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(54) **Title:** NUTRITIONAL PRODUCTS HAVING IMPROVED QUALITY AND METHODS AND SYSTEMS REGARDING SAME

(57) **Abstract:** Nutritional formulas and methods for producing same are provided. In an embodiment, the present invention provides a nutritional composition produced in a process requiring a heating step, the composition comprising a reduced amount of undesirable reaction products formed from chemical reactions between proteins and carbohydrates during exposure to heat. For example, the composition can have a reduced amount of AGEs compared to similar products made by conventional heat treatment processes.

## TITLE

**NUTRITIONAL PRODUCTS HAVING IMPROVED QUALITY AND METHODS AND SYSTEMS REGARDING SAME**

## BACKGROUND

[0001] The present invention generally relates to improved nutritional products. More specifically, in an embodiment, the present invention relates to improved infant formulas and methods and systems regarding same.

[0002] There are a wide variety of nutritional products that are manufactured. The purpose of these products, in part, is to provide necessary nutrition to the consumer. In addition to providing nutrition to the consumer, it is important that these products are safe for consumption. Thus, for at least certain products, issues of sterility and shelf-life must be considered during the manufacturing process.

[0003] An example of a nutritional product is infant formula. For almost a century, an aim of the infant formula industry has been to develop products that at least approximate the composition of human breast milk. The most recent example of this "composition focused" innovation was the introduction of products that were enriched with long-chain polyunsaturated fatty acids, DHA and ARA, unstable ingredients that were blended into the formulation during manufacturing. Infant formula manufacturers at the same time must reconcile several opposing constraints of modern food formulation with varying infant nutrient requirements. Such opposing demands have led at times to compromises in the opportunities to provide certain qualities of human milk to the formulas delivered to infants.

[0004] These demands include issues of sterility and shelf-life. Of course, food manufacturing practices must achieve final products with assured microbial safety, e.g., sterility. Traditionally, this means products must be heat processed to reduce any potential microbial contamination to meet or exceed the levels of sterility prescribed for such products in national and international legislation. In addition, products typically must be stored for extended periods of time and hence unstable components cannot be included without deterioration or must be over-dosed to ensure that minimal quantities remain at point of consumption. It is, of course, desirable that products contain all of the essential nutrients needed for human infant growth and

development. This results in compositions that are designed for the average requirements in spite of varying needs by infants of different ages, sizes or physiological states.

[0005] These formula demands and industrial production constraints have limited the opportunities to approach the highly personal, biologically active, compositionally dynamic and interactive experience of nourishment achieved by human breast feeding. To date, the inventors believe that no truly integrated infant formula production system has been developed that can simultaneously optimize the manufacturing process to minimize the effects of processing on the biological and nutritional quality of infant formula and yet provide the flexibility to deliver customized formulations to individual infants.

[0006] A prerequisite to an infant formula is that the final product must be microbiologically safe, and for that reason traditional processing mandates that the final product be adequately heat processed. Thus, products in powder form are typically heat treated before spray-drying. Although such powders have very low bacterial counts, they are not sterile in the sense that this word is used in medicine. Products in liquid form, however, are subject to a more rigorous treatment typically by exposure to high temperatures for short time (UHT – aseptic process) or by retorting. The retort sterilization is in fact recommended for products used in hospitals to feed premature and term newborn babies. Such products are still not completely sterile as bacterial spores may not be completely destroyed by the heat treatment.

[0007] While these thermal treatments are successful in assuring microbial safety, they can adversely affect the molecular components and structures that are ingredients in infant formulas. Invariably, heat-treating complex infant formula mixtures leads to various reactions of individual molecules and to interactions between different components. The current strategy to resolve the losses caused by these destructive reactions with respect to the final quantities of components of formula is to include a sufficient excess of the ingredients as a quantitative function of the instability to ensure that sufficient levels of essential nutrients remain in the final product. The strategy of using excess nutrients prior to processing the formula, ignores the potential implications to the infant of consuming thermal reaction products formed during processing. Thus, although necessary, the thermal processing of nutritional

components can generate compounds or intermediates that may have undesirable nutritional consequences.

[0008] Thermal processing can generate advanced glycation endproducts (AGEs). Through the Maillard reaction, certain amino acids such as lysine can react with aldehyde groups of glucose to create first Schiff bases and then rearrange to Amadori products. These reactions produce various glycooxidation and lipoxidation products which are collectively known as AGEs. For example, AGEs are formed by the Maillard reaction during food processing when mixtures containing protein and carbohydrates are heated. However, AGEs may also be formed endogenously in the body and probably contribute to the natural aging process.

[0009] As the term indicates, AGEs are end-products that in general retain little chemical reactivity. They are formed via complex chemical reactions which may include oxidation reactions and formation of reactive intermediates. Thus, AGEs can be considered markers for the formation of these reactive intermediates. These intermediates include glyoxal, methylglyoxal, 3-deoxyglucosone, glyceraldehyde, and others. Examples of AGEs are lactuloselysine, hydroxymethylfurfural, oxalic acid monolysinylamide, and carboxymethyllysine

[0010] Recently, it has been suggested that AGEs may be linked to chronic low level inflammation. This is due in part to oxidative stress caused by the AGEs. Chronic low level inflammation has been linked to a number of diseases. For example, it is hypothesized that chronic low level inflammation may be linked to diabetes, cardiovascular disease, Alzheimer, cancer, and even weight gain and aging. A reduction in AGEs in the diet may lead to: extension of life span, prevention/reduction of weight gain; prevention of insulin resistance; prevention of heart disease; and improvement of oxidative stress. Many scientific papers have been written postulating links between AGEs and various disease states. One example is a paper entitled "Advanced Glycation Endproducts" by Wauthier and Guillemeau, *Diabetes Metab (Paris)* 2001, 27, 535 – 542.

[0011] Therefore, there is a need to provide improved nutritional products having reduced levels of AGEs.

## SUMMARY

[0012] The present invention provides improved formulations, processes, assembly, and delivery of nutritional products. In an embodiment, the present invention provides nutritional products that have a reduced amount of AGEs or are substantially free of AGEs. Although, in a preferred embodiment, the present invention relates to infant formulas, the present invention has application to a wide variety of other nutritional products.

[0013] In another embodiment, the present invention provides a nutritional composition produced in a process requiring a heating step. For example, the composition comprises a reduced amount of undesirable reaction products formed from chemical reactions between proteins and carbohydrates and/or lipids and carbohydrates during exposure to heat.

[0014] In an embodiment, the undesirable reaction products are selected from the group consisting of AGEs, intermediates of AGEs and combinations thereof.

[0015] In an embodiment, the composition is substantially free of AGEs and intermediates of AGEs.

[0016] In an embodiment, the reaction products are quantified by measuring the percentage of blocked lysine of the nutritional composition.

[0017] In an embodiment, the percentage of blocked lysine of the nutritional composition is used as a marker for the level of AGEs and intermediates of AGEs formed in the nutritional composition.

[0018] In an embodiment, the composition is a powder.

[0019] In an embodiment, the composition is a liquid.

[0020] In an embodiment, the composition is an infant formula.

[0021] In an embodiment, the composition is a dairy product.

[0022] In an embodiment, the composition includes one or more components selected from the group consisting of a protein source, a carbohydrate source, a lipid source and combinations thereof.

[0023] In an embodiment, the composition includes at least one heat labile component.

[0024] In an embodiment, the composition is sterilized. For example, the composition can be sterilized by a process selected from the group consisting of

bacterial filtration, high pressure sterilization, irradiation, retorting, aseptic processing, heat treatment, pasteurization and combinations thereof.

[0025] In another embodiment, the present invention provides a method of producing a nutritional composition. For example, the method comprises providing a protein component, providing a carbohydrate component, treating at least one of the protein component and the carbohydrate component separately from the other component. The components can be treated, for example, to at least reduce bacterial loads therein. The protein component and carbohydrate component are combined after treatment to form the nutritional composition. The method can also comprise separately treating the protein component and the carbohydrate component.

[0026] In an embodiment, the nutritional composition comprises a reduced amount of compounds from the group consisting of AGEs, intermediates of AGEs and combinations thereof.

[0027] In an embodiment, the carbohydrate component or phase is substantially free of proteins or has a reduced level of proteins. For example, any protein associated with the carbohydrate component may be removed or reduced by any suitable process.

[0028] In an embodiment, the protein component or phase is substantially free of carbohydrates or has a reduced level of carbohydrates. For example, any carbohydrate associated with the protein component may be removed or reduced by any suitable process.

[0029] In an embodiment, sterilizing the carbohydrate component and sterilizing the protein component can be done by a process selected from the group consisting of bacterial filtration, high pressure sterilization, irradiation, retorting, aseptic processing, thermal treatment and combinations thereof.

[0030] In an alternative embodiment, the present invention provides a system for producing a commercially sterile nutritional composition. For example, the system comprises a protein phase and a carbohydrate phase. At least one of the protein phase and the carbohydrate phase can be treated separately from the other phase or both the protein phase and the carbohydrate phase can be treated separately. The treatment can be, for example, to reduce the bacterial load of the phase being treated. The system also comprises a storage component for holding the protein phase and carbohydrate

phase separately or together, and a dispensing device for combining the protein phase and carbohydrate phase to form the nutritional composition.

[0031] In an embodiment, the dispensing device is capable of combining specific levels of the protein phase and carbohydrate phase according to the nutritional needs of a consumer.

[0032] In another embodiment, the present invention provides a method of producing a commercially sterile nutritional composition. For example, the method comprises providing a composition having a protein component and a carbohydrate component; and treating the composition. The treated composition can have a reduced amount of undesirable compounds selected from the group consisting of AGEs, intermediates of AGEs and combinations thereof.

[0033] In an embodiment, the composition includes at least one heat labile component.

[0034] In an embodiment, treating is by a process selected from the group consisting of microfiltration, high pressure sterilization, irradiation and combinations thereof.

[0035] In an alternative embodiment, the present invention provides a method of producing a commercially sterile powdered nutritional composition including a source of proteins, a source of lipids and a source of carbohydrates. For example, the method comprises dissolving the source of proteins in water, adding the lipid source, homogenizing the protein/lipid mixture, heat treating the mixture to reduce bacterial loads, concentrating the heat treated mixture, adding the carbohydrate source and spray-drying the mixture.

[0036] In an embodiment, at least part of the remainder of the carbohydrate source is added to the spray dried powder in an additional dry-mixing step.

[0037] In an alternative embodiment, the present invention provides a method of producing a commercially sterile powdered nutritional composition including a source of proteins, a source of lipids and a source of carbohydrates by spray drying. For example, the method comprises dissolving the source of proteins in water together with the minimum amount of carbohydrate necessary to facilitate the spray drying, adding the lipid source, homogenizing the protein/lipid mixture, heat treating the

mixture to reduce bacterial loads, concentrating the heat treated mixture, spray-drying the mixture and adding the remainder of the carbohydrate source.

[0038] In an embodiment, at least part of the remainder of the carbohydrate source is added during the spray drying step by blowing into the spray dryer.

[0039] It is an advantage of the present invention to provide new methods of producing nutritional products.

[0040] Another advantage of the present invention is to provide improved infant formulas.

[0041] Moreover, an advantage of the present invention is to provide improved methods for producing infant formulas.

[0042] Still another advantage of the present invention is to reduce or substantially eliminate in nutritional products unwanted products generated during manufacturing processes.

[0043] Furthermore, an advantage of the present invention is to reduce or substantially eliminate AGEs in nutritional products.

[0044] Moreover, an advantage of the present invention is to reduce or substantially eliminate AGEs in infant formulas.

[0045] Still an advantage of the present invention is to provide nutritional products that reduce oxidative stress as compared to prior art nutritional products.

[0046] Another advantage of the present invention is that it provides nutritional formulations that reduce the potential for causing chronic low level inflammation.

[0047] And an advantage of the present invention is that it reduces or eliminates the need to use excess components such as vitamins during the manufacturing process.

[0048] Further, an advantage of the present invention is to provide customized infant formulas.

[0049] Additional features and advantages of the present invention are described in, and will be apparent from, the following Detailed Description.

#### DETAILED DESCRIPTION

[0050] The present invention provides improved nutritional products and methods and systems regarding same. In an embodiment, the nutritional products and

methods and systems regarding same will have a reduced amount of AGEs or be substantially free of AGEs. In the present specification, the term “reduced AGEs” or “reduced amount of AGEs” should be understood to mean a nutritional composition having a lower level of AGEs than would be found in the same nutritional composition produced by conventional processing, for example, such as heat treatment. In the present specification, the phrase “substantially free of AGEs” should be understood to mean that the AGEs are present at a level that is sufficiently low as to not produce chronic low-level inflammation. This level is at least lower than a corresponding commercially-available product currently available.

[0051] In an embodiment, the reduction of AGEs in nutritional compositions of the present invention can be quantified by measuring the percentage of blocked lysine. As will be appreciated from the foregoing, numerous AGEs and their reactive precursors exist. Various tests for AGEs have been proposed in the literature but it will be appreciated that it is impractical to test for every possible compound that might be present. However, a universal feature of nutritional compositions containing proteins and carbohydrates that have undergone a heat treatment is a reduction in the amount of available lysine in the heat treated composition. Thus, measurement of blocked lysine is an indicator not only of the specific reaction of reducing sugars with free lysine groups but also a marker for the presence of other AGEs and the temporary presence of earlier reactive intermediates. For example, the percentage of blocked lysine in products which are commercially available varies between 3 and 17% depending upon the composition of the product with products containing lactose at the higher end of this scale and lactose free products at the lower end of the scale.

[0052] It should be appreciated that the measurement of AGEs and intermediates thereof can also be determined by any currently available analytical techniques or methods known to one skilled in the art. For example, one such alternative method is the quantification of carboxymethyllysine which is described in “Advanced glycoxidation end products in commonly consumed foods” by Goldberg et al, J. Am Diet Assoc 2004, 104(8) 1287 – 91.

[0053] In another embodiment, the individual macro-components of, for example, the infant formula or shelf stable dairy products, are processed separately and with a minimum amount of treatment required to ensure product safety. The potential

for formation of AGEs is thereby greatly reduced. Thus, the present invention allows for the production of compositions which have a reduced level of AGEs or are substantially free of AGEs

[0054] In addition, the methods of the present invention provide other benefits such as reducing or eliminating the need to use excess microcomponents to ensure that sufficient microcomponents survive the heat treatment to be effective. Sensitive microcomponents such as those which cannot survive the current heat treatment can also now be included. The present invention also allows for the possibility of customization of formulas. If individual components are processed separately, they can be supplied separately allowing a hospital to make up oral or enteral feeds to suit individual patients.

[0055] In an embodiment, the nutritional composition contains lactose and has a level of blocked lysine of less than 8%, more preferably less than 5%. An example of such a composition is an infant formula. Alternatively, the nutritional composition may contain maltodextrin and have a level of blocked lysine of less than 3%, more preferably less than 2%. An example of such a composition is an enteral formula.

[0056] Typically, infant formula must be pre-processed to achieve the final composition and to uniformly disperse and solubilize all formula ingredients (proteins, carbohydrates, lipids and other nutrients) and to produce a homogenous emulsion. The emulsion is further processed by high pressure homogenizations and heating to assure homogeneity and reduce bacterial load. If a powdered product is desired, the emulsion is spray-dried and filled into appropriate packaging. If a ready-to-feed liquid is desired, the emulsion is filled into appropriate packaging and subjected to a further heat treatment. The heat treatment may be applied either before filling in which case filling is carried out under aseptic conditions or the filled containers may themselves be heat treated in a so-called retort process. In addition, a small proportion of infant formulas are produced and packaged for the first feeding in hospitals. Virtually all hospital-targeted products are produced in ready-to feed liquid form in small bottles called nursettes. Most of the hospital products are sterilized in these containers by retort processing.

[0057] The majority of destructive reactions and of undesirable Maillard complexation reactions that lead to various decomposition and polymerization

products including AGEs occur when proteins, lipids and carbohydrates are heated in a liquid phase. This intensive heating is also a factor that leads to the decomposition of various heat labile nutrients. Once they begin during the heating process, many chemical reactions continue, although at slower reaction rates, throughout the storage of either liquid or dry products at room temperature. It should also be noted that under factory conditions it may occasionally be necessary for batches of liquid product to be kept in holding tanks at various stages in the manufacturing process for reasons such as unplanned work on necessary processing equipment. Any delays occurring in this way will increase the potential for AGE formation.

[0058] The present invention, in an alternative embodiment, provides a comprehensive integrated system for producing infant formulas and similar products capable of delivering to the consumer, enteral compositions in powder or liquid form. Pursuant to an embodiment of the present invention, a production and delivery process is provided in which the interaction of enteral composition ingredients and consequent formation of undesirable reaction products are eliminated or minimized.

[0059] By way of example and not limitation, examples of enteral compositions of the present invention include: products for feeding infants, also known as starter and follow on infant formula; infant formula specialties and products for feeding premature and low weight infants; enteral compositions for feeding infants and children in need of special nutrients and requiring specialized nutrition (e.g. compositions based on amino acids and peptides, essentially free of intact proteins free of proteins); and enteral compositions for feeding patients and/or treating specific disease states.

[0060] In an embodiment, methods of the present invention include methods of producing enteral composition (formula) containing heat labile components such as vitamins, hormones, growth factors and beneficial bacteria, which can be added at concentrations and quantities desired for their optimal nutritional or physiological effects. The methods of the present invention, for example, produce a number of distinct benefits to the final product including: permitting the inclusion of labile components not currently used in infant formula; avoiding the use of excessive components necessary to compensate for the destruction or decomposition of such heat labile components; avoiding hydrolysis, rearrangement, isomerization, complexation,

condensation and polymerization reactions and their products; customizing final product formulations according to varying requirements of consumers; detailing of individual portion containers; and extended shelf stability of infant and enteral ingredients.

[0061] In an embodiment, the nutritional composition is provided as a dry formulation, in which the final form is a powder. The production process may consist of dry mixing of commercially sterile powder forms of all formula components, typically including proteins, carbohydrates, lipids and micronutrients.

[0062] Typically, the nutritional composition will include proteins, carbohydrates, and lipids. The proteins that can be used include, but are not limited to, milk or vegetable proteins or fractions of milk proteins such as whey proteins and caseins or fraction of those such as but not limited to alpha-lactalbumin, beta-lactoglobulin, lactoferrin and their hydrolyzed forms. The carbohydrates can include, by way of example and not limitation, lactose, glucose, sucrose, maltodextrins, galactooligosaccharides, glucooligosaccharides, fructooligosaccharides or other oligosaccharides known to provide explicit physiological benefits or to be present in human and other mammalian milks.

[0063] The lipids include, but are not limited to, those of animal, plant or microbial origin and have been converted to a powdered or dry dispersible form by use of an inert carrier, including carbohydrates such as maltodextrin or lactose, or proteins from the group described above. The conversion of lipid, which typically is in the liquid form to a powder form, is a technologically feasible process and such products are commercially available. A wide range of free flowing fat powders is available from Prince International of The Netherlands under the trade mark O2P. Encapsulated docosahexaenoic acid is available from Firmenich under the trade mark DURALIFE where the encapsulation material is a matrix of a food-based carbohydrate. Other spray dried fats are commercialized by Nutri Pharmaceuticals Research Inc. of Las Vegas

[0064] A large number of nutritional products also include micronutrients. The micronutrients that can be included in the products and methods of the present invention include, but are not limited to, minerals, vitamins, hormones, growth factors, nucleotides, polynucleotides, and biopolymers mixtures of proteins, carbohydrates

and/or nucleotides. If desired, living organisms including, but not limited to, beneficial bacteria known as probiotics and their products, beneficial viruses termed bacteriophages, and their products and yeasts, molds and fungi can be used in the nutritional formulations.

[0065] It is important that all components of the formula in an embodiment of the present invention are commercially sterile. In the present specification, the term "commercially sterile" should be understood to mean that the product in question complies with the respective microbiological standard prescribed for products of that type in national and international legislation. For example, the formula components in embodiments of the present invention can be rendered commercially sterile by techniques which are explicitly designed to reduce or eliminate interactions and heat reactions of proteins and lipids, proteins and carbohydrates and/or to reduce damage to or decomposition of heat labile macro- and micronutrients such as nucleotides, vitamins, probiotics, long chain polyunsaturated fatty acids etc. A variety of suitable techniques are available. Some of these techniques rely on the application of heat, for example, such as retorting and aseptic processing. Other non-heat techniques include, for example, bacterial filtration or microfiltration, high pressure sterilization and irradiation. These techniques may be selected and combined as appropriate in the production of specific formulas according to the intended use of the formulas of the present invention.

[0066] Proteins that, at the initial phase of their production, are in powder form can be dissolved in water and heat treated to render them commercially sterile. Proteins in the liquid form (milk, whey, protein hydrolyzates, casein) can be treated by heat at conditions, which eliminate or minimize interactions with carbohydrates. In an embodiment, it is particularly preferred to use protein sources free or nearly free of carbohydrates, such as high protein concentrates and protein isolates. An example is the whey protein isolate supplied under the trade mark Bipro by Davisco Foods which contains 95% protein. Such high protein concentrates can be sterilized using relatively high heat conditions, while protein concentrates containing appreciable quantities of carbohydrates, typically exceeding 5% (w/w) can be heat treated by pasteurization.

[0067] Alternatively, microbial filtration, UV and gamma irradiations can be used to render protein solutions containing carbohydrates commercially sterile.

Commercially sterile solutions and suspensions of proteins may be dried if desired. Suitable drying techniques include, but are not limited to, spray drying and freeze-drying. Similarly, vitamins and other micronutrients can be produced in powder forms, commercially sterile, using currently available technologies.

[0068] In an embodiment, the present invention also provides individual containers or capsules that can be used to produce ready-to-drink formula in a hospital, home, car, or portable devices. Predetermined quantities of formula ingredients in powdered form and essentially free of undesirable products typically described as advanced glycation endproducts, Maillard reaction products and decomposition products of vitamins degradation are produced and filled into capsules. At the time of use a capsule is opened and the contents are mixed with an appropriate quantity of sterile water to produce a single serving of ready to drink infant formula. Generally, the dispensing system may be similar to those used by food service operations to produce ready-to-drink liquids such as coffee or milk-based beverages. The system allows accurate preparation of desired volumes of the formula, virtually eliminating risks of errors in reconstitution of formula from powder, which is common in current practice.

[0069] In another embodiment, the present invention utilizes the technologies of powder portioning, water sterilization, water temperature control, formulation blending and homogenization, container filling and labeling. The enteral products that can be assembled by this system include, for example, emulsions, solutions or suspensions that are commercially sterile, stable, uniformly mixed and suitable for immediate consumption by infants. In addition, the methods of the present invention can utilize electronic balance recording devices that are capable of measuring weights of product dispensed and maintaining records of total nutrients consumed over time. Optional devices to measure and record unconsumed product to be subtracted from dispensed product are also included in the invention specifications.

[0070] In an embodiment of the method, a predetermined quantity of powder from a process described above is placed in a suitable container which allows for an effective and safe separation of powder and liquid. So-called two compartment packaging devices are commercially available (e.g. Twist-'N Feed) or can be developed to suit the intended purpose. At the time of intended use, applying the

mechanisms specific to the two compartment device, admixture of water and powder is initiated, resulting in a product suitable for feeding an infant.

[0071] Various permutations and combinations of liquid and powdered ingredients can be used. For example, the carbohydrate component of the powder can be present separately in the liquid phase containing the water component of the enteral formulation. In such a case, the powder component of the formula is free or partially free of carbohydrates, while the water component contains the remaining quantity of the carbohydrate component of the formula.

[0072] In an alternative embodiment, a complete formula is produced in a liquid form. In a significant departure from processes currently used by infant formula manufacturers, individual formula components, may be sterilized separately using technologies and methods which do not damage, destroy or decompose heat labile components.

[0073] It is important that in the processes used to render individual formula components commercially sterile, the chemical interactions of proteins and carbohydrates, proteins and lipids, lipids and carbohydrates, proteins and carbohydrates and lipids, as well as the heat induced destruction of vitamins, hormones, bioactive peptides and other labile components of the composition are reduced or effectively prevented. The commercially sterile components of the formula are designed to be mixed in certain proportions to achieve desirable final composition under conditions preventing contamination and the complete liquid product is dispensed aseptically into suitable containers. Alternatively, the components may be dispensed separately into the desired containers such that the components do not mix until they reach the containers. In this case, it may be desirable to subject the filled and sealed containers to agitation or ultra-sound treatment for example to ensure that the lipid phase is satisfactorily dispersed in the product.

[0074] By way of comparison and not limitation, comparing the present invention to the prior art methods, the differences include absence of products formed by decomposition of heat labile components such as vitamins, absence of new chemical forms of minerals salts formed during heat processing, absence of compounds generally described as early or late Maillard reaction products and/or absence of chemical individuals generally described as precursors to formation or

formed advanced glycation end products (AGEs). Visually, the products according to an embodiment of the present invention are whiter and more milk-like looking than the prior art method made products.

[0075] Once the formulas are prepared, they can be stored in a variety of containers. Containers into which formulations are dispensed can include glass or plastic bottles, pouch or bottle inserts, metal cans, unit dose capsules or any other suitable container. An intermediate mixing step to produce a "stock" solution of the product can be included or eliminated and the formula components dispensed into the final container which can vary in volume from few milliliters to several liters.

[0076] In another embodiment, a system similar to existing parenteral nutrition mixing system can be used to produce infant formula. For example, the key components of a formula (proteins, carbohydrates, lipids and micronutrients) are prepared as liquid phases and treated to render them commercially sterile. Heat treatments can be used for heat stable components (e.g. carbohydrates, lipids, possibly proteins) while suitable non-heat treatments such as bacterial filtration can be used for heat labile components such as vitamins. When the product is required, calculated volumes of liquids from separate compartments (bags or syringes) can be dispensed into infant bottles or other suitable containers for consumption or redistribution. The mixing system can be linked to a mechanical or computerized system, which allows for delivery of an unlimited number of combinations of nutritional compositions. Optionally, the mixing system can include means for homogenizing the compounded formula to emulsify the lipid phase and render the product visually appealing to medical staff and other care givers.

#### [0077] EXAMPLES

[0078] By way of example and not limitation, the following examples are illustrative of various embodiments of the present invention and further illustrate experimental testing conducted in accordance with embodiments of the present invention.

[0079] EXAMPLE 1: Production of Infant Formula – Powder

[0080] 30 kg of casein and a required quantity of calcium and potassium hydroxides to convert the casein into soluble form are dissolved in 1000 liters of demineralized water. To this mixture, 65 kg of whey protein isolate, 116 kg of maltodextrin and 270 kg of fat composed of coconut oil, low erucic acid rapeseed oil, corn oil, fish oil and vegetable oils from *Mortierella alpina* and emulsifiers (typically lecithins and monoglycerides) is added with intense agitation. The resulting mixture is homogenized, heated to 90°C and spray-dried. Resulting powder is well mixed with 464 kg of edible crystalline lactose, 20 kg of mixture of minerals containing sodium, potassium, calcium magnesium, manganese, iron, zinc and selenium, in form of chlorides, phosphates, citrates, sulphates or other forms known to those skilled in the art of infant nutrition. Finally, a mixture of vitamins in forms of micronutrient premix and containing all those required by regulations is added, in quantities not exceeding the declared label values, other than by GMP.

[0081] The resulting powder should have an appreciably lower content of Maillard reaction products and other nutritionally undesirable products, including those formed from heat decomposition of vitamins than a formula with the same composition produced by conventional processing, and is ready for reconstitution in water and consumption.

[0082] EXAMPLE 2: Production of Infant Formula – Powder

[0083] 58 kg of whey protein isolate is dry mixed with 100 kg of non-fat dry milk solids. Both protein sources are of edible quality and of low microbial counts. To this mixture, 550 kg of spray-dried fat composition containing 270 kg of fat (coconut oil, low erucic acid rapeseed oil, corn oil, fish oil and vegetable oils from *Mortierella alpina* and emulsifiers) and 280 kg of maltodextrin carrier is added. This mixture is homogenized and heat treated as described in Example 1 and then spray dried. 160 kg of edible lactose, is blown into the spray dryer and a further 100 kg is dry mixed with the mixtures of mineral and micronutrients in powder form to fulfill regulatory, nutritional and label requirements are added.

[0084] The resulting powder should have an appreciably lower content of Maillard reaction products and other nutritionally undesirable products, including

those formed from heat decomposition of vitamins than a formula with the same composition produced by conventional processing, and is ready for reconstitution in water and consumption.

[0085] EXAMPLE 3: Production of Infant Formula – Liquid

[0086] 65 kg of whey protein isolate and 30 kg of calcium/potassium caseinate are dissolved in 2000 liters of demineralized water. To this mixture, 270 kg of fat composed of coconut oil, low erucic acid rapeseed oil corn oil, fish oil and vegetable oils from *Mortierella alpina* and emulsifiers (typically lecithins and monoglycerides) is added with intense agitation. The resulting mixture is standardized, homogenized, processed through HTST (high temperature, short time) aseptic system and delivered into a sterile tank furnished with the agitation system.

[0087] 260 kg of edible lactose is dissolved in 500 liters of demineralized water and sterilized by processing through HTST aseptic system and added to the sterile protein-fat mixture. Finally, a mixture of micronutrients and vitamins is dissolved in 300 liters of water and sterilized by passing through bacterial filtration system and added to the mixture of proteins, lipids and carbohydrates. The final composition is adjusted to required acidity (pH) by sterile solution of sodium hydroxide and/or citric acid, adjusted to required solids concentration (13% for product ready to feed and 26% for infant formula concentrate to be used after dilution with water) and aseptically filled into glass, plastic or metal containers, using technology know to those skilled in art of aseptic processing.

[0088] The resulting liquid should have an appreciably lower content of Maillard reaction products and other nutritionally undesirable products, including those formed from heat decomposition of vitamins than a formula with the same composition produced by conventional processing, and is ready for consumption

[0089] EXAMPLE 4: Other Enteral Formula (Liquid)

[0090] 40 kg of potassium-calcium caseinate is dissolved in 500 liters of demineralized water. To this mixture, 340 kg of fat composed of low erucic rapeseed oil (canola), medium chain triglycerides, corn oil and soy lecithin is added with intense agitation. The resulting mixture is homogenized, processed through HTST (high

temperature, short time) aseptic system and delivered into sterile tank furnished with the agitation system.

[0091] 77 kg of maltodextrins mixtures of DE 14-32, 29 kg of sucrose, 10 kg of fiber (pea, fructooligosaccharides) and a small quantity of carrageenan is dissolved in 200 liters of demineralized water and sterilized by processing through HTST aseptic system and added to the sterile protein-fat mixture. Finally, a mixture of flavorings, colorings, micronutrients and vitamins is dissolved in 100 liters of water and sterilized by passing through bacterial filtration system and added to the mixture of proteins, lipids and carbohydrates. The final composition is adjusted to required acidity (pH) by sterile solution of sodium hydroxide and/or citric acid, adjusted to required solids concentration and aseptically filled into glass, plastic or metal containers, using technology know to those skilled in art of enteral product manufacturing.

[0092] The resulting liquid should have an appreciably lower content of Maillard reaction products and other nutritionally undesirable products, including those formed from heat decomposition of vitamins than a formula with the same composition produced by conventional processing, and is ready for consumption

#### [0093] EXAMPLE 5

[0094] This example demonstrates the effect of preparing an infant formula according to the present invention on AGE content in the finished product as measured by % of blocked lysine compared with the same composition conventionally produced. The infant formula was based on partially hydrolyzed whey protein as the hydrolysis and enzyme activation processes offers an additional opportunity for AGE formation as compared to formulas containing intact proteins. In both cases, the ingredients were 12.2% of Bipro whey protein isolate and 40.4% lactose. In both cases, the protein was subject to hydrolysis as described in European Patent No. 322 589, the contents of which are incorporated herein by reference.

[0095] For the conventional sample, the lactose was included in the hydrolysis process as is usual because commercially available lactose is always contaminated by small amounts of cows milk proteins. For the experimental sample, the lactose was not included in the hydrolysis process. The hydrolyzed proteins were then preheated to a temperature in the range of about 50°C to about 70°C, mixed with the fat (which

had itself been preheated to between 35°C and 55°C) and homogenized in two stages at about 25 MPa in the first stage and about 5 MPa in the second stage. The homogenized liquid mixture was rapidly heated to a temperature of 145°C for 11 seconds to reduce bacterial loads. The liquid mixture was then cooled to about 3°C to about 10°C.

[0096] Meanwhile, the lactose for the experimental sample was dissolved in demineralized water, heat treated as described above and cooled. For the conventional sample, the homogenized mixture was filled into suitable containers under aseptic conditions as is well known in the art. For the experimental sample, the homogenized protein/fat mixture was filled into container as for the conventional sample and the lactose mixture was added still under aseptic conditions.

[0097] The percentage of blocked lysine in the two products was determined using the method described in Finot *et al.* (1981): *The extent of Maillard reaction during the processing of milk*. Prog Food Nutr Sci 5, 345. It was found that the percentage of blocked lysine in the experimental sample was only very slightly higher than that of the starting material and significantly lower than that of the conventional sample.

#### [0098] EXAMPLE 6: Delivery System for Personalized Nutrition of Infants

[0099] This system is similar to existing parenteral nutrition mixing systems, although larger in size to fulfill needs of neonatal units in a hospital, where such a system would find its best utility. The systems consist of bags and syringes filled with separate commercially sterilize solutions of proteins, consisting typically of mixtures of whey proteins and caseins to provide best amino acid composition, similar to that of breast milk. Alternatively, the proteins are in hydrolyzed form, either partially or extensively for reduction of allergenicity or facilitation of protein absorption and metabolism.

[00100] Other containers hold sterile solutions of carbohydrates, typically lactose, although sucrose, maltodextrins, glucooligosaccharides, fructooligosaccharides, galactooligosaccharides and other carbohydrates similar or identical to those present in breast milk and those known to have physiologically beneficial functions for developing infant can also be considered. Other container hold

emulsion of lipids generally used in formulations of infant and other enteral products, while still other containers hold emulsions of specialty lipids, such as fish oil, microbial oils containing docosahexaenoic acid (DHA), vegetable oil containing arachidonic acid (ARA) and their derivatives in forms of mono- and diglycerides.

[00101] Still other containers hold emulsions, suspensions and solutions of vitamins and minerals and other physiologically or biologically beneficial constituents some of which are to be only discovered, in form of premixes or individual components. Finally, a container with sterile water is there for adjusting the proper concentration of above described nutrients.

[00102] At the time of need, a computerized system governing functions of pumps and syringes provides signal for dispensing certain volumes of formula ingredients to match nutritional needs of a consumer with formula composition.

[00103] It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present subject matter and without diminishing its intended advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

## CLAIMS

The invention is claimed as follows:

1. A nutritional composition produced in a process requiring a heating step, the composition comprising a reduced amount of undesirable reaction products formed from chemical reactions between carbohydrates and a compound selected from the group consisting of proteins, lipids and combinations thereof during exposure to heat.
2. The nutritional composition of Claim 1, wherein the undesirable reaction products are selected from the group consisting of AGEs, intermediates of AGEs and combinations thereof.
3. The nutritional composition of Claim 2, wherein the composition is substantially free of AGEs and intermediates of AGEs.
4. The nutritional composition of Claim 1, wherein the reaction products are quantified by measuring the percentage of blocked lysine of the nutritional composition.
5. The nutritional composition of Claim 1, wherein the percentage of blocked lysine of the nutritional composition is used as a marker for the level of AGEs and intermediates of AGEs formed in the nutritional composition.
6. The nutritional composition of Claim 1, wherein the composition is a powder.
7. The nutritional composition of Claim 1, wherein the composition is a liquid.
8. The nutritional composition of Claim 1, wherein the composition is an infant formula.

9. The nutritional composition of Claim 1, wherein the composition is a dairy product.

10. The nutritional composition of Claim 1, wherein the composition includes at least one component selected from the group consisting of a protein source, a carbohydrate source, a lipid source and combinations thereof.

11. The nutritional composition of Claim 1, wherein the composition includes at least one heat labile component.

12. The nutritional composition of Claim 1, wherein the composition is a sterile liquid.

13. The composition of Claim 1, wherein the composition is sterilized by a process selected from the group consisting of bacterial filtration, high pressure sterilization, irradiation, retorting, aseptic processing, heat treatment, pasteurization and combinations thereof.

14. A method of producing a commercially sterile nutritional composition, the method comprising:

providing a protein component;

providing a carbohydrate component;

treating separately at least one of the protein component and the carbohydrate component; and

combining the protein component and carbohydrate component to form the nutritional composition.

15. The method of Claim 14, wherein treating separately at least one of the protein component and the carbohydrate component at least reduces bacterial loads of the treated component.

16. The method of Claim 14, wherein the nutritional composition comprises a reduced amount of compounds from the group consisting of AGEs, intermediates of AGEs and combinations thereof.

17. The method of Claim 14, wherein the carbohydrate component is substantially free of proteins.

18. The method of Claim 14, wherein the protein component is substantially free of carbohydrates.

19. The method of Claim 14, wherein at least one of the carbohydrate component and the protein component are treated to at least reduce the bacterial load within the treated component by a process selected from the group consisting of bacterial filtration, high pressure sterilization, irradiation, retorting, aseptic processing, heat treatment, pasteurization and combinations thereof.

20. The nutritional composition of Claim 14, wherein the composition is a powder.

21. The nutritional composition of Claim 14, wherein the composition is a liquid.

22. A system for producing a commercially sterile nutritional composition, the system comprising:

a protein phase and a carbohydrate phase, wherein at least one of the protein phase and the carbohydrate phase was treated separately from the other phase;

a storage component for holding the protein phase and carbohydrate phase; and

a dispensing device for combining the protein phase and carbohydrate phase to form the nutritional composition.

23. The system of Claim 22, wherein the nutritional composition comprises a reduced amount of compounds from the group consisting of AGEs, intermediates of AGEs and combinations thereof.

24. The system of Claim 22, wherein treating separately at least one of the protein phase and the carbohydrate phase at least reduces bacterial loads of the treated component.

25. The system of Claim 22, wherein treating is by a process selected from the group consisting of bacterial filtration, high pressure sterilization, irradiation, retorting, aseptic processing, heat treatment, pasteurization and combinations thereof.

26. The system of Claim 22, wherein the dispensing device is capable of combining specific levels of the protein phase and carbohydrate phase according to the nutritional needs of a consumer.

27. The system of Claim 22, wherein the carbohydrate phase is substantially free of proteins.

28. The system of Claim 22, wherein the protein phase is substantially free of carbohydrates.

29. A method of producing a commercially sterile nutritional composition, the method comprising:

providing a composition having a protein component and a carbohydrate component; and

treating the composition, wherein the treated composition has a reduced amount of undesirable compounds selected from the group consisting of AGEs, intermediates of AGEs and combinations thereof.

30. The method of Claim 29, wherein the composition includes at least one heat labile component.

31. The method of Claim 29, wherein treating is by a process selected from the group consisting of microfiltration, high pressure sterilization, irradiation and combinations thereof.

32. A method of producing a commercially sterile powdered nutritional composition including a source of proteins, a source of lipids and a source of carbohydrates, the method comprising dissolving the source of proteins in water, adding the lipid source, homogenizing the protein/lipid mixture, heat treating the mixture to reduce bacterial loads, concentrating the heat treated mixture, adding the carbohydrate source and spray-drying the mixture.

33. The method of Claim 32, wherein at least part of the remainder of the carbohydrate source is added to the spray dried powder in an additional dry-mixing step.

34. A method of producing a commercially sterile powdered nutritional composition including a source of proteins, a source of lipids and a source of carbohydrates by spray drying, the method comprising dissolving the source of proteins in water together with the minimum amount of carbohydrate necessary to facilitate the spray drying, adding the lipid source, homogenizing the protein/lipid mixture, heat treating the mixture to reduce bacterial loads, concentrating the heat treated mixture, spray-drying the mixture and adding the remainder of the carbohydrate source.

35. The method of Claim 34, wherein at least part of the remainder of the carbohydrate source is added during the spray drying step by blowing into the spray dryer.

# INTERNATIONAL SEARCH REPORT

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PCT/US2005/032116

**A. CLASSIFICATION OF SUBJECT MATTER**  
A23L1/29      A23L1/305

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)  
A23L A23C

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)

EPO-Internal, WPI Data, PAJ, FSTA, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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X	US 4 640 840 A (ASSINDER ET AL) 3 February 1987 (1987-02-03) column 1, lines 5-8, 36-65 column 2, lines 11-16, 57 column 2, line 67 - column 3, line 18 examples I-III figure 1  -----  -/--	1-7, 9-28

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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## INTERNATIONAL SEARCH REPORT

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A	column 6, line 63 - column 7, line 1	14-19, 32-35
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Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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