

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

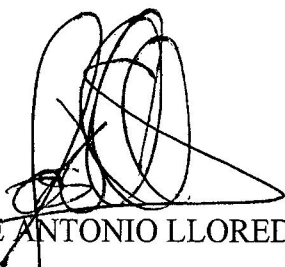
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SUPERINDUSTRIA Y COMERCIO
Radicación: 00025252 00000001
Fecha (FMD): 2000-05-19 16:29:52
Trámite: 002 PATENTES D 1 REGISTRO/ 329 COMPLETAR
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES
Folios: 27

Re: P1.- ABBOTT LABORATORIES.- Solicitud de Patente de Invención para
"FORTALECEDOR EN POLVO PARA LECHE HUMANA".- Clase
A23.-Expediente número 00-025.252 .-

1. Me refiero a mi solicitud de patente arriba nombrada de fecha 6 de Abril de 2000.
2. Anexos me permito presentar a usted:
 - (1) Copia autentica, debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad**, a saber la solicitud estadinense número 60/128.575 de 9 de Abril de 1999, junto con su traducción oficial No. 5722 correspondiente a las legalizaciones y reivindicaciones de dicho documento; y
 - (2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial de la señora María Luisa Brigard de Restrepo quien elaboró la traducción de la legalizaciones de la solicitud estadinense número 60/128.575 de 9 de Abril de 1999.
3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.
Señor Superintendente,


JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

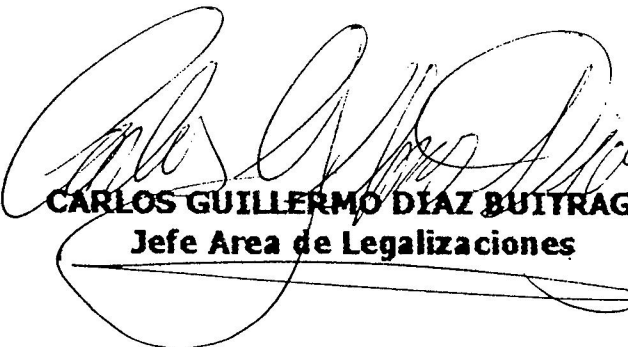
**EL SUSCRITO JEFE DEL AREA DE
LEGALIZACIONES DEL MINISTERIO DE
RELACIONES EXTERIORES**

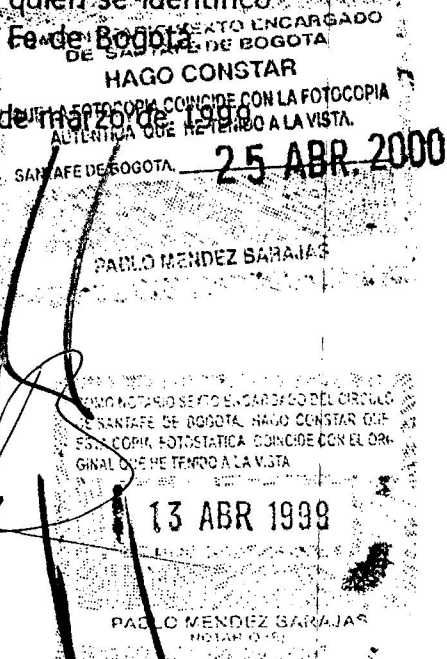
CERTIFICA

Que revisados los registros que se llevan en la oficina de Legalizaciones aparece la firma de la señora **MARIA LUISA DE BRIGARD DE RESTREPO**, como traductora e intérprete oficial para los idiomas **INGLES - ESPAÑOL, ESPAÑOL-INGLES**, según resolución 0793 del 21 de marzo de 1958

La anterior certificación se expide a solicitud de la interesada, quien se identificó con cédula de ciudadanía No. 20.024.691 expedida en Santa Fe de Bogotá

Dada en Santa Fe de Bogotá, D.C. a los veinticinco (25) días de marzo de 1999


CARLOS GUILLERMO DIAZ BUITRAGO
Jefe Area de Legalizaciones



91-88

TRADUCCION OFICIAL No. 5.722

de un documento escrito en INGLES, el cual para su identificación se sella con el sello del Traductor al mismo tiempo que la presente. -

ESTADOS UNIDOS DE AMERICA

A CUANTOS LLEGAREN LAS PRESENTES:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS 5.722

Oficina de Patentes y Marcas de Fábrica de los Estados Unidos

Handwritten signature and stamp:
Sello de la Oficina de Patentes y Marcas de Fábrica de los Estados Unidos
24 de mayo del 2000

POR LA PRESENTE SE CERTIFICA QUE ANEXA AQUI SE ENCUENTRA UNA COPIA FIEL , TOMADA DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE FABRICA DE LOS ESTADOS UNIDOS, DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA ABAJO QUE SATISFACEN LOS REQUISITOS PARA QUE SEA OTORGADA UNA FECHA DE REGISTRO SEGUN 35 USC 111.

NUMERO DE SOLICITUD: 60/128,575

FECHA DE REGISTRO: 9 de abril de 1999.

Por Autorización del

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COMISIONADO DE PATENTES Y MARCAS DE FABRICA

(Firma)

H. L. JACKSON

Funcionario Certificador

Sello: OFICINA DE PATENTES Y MARCAS DE FABRICA - ESTADOS UNIDOS DE AMERICA -

Reivindicamos:

5.722
TRANSCODI. OFICIAL NO.
Marta Luisa Brizuela de Restrepo
Intérprete Oficial
No. 0782 del Min. de Justicia

1. Un fortificador de la leche humana, en polvo, que comprende:
 - a. un componente de proteína de cerca de 24% hasta cerca de 55% peso/peso, y
 - b. un componente de grasa de cerca de 1% hasta cerca de 30% peso/peso.
2. Un método para proporcionar nutrientes suplementarios a infantes predeterminados, que consiste en agregar un polvo fortificador a la leche humana y administrar la leche humana fortificada a un infante prematuro,

en el que dicho polvo fortificador comprende:

- a. un componente de proteína de cerca de 24% hasta cerca de 55% peso/peso, y
- b. un componente de grasa de cerca de 1% hasta cerca de 30% peso/peso.

3. Una dosis unitaria de polvo fortificador de la leche humana que comprende

- a. un recipiente,
- b. un componente de proteína de cerca de 24% hasta cerca de 55% peso/peso, y
- c. un componente de grasa de cerca de 1% hasta cerca de 30% peso/peso.

4. Un método para promover el crecimiento de un infante prematuro, que consiste en administrar al mismo leche humana fortificada que comprende:

- a. leche humana, y
- b. fortificador en polvo,

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en el que dicho fortificador en polvo comprende:

- a. un componente de proteína de cerca de 24% hasta cerca de 55% peso/peso, y
- b. un componente de grasa de cerca de 1% hasta cerca de 30% peso/peso.

5. Un método para incrementar la estabilidad de la leche humana, que consiste en agregar un emulsionador a la leche humana.

ES TRADUCCION FIEL Y COMPLETA, de la cual queda copia en los archivos de esta oficina de traducciones, para su confrontación y a la que me remito.

Derechos de Traducción: \$36.000,00

BOGOTA, 6 DE JUNIO DEL 2000.

TRADUCCION OFICIAL No 5-722

Maria Luisa Brigard de Restrepo
Maria Luisa Brigard de Restrepo
Intérprete Oficial
Cm No 0722 del Min de Justicia

PA 251595

THE UNITED STATES OF AMERICA**TO ALL TO WHOM THESE PRESENTS SHALL COME:****UNITED STATES DEPARTMENT OF COMMERCE****United States Patent and Trademark Office**

May 24, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK
OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/128,575

FILING DATE: April 09, 1999



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

H. L. Jackson
H. L. JACKSON
Certifying Officer

TRANSLACION OFICIAL No. 5. 2
Marka de Registro de Resolucion
Intendencia de Comercio
del Min. de Justicia

04/09/99
jc649 U.S. PTO

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PTO/SB/16 (2-98)
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

INVENTOR(S)					
Given Name (first and middle (if any))		Family Name or Surname		Residence (City and either State or Foreign Country)	
Bridget Barrett		Reis		Dublin, Ohio	
☒ Additional inventors are being named on the ___ separately numbered sheets attached hereto					
TITLE OF THE INVENTION (280 characters max)					
HUMAN MILK FORTIFIER					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
☐ Customer Number				Place Customer Number Bar Code Label here	
OR Type Customer Number here					
☒ Firm or Individual Name		J. Michael Dixon, Ross Product Division, Abbott Laboratories			
Address		625 Cleveland Avenue			
Address					
City		Columbus	State	Ohio	ZIP 43215
Country		United States	Telephone	614-624-5686	Fax 614-624-3074
ENCLOSED APPLICATION PARTS (check all that apply)					
☒ Specification Number of Pages		17		☐ Small Entity Statement	
☐ Drawing(s) Number of Sheets				☐ Other (specify)	
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)					
☐ A check or money order is enclosed to cover the filing fees				FILING FEE AMOUNT (\$)	
☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 01-0025				\$150.00	
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
☒ No.					
☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____					

Respectfully submitted,

SIGNATURE

J. Michael Dixon

Date 4 / 9 / 99

TYPED or PRINTED NAME

J. Michael Dixon

REGISTRATION NO.
(if appropriate)

32,410

TELEPHONE

614-624-5686

Docket Number:

6483.US.Z1

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C., 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C., 20231.

Powder Human Milk Fortifier

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INTRODUCTION

Preterm infants are commonly fed either a commercial infant formula designed specifically for these infants or their own mother's milk. The exact nutrition requirements of these infants are still unknown; however, numerous studies have documented that unsupplemented preterm milk and banked term milk provide inadequate quantities of several nutrients to meet the needs of these infants (Davies DP, Adequacy of expressed breast milk for early growth of preterm infants. *Archives of Disease in Childhood*, 52, p. 296-301, 1997; Gross SJ, Growth and biochemical response of preterm infants fed human milk or modified infant formula. *New England Journal of Medicine*, 308, p.237-241, 1983; Mondanlau et al Growth, biochemical status, and mineral metabolism in very-low-birth-weight infants receiving fortified preterm human milk. *Journal Pediatric Gastroenterology and Nutrition*, 5, p.762-767, 1986; Putet et al, Nutrient balance, energy utilization, and composition of weight gain in very-low-birth-weight infants fed pooled human milk or a preterm formula. *Journal of Pediatrics*, 105, p.105-179, 1983.) Thus, it has been recommended that when preterm infants are fed preterm human milk, the human milk be fortified to better meet the nutritional needs of the preterm infant. Fortification of preterm human milk is deemed of lesser importance in early lactation due to the high concentrations of protein and sodium and other nutrients present in colostrum and transitional milk. Concentrations of these nutrients decrease as the milk supply matures. It is generally agreed that preterm human milk supplies insufficient quantities of energy, protein and several vitamins and minerals, most notably calcium and phosphorus, to support adequate growth and bone mineralization.

Moro et al studied an alternate fortification regimen for very-low-birth-weight infants with a new powder fortifier in Fortification of Human Milk: Evaluation of a Novel Fortification Scheme and of a New Fortifier, *Journal of Pediatric Gastroenterology and Nutrition*, 20, pp 162-172, 1995. A new powder fortifier based on bovine milk proteins performed equally to the human milk protein concentrate fortifier in the new regimen. The bovine milk protein-based fortifier added 0.79 gm of protein (40% casein/ 60% whey), 0.36gm medium chain triglycerides, 1.7 gm maltodextrin, 121 mg calcium, 61 mg phosphorus, 8 mg magnesium, 15.4 mg sodium, 63 mg potassium, 37.7 mg chloride, 0.35 mg iron, 1.04 mg zinc, 0.17 mg copper, 18.3 mcg mangnaese, 3.6 mg taurine, 156 IU vitamin A, 120 IU vitamin D, 2.2 IU vitamin E, 8.3 mcg

vitamin K, 25 mcg vitamin C, 233 mcg vitamin B1, 417 mcg vitamin B2, 211 mcg vitamin B6, 0.64 mcg vitamin B12, 3.57 mg niacin, 23 mcg folic acid, 1.51. mcg pantothenic acid, 26.3 mcg biotin, 12.1 mg choline and 3.85 mg m-inositol to 100 ml of human milk. The protein content of the powder fortifier of the instant invention is higher than that of the bovine protein based fortifier of Moro et al.

Liquid and powder forms of preterm milk fortifiers have been marketed in response to this recognized need. The nutrient compositions of mature human milk and a variety of commercially available fortifiers are presented in Table 1.

Table 1: Energy and Nutrient Composition of Human Milk and Human Milk Fortifiers

Nutrients	Mature Human Milk (100 mL)	Enfamil Human Milk Fortifier Powder (3.8g)	Similac Natural Care Liquid (100 ml)
Energy, Kcal	67	14	81
Protein , gm	1.4	0.7	2.2
source	human milk	whey protein concentrate, sodium caseinate	nonfat milk, whey protein concentrate
Fat, gm	3. 9	<0.1	4.4
source	human milk	none added	MCT, soy, coconut
Carbohydrate, gm	6.6	2.7	8.6
source	lactose	corn syrup solids	corn syrup solids, lactose
Minerals			
calcium, mg	25	90	171
phosphorus, mg	13	45	94
magnesium, mg	3.2	1	10
zinc, mg	0.34	0.71	1.22
manganese, mcg	0.6	4.7	9.8
copper, mg	64	0.06	0.2
sodium, mg	25	7	35
potassium, mg	57	15.6	105
chloride, mg	55	17.7	66
iron, mg	0.12	none added	0.3
selenium, mcg	2.3	none added	1.46
Vitamins			
A, IU	389	950	1,008
D, IU	2	210	122
E, IU	1	4.6	3.2
K, mcg	0.21	4.4	10
Thiamin, mg	0.02	0.15	0.2
Riboflavin, mg	0.04	0.21	0.5
B6, mg	0.15	0.11	0.2
B12, mg	0.05	0.18	0.45
Niacin, mg	0.15	3	4
Folic acid, mcg	3.3	25	30

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Pantothenic acid, mg	0.18	0.73	1.54
Biotin, mcg	0.4	2.7	30
C, mg	11	11.6	30
Enfamil Human Milk Fortifier (Mead Johnson Nutritionals, Evansville, Ind.) Values are label claim.			
Similac Natural care (Ross Products Division of Abbott Laboratories, Chicago, ILL.) Values are label claim.			

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Similac Natural Care and Enfamil are commercially available human milk fortifiers. The fortifiers differ with respect to their form, source of ingredients and energy and nutrient composition. There is need in the neonatal intensive care unit for both liquid and powdered human milk fortifiers. When a mom is able to produce and pump sufficient milk to meet the volume needs of her infant, it is advantageous to minimize the dilution of mother's milk. However, if mom's milk supply is limited, a liquid fortifier may be used to stretch her supply of human milk. Similac Natural Care is designed to be added to preterm milk in a one-to-one ratio or fed alternately with human milk meeting a need in the neonatal intensive care unit. The primary advantage of the powdered fortifier is that there is minimal dilution of human milk. There is currently only one powder human milk fortifier available on the domestic market (Enfamil Human Milk Fortifier). Four packets of powder Enfamil (0.96 g powder/packet) is added to 100 mL of preterm milk. A study conducted by Schanler, Suitability of human milk for the low-birth weight infant, Clinics in Perinatology, 22, pp. 207-222, 1995 in preterm infants receiving this powder fortifier demonstrated poor fat absorption. Poor fat absorption can have a negative impact on growth. Another recent study by Lucas et al, Randomized outcome trial of human milk fortification and development outcome in preterm infants, American Journal Clinical Nutrition, 64, pp142-151,1996 evaluating this powdered human milk fortifier found a greater rise in alkaline phosphatase by week 6 and more clinical infections as compared to a control group. In addition, physical stability issues are observed when the Enfamil powder fortifier is added to the human milk.

A fortifier that promotes physical stability of the human milk/fortifier admixture and maximizes the short and long-term nutritional needs of a premature infant and the health benefits of human milk while addressing the variability of human milk as a sole source of energy, protein, calcium, phosphorus, sodium and other micronutrients is needed to support the growth of the premature infant.

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SUMMARY OF THE INVENTION

The instant invention relates to a powder fortifier comprising a protein component present in a quantity of from about 24% to about 55% wt/wt, and a fat component present in a quantity of from about 1% to about 30% wt./wt. Typically, an emulsifier is present in a quantity of from about 1% to about 10% wt/wt of the fat system or 0.1% to about 1% wt/wt of said powder fortifier. Preferably, the powder fortifier is provided in a unit dose container which holds from about 0.5gm to about 10gm of said powder fortifier. The instant invention also relates to a method of providing nutrition to preterm infants by adding said powder fortifier to human milk and administering said fortified human milk to a premature infant. The invention further provides a method of promoting growth of a premature infant by administering said fortified human milk to a premature infant. The invention also relates to a method for enhancing the physical stability of human milk by adding an emulsifier to the human milk.

DETAILED DESCRIPTION OF THE INVENTION

It is a principal object of the invention to provide an improved human milk fortifier for premature infants who require additional nutrients to support their growth. The invention is to provide a powder which when added to human milk supplements the levels of protein, fat, vitamins and minerals. Another object of this invention is to provide a method for providing supplemental nutrients to a premature infant who requires additional nutrients for growth.

The terms "premature", "preterm" and "low-birth-weight" infants are used interchangeably herein and refer to infants born less than 37 weeks gestational age and/or with birth weights less than 2500 gm.

"A unit dose" as used herein refers to individual packages of powder fortifier containing an amount of fortifier that will be used in one feeding. There will be no leftover fortifier requiring storage.

The term "growth" used herein refers to gains in weight, length and/or head circumference.

The powder fortifier of this invention will typically provide the following nutrient distribution. The protein system will typically be present in an amount of from about 24% to about 55% wt./wt., more preferably from about 25% to about 42% wt./wt., most preferably from about 28% to about 36% wt./wt.. The fat system will typically be present in an amount of from about 1% to about 30% wt./wt., more preferably about 5% to about 20% wt./wt., most preferably

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about 8% to about 18% wt./wt.. The carbohydrate system will typically be present in an amount of from about 15% to about 75% wt./wt., more preferably from about 38% to about 70% wt./wt., most preferably from about 46% to about 64% wt./wt.. The amount of powder required to provide a unit dose of the fortifier will typically range from about 0.5gm to about 10 gm, more preferably from about 0.8 gm to about 5.0 gm, most preferably from about 0.85 gm to about 2.0 gm. The caloric density is typically from about 1.0 kcal/gm powder to about 8.5 kcal/gm powder.

The first component of the powder fortifier of this invention is the protein system. As stated above, the protein system will typically be present in an amount of from about 24% to about 55% wt./wt.. Examples of suitable protein for a premature infant comprise casein, whey, condensed skim milk, nonfat milk, soy, pea, rice, corn, hydrolyzed protein and mixtures thereof. The preferred protein system will typically be comprised of about 51% whey protein concentrate and about 49% nonfat dry milk which corresponds to about 60% whey and about 40% casein.

The second component of the powder fortifier of this invention is the fat system. As stated above, the fat system will typically be present in an amount of from about 1% to about 30% wt./wt.. Examples of suitable fat sources comprise high oleic safflower oil, soy oil, fractionated coconut oil (medium chain triglycerides, MCT oil), high oleic sunflower oil, corn oil, canola oil and mixtures thereof. The preferred fat system comprises 100% MCT oil. This fat source at this level provides well tolerated fat calories to the premature infant in addition to providing a vehicle for fat soluble vitamins and an emulsifier.

The emulsifier helps the water soluble and insoluble components of the nutritional powder incorporate into the human milk. It is also thought to help prevent separation of expressed human milk due to extreme storage conditions, such as freezing. Examples of suitable emulsifiers comprise soya bean lecithin, polyoxyethylene stearate, polyoxyethylene sorbitan mono-oleate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, ammonium phosphatides, polyoxyethylene sorbitan monolaurate, citric acid esters of mono and diglycerides of fatty acids, tartaric acid esters of mono and diglycerides of fatty acids. The preferred emulsifier source is natural soy lecithin. The amount of emulsifier will typically be present in an amount of from about 1% to about 10% wt/wt of the fat system or 0.1% to about 1% wt/wt of the powder fortifier, more preferably from about 1.5% to about 5% wt/wt of the fat system.

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The third component of the powder fortifier of this invention is a source of carbohydrates. The carbohydrates that may be used in the powder fortifier can vary widely. Examples of carbohydrates suitable for preterm infants include hydrolyzed corn starch, maltodextrin, glucose polymers, sucrose, corn syrup solids, glucose, fructose, lactose, high fructose corn syrup and fructooligosaccharides.

Maltodextrins and corn syrup solids are complex carbohydrates routinely used in nutritional formulations because of their excellent digestibility and functional properties. Specifically, they are good water binders and provide products with desired texture and mouth feel. Maltodextrins are polysaccharides obtained from the acid or enzyme hydrolysis of corn starch. Their classification is based on the degree of hydrolysis and is reported as dextrose equivalence (DE). The FDA defines maltodextrins as non-sweet, nutritive polysaccharides that have a DE less than 20. Corn syrup solids are defined as having DE's greater than 20. Corn syrup solids consist of dextrose chains about 3 to 4 units long while maltodextrins are less hydrolyzed and contain longer dextrose chains. The difference in polymer length results in different functionality, viscosity, mouth feel and osmolality.

As noted above, the carbohydrates will typically be present in an amount of from about 15% to about 75% wt./wt.. Any single carbohydrate listed above, or any combination thereof, as appropriate may be utilized. The preferred carbohydrate level and source has been selected to decrease osmolality and viscosity. The preferred carbohydrate source is 100% corn syrup solids.

The fourth component of the powder fortifier of the present invention typically includes supplemented vitamins and minerals. The variability of human milk vitamin and mineral concentrations requires a minimal fortification to ensure that a developing premature infant is receiving adequate amounts of vitamins and minerals while not over fortifying and possibly causing, for example, hypercalcemia. Table 2 lists typical ranges for the vitamins and minerals per serving (4 pouches of 0.9gm) of powder human milk fortifier. The ranges listed in Table 2 are not intended to limit the invention but are to be used as guidelines by those knowledgeable in the art.

Table 2 Vitamin and Mineral Ranges per 3.6 gm

Vitamins		
A, IU	620	905
D, IU	121	145
E, IU	3.4	3.9
K, mcg	8.50	9.90
Thiamin (B-1), mg	0.240	0.310
Riboflavin (B-2), mg	0.418	0.500
B-6, mg	0.205	0.256
B-12, mg	0.660	0.994
Niacin, mg	4.0	4.75
Folic acid, mg	25	34
Pantothenic acid, mg	1.53	2.07
Biotin, mg	26.5	39.7
C, mg	25.0	67.7
m-inositol, mg	107	127
Minerals		
Calcium, mg	117	145
Phosphorus, mg	67	82
Magnesium, mg	7.0	9.3
Zinc, mg	1.04	1.26
Manganese, mcg	4.5	13.5
Copper, mg	0.169	0.238
Sodium, mg	15.4	18.4
Potassium, mg	63.0	75.6
Chloride, mg	37.7	44.9
Iron, mg	0.35	0.42
Selenium, mcg	0.72	1.44

Desirably, the nutritional powder will include the natural form of vitamin E (RRR-d-alpha-tocopherol acetate). The term "vitamin E" means a group of tocopherols that differ only in the number and position of methyl groups on the ring. The most active form of vitamin E, is also the most widely distributed in nature. When tocopherol was first synthesized, the synthetic material was found to have a slightly lower biological activity than the tocopherol from plants. Because of this phenomena, the natural occurring form has been designated RRR-"-tocopherol. For dietary purposes, vitamin E activity is expressed as RRR-"-tocopherol equivalents (TEs). One TE is the activity of 1 mg of RRR-"-tocopherol. One mg of RRR-"-tocopherol is equivalent to 1.49 IU of vitamin E.

While not fully evaluated, the characteristics, specifically solubility, of some of the minerals in the powder fortifier may be important in product stability, formula tolerance and mineral bioavailability characteristics of the fortified human milk. It is known that soluble minerals, particularly calcium, are capable of interacting with proteins. The destabilization of proteins results in denatured protein that precipitates out of solution or clings to the sides of the

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delivery container. Consequently, the protein is not actually delivered to the infant. Preferably, the current invention uses insoluble calcium sources and address mineral precipitation issues first by making the fortifier a powder and secondly by using particle sizes small enough (ultra micronized) to stay in solution during feeding.

The nutritional powder of this invention can be manufactured using techniques well known to those skilled in the art. While manufacturing variations are certainly well known to those skilled in the nutritional formulation arts, a few of the manufacturing techniques are described in detail in the Examples. Generally speaking an oil blend is prepared containing all oils, any emulsifier, and the fat soluble vitamins. Two more slurries (carbohydrate and protein) are prepared separately by mixing the carbohydrate and minerals together and the protein in water. The two slurries are then mixed together with the oil blend. The resulting mixture is homogenized, heat processed, standardized with water soluble vitamins, and dried. The resulting powder may be milled to a specific particle size and /or agglomerized to modify particle size and mixability characteristics. Those skilled in the nutritional formulation arts would also be able to dry blend the individual starting materials and add the fat through agglomeration or during the dry blending step.

Individual unit dose size packages are preferred over bulk packaging. Because of the small volumes of milk administered to premature infants over the course of a days feeding, small volumes of fortified human milk are prepared. Powder sterility in a bulk container that has been repeatedly opened, powder scooped out, recovered and stored is always a concern in a hospital environment. Individual unit doses allow for addition of small amounts of powder to human milk without the possibility of contamination of the remaining powder since all of the powder is used in a single serving. As noted above, the unit dose of the invention typically is the amount of from about 0.5 gm to about 10gm of powder fortifier.

EXAMPLE I

A 8,172 kg powder batch consists of one carbohydrate/mineral (CHO/MIN) slurry, one oil blend and one protein in water slurry (PIW). The CHO/MIN, oil blend and PIW slurries are mixed together to form the final blend. The final blend is then processed with an UHTST treatment. After standardization, the final blend is spray dried. The resultant powder may be used as is or agglomerated to modify mixability characteristics of the powder.

Table 3 presents a bill of materials for manufacturing 8,172 kg of nutritional powder human milk fortifier. A detailed description of its manufacture follows.

Table 3 Bill of materials

Ingredient	Amount
Ingredient water	16,205 L
Corn syrup solids	1603 kg
Magnesium chloride	96.2 kg
Potassium citrate	223.8 kg
Sodium citrate	6.6 kg
Sodium chloride	15.4 kg
MCT oil	801 kg
Lecithin	16.6 kg
Vitamin A	1.98 kg
Vitamin D	359.3 g
Vitamin K	23.3 g
Natural Vitamin E	7.6 kg
Calcium carbonate	33.1 kg
UM-Tricalcium phosphate	571.5 kg
Whey protein concentrate	1506 kg
Non fat dry milk	3307 kg
potassium citrate	257.2 g
ferrous sulfate	3.7 kg
Zinc sulfate	11.1 kg
Copper sulfate	1.84 kg
Manganese sulfate	0.320 kg
Sodium selenate	0.001 kg
Niacinamide	0.98 kg
Riboflavin	1.14 kg
Calcium pantothenate	4.08 kg
Pyridoxine hydrochloride	0.655 kg
m-inositol	9.55 kg
Biotin	0.0727 kg
Folic acid	0.0775 kg
Cyanocobalamin	0.0016 kg
Ascorbic acid	153.5 kg

A carbohydrate/mineral slurry is prepared by heating 2,763 liters of ingredient water to 130°F- 145°F. With agitation, the specified amounts of corn syrup solids (Maltrin M200 distributed by Grain Processing Corporation, Muscatine, Iowa), magnesium chloride, sodium chloride, sodium citrate, potassium citrate, ultra micronized tricalcium phosphate and calcium

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carbonate are added to the heated water. The slurry is held under agitation at 130°F-145°F for not longer than six hours until it is blended with the other slurries.

An oil blend is prepared by heating the specified amount of MCT oil (distributed by Stepan, Maywood, New Jersey) to 90°F-100°F with agitation. An emulsifier (standard fluid lecithin distributed by Central Soya, Ft. Wayne, Indiana) is then added under agitation and allowed to dissolve. Vitamin A,D,K and Natural Vitamin E (distributed by Vitamins, Inc., Chicago, Illinois) are then added to the slurry with agitation. The completed oil slurry is held under moderate agitation at a temperature from 80°F to 120°F for a period of no longer than six hours until it is blended with the other slurries.

A protein-in-water slurry is prepared by heating 9,053 liters of ingredient water to 130°F-145°F. With agitation, the specified amount of whey protein concentrate (AMP 800 distributed by AMPC, Inc. Ames, Iowa) and nonfat dry milk is added to the heated water. The completed protein-in-water slurry is not held but blended directly with the other slurries.

The protein-in-water, oil blend and carbohydrate/mineral slurries are blended together with agitation and the resultant blend is maintained at a temperature from 125°F to 140°F. After waiting for at least five minutes with agitation the final blend pH is adjusted with 1N KOH to a pH from 6.45 to 6.60. The total solids of the final blend is 40%. The final blend is held for no longer than two hours after the pH check.

After waiting for a period of not less than five minutes nor greater than two hours, the blend is subjected to deaeration, ultrahigh-temperature-short-time heat treatment, and homogenization, as follows:

- A. deaerate the blend at 10-15 inches Hg;
- B. emulsify the blend at 900-1100 psig in a single stage homogenizer;
- C. pass the blend through a plate/coil heater and heat the mix to 160°F to 180°F;
- D. homogenize the blend at 3900 to 4100 / 400 to 600 psig in a double stage homogenizer;
- E. pass the blend through a 16 second hold tube at a temperature from 165°F to 185°F;
- F. cool the blend to a temperature from 34°F to 45°F; and
- G. store the blend at a temperature from 34°F to 45°F.

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After the above steps have been completed, appropriate analytical testing for quality control is conducted. Based on the analytical results of the quality control tests, batch corrections are made if need be. Final blend total solids are from 39% to 41%.

A water soluble vitamin solution, ascorbic acid solution and trace mineral solution are prepared separately and added to the processed blend.

The ascorbic acid solution is prepared by adding to 3,686 liters of 50°F to 100°F water the required amount of ascorbic acid with agitation.

The mineral solution is prepared by heating 321 liters of ingredient water to 100°F to 150°F. Under agitation, add the required amount of potassium citrate and ferrous sulfate. Allow to agitate until the solution is a clear green color. Add the required amounts of zinc sulfate, copper sulfate, manganese sulfate and sodium selenate to the green mineral solution. Agitate five minutes minimum.

The water soluble vitamin solution is prepared by heating 382 liters of ingredient water to 100°F to 150°F. The required quantities of niacinamide, riboflavin, calcium pantothenate, pyridoxine hydrochloride, thiamine hydrochloride, myo-inositol, biotin, folic acid and cyanocobalamin are added to the heated water.

All of the ascorbic acid solution, the mineral solution and water soluble vitamin solution is then added to the blended slurry under agitation.

The final mix is preheated through a plate heater to 160°F-180°F before going to a surge tank. The mix leaves the surge tank and passes through the steam injector where it is heated to 217°F-250°F. The mix enters the vapor-flash chamber where it is cooled to 160°F-180°F, then pumped through an in-line 200 micro filter prior to the high pressure pump and into the dryer. The dryer settings are as follows:

Nozzle pressure	3000 - 5000 psig
Liquid flow rate	10 gpm max.
Ingoing Air Temperature	320°F-405°F
Outgoing Air Temperature	180°F-228°F

To control bulk density, dispersibility, particle size, moisture and physical stability, the specific spray nozzle, nozzle pressure, drying temperatures and fine reinjection parameters may vary depending upon the drying conditions of the day. The powder passes from the dryer into the powder cooler where the powder is cooled to below 110°F. The cooled powder is stored in appropriate containers until being filed in bulk containers or individual packets.

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EXAMPLE II

The primary objective of the study was to demonstrate that the nutritional powder fortifier of the instant invention added to human milk (HM) would support acceptable growth in preterm infants. A second objective was to evaluate the serum biochemistries (ie, protein status, calcium, alkaline phosphatase), tolerance, clinical problems, and morbidity of premature infants consuming the nutritional module. Another secondary objective was to compare the nutritional powder of the instant invention to a commercial powder fortifier that has been in use for a number of years.

An intent-to-treat, prospective, randomized, double-blinded multicenter study was conducted to evaluate preterm infants receiving preterm milk supplemented with either a commercial powder human milk fortifier (Enfamil Human Milk Fortifier, EHMF) or the nutritional powder of the current invention (NPF) at every feeding. Subjects were enrolled and randomized to each fortifier prior to 21 days of life. Study Day 1 was when fortification of the study fortifier had begun and the subject reached an intake of at least 100 mL/kg/day. Anthropometric indices, serum biochemistries, intake, tolerance, and morbidity data were assessed. Each infant was studied until hospital discharge; only anthropometric variables (weight, length, and head circumference) were collected after Study Day 29.

Premature infants were recruited from neonatal intensive care units (NICUs) that had agreed to collaborate with study investigators located in Salt Lake City, UT; Houston, TX; Indianapolis, IN; Kansas City, MO; Louisville, KY; and Omaha, NE.

Single, twin, or triplet infants born ≤ 33 weeks gestational age, with appropriate weight for gestational age, and weighing ≤ 1600 g were eligible to participate. One-hundred and forty-four infants were randomized to either EHMF or NPF; 70 preterm infants were randomized to the EHMF group and 74 preterm infants were randomized to the NPF group. The randomization was proportional for birth weight (< 1100 g and ≤ 1100 g) and gender.

The nutrient content of the two powder fortifiers added to human milk is listed in Table 4.

Table 4 Nutrient Content of Human Milk, EHMf and NPF

Nutrients	Preterm Milk-Mature* (per 100 mL)	EHMF† (per 3.8 g)	NPF‡ (per 3.6 g)	
			Batch 1	Batch 2
Energy	67	14	13.8	14
Protein, g source	1.4 mature human milk	0.7 whey protein concentrate/ sodium caseinate	1.0 whey protein concentrate/ nonfat dry milk	1.0 whey protein concentrate/ nonfat dry milk
Fat, g source	3.9 mature human milk	<0.1 none added	0.41 MCT oil	0.37 MCT oil
Carbohydrate, g source	6.6 lactose	2.7 corn syrup solids	1.6 corn syrup solids	1.7 corn syrup solids
Vitamins				
A, IU	389	950	640	763
D, IU	2.0	210	134	145
E, IU	1.0	4.6	3.4	3.5
K, mcg	0.21§	4.40	8.50	8.60
Thiamin (B-1), mg	0.021§	0.151	0.270	0.300
Riboflavin (B-2), mg	0.048	0.210	0.460	0.500
B-6, mg	0.015	0.114	0.230	0.240
B-12, mcg	0.05§	0.18	0.85	0.83
Niacin, mg	0.15§	3.0	0.40	0.42
Folic acid, mcg	3.3	25	30	27
Pantothenic acid, mg	0.18§	0.73	1.60	1.40
Biotin, mcg	0.4	2.7	30.0	33.0
C, mg	11	11.6	23.3	60.0
Minerals				
Calcium, mg	25	90	131	118
Phosphorus, mg	13	45	68	67
Magnesium, mg	3.2	1.0	7.7	7.7
Zinc, mg	0.34	0.71	1.30	1.2
Manganese, mcg	0.6	4.7	9.2	12.0
Copper, mg	0.064	0.062	0.200	0.200
Sodium, mg	25.0	7.0	17.5	17.5
Potassium, mg	57	15.6	72.0	72.0
Chloride, mg	55.0	17.7	40.0	40.0
Iron, mg	0.12	—	0.35	0.45
Selenium, µg	2.3	—	1.4	0.99
† Amounts added to each 100 mL human milk (4 packets of fortifier). Values are label claim.				
‡ Amounts added to each 100 mL milk (4 packets of fortifier). Values are analyzed values.				
§ Values for mature human milk were used.				

The independent variables (treatments) were EHMf and NPF which were added to HM. Both fortifiers were provided in small packets in powdered form and were added to 25 mL HM.

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The primary outcome variable was weight gain (g/kg/day) from study day 1 to study day 29 or discharge, whichever came first. Secondary outcome variables were length gain (mm/day) and serum biochemistries to evaluate protein status, electrolyte status, mineral homeostasis, and vitamin A and E status. Serum biochemistries also included unscheduled laboratory results recorded in the medical chart. Tertiary variables included head circumference gain (mm/day), clinical history, intake, tolerance, clinical problems/morbidity, respiratory status, antibiotic use, and the number of transfusions.

Mean total energy intakes during the study period was not different between the two groups. Infants fed EHMF fortified human milk received 118.0 ± 2.2 kcal/kg/day while the infants fed NPF fortified human milk received 118.0 ± 1.6 kcal/kg/day. There was a difference in mean protein intake between the two groups. Infants fed EHMF fortified human milk received 3.1 ± 0.1 g protein/kg/day while infants fed NPF fortified human milk received 3.5 ± 0.1 g protein/kg/day which is consistent with the slightly higher protein content of NPF.

There were consistent differences among infants in the two fortifier groups with respect to growth (weight, length, head circumference) with the EHMF group always growing more slowly. The significant difference in weight gain for the primary analysis between the groups was 2.6 g/kg/day (NF > EHMF; $p < 0.0005$). The significant difference in length gain for the primary analysis between the groups was 0.2 mm/day (NF > EHMF; $p < 0.05$). Although the primary analysis for head circumference gain was not different between the groups, there was a significant difference in head circumference gain of 0.15 mm/day when analyzed from study day 1 to last fortifier feeding (NF > EHMF; $p < 0.05$). Furthermore, the differences in weight, length, and head circumference gains between the groups were even greater in the evaluable group of infants than in the intent-to-treat group of infants. The significant differences in weight, length, and head circumference gains ($p < 0.0005$; $p < 0.05$; and $p < 0.001$, respectively) for the primary analyses were 4.07 g/kg/day, 0.23 mm/day, and 0.30 mm/day, respectively, with the EHMF group growing more slowly.

The differences in serum biochemistries between the groups were also very consistent between the intent-to-treat and evaluable groups. Of most clinical significance were the mean alkaline phosphatase and calcium values. In the intent-to-treat group, mean alkaline phosphatase values among infants randomized to the NPF group appeared to be higher compared to the infants randomized to the EHMF group (327 U/L vs 272 U/L, respectively); however, mean values for both groups were decreased by study day 29. In addition, mean

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alkaline phosphatase was in the normal range for both groups. Results were similar in the evaluable group. In contrast, in the intent-to-treat group, the mean serum calcium values among infants fed EHMF tended to be higher overall than among infants fed NPF($p=0.069$). As expected, in the evaluable group the overall differences were greater with mean calcium values of 11.2 mg/dL in the EHMF group and 10.3 mg/dL in the NPF group($p=0.016$). A value greater than 11 mg/dL is considered in the upper range and is suggestive of hypercalcemia.

There were no significant differences between the groups in respect to clinical problems or morbidity data. Overall tolerance to both products was excellent. The only difference was in the episodes of vomiting with the EHMF group having a greater number (percent) of days with vomiting episodes than the NM group (18% vs 11%; $p<0.01$). The EHMF group also had a statistically greater number of infants who exited early from the study for reasons of gastric residuals and/or abdominal distention than did the NPF group (6 vs 0; $p=0.012$).

The primary findings of this study suggest that increases in protein and the addition of fat in a powder fortifier results in dramatic improvements in growth performance of low-birth-weight infants even though the caloric density has not been changed.

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We claim:

1. A powder human milk fortifier comprising:
 - a. a protein component from about 24% to about 55% wt/wt, and
 - b. a fat component from about 1% to about 30% wt./wt.
2. A method of providing supplemental nutrients to preterm infants comprising adding a powder fortifier to human milk and administering the fortified human milk to a premature infant, said powder fortifier comprising:
 - a. a protein component from about 24% to about 55% wt/wt, and
 - b. a fat component from about 1% to about 30% wt./wt.
3. A unit dose of powder human milk fortifier comprising:
 - a. a container,
 - b. a protein component from about 24% to about 55% wt/wt, and
 - c. a fat component from about 1% to about 30% wt./wt.
4. A method for promoting growth of a premature infant comprising administering fortified human milk to a premature infant, said fortified human milk comprises:
 - a. human milk, and
 - b. powder fortifier,said powder fortifier comprises:
 - a. a protein component from about 24% to about 55% wt/wt, and
 - b. a fat component from about 1% to about 30% wt./wt.
5. A method for enhancing the stability of human milk comprising adding an emulsifier to human milk.

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ABSTRACT

The invention relates to a powder human milk fortifier comprising a protein component typically present in an amount of from about 24% to about 55% wt/wt, and a fat component typically present in an amount of from about 1% to about 30% wt./wt. Preferably, the powder human milk fortifier is provided in a unit dose container which holds from about 0.5gm to about 10gm of powder. The instant invention also relates to a method of providing nutrition to preterm infants by adding a powder fortifier to human milk and administering the fortified human milk to a premature infant. The invention further provides a method of promoting growth of a premature infant by administering fortified human milk to a premature infant.