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(54) Title: CALCIUM–CONTAINING COMPOSITION

(57) Abstract

The invention provides a liquid emulsion composition having a continuous aqueous phase containing a viscosity modifier and a dissolved physiologically tolerable calcium compound, and a discontinuous triglyceride phase comprising vitamin D and an edible triglyceride, said emulsion composition further containing at least one emulsifying agent selected from edible phospholipids and fatty acid esters.

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Calcium-containing composition

This invention relates to a calcium and vitamin D formulation in liquid form, for example a syrup or a liquid concentrate, and to a process for its manufacture.

Calcium carbonate tablets are widely used as a source of the essential nutrient calcium, especially for individuals in periods of rapid growth (e.g. in infancy or adolescence), or those suffering from or at risk of osteoporosis.

Calcium uptake is reduced in patients with vitamin D deficiency and accordingly calcium carbonate is often formulated together with vitamin D, e.g. as in the Orocal-Vitamin D_3 tablets of Theramex (Monaco).

However there is a need for alternative dosage forms for the administration of calcium and vitamin D. Different age groups will have different preferences for specific products and this represents a challenge to the pharmaceutical and food industry. Increased attention has been focused on the fact that an increased peak bone density at the end of adolescence reduces the risk of osteoporosis later on in life. This shifts the emphasis towards prevention efforts directed at young children and especially adolescent females. The recommended calcium intake for young women (11-24 years) is as high as 1200-1500 mg of elemental calcium per day. Vitamin D metabolites enhance calcium absorption and an intake of 600 to 800 IU/day of vitamin D is recommended. Population surveys of girls and young women 12-19 years of age show their average calcium intake to be less than 900 mg/day. It is important to increase the awareness of this problem and to improve the dietary calcium intake in this age group. One measure is to offer to this age group dietary supplements and fortified foods

containing calcium and vitamin D which they find attractive and convenient to take.

Accordingly, since the calcium dosage desired for an individual may vary depending on age and condition, and since the calcium tablets available commercially are rather large (e.g. about 1.7 to 2.5g in weight per tablet), it is desirable to provide such calcium and vitamin D supplements in an acceptable liquid form, e.g. as a syrup or as a liquid concentrate for dilution before consumption.

Formulating calcium and vitamin D in a liquid composition however provides its own problems, in particular related to the stability of the vitamin D. Thus typically vitamin D activity (ie. content) of such liquid compositions deteriorates rapidly.

By way of example GB-A-2196523, which acknowledges the problem of vitamin D deterioration, describes two beverages which, after 3 months storage, had lost in one case a third of vitamin D and in the other case all vitamin D.

Calcium and vitamin D supplement products need to be storage stable for prolonged periods in order to be commercially viable and in order for the user to receive the desired dosages of calcium and vitamin D. To some extent, vitamin D deterioration may be compensated for by use of an "overage", a higher initial vitamin D content; however, the overage must be relatively small (e.g. 10% or less) otherwise doses received when using relatively fresh product would be above the desired levels.

We have now found that liquid calcium and vitamin D compositions with very long storage lives can be produced if the vitamin D is present in the oil-phase of an aqueous oil-in-water emulsion in which the oil phase derives from an edible triglyceride and a phospholipid.

Thus viewed from one aspect the invention provides a liquid emulsion composition having a continuous

aqueous phase containing a viscosity modifier and a dissolved physiologically tolerable calcium compound, and a discontinuous triglyceride phase comprising vitamin D and an edible triglyceride, said emulsion composition further containing at least one emulsifying agent selected from edible phospholipids and fatty acid esters.

In the compositions of the invention, the edible triglyceride is preferably a fish oil or more preferably a plant oil, optionally wholly or partially hydrogenated, e.g. coconut oil, soybean oil, rape seed oil, sunflower oil, safflower oil, mustard seed oil, olive oil, etc. Particularly preferably the oil will be one rich in relatively short fatty acid chains, e.g. having a high abundance of C_6 to C_{18} or more preferably C_8 to C_{12} fatty acid residues. Particularly preferably, the weight average fatty acid carbon content is in the range C_8 to C_{12}. Fatty acid profiles can be adjusted as desired by fractionating plant oil or by mixing plant oils from different sources. Highly unsaturated fatty acids are in general not preferred. The edible triglyceride preferably constitutes up to 5% by weight of the total composition, more preferably up to 3% by weight, still more preferably up to 1% by weight, e.g. 0.1 to 0.5% by weight.

The edible triglyceride is preferably used in a ratio of 1000 000 IU vitamin D to 50 to 400g, more preferably 175 to 300g, especially 190 to 250g, more especially 200 to 225g triglyceride.

In place of, or in addition to, the phospholipid in the compositions of the invention, other fatty acid ester emulsifying agents may be used, e.g. esters of fatty acids (e.g. C_{16-22}, especially C_{18} fatty acids) and polyhydric alcohols (especially C_6 alcohols) or polyoxyethylated derivatives thereof, in particular the span and tween non-ionic surfactants, especially polysorbate 80 (i.e. Tween 80). However while such

emulsifiers, in particular polysorbate 80, have found use in the pharmaceutical and dietary supplement area, they are not generally preferred for use in foodstuffs and the use of phopholipids in the compositions of the invention is preferred.

The phospholipid used in the compositions of the invention is preferably a glycerophospholipid, a lysophospholipid or a sphingophospholipid, e.g. a sphingomyelin (SPH), cerebroside or ganglioside. Examples of glycerophospholipids include phosphatidic acids (PA), phosphatidylethanolamines (PE), phosphatidylcholines (PC), phosphatidyl-glycero-phosphates, N-acyl-phosphatidyl-ethanolamines, phosphatidylserines (PS), phosphatidylinositols (PI), phosphatidylglycerols, diphosphatidylglycerols and plasmalogens. Examples of lysophospholipids include lysophosphatidylcholines, lysophosphotidylethanolamines, lysophosphatidylinositols, lysophosphatidylserines, lysophosphatidylglycerols, lysophosphatidylglycerophosphates, lysodiphosphatidylglycerols, lyso-N-acyl-phosphatidylethanolamines and lysophosphatidic acids, Glycerophospholipids, for example phosphatidylcholines, are particularly preferred. The phospholipid may be naturally occurring, synthetic or semisynthetic; however arian egg phospholipids or plant-derived natural phospholipids such as lecithins are especially preferred, e.g. soybean, sunflower, rapeseed, corn or peanut lecithins. By semisynthetic phospholipids is meant a natural phospholipid which has been subjected to chemical modification, e.g. hydrolysis, for example enzymatic hydrolysis with phospholipases such as phospholipase A_1, A_2, B, C, or D, especially phospholipase A_2. Single phospholipids or combinations of two or more phospholipids may be used. Plant derived lecithins generally contain a mixture of phospholipids, e.g. PC together with one or more of PE, PI, PS, PA and

SPH. One example of a particularly suitable commercially available food grade phospholipid is Emultop (available from Lucas Meyer GmbH, Hamburg, DE), a deoiled, enzymatically hydrolysed, powdered soybean lecithin enriched with lysophospholipids. Lecithins are also particularly preferred for use as the phospholipids due to their tocopherol content and inherent antioxidative properties.

The phospholipids or fatty acid ester emulsifiers are preferably used at a weight ratio relative to the triglyceride of 1:10 to 1:60, more preferably 1:20 to 1:40, especially 1:25 to 1:35.

It is thought that the phospholipid or fatty acid ester provides the triglyceride droplets in the emulsion with an at least partial surface membrane which serves to promote stability both of the emulsion and of the vitamin D dispersed in the triglyceride droplets. The protection of the vitamin D may arise as a result of reduced oxygen diffusion across the oil-water interface of the emulsion droplets and desirably the vitamin D concentration in the oil phase is relatively low in order to have a low ratio between vitamin D-in-oil concentration and oil-water interface surface area.

The vitamin D used in the compositions of the invention may be in any one of its various active forms including metabolites and bioprecursors, e.g. cholecalciferol (vitamin D_3), ergocalciferol (vitamin D_2), 1α,25-dihydroxy vitamin D, 25-hydroxy vitamin D, 1α-hydroxy vitamin D, etc. Ergocalciferol and, even more so, cholecalciferol are preferred. Vitamin D_3 is readily available commercially in an edible oil base, e.g. from Roche. Such forms may include edible triglycerides and it should be noted that the total quantity of edible triglycerides in the composition may include some deriving from the vitamin D mix.

The calcium compound used in the compositions of the invention may be any calcium compound capable of

acting as a calcium source on oral administration. The compound may be in dissolved or dissolved and suspended form in the final composition; while soluble calcium salts are preferred, insoluble calcium salts may be included to further increase the calcium concentration of the compositions.

However, where insoluble calcium salts are used, it is desirable to use them in finely divided form, e.g. with a mean particle size below 5 μm, to prevent sedimentation during storage and to avoid any "gritty" taste on consumption. By "soluble" is meant soluble in the continuous aqueous phase of the composition. Examples of calcium sources include calcium carbonate, calcium lactate, calcium gluconate, calcium citrate, calcium malate, calcium hydroxide, calcium glycerophosphate, calcium phosphate, calcium hydrogen phosphate (in tribasic, dibasic and monobasic forms, ie. $Ca_3(PO_4)_2$, $CaHPO_4.2H_2O$ and $Ca(HPO_4)_2.H_2O$), calcium glucuronate, calcium aspartate, calcium glucoheptonate, calcium chloride, etc. As a soluble calcium salt, calcium lactate (e.g. calcium lactate pentahydrate) which has a mild, neutral taste is preferred. As an insoluble calcium salt, calcium carbonate is preferred.

If the calcium is to be kept in dissolved form in the emulsions of the invention, the calcium concentration should be selected to be below its solubility limit, a limit which may be pH and temperature dependant and may be dependant on the presence or absence of other components in the aqueous phase, e.g. acidifiers. If for any particular formulation, a precipitation or flocculation problem occurs, this can readily be remedied by increasing the water content, i.e. by reducing the calcium concentration in the aqueous phase.

Where desired, the calcium salt may be formed in the production of the compositions of the invention, e.g. by reaction of calcium carbonate or calcium

hydroxide with an acid source of the desired counterion, e.g. lactic acid, malic acid or citric acid (especially (+)-lactic acid) for the preparation of calcium lactate).

In the composition of the invention, the calcium content will preferably be 1000 mg Ca per 200-1200 IU vitamin D, more preferably 1000 mg/400-1000 IU, most especially about 1000 mg/700-900 IU. In general, the composition, in concentrate or syrup form, will contain 0.5 to 10% w/w of calcium and 0.5 to 100 IU/g vitamin D, preferably 1 to 6% w/w calcium and 1 to 50 IU/g, more preferably 1 to 5% w/w calcium and 9 to 40 IU/g. For administration, the emulsion may be taken neat or may first be diluted, e.g. with water or a selected beverage, for example in a 1 part emulsion to 2 to 10 parts, more especially 5 parts, water ratio.

Besides the calcium compound, the triglyceride, the emulsifying agent (e.g. phospholipid), the vitamin D and water, the compositions according to the invention may, and indeed generally will, contain other physiologically tolerable components, for example sweeteners, viscosity modifiers (e.g. gelling agents, gums, starches, and other thickeners), antioxidants (e.g. tocopherols, such as d,l-α-tocopherol, and ascorbyl palmitate), essential nutrients (e.g. vitamins other than vitamin D (e.g. vitamins A, B, C, E and K), isoflavones, betacarotene, lycopene, soluble and insoluble fibre and minerals other than calcium), colouring agents, pharmaceuticals, pH modifiers (e.g. buffering agents or acidifiers, for example citric acid, lactic acid, malic acid, etc.) preservatives (e.g. benzoates and sorbates), flavours, etc.

The compositions of the invention also contain a viscosity modifier, ie. a material which increases the viscosity of the aqueous phase, most preferably the combination of a thickener and a gelling agent, for example agar agar and an edible gum such as locust bean

gum, guar gum, xanthan gum, gum arabic, or gum tragacanth. The viscosity modifier will generally be used at total concentrations of 0.01 to 5% w/w of the total liquid emulsion composition, more preferably 0.05 to 3% w/w, especially 0.3 to 1.5% w/w. The viscosity modifiers serve to enhance the physical stability of the emulsion and advantageously at least one of the viscosity modifiers used is a gelling agent, ie. a material capable of forming a gel on dissolution in water. The gelling agent is preferably used at a concentration of 0.05 to 1% w/w of the total composition, more preferably 0.06 to 0.4% w/w, especially 0.07 to 0.3% w/w. One particularly preferred gelling agent is agar agar and this is especially preferably used together with one or more edible gums, e.g. locust bean gum and guar gum. The thickener is preferably used at a concentration of 0.05 to 3% by weight of the total composition.

The compositions of the invention are intended for oral ingestion and thus desirably contain sweeteners and flavours to enhance their acceptability to the consumer. The sweeteners used may be natural sweeteners, e.g. mono, di and polysacchrides, for example sucrose, fructose, fructooligosaccharides (oligofructoses), glucose, glucose syrup, invert sugar, maltodextrins or sugar alcohols such as sorbitol, mannitol, xylitol, isomalt, etc., or artificial sweeteners. However intense artificial sweeteners, and especially non-cariogenic sweeteners are preferred. Examples include aspartame, acesulfam K, neohesperidine dihydrochalcone, thaumatin, saccharin, saccharin salts and cyclamates. A single sweetener or a combination of two or more sweeteners may be used. Preferred natural sweeteners are sugar and fructose conveniently used as syrups with 70% solids (on drying), and fructooligosaccharides. A particularly preferred combination is aspartame and acesulfam K, e.g. in a 2:1 to 1:2 weight ratio, especially a 0.9:1 to 1:0.9 ratio.

Especially preferred a combination of aspartame, acesulfam and inulin and/or fructooligosaccherides is used as the combination has a synergistic taste effect, relatively effectively mimicking the sweetening effect of sugar and masking any harsh taste of the artificial sweeteners. Fructooligosaccharides can be obtained by partial hydrolysis of inulin and are available under the trade name Raftilose from Orafti SA, Tienen, Belgium, which firm also supplies inulins under the trade name Raftiline. Fructooligosaccharides are also available under the trade name Actilight from Beghin-Meiji Industries, Neuilly-sur-Seine, France. Generally the inulin or fructooligosaccharide will be used in 100-5000 parts by weight per 2 parts by weight of aspartame and acesulfam.

The content of sweetener in the compositions of the invention will depend upon the particular sweeteners used and on whether the composition is to be diluted before consumption. Thus the sweetener content will be chosen so as to give a pleasant sweetness on consumption. Typically the sweetener content will be 0.05 to 1% w/w where intense artificial sweeteners are used, e.g. about 0.1% w/w. Where natural sweeteners (e.g. invert sugar or fructose) are used, they can typically make up 20-50% w/w, more preferably 30-50% w/w of the overall composition on a dry solids basis.

While polyols such as sorbitol, mannitol, xylitol and isomalt may be used as mentioned above, these may result in a laxative effect if used in large quantities and they are thus less preferred than the intense artificial sweeteners.

The use of prebiotics such as inulin and fructooligosaccharides is also preferred as it appears that they serve as a substrate for the bifidobacteria in the colon, resulting in certain circumstances in improved uptake of calcium. The use of fructooligosaccharides in oral calcium compositions is

novel and forms a further aspect of the present invention. Viewed from this aspect the invention provides an orally administrable calcium supplement comprising a physiologically tolerable calcium compound, a prebiotic (e.g. fructooligosaccharide or inulin) and preferably also a vitamin D. Such supplements may be in any convenient form, e.g. tablets (for example as described in WO96/09036 (Innothera), powders, capsules, dispersions, emulsions, syrups, gels, etc.

For compositions intended for adolescent females and children not in need of low calorie products, natural sweeteners may be preferred over artificial sweeteners. However, for products intended for calorie-conscious adults, artificial sweeteners may be preferred.

Examples of flavouring agents useful in the compositions of the invention include fruit (e.g. pineapple or citrus) concentrates and concentrated aqueous or non-aqueous flavours such as flavour oils, e.g. citrus oils, for example cold pressed orange oil (B.P.). Orange concentrate, e.g. 65 Brix orange concentrate is particularly suitable. The flavouring agent will be used at a concentration sufficient to give the composition, optionally after dilution, a pleasant taste. By way of example 65 Brix orange concentrate may be used at a concentration of 1 to 20% w/w relative to the total emulsion, preferably 2 to 15% w/w. Alternatively cold pressed orange oil BP may be used at a concentration of 0.04 to 0.3% w/w, preferably 0.06 to 0.2% w/w, relatively to the total emulsion.

It should be recognised that the use of flavours or acidifiers which are soluble in the aqueous phase (e.g. fruit concentrates or citric acid) may affect the solubility of the calcium compound in that phase and that it may be necessary in such cases to dilute the aqueous phase to prevent precipitation. Accordingly, acidifiers such as lactic acid and water-insoluble

flavours such as citrus oils or water-soluble flavours such as strawberry, raspberry, passion fruit, exotic fruit, peach and apricot flavours and other non-citrus flavours such as pineapple concentrate are preferred.

Where a flavour oil is used, it may be dispersed in the triglyceride together with the vitamin D or alternatively and preferably it and the vitamin D are separately dispersed in the overall emulsion - in this way any effect of the flavour oil on vitamin D stability may be minimized. In these circumstances a phospholipid or another emulsifier is preferably dissolved in the flavour oil and two oil phases, one containing flavour oil and the other containing vitamin D are intensively mixed with the aqueous phase. This can be done separately (with the two emulsions then being mixed together) or sequentially (with one oil phase, generally the vitamin D phase, being intensively mixed with some or all of the aqueous phase and the second oil phase then being intensively mixed with the resulting emulsion (optionally after dilution of this emulsion).

Suitable preservatives for use in the compositions of the invention include food grade preservatives, for example the potassium and sodium salts of sorbic, benzoic and parahydroxybenzoic acids. Potassium sorbate is especially preferred. The preservative will generally be used at concentrations of 0.05 to 1.5% w/w relative to the total emulsion, preferably 0.1 to 0.3 w/w.

Vitamin C is desirably included in the compositions of the invention, e.g. at a concentration of 1-3 mg/mL, especially 1.5-2.0 mg/mL.

As a colouring agent, beta-carotene may for example be used. Beta-carotene gives the emulsion an orange colour which matches the orange flavour where an orange flavour is used. Cold-water soluble beta-carotene is preferred as it disperses easily in the aqueous phase. Beta-carotene 7% CWS from Roche, which gives the product

a clear transparent orange colour is especially preferred.

Acidifying agents, e.g. lactic or malic acid, may be included in the compositions of the invention. Lactic acid, available in 80% solution as Purac 80 from Purac biochem bv is preferred. Preferably the pH of the emulsion should be adjusted to below 6, more preferably below 5, e.g. in the range 3 to 5. The particular pH selected should be sufficient to maintain all or the desired fraction of the calcium compound in solution. Where fructooligosaccharides are used in the compositions of the invention, the pH is desirably kept above 4 to avoid hydrolysis.

The compositions of the invention are oil-in-water emulsions, preferably with a narrow oil (triglyceride) droplet size distribution with the mean droplet size (measured for example by light microscopy and comparison with a 1 to 10 μm scale) in the range 1 to 5 μm, more preferably 1 to 4 μm. Emulsification is preferably effected in such a way as to have only a small oversize fraction of droplets, ie. droplets above 5 μm in diameter. This may be achieved by mixing the aqueous phase and the oil phase using a high intensity mixer, for example a high shear rotor stator mixer, available for example from Ystral GmbH, Dottingen, DE. One example of a suitable mixer is the Diax 600 with a 20G or 20F shaft. An in-line dispersion chamber (eg Diax 600, type 22/Z is preferably used as this can ensure that little or no air is introduced into the emulsion.

It may be more efficient to create an emulsion using only part of the aqueous phase and then to add the emulsion to the remaining portion or portions of the aqueous phase.

The preparation of the emulsion of the invention forms a further aspect of the invention. Viewed from this aspect the invention provides a process for the preparation of a liquid emulsion composition according to the invention, said process comprising:

forming an aqueous composition comprising an aqueous solution of a viscosity modifier;

forming a triglyceride composition comprising a solution of a Vitamin D and at least one emulsifying agent selected from edible phospholipids and fatty acid esters;

mixing said triglyceride composition with at least part of said aqueous composition whereby to form an oil-in-water emulsion; and

if necessary mixing further components with said emulsion whereby to form said liquid emulsion composition, e.g. mixing in further aqueous or non-aqueous compositions containing a physiologically tolerable calcium compound, sweeteners, a further viscosity modifier (e.g. a gelling agent), further vitamins or minerals, flavours, colours, preservatives etc.

On a small scale, the process of the invention preferably involves preparing at least two, and more preferably at least three, aqueous compositions and at least one, preferably two, non-aqueous compositions. The first aqueous composition comprises a solution of a thickening agent (e.g. a vegetable gum or a mixture of vegetable gums, e.g. galactomannans) and a portion of this may be used for the preparation of the emulsion, the remainder being combined with a second aqueous composition which is an aqueous solution of a gelling agent (e.g. agar agar). The calcium compound may be dissolved or dispersed in either of the first or second aqueous solutions or in the combined aqueous composition; preferably however the calcium compound is dispersed in a third aqueous composition, optionally together with further components such as sweeteners and preservatives, and this third aqueous composition is mixed in with the combined aqueous composition before or preferably after which the emulsion is also mixed in. Where an oil component such as a flavour oil is used which has the potential to reduce vitamin D stability,

it is preferred to prepare two oil compositions, a first containing the vitamin D and the phospholipid and a second containing an emulsifier (e.g. the same phospholipid) and the further other oil component.

The first oil composition is preferably emulsified with the portion of the first aqueous composition that has been set aside for emulsion formation whereafter the second oil composition may be intensively mixed in with the resultant emulsion.

The overall volume of water used is preferably kept to the minimum required to keep the calcium compound stably in solution. The proportions of this water used to prepare the different aqueous compositions will generally be selected to be at least the minimum required to produce compositions which can be poured and mixed together, the total desired water content can be made up by addition of aqueous solutions of further components (such as vitamin C) or of water. In this way evaporation losses can be compensated for.

Preferably all composition production and handling is carried out under an inert (e.g. nitrogen or inert (e.g. noble) gas) atmosphere, under a partial vacuum or with nitrogen injection so as to minimize the oxygen contact with the vitamin D. Alternatively oxygen contact may be reduced by preparing the vitamin D-triglyceride composition, and emulsifying this with the thickener solution under an inert atmosphere.

One preferred embodiment of a small scale preparation of an emulsion according to the invention comprises the following steps:

1. Heat a first batch of water to 60°C.

2. Add agar agar and disperse with a high speed mixer.

3. Heat to 95°C to dissolve the agar agar to produce liquid (A).

4. Maintain liquid (A) above the gel point (30-40°C), e.g. at 50°C.

5. Heat a second batch of water to 70°C.

6. Add a 65:35 locust bean gum: guar gum mixture and disperse with a high speed mixer to produce liquid (B).

7. Maintain liquid (B) at a temperature above the gel point of liquid (A), e.g. at 50°C.

8. Remove a fraction, e.g. 5-10%, of liquid (B), cool to about 30°C and dilute with water to reduce viscosity to a level suitable for emulsification and to reduce exposure of vitamin D to elevated temperatures. The resulting liquid is liquid (C).

9. Combine the remainder of the liquid (B) with liquid (A) and maintain the resulting liquid, liquid (D) above the gel point, e.g. at 50°C.

10. Add sweeteners (e.g. acesulfam and aspartame) and preservatives (e.g. potassium sorbate) to a third batch of water at ambient temperature.

11. Add calcium lactate and disperse to produce a thick suspension, liquid (E).

12. Add liquid (E) to liquid (D) keeping the temperature of the resulting mixture above the gel point, e.g at 50°C. The calcium lactate will dissolve to yield a clear solution. If desired colorants, acidifier (e.g. lactic acid), fructooligosaccharides, etc. can be added at this stage. The resulting liquid is liquid (F).

13. Cool liquid (F) slowly through its gel point, e.g. to 25-28°C, with constant gentle stirring to prevent gelling at container sides. The result is a pourable, viscous, liquid.

14. Add lecithin to triglyceride at ambient temperature, heat to 50°C to dissolve the lecithin and cool to about 30°C.

15. Add vitamin D to produce liquid (G).

16. Mix citrus oil (e.g. orange oil) with lecithin and warm slightly, e.g. to about 30°C to dissolve the lecithin. The resultant liquid is liquid (H).

17. Mix liquid (G) and liquid (C) with a high intensity mixer to produce an emulsion. Then mix in liquid (H) also with a high intensity mixer, e.g. a rotor stator. Allow the resulting emulsion, liquid (I), to cool to 25-30°C.

15. With gentle stirring mix liquid (I) into liquid (F), and vitamin C solution, cool to below 25°C, add water if required to make up volume and fill into bottles and seal under nitrogen.

The containers used may be single dose containers, e.g. bottles, sachets, vials, etc; however multi-dose containers are preferred, e.g. 50 to 1000 mL bottles, preferably 500 mL bottles. If the containers are light transmitting, they are preferably brown-coloured, e.g. brown coloured PET. Before the containers are sealed, the head space above the emulsion may if desired be flushed with an oxygen-free gas, e.g. nitrogen.

As mentioned above, deaeration or nitrogen injection is preferably used during the preparation of the emulsion product to exclude oxygen.

The emulsion is preferably administered (optionally after dilution) in doses containing 100 to 1500 mg Ca, preferably 200 to 500 mg Ca, with sufficient doses being taken over the day to provide a 200 to 1200 mg Ca daily dosage, more preferably a 500 to 1000 mg Ca daily dosage. For prophylactic use, the daily dosage is preferably 400 to 600 mg Ca, more preferably 500 mg Ca while for therapeutic use, e.g. in osteoporosis, the daily dosage is preferably 900 to 1100 mg Ca, more preferably 1000 mg Ca. Individual doses preferably contain 500 mg Ca or less in order to optimise calcium uptake.

The vitamin D dosage is preferably 100 to 1000 IU per day, more preferably 300 to 500 IU/day for prophylactic use and 700 to 900 IU/day for therapeutic use. The calcium to vitamin D ratio is preferably 500 mg Ca: 150-500 IU, more preferably 500 mg Ca: 200-450

IU, especially 500 mg Ca: 200-220 IU and 500 mg Ca: 400-450 IU for prophylactic and therapeutic use respectively.

The calcium content of the emulsion according to the invention is preferably 10-27.5 mg Ca/mL, especially 12.5 or 25 mg Ca/mL. Such emulsions may conveniently be diluted 1 part with 5 parts by volume of diluent, e.g. tap water or mineral water, milk, fruit juice, or any other alcohol-free beverage. Where water is used the resultant diluted composition may be a clear liquid with an acceptable flavour.

Doses of the composition of the invention may be taken between meals or with meals and are suitable for older people with reduced gastric acid secretion.

The compositions of the invention may be used in therapeutic or prophylactic treatment and this forms a further aspect of the invention. Viewed from this aspect the invention provides a method of treatment of a human or non-human mammal subject to combat conditions associated with calcium deficiency (e.g. osteoporosis), said method comprising orally administering said subject a composition or supplement according to the invention, optionally following dilution thereof in a physiologically tolerable aqueous liquid.

The invention will now be described further with reference to the following non-limiting Examples:

EXAMPLE 1

Preparation of a liquid beverage concentrate

Ingredients:

Potassium sorbate		4g
Calcium lactate pentahydrate		175g
Agar agar		3.2g
Guar gum		4.5g
Locust bean gum		8.3g
Aspartame		1g
Acesulfam K		1g
Lactic acid (80%)		8g
Betacarotene (7% CWS)		170mg
Orange oil BP		3g
Vitamin D_3 (1 MIU/g from Roche)		22mg
Lecithin (Emultop)		315mg
Fractionated coconut oil		4.7g
Purified water	to	2000 mL

The agar agar is mixed with 350 ml of purified water with an intensive mixer and heated up until dissolved at a temperature of 95°C.

The locust bean gum and guar gum are mixed together with 900 mL of purified water at a temperature of 70°C. 70 mL of this mixture is removed and diluted to 150 mL with purified water and set aside for use in emulsification.

The agar agar solution and the remaining gum solution are mixed and kept above 50°C to form the main solution.

Aspartame, acesulfam K and potassium sorbate are added to 600 ml of purified water and dissolved by the aid of

an intensive mixer. 175 gram of calcium lactate pentahydrate is then gradually added to form a suspension by the aid of the same intensive mixer.

The suspension is transferred to the main solution where calcium lactate dissolves completely to form a clear solution.

Lactic acid (80%) and betacarotene 7% CWS are added and the container is placed in a waterbath for cooling while continuously being stirred by a slow moving stirrer.

The triglyceride and 190 mg lecithin are heated up until approximately 50°C until a solution is achieved. The clear brown solution is then cooled down to approximately 30°C whereupon vitamin D is added.

The orange oil and 125 mg lecithin are mixed; only slight heating is necessary in this case in order to dissolve the lecithin.

The triglyceride phase is then emulsified into the 150 ml diluted gum solution with an intensive mixer at high speed to produce an emulsion. Likewise the orange oil is then emulsified into the same 150 ml. The emulsion is then added to the main solution when the temperature in this solution is at approximately 28°C.

The temperature is further brought down below 20°C at which the volume is corrected with purified water to 2000 ml. The product is then filled into coloured 250 - 1000 ml PET or glass bottles.

The resulting beverage concentrate contains 250 mg of elemental calcium and 220 IU of vitamin D_3 per 20 ml of serving. The beverage concentrate has the following properties:

Viscosity (Brookfield):	1280 mPa.s
Density:	1.01 g/ml
pH:	4.7
Average droplet size	2-4 μm

The viscosity is measured by the aid of a Brookfield DV-2 viscosimeter, spindle 2 and with a rotation speed of 10 rpm. A 600 ml sample is used and the measurement is taken at room temperature.

EXAMPLE 2

Preparation of a liquid beverage concentrate

Ingredients:

Agar agar	2.6g
Locust bean gum	6.8g
Guar gum	3.6g
Calcium lactate pentahydrate	175g
Potassium sorbate	4g
Aspartame	1g
Acesulfam K	1g
Fructooligosaccharides (Raftilose L95/75)	210g
Lactic acid 80%	8g
Betacarotene 7% CWS	200mg
Fractionated coconut oil	4.7g
Lecithin (Emultop)	315mg
Vitamin D_3 (1 mill IU/g from Roche)	22mg
Orange oil, BP	3g
Purified water to	2500 ml

The beverage concentrate is prepared analogously to Example 1. The fructooligosaccharide is added at the time when the cooling down process starts in order to avoid unnecessary exposure to high temperatures.

The beverage concentrate contains 250 mg of elemental calcium, 220 IU of vitamin D_3 and 1.5 grams of fructo oligosaccharides per 25 ml of serving. The beverage concentrate has the following properties:

Viscosity (Brookfield):	916 mPa.s
Density:	1.00 g/ml
pH:	4.7
Average droplet size	1-3 μm

EXAMPLE 3

Preparation of a liquid beverage concentrate

Ingredients:

Agar agar	2.6g
Locust bean gum	6.8g
Guar gum	3.6g
Calcium lactate pentahydrate	175g
Potassium sorbate	4g
Aspartame	1g
Acesulfam K	1g
Fructooligosaccharides (Raftilose L95/75)	210g
Lactic acid 80%	8g
Betacarotene 7% CWS	200mg
Fractionated coconut oil	4.7g
Lecithin (Emultop)	315mg
Vitamin D_3 (1 mill IU/g from Roche)	22mg
Orange oil, BP	3g

Ascorbic acid	3.9g
Purified water to	2500 ml

The beverage concentrate is prepared analogously to Example 2, except that vitamin C is dissolved in approximately 100 ml of purified water and added at the end of the process together with the triglyceride and orange oil emulsion.

The beverage concentrate contains 250 mg of elemental calcium, 220 IU of vitamin D_3, 39 mg of vitamin C and 1.5 grams of fructooligosaccharides per 25 ml of serving. The beverage concentrate has the following properties:

Viscosity (Brookfield):	1130 mPa.s
Density:	1.02 g/ml
pH:	4.6
Average droplet size	1-3 μm

EXAMPLE 4

A stability study was carried out in order to investigate the physical and chemical stability of the liquid calcium composition product. A 2^3 factorial design was set up in order to demonstrate the effect of three formulation variables. These were the type of emulsifying agent, presence of vitamin C and presence of oligofructose. The following combinations of formulation variables were used in all together 8 combinations and executed in a random order:

Batch	Emulsifying agent	Vitamin C	Oligofructose
1	Emultop	39.0 mg	1.5 g
2	Emultop	2.0 mg	1.5 g
3	Emultop	39.0 mg	-
4	Tween 80	39.0 mg	1.5 g
5	Tween 80	2.0 mg	-
6	Tween 80	2.0 mg	1.5 g
7	Tween 80	39.0 mg	-
8	Emultop	2.0 mg	-
9	Emultop	2.0 mg	-
10	Emultop	2.0 mg	-

Batches 9 and 10 were identical to batch 8 and were produced in order to demonstrate the variability of the analytical methods employed.

The type of emulsifying agent was investigated for influence on the stability of vitamin D_3 and effect on the physical stability of the emulsion. Effects on physical stability investigated included any evidence of creaming or phase separation as well as the measurement of the mean droplet size as a function of time.

The possible effect of two concentrations of vitamin C and the presence of oligofructose on the stability of vitamin D_3 was also investigated.

The calcium content per dosage of 20 or 25 ml was 200 mg of elemental calcium and the content of vitamin D_3 was 4 μg (160 IU) per dosage (i.e. 4.4 μg (176 IU) including overage (10%)).

The amount of the gelling agent (agar-agar) and the thickeners (locust bean gum and guar gum) was selected in order to maintain a satisfactory viscosity in the

product.

The low level of vitamin C (2 mg) was added to the formulations in order to function as an antioxidant to prevent the discolouring of betacarotene.

Two minor modifications to the production method previously described were employed. Firstly, the vitamin D_3 and the orange oil were separately emulsified into two different pre-emulsions and added after each other into the main solution at a temperature of 28°C. Secondly the emulsion was homogenised with a Diax 600 high intensity mixer for two minutes after the volume correction at the very end of the production.

A vitamin D_3 premixture containing vitamin D_3, emulsifying agent and triglyceride which was enough for ten batches was made for practical reasons and due to the small amount of vitamin D_3 per batch. The same procedure was carried out for the orange oil and lecithin components.

Table 1 below gives the exact composition of the 10 batches

Table 1

Component/Batch No.	1	2	3	4	5	6	7	8	9	10
Agar agar	3.84 g	3.84 g	4.80 g	3.84 g	4.80 g	3.84 g	4.80 g	4.80 g	4.80 g	4.80 g
Locust bean gum	10.00 g	10.00 g	12.5 g	10.00 g	12.5 g	10.00 g	12.5 g	12.5 g	12.5 g	12.5 g
Guar gum	5.40 g	5.40 g	6.7 g	5.40 g	6.7 g	5.40 g	6.7 g	6.7 g	6.7 g	6.7 g
Calcium lactate penthydrate	168 g	168 g	209 g	168 g	209 g	168 g	209 g	209 g	209 g	209 g
Potassium sorbate	4.80 g	4.80 g	4.80 g	4.80 g	4.80 g	4.80 g	4.80 g	4.80 g	4.80 g	4.80 g
Aspartame	1.20 g	1.20 g	1.50 g	1.20 g	1.50 g	1.20 g	1.50 g	1.50 g	1.5 g	1.50 g
Acesulfam K	1.20 g	1.20 g	1.50 g	1.20 g	1.50 g	1.20 g	1.50 g	1.50 g	1.5 g	1.50 g
Lactic acid (80%)	9.60 g	9.60 g	12.0 g	9.60 g	12.0 g	9.60 g	12.0 g	12.0 g	12.0 g	12.0 g
Fructooligosaccharides (Raftilose L95/75)	252 g	252 g		252 g		252g				
Betacarotene 7% CWS	240 mg	240 mg	300 mg	600 g	300 mg	240 mg	300 mg	300 mg	300 mg	300 mg
Lecithin (Emultop)	432 mg	432 mg	516 mg					516 mg	516 mg	516 mg
Polysorbate 80				432 mg	516 mg	432 mg	516 mg			
Vitamin D_3 (1 mill IU/g)	21.1 mg	21.1 mg	26.4 mg	21.1 mg	26.4 mg	21.1 mg	26.4 mg	26.4 mg	26.4 mg	26.4 mg
Fractionated coconut oil	4.54 g	4.54 g	5.68 g	4.54 g	5.68 g	4.54 g	5.68 g	5.68 g	5.68 g	5.68 g
Orange oil	3.60 g	3.60 g	4.50 g	3.60 g	4.50 g	3.60 g	4.50 g	4.50 g	4.50 g	4.50 g
Ascorbic acid	4.68 g	240 mg	5.85 g	4.68 g	300 mg	240 mg	5.85 g	300 mg	300 mg	300 mg
Purified water to:	3000 ml	3000 ml	3000 ml	3000 ml	3000 ml	3000 ml	3000 ml	3000 ml	3000 ml	3000 ml
Dosage	25 ml	25 ml	20 ml	25 ml	20 ml	25 ml	20 ml	20 ml	20 ml	20 ml
Calcium per dosage	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Vitamin D_3 per dosage	4.4 µg	4.4 µg	4.4 µg	4.4 µg	4.4 µg	4.4 µg	4.4 µg	4.4 µg	4.4 µg	4.4 µg
Fructooligosaccharides per dosage	1.5 g	1.5 g		1.5 g		1.5 g				
Vitamin C per dosage	39 mg	2 mg	39 mg	39 mg	2 mg	2 mg	39 mg	2 mg	2 mg	2 mg

The emulsions were filled into 200 ml amber glass bottles with a screw cap and set aside for the stability trial. The stability conditions were chosen to be 25°C and 60% relative humidity as this would closely resemble the actual storage conditions in a retail situation.

The 10 batches were analysed initially and after 2, 4 and 6 months with respect to the content of vitamin D_3, emulsion droplet size and appearance. Two of the formulations were analysed at 3 months instead of 2 months with respect to vitamin D_3. Viscosity, microbiological quality, pH, oxygen content and taste were analysed initially and after 6 months.

Vitamin D_3 content analysis was carried out by a single one-step extraction of the fat-soluble vitamins from a product sample into hexane, followed by solid phase extraction (SPE) to further purify and enrich the vitamin D_3.

Vitamin D_3 was then analysed on a reversed phase Supelcosil HPLC column using a mobile phase containing acetonitrile and methanol for the separation.

The results after 6 months as a whole showed that vitamin D_3 is stable in the 10 batches, the measured vitamin D_3 contents, expressed on percentages of the theoretical vitamin D_3 content being no lower than 97.7% for batches 1 to 8. (The initial vitamin D_3 content in the premixes for batches 9 and 10 was not analysed). In this study, previtamin D_3 (a common vitamin D_3 degradation component) did not increase indicating that no vitamin D_3 degradation had occured in this product. (Previtamin D_3 was studied using HPLC).

The statistical evaluation of the results of changing the three formulation variables (emulsifying agent,

vitamin C and oligofructose) indicated that none of these affected the vitamin D_3 content. This indicates a very robust formulation where major formulation changes can be carried out without affecting the stability of vitamin D_3.

No evidence of precipitation was seen in any of the samples after 6 months.

The effect of time on measured emulsion droplet size, viscosity, pH and appearance is set out in Table 2 below:

Table 2

Batch	Droplet size* (μm) after 0, 2, 4 and 6 months				Viscosity (cp)		pH		Oxygen content (ppm)	
	0	2	4	6	Initial	6 mths	Initial	6 mths	Initial	6 mths
1	5.5	6.3	3.5	2.6	444	328	4.55	4.51	3.2	0.52
2	5	4	3.1	2.2	648	400	4.70	4.61	4.1	5.50
3	5	5.5	2	2.2	820	560	4.55	4.45	6.3	3.54
4	3.5	2.5	3.5	1.9	396	256	4.60	4.47	2.4	0.84
5	3.5	3.8	1.8	1.9	664	408	4.65	4.51	0.7	1.73
6	3.5	4	2	1.9	708	368	4.65	4.54	3.0	2.02
7	3.5	2.5	1.7	1.9	1090	728	4.55	4.40	1.9	0.47
8	6	3.5	2.6	2.2	1030	616	4.65	4.56	2.3	2.16
9	4.5	7.5	1.9	4.8	400	524	4.59	4.52	0.7	2.19
10	6.0	5.5	1.8	4.2	680	672	4.57	4.52	0.9	2.48

* The method of measuring the droplet size was changed before the 4 month measurement point. The new method included a more accurate and statistically better method for calculating the mean droplet size involving determining the mean for 10 to 25 droplets from a 40x microscope picture.

There was no evidence of creaming or phase separation in any of the batches at the various time points during the stability trial.

The viscosity decreased slightly for all the batches. This was an expected result as the polymeric substances in the gelling and thickener system contract and go into an relaxed state with a resultant decrease in viscosity.

The pH for the formulations are all in the region of 4.4 to 4.6 and no significant changes over time were seen.

The amount of dissolved oxygen in the batches were measured with a Moca 3600 oxygen sensor from Orbisphere Laboratories. The mean values for the oxygen content were 2.55 and 2.14 ppm respectively for the initial analysis and after 6 months.

Claims

1. A liquid emulsion composition having a continuous aqueous phase containing a viscosity modifier and a dissolved physiologically tolerable calcium compound, and a discontinuous triglyceride phase comprising vitamin D and an edible triglyceride, said emulsion composition further containing at least one emulsifying agent selected from edible phospholipids and fatty acid esters.

2. A composition as claimed in claim 1 wherein said emulsifying agent is an edible phospholipid.

3. A composition as claimed in claim 2 containing a lecithin as an emulsifying agent.

4. A composition as claimed in any one of claims 1 to 3 containing said emulsifying agent and said triglyceride in a weight ratio of from 1:10 to 1:60.

5. A composition as claimed in any one of claims 1 to 4 containing said edible triglyceride and said vitamin D in a ratio of from 50 to 400g triglyceride to 1,000,000 IU vitamin D.

6. A composition as claimed in any one of claims 1 to 5 containing a plant oil as said triglyceride.

7. A composition as claimed in any one of claims 1 to 6 containing up to 5% by weight of said triglyceride.

8. A composition as claimed in any one of claims 1 to 7 containing calcium lactate.

9. A composition as claimed in any one of claims 1 to 8 containing said calcium compound and said vitamin D in

a ratio of 1000 mg Ca to 200 to 1200 IU vitamin D.

10. A composition as claimed in any one of claims 1 to 9 containing 0.05 to 1% by weight of said gelling agent.

11. A composition as claimed in any one of claims 1 to 10 containing 0.05 to 3% by weight of said thickener.

12. A composition as claimed in any one of claims 1 to 11 containing a gelling agent and a thickener as said viscosity modifer.

13. A composition as claimed in claim 12 to containing agar agar and an edible gum as said gelling agent and said thickener.

14. A composition as claimed in any one of the preceding claims further containing a sweetener.

15. A composition as claimed in claim 14 wherein said sweetener is selected from sucrose, fructose, oligosaccharides, inulin, aspartame, acesulfam and mixtures thereof.

16. A composition as claimed in any one of the preceding claims further containing vitamin C.

17. A composition as claimed in any one of the preceding claims further containing a water-insoluble physiologically tolerable calcium compound.

18. A process for the preparation of a liquid emulsion composition as claimed in any one of claims 1 to 17 according to the invention, said process comprising:

forming an aqueous composition comprising an aqueous solution of a viscosity modifier;

forming a triglyceride composition comprising a

solution of a vitamin D and at least one emulsifying agent selected from edible phospholipids and fatty acid esters;

mixing said triglyceride composition with at least part of said aqueous composition whereby to form an oil-in-water emulsion; and

if necessary mixing further components with said emulsion whereby to form said liquid emulsion composition.

19. An orally administratable calcium supplement comprising a physiologically tolerable calcium compound and a prebiotic.

20. A supplement as claimed in claim 19 further containing vitamin D.

21. A method of treatment of a human or non-human mammal subject to combat conditions associated with calcium deficiency, said method comprising orally administering said subject a composition or supplement according to any one of claims 1 to 17, 19 and 20, optionally following dilution thereof in a physiologically tolerable aqueous liquid.

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/GB 00/00986

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P3/02 A61K9/00 A61K9/107 A23L1/303 A23L1/304

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)
IPC 7 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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 96 31130 A (ABBOTT LAB) 10 October 1996 (1996-10-10) page 9, paragraph 2 - paragraph 3; tables 3,4 page 16, paragraph 2 - paragraph 3 page 21, paragraph 1 - paragraph 2 page 23, paragraph 1 - last paragraph; table 11 page 29, paragraph 2; tables 19,20 example 1; table 22 claims 1-6,9 --- -/--	1,6-8, 14-17,21 10,11,13

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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"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
16 June 2000	28/06/2000

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, E

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INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/GB 00/00986

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	column 2, line 63 - last line column 3, line 18 - line 27 column 3, line 29 - line 32 column 6, line 22 - line 34 column 6, line 55 -column 8, line 2; claims 1,3,5,7,8,13,14 ---	10,11,13
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A	column 1, line 46 - line 60 column 2, line 21 - line 43 column 3, line 13 - line 25 column 4, line 9 - line 28; examples 1,3 ---	10,11,13
X	US 5 785 990 A (LANGREHR JANA S) 28 July 1998 (1998-07-28) column 3, line 11 - line 19 column 3, line 36 column 3, line 40 column 3, line 57; tables 2,4 column 10, line 20 - line 31; claim 1 ---	19-21
X	EP 0 753 302 A (MEIJI SEIKA KAISHA) 15 January 1997 (1997-01-15) page 2, line 33 - line 37 page 2, line 45 - line 48 page 2, last paragraph page 3, line 7 - line 8 page 2, line 40 - line 43; claims; examples 1,2 ---	19,21
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 00 /00986

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-18, 21 (part.)

   Emulsion with in aqueous phase viscosity modifier, dissolved calcium compound and in discontinuous phase vitamin D and triglyceride, further comprising an emulsifying agent. Process for preparation of the emulsion.

2. Claims: 19, 20, 21 (part.)

   Oral calcium supplement with prebiotic.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte onal Application No
PCT/GB 00/00986

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