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(54) Title: MULTIFUNCTIONAL FAT ABSORPTION AND BLOOD CHOLESTEROL REDUCING FORMULATION CONTAINING CHITOSAN AND NICOTINIC ACID

(57) Abstract

Chitosan is formulated with nicotinic acid and may additionally contain one or more other vitamin acids, such as ascorbic acid, folic acid, pantothenic acid, or biotin, for oral administration to enhance cholesterol reduction and high-density lipoprotein elevation in blood serum. In addition, such formulations reduce the pH of large intestine which is beneficial in colon etiology. The formulation may be in dosage unit form for daily administration of, par example, 2-18 g of chitosan and 50-3,000 mg of nicotinic acid.

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MULTIFUNCTIONAL FAT ABSORPTION AND BLOOD CHOLESTEROL REDUCING FORMULATION CONTAINING CHITOSAN AND NICOTINIC ACID

Background of the Invention

In my United States Patent 4,223,023 of September 16, 1980, the use of chitosan to reduce lipid absorption by oral administration is described. The chitosan may be used as such, i.e., as the free base, or in the form of a fatty acid complex.

Chitosan (1-4-8-D-polyglucosamine), usually containing about 0-30% of N-acetylglucosamine residues, has been confirmed in numerous animal and clinical studies as being an effective cholesterol-reducing agent. It, additionally, has been shown to act as a powerful fat binder, binding dietary fats in vivo and thus rendering them nutritionally unavailable. The bound fats, instead of being absorbed and utilized, are excreted. While the mechanism of chitosan's activity in mammals is complex, and several different modes of action have been proposed, it is believed that chitosan acts in a non-systemic manner, and the critical process takes place in the digestive tract of the mammal.

Summary of the Invention

An object of this invention is a chitosan formulation that has improved hypolipidemic efficiency, is more effective in elevating high-density lipoprotein fraction (HDL) in blood serum, reduces the pH of the large intestine, and has a better nutritional profile. These and further objects will become apparent from the following description.

Detailed Description of the Presently Preferred Embodiments

In accordance with the invention, chitosan is formulated with nicotinic acid in a form which may be orally administered to mammals, such as humans. The formulation should be in a form to allow administration of about

2-18 grams per day of chitosan with 50-3,000 milligrams per day of nicotinic acid. The formulation is preferably in the form of a powder mixture and should contain a weight ratio of chitosan to nicotinic acid between about 0.67 and 360. The powder may, for example, be incorporated into individual gelatin capsules in dosage unit form, or may be formed into tablets, or the like, by conventional procedures.

The chitosan and nicotinic acid may be formulated by dry mixing the components in powder form, or, for example, by treating chitosan free base with an aqueous solution of nicotinic acid (niacin) to form chitosan-nicotinate salt, followed by drying.

The formulation, preferably, additionally contains one or more other water-soluble vitamin acids, such as ascorbic acid, folic acid, pantothenic acid, or biotin. These additional acids should preferably be present in amounts to provide a daily dosage of, for example, 50-3,000 mg/day ascorbic acid, 200-400 mcg/day folic acid, 5-10 mg/day pantothenic acid, and 150-300 mcg/day biotin. These acids may be added as a dry mix or by neutralization of the chitosan as a free base with an aqueous solution of one or more of such vitamin acids to prepare corresponding salts, followed by drying.

The combination of the chitosan with the nicotinic acid and/or with the other water-soluble vitamin acids has an additional and unique effect in that the chitosan delays vitamin rapid absorption. This is achieved by ionic binding of vitamin acids to unabsorbable chitosan as well as by increased viscosity caused by the administered or in situ formed chitosan-vitamin acid salts. The presence of water soluble vitamin acids in the lower digestive tract results in lowering of its pH which is beneficial in reducing the risk of large bowel cancer development.

The chitosan, as used herein, in addition to being in the form of the free base in which it normally exists, can be in the form of the hydrochloride or other chitosan salts, after being partially neutralized by hydrochloric or other acids.

Unexpectedly, the components of the formulation in accordance with the invention synergistically act when orally administered to mammals, such

as humans, to enhance reduction of serum lipids, namely total cholesterol and LDL, while increasing HDL, thus providing benefits for individuals who desire to reduce the risks associated with coronary heart disease, high blood pressure and obesity.

The formulation in accordance with the invention additionally provides a better nutritional profile.

The formulation furthermore minimizes the recognized adverse side effects caused by nicotinic acid when used in high doses.

The formulation, because of the presence of vitamin acids, insures a more complete solubilization of the chitosan under gastric conditions. The increased solubilization increases the chitosan surface area and its initial intestinal viscosity as it enters the upper gastrointestinal tract, namely the duodenum and jejunum. It is known that greater intestinal viscosity enhances the hypocholesterolemic effect of unabsorbable fibers, which is reflected in blood serum. It is also known, however, that a very high concentration of ascorbic acid or its sodium salt enhances chitosan's fat binding, as reflected by increased fat excretion. This effect, in contrast to the enhanced blood cholesterol reduction, is believed to be due to reduced gastric viscosity or to other factors caused by the very high level of these compounds in the diet of experimental animals (1.5%).

The formulation may additionally contain other water-soluble vitamins and oil-soluble vitamins, such as Vitamin A, E, D and K, as well as B-Carotene, for their nutritional value, though the same have not been shown to improve the hypolipidemic efficiency.

The formulation of the chitosan with the water-soluble vitamin acids furthermore comprises an unique system for the delivery of these biologically active vitamin acids. Chitosan has been found to bind these vitamin acids, providing a viscous environment, thus slowing down their absorption, in effect, acting as a slow-release agent. Additionally, as their absorption is slowed down, they can partially reach the large intestine, having a desirable effect on colonic pH. The chitosan can enhance delayed absorption of both

basic water-soluble vitamins, such as thiamine, riboflavin, pyridoxine and Vitamin B_{12}, and oil-soluble vitamins.

The following examples are given by way of illustration and not limitation.

Example 1.

Preparation of Chitosan - Nicotinic Acid Dry Mix for Oral Administration

Ingredients	Grams
Chitosan powder	983.3
Nicotinic acid powder	16.7

An intimate mixture of these ingredients is prepared in a mixer or blender and is then packed into individual gelatin capsules containing 250 milligrams of powder. The dosage is five to eight capsules, ingested during or after a meal, preferably with a generous amount of liquid (approximately 8 fluid ounces) three times daily. The maximum total daily intake of chitosan in that case (24 capsules) is 5.9 grams, and that of nicotinic acid is 100 mg, which represents 500% RDA for nicotinic acid.

Example 2.

Preparation of Chitosan-Nicotinate by Partial Neutralization of Chitosan with Nicotinic Acid

Fine powder of chitosan free base (90.00 g) is dispersed in 1000 ml of aqueous solution of nicotinic acid (10.00 g). The dispersion is stirred vigorously for two hours at room temperature. The dispersion is then filtered or centrifuged, and the product is washed with water and alcohol, and dried. The dried powder is then formed into tablets with tableting aids, or packed

into individual gelatin capsules containing 250 mg of powder. The dosage is five to eight capsules, ingested during or after a meal, preferably with a generous amount of liquid (approximately 8 fluid ounces) three times daily.

Example 3.

Preparation of Chitosan-Vitamin Acids Dry Mix for Oral Administration

Ingredients	Grams
Chitosan powder	814.45
Nicotinic acid	167.00
Pantothenic acid	1.68
Ascorbic acid	16.80
Folic acid	0.067
Biotin	0.050

An intimate mixture of these ingredients is prepared in a mixer or blender and is then packed into individual gelatin capsules containing 250 milligrams of powder. The dosage is five to eight capsules, ingested during or after a meal, preferably with a generous amount of liquid (approximately 8 fluid ounces) three times daily. The maximum daily intake of 24 capsules would correspond, in that case, to

Acid	mg	%RDA
Nicotinic	1,000	5,000
Pantothenic	10	100
Ascorbic	100	167
Folic	0.4	100
Biotin	0.3	100

Although the invention has been described in detail with reference to certain specific embodiments, various changes and modifications will become apparent to those skilled in the art. The invention is only intended to be limited by the appended claims or their equivalents.

Claims

1. A cholesterol reduction formulation comprising chitosan and nicotinic acid, said chitosan being present in a weight amount relative to the nicotinic acid of between 0.67 and 360.

2. The formulation according to claim 1, in which said formulation is in the form of a dry powder mixture of chitosan and nicotinic acid.

3. The formulation according to claim 1, in which said chitosan and nicotinic acid are present in said formulation at least partially in the form of chitosan-nicotinate salt and prepared by treating chitosan free base with an aqueous solution of niacin.

4. The formulation according to claim 1 in dosage unit form.

5. The formulation according to claim 4, in which said dosage unit formulation is in the form of gelatin capsules containing a powder mixture of the formulation.

6. The formulation according to claim 1, containing at least one additional water-soluble vitamin acid.

7. The formulation according to claim 6, in which said water-soluble vitamin acid is selected from the group consisting of ascorbic acid, folic acid, pantothenic acid, and biotin.

8. A method for administering water soluble vitamin acids with delayed absorption thereof, and with a reduction of the pH of the large intestine, which comprises administering the water soluble vitamin acid with an amount of chitosan sufficient to cause this effect.

9. A method of reducing cholesterol in blood serum, which comprises orally administering a combination of chitosan and nicotinic acid at a relative weight ratio of chitosan to nicotinic acid of between 0.67 and 360, in an amount effective to substantially effect such cholesterol reduction in the blood serum.

10. A method for increasing the level of high density lipoproteins (HDL) in blood serum, which comprises orally administering a dry mixture of chitosan and nicotinic acid in an amount effective to cause such increase.

11. The method according to claim 9, in which the chitosan and nicotinic acid are at least partially present in the form of a chitosan-nicotinate salt.

12. The method according to claim 9, in which a vitamin selected from the group consisting of ascorbic acid, folic acid, pantothenic acid, and biotin is additionally administered with the mixture.

13. The method according to claim 9, in which 2-18 grams per day of chitosan and 50-3,000 milligrams per day of nicotinic acid are administered.

14. The use of water soluble vitamin acids and chitosan for the manufacture of a medicament to delay absorption of the water soluble vitamin acids and reduce the pH of the large intestine.

15. The use of a combination of chitosan and nicotinic acid at a relative weight ratio of chitosan to nicotinic acid of between 0.67 and 360 for the manufacture of a medicament for the reduction of cholesterol in blood serum.

16. The use of a dry mixture of chitosan and nicotinic acid for the manufacture of a medicament for increasing the level of high density lipoproteins (HDL) in blood serum.

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/01635

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/715 //(A61K31/715,31:455)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 408 017 A (UNION CARBIDE CHEM PLASTIC) 16 January 1991 see page 8, line 51-56 see page 10, line 19-43 see page 13; example 5	1-16
A	EP 0 368 253 A (UNION CARBIDE CHEM PLASTIC) 16 May 1990 see column 7, line 8-19 see column 9, line 28-37	1-16
A	US 5 420 197 A (LORENZ DONALD H ET AL) 30 May 1995 see column 5, line 45-54 see claims 17,18	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
23 May 1997	09.06.97

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/01635

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 8-13
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCI/US 97/01635

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