POLYMERIC LAXATIVE COMPOSITION AND METHOD OF USING SAME

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The present invention relates to a therapeutic composition and is more particularly concerned with a composition for use as a fecal softening agent, such compositions containing a non-ionic surface active component. The invention further relates to compositions containing other therapeutically active medicaments in addition to the non-ionic component.

Hereinafter, a wide variety of therapeutic compositions have been utilized as fecal softening agents. These include proprietary compounds and more recently developed softening agents, e.g. diocyl sodium sulfosuccinate and thimino diocyl sulfosuccinate. Some compositions have incorporated other anionic and cationic detergents or surface active compounds. The function of these therapeutic compositions is merely to soften the contents of the intestine and to relieve constipation. Such compositions exert a softening effect but do not stimulate peristaltic movement. Consequently, peristaltic stimulants are frequently administered in conjunction with the use of fecal softening agents.

Among the most effective ionic wetting agents reported to date are diocyl sodium sulfosuccinate (sarsol®) and thimino diocyl sulfosuccinate. These compounds, however, have a pronounced obnoxious odor and are very bitter to the taste. Further, the compounds are not readily water-soluble. They are waxy in nature and formulations containing them are difficult to prepare. Further, because of their ionic nature these compounds frequently cause irritation to the skin and they tend to be unstable in the presence of acids and alkalies. In addition, these compounds are precipitated by most metal ions. Thus, it is an object of the present invention to provide a novel composition for use as an orally ingested fecal softening agent.

An additional object of the present invention is to provide a therapeutic composition containing as an active component a compound that is substantially odorless and tasteless, that is stable in the presence of acids and alkalies and that does not readily react with metal ions.

It is a further object of the present invention to provide a therapeutic composition that is readily dispersible in the contents of the stomach and intestines and whose primary active component is substantially soluble in water at room temperature in all proportions and is itself readily dispersed in the intestinal tract.

Still another object of the present invention is to provide a therapeutic composition in dosage unit form containing a non-ionic surface active agent and having, in addition to a softening property, pronounced effect in reducing blood serum cholesterol content.

These and other objects of the present invention will become apparent to one skilled in the art as the description of the present invention proceeds.

It has now been found that a therapeutic composition can be prepared for use as an orally ingested, fecal softening agent comprising a non-ionic, polyoxyethylene material, such as a condensation product of ethylene oxide and polyoxypropylene glycol, and a pharmaceutical carrier. Such preferred condensation products are non-ionic in character and the preferred products are substantially water-soluble, having molecular weights of between about one thousand and about eleven thousand. The ethylene oxide proportion of the total weight of the molecule may vary from as low as about 10 percent to about 90 percent.

The pharmaceutical carrier comprises both solid and liquid materials and the therapeutic composition of the present invention may be packaged in capsule, liquid and tablet form. The therapeutic composition of the present invention has utility as a fecal softening agent generally. It is useful in relieving constipation, especially constipation induced by the intake of antacids containing aluminum hydroxide and similar compounds. It is useful in the treatment of diverticulosis.

Structurally, the active non-ionic agents in the therapeutic compositions of this invention are unrelated to the active components of the widely used proprietary products and the sulfonated dicarboxylic acid esters, e.g. diocyl sodium sulfosuccinate (bis(2-ethoxyethyl)sodium sulfosuccinate). The compositions of the present invention are basically resin or plastic materials and are more specifically block-polymers having surface active properties. These resins are linear in nature and contain both hydrophilic and hydrophobic units. The term, "non-ionic, surface active polyoxyalkylene materials" is used in the broadest sense and denote these resins compositions containing both hydrophilic and hydrophobic units. The term includes both the fatty acid esters or fatty alcohol ether types of non-ionic surfactants. Generally these are condensation products of alkylene oxides, such as ethylene or propylene oxide, and polyols, such as the glycols, sorbitols, polyoxylalkylene glycols and the like. In the preferred compositions, for example, the hydrophobic or water-insoluble portion of the polymers are polyoxypropylene compounds whereas the hydrophilic portions of the polymers are polyoxyethylene compounds. These preferred resins can be represented structurally as follows:

\[ \text{HO(C}_2\text{H}_4\text{O})_n\text{CO(H}_2\text{O})_m\text{C}_3\text{H}_7\text{O})_2\text{H} \]

wherein the \((\text{C}_2\text{H}_4\text{O})_n\) represents the polyoxypropylene hydrophilic base component and the \((\text{C}_3\text{H}_7\text{O})_2\text{H}\) represent the polyoxyethylene hydrophilic constituents. The molecular weight of the preferred polymers useful in the compositions of the present invention may be as low as about 1000 and as high as about 11,000 and wherein the polyoxyethylene portion of the polymer may vary from as little as 10 percent to as high as 90 percent, respectively. The higher the polyoxyethylene percentage, the more water-soluble becomes the total molecule or polymer. Thus, the substantially water-soluble polymers in the molecular weight range of between about five and about eleven thousand are preferred. The resins through this molecular weight range may be liquids, pastes and even crystalline flakes or powders. The preferred resin embodiment is a polymer having a molecular weight of about seven thousand five hundred, an ethylene oxide content of about eighty and ninety percent by weight of the total molecule, and a melting point of 51—54 degrees centigrade. The polymer is substantially water-soluble and is readily compatible with the selected pharmaceutical carriers.

These resin compositions have excellent surface active properties, including good wetting, and exhibit low toxicity, especially when compared with other surface active agents or detergents. These compounds are stable to acids, alkalis and metal ions, due in part to their non-ionic character. The polymers, especially in the higher molecular weight ranges, are virtually odorless and tasteless. These properties are especially valuable since there is less tendency for them to react with vitamins, minerals, enzymes and the like in the stomach and intestines than for conventional anionic and cationic agents. Because these polymers are non-ionic and are virtually neutral
in pH they are less irritating to the skin than the more reactive ionic wetting agents. In FIGURE 1 below are comparative data showing the stability of the resins and compounds of the present invention in various media with which they are associated in use. Comparison of a preferred member of this resin series has been made with dioctyl sodium sulfosuccinate, the most effective of the known floc forming ionic wetting agents. Equal volume portions (10 ccs, each) of the conventional ionic wetting agent and the non-ionic polyoxypropylene glycol-ethylene oxide condensation product, respectively, were compared with equal volumes of the selected test material. FIGURE 1

<table>
<thead>
<tr>
<th>Material tested</th>
<th>Dioctyl Sodium Sulfosuccinate, %</th>
<th>Polyoxypropylene glycol-ethylene oxide condensation product (Pluronic F-68), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2M NaOH</td>
<td>Hazily cloudy</td>
<td>Clear</td>
</tr>
<tr>
<td>2M HCl</td>
<td>Slight haze</td>
<td>Do</td>
</tr>
<tr>
<td>Artificial Gastric Juice</td>
<td>do</td>
<td>Do</td>
</tr>
<tr>
<td>Artificial Intestinal Juice</td>
<td>do</td>
<td>Do</td>
</tr>
<tr>
<td>ATMorphine Sulfate</td>
<td>Heavy precipitate</td>
<td>Do</td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>Slight precipitate</td>
<td>Do</td>
</tr>
<tr>
<td>Sod. Pentobartal</td>
<td>Very slight haze</td>
<td>Do</td>
</tr>
<tr>
<td>Vitamin B</td>
<td>Heavy precipitate</td>
<td>Do</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Clear</td>
<td>Do</td>
</tr>
<tr>
<td>Ferrous Gluconate</td>
<td>Deposit settles out and</td>
<td>Do</td>
</tr>
<tr>
<td>NACI</td>
<td>Precipitate (filtered)</td>
<td>Do</td>
</tr>
<tr>
<td>Liver Concentrate Solution</td>
<td>Slight</td>
<td>Do</td>
</tr>
<tr>
<td>1% Phenol</td>
<td>Clear</td>
<td>Do</td>
</tr>
<tr>
<td>Extract of Hog Bile</td>
<td>do</td>
<td>Do</td>
</tr>
<tr>
<td>Caffeine</td>
<td>do</td>
<td>Do</td>
</tr>
</tbody>
</table>

In further testing with non-ionic compositions, polyoxyethylene sorbitan monooleate (Twee 80)—1 percent, was tested against vitamin B1, artificial gastric juice, hydrochloric acid—2 percent, atropine sulfate dilution—1 percent, ferrous gluconate solution—1 percent, phenol—1 percent, D1-amphetamine sulfate—1 percent, and pyrillamine maleate—1 percent. Turbidity was not produced. In like manner, another polyoxyalkylene material (Triton X-100) was tested under comparable conditions and produced slight turbidity with only one percent phenol solution. Thus, both of these latter compositions are operative. However, both of these are liquids with a somewhat bitter taste and are thus not preferred embodiments of the present invention.

Several of these preferred non-ionic agents are commercially available under the trademark, “Pluronic” (Wyandotte Chemical Company). Others have been synthesized by controlled reaction of the appropriate polyoxypropylene base, formed by condensation of propylene oxide with propylene glycol, with ethylene oxide. For example, the non-ionic polyalkylene glycol ethers are available as “Tergitol” (Carbide and Carbon Chemicals Company), such as the “Tergitol” XD, a solid surfactant that is stable in the presence of most of the materials listed above.

In preparing the therapeutic compositions of the present invention, non-toxic pharmaceutical carriers or diluents are employed, such as corn starch, distilled water, powdered milk sugar, gum acacia, talc, glycerin, and the like. Flavoring agents, viscosity regulators, excipients and lubricants may be employed, where desired. The carrier chosen will depend on the ultimate form of the therapeutic dosage, i.e. capsule, liquid or tablet.

The amount of active non-ionic agent employed varies with the dosage form utilized and may be as low as about 10 milligrams and as high as 500 milligrams or more, in view of the very low toxicity of such polymeric com-dehydration of waste material in the colon. Where use of antacids containing aluminum hydroxide or other gels or bulking agents has caused severe dehydration of the fecal matter, the compositions have been found useful in softening the compacted material. Pronounced symptomatic relief in persons having diverticulitis of the colon has been observed upon administration of the therapeutic compositions.

Unexpectedly, it has been found that the compositions of the present invention may be successfully employed in some instances in the treatment of hypercholesteremic conditions. For example, it has been demonstrated clinically that the orally ingested therapeutic compositions caused a reduction in blood serum cholesterol content in persons showing elevated cholesterol, i.e. 270-320 milligrams of cholesterol per 100 milliliters of blood serum. Substantial reductions were observed without any change in the diet of the patient. While the compositions illustrated in Examples 1 and 2 have been found operable for this purpose, the compositions of Examples 3 and 5, respectively, may yield better results, apparently due in part to the inclusion of compounds containing alkaline earth metals. In general, compounds containing elements from the Group II of the periodic classification of the elements are preferably incorporated with the non-ionic polymeric agent. Metals containing two electrons in their outer shells, such as beryllium, strontium, and magnesium, are preferred. The preferred embodiment is the magnesium ion. Where the use of these novel therapeutic compositions in the treatment of hypercholesteremia is indicated, a compound selected from the group consisting of non-toxic unsaturated oils and unsaturated oil fatty acids may be incorporated, if desired. When the composition of Example 1 below was administered orally to clinical patients, a statistically significant lowering of the total serum cholesterol was observed within 24 to 36 hours following ingestion.
The following examples illustrate the compositions of the present invention:

Example 1.—Capsule form (per capsule)
Non-ionic agent (Pluronic F-68; molecular weight about 7500; M.P. 51–54 degrees C.; ethylene oxide content 80–90 percent) 250 milligrams.
Dried corn starch 138.8 milligrams
(i.e., sufficient corn starch to maintain a six gram capsule).

In preparation, the non-ionic agent was admixed with the previously dried corn starch and the resulting admixture milled through a Fitzpatrick machine using a number 20 mesh screen. The resulting, intimately mixed formulation was incorporated into soft gel capsules. The starch prevents the non-ionic agent from tending to coalesce and yet permits it to be dispersed readily in the contents of the stomach and intestines.

Example 2.—Liquid form (per 5 cc. dosage unit)
Non-ionic agent (Pluronic F-68) 250 milligrams.
Distilled water 3.0 cc.
Glycerin 0.50 cc.
Flavoring agent, q.s.

In preparation, the non-ionic agent was dispersed easily in the aqueous components.
In like manner, another non-ionic agent (Pluronic L-62), being in liquid form and having a molecular weight of about 2000, can be utilized in place of the above non-ionic agent.

Example 3.—Tablet form (per tablet)
Non-ionic agent (Pluronic F-68) 250 milligrams.
Milk sugar 350 do.
Gum acacia (gum arabic) 50 do.
Magnesium stearate 1.0 do.
Starch, q.s. to weight.

In preparation the above components were admixed thoroughly and tableted in a conventional tablet machine.

Example 4.—Capsule (per capsule)
Non-ionic agent (Pluronic F-75) — molecular weight about 3,500 10 milligrams.
Dried corn starch 378 milligrams
(i.e., sufficient corn starch to maintain a six gram capsule).

Example 5.—Liquid emulsion (per 30 cc.)
Non-ionic agent 1.0 gram.
Salinum (oil or linoleic acid) 20 cc.
Distilled water, q.s. ad.
Flavoring agent 5 min.

Example 6.—Capsule (per capsule)
Non-ionic agent (Pluronic F-68) 250 milligrams.
Magnesium stearate 10 milligrams.
Dried corn starch 128.8 milligrams
(i.e., sufficient corn starch to maintain a six gram capsule).

Example 7.—Bulk type laxative preparation (per teaspoon dosage)
Psyllium seed husks 3.5 grams.
Gum karaya 0.5 do.
Non-ionic agent (Pluronic F-68) 250 milligrams.
Powdered dextrose 0.75 grams.

The bulk laxative was produced by finely milling the above components and subsequently wetting the admixture to produce granules. (Alternatively, the preparation has been made by dissolving the non-ionic agent in the water utilized to produce the granules.)

Example 8.—Bulk type laxative preparation (per tablespoon dosage)
Psyllium seed husks (aqueous extractive) 2.0 grams.
Powdered anhydrous dextrose 2.0 do.
Non-ionic agent (Pluronic F-68) 300 milligrams.

Example 9.—Bulk type laxative preparation (per teaspoon dosage)
Psyllium seed husks 4.5 grams.
Non-ionic agent (Pluronic F-68) 350 milligrams.

These components were finely milled and wetted with water to provide the desired granules.
Other components may be added in varying amounts, e.g., karaya gum, pectin, and agar.
In still another embodiment, honey, thinned with water, has been applied to the seed husks in the above formulation. The treated husks were then dried and admixed with the non-ionic agent. If desired, thiamine hydrochlorides may be incorporated in the above composition at the rate of about 2 milligrams per teaspoonful.

Example 10.—Laxative (per capsule)
Non-ionic agent (Pluronic F-68) 250 milligrams.
Danthron 50 do.
Dried corn starch 138.8 do.

This composition was prepared in the manner of Example 1.

Example 11.—Laxative (per capsule)
Desiccated hog bile (equivalent to about 2.5 cc. of fresh hog bile) 325 milligrams.
Non-ionic agent (Pluronic F-68) 250 milligrams.

Example 12.—Gastric antacid preparation (per tablet)
Aluminum hydroxide gel (dried) 10 grams.
Non-ionic agent (Pluronic F-68) 100 milligrams.

The amount of non-ionic agent has been varied from between about 50 and 250 milligrams per 10 grain antacid tablet.

In practice, the compositions of Examples 1 to 12, inclusive, may be administered daily in from one to as many as six or more of the unit doses set forth above.
In like manner, other non-ionic, surface active polyoxyalkylene materials, especially the condensation products of ethylene oxide and polyoxypropylene glycol having molecular weights of between about one and about eleven thousand and ethylene oxide contents of between about 10 and 90 percent, respectively, by weight, have been successfully substituted for the non-ionic agents of the above examples. Also, other alkaline earth compounds, wherein the alkaline earth metal per se has two electrons in their outer shells, such as beryllium, strontium, barium, magnesium, and the like, have been used successfully in place of the magnesium compounds set forth in the above examples. Among the preferred fatty acids useful in the above compositions are linoleic and arachidonic.

While the therapeutic compositions of the present invention have been described with primary reference to dosage unit form as fecal softening agents, the active non-
ionic compositions can be administered concomitantly with other medicaments, especially peristaltic stimulants and the like, wherein such agents continue to function as fecal softening promoters in the presence of the other medicaments. Examples 7 to 11, illustrate the combined use of the non-ionic composition in admixture with other components having therapeutic activity as laxatives and choleraics. Example 12 above illustrates the use of the preferred compositions with gastric antacid preparations, wherein the non-ionic agent continues to function as a fecal softening compound. Likewise, in the preparation of baby foods, the compounds of the present invention have been incorporated as fecal softening material. Thus, the present invention further contemplates these therapeutic compositions which comprise as their essentially active components other medicaments or therapeutics, as well as the non-ionic, surface active, fecal softening polyoxyalkylene materials.

The present invention also includes a method for preparing a composition exhibiting fecal softening properties and which generally comprises the admixing of a non-ionic, surface active polyoxyalkylene material and a pharmaceutical carrier.

As noted in the specification, the compositions intended are fecal softening compositions and methods for their use and are applied to persons, patients and babies (see column 4, line 43, column 7, line 11, etc.) and are clearly intended for human therapy. Thus, these compositions of the present invention are orally administered to humans to soften the fecal matter as above discussed. Other modifications can be made in the compositions and methods of the present invention without departing from the spirit or the scope thereof and it is to be understood that such modifications are included within the scope of the appended claims.

I claim:

1. The method for treating constipation in humans comprising orally administering an effective amount of a composition consisting essentially of a compound having the formula:

\[ \text{HO(C}_2\text{H}_4\text{O)}_n\text{C}_2\text{H}_5\text{OH)H} \]

wherein the mol-weight of the \((C_2H_4O)\) groups is 10% to 90% of the polymer and \(n\) is an integer between about 25-32.

2. The method of softening human fecal matter which comprises: orally administering a dosage unit of a composition comprising the polymer of the formula:

\[ \text{HO(C}_2\text{H}_4\text{O)}_n\text{C}_2\text{H}_5\text{OH;H} \]

wherein \(n\) and \(c\) comprise between about ten to about ninety percent by weight of the polymer and wherein the polymer has a molecular weight between about one thousand and about eleven thousand, the composition containing a melting point of about fifty-one to fifty-four degrees centigrade and wherein \(n\) and \(c\) comprise about eighty to ninety percent by weight of the polymer.

3. Claim 2 wherein the composition contains between about ten and about three hundred milligrams of the polymer per dosage unit.

4. Claim 2 wherein the composition contains between about ten and about three hundred milligrams of polymer per dosage unit, wherein the polymer has a molecular weight of about seven thousand five hundred and a melting point of about fifty-one to fifty-four degrees centigrade and wherein \(n\) and \(c\) comprise about eighty to ninety percent by weight of the polymer.

5. Claim 2 wherein in addition the composition contains a peristalsis stimulating laxative.

6. Claim 2 wherein the composition contains between about ten and about three hundred milligrams of polymer per dosage unit and in addition the composition contains a pharmaceutical carrier.

7. Claim 2 wherein in addition the composition contains a pharmaceutical carrier.

8. A composition in dosage unit form for use as an orally ingested human fecal softener which comprises:

(a) a polymer of the formula:

\[ \text{HO(C}_2\text{H}_4\text{O)}_n\text{C}_2\text{H}_5\text{OH;H} \]

wherein \(n\) and \(c\) comprise between about ten to about ninety percent by weight of the polymer and wherein the polymer has a molecular weight between about one thousand and about eleven thousand; and

(b) a peristalsis stimulating laxative, the composition containing that amount of polymer per dosage unit necessary to induce softening of the fecal matter and thus to facilitate evacuation of the fecal matter.

9. Claim 8 wherein the peristalsis stimulating laxative is psyllium.

10. Claim 8 wherein the peristalsis stimulating laxative is bile.

11. Claim 8 wherein the composition contains between about ten and about three hundred milligrams of polymer per dosage unit.

12. Claim 8 wherein the composition contains between about ten and about three hundred milligrams of polymer per dosage unit, wherein the polymer has a molecular weight of about seven thousand five hundred and a melting point of about fifty-one to fifty-four degrees centigrade and wherein \(n\) and \(c\) comprise about eighty to ninety percent by weight of the polymer.

13. Claim 8 wherein in addition the composition contains a pharmaceutical carrier.

References Cited by the Examiner


JULIAN S. LEVITT, Primary Examiner.

MORRIS O. WOLK, WILLIAM B. KNIGHT, Examiners.