using dip molding equipment. The aqueous dipping composition was heated to 65 °C. The pins were maintained at 30 °C.

[0121] The mold pins were lubricated with a mixture of sunflower lecithin and coconut oil at a ratio of 70/30 sunflower lecithin/coconut oil.

[0122] The resulting capsules had the following composition

[0123] Excluding water:

Ingredient	Wt%
Pullulan	97.43
Potassium chloride	1.61
Kappa Carrageenan	0.45
Sucrose cocoate	0.52

[0124] Including water:

Ingredient	Wt%
Pullulan	85.73
Potassium chloride	1.41
Kappa Carrageenan	0.39
Sucrose cocoate	0.45
Water	12.01

**[0125] Example 2**

[0126] In this example, capsules produced from organic pullulan made according to Example 1 (Capsule A) and Plantcaps® capsules from Capsugel, Greenwood, SC, (Capsule B) were analyzed for Mg<sup>2+</sup> and K<sup>+</sup> content using the standard protocol SM3111B using Flame Atomic Absorption Spectroscopy. In addition, Ca<sup>2+</sup> content in these capsule was also measured using the standard protocol SM3111D using Flame Atomic Absorption Spectroscopy. Each capsule batch was analyzed in triplicate. From this analysis it was determined that the concentration of both Mg<sup>2+</sup> and Ca<sup>2+</sup> is higher in Capsule A than Capsule B. In addition, Capsule A capsules have a lower ratio of monovalent cation (K<sup>+</sup>) to divalent cations (Mg<sup>2+</sup> and Ca<sup>2+</sup>).

**Table 1.** Results of Metal Analysis of Capsules

	Capsule A				Capsule B			
	Mg <sup>2+</sup> (mg/kg)	Ca <sup>2+</sup> (mg/kg)	K <sup>+</sup> (mg/kg)	<u>K+</u> (Mg <sup>2+</sup> +Ca <sup>2+</sup> ) )	Mg <sup>2+</sup> (mg/kg)	Ca <sup>2+</sup> (mg/kg)	K <sup>+</sup> (mg/kg)	<u>K+</u> (Mg <sup>2+</sup> +Ca <sup>2+</sup> ) )
Replicat e 1	58.6	704	7920	10.4	18.2	104	7500	61.4
Replicat e 2	58.2	680	7740	10.5	18.4	101	7410	62.1
Replicat e 3	59.4	680	7590	10.3	19	98.3	7560	64.5
Mean ±	58.7±0.	688±13.	7750±16	10.4±0.1	18.5±0.	101±2.	7490±7	62.6±1.6
St. Dev	6	9	5		4	9	5	

Values expressed in mg metal per kilogram capsule

## WHAT IS CLAIMED IS:

1. A capsule comprising:
  - a) pullulan in an amount of at least 70wt% of said capsule;
  - b) a setting system in an amount of at least 0.01wt% of said capsule;
  - c) a surfactant comprising a sucroglyceride or a sugar fatty acid ester or mixture thereof;wherein said wt% amounts are exclusive of water present in the capsule.
2. A capsule consisting essentially of:
  - a) pullulan in an amount of at least 70wt% of said capsule;
  - b) a setting system in an amount of at least 0.01wt% of said capsule;
  - c) a surfactant selected from the group consisting of sucroglycerides, sugar fatty acid sugar esters, and mixtures thereof in an amount of at least 0.2wt% of said capsule;wherein said wt% amounts are exclusive of water present in the capsule.
3. The capsule of claim 1 or 2 wherein said pullulan is manufactured using an organic fermentation process.
4. The capsule of claim 1 or 2 wherein said sugar fatty acid ester comprises a sugar head group selected from the group consisting of glucose, fructose, galactose, sucrose, maltose, trehalose, lactose, and raffinose.
5. The capsule of claim 1 or 2 wherein said sucroglyceride or said sugar fatty acid ester comprises a lipophilic group derived from the fatty acid esters of a vegetable oil selected from the group consisting of coconut oil, palm oil, palmist oil, soy oil, rapeseed oil, sunflower oil, cottonseed oil, peanut oil, olive oil, canola oil, castor oil, corn oil, flaxseed oil, safflower oil, and sesame oil.
6. The capsule of claim 1 or 2 wherein said surfactant is a sucrose fatty acid ester.
7. The capsule of claim 1 or 2 wherein said surfactant is a sucroglyceride.
8. The capsule of claim 6 or 7 wherein said surfactant is derived from the fatty acids of coconut oil.
9. The capsule of claim 1 or 2 wherein said surfactant is sucrose cocoate.
10. The capsule of any of the preceding claims wherein said surfactant is present in an amount of from 0.2wt% to 2wt% of the composition, or from 0.4wt% to 1.5wt% of the capsule composition, or from 0.5wt% to 1wt% of the capsule composition (exclusive of water).
11. The capsule according to any of the preceding claims, further comprising at least one sequestering agent.
12. The capsule according to any of the preceding claims, further comprising plasticizers or/and flavoring agents.

13. The capsule according to any of the preceding claims, further comprising coloring agents in a range from about 0% to 10% based upon the weight of the composition.

14. The capsule according to any of the preceding claims, wherein the capsule comprises a coating.

15. A caplet encapsulated in a capsule according to claim 1 or 2.

16. A method for manufacturing the capsule of claim 1 or 2, comprising:

a) providing an aqueous dipping composition comprising pullulan, said setting system, and said surfactant;

b) dipping mold pins in the aqueous dipping composition;

c) extracting the mold pins from the aqueous dipping composition such that a film is formed over each of the mold pins;

d) drying the film to form a solid coating on the mold pins;

e) removing the solid coating from the mold pins to provide capsule shells.

17. The method of claim 13 wherein said mold pins are lubricated with a mixture of lecithin and a vegetable oil.

18. The method of claim 13 wherein said solid coating is lubricated with a mixture of lecithin and a vegetable oil.

19. The method of claim 17 or 18 wherein said lecithin is selected from the group consisting of soybean lecithin, peanut lecithin, cottonseed lecithin, sunflower lecithin, rapeseed lecithin, corn lecithin, and groundnut lecithin. In a preferred embodiment, the lecithin is sunflower lecithin.

20. The method of claim 17 or 18 wherein said vegetable oil is selected from the group consisting of coconut oil, palm oil, palmist oil, soy oil, rapeseed oil, sunflower oil, cottonseed oil, peanut oil, olive oil, canola oil, castor oil, corn oil, flaxseed oil, safflower oil, and sesame oil.

21. The method of claim 14 wherein said lubricant comprises a mixture of coconut oil and sunflower lecithin.

22. The method of claim 14 wherein said lubricant comprises a sucroglyceride or a mixture of a sucroglyceride and lecithin.

23. A capsule comprising:

a) pullulan in an amount of at least 70wt% of said capsule;

b) a setting system in an amount of at least 0.01wt% of said capsule;

c) a surfactant comprising a sucroglyceride or a sugar fatty acid ester or mixture thereof;

wherein said wt% amounts are exclusive of water present in the capsule; and

wherein the capsules have a Ca<sup>2+</sup> content of at least 200mg/kg, or at least 300mg/kg, or even at least 500 mg/kg.

24. The capsule of claim 23 wherein the capsules have a Mg<sup>2+</sup> content of at least 30mg/kg, or at least 40 mg/kg, or even at least 50mg/kg.

25. The capsule of claim 23 wherein the ratio of K<sup>+</sup>/(Mg<sup>2+</sup> + Ca<sup>2+</sup>) is less than 50, or less than 40, or less than 30, or even less than 20.

FIG. 1

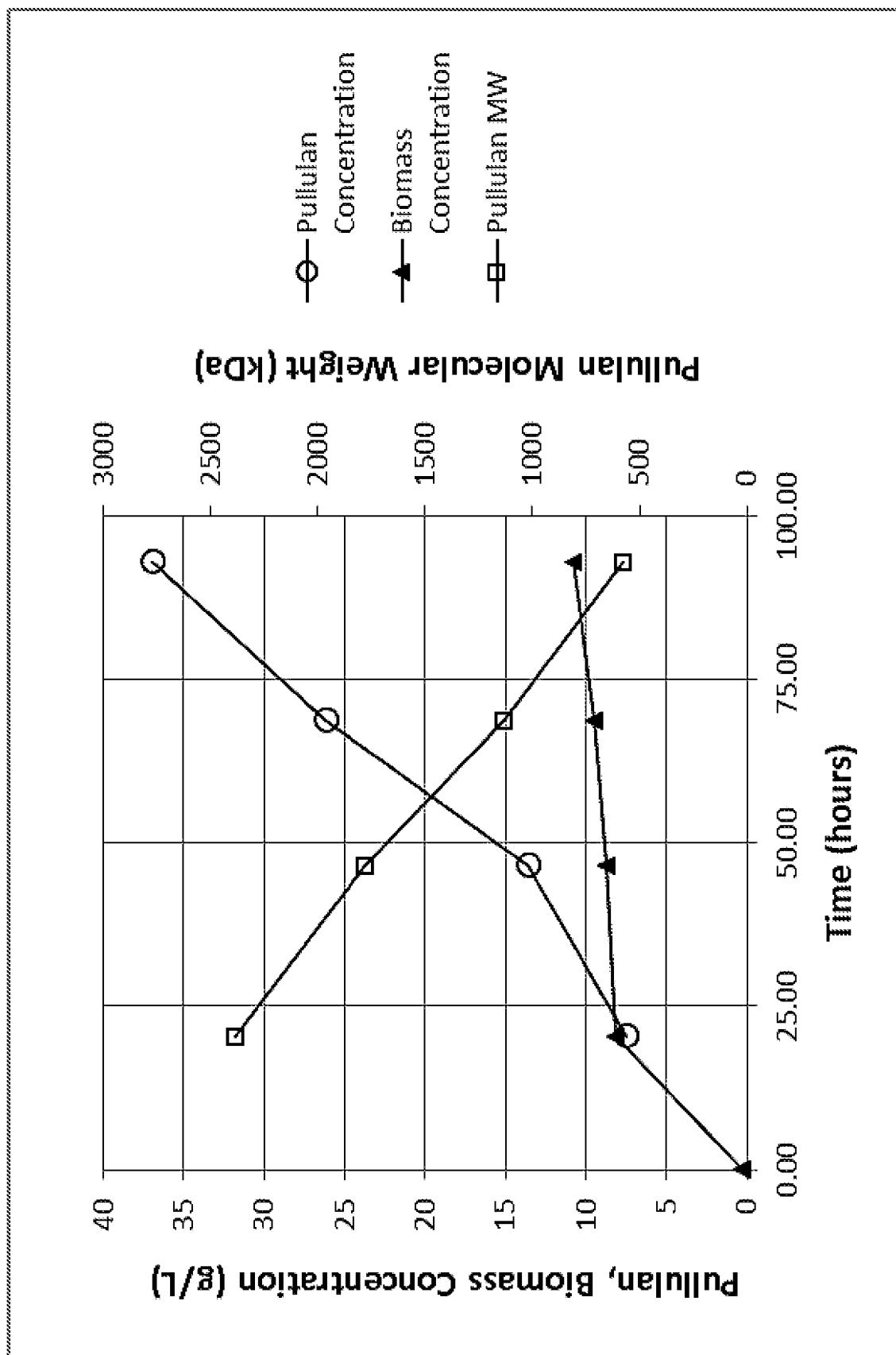


FIG. 2B

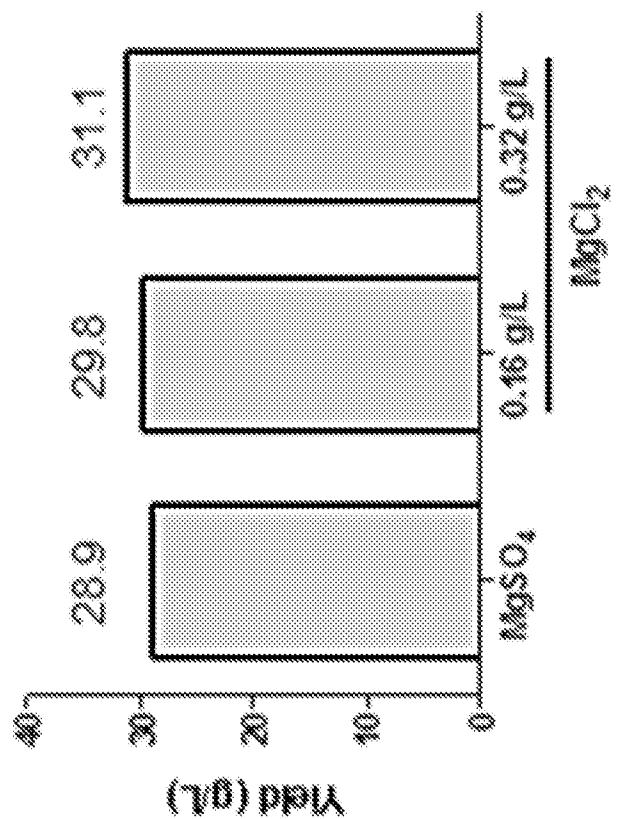
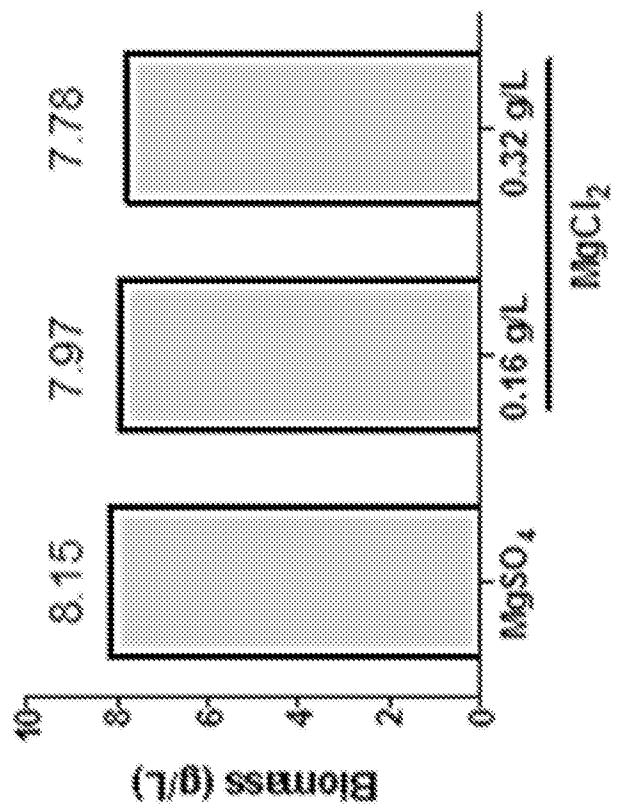


FIG. 2A



# INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2018/000448

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K9/48

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, BIOSIS, EMBASE, 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	US 2015/111862 A1 (PODOLSKI JOSEPH S [US] ET AL) 23 April 2015 (2015-04-23) paragraph [0033] - paragraph [0036] -----	1
Y	WO 2004/096283 A1 (HAYASHIBARA BIOCHEM LAB [JP]; KUMOOKA NORIYOSHI [JP]; KATO KOSO [JP];) 11 November 2004 (2004-11-11) paragraph [0021] paragraph [0100] - paragraph [0103] -----	1-25



Further documents are listed in the continuation of Box C.



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 July 2018

17/07/2018

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

Authorized officer

Sindel, Ulrike

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2018/000448

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