



Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

Canadian
Intellectual Property
Office

An agency of
Industry Canada

CA 2695366 A1 2009/02/12

(21) **2 695 366**

(12) **DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION**

(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2008/08/04
(87) Date publication PCT/PCT Publication Date: 2009/02/12
(85) Entrée phase nationale/National Entry: 2010/02/01
(86) N° demande PCT/PCT Application No.: US 2008/009399
(87) N° publication PCT/PCT Publication No.: 2009/020595
(30) Priorités/Priorities: 2007/08/03 (US60/953,944);
2007/08/03 (US60/953,934)

(51) Cl.Int./Int.Cl. *A61K 9/48* (2006.01),
A23L 1/30 (2006.01)
(71) Demandeur/Applicant:
SHAKLEE CORPORATION, US
(72) Inventeurs/Inventors:
CHANG, KUEI-TU, US;
SMIDT, CARSTEN R., US;
CASTILLO, JOHN, US;
MERGENS, WILLIAM J., US
(74) Agent: SMART & BIGGAR

(54) Titre : SYSTEME DE COMPLEMENT NUTRITIONNEL
(54) Title: NUTRITIONAL SUPPLEMENT SYSTEM

(57) **Abrégé/Abstract:**

A multi-part nutritional supplement system supplies nutrients to a user at advantageous locations in the digestive tract.



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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 February 2009 (12.02.2009)

PCT

(10) International Publication Number
WO 2009/020595 A3

(51) International Patent Classification:

A61K 9/48 (2006.01) A23L 1/30 (2006.01)

(21) International Application Number:

PCT/US2008/009399

(22) International Filing Date: 4 August 2008 (04.08.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/953,934 3 August 2007 (03.08.2007) US
60/953,944 3 August 2007 (03.08.2007) US

(71) Applicant (for all designated States except US): **SHAK-LEE CORPORATION** [US/US]; 4747 Willow Road, Pleasanton, CA 94588 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CHANG, Kuei-tu** [US/US]; 2753 Glauser Drive, San Jose, CA 95133 (US). **SMIDT, Carsten, R.** [DE/US]; 5739 Ohana Place, Pleasanton, CA 94566 (US). **CASTILLO, John** [US/US]; 37889 Rockspray Street, Newark, CA 94560 (US). **MERGENS, William, J.** [US/US]; 1639 Breakers West Blvd., West Palm Beach, FL 33411 (US).

(74) Agent: **POLLEY, Richard, J.**; Klarquist Sparkman, LLP, One World Trade Center, Suite 1600, 121 Sw Salmon Street, Portland, OR 97204 (US).

(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, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

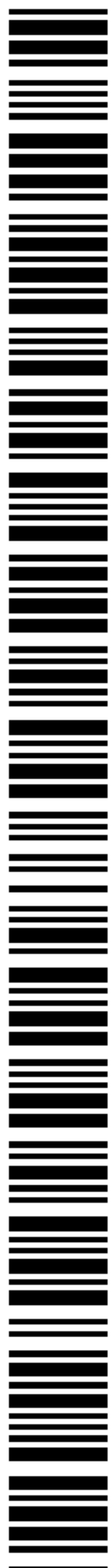
Published:

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
9 April 2009

(54) Title: NUTRITIONAL SUPPLEMENT SYSTEM

(57) Abstract: A multi-part nutritional supplement system supplies nutrients to a user at advantageous locations in the digestive tract.



WO 2009/020595 A3

NUTRITIONAL SUPPLEMENT SYSTEM

Cross Reference to Related Applications

This claims the benefit of U.S. Provisional Application No. 60/953,934 filed
5 August 3, 2007 and U.S. Provisional Application No. 60/953,944 filed August 3,
2007, both herein incorporated by reference.

Background and Summary

Described herein is a nutritional supplement system for the delivery of
10 vitamins, minerals, and/or probiotics for sustaining the health of human subjects.

Vitamin and mineral preparations are commonly administered as general
nutritional supplements. Micronutrients are elements or compounds which are
present in foods and herbs in small or trace amounts. These include vitamins,
minerals, or other elements, and substances found in foods. The macronutrients
15 consist of carbohydrates, fats, and proteins, which supply nutrients and calories.
Some elements such as calcium, sodium, potassium, chloride, and phosphorus are
consumed in relatively large amounts, while many such as iron, iodine, and zinc are
consumed in small amounts. Vitamins, such as vitamin B12 and folic acid, and the
minerals copper, selenium, and chromium are consumed in very small or trace
20 amounts.

Inasmuch as the human body does not synthesize many compounds which
are essential to the human body, certain vitamins, minerals, and other nutrients can
be obtained from only two sources, food and supplements. The primary source of
all nutrients is food. However, many people do not acquire optimal amounts of the
25 essential compounds and elements from the foods they eat. Thus, nutritional
supplementation has become a recognized method of preserving good health.

The consumption of probiotic supplements also can be beneficial to the well
being of humans. It has been recognized that temporary or chronic digestive
symptoms can be caused by a damaged or disordered intestinal flora. Consumption
30 of a nutritional supplement preparation containing suitable microorganisms is often
sufficient to alleviate or to eliminate the symptoms caused by a disordered or
damaged intestinal flora.

As used herein, "probiotics" refers to live micro-organisms, delivered in food supplements, which beneficially affect the host animal by improving its intestinal microbial balance. Antibiotics and other related compounds are not included in this definition. (*J. Nutr.* 1995;125:1401-12). For humans, lactobacilli are commonly
5 provided as probiotics, either as single species or in mixed culture with other bacteria. Other genera that have been used are bifidobacteria and streptococci. "Prebiotics" refers to non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of bacteria in the colon.

It has been a problem with many prior nutritional supplement systems that
10 they provide incomplete nutrition or that a multiplicity of doses of nutrients must be taken at multiple different times to achieve a well balanced and appropriately timed delivery of nutrients to a user. Prior nutritional supplement systems have in some cases delivered nutrients to a location in the digestive tract where, although effective for uptake of the nutrients, have caused user discomfort. In other cases, one or more
15 nutrients are released in a location that is not optimal for uptake by the body. When nutrients or probiotics are released in locations that are unfavorable reduce biological activity can result. For example, probiotics typically do not survive exposure to stomach acid.

It has been a specific problem in the formulation of supplements for the
20 delivery of vitamin B12 that the absorption of vitamin B12 has been found to require secretion of a glycoprotein, known as "intrinsic factor," from cells lining the stomach. Normally, vitamin B12 is readily absorbed in the last part of the small intestine (ileum), which leads to the large intestine. However, to be absorbed, the vitamin must combine with intrinsic factor. As a result of passage through the
25 stomach, vitamin B12 is attaches to intrinsic factor for transfer. This combination of the vitamin and intrinsic factor can then be "caught" by the ileal receptor. Without intrinsic factor, significant amounts of vitamin B12 can remain in the intestine and are excreted in the stool. Previously it has been thought that, to maximize the absorption of vitamin B12, a supplement should be formulated to deliver vitamin
30 B12 in the stomach to maximize binding to intrinsic factor and optimize uptake of the intrinsic factor/B12 complex. But there are difficulties with supplements that provide for rapid release vitamin B12 in the stomach.

There thus is a continuing need for user friendly systems for effectively delivering beneficial substances to the body.

In answer to that need a nutritional supplement system is provided that supplies nutrients and/or probiotics at various appropriate locations in the digestive tract.

One particular element of such a system is a dosage unit formulated to release vitamin B12 over time in both the stomach and the intestines of the upper GI tract.

Detailed Description

A multi-component oral nutritional supplement system supplies a combination of nutrients and/or probiotics at optimal locations throughout the digestive tract of a human subject for efficient nutrient utilization and user comfort and convenience.

An optimal system includes four dosage units, although certain other beneficial systems may include two or three dosage units.

A first dosage unit that is formulated to quickly release one or more nutrients in the stomach of a human subject. This dosage unit advantageously includes vitamins and minerals or other dietary supplement ingredients that benefit from release in the stomach and exposure to stomach acid, or are not adversely affected by such release or exposure, and/or properly are dispersed in the stomach for optimal absorption further down in the GI tract. This dosage unit advantageously is in the form of a tablet or caplet formed by compression. The tablet may be coated with a layer containing one or more nutrients that best are delivered in the stomach particularly rapidly. In general, the first dosage unit should not contain substances that are not well tolerated by the stomach or that would be harmed by the acidic environment of the stomach; such substances should be delivered in one of the other dosage units described herein.

A second dosage unit is formulated to contain nutrients that do not require release in the stomach and exposure to stomach acid for efficient digestion and absorption, and which may cause tolerance problems (repeating, stomach upset, nausea) or loss in biological activity when released in the stomach. This dosage unit

advantageously is used to deliver certain nutritional oils, notably fish oil constituents, other omega-3 fatty acid containing oils, and may also include fat-soluble micronutrients that do not require stomach digestion, such as vitamins A, D, E, and carotenoids. The dosage unit advantageously is a sealed gelatin
5 encapsulation that can pass through the stomach before releasing the encapsulated nutrients.

A third dosage unit is formulated to contain water-soluble nutrients and other nutrients that are typically very rapidly absorbed and therefore best delivered by sustained release so as to maintain an elevated concentration in the body over time.
10 This dosage unit is designed to slowly, in generally linear fashion, release one or more water-soluble nutrients. The release of these nutrients is initially in the stomach and continues into the intestines of the upper GI tract. This dosage unit advantageously is formulated to release vitamin B12. The dosage unit also is useful to deliver other B-vitamins and vitamin C.

15 A fourth dosage unit contains nutrients and/or other supplement ingredients such as probiotics that are adversely affected by exposure to stomach acid or stomach digestion, and that should be delivered into the lower parts of the small intestine for full activity in the large intestine. This dosage unit is formulated to protect the probiotic microorganisms from potentially lethal acid exposure during
20 passage of the dosage unit through the stomach. Advantageously it is in the form of a three-layer capsule.

These four dosage units are formulated for administration one time each day, and can be taken substantially simultaneously, to provide complete and appropriately timed delivery of a full range of nutrients and probiotics.

25 All the dosage units of complete daily dose of the nutritional supplement system advantageously are packaged together as a multi-element package so that a user will not need to remember to combine various individual dosage units to make a complete daily dose. In some cases, to avoid the use of uncomfortably large tablets, caplets, or capsules, certain of the dosage units can be split into two or more
30 tablets, caplets, or capsules. Because a balanced supplement system requires relatively large amount of the nutrients of the first and second dosage units, in a particularly advantageous arrangement the first dosage unit is in the form of two

separate dosage elements, preferably tablets or caplets, and the second dosage unit is in the form of two separate dosage elements, preferably gel encapsulations. With that arrangement, the two first dosage unit elements, the two second dosage unit elements, one third dosage unit element, and one fourth dosage unit element can be
5 provided together, for example in a single blister pack card or strip, so that a user will immediately know that the six elements together are a day's dose. A typical blister pack arrangement will have six attached blister strips, separated by perforated detachment lines, with each strip holding the six dosage elements that together comprise a day's dose.

10 The dosage units advantageously employ various forms of extended release excipients or coatings along with immediate release excipients or coatings to deliver the various vitamins and mineral supplements over various optimum rates of release. For example, a folic acid micro-coating can be employed to release folic acid from the multi-vitamin and mineral supplement within minutes after entry into the
15 stomach. Gel diffusion technology can be used to maximize the intestinal adsorption of vitamins B and C for over twelve hours. Providing fish oil in delayed release capsules results in rapid release in the intestines of upper GI tract, which gives maximum bioavailability and minimum stomach discomfort. And a triple layer encapsulation system provides for targeted release of probiotics to the lower
20 GI tract.

In general, those of ordinary skill know how to formulate dosage units with various different release profiles. Nutritional supplement dosage units may employ one or more forms of release, including, without limitation, immediate release, extended release, pulse release, variable release, controlled release, timed release,
25 sustained release, delayed release, long acting, and combinations thereon. The various types of release can be accomplished using well known procedures and techniques.

The time release characteristics for the release of the components may be varied by modifying the composition of layers, including modifying any of the excipients or coatings which may be present. For example, changing the
30 composition or amount of the covering or coating layers may be used to control the release of the components. Similarly, when modified release is facilitated by the

inclusion of a specific matrix material, controlling the choice and amount of modified release matrix material utilized may be used to control the release of the active components. The matrix material may be present, either surrounding individual components of the composition or over a layer of the composition, in any amount that is sufficient to yield the desired time release or time lag between release of the components.

Various coating materials that modify the release of the components in the desired manner may be used. In particular, coating materials suitable for use in the practice include, but are not limited to polymer coating materials, hydrogels and gel-forming materials and hydrophilic polymers. Preferred polymer coating materials are cellulose acetate phthalate, cellulose acetate trimaletate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, amino methacrylate copolymers such as Eudragit.RTM. RS and RL, polyacrylic acid and polyacrylate and methacrylate copolymers such as Eudragit.RTM. S and L, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, and shellac.

Preferred hydrogels and gel-forming materials include carboxyvinyl polymers, sodium alginate, sodium carmellose, calcium carmellose, sodium carboxymethyl starch, polyvinyl alcohol, hydroxyethyl cellulose, methyl cellulose, gelatin, starch, and cellulose based cross-linked polymers in which the degree of crosslinking is low so as to facilitate adsorption of water and expansion of the polymer matrix, hydroxypropyl cellulose, hydroxypropyl methylcellulose, crosslinked starch, microcrystalline cellulose, chitin, aminoacryl-methacrylate copolymer (Eudragit.RTM. RS-PM), pullulan, collagen, casein, agar, gum arabic, sodium carboxymethyl cellulose, (swellable hydrophilic polymers) poly(hydroxyalkyl methacrylate) (molecular weight about 5 k-5,000 k), polyvinylpyrrolidone (molecular weight about 10 k-360 k), anionic and cationic hydrogels, polyvinyl alcohol having a low acetate residual, a swellable mixture of agar and carboxymethyl cellulose, copolymers of maleic anhydride and styrene, ethylene, propylene or isobutylene pectin (molecular weight about 30 k-300 k), polysaccharides such as agar, acacia, karaya, tragacanth, algin and guar, polyacrylamides, Polyox.RTM. polyethylene oxides (molecular weight about 100 k-

5,000 k), AquaKeep.RTM. acrylate polymers, diesters of polyglucan, crosslinked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, and sodium starch glycolate (e.g., Explotab.RTM.).

Preferred hydrophilic polymers include polysaccharides, methyl cellulose,
 5 sodium or calcium carboxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, nitrocellulose, carboxymethyl cellulose, cellulose ethers, polyethylene oxides (e.g. Polyox.RTM., Union Carbide), methylethyl cellulose, ethylhydroxy ethylcellulose, cellulose acetate, cellulose butyrate, cellulose propionate, gelatin, collagen, starch, maltodextrin, pullulan,
 10 polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic acid, copolymers of methacrylic acid or methacrylic acid (e.g., Eudragit.RTM.), other acrylic acid derivatives, sorbitan esters, natural gums, lecithins, pectin, alginates, ammonia alginate, sodium, calcium, potassium alginates, propylene glycol alginate, agar, and gums such as arabic, karaya, locust
 15 bean, tragacanth, carrageens, guar, xanthan, scleroglucan and mixtures and blends thereof.

Excipients such as plasticisers, lubricants, solvents and the like may be added to a coating. Suitable plasticisers include for example hydroxylated soy lecithin, acetylated monoglycerides, butyl phthalyl butyl glycolate, dibutyl tartrate, diethyl
 20 phthalate, dimethyl phthalate, ethyl phthalyl ethyl glycolate, glycerin, propylene glycol, triacetin, citrate, tripropioin, diacetin, dibutyl phthalate, acetyl monoglyceride, polyethylene glycols, castor oil, triethyl citrate, polyhydric alcohols, glycerol, acetate esters, glycerol triacetate, acetyl triethyl citrate, dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, diisononyl phthalate, butyl octyl phthalate,
 25 dioctyl azelate, epoxidized tallate, triisooctyl trimellitate, diethylhexyl phthalate, di-n-octyl phthalate, di-i-octyl phthalate, di-i-decyl phthalate, di-n-undecyl phthalate, di-n-tridecyl phthalate, tri-2-ethylhexyl trimellitate, di-2-ethylhexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate.

A coating layer may be any suitable modified release matrix material or
 30 suitable combination of modified release matrix materials. Such materials are known to those skilled in the art. Modified release matrix materials suitable for the practice of the present invention include, but are not limited to, microcrystalline cellulose,

sodium carboxymethylcellulose, hydroxyalkylcelluloses (e.g., hydroxypropylmethylcellulose and hydroxypropylcellulose), polyethylene oxide, alkylcelluloses (e.g., methylcellulose and ethylcellulose), polyethylene glycol, polyvinylpyrrolidone, cellulose acetate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose acetate trimellitate, polyvinylacetate phthalate, polyalkylmethacrylates, polyvinyl acetate and mixtures thereof.

The dissolution characteristics of a dosage form can be manipulated not only through the quantity of the excipients in the finished dosage form and size of the finished dosage form, but also by a judicious selection and blending of various molecular weights of a given polymer or polymers, as is known to those skilled in the art.

Film coated tablets may be prepared by coating tablets using techniques such as rotating pan coating methods or air suspension methods to deposit a contiguous film layer on a tablet. This procedure is often done to improve the aesthetic appearance of tablets, but may also be done to improve the swallowing of tablets, to mask an obnoxious odor or taste, or to improve to usual properties of an unsightly uncoated tablet. Compressed tablets, for example, without limitation, may be prepared by mixing the components with excipients intended to add binding or disintegration qualities. The mixture is either directly compressed, or granulated then compressed, using methods and machinery quite well known to those in the industry.

One or more of the dosage units of the nutritional supplement system described herein can also be used to deliver prebiotics. Example prebiotics include oligosaccharides such as glucose, fructose, xylose, galactose, lactose, mannose, arabinose, D-fucose, L-fucose, rhamnose, Actilight, Biotose, Palatinose, IMO, cellobiose, gentiobiose, laevan, maltodextrin, maltose, melibiose, raffinose, lactose, panorich, melezitose, raftiline, raftilose, stachyose, sucrose, tagatose, xylan, fructooligosaccharide (FOS), galactooligosaccharide (GOS), soy oligosaccharide, lactosucrose, maltooligosaccharide, xylooligosaccharide, inulin and fractionated inulin as well as one or more dietary fiber components such as coconut (including coconut endosperm fibber), beet pulp (such as sugarbeet pulp), chicory (including chicory pulp), oat bran concentrate, rice bran, carob bean, gum talhar and guar gum.

The nutritional supplement system will be better understood with reference to the following specific discussion and examples which detail certain procedures for the preparation of the dosage units. All references made to specific examples are for the purposes of illustration. They are not to be considered limiting as to the scope and nature of the present invention.

First Dosage Unit

The first dosage unit is formulated to contain vitamins and minerals, typically at or near their USFDA Daily Value (DV) level, that best are delivered in the stomach. Such nutrients include vitamins, minerals and other dietary supplement ingredients that benefit from release in the stomach and exposure to stomach acid, or that are not adversely affected by such release or exposure, and/or that properly are dispersed in the stomach for optimal absorption further down the GI tract.

This dosage unit advantageously is in the form of a tablet or caplet formed by compression of a blend containing vitamins, minerals and appropriate excipients. Because rapid delivery of nutrients is desired, the first dosage unit should be formulated for release in less than one hour, and best within 0.75 hour.

The tablet or caplet may be coated with a layer containing one or more nutrients that best are delivered particularly rapidly. Advantageously, the coating will include folic acid (folate) for rapid release. As described in U.S. Patents Nos. 6,852,335 and 6,465,013, folic acid in an outer coating is released more rapidly than when folic acid is contained in the core of a tablet, resulting in increased bioavailability.

The first dosage unit optimally is formulated to include:

from 0 mg to 600 mg of phosphorus,
from 50 mg to 600 mg of magnesium,
from 30 mg to 500 mg of vitamin C,
from 1 mg to 30 mg of zinc,
from 30 IU to 400 IU of vitamin E,
from 0 mg to 5 mg of manganese,
from 5 mg to 50 mg of vitamin B3,
from 0 mg to 5 mg of boron,

from 0.5 mg to 5 mg of copper,
 from 0 IU to 10,000 IU of vitamin A,
 from 0 mg to 6 mg of beta carotene,
 from 1 mg to 30 mg of pantothenic acid,
 5 from 0 mg to 200 mcg of trace mineral protein hydrolysate for
 chromium, molybdenum, nickel, tin, vanadium, and selenium,
 from 0 mcg to 200 mcg of vitamin K,
 from 0 mg to 100 mg of N-acetyl cysteine,
 from 0 mg to 25 mg of silicon,
 10 from 1 mg to 10 mg of vitamin B6,
 from 1 mg to 10 mg of vitamin B1,
 from 1 mg to 10 mg of vitamin B2,
 from 3 mcg to 25 mcg of vitamin B12,
 from 200 IU to 800 IU of vitamin D3,
 15 from 100 mcg to 800 mcg of folate,
 from 50 mcg to 600 mcg of biotin, and
 from 50 mcg to 500 mcg of iodine.

Example formulations of a first nutritional supplement dosage unit, in the
 form of immediate release tablets, are shown in the following table:

20

	Men's Vitamin/Mineral Tablet		Women's Vitamin/Mineral Tablet		Senior's Vitamin/Mineral Tablet	
Ingredient	Label Claim (per dose)		Label Claim (per dose)		Label Claim (per dose)	
Dicalcium phosphate (Ca)	450 mg		450 mg		450 mg	
Dicalcium phosphate (P)	350 mg		350 mg		350 mg	
Magnesium oxide	200 mg		200 mg		200 mg	
Microcrystalline cellulose	n/a		n/a		n/a	
Ascorbic acid	120 mg		120 mg		120 mg	
Zinc gluconate	15 mg		15 mg		22.5 mg	
Ferrous fumarate	18 mg		n/a		n/a	
Hydroxypropyl methylcellulose	n/a		n/a		n/a	
Vitamin E succinate	60 IU		60 IU		60 IU	
Manganese gluconate	2 mg		2 mg		2 mg	
Croscarmellose sodium	n/a		n/a		n/a	
Niacinamide	20 mg		20 mg		30 mg	
Boron protein hydrolysate	1 mg		1 mg		1 mg	
Magnesium stearate	n/a		n/a		n/a	
Copper gluconate	2 mg		2 mg		2 mg	

Vitamin A acetate	2500 IU		2500 IU		1500 IU	
Beta carotene	2500 IU		2500 IU		1500 IU	
d-Calcium pantothenate	10 mg		10 mg		15 mg	
Sea kelp powder	n/a		n/a		n/a	
Selenium*	70 mcg		70 mcg		70 mcg	
Chromium*	120 mcg		120 mcg		120 mcg	
Molybdenum*	75 mcg		75 mcg		75 mcg	
Nickel*	15 mcg		15 mcg		5 mcg	
Tin*	10 mcg		10 mcg		10 mcg	
Vanadium*	20 mcg		20 mcg		20 mcg	
Vitamin K	80 mcg		80 mcg		80 mcg	
N-acetyl cysteine	n/a		n/a		25 mg	
Spirulina	n/a		n/a		n/a	
Inositol	n/a		n/a		n/a	
Choline bitartrate	n/a		n/a		n/a	
Alfalfa powder	n/a		n/a		n/a	
Grapefruit bioflavonoid	n/a		n/a		n/a	
Hesperidin complex	n/a		n/a		n/a	
Lemon bioflavonoid	n/a		n/a		n/a	
Mixed tocopherols	n/a		n/a		n/a	
Orange bioflavonoid	n/a		n/a		n/a	
Rice bran powder	n/a		n/a		n/a	
Rose hips powder	n/a		n/a		n/a	
Acerola extract	n/a		n/a		n/a	
Silicon dioxide	2 mg		2 mg		2 mg	
Pyridoxine hydrochloride	2 mg		2 mg		4 mg	
Thiamine mononitrate	1.5 mg		1.5 mg		2.25 mg	
Riboflavin (nutrient)	1.7 mg		1.7 mg		2.55 mg	
Riboflavin (color)	n/a		n/a		n/a	
Hydroxylated soy lecithin	n/a		n/a		n/a	
Carnauba wax	n/a		n/a		n/a	
Vitamin B ₁₂	6 mcg		6 mcg		24 mcg	
Vitamin D ₃	400 IU		400 IU		800 IU	
Folic acid	400 mcg		400 mcg		400 mcg	
Biotin	300 mcg		300 mcg		300 mcg	
Potassium iodide (I)	150 mcg		150 mcg		150 mcg	
* Supplied as a trace mineral protein hydrolysate						

Coated tablets were assembled by combining the ingredients to form the blend for a core and compressing the blend to form tablets. The tablets were then coated with a film coating solution. Two such tablets served as one day's dose of the first dosage unit.

Second Dosage Unit

The second dosage unit is formulated to contain nutrients that do not require release in the stomach and exposure to stomach acid for efficient digestion and

absorption, and which may cause tolerance problems (repeating, stomach upset, nausea) or loss in biological activity when released in the stomach. This dosage unit advantageously is used to deliver certain nutritional oils, notably fish oil constituents, other omega-3 fatty acid containing oils, and may also include fat-soluble micronutrients that do not require stomach digestion, such as vitamins A, D, E, and carotenoids.

The dosage unit advantageously is a sealed gelatin encapsulation that can pass through the stomach before releasing the encapsulated nutrients.

This dosage unit is formulated to pass through the stomach without releasing its contents, notably fish oil, and remain unopened until after it naturally passes into the intestines of the upper GI tract. Release in the stomach can lead to an unpleasant taste caused by repeating fish oil aroma ("fish burp") in the mouth of a user.

This dosage form thus advantageously is a soft capsule having a coating resistant to gastric juice to achieve a delayed release of the fish oil in the intestine, advantageously a coating of a polymer such as methacrylic acid. Delayed release can also be accomplished or enhanced by cross-linking of gelatin used to form such a capsule or by providing derivates of starch in the casing of such a capsule.

The second dosage unit optimally is formulated to include:

from 0 mg to 10 mg of lutein,
from 0 mg to 10 mg of lycopene,
from 50 IU to 400 IU of vitamin D3,
from 50 IU to 400 IU of vitamin E,
from 50 mg to 3500 mg of total omega-3 fatty acids (fish oil), and
from 0 mg to 250 mg of gamma-tocopherol.

An example formulation of a second nutritional supplement dosage unit, in the form of a soft gelatin capsule, is shown in the following table:

Ingredient	Enteric Coated Fat Soluble Nutrients	
	Label Claim (per dose)	
Lutein ester suspension	2 mg	
Lycopene suspension	2.5 mg	
Vitamin D ₃	200 IU	
Mixed tocotrienols & tocopherols	1 mg	
Vitamin E (α-tocopherol concentrate)	140 IU	
Total omega-3 fatty acids	500 mg	
Gamma tocopherol	25 mg	
Beta and delta tocopherol	10 mg	
Silicon dioxide	n/a	
Beeswax	n/a	
Glycerin	n/a	
Gelatin	n/a	
Annatto suspension (Ultrabix 03190)	n/a	
Water	n/a	
Enteric coating (TM29Z19241 Clear)	n/a	
Surelease (E-7-19040)	n/a	
Natural vanillin	n/a	

The nutritional ingredients were mixed to form a fill mixture. Gel mass ingredients were mixed to form a gel mass. Formed halves were injected with the fill mixture and then joined to form capsules. Coating ingredients were mixed to make a coating mixture; and then the formed capsules were coated with the mixture in a tablet coating apparatus. The finished product was then dried.

Two of the resulting encapsulations served as one day's dose of the second dosage unit.

Third Dosage Unit

The third dosage unit is formulated to contain one or more water-soluble nutrients and/or other nutrients that are typically very rapidly absorbed and therefore best delivered by sustained release so as to maintain an elevated concentration in the body over time.

Certain rapidly-absorbed, typically water-soluble nutrients are best delivered by sustained release so as to maintain an elevated concentration in the body over time. These include B-vitamins and vitamin C. If given in an immediate release

dosage unit, the concentrations of such vitamins in the body rapidly decline after an initial peak. Moreover, the absorptive sites and nutrient uptake mechanisms in the intestinal wall can be overwhelmed by the high intestinal nutrient concentrations caused by immediate release dosage units, which is known to reduce the overall amount that can be taken up by the body. Sustained release dosage units of such vitamins have been used to overcome these problems. But sustained release dosage units of such vitamins have typically excluded vitamin B12 because of the perceived need to deliver an entire dose of vitamin B12 to the stomach so that it can be combined with intrinsic factor.

Testing now shows that vitamin B12, delivered by sustained release, can result in improved bioavailability of vitamin B12 as compared to immediate release in the stomach. In the particular tests conducted, subjects were given a tablet containing 9.8 mg vitamin B1, 11.5 mg vitamin B2, 13.1 mg vitamin B6, 90 µg vitamin B12 and 518 mg vitamin C. For the B vitamins, ingestion of a comparable immediate-release formulation produced peak plasma concentrations for B1, B2 and B6 at 2 hours post ingestion and at 3 hours for serum vitamin B12. B-vitamin concentrations then declined rapidly from peak concentrations, returning to baseline by 6 hr for B1 and B6 and by 12 hr for B2 and B12. In contrast, ingestion of the sustained release formulation resulted in delayed peak serum and plasma concentrations until 4 hr for B1 and B2 and 5 hr for B6 and B12. Sustained-release tablet delivery was found to improve the bioavailability of vitamin C and at least three B-vitamins, including vitamin B12, in comparison to immediate release delivery.

The third dosage unit thus is formulated to release vitamin B12 in the stomach and intestines of the upper GI tract, advantageously in an amount that is greater than or at multiple levels of the DV (Daily Value) of vitamin B12. This is accomplished by including vitamin B12 in an amount of from 3 mcg to 500 mcg, with best results at a vitamin B12 amount of from 6 mcg to 500 mcg.

Best results for the delivery of vitamin B12 are achieved with a dosage unit that releases vitamin B12, as determined by USP dissolution apparatus at 37°C at 50 RPM paddle speed in 900 ml of 0.1N HCl, continuously and generally linearly over a period of 6 hours. It is particularly advantageous for the dosage unit to be

formulated to allow at least 15% of the vitamin B12 to dissolve in one hour in 900 ml of 0.1N HCl at 37°C. This dosage form, after ingestion by a subject, will sustain plasma levels of the vitamin B12 for a period 12 hours. Good delivery of vitamin B12 is achieved, for example, with third dosage unit tablet of 350 mg to 1500 mg total weight, where the tablet contains 20 mcg to 100 mcg of vitamin B12 and contains 5% to 20% HPMC K100/ E15 by weight. Superior results are achieved with tablets having 9.5% to 14% HPMC K100/E15.

The third dosage unit also can be used to deliver one or more other water-soluble nutrients, particularly other B-vitamins and vitamin C, advantageously at or above or at multiple levels of their DVs (Daily Values) where applicable. The dosage unit thus advantageously will include 30 mg to 1000 mg of vitamin C, 1 mg to 40 mg of vitamin B1, 1 mg to 40 mg of vitamin B2, 10 mg to 300 mg of niacin, 10 mg to 300 mg of vitamin B5, and 1 mg to 40 mg of vitamin B6. A particularly useful formulation includes from 30 mg to 750 mg of vitamin C, from 25 mg to 400 mg of calcium, from 1 mg to 40 mg of vitamin B1, from 1 mg to 40 mg of vitamin B2, from 10 mg to 300 mg of vitamin B5, from 1 mg to 40 mg of vitamin B6, from 6 mcg to 500 mcg of vitamin B12, from 1 mg to 100 mg of bioflavonoid complex, and from 5 mg to 300 mg of quercetin.

The third dosage unit is designed to slowly, in a generally linear fashion, release the one or more of such water-soluble nutrients. The release of the water-soluble nutrients in general should occur in the stomach and small intestine (duodenum, jejunum and ileum).

Generally, when a supplement is taken with a meal, as commonly recommended, it takes about 6-12 hours to pass through stomach and small intestine. Therefore release of the water-soluble vitamins from the third dosage unit should extend for at least three hours after ingestion, and advantageously for up to a full twelve hours after ingestion. The third dosage unit also advantageously will be formulated to release vitamin B12 such that plasma levels of the vitamin B12 are sustained for a period of at least 6 hours, with best results achieved when formulated such that plasma levels of the vitamin B12 are sustained during the period of from 30 minutes to 24 hours after ingestion.

An example formulation of a third nutritional supplement dosage unit, in the form of a sustained release tablet, is shown in the following table:

5

	Sustained Release Vitamin B + C Tablet	
Ingredient	Label Claim (per dose)	
Calcium ascorbate (Ca)	43 mg	
Calcium ascorbate (Vitamin C)	380 mg	
Calcium carbonate (Ca)	7 mg	
Thiamin mononitrate	7.5 mg	
Riboflavin	8.5 mg	
Niacinamide	100 mg	
Calcium pantothenate	50 mg	
Pyridoxine hydrochloride	10 mg	
Vitamin B ₁₂	30 mcg	
Citrus bioflavonoids	25 mg	
Quercetin	50 mg	
Microcrystalline cellulose	n/a	
Magnesium stearate	n/a	
Silicon dioxide	n/a	
Hydroxypropyl methylcellulose	n/a	
Hydroxylated soy lecithin	n/a	

Tablet contents were mixed, and tablets were formed from the resulting mixture. Coating ingredients were mixed, and the resulting mixture was used to coat the tablets.

10

Fourth Dosage Unit

The fourth dosage unit contains nutrients and/or other supplement ingredients, such as probiotics, that are adversely affected by exposure to stomach acid or stomach digestion and that should be delivered into the lower parts of the small intestine for full activity in the large intestine.

15

This dosage unit is formulated to protect the probiotic microorganisms from potentially lethal acid exposure during passage through the stomach. This can be accomplished using coated or enteric-coated tablets or capsules and other solid dosage delivery forms, where the coating is designed to deliver the ingredients into the lower intestinal tract (ileum and colon).

20

In one arrangement the fourth dosage unit is in the form of layered capsule as described in U.S. Patent No. 5,478,570.

Particularly useful is a triple layer, enteric release encapsulation which protects live probiotic organisms from the acidic gastric environment and releases the organisms in the intestinal tract where they can flourish and provide their health benefits.

5 For the triple layer delivery system, the inner layer or core contains the probiotic organisms (preferably *Lactobacillus acidophilus* and *Bifidobacterium longum*) suspended in vegetable oil. The middle layer, composed of hardened vegetable oil, surrounds and protects the inner layer. The outer layer or primary protective shell is composed of gelatin, pectin and glycerine and provides stability
10 from heat, freezing and acid.

The capsule has an outer shell that does not dissolve under pH 4 (at 37°C) and thus is adapted to pass through the stomach intact. Once the capsule reaches the higher pH environment in the intestines, the outer gelatin shell begins to slowly dissolve, gradually exposing the inner lipid layers. The probiotics are then gradually
15 released by the further action of lipolytic enzymes and the motion of the intestinal tract.

The fourth dosage unit optimally is formulated to include:

from 250,000 cfu to 20 billion cfu of *Lactobacillus acidophilus*,
and from 250,000 cfu to 20 billion cfu of *Buifodobacterium longum*.

20 An example formulation of a fourth nutritional supplement dosage unit, in the form of a delayed release capsule, is shown in the following table:

Ingredient	Triple-Layer Probiotic Capsule	
	Label Claim (per dose)	
<i>Lactobacillus acidophilus</i>	250M CFU	
<i>Bifidobacterium longum</i>	250M CFU	
Coconut/palm oil	n/a	
Gelatin	n/a	
Glycerin	n/a	
Soy lecithin	n/a	
Pectin	n/a	

The ingredients were combined in layered capsules. A core of each capsule contained the *Lactobacillus acidophilus* and *Buifodobacterium longum*.

The core was covered by a layer of the vegetable oil to protect the beneficial bacteria during passage through the stomach. The gelatin was provided as an outer shell over the vegetable oil to provide further protection from the acidic stomach environment.

5 In a second example arrangement, the forth dosage unit can be formed using a sodium alginate-ethylcellulose enteric coating system for soft gelatin capsules.

In this arrangement, the composition of enteric film basically consists of sodium alginate and ethylcellulose. The sodium alginate is insoluble in acids where the pH of the resulting solution (coating solution) falls below 3.0. The
10 ethylcellulose is insoluble in water, but it is a very good film forming and adhesive polymer while the sodium alginate is a crystalline powder which does not have filming capability.

An ethylcellulose coating solution can be formed by processing ethylcellulose in an alkaline aqueous solution (ammonia solution) to form a latex
15 solution, for example, Surelease[®] coating, by Colorcon, West Point, PA, USA. Small ethylcellulose particles (latex) are able to disperse uniformly in a solution for coating applications. By spraying the ethylcellulose latex aqueous solution on tablets in a coating system upon heating, the ammonia and water are evaporated and the ethylcellulose latexes are left on the tablet surface. Under heated condition, the
20 latexes then can be annealed together to form a non-water soluble film on the tablet surface.

Small molecular sodium alginate can be provided in the ethylcellulose aqueous solution. The sodium alginate will dissolve in the latex alkaline solution to form an enteric coating solution. Once the enteric coating solution is sprayed on the
25 tablets (2-4 percent solid gain), the ammonia and water are evaporated. Ethylcellulose latexes then can be annealed to form a film. The sodium alginate and ethylcellulose (sodium alginate-ethylcellulose solid solution) is molecularly mixed and uniformly coated on the tablet surface.

Once the enteric coated tablets are administered and reach stomach, the
30 enteric coated tablets will stay intact in the acid condition (pH 2.6) for 6-12 hours. Both sodium alginate and ethylcellulose do not dissolve and will prevent water from penetrating into the core tablet to avoid premature release of the active ingredient.

Once the tablets reach the intestine, the film starts to dissolve and the content of tablets are released instantly. The ratio of sodium alginate and ethylcellulose can be varied to control the release pattern and insure an instant, full release in the target physiological site for the best bioavailability.

5

Preferred Formulation

In its entirety, a preferred nutritional supplement system includes vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin C, vitamin D3, vitamin E, vitamin B5,
 10 vitamin B6, vitamin B12, vitamin B, vitamin K, lutein, lycopene, omega-3 fatty acids (from fish oil), gamma-tocopherol, silicon, beeswax, calcium, niacin, bioflavonoid complex, quercetin, phosphorus, magnesium, zinc, manganese, boron, copper, beta carotene, trace mineral protein hydrolysate for chromium, molybdenum, nickel, tin, vanadium, boron and selenium, N-acetyl cysteine,
 15 spirulina, folate, biotin, iodine, probiotic Acidopholis, and probiotic Bifidus.

A particularly complete and advantageous system comprises
 from 0 mg to 10 mg of lutein,
 from 0 mg to 10 mg of lycopene,
 from 200 IU to 2000 IU of vitamin D3,
 20 from 80 IU to 450 IU of vitamin E,
 from 50 mg to 3500 mg of total omega-3 fatty acids (fish oil),
 from 0 mg to 250 mg of gamma-tocopherol,
 from 0 mg to 25 mg of silicon,
 from 30 mg to 1000 mg of vitamin C,
 25 from 25 mg to 1200 mg of elemental calcium, dosed in the form of a pharmaceutically acceptable calcium compound,
 from 1 mg to 41 mg of vitamin B1,
 from 1 mg to 41 mg of vitamin B2,
 from 5 mg to 300 mg of niacin,
 30 from 10 mg to 300 mg of vitamin B5,
 from 1 mg to 40 mg of vitamin B6,
 from 3 mcg to 503 mcg of vitamin B12,

- from 0 mg to 100 mg of bioflavonoid complex,
- from 0 mg to 300 mg of quercetin,
- from 0 mg to 25 mg of silicon,
- from 0 mg to 1200 mg of phosphorus,
- 5 from 50 mg to 600 mg of magnesium,
- from 1 mg to 30 mg of zinc,
- from 0 mg to 10 mg of manganese,
- from 0 mg to 10 mg of boron,
- from 0.5 mg to 5 mg of copper,
- 10 from 0 IU to 10,000 IU of vitamin A,
- from 0 mg to 12 mg of beta carotene,
- from 0 mg to 200 mcg of chromium, molybdenum, nickel, tin, vanadium,
- and selenium,
- from 0 mcg to 200 mcg of vitamin K,
- 15 from 0 mg to 100 mg of N-acetyl cysteine,
- from 100 mcg to 1000 mcg of folate,
- from 10 mcg to 600 mcg of biotin,
- from 50 mcg to 500 mcg of iodine,
- from 250,000 cfu to 20 billion cfu of probiotic Acidopholis, and
- 20 from 250,000 cfu to 20 billion cfu of probiotic Bifidus.

In one embodiment for women, the supplement system is additionally comprised of from 5 mg to 30 mg of iron.

In one embodiment formulated for users above the age of fifty, the supplement system is additionally comprised of 100 mcg to 1000 mcg of additional
25 folic acid.

It will be appreciated that advantageous systems for the delivery of nutrients also can employ fewer than all four of the dosage units in some instances. A nutritional supplement delivery system, particularly well adapted for the delivery of nutrients, consists of the first, second, and third dosage units. A nutritional
30 supplement system, particularly well adapted for the delivery of water-soluble nutrients, consists of the first and third dosage units.

In view of the many possible embodiments to which the principles of the disclosed invention may be applied, it should be recognized that the illustrated embodiments are only preferred examples of the invention and should not be taken as limiting the scope of the invention. Rather, the scope of the invention is defined
5 by the following claims.

Claims:

1. A nutritional supplement system for human subjects consisting essentially of:

- 5 a first nutritional supplement dosage unit, the first dosage unit being formulated to release one or more nutrients in the stomach of a human subject;
- a second nutritional supplement dosage unit, the second dosage unit being formulated to release one or more nutrients in the upper intestinal tract of the subject, the one or more nutrients being selected from the group consisting of
- 10 nutrients that do not require release in the stomach and exposure to stomach acid for efficient digestion and absorption and that cause tolerance problems or are subject to a loss in biological activity when released in the stomach;
- a third nutritional supplement dosage unit, the third dosage unit being formulated to continually release one or more nutrients starting in the stomach and
- 15 continuing into the upper intestinal tract of the subject, the one or more nutrients being selected from the group consisting of water-soluble nutrients and other nutrients that are typically very rapidly absorbed and are best delivered by sustained release so as to maintain an elevated concentration in the body over time; and
- a fourth nutritional supplement dosage unit, the fourth dosage unit being
- 20 formulated to release one or more supplement ingredients in the lower intestinal tract of the subject, the supplement ingredients being selected from the group consisting of nutrients and other supplement ingredients that are adversely affected by exposure to stomach acid or stomach digestion.

25 2. The system of claim 1 wherein:

- the first nutritional supplement dosage unit comprises a plurality of vitamins and minerals and is formulated for immediate release in the subject's stomach;
- the second nutritional supplement dosage unit comprises nutritional oils including omega-3 fatty acids;
- 30 the third nutritional supplement dosage unit comprises vitamin B12 and is formulated for sustained release of vitamin B12 starting in the stomach and continuing into the intestines of the subject; and

the fourth nutritional supplement dosage unit comprises *Lactobacillus acidophilus* and *Buifodobacterium longum*.

3. The system of claim 2 wherein the third dosage unit further comprises:
5 one or more additional B-vitamin(s); and
vitamin C.

4. The system of claim 1 wherein the third nutritional supplement dosage unit comprises vitamin B12 and is formulated to provide elevated plasma levels of
10 vitamin B12 for a period of at least 12 hours after ingestion.

5. The system of claim 1 wherein the third nutritional supplement dosage unit comprises vitamin B12 and is formulated to allow at least 15% of the vitamin B12 to dissolve in one hour in 900 ml of 0.1N HCl at 37°C.
15

6. The system of claim 1 wherein:
the first nutritional supplement dosage unit consists of two tablets or two caplets;
the second nutritional supplement dosage unit consists of two gel
20 encapsulations;
the third nutritional supplement dosage unit consists of one tablet or caplet;
and
the fourth nutritional supplement dosage unit consists of one layered tablet.

7. The system of claim 6 wherein the six dosage unit elements of the first, second, third, and fourth dosage units are packaged in a common blister pack such that a day's complete dose is packaged together.
25

8. The system of claim 1 wherein:
30 the first nutritional supplement dosage unit comprises:
from 0 mg to 600 mg of phosphorus,
from 50 mg to 600 mg of magnesium,

- from 30 mg to 500 mg of vitamin C,
 from 1 mg to 30 mg of zinc,
 from 30 IU to 400 IU of vitamin E,
 from 0 mg to 5 mg of manganese,
 5 from 5 mg to 50 mg of vitamin B3,
 from 0 mg to 5 mg of boron,
 from 0.5 mg to 5 mg of copper,
 from 0 IU to 10,000 IU of vitamin A,
 from 0 mg to 6 mg of beta carotene,
 10 from 1 mg to 30 mg of pantothenic acid,
 from 0 mg to 200 mcg of trace mineral protein hydrolysate for
 chromium, molybdenum, nickel, tin, vanadium, and selenium,
 from 0 mcg to about 200 mcg of vitamin K,
 from 0 mg to 100 mg of N-acetyl cysteine,
 15 from 0 mg to 25 mg of silicon,
 from 1 mg to 10 mg of vitamin B6,
 from 1 mg to 10 mg of vitamin B1,
 from 1 mg to 10 mg of vitamin B2,
 from 3 mcg to 25 mcg of vitamin B12,
 20 from 200 IU to 800 IU of vitamin D3,
 from 100 mcg to 800 mcg of folate,
 from 50 mcg to 600 mcg of biotin, and
 from 50 mcg to 500 mcg of iodine;
 the second nutritional supplement dosage unit comprises:
 25 from 0 mg to 10 mg of lutein,
 from 0 mg to 10 mg of lycopene,
 from 50 IU to 400 IU of vitamin D3,
 from 50 IU to 400 IU of vitamin E,
 from 50 mg to 3500 mg of total omega-3 fatty acids (fish oil), and
 30 from 0 mg to 250 mg of gamma-tocopherol;
 the third nutritional supplement dosage unit comprises
 from 30 mg to 750 mg of vitamin C,

from 25 mg to 400 mg of calcium,
from 1 mg to 40 mg of vitamin B1,
from 1 mg to 40 mg of vitamin B2,
from 10 mg to 300 mg of vitamin B5,
5 from 1 mg to 40 mg of vitamin B6,
from 6 mcg to 500 mcg of vitamin B12,
from 0 mg to 100 mg of bioflavonoid complex,
from 0 mg to 300 mg of quercetin; and
the fourth nutritional supplement dosage unit comprises:
10 from 250,000 cfu to 20 billion cfu of *Lactobacillus acidophilus*,
and from 250,000 cfu to 20 billion cfu of *Buifodobacterium longum*.

9. The system of claim 8 wherein the first nutritional supplement dosage unit further comprises from 5 mg to 30 mg of iron.

15

10. The system of claim 8 wherein the first nutritional supplement dosage unit further comprises from 100 mcg to 1000 mcg of folic acid.

11. A method for delivering nutrients and probiotics to a human subject, the method comprising orally administering a nutritional supplement system consisting essentially of:

a first nutritional supplement dosage unit, the first dosage unit being formulated to release one or more nutrients in the stomach of a human subject;
a second nutritional supplement dosage unit, the second dosage unit being
25 formulated to release one or more nutrients in the upper intestinal tract of the subject, the one or more nutrients being selected from the group consisting of nutrients that do not require release in the stomach and exposure to stomach acid for efficient digestion and absorption and that cause tolerance problems or are subject to a loss in biological activity when released in the stomach;
30 a third nutritional supplement dosage unit, the third dosage unit being formulated to continually release one or more nutrients starting in the stomach and continuing into the upper intestinal tract of the subject, the one or more nutrients

being selected from the group consisting of water-soluble nutrients and other nutrients that are typically very rapidly absorbed and are best delivered by sustained release so as to maintain an elevated concentration in the body over time; and

5 a fourth nutritional supplement dosage unit, the fourth dosage unit being formulated to release one or more supplement ingredients in the lower intestinal tract of the subject, the supplement ingredients being selected from the group consisting of nutrients and other supplement ingredients that are adversely affected by exposure to stomach acid or stomach digestion.

10 12. The method of claim 11 wherein:

the first nutritional supplement dosage unit comprises a plurality of vitamins and minerals and is formulated for immediate release in the subject's stomach;

the second nutritional supplement dosage unit comprises omega-3 fatty acids;

15 the third nutritional supplement dosage unit comprises vitamin B12 and is formulated for sustained release of vitamin B12 starting in the stomach and continuing into the intestines of the subject sufficient to provide elevated plasma levels of vitamin B12 for a period 12 hours after ingestion; and

20 the fourth nutritional supplement dosage unit comprises *Lactobacillus acidophilus* and *Buifodobacterium longum*.

13. The method of claim 12 wherein the third dosage unit further comprises: one or more additional B-vitamin(s); and vitamin C.

25

14. The method of claim 11 wherein the third nutritional supplement dosage unit comprises vitamin B12 and is formulated to provide elevated plasma levels of vitamin B12 for a period of at least 12 hours after ingestion.

30 15. The method of claim 11 wherein the third nutritional supplement dosage unit comprises vitamin B12 and is formulated to allow at least 15% of the vitamin B12 to dissolve in one hour in 900 ml of 0.1N HCl at 37°C.

16. The method of claim 11 wherein:

the first nutritional supplement dosage unit consists of two tablets or two caplets;

5 the second nutritional supplement dosage unit consists of two gel encapsulations;

the third nutritional supplement dosage unit consists of one tablet or caplet; and

10 the fourth nutritional supplement dosage unit consists of one layered tablet.

17. The method of claim 16 wherein the six dosage unit elements of the first, second, third, and fourth dosage units are packaged in a common blister pack such that a day's complete dose is packaged together.

15 18. The method of claim 11 wherein the first, second, third and fourth nutritional supplement dosage units are administered substantially simultaneously.

19. A nutritional supplement system for human subjects consisting essentially of:

20 a first nutritional supplement dosage unit, the first dosage unit being formulated to release one or more nutrients in the stomach of a human subject;

a second nutritional supplement dosage unit, the second dosage unit being formulated to release one or more nutrients in the upper intestinal tract of the subject, the one or more nutrients being selected from the group consisting of
25 nutrients that do not require release in the stomach and exposure to stomach acid for efficient digestion and absorption and that cause tolerance problems or are subject to a loss in biological activity when released in the stomach; and

a third nutritional supplement dosage unit, the third dosage unit being formulated to continually release one or more nutrients starting in the stomach and
30 continuing into the upper intestinal tract of the subject, the one or more nutrients being selected from the group consisting of water-soluble nutrients and other

nutrients that are typically very rapidly absorbed and are best delivered by sustained release so as to maintain an elevated concentration in the body over time.

20. The system of claim 19 wherein:

- 5 the first nutritional supplement dosage unit comprises a plurality of vitamins and minerals and is formulated for immediate release in the subject's stomach;
- the second nutritional supplement dosage unit comprises nutritional oils including omega-3 fatty acids; and
- the third nutritional supplement dosage unit comprises vitamin B12 and is
- 10 formulated for sustained release of vitamin B12 starting in the stomach and continuing into the intestines of the subject.

21. The system of claim 20 wherein the third dosage unit further comprises:

 one or more additional B-vitamin(s); and

15 vitamin C.

22. The system of claim 19 wherein the third nutritional supplement dosage unit comprises vitamin B12 and is formulated to provide elevated plasma levels of vitamin B12 for a period of at least 12 hours after ingestion.

20

23. The system of claim 19 wherein the third nutritional supplement dosage unit comprises vitamin B12 and is formulated to allow at least 15% of the vitamin B12 to dissolve in one hour in 900 ml of 0.1N HCl at 37°C.

25

24. The system of claim 19 wherein:

- the first nutritional supplement dosage unit consists of two tablets or two caplets;
- the second nutritional supplement dosage unit consists of two gel encapsulations; and
- 30 the third nutritional supplement dosage unit consists of one tablet or caplet.

25. The system of claim 24 wherein the five dosage unit elements of the first, second, and third dosage units are packaged in a common blister pack such that a day's complete dose is packaged together.

5 26. A method for delivering nutrients to a human subject, the method comprising orally administering a nutritional supplement system consisting essentially of:

 a first nutritional supplement dosage unit, the first dosage unit being formulated to release one or more nutrients in the stomach of a human subject;

10 a second nutritional supplement dosage unit, the second dosage unit being formulated to release one or more nutrients in the upper intestinal tract of the subject, the one or more nutrients being selected from the group consisting of nutrients that do not require release in the stomach and exposure to stomach acid for efficient digestion and absorption and that cause tolerance problems or are subject to
15 a loss in biological activity when released in the stomach; and

 a third nutritional supplement dosage unit, the third dosage unit being formulated to continually release one or more nutrients starting in the stomach and continuing into the upper intestinal tract of the subject, the one or more nutrients being selected from the group consisting of water-soluble nutrients and other
20 nutrients that are typically very rapidly absorbed and are best delivered by sustained release so as to maintain an elevated concentration in the body over time.

27. The method of claim 26 wherein:

 the first nutritional supplement dosage unit comprises a plurality of vitamins
25 and minerals and is formulated for immediate release in the subject's stomach;

 the second nutritional supplement dosage unit comprises omega-3 fatty acids; and

 the third nutritional supplement dosage unit comprises vitamin B12 and is formulated for sustained release of vitamin B12 starting in the stomach and
30 continuing into the intestines of the subject sufficient to provide elevated plasma levels of vitamin B12 for a period 12 hours after ingestion.

28. The method of claim 27 wherein the third dosage unit further comprises:
one or more additional B-vitamin(s); and
vitamin C.

5 29. The method of claim 26 wherein the third nutritional supplement dosage
unit comprises vitamin B12 and is formulated to provide elevated plasma levels of
vitamin B12 for a period of at least 12 hours after ingestion.

10 30. The method of claim 26 wherein the third nutritional supplement dosage
unit comprises vitamin B12 and is formulated to allow at least 15% of the vitamin
B12 to dissolve in one hour in 900 ml of 0.1N HCl at 37°C.

 31. The method of claim 26 wherein:
the first nutritional supplement dosage unit consists of two tablets or two
15 caplets;
the second nutritional supplement dosage unit consists of two gel
encapsulations; and
the third nutritional supplement dosage unit consists of one tablet or caplet.

20 32. The method of claim 31 wherein the five dosage unit elements of the
first, second, and third dosage units are packaged in a common blister pack such that
a day's complete dose is packaged together.

 33. The method of claim 26 wherein the first, second, and third nutritional
25 supplement dosage units are administered substantially simultaneously.

 34. A nutritional supplement system for human subjects consisting
essentially of:
a immediate release nutritional supplement dosage unit, the dosage unit
30 being formulated to release one or more nutrients in the stomach of a human subject;
and

a sustained release nutritional supplement dosage unit, the sustained release dosage unit being formulated to continually release one or more nutrients starting in the stomach and continuing into the upper intestinal tract of the subject, the one or more nutrients being selected from the group consisting of water-soluble nutrients and other nutrients that are typically very rapidly absorbed and are best delivered by sustained release so as to maintain an elevated concentration in the body over time.

35. The system of claim 34 wherein:

the immediate release nutritional supplement dosage unit comprises a plurality of vitamins and minerals and is formulated for immediate release in the subject's stomach; and

the sustained release nutritional supplement dosage unit comprises vitamin B12 and is formulated for sustained release of vitamin B12 starting in the stomach and continuing into the intestines of the subject.

15

36. The system of claim 35 wherein the sustained release dosage unit further comprises:

one or more additional B-vitamin(s); and
vitamin C.

20

37. The system of claim 34 wherein the sustained release nutritional supplement dosage unit comprises vitamin B12 and is formulated to provide elevated plasma levels of vitamin B12 for a period of at least 12 hours after ingestion.

25

38. The system of claim 34 wherein the sustained release nutritional supplement dosage unit comprises vitamin B12 and is formulated to allow at least 15% of the vitamin B12 to dissolve in one hour in 900 ml of 0.1N HCl at 37°C.

30

39. The system of claim 34 wherein:

the immediate release nutritional supplement dosage unit consists of two tablets or two caplets; and

the sustained release nutritional supplement dosage unit consists of one tablet or caplet.

40. The system of claim 24 wherein the three dosage unit elements of the immediate release and sustained release dosage units are packaged in a common blister pack such that a day's complete dose is packaged together.

41. A method for delivering nutrients to a human subject, the method comprising orally administering a nutritional supplement system consisting essentially of:

a immediate release nutritional supplement dosage unit, the immediate release dosage unit being formulated to release one or more nutrients in the stomach of a human subject; and

a sustained release nutritional supplement dosage unit, the sustained release dosage unit being formulated to continually release one or more nutrients starting in the stomach and continuing into the upper intestinal tract of the subject, the one or more nutrients being selected from the group consisting of water-soluble nutrients and other nutrients that are typically very rapidly absorbed and are best delivered by sustained release so as to maintain an elevated concentration in the body over time.

20

42. The method of claim 41 wherein:

the immediate release nutritional supplement dosage unit comprises a plurality of vitamins and minerals and is formulated for immediate release in the subject's stomach; and

25 the sustained release nutritional supplement dosage unit comprises vitamin B12 and is formulated for sustained release of vitamin B12 starting in the stomach and continuing into the intestines of the subject sufficient to provide elevated plasma levels of vitamin B12 for a period 12 hours after ingestion.

30

43. The method of claim 42 wherein the sustained release dosage unit further comprises:

one or more additional B-vitamin(s); and
vitamin C.

5

44. The method of claim 41 wherein the sustained release nutritional supplement dosage unit comprises vitamin B12 and is formulated to provide elevated plasma levels of vitamin B12 for a period of at least 12 hours after ingestion.

10

45. The method of claim 41 wherein the sustained release nutritional supplement dosage unit comprises vitamin B12 and is formulated to allow at least 15% of the vitamin B12 to dissolve in one hour in 900 ml of 0.1N HCl at 37°C.

15

46. The method of claim 41 wherein:

the immediate release nutritional supplement dosage unit consists of two tablets or two caplets; and

the sustained release nutritional supplement dosage unit consists of one tablet or caplet.

20

47. The method of claim 46 wherein the three dosage unit elements of the immediate release and sustained release dosage units are packaged in a common blister pack such that a day's complete dose is packaged together.

25

48. The method of claim 41 wherein the immediate release and sustained release nutritional supplement dosage units are administered substantially simultaneously.

30

49. A method for delivering nutrients and probiotics to a human subject, the method comprising:

providing one or more nutrients in the stomach of a human subject;

providing one or more nutrients in the upper intestinal tract of the subject,

5 the one or more nutrients being selected from the group consisting of nutrients that do not require release in the stomach and exposure to stomach acid for efficient digestion and absorption and that cause tolerance problems or are subject to a loss in biological activity when released in the stomach;

continually providing one or more nutrients starting in the stomach and
10 continuing into the upper intestinal tract of the subject, the one or more nutrients being selected from the group consisting of water-soluble nutrients and other nutrients that are typically very rapidly absorbed and are best delivered by sustained release so as to maintain an elevated concentration in the body over time; and

providing one or more supplement ingredients in the lower intestinal tract of
15 the subject, the supplement ingredients being selected from the group consisting of nutrients and other supplement ingredients that are adversely affected by exposure to stomach acid or stomach digestion.

50. The method of claim 49 wherein:

20 the one or more nutrients provided in the stomach of a human subject comprise a plurality of vitamins and minerals that are immediate released in the subject's stomach;

the one or more nutrients provided in the upper intestinal tract comprise omega-3 fatty acids;

25 the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract comprise vitamin B12, and the vitamin B12 is provided in an amount sufficient to provide elevated plasma levels of vitamin B12 for a period 12 hours after ingestion; and

the one or more supplement ingredients provided in the lower intestinal tract
30 comprise *Lactobacillus acidophilus* and *Buifodobacterium longum*.

51. The method of claim 50 wherein the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract further comprise:

5 one or more additional B-vitamin(s); and
 vitamin C.

52. The method of claim 49 wherein the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract comprises vitamin B12 in an amount sufficient to provide elevated plasma levels of vitamin
10 B12 for a period of at least 12 hours after ingestion.

53. The method of claim 49 wherein the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract comprise vitamin B12 and in an amount sufficient to allow at least 15% of the vitamin B12 to
15 dissolve in one hour in 900 ml of 0.1N HCl at 37°C.

54. The method of claim 49 wherein:
 the one or more nutrients provided in the stomach of a human subject are released from two tablets or two caplets that release nutrients in the stomach;
20 the one or more nutrients provided in the upper intestinal tract are released from two gel encapsulations that release in the intestinal tract;
 the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract are released from one tablet or caplet; and
 the one or more supplement ingredients provided in the lower intestinal tract
25 are released from one layered tablet.

55. A method for delivering nutrients to a human subject, the method comprising:
 providing one or more nutrients in the stomach of a human subject;
30 providing one or more nutrients in the upper intestinal tract of the subject, the one or more nutrients being selected from the group consisting of nutrients that do not require release in the stomach and exposure to stomach acid for efficient

digestion and absorption and that cause tolerance problems or are subject to a loss in biological activity when released in the stomach; and

continually providing one or more nutrients starting in the stomach and continuing into the upper intestinal tract of the subject, the one or more nutrients
5 being selected from the group consisting of water-soluble nutrients and other nutrients that are typically very rapidly absorbed and are best delivered by sustained release so as to maintain an elevated concentration in the body over time.

56. The method of claim 55 wherein:

10 the one or more nutrients provided in the stomach of a human subject comprise a plurality of vitamins and minerals that are immediate released in the subject's stomach;

the one or more nutrients provided in the upper intestinal tract comprise omega-3 fatty acids; and

15 the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract comprise vitamin B12, and the vitamin B12 is provided in an amount sufficient to provide elevated plasma levels of vitamin B12 for a period 12 hours after ingestion.

20 57. The method of claim 56 wherein the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract further comprise:

one or more additional B-vitamin(s); and
vitamin C.

25

58. The method of claim 55 wherein the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract comprises vitamin B12 in an amount sufficient to provide elevated plasma levels of vitamin
B12 for a period of at least 12 hours after ingestion.

30

59. The method of claim 55 wherein the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract comprise

vitamin B12 and in an amount sufficient to allow at least 15% of the vitamin B12 to dissolve in one hour in 900 ml of 0.1N HCl at 37°C.

60. The method of claim 55 wherein:

- 5 the one or more nutrients provided in the stomach of a human subject are released from two tablets or two caplets that release nutrients in the stomach;
- the one or more nutrients provided in the upper intestinal tract are released from two gel encapsulations that release in the intestinal tract; and
- the one or more nutrients provided starting in the stomach and continuing
10 into the upper intestinal tract are released from one tablet or caplet.

61. A method for delivering nutrients to a human subject, the method comprising:

- providing one or more nutrients in the stomach of a human subject; and
15 continually providing one or more nutrients starting in the stomach and continuing into the upper intestinal tract of the subject, the one or more nutrients being selected from the group consisting of water-soluble nutrients and other nutrients that are typically very rapidly absorbed and are best delivered by sustained release so as to maintain an elevated concentration in the body over time.

20

62. The method of claim 61 wherein:

- the one or more nutrients provided in the stomach of a human subject comprise a plurality of vitamins and minerals that are immediate released in the subject's stomach; and
- 25 the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract comprise vitamin B12, and the vitamin B12 is provided in an amount sufficient to provide elevated plasma levels of vitamin B12 for a period 12 hours after ingestion.

30

63. The method of claim 62 wherein the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract further comprise:

5 one or more additional B-vitamin(s); and
 vitamin C.

64. The method of claim 61 wherein the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract comprises vitamin B12 in an amount sufficient to provide elevated plasma levels of vitamin
10 B12 for a period of at least 12 hours after ingestion.

65. The method of claim 61 wherein the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract comprise vitamin B12 and in an amount sufficient to allow at least 15% of the vitamin B12 to
15 dissolve in one hour in 900 ml of 0.1N HCl at 37°C.

66. The method of claim 61 wherein:
 the one or more nutrients provided in the stomach of a human subject are released from two tablets or two caplets that release nutrients in the stomach; and
20 the one or more nutrients provided starting in the stomach and continuing into the upper intestinal tract are released from one tablet or caplet.