INSTRUCTIONS
(a) If Convention application insert "Convention"

AMENDED

(a) CONVENTION

AUSTRALIA *Patents Act* 610556

(b) Delete one

APPLICATION FOR A (b) STANDARD ~~XXXXXXX~~ PATENT

(c) Insert FULL name(s) of applicant(s)

I/We (c) THE DOW CHEMICAL COMPANY

(d) Insert FULL address(es) of applicant(s)

of (d) 2030 Dow Center
Abbott Road
Midland, Michigan 48640
UNITED STATES OF AMERICA

(e) Delete one

hereby apply for the grant of a (e) Standard ~~Xxxx~~ Patent for an invention entitled

(f) Insert TITLE of invention

(f) CHOLESTYRAMINE COMPOSITION AND PROCESS FOR ITS PREPARATION

(g) Insert "complete" or "provisional" or "petty patent"

which is described in the accompanying (g) complete specification.

(Note: The following applies only to Convention applications)

Details of basic application(s)

(h) Insert number, country and filing date for the/or each basic application

Application No.	Country	Filing Date
(h) 012,470	UNITED STATES OF AMERICA	9 February 1987
140,696	UNITED STATES OF AMERICA	4 January 1988

Address for Service: PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia 3000

(i) Insert date of signing

Dated (i) 17th February, 1988

(j) Signature of applicant(s) (For body corporate see headnote*)

(k) Corporate seal if any

(k)

(j) PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
THE DOW CHEMICAL COMPANY

Note: No legalization or other witness required

PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia

P17/2/83

35367A

AUSTRALIA

Patents Act

AUSTRALIA
Patent Declaration

DECLARATION FOR A PATENT APPLICATION

▼ INSTRUCTIONS

(a) Insert "Convention" if applicable

(b) Insert FULL name(s) of applicant(s)

(c) Insert "of addition" if applicable

(d) Insert TITLE of invention

(e) Insert FULL name(s) AND address(es) of declarant(s) (See headnote*)

(f) Insert FULL name(s) AND address(es) of actual inventor(s)

(g) Recite how applicant(s)' derive(s) title from actual inventor(s) (See headnote**)

(h) Insert country, filing date, and basic applicant(s) for the, or EACH basic application

(k) Insert PLACE of signing

(l) Insert DATE of signing

(m) Signature(s) of declarant(s)

Note: No legalization or other witness required

In support of the (a) CONVENTION application made by
(b) THE DOW CHEMICAL COMPANY
2030 Dow Center, Abbott Road,
Midland, Michigan 48640, U.S.A.

(hereinafter called "applicant(s) for a patent (c) for an invention entitled (d) CHOLESTYRAMINE COMPOSITION AND PROCESS FOR ITS PREPARATION

I/~~We~~ (e) Richard G. Waterman, General Patent Counsel
THE DOW CHEMICAL COMPANY
2030 Dow Center, Abbott Road,
Midland, Michigan 48640, U.S.A.
do solemnly and sincerely declare as follows:

1. ~~I am/We are the applicant(s).~~
(or, in the case of an application by a body corporate)
1. I am/~~We are~~ authorized to make this declaration on behalf of the applicant~~(s)~~.
2. ~~I am/We are the actual inventor(s) of the invention.~~
(or, where the applicant(s) is/are not the actual inventor(s))
2. (f) Gary J. Schulz, 81 Oaklawn,
Midland, Michigan 48640, USA

is/~~are~~ the actual inventor(s) of the invention and the facts upon which the applicant(s) is/~~are~~ entitled to make the application are as follows:
(g) The applicant Company is the assignee of the said invention from the said actual inventor(~~s~~).

(Note: Paragraphs 3 and 4 apply only to Convention applications)

3. The basic application(s) for patent or similar protection on which the application is based ~~is/~~are identified by **country, filing date, and basic applicant(s)** as follows:
(h) US, filed February 9, 1987 in the name of Gary J. Schulz; in United States of America

US, filed January 4, 1988 in the name of Gary J. Schulz, in United States of America

4. The basic application(s) referred to in paragraph 3 hereof ~~was/~~were the first application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at (k) Midland, Michigan, 48640, U.S.A.
Dated (l) January 18 1988

(m) THE DOW CHEMICAL COMPANY

CORP. SEAL

SIGNATURE

To: The Commissioner of Patents By: R. Waterman
RICHARD G. WATERMAN
General Patent Counsel

Agent:
Phillips Ormonde & Fitzpatrick

No legalization or other

(12) PATENT ABRIDGMENT (11) Document No. AU-B-11266/88
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CHOLESTYRAMINE COMPOSITION AND PROCESS FOR ITS PREPARATION

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PHILLIPS ORMONDE & FITZPATRICK, 367 Collins Street, MELBOURNE VIC 3000

(56) Prior Art Documents
US 3974272
AU 52274/86 A23L A23G A61K

(57) Claim

1. A composition of granules or tablets which comprises cholestyramine particles immobilized by a gum such that when the granules or tablets are added to an aqueous media, approximately the same number of cholestyramine particles remain immobilized by the gum, wherein the granules or tablets are prepared by a process comprising:

(a) forming a paste of cholestyramine, a gum, and water, wherein the gum is not pre-swelled before admixture with the cholestyramine;

(b) extruding the paste to form an extrudate;

(c) drying the extrudate;

(d) pulverising the dried extrudate to form dry, water-dispersible granules; and

(e) optionally, pressing the granules into tablets.

9. A method for treating a patient suffering from hypocholesteremia which comprises orally administering to said patient a formulation having:

.../2

(a) an aqueous medium which is water, milk or fruit juice; and

(b) a composition of granules or tablets having a pharmaceutically effective amount of cholestyramine particles immobilized by a gum such that when the granules or tablets are added to the aqueous media, approximately the same number of cholestyramine particles remain immobilized by the gum, wherein the granules or tablets are prepared by a process comprising:

(i) forming a paste of cholestyramine, a gum, and water, wherein the gum is not pre-swelled before admixture with the cholestyramine;

(ii) extruding the paste to form an extrudate;

(iii) drying the extrudate;

(iv) pulverising the dried extrudate to form dry, water-dispersible granules; and

(v) optionally, pressing the granules into tablets.

AUSTRALIA

Patents Act

610556

COMPLETE SPECIFICATION
(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

APPLICANT'S REFERENCE: Dow Case 35,367A-F

Name(s) of Applicant(s):

The Dow Chemical Company

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Address for Service is:

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Patent and Trade Mark Attorneys
367 Collins Street
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Complete Specification for the invention entitled:

CHOLESTYRAMINE COMPOSITION AND PROCESS FOR ITS PREPARATION

Our Ref : 82169
POF Code: 1037/1037

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

CHOLESTYRAMINE COMPOSITION AND PROCESS FOR ITS PREPARATION

The present invention concerns a palatable cholestyramine composition and a process for its preparation.

Cholestyramine is a compound known to be effective in controlling hypocholesteremia, also known as high blood cholesterol levels, believed to be responsible in many cases for arteriosclerosis as described in U.S. Patent 3,383,281. Cholestyramine, which is orally consumed in order to effect its cholesterol lowering or controlling properties, is astringent and unpleasant to swallow. The cholestyramine also has the side effect of inducing constipation.

Processes and compositions for using cholestyramine are known such as those described in U.S. Patents 3,308,020, 3,499,960 and 3,947,272. For example, U.S. Patent 3,974,272 teaches combining cholestyramine with a modified gum, together with a flavoring agent to form a coascervate in an aqueous medium such as water, milk and fruit juice. Although pharmaceutically effective, these known compositions

are still very undesirable to drink, since the compositions form a gritty coating on the surface inside of the mouth and require at least an additional glass of water to rinse off the gritty coating. Another disadvantage is that the solids of such compositions, including the cholestyramine particles, quickly settle after being added to the aqueous medium, requiring the consumer to frequently stir the medium in order to maintain the cholestyramine in suspension. A further disadvantage of the compositions prepared in accordance with U.S. Patent 3,947,272 is that they do not readily disperse when added to an aqueous medium. Instead, clumps form which require several minutes stirring before the drink can be consumed. Such disadvantages become particularly pronounced for individuals who need to consume the cholestyramine compositions several times a day for periods of months or even years.

Evidence of the unpalatability of cholestyramine compositions currently being marketed is the low rate of compliance by patients to adhere to a diet requiring daily consumption of the cholestyramine product. This low compliance rate indicates a definite need for cholestyramine compositions which are more palatable than the known compositions.

One embodiment of the present invention discloses a process for preparing a palatable cholestyramine composition which process comprises:

(a) forming a paste of cholestyramine, a gum and water; and

One embodiment of the present invention discloses a composition of granules or tablets which comprises cholestyramine particles immobilized by a gum such that when the granules or tablets are added to an aqueous media, approximately the same number of cholestyramine particles remain immobilized by the gum, wherein the granules or tablets are prepared by a process comprising:

(a) forming a paste of cholestyramine, a gum, and water, wherein the gum is not pre-swelled before admixture with the cholestyramine;

(b) extruding the paste to form an extrudate;

(c) drying the extrudate;

(d) pulverising the dried extrudate to form dry, water-dispersible granules; and

(e) optionally, pressing the granules into tablets.

Another embodiment of the present invention discloses a method for treating a patient suffering from hypocholesteremia which comprises orally administering to said patient a formulation having:

(a) an aqueous medium which is water, milk or fruit juice; and

(b) a composition of granules or tablets having a pharmaceutically effective amount of cholestyramine particles immobilized by a gum such that when the granules or tablets are added to the aqueous media, approximately the same number of cholestyramine particles remain immobilized by the gum, wherein the granules or tablets are prepared by a process comprising:

(i) forming a paste of cholestyramine, a gum, and water, wherein the gum is not pre-swelled before admixture with the cholestyramine;

(ii) extruding the paste to form an extrudate;

(iii) drying the extrudate;

(iv) pulverising the dried extrudate to form dry, water-dispersible granules; and

(v) optionally, pressing the granules into tablets.

Yet another embodiment of the present invention discloses a process for preparing a palatable cholestyramine

composition comprising:

(a) forming a paste of cholestyramine, a gum, and water, wherein the gum is not pre-swelled before admixture with the cholestyramine;

(b) extruding the paste to form an extrudate;

(c) drying the extrudate;

(d) pulverising the dried extrudate to form dry, water-dispersible granules; and

(e) optionally, pressing the granules into tablets,

wherein said granules to tablets are made of cholestyramine particles immobilized by the gum such that when the granules or tablets are added to an aqueous media, approximately the same number of cholestyramine particles remain immobilized by the gum.

The present invention has the advantage of providing granules or tablets which are more palatable

than known compositions containing cholestyramine. Another advantage of the present invention is that the granules prepared therefrom are larger than granules taught in known compositions and allow for improved palatability. A further advantage of the present invention is that it provides granules which are much more readily dispersible in an aqueous medium, do not clump, and require only a few seconds stirring before the drink is consumed. And yet another advantage of the present invention is that it provides granules and tablets, which when added to an aqueous medium, remain suspended in the medium and require little or no stirring thereafter.

In order to more fully understand the present invention, the following discussion of the drawings is provided.

In Figure 1 is shown an enlargement of a microscopic sketch of the wet heterogeneous paste 2 used to prepare granules or tablets of the cholestyramine composition of the present invention. Paste 2 is made of swollen cholestyramine particles 4 and swollen gelled gum 6 which extends continuously throughout paste 2. The swelling of the cholestyramine particles 4 and gum 6 is due to the absorption of water.

In Figure 2 is shown an enlargement of a microscopic sketch of dry, water-dispersible granules 5. Granules 5 are formed by removal of most of the water from paste 2 in Figure 1, followed by subsequent pulverization to smaller-sized granules 5 ($\leq$3000 microns (μ) i.e., 3 mm or less). After removal of the

water, cholestyramine particles 7 in dry granule 5 remain immobilized by gum 9.

In Figure 3 is shown a container 11, such as a drinking glass, containing an aqueous medium 8 wherein dry granules 5 are added to and dispersed in the aqueous medium to form water swollen granules 10. Water swollen granules 10 maintain their identity with the dry granule 5 from which each is derived, since the gum in each swollen granule 10 still immobilizes approximately the same number of cholestyramine particles.

In Figure 4, individual water swollen granule 10 is made of swollen cholestyramine particles 12 which remain immobilized by a swollen gum 14 which extends continuously throughout water swollen granule 10. Approximately the same number of cholestyramine particles are occluded within water swollen granule 10 as from dry granule 5 from which water swollen granule 10 is derived. Granule 10 is from 75 to 3000μ in diameter, more preferably from 300 to 1000μ.

In a similar manner, tablets, which are made by compressing and drying the paste of Figure 1, are used in Figure 3.

The term "cholestyramine", or "cholestyramine particle", is intended to mean a synthetic, strongly basic anion exchange resin containing quaternary ammonium functional groups which are attached to a styrene-divinylbenzene copolymer, such as described in U.S. Patents 3,308,020, 3,383,281, 3,499,960 and 3,974,272. Cholestyramine is known to be effective in controlling the level of blood cholesterol.

Although cholestyramine is the most preferred cholesterol controlling or lowering agent, the process of the present invention can be used to prepare palatable granules or tablets of any solid cholesterol controlling or reducing compound which is relatively water insoluble, is gritty and/or has charged surfaces.

The term "flavoring agent" is intended to mean a reagent which imparts a flavor to the compositions of the present invention to improve their palatability.

The term "gum" is meant to mean hydrophobic colloid of carbohydrates such as methylcellulose, ethylcellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and charged anionic gums such as carrageenan, sodium alginate, potassium alginate, propylene glycol alginate, Xantham, gum arabic, augar and pectins. Particularly preferred gums are hydroxypropylmethyl cellulose and methylcellulose, most preferably methylcellulose. Synthetic gums include polyvinyl alcohol and polyvinyl pyrrolidone starch. Viscous gums are preferred over less-viscous gums due to the higher bonding efficiency of the viscous gums to the cholestyramine particles to form more stable water-dispersible granules or tablets. Generally, viscous gums tend to have a higher molecular weight than less viscous gums. Generally, the viscosity of the gum can range between 5 to 400,000 centipoise, preferably from 4000 to 100,000, based upon a 2 percent by weight solution of the gum in water. Viscosities of the gum can be determined by known methods, such as those described in U.S. Pharmacopeia National Formulary, Volume XXI, USP, Procedure 911, page 1278.

The term "immobilized" refers to the bonding of the cholestyramine particle by the gum, either dry or swollen, such that the relative movement of approximately the same number of cholestyramine particles associated with the gum is hindered, especially from leaving either the dry or swollen granule.

The term "aqueous medium" is meant to mean any medium containing water within which cholestyramine granules can be dispersed. Representative aqueous mediums which can be employed in the practice of this invention are water, milk, and fruit juices such as orange, grapefruit, tomato, pineapple and the like, and soft drinks such as colas, sodas, pops, uncolas and the like.

The term "swollen" is meant to mean the expansion of size or volume of cholestyramine or gum particles beyond their dry size or volume.

The term "gell" is meant to mean hydrating a substance to the extent that it does not tend to flow under its own weight, but does flow upon external mechanical force.

The term "dry granule" is meant to mean granules approximately devoid of water in which cholestyramine is immobilized by a gum. When the dry granules are added to an aqueous media, approximately the same number of cholestyramine particles continue to remain immobilized by the gum, even though the entire granule is swollen with water. Generally, the dry granules have a particle size diameter ranging from 3000 to 50μ, preferably from 850 to 150μ, more

preferably from 500 to 150μ, most preferably about 500μ.

The term "water swollen granule" is meant to mean particles of swollen cholestyramine immobilized by a swollen gum phase.

The term "paste" as used herein is meant to mean the mixture of cholestyramine and the gum which has been moistened with sufficient water to form a soft, viscous mass of cholestyramine particles and gelled gum which extends continuously throughout the paste, i.e., the cholestyramine is dispersed as a discontinuous phase in the gum which extends as a continuous phase throughout the paste. The mixture of cholestyramine and gum is moistened with sufficient water to form a paste containing from 45 to 90 percent water (weight basis), preferably from 65 to 75 percent by weight water, most preferably about 70 percent.

The number of cholestyramine particles immobilized per dry granule can vary greatly, depending in part upon the size of the cholestyramine particles and the size or diameter of the granule. Generally, the smaller the cholestyramine particle, the larger the number of cholestyramine particles that can be immobilized by gum in the granule. Similarly, larger granules can accommodate a greater number of cholestyramine particles. The following Table gives an estimation of the number of cholestyramine particles for various sized granules, assuming a fixed cholestyramine particle size diameter of 50μ.

Granule Mesh Size	Granule Diameter Size (μ)	Number of Cholestyramine Particles
20	850	2457
35	500	500
60	250	62
80	180	23
100	150	13

One feature of granules of the present invention is that upon their application to an aqueous medium, they do not coacervate or form coacervate solutions within minutes as taught in U.S. Patent 3,974,272. That is, in U.S. Patent 3,974,272 the cholestyramine particles are free to floc to form loosely held small clumps from suspension. In comparison, the cholestyramine particles in the present granules are generally not free to floc and do not form small clumps since they are already immobilized by the gum. Also, U.S. Patent 3,974,272 teaches the gum is the flocculant which loosely adheres or flocs the cholestyramine particles. In contrast, in the present invention, the gum is generally not available for flocculating the cholestyramine particles since the gum is already immobilizing the cholestyramine particles in the granule.

Granules or tablets of the present invention, optionally and preferably, contain a small amount of a flavoring, such as strawberry, orange, grape, raspberry, lemon, lime, cherry, licorice, spearmint, wintergreen, chocolate, eggnog, butterscotch, vanilla, banana and the like in order to enhance the sweetness or flavor of aqueous compositions prepared therefrom.

Flavoring agents to improve sweetness such as sucrose or fructose sugars or artificial sweeteners such as aspartame can be employed. Such natural and artificial flavorings are well known, and all are suitably employed herein. Citric acid is commonly employed in conjunction with fruit flavorings. The flavoring agent can comprise from 1 to 90 weight percent of the composition, preferably 70 to 80 percent. The flavoring agent can be blended with the dry granules in order to prepare the compositions of the present invention. Alternatively, the flavoring reagent can be mixed with the wet paste prior to preparation of the granules. Liquid or oily flavors may be employed herein so long as they are thoroughly mixed with the other components of the cholestyramine mixture in a way that the cholestyramine mixture is a dispersible particulate. Such oily flavorings often improve the dispersibility of the gum due to their hydrophobic character.

The manner in which the paste is prepared is not critical to the invention. Preferably dry cholestyramine is admixed with dry gum to form a mixture or blend which can be moistened to the requisite water content, forming the paste. Alternatively, the gum can be moistened to the requisite water content before addition of the cholestyramine. Conversely, the cholestyramine can be moistened first to the requisite water content before addition of the gum. Alternatively, cholestyramine, gum and water can be admixed simultaneously in order to prepare the paste.

Cholestyramine is admixed with the gum in a ratio ranging from 10 to 0.1 parts by weight of cholestyramine to one part of gum, preferably from 1 to

4 parts by weight of cholestyramine to one part by weight gum, most preferably 2 parts by weight cholestyramine to one part gum.

The paste used in preparing the compositions of the present invention are conveniently and preferably prepared in a device known as an Extructor®, trademark of the Rietz Division, Bepex Corporation, Santa Rosa, California. The Extructor® is adaptable to the continuous mixing of solids and liquids where very viscous pastes and plastic masses are handled.

After the paste is prepared, it is optionally and preferably wet extruded into strands which are then chopped into wet pellets. The water content of the paste should not be so high that the extrudate strands formed therefrom (as by an extruder) readily stick together and reagglomerate or that they become fragile or "runny." Such pellets can range from 0.001 to 0.5 centimeters (cm) in diameter. The wet pellets are conveniently dried by any convenient method, such as by air drying or oven drying.

The dry pellets can be pulverized into the desired water dispersible granules by any suitable method or device of such purpose. For example, the dry pellets can be pulverized into water-dispersible granules of the desired particle size with a device such as the Micro ACM pulverizer of the Mikropul Corporation, Summit, New Jersey.

Alternatively, the paste, wet pellets or dry granules as prepared hereinabove can be pressed directly into a tablet using any known method or device.

The tablets of the present invention can be made even more palatable by the further addition of base such as sodium bicarbonate together with a suitable organic acid such as citric acid or ascorbic acid. The addition of moisture either by water or saliva will cause the bicarbonate to contact the citric or ascorbic acid and form gaseous carbon dioxide. The formation of the carbon dioxide aids in the disintegration of the tablet in the mouth, improving chewability or palatability. When added to aqueous media, the formation of the carbon dioxide aids the dispersion of the tablet in water. Approximately equivalent ratios of base to acid are employed. For example, one mole of citric acid has three equivalents of acid, and would require three moles of sodium bicarbonate (which has one equivalent base per mole) to neutralize both the acid and base. The combined amounts of acid and base present in the tablet can range from 1 to 20 percent by weight, preferably between 1 to 5 percent by weight.

Once prepared, the dry granules or tablets can be added from 6 to 8 ounces of an aqueous medium to make a non-gritty tasting slurry that sticks to the sides of the mouth much less than compositions previously taught. After an extended period of time, the swollen gum likely will continue to swell with water, thereby lowering the viscosity of the gum to the point the highly swollen gum may no longer be capable of immobilizing the swollen cholestyramine particles. Under a normal period for consumption (i.e. within several minutes), it is anticipated the compositions containing the cholestyramine particles will be consumed long before the gum is too swollen to

immobilize the cholestyramine particles. The slurry thus prepared can be consumed within zero to 60 minutes after the granules have been added to the aqueous medium, preferably from zero to 10 minutes.

Where the granules or tablets are to be orally administered in an aqueous medium, the recommended dose of cholestyramine is 4 to 12 grams (g) three times a day. The recommended dosage of the gum is from one to 2 grams, three times a day, especially for methylcellulose as a bulking laxative.

The following examples illustrate the present invention and the manner by which it can be practiced but, as such, should not be construed as limitations upon the overall scope of the same.

Example 1 Preparation of Granulated Cholestyramine/-Methylcellulose Ether Powdered Blend

Approximately 10 lbs (4.5 kg) of a heterogeneous mixture was made by first blending three parts cholestyramine powder with one part Methocel® A4M, trademark of The Dow Chemical Company, Midland, Michigan. Methocel A4M® is an untreated powder of methylcellulose ether having a viscosity of 4000 centipoise. To this powder blend, water was added to make a paste having a water content of about 75 percent. The water proportionates between the cholestyramine and the Methocel® powder. The cholestyramine swells, but does not dissolve. The Methocel® powder hydrates and dissolves forming a gelled gum which extends continuously throughout the paste to immobilize the cholestyramine particles.

This heterogeneous paste was then extruded with an RE-6 Extructor® with 1/16 inch (0.16 cm) die holes, and the moist extrudate was chopped into wet pellets. The wet pellets were dried in a tray dryer and ground with a 6 inch (15 cm) Wiley knife mill using a 20 mesh (U.S. Standard) internal screen to the following particle size distribution:

Mesh	% On Screen
16	0.0
20	1.3
30	32.7
40	29.2
60	21.3
80	3.7
100	1.6
140	1.9
PAN	5.0

A cut from 30 to 60 mesh was obtained by screening. Generally, a 35 mesh is equivalent to 500 microns and a 60 mesh is equivalent to 250 microns. The cut was blended with a flavoring agent base at 2.7 parts of the cut to 8.0 parts flavoring agent base. Then about 21 g of this blend was mixed in approximately 6 ounces (oz) water to form a smooth, good tasting orange drink with good palatability.

Example 2 Simultaneous Wetting/Extrusion of Powdered Blend of Cholestyramine/Methylcellulose

One part Methocel® A4M powder having a viscosity of 4000 centipoise was blended with two parts cholestyramine powder at a weight ratio of 1:2 respectively. As this blend was fed to an RE-6

Extructor® at a rate of 56.2 pounds per hour (lbs/hr) (71×10^{-4} kg/s), water was fed to the Extructor® at 131 lbs/hr (165×10^{-4} kg/s) to form a heterogeneous paste mixture having a moisture content of 70 percent. This paste was extruded into moist 1/16 inch (0.16 cm) diameter strands which were chopped into 1/8 to 3/4 inch (0.3 to 1.9 cm) pellets. The pellets were dried in a fluid bed dryer and ground with a Mikropulverizer 10 ACM granules mill to the following particle size distribution:

Mesh Size	Granule Diameter (μ)	Accumulative %
30	600	18.5
40	425	38.7
45	355	55.3
60	250	70.3
80	180	79.3
100	150	83.7
140	106	87.8
200	75	91.3

The 35-80 mesh fraction was blended with an orange flavoring agent (6 parts 35-80 mesh fraction/16 parts flavoring agent). About 22 g of the flavored granules were mixed with 4 to 10 oz. water to form a palatable, good tasting orange drink.

Example 3

A 7.25 g portion of the cholestyramine/-methylcellulose granules from the 35-80 mesh fraction containing a flavoring agent prepared as in Example 2 was compressed into a 1/4 inch by 1 1/4 inch (0.64 cm by 3.2 cm) diameter tablet at a pressure of 4000 pounds per square inch (psi) (27.6 MPa). Four of these

tablets are equivalent to a pharmaceutically acceptable dosage for an adult. The tablets can be chewed without water.

Example 4

Four tablets of cholestyramine/methylcellulose prepared as in Example 3 were added to 4 to 10 oz. of water and briefly stirred. Within 1 to 2 minutes the tablets dispersed, forming a smooth, good tasting orange drink.

Example 5

A 252 g portion of Methocel K100M® having a viscosity of 100,000 centipoise was hydrated with 434 g of cold water. Then 3.86 kilograms (kg) of wet (73.8% by weight water) cholestyramine was mixed into the prehydrated Methocel K100M®. This mixture was then extruded with an RE-6 Extructor® through 1/16 inch (0.16 cm) die holes. The extruded strands were chopped up into 1/8 inch to 3/4 inch (0.3 to 1.9 cm) pellets. The pellets were dried in a tray dryer and milled with an Alpine 100 UPZ mill. The milled material was screened to give a 35 to 80 mesh product. Flavors were added to these granules to give a palatable good tasting drink.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A composition of granules or tablets which comprises cholestyramine particles immobilized by a gum such that when the granules or tablets are added to an aqueous media, approximately the same number of cholestyramine particles remain immobilized by the gum, wherein the granules or tablets are prepared by a process comprising:

(a) forming a paste of cholestyramine, a gum, and water, wherein the gum is not pre-swelled before admixture with the cholestyramine;

(b) extruding the paste to form an extrudate;

(c) drying the extrudate;

(d) pulverising the dried extrudate to form dry, water-dispersible granules; and

(e) optionally, pressing the granules into tablets.

2. A composition as claimed in claim 1 wherein the gum is hydroxypropylmethyl cellulose or methylcellulose.

3. A composition as claimed in claim 1 or claim 2 wherein the ratio of cholestyramine to gum in the compostion ranges from 10 to 0.1 parts by weight cholestyramine to one part by weight gum.

4. A composition as claimed in claim 3 wherein the ratio of cholestyramine to gum in the composition ranges from 4 to 1 part by weight cholestyramine to one part by weight gum.

5. A composition as claimed in any one of claims 1 to 4 wherein the granules range in diameter from 3000 to 50 microns.

6. A composition as claimed in any one of claims 1 to 5 further comprising a flavoring agent.

7. A composition as claimed in claim 6 wherein the flavoring agent is from 1 to 90 percent by weight of the granules.

8. A composition as claimed in claim 6 or claim 7 wherein the flavoring agent is sucrose sugar, fructose sugar, citric acid, potassium citrate, orange flavor, or aspartame.

9. A method for treating a patient suffering from hypocholesteremia which comprises orally administering to said patient a formulation having:

(a) an aqueous medium which is water, milk or fruit juice; and

(b) a composition of granules or tablets having a pharmaceutically effective amount of cholestyramine particles immobilized by a gum such that when the granules or tablets are added to the aqueous media, approximately the same number of cholestyramine particles remain immobilized by the gum, wherein the granules or tablets are prepared by a process comprising:

(i) forming a paste of cholestyramine, a gum, and water, wherein the gum is not pre-swelled before admixture with the cholestyramine;

(ii) extruding the paste to form an extrudate;

(iii) drying the extrudate;

(iv) pulverising the dried extrudate to form dry, water-dispersible granules; and

(v) optionally, pressing the granules into tablets.

10. A method as claimed in claim 9 wherein the dose of cholestyramine is 4 to 12 grams three times a day.

11. A method as claimed in claim 9 or claim 10 wherein the weight of the aqueous medium of part (a) is 6 to 8 ounces.

12. A method as claimed in any one of claims 9 to 11 wherein the composition of part (b) is defined as in any one of claims 1 to 8.

13. A process for preparing a palatable cholestyramine composition comprising:

(a) forming a paste of cholestyramine, a gum, and water, wherein the gum is not pre-swelled before admixture with the cholestyramine;

(b) extruding the paste to form an extrudate;

(c) drying the extrudate;

(d) pulverising the dried extrudate to form dry, water-dispersible granules; and

(e) optionally, pressing the granules into tablets,

wherein said granules to tablets are made of cholestyramine particles immobilized by the gum such that when the granules or tablets are added to an aqueous media, approximately the

same number of cholestyramine particles remain immobilized by the gum.

14. A process as claimed in claim 13 wherein the ratio of cholestyramine to gum in the paste ranges from 10 to 0.1 parts by weight cholestyramine to one part by weight gum.

15. A process as claimed in claim 13 wherein the ratio of cholestyramine to gum in the paste ranges from 1 to 4 parts by weight cholestyramine to one part by weight gum.

16. A process as claimed in any one of claims 13 to 15 wherein said paste contains from 45 to 90 percent by weight water.

17. A process as claimed in any one of claims 13 to 16 wherein said paste is wet extruded and chopped into wet pellets.

18. A process as claimed in any one of claims 13 to 17 wherein the pellets range from 0.001 to 0.5 centimeters in diameter.

19. A process as claimed in claim 17 wherein said wet pellets are dried.

20. A process as claimed in claim 19 wherein said dry pellets are pulverised into water-dispersible granules.

21. A process are claimed in claim 20 wherein said dry granules have a particle size ranging from 850 microns to 150 microns.

22. A process as claimed in any one of claims 13 to 16 wherein said paste is pressed into tablets.

23. A process as claimed in claim 20 wherein said dry granules are pressed into tablets.

24. A process as claimed in any one of claims 13 to 23 further comprising adding a flavoring agent to said granules.

25. A composition as claimed in claim 1 substantially as hereinbefore described with reference to any one of the examples.

26. A method as claimed in claim 9 substantially as hereinbefore described with reference to any one of the examples.

27. A process as claimed in claim 13 substantially as hereinbefore described with reference to any one of the

examples.

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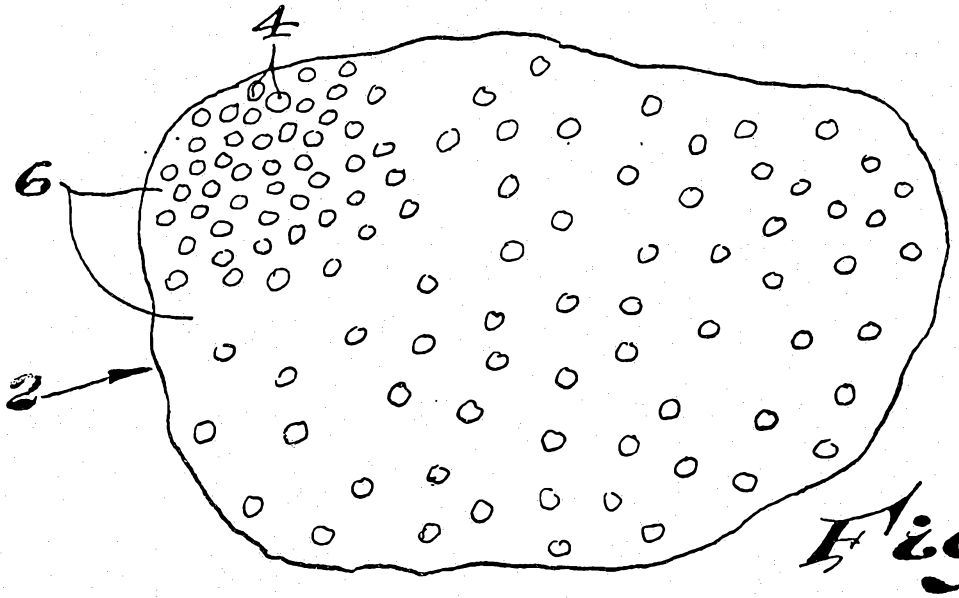

Fig. 1

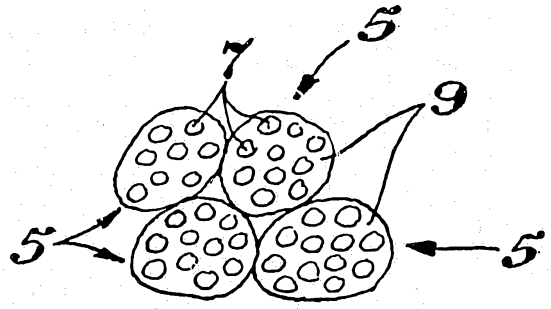

Fig. 2

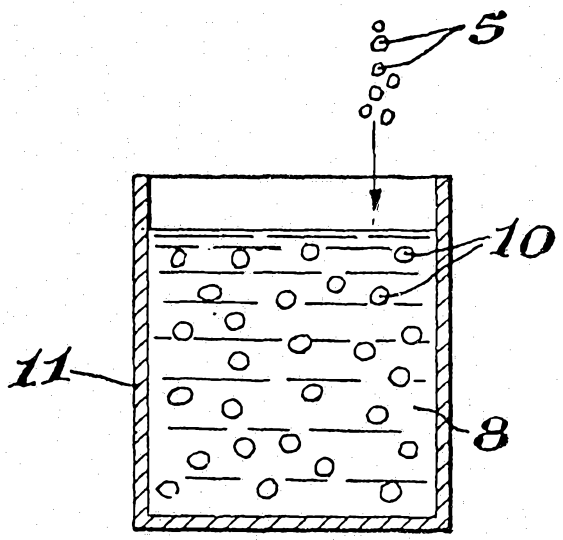

Fig. 3

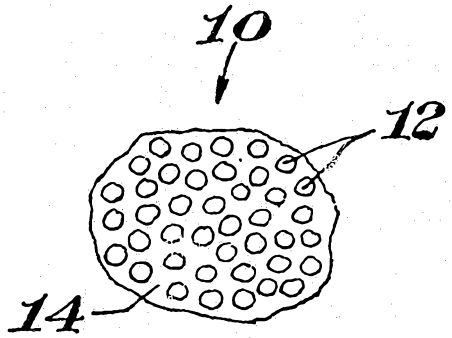

Fig. 4