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(54) **Cholesterol lowering drink mix compositions**

Trinklösung zur Verminderung des Cholesterolspiegels

Solutions buvables destinées à la diminution du taux de cholestérol

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(56) References cited:
**EP-A- 0 278 464 EP-A- 0 320 519
WO-A-94/04136 US-A- 4 895 723**

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Description

[0001] High blood cholesterol levels are associated with life threatening cardiovascular diseases. Cholestyramine and colestipol hydrochloride are drugs used in treating hypercholesterolemia. These drugs are known as basic anion exchange resins. They help to lower blood cholesterol levels apparently by binding to bile acids in the intestine. It is believed that this in turn causes an increase in hepatic metabolism of cholesterol to replenish the bile acids lost to complexation with the anion exchange resins.

[0002] Cholestyramine is usually dosed at four grammes (anhydrous weight), one to six times daily. At the present time cholestyramine is commercially available as Questran® and Questran® Light (manufactured by the Bristol-Myers Squibb Company) in a four gramme unit dose powder packet or in bulk powder. [Physicians Desk Reference, 49th Edition, pages 735-739 (1995).] Cholestyramine is commercially available as Duolite AP-143 resin (Rohm & Haas Co.).

[0003] Colestipol hydrochloride is usually administered at five to thirty grammes daily given once or in divided doses. Colestipol hydrochloride is commercially available under the tradename Colestid® (colestipol hydrochloride granules, manufactured by The Upjohn Company). It is sold in a five gramme unit dose powder packet or in bulk powder. [Physicians Desk Reference, 49th Edition, pages 2531-2534 (1995)].

[0004] While the benefits of anion exchange resins are well known and appreciated, the aesthetics (e.g., mouthfeel, taste, and throat sticking) are considered by many users to be very unacceptable. The unpleasant mouthfeel of cholestyramine is frequently described as a sandy, gritty texture which tends to stick to the back of the mouth and throat upon ingestion and which leaves an unpleasant fishy taste in the mouth. Colestipol hydrochloride is described as having an astringent taste and a sandy, gritty texture which sticks to the mouth and teeth after ingestion. Obviously, poor aesthetics raise concern about how closely patients will comply with any treatment regimen using these agents.

[0005] Research has been done in an effort to improve the palatability of anion exchange resins. Patents which disclose such efforts include: French Medical Patent 6,888 M published June 4, 1964 by Mead Johnson & Company which describes dry mixing acacia gum with cholestyramine resin to aid in making the astringency of cholestyramine disappear; and U.S. Patent 3,974,272 to Polli et al., issued August 10, 1976 which describes a palatable oral coacervate composition containing cholestyramine and a modified gum selected from hydrophilic colloid of cellulosic material and charged anionic gum in an aqueous medium.

[0006] Despite the research aimed at improving the compositions containing anion exchange resins, a great need still exists for compositions that provide therapeutic benefit while maintaining an agreeable texture and taste, thereby encouraging patient compliance with the treatment regimen. It has been discovered in the present invention that combining an anion exchange resin, such as cholestyramine or colestipol hydrochloride, with xanthan gum aids in masking the unpleasant taste and mouthfeel associated with these resins. It has also been discovered that such compositions can be formulated as aesthetically pleasing drink mix compositions. This improvement in aesthetics has the advantage of further enhancing compliance of an individual receiving an anion exchange resin therapeutic regimen.

[0007] These and other objects of the present invention will become readily apparent from the detailed description which follows. All percentages and ratios used herein are by weight unless otherwise specified. Screen mesh sizes used herein are based on U.S. standards. The abbreviation "g", as used herein refers to "grammes".

SUMMARY OF THE INVENTION

[0008] The present invention relates to a drink mix composition in the form of a dry powder comprising a therapeutically effective dose of an anion exchange resin selected from cholestyramine and colestipol hydrochloride; and from 0.01g to 1.25g of xanthan gum per 4g dose cholestyramine or 5g dose colestipol hydrochloride; and one or more carriers, comprising an agglomeration agent.

DETAILED DESCRIPTION OF THE INVENTION

[0009] The drink mix compositions of the present invention are compositions useful for reducing serum cholesterol levels containing an anion exchange resin and xanthan gum, in a form mixable with a liquid to form a suspension of the anion exchange resin and xanthan gum. Preferred form is a dry powder in bulk or unit dose form which readily mixes and disperses in a liquid. Suitable liquids include any liquid suitable for human consumption such as water, juices and milk .

[0010] The levels of xanthan gum disclosed herein are based on a preferred therapeutically effective dose of anion exchange resin (i.e., 4g anhydrous weight per dose of cholestyramine or 5g per dose of colestipol hydrochloride) in 170g (6 ounces) of a liquid. Also included in the present invention are compositions which vary in delivered dose of anion exchange resin or amount of liquid or both. Such compositions may be formulated by varying the level of components in proportion to the levels of components disclosed herein.

[0011] The essential and optional components of the compositions according to the present invention, and repre-

sentative amounts, are described in detail as follows.

Anion Exchange Resin:

5 **[0012]** The term "anion exchange resin", as used herein, means cholestyramine or colestipol hydrochloride.

[0013] Cholestyramine is a strongly basic anion exchange resin, which contains quaternary ammonium functional groups attached to a styrene-divinylbenzene copolymer. [The Merck Index, 10th Edition, published by Merck & Co., No. 2182 (1983)].

10 **[0014]** Colestipol hydrochloride is an insoluble, high molecular weight basic anion-exchange copolymer of diethylene triamine and 1-chloro-2,3-epoxypropane with approximately 1 out of 5 amine nitrogens protonated (chloride form). [The Merck Index, 11th edition, published by Merck & Co., No. 2472 (1989)].

[0015] The present compositions comprise a therapeutically effective dose of the anion exchange resin. The term "therapeutically effective amount", as used herein, means 4g anhydrous weight per dose of cholestyramine, and 5g per dose of colestipol hydrochloride.

Xanthan Gum

20 **[0016]** The present drink mix compositions contain xanthan gum. Xanthan gum is a polysaccharide gum produce by the bacterium *Xanthomonas campestris*. Xanthan gum is a cream-colored, free-flowing, odorless powder which dissolves in water to provide highly viscous solutions at low concentrations. The Merck Index, Tenth Edition, published by Merck & Co., No. 9868, (1983). Xanthan gum is available commercially under the tradename Keltrol®, by the Kelco Division of Monsanto & Co., San Diego California. Keltrol® is available in various particles sizes such as Keltrol® F (fine grade of xanthan gum), and Keltrol® 1000. All such xanthan gum formulations are considered suitable for use in the present invention, however the amount of xanthan gum utilized may vary depending on the particle size. For example, a smaller amount of a fine grade xanthan gum will be needed in the present compositions, in comparison to a coarser grade, due to the greater surface area of the small particles.

25 **[0017]** Xanthan gum, utilizing a grade such as Keltrol® 1000, may be used in the present compositions at a level of from 0.08g to 1.25g, preferably from 0.15g to 1.2g, more preferably from 0.3g to 1.1g, and most preferably from 0.5g to 0.95g. A finer grade of xanthan gum such as Keltrol® F, may be used at a level of from 0.01g to 0.5g, preferably from 0.02g to 0.4g, more preferably from 0.05g to 0.35g, and most preferably from 0.1g to 0.25g.

30 **[0018]** Formulations containing anion exchange resins and adequate amounts of xanthan gum to improve the palatability of the anion exchange resin may exhibit less than desirable mixing properties. It is preferred that appropriate levels of a diluent/wetting agent such as maltodextrin be added to such anion exchange resin/xanthan gum-containing compositions as required to improve the mixability and/or dispersion properties of the compositions.

Carriers

35 **[0019]** The present invention may optionally contain one or more carriers. Suitable carriers must be safe for oral administration to humans, and may be chosen by one of ordinary skill in the art as appropriate for the drink mix form and use intended for the product.

40 **[0020]** Suitable carriers herein, depending on desired properties and intended end use, are selected from the group consisting of suspending agents, solubilizing agents, diluents, surfactants, buffers, lubricants, thickeners, agglomerating materials, fillers, extenders, emulsifiers, flavoring agents, coloring agents, humectants, edible acids, sweetening agents, binders, disintegrating agents, flow-inducing agents, plasticizers, wetting agents, antioxidants and stabilizers. One or more of the carriers may be added to the present anion exchange resin/xanthan gum drink mix compositions in quantities sufficient to achieve desired formulation characteristics according to the formulator's preference.

45 **[0021]** The products of the present invention are in the form of a dry powder form suitable for mixing in a liquid to form a xanthan gum/anion exchange resin-containing drink. Preferred carriers for such powder forms are known and are also described in detail, for example, in U.S. Patents 4,459,280 and 4,548,806. Preferred are such powders comprising maltodextrin. The compositions of the present invention may be prepared by dry blending the components. Such dry blending techniques are well-known in the art such as Ribbon mixers, V-blenders, Paddle mixers, Nauta mixers, Tote mixers, and Forberg mixers.

50 **[0022]** It is preferred that the compositions of the present invention be prepared by agglomeration and/or other means of composition coating for improved aesthetics and mixing. In the present invention, suitable techniques for agglomeration include any technique well-known in the art, such as fluid bed agglomeration. Preferred are agglomerates of xanthan gum and/or coated xanthan gum, especially agglomerated with maltodextrin and/or sucrose. However, agglomerates of xanthan gum may also include one or more of an edible acid, sweetening agents, coloring agents, dietary fibers. Also, some or all of the anion exchange resin may also be included.

[0023] Agglomerating materials preferred for use herein are known. These agglomerating materials include those selected from the group consisting of water dispersible hydrolyzed starch oligosaccharide, mono-saccharide, di-saccharide, polyglucose, polymaltose, polyvinyl pyrrolidone, and mixtures thereof.

[0024] The present compositions may optionally comprise an edible acid. The term "edible acids", as used herein, means any water soluble acid material having a pK_a of less than about 5, preferably within the range of from 2 to 5, and is safe for ingestion by humans. Examples of edible acids include, but are not limited to, citric acid, ascorbic acid, malic acid, succinic acid, tartaric acid, phosphoric acid, monopotassium phosphate and mixtures thereof. Preferred are ascorbic acid, phosphoric acid, malic acid, and citric acid, with citric acid being most preferred. Preferred compositions of the present invention are those which have some or all of the edible acid coated on the xanthan gum.

[0025] The present compositions may optionally contain one or more sweetening agents. Suitable sweetening agents include saccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch or corn syrup solids and sugar alcohols. Sugar components also include materials such as invert sugar syrups, brown sugar, honey, molasses and maple syrups.

[0026] Artificial sweetening agents may also be included. Such agents include aspartame, saccharin, cyclamate, acesulfame, gem sweet, L-sugars, trichloro sucrose, aspartyl-D-valine, glycyrrhizin, p-phenetylurea, and neohesperidin hydrochalcone. Preferred artificial sweeteners are saccharin, cyclamate, acesulfame K, and aspartame, sold as Nutrasweet® By G.D. Searle.

[0027] One or more flavoring agents may also be included. Such agents may be volatile oils, liquids or dry agents which are pharmaceutically acceptable for internal ingestion by humans. Examples of flavoring agents include but are not limited to citrus flavors such as orange and grapefruit; strawberry; cherry; apricot; peach; banana; chocolate; vanilla and vanilla cream; mint flavors such as peppermint and spearmint; spices such as cinnamon, clove and nutmeg; and nut flavors such as hazelnut, peanut butter and almond.

[0028] Additional dietary fibers may also be included as optional carriers. Preferred is psyllium husk fiber but other dietary fibers such as cellulose derivatives (i.e, methylcellulose, hydroxypropylmethyl cellulose, and hydroxypropyl cellulose), and cereal brans such as wheat, corn, barley, rye, oats, rice, and soybean may also be used.

[0029] The present compositions may also include a humectant which provides the benefit of a mixing agent. Preferred is glycerin, which is commercially available in food grade quality.

[0030] The present compositions may also optionally comprise other additives which include milk products such as whole milk, skim milk, whey, various milk powders, egg products, other protein sources such as soy protein, preservatives such as sorbic acid, polyhydric alcohols such as glycerol and propylene glycol, emulsifiers such as lecithin, modified celluloses, antioxidants such as ascorbic acid, and coloring agents and dyes.

[0031] The products of the present invention may be orally administered to a human or lower animal patient in need of having a lowered blood cholesterol level a safe and effective amount of an aqueous liquid suspension of a xanthan gum/anion exchange resin-containing composition according to the present invention. The term "safe and effective amount", as used herein, means an amount of the drink mix composition high enough to significantly positively modify the hypercholesterolemic condition being treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount will vary with the age and physical condition of the patient being treated, the nature of the condition, the duration of treatment, the nature of concurrent therapy, and like factors within the knowledge and expertise of the attending physician. However, a patient in need of such treatment will typically receive 4g to 24g daily of cholestyramine, or from 5g to 30g daily of colestipol hydrochloride.

[0032] The following examples further describe and demonstrate embodiments within the scope of the present invention. These examples are given solely for the purpose of illustration.

EXAMPLE 1

[0033]

Components	Grams/dose
Cholestyramine ^(a)	4.400
Maltodextrin, NF ^(b)	1.250
Xanthan Gum, NF ^(c)	0.850
Citric Acid, USP (anhydrous, fine)	0.250

(a) equal to about 4g anhydrous weight

(b) Maltrin M100 sold by Grain Processing Inc., (Muscatine, Iowa)

(c) Keltrol® 1000 sold by the Kelco Division of Monsanto & Co., (San Diego, California).

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(continued)

Components	Grams/dose
Orange Flavor	0.600
Vanilla Cream Flavor	0.040
Aspartame	0.060
D&C Yellow #10	0.004
FD&C Yellow #6	0.002

[0034] Prepare Example 1 using wet agglomeration and granulation as follows: charge cholestyramine, xanthan gum and maltodextrin to a fluid bed dryer such as Glatt, and allow to mix. Spray water on cholestyramine mix to form agglomerates/granules. Note: other ingredients such as citric acid, dyes, etc. can be added to the binder solution, but process cycle time may increase. Dry agglomerates to desired moisture content (e.g. loss on drying equals about 5-10%). Dry blend remainder of ingredients after drying. The dose weight of the composition in Example 1 is about 7.46g. The 7.46g of the composition in Example 1 is dispersed in 170g (6 ounces) of water and then consumed by a person in need of treatment for hypercholesterolemia, delivering about 4g per dose of cholestyramine.

EXAMPLE 2

[0035]

Components	Grams/dose
Aspartame	0.0510
Citric Acid	0.2980
D & C Yellow #10	0.0040
Cholestyramine ^(a)	4.4740
Calcium Carbonate	0.0430
Malic Acid	0.0850
Sodium Citrate	0.1700
Maltodextrin	0.5100
Xanthan Gum ^(b)	0.2000
FD&C Yellow #6	0.0030
Peach Flavor	0.4680
Apricot Flavor	0.0340

^(a) equals about 4g anhydrous weight

^(b) Keltrol® F sold by the Kelco Division of Monsanto & Co., (San Diego, California)

[0036] Prepare Example 2 in dry mix form by blending all powders in a mixer with no other processing steps. A ribbon blender, paddle mixer, V-blender or other comparable mixer may be used. The dose weight of the composition in Example 2 is about 6.3400g. The 6.3400g of the composition in Example 2 may be dispersed in 170g (6 ounces) of water and then consumed by a person in need of treatment for hypercholesterolemia, delivering about 4g of cholestyramine.

EXAMPLE 3

[0037]

Components	Grams/dose
Aspartame	0.0600
Calcium Carbonate	0.0500
Colestipol Hydrochloride	5.0000
Xanthan Gum ^(a)	0.2

^(a) Keltrol® F, sold by Kelco Division of Monsanto & Co. (San Diego, California)

(continued)

Components	Grams/dose
Citric Acid	0.3500
D&C Yellow #10	0.0050
FD&C Yellow #6	0.0030
Malic Acid	0.1000
Strawberry Flavor	0.5500
Maltodextrin	0.6000
Sodium Citrate	0.2000
Vanilla Cream Flavor	0.0400

[0038] Prepare Example 3 by adding aspartame, citric acid, calcium carbonate, malic acid, strawberry flavor, vanilla flavor, sodium citrate, FD & C Yellow #6 and #10 in a Hobart bowl and mixing for 4 minutes using speed #1. Next add colestipol hydrochloride and xanthan gum and mix for 5 minutes or until uniform. The dose weight of the composition in Example 3 is about 7.16g. The 7.16g of the composition in Example 3 may be dispersed in 170g (6 ounces) of water and then consumed by a person in need of treatment for hypercholesterolemia, delivering about 5g of colestipol hydrochloride.

Claims

1. A drink mix composition, in the form of a dry powder, comprising:

(a) a therapeutically effective dose of an anion exchange resin selected from cholestyramine and colestipol hydrochloride;

(b) an agglomerate of xanthan gum, comprising from 0.01g to 1.25g of xanthan gum per 4g dose cholestyramine or 5g dose colestipol hydrochloride; and

(c) one or more carriers, comprising an agglomerating agent;

wherein the composition is in a form mixable with a liquid to form a suspension of the anion exchange resin and xanthan gum.

2. The composition according to Claim 1 wherein the agglomerating agent is maltodextrin.

3. The composition according to any preceding claim wherein the anion exchange resin is cholestyramine.

4. The composition according to any preceding claim wherein the carriers further comprise an edible acid, a sweetening agent, one or more colouring agents, and one or more flavouring agents.

5. The composition according to any preceding claim wherein the composition comprises an edible acid selected from citric acid, phosphoric acid, and mixtures thereof.

Patentansprüche

1. Getränkegemischzusammensetzung in Form eines trockenen Pulvers, umfassend:

(a) eine therapeutisch wirksame Dosis eines Anionenaustauscherharzes, ausgewählt unter Cholestyramin und Cholestipolhydrochlorid;

(b) ein Xanthangummiagglomerat umfassend 0,01 g bis 1,25 g Xanthangummi pro 4 g Dosis Cholestyramin oder 5 g Dosis Cholestipolhydrochlorid; und

(c) einen oder mehrere Träger, umfassend ein Agglomerierungsmittel;

wobei die Zusammensetzung in einer mit einer Flüssigkeit mischbaren Form vorliegt, um eine Suspension aus dem Anionenaustauscherharz und Xanthangummi auszubilden.

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2. Zusammensetzung nach Anspruch 1, worin das Agglomerierungsmittel Maltodextrin ist.
3. Zusammensetzung nach einem der vorstehenden Ansprüche, worin das Anionenaustauscherharz Cholestyramin ist.
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4. Zusammensetzung nach einem der vorstehenden Ansprüche, worin die Träger ferner eine genießbare Säure, ein Süßungsmittel, ein oder mehrere Färbemittel und ein oder mehrere Geschmacksstoffmittel umfassen.
5. Zusammensetzung nach einem der vorstehenden Ansprüche, wobei die Zusammensetzung eine genießbare Säure umfaßt, die unter Zitronensäure, Phosphorsäure und Gemischen hievon ausgewählt ist.

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Revendications

1. Composition de préparation pour boisson sous la forme d'une poudre sèche, comprenant :

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- (a) une dose efficace sur le plan thérapeutique d'une résine échangeuse d'anions sélectionnée parmi la cholestyramine et le chlorhydrate de cholestipol ;
(b) un agglomérat de gomme de xanthane, comprenant 0,01 g à 1,25 g de gomme de xanthane pour une dose de 4 g de cholestyramine ou une dose de 5 g de chlorhydrate de cholestipol ; et
(c) un ou plusieurs véhicules, comprenant un agent d'agglomération ;

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dans laquelle la composition se présente sous une forme susceptible d'être mélangée avec un liquide pour former une suspension de résine échangeuse d'anions et de gomme de xanthane.

2. Composition selon la revendication 1, dans laquelle l'agent d'agglomération est de la maltodextrine.
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3. Composition selon l'une quelconque des revendications précédentes, dans laquelle la résine échangeuse d'anions est la cholestyramine.
4. Composition selon l'une quelconque des revendications précédentes, dans laquelle les véhicules comprennent en outre un acide comestible, un agent édulcorant, un ou plusieurs agents colorants, et un ou plusieurs agents aromatisants.
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5. Composition selon l'une quelconque des revendications précédentes, dans laquelle la composition comprend un acide comestible sélectionné parmi l'acide citrique, l'acide phosphorique, et des mélanges de ceux-ci.

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