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(54) **Title**: ORAL CHOLESTYRAMINE FORMULATION AND USE THEREOF

(57) **Abstract**: The invention relates to an oral formulation for targeted delivery of cholestyramine to the colon, comprising a plurality of cholestyramine pellets that are coated with a colon release coating. The invention also relates to the use of this formulation in the treatment of bile acid malabsorption.

ORAL CHOLESTYRAMINE FORMULATION AND USE THEREOF

The invention relates to an oral formulation for targeted delivery of cholestyramine to the colon, comprising a plurality of cholestyramine pellets that are coated with a colon release coating. The invention also relates to the use of this formulation in the treatment of bile acid malabsorption.

BACKGROUND

Bile acid malabsorption is a condition characterized by an excess of bile acids in the colon, often leading to chronic diarrhoea. Bile acids are steroid acids that are synthesized and conjugated in the liver. From the liver, they are excreted through the biliary tree into the small intestine where they participate in the solubilisation and absorption of dietary lipids and fat-soluble vitamins. When they reach the ileum, bile acids are reabsorbed into the portal circulation and returned to the liver. A small proportion of the secreted bile acids is not reabsorbed in the ileum and reaches the colon. Here, bacterial action results in deconjugation and dehydroxylation of the bile acids, producing the secondary bile acids deoxycholate and lithocholate.

In the colon, bile acids (in particular the dehydroxylated bile acids chenodeoxycholate and deoxycholate) stimulate the secretion of electrolytes and water. This increases the colonic motility and shortens the colonic transit time. If present in excess, bile acids produce diarrhoea with other gastrointestinal symptoms such as bloating, urgency and faecal incontinence. There have been several recent advances in the understanding of this condition of bile salt or bile acid malabsorption, or BAM (Pattni and Walters, *Br. Med. Bull*. 2009, vol 92, p. 79-93; Islam and Di Baise, *Pract. Gastroenterol*. 2012, vol. 36(10), p. 32-44). Dependent on the cause of the failure of the distal ileum to absorb bile acids, bile acid malabsorption may be divided into Type 1, Type 2 and Type 3 BAM.

Diarrhoea may also be the result of high concentrations of bile acid in the large intestine following treatment with drugs that increase the production of bile acids and/or influence the reabsorption of bile acids by the small intestine, such as treatment with ileal bile acid absorption (IBAT) inhibitors.

The current treatment of bile acid malabsorption aims at binding excess bile acids in the gastrointestinal tract, beginning in the proximal part of the small bowel, thereby reducing the secretory actions of the bile acids. For this purpose, cholestyramine is commonly used as the bile acid sequestrant. Cholestyramine (or colestyramine; CAS Number 11041-12-6) is a strongly basic anion-exchange resin that is practically insoluble in water and is not absorbed from the gastrointestinal

tract. Instead, it absorbs and combines with the bile acids in the intestine to form an insoluble complex. The complex that is formed upon binding of the bile acids to the resin is excreted in the faeces. The resin thereby prevents the normal reabsorption of bile acids through the enterohepatic circulation, leading to an increased conversion of cholesterol to bile acids to replace those removed from reabsorption. This conversion lowers plasma cholesterol concentrations, mainly by lowering of the low-density lipoprotein (LDL)-cholesterol.

Cholestyramine is also used as hypolipidaemic agents in the treatment of hypercholesterolemia, type II hyperlipoproteinaemia and in type 2 diabetes mellitus. It is furthermore used for the relief of diarrhoea associated with ileal resection, Crohn´s disease, vagotomy, diabetic vagal neuropathy and radiation, as well as for the treatment of pruritus in patients with cholestasis.

In the current treatment of hyperlipidaemias and diarrhoea, the oral cholestyramine dose is 12 to 24 g daily, administered as a single dose or in up to 4 divided doses. In the treatment of pruritus, doses of 4 to 8 g are usually sufficient. Cholestyramine may be introduced gradually over 3 to 4 weeks to minimize the gastrointestinal effects. The most common side-effect is constipation, while other gastrointestinal side-effects are bloating, abdominal discomfort and pain, heartburn, flatulence and nausea/vomiting. There is an increased risk for gallstones due to increased cholesterol concentration in bile. High doses may cause steatorrhoea by interference with the gastrointestinal absorption of fats and concomitant decreased absorption of fat-soluble vitamins. Chronic administration may result in an increased bleeding tendency due to hypoprothrombinaemia associated with vitamin K deficiency or may lead to osteoporosis due to impaired calcium and vitamin D absorption. There are also occasional reports of skin rashes and pruritus of the tongue, skin and perianal region. Due to poor taste and texture and the various side effects, >50% of patients discontinue therapy within 12 months.

Another drawback with the current treatment using cholestyramine is that this agent reduces the absorption of other drugs administered concomitantly, such as oestrogens, thiazide diuretics, digoxin and related alkaloids, loperamide, phenylbutazone, barbiturates, thyroid hormones, warfarin and some antibiotics. It is therefore recommended that other drugs should be taken at least 1 hour before or 4 to 6 hours after the administration of cholestyramine. Dose adjustments of concomitantly taken drugs may still be necessary to perform.

In view of these side effects, it would be desirable if cholestyramine could be formulated as a colon release formulation, i.e. for release of the cholestyramine in the proximal part of the colon. Such a

formulation may require a lower dose of cholestyramine and should have better properties regarding texture and taste, and may therefore be better tolerated by the patients. More importantly, colonic release of cholestyramine should be devoid of producing interactions with other drugs and should not induce risks for malabsorption of fat and fat-soluble vitamins, while still binding bile acids in order to reduce the increased colonic secretion and motility. For reasons of patient compliance, it would furthermore be desirable if the number of pills to be taken could be kept as low as possible. Each pill should therefore contain as much cholestyramine as possible.

EP 1273307 discloses preparations for preventing bile acid diarrhoea, comprising a bile acid adsorbent coated with a polymer so as to allow the release of the bile acid adsorbent around an area from the lower part of the small intestine to the cecum. It is shown that cholestyramine granules coated with HPMCAS-HF or ethyl cellulose displayed extensive swelling and bursting under conditions simulating the gastric environment.

Jacobsen et al. (*Br. Med. J*. 1985, vol. 290, p. 1315-1318) describe a study wherein patients who had undergone ileal resection were administered 500 mg cholestyramine tablets coated with cellulose acetate phthalate (12 tablets daily). In five of the 14 patients in this study, the tablets did not disintegrate in the desired place.

Despite progress made in this area, there still is a need for further improved cholestyramine formulations. In particular, there is a need for oral formulations for targeted delivery of cholestyramine to the colon.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the sequestration profiles for different formulations in an assay simulating the pH of the stomach and the small intestine. FIG. 1A shows the results for formulations A, B and C during 6 hours at pH 5.5. FIG. 1B shows the results for formulations A and C during 2 hours at pH 1 followed by 4 hours at pH 6.8. FIG. 1C shows the results for formulation C during 2 hours at pH 1 followed by 4 hours at pH 7.4.

FIG. 2 shows the relative concentration of cholic acid (%) vs. incubation time (h) for formulations A, B and C in an *in vitro* SHIME® assay. The results for a comparative experiment using pure cholestyramine powder and a control experiment without cholestyramine are also shown.

FIG. 3 shows the relative concentration of chenodeoxycholic acid (%) vs. incubation time (h) for formulations A, B and C in an *in vitro* SHIME® assay. The results for a comparative experiment using pure cholestyramine powder and a control experiment without cholestyramine are also shown.

FIG. 4 shows the relative concentration of deoxycholic acid (%) vs. incubation time (h) for formulations A, B and C in an *in vitro* SHIME® assay. The results for a comparative experiment using pure cholestyramine powder and a control experiment without cholestyramine are also shown.

DETAILED DESCRIPTION OF THE INVENTION

It has been discovered that small and stable pellets of cholestyramine can be obtained, and that these pellets can be coated with a coating layer that prevents release of the pellets until they reach the colon. The combination of small cholestyramine pellets and a colon release coating allows the dose of cholestyramine to be reduced to for example 1.5 g twice daily. It is believed that this dose of cholestyramine is sufficient for binding an excess of bile acids in the colon. The formulation disclosed herein further reduces undesired interactions of cholestyramine with other components in the gastrointestinal tract, such as other drugs or nutrients.

In one aspect, the invention relates to an oral formulation for targeted delivery of cholestyramine to the colon, comprising:

a) a plurality of pellets comprising cholestyramine; and
b) a colon release coating around said pellets,

wherein more than 70% of the cholestyramine is released in the colon.

Preferably, more than 75% of the cholestyramine is released in the colon, such as more than 80%, or such as more than 85%. More preferably, more than 90% of the cholestyramine is released in the colon.

In another aspect, the invention relates to an oral formulation for targeted delivery of cholestyramine to the colon, comprising:

a) a plurality of pellets comprising cholestyramine; and
b) a colon release coating around said pellets,

wherein less than 30% of the cholestyramine is released in the small intestine.

Preferably, less than 25% of the cholestyramine is released in the small intestine, such as less than 20%, or such as less than 15%. More preferably, less than 10% of the cholestyramine is released in the small intestine.

The cholestyramine content of the pellets should be as high as possible. The uncoated pellets therefore preferably contain at least 70% w/w cholestyramine, more preferably at least 75% w/w cholestyramine, more preferably at least 80% w/w cholestyramine, even more preferably at least 85% w/w cholestyramine and most preferably at least 90% w/w cholestyramine.

In another aspect, the invention relates to an oral formulation for targeted delivery of cholestyramine to the colon, comprising:

a) a plurality of pellets comprising cholestyramine and
   i. at least 7% w/w of a vinylpyrrolidone-based polymer; or
   ii. a combination of at least 6% w/w of a vinylpyrrolidone-based polymer and at least 2% w/w of an acrylate copolymer; or
   iii. a combination of at least 5% w/w of a vinylpyrrolidone-based polymer and at least 3% w/w of an acrylate copolymer; or
   iv. a combination of at least 6% w/w of a vinylpyrrolidone-based polymer, at least 1% w/w of an acrylate copolymer at least 10% w/w microcrystalline cellulose; or
   v. a combination of at least 5% w/w of a vinylpyrrolidone-based polymer, at least 2% w/w of an acrylate copolymer at least 20% w/w microcrystalline cellulose; and
b) a colon release coating around said pellets.

In one embodiment, more than 70% of the cholestyramine is released in the colon, preferably more than 75%, such as more than 80%, or such as more than 85%. More preferably, more than 90% of the cholestyramine is released in the colon.

In another embodiment, less than 30% of the cholestyramine is released in the small intestine, preferably less than 25%, such as less than 20%, or such as less than 15%. More preferably, less than 10% of the cholestyramine is released in the small intestine.

The presence of specific amounts of a vinylpyrrolidone-based polymer, or of a combination of a vinylpyrrolidone-based polymer and an acrylate copolymer, in the composition of the pellets allows for a high cholestyramine content. The resulting pellets are stable enough to withstand the conditions necessary for applying the coating layer onto the pellets.

The colon release coating substantially prevents release of cholestyramine from the pellets until they reach the large intestine, in particular the proximal colon. Additionally, the coating prevents the pellets from bursting. When water that diffuses through the coating is absorbed by the cholestyramine, the increasing volume of the cholestyramine leads to swelling of the pellets. The coating of the pellets is elastic and is therefore able to withstand the swelling of the pellets. The coating thereby prevents burst of the pellets and premature release of the cholestyramine.

Because of its very low solubility, cholestyramine is not "released" from the formulation in that it dissolves from the formulation and diffuses into the intestine. Instead, the cholestyramine probably stays within the gradually degrading structure of the coated pellet. Therefore, as used herein, the term "release" of the cholestyramine refers to the availability of the cholestyramine to the intestinal content in order to bind components (i.e., bile acids) therein.

Pellets

As used herein, the term "pellets" refers to extruded pellets, i.e. pellets obtained through extrusion and spheronization. The preparation of extruded pellets typically comprises the steps of mixing a powder with a liquid to obtain a wet mass, extruding the wet mass, spheronizing the extrudate and drying of the wet pellets.

It is essential that the pellets are stable enough to withstand mechanical stress during handling, such as during drying and coating of the pellets. The stability of the pellets may be expressed in terms of friability, which is the ability of a solid substance (such as a tablet, granule, sphere or pellet) to be reduced to smaller pieces, e.g. by abrasion, breakage or deformation. A low degree of friability means that the solid substance breaks into smaller pieces only to a low extent. As used herein, friability is defined as the reduction in the mass of the pellets occurring when the pellets are subjected to mechanical strain, such as tumbling, vibration, fluidization, etc. Methods for measuring friability are known in the art (e.g., European Pharmacopoeia 8.0, tests 2.9.7 or 2.9.41).

Experiments have shown that the inclusion of smaller amounts of vinylpyrrolidone-based polymer and/or acrylate copolymer than specified above results in lower yield and higher friability of the pellets. Although it is not possible to define acceptable friability limits for pellets in general, friability values of <1.7% w/w friability have been reported as acceptable to withstand stresses associated with fluid bed coating, handling and other processes (Vertommen and Kinget, *Drug Dev. Ind. Pharm*.

1997, vol. 23, p. 39-46). For the cholestyramine pellets of the present invention, it has been found that a friability of 2.1% is still acceptable. The friability is preferably lower than 2.0%, more preferably lower than 1.5%, and even more preferably lower than 1.0%.

The vinylpyrrolidone-based polymer in the pellets may be polyvinylpyrrolidone (povidone) or a vinylpyrrolidone-vinyl acetate copolymer (copovidone). Povidone is a linear, water-soluble polymer made from N-vinylpyrrolidone. Copovidone (also known as copolyvidone) is a linear, water-soluble copolymer of 1-vinyl-2-pyrrolidone (povidone) and vinyl acetate in a ratio of 6:4 by mass. In a preferred embodiment, the vinylpyrrolidone-based polymer is copovidone.

The acrylate copolymer in the pellets may be any pharmaceutically acceptable copolymer comprising acrylate monomers. Examples of acrylate monomers include, but are not limited to, acrylate (acrylic acid), methyl acrylate, ethyl acrylate, methacrylic acid (methacrylate), methyl methacrylate, butyl methacrylate, trimethylammonioethyl methacrylate and dimethylaminoethyl methacrylate. Several acrylate copolymers are known under the trade name Eudragit®.

Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) is a copolymer of ethyl acrylate, methyl methacrylate and a low content of trimethylammonioethyl methacrylate chloride (a methacrylic acid ester with quaternary ammonium groups). The copolymer is also referred to as ammonio methacrylate copolymer. It is insoluble but the presence of the ammonium salts groups makes the copolymer permeable. The copolymer is available as a 1:2:0.2 mixture (Type A) or as a 1:2:0.1 mixture (Type B). 30% aqueous dispersions of Type A and Type B are sold under the trade names Eudragit® RL 30 D and Eudragit® RS 30 D, respectively.

Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1 is a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid. It is insoluble in acidic media but dissolves by salt formation above pH 7.0. A 30% aqueous dispersion is sold under the trade name Eudragit® FS 30 D.

Poly(methacrylic acid-co-ethyl acrylate) 1:1 is a copolymer of ethyl acrylate and methacrylic acid. It is insoluble in acidic media below a pH of 5.5 but dissolves above this pH by salt formation. A 30% aqueous dispersion is sold under the trade name Eudragit® L 30 D-55.

Further suitable acrylate copolymers include poly(ethyl acrylate-co-methyl methacrylate) 2:1, which is a water-insoluble copolymer of ethyl acrylate and methyl methacrylate. 30% aqueous dispersions are sold under the trade names Eudragit® NE 30 D and Eudragit® NM 30 D.

Preferred acrylate copolymers are ammonio methacrylate copolymer, poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1, and poly(methacrylic acid-co-ethyl acrylate) 1:1. More preferably, the acrylate polymer is ammonio methacrylate copolymer, and most preferably the acrylate polymer is poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2.

In one embodiment, the pellets comprise cholestyramine and

i. at least 7% w/w of a vinylpyrrolidone-based polymer; or
ii. a combination of at least 6% w/w of a vinylpyrrolidone-based polymer and at least 2% w/w of an acrylate copolymer.

In a more preferred embodiment, the pellets comprise cholestyramine and

i. at least 7% w/w copovidone; or
ii. a combination of at least 6% w/w copovidone and at least 2% w/w ammonio methacrylate copolymer.

The pellets may further comprise an excipient such as microcrystalline cellulose. In one embodiment, the pellets comprise from 0 to 20% w/w microcrystalline cellulose, such as from 0 to 10% w/w microcrystalline cellulose. In a more preferred embodiment, the pellets comprise from 0 to 5% w/w microcrystalline cellulose.

In another embodiment, the pellets are free from microcrystalline cellulose.

In one embodiment, the pellets comprise from 70 to 92% w/w cholestyramine, from 6 to 12% w/w of a vinylpyrrolidone-based polymer, from 2 to 5% w/w of an acrylate copolymer and from 0 to 20% w/w microcrystalline cellulose. More preferably, the pellets comprise from 80 to 92% w/w cholestyramine, from 6 to 12% w/w of a vinylpyrrolidone-based polymer, from 2 to 5% w/w of an acrylate copolymer and from 0 to 5% w/w microcrystalline cellulose.

In another embodiment, the pellets comprise from 70 to 92% w/w cholestyramine, from 6 to 12% w/w copovidone, from 2 to 5% w/w ammonio methacrylate copolymer and from 0 to 20% w/w microcrystalline cellulose. More preferably, the pellets comprise from 80 to 92% w/w cholestyramine, from 6 to 12% w/w copovidone, from 2 to 5% w/w ammonio methacrylate copolymer and from 0 to 5% w/w microcrystalline cellulose.

In another embodiment, the pellets comprise from 70 to 93% w/w cholestyramine, from 7 to 12% w/w of a vinylpyrrolidone-based polymer and from 0 to 20% w/w microcrystalline cellulose. More preferably, the pellets comprise from 70 to 93% w/w cholestyramine, from 7 to 12% w/w copovidone and from 0 to 20% w/w microcrystalline cellulose.

In yet another embodiment, the pellets comprise from 80 to 93% w/w cholestyramine, from 7 to 12% w/w of a vinylpyrrolidone-based polymer and from 0 to 10% w/w microcrystalline cellulose. More preferably, the pellets comprise from 80 to 93% w/w cholestyramine, from 7 to 12% w/w copovidone and from 0 to 10% w/w microcrystalline cellulose.

The uncoated pellets rapidly disintegrate under aqueous conditions. However, they are stable enough to withstand the conditions necessary for applying the colon release coating onto the pellets.

Colon release coating

The colon release coating around the pellets allows for enzyme controlled release of the cholestyramine. The coating comprises a biodegradable polymer that is degraded by bacterial enzymes present in the colon, but that is not degraded by the human enzymes present in the gastrointestinal tract. The release of the cholestyramine from the pellets is thus triggered by changes in the bacterial environment and substantially prevented until the coated pellets reach the colon.

The biodegradable polymer may be an azo polymer or a polysaccharide. Examples of bacterially degradable polysaccharides include chitosan, pectin, guar gum, dextran, inulin, starch and amylose, as well as derivatives thereof (Sinha and Kumria, *Eur. J. Pharm. Sci.* 2003, vol. 18, p. 3-18). The colon release coating preferably comprises starch.

The structure of starch generally comprises 20-30% (w/w) amylose, which is less easily degraded by intestinal microbiota, and 70-80% (w/w) amylopectin, which is more easily degraded by intestinal microbiota. Thus, depending on the specific amounts of amylose and amylopectin present in the structure, different types of starch have different degradation profiles. Resistant starch has a high amylose content and generally escapes from digestion in the small intestine. Such starch is instead digested by bacteria in the colon. Depending on the natural source of the starch and how it has been treated, resistant starch can be categorized into four types (RS1 to RS4), each having different properties. Resistant starch type 2 (RS2), such as in high amylose maize starch (or high amylose corn

starch) is less accessible to enzymes due to the conformation of the starch. The colon release coating around the cholestyramine pellets preferably comprises resistant starch type 2 (RS2). When RS2 is cooked or heated, realignment of the amylose and amylopectin crystalline structures occurs in a process called retrogradation, leading to resistant starch type 3 (RS3).

In addition to the biodegradable polymer, the colon release coating comprises one or more further organic polymers. Examples of suitable organic polymers include, but are not limited to, poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1 (Eudragit® FS 30 D), poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2 (Eudragit® RL 30 D), poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1 (Eudragit® RS 30 D), poly(ethyl acrylate-co-methyl methacrylate) 2:1 (Eudragit® NE 30 D or Eudragit® NM 30 D) and poly(vinyl acetate) (e.g., Kollicoat® SR 30 D). In a preferred embodiment, the organic polymer is poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1 (Eudragit® FS 30 D).

When water is absorbed by the cholestyramine, the increasing volume of the cholestyramine leads to swelling of the pellets. It is therefore preferred that the colon release coating is elastic (i.e., has high elongation at break). Because of the elasticity of the coating, the coating is able to withstand this swelling. Burst of the pellets and premature release of the cholestyramine is thereby avoided. The elasticity of the coating may be the result of the elasticity of the organic polymer(s) itself, or may be induced by the addition of a plasticizer. Examples of suitable plasticizers include, but are not limited to, triethyl citrate, glyceryl triacetate, tributyl citrate, diethyl phthalate, acetyl tributyl citrate, dibutyl phthalate and dibutyl sebacate.

The colon release coating may comprise one or more further additives, such as acids and bases, glidants, and surfactants. Examples of suitable acids include organic acids such as citric acid, acetic acid, trifluoroacetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, ascorbic acid, pamoic acid, maleic acid, hydroxymaleic acid, phenylacetic acid, glutamic acid, benzoic acid, salicylic acid, mesylic acid, esylic acid, besylic acid, sulfanilic acid, 2-acetoxybenzoic acid, fumaric acid, toluenesulfonic acid, methanesulfonic acid, ethane disulfonic acid and oxalic acid, and inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, sulfamic acid, phosphoric acid and nitric acid. Examples of suitable bases include inorganic bases such as sodium bicarbonate, sodium hydroxide and ammonium hydroxide. Examples of suitable glidants include talc, glyceryl monostearate, oleic acid, medium chain triglycerides and colloidal silicon dioxide. Examples of suitable surfactants include sodium dodecyl sulfate, polysorbate 80 and sorbitan monooleate.

In order to improve the adherence of the coating layer onto the cholestyramine pellets, or in order to minimize the interaction between the coating layer and the cholestyramine in the pellets, a barrier coating may optionally be present as an additional layer between the pellets and the coating layer. A barrier coating may also be present when two different coating layers should be kept physically separated from each other. A particularly suitable material for the barrier coating is hydroxypropyl methylcellulose (HPMC).

A thin layer of a non-sticking agent may ultimately be applied to the coated pellets. This outer layer prevents the coated pellets from sticking together, e.g. during storage. Examples of suitable non-sticking agents include fumed silica, talc and magnesium stearate.

The colon release coating substantially prevents release of the cholestyramine from the pellets until they have reached the large intestine. Preferably, there should be no exposure of the cholestyramine in the small intestine, whereas the exposure should be quick once the multiparticulates have passed the ileocecal valve. In one embodiment, less than 30% of the cholestyramine is released in the small intestine, such as less than 20%, such as less than 10%. In a more preferred embodiment, less than 5% of the cholestyramine is released in the small intestine. In another embodiment, more than 70% of the cholestyramine is released in the colon, such as more than 80%, such as more than 90%. In a more preferred embodiment, more than 95% of the cholestyramine is released in the colon.

The colon release coating adds further weight and volume to the pellets. The smaller the size of the pellets, the larger is the impact of the coating on the volume of the final formulation. However, for reasons of patient compliance, it is desirable that the total volume of the formulation is kept as low as possible. The coating layer should therefore be as thin as possible. Preferably, the amount of coating in the final formulation (on dry weight basis) is less than 45% w/w, more preferably less than 40% w/w and even more preferably less than 35% w/w.

The cholestyramine content of the pellets should be as high as possible. The uncoated pellets therefore preferably contain at least 70% w/w cholestyramine, more preferably at least 75% w/w cholestyramine, more preferably at least 80% w/w cholestyramine, even more preferably at least 85% w/w cholestyramine and most preferably at least 90% w/w cholestyramine. The cholestyramine content of the final formulation (on dry weight basis) is preferably at least 50% w/w, and more preferably at least 55% w/w.

The size of the pellets is initially governed by the diameter of the screen used in the extrusion step. After the extrusion and spheronization steps, the pellets may be sieved to obtain a pellet fraction with a narrow size distribution. The diameter of the uncoated cholestyramine pellets is preferably from 500 µm to 3000 µm, more preferably from 750 µm to 2000 µm and even more preferably from 1000 to 1600 µm. In a most preferred embodiment, the diameter of the pellets is from 1000 to 1400 µm.

The cholestyramine pellets may be prepared in a process comprising the steps of:

i) mixing the dry ingredients;

ii) adding water, and optionally the acrylate copolymer, to obtain a wet mass;

iii) extruding the wet mass;

iv) spheronizing the extrudate; and

v) drying the obtained pellets.

The dried pellets may thereafter be sieved in order to obtain pellets of uniform size.

The dry ingredients in step i) comprise cholestyramine and the vinylpyrrolidone-based polymer, and may optionally comprise microcrystalline cellulose.

Because of its physical nature, cholestyramine powder is able to absorb large amounts of water, which results in considerable swelling of the material. In order to prepare a wet mass from dry cholestyramine, it is therefore necessary to add more water than normally would be used for preparing a wet mass from dry ingredients. Preferably, water is added to the mix of dry ingredients in an amount of at least 1.5 times the amount of cholestyramine (w/w), more preferably in an amount of at least 1.75 times the amount of cholestyramine (w/w), and even more preferably in an amount of at least 2 times the amount of cholestyramine (w/w).

The coating may be applied onto the cholestyramine pellets by methods known in the art, such as by film coating involving perforated pans and fluidized beds.

The oral formulation described herein may be administered to a patient in different forms, depending on factors such as the age and general physical condition of the patient. For example, the formulation may be administered in the form of one or more capsules wherein the coated pellets are contained. Such capsules conventionally comprise a degradable material, such as gelatin, hydroxypropyl methylcellulose (HPMC), pullulan or starch, which easily disintegrates under the acidic

conditions in the stomach. The coated pellets are thereby quickly released into the stomach. Thus, in one aspect, the invention relates to a capsule comprising the oral formulation disclosed herein.

Alternatively, the coated pellets may be administered as a sprinkle formulation, the contents of which can be dispersed in liquid or soft food. Such a formulation does not require the swallowing of larger capsules and is therefore particularly useful for infants and small children as well as for older adults. Thus, in another aspect, the invention relates to a sprinkle formulation comprising the oral formulation disclosed herein. In such a formulation, the coated pellets may be contained within a capsule, sachet or stick pack.

The oral formulation disclosed herein provides several advantages over other formulations. The small coated pellets (multiparticulates) according to the present invention are able to easily pass the gastrointestinal tract. This eliminates the risk that the formulation is temporarily held up in the gastrointestinal tract, such as at the stomach or at the ileocecal valve, as is sometimes encountered with monolithic formulations (such as tablets or capsules that do not disintegrate in the stomach). Furthermore, the cholestyramine is made available to the intestinal content only when the coating starts being degraded as a result of the bacteria present in, and the higher pH at, the lower gastrointestinal tract, in particular the colon. The contents of the stomach and the small intestine are therefore effectively protected from the cholestyramine, which is a major improvement over formulations that directly release the cholestyramine in the stomach or the small intestine.

The low solubility of cholestyramine in aqueous environment prevents the release of cholestyramine from the formulation to be measured directly. The availability of the cholestyramine to the intestinal content over time and at different pH values can instead be determined *in vitro*, such as by measuring the sequestering capacity of the formulation under simulated conditions for the gastrointestinal tract. Such a method involves measuring the decreasing amount of free bile acid (i.e., the compound to be sequestered) in a liquid medium representative of the gastrointestinal tract, as described in the experimental section. See also the Official Monograph for cholestyramine resin (USP 40, page 3404).

In another aspect, the invention relates to the formulation disclosed herein for use in the treatment or prevention of bile acid malabsorption.

The invention also relates to the use of the formulation disclosed herein in the manufacture of a medicament for the treatment or prevention of bile acid malabsorption. The invention further

relates to a method for the treatment or prevention of bile acid malabsorption comprising administering to a mammal in need of such treatment or prevention a therapeutically effective amount of the formulation disclosed herein.

Bile acid malabsorption may be divided into three different types, dependent on the cause of the failure of the distal ileum to absorb bile acids. Type 1 BAM is the result of (terminal) ileal disease (such as Crohn's disease) or (terminal) ileal resection or bypass. Type 2 BAM is often referred to as idiopathic bile acid malabsorption or primary bile acid diarrhoea (BAD) and is believed to be the result of an overproduction of bile acids or caused by a defective feedback inhibition of hepatic bile acid synthesis. This feedback regulation is mediated by the ileal hormone fibroblast growth factor 19 (FGF19) in man. Finally, type 3 BAM may be the result of cholecystectomy, vagotomy, small intestinal bacterial overgrowth (SIBO), coeliac disease, pancreatic insufficiency (chronic pancreatitis, cystic fibrosis), pancreatic transplant, radiation enteritis, collagenous colitis, microscopic colitis, lymphocytic colitis, ulcerative colitis or irritable bowel syndrome (i.e., diarrhoea-predominant irritable bowel syndrome (IBS-D)).

The formulation may also be used in combination with an Ileal Bile Acid Absorption (IBAT) inhibitor. Treatment with IBAT inhibitors, such as in the treatment of liver diseases, disorders of fatty acid metabolism or glucose utilization disorders, may result in increased levels of bile acids and/or influence the reabsorption of bile acids by the small intestine, leading to high concentrations of bile acid in the large intestine and thus causing diarrhoea. This side effect of the treatment with IBAT inhibitors may be treated or prevented by treatment with the formulation as disclosed herein. The formulation and the IBAT inhibitor may be administered simultaneously, sequentially or separately.

Thus, in another aspect, the invention relates to the formulation disclosed herein, for use in the treatment or prevention of diarrhoea upon oral administration of an IBAT inhibitor.

The invention also relates to the use of the formulation disclosed herein in the manufacture of a medicament for the treatment or prevention of diarrhoea upon oral administration of an IBAT inhibitor. The invention further relates to a method for the treatment or prevention of diarrhoea upon oral administration of an IBAT inhibitor, comprising administering to a mammal in need of such treatment or prevention therapeutically effective amounts of an IBAT inhibitor and of the formulation disclosed herein.

In a preferred embodiment, the invention relates to the formulation disclosed herein, for use in the treatment or prevention of bile acid diarrhoea upon treatment of a liver disease, such as a cholestatic liver disease, comprising oral administration of an IBAT inhibitor. In particular, the invention relates to the formulation disclosed herein for use in the treatment or prevention of diarrhoea upon treatment of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), autoimmune hepatitis, cholestatic pruritus, non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) comprising oral administration of an IBAT inhibitor.

In another embodiment, the invention relates to a method for the treatment or prevention of bile acid diarrhoea upon treatment of a liver disease comprising oral administration of an IBAT inhibitor, comprising administering to a mammal in need of such treatment or prevention a therapeutically effective amount of the formulation disclosed herein. In particular, the invention relates to such a method for the treatment or prevention of diarrhoea wherein the liver disease is Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), autoimmune hepatitis, cholestatic pruritus, non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH).

A liver disease as defined herein is any bile acid-dependent disease in the liver and in organs connected therewith, such as the pancreas, portal vein, the liver parenchyma, the intrahepatic biliary tree, the extrahepatic biliary tree, and the gall bladder. Liver diseases include, but are not limited to an inherited metabolic disorder of the liver; inborn errors of bile acid synthesis; congenital bile duct anomalies; biliary atresia; neonatal hepatitis; neonatal cholestasis; hereditary forms of cholestasis; cerebrotendinous xanthomatosis; a secondary defect of BA synthesis; Zellweger´s syndrome; cystic fibrosis (manifestations in the liver); alpha1-antitrypsin deficiency; Alagilles syndrome (ALGS); Byler syndrome; a primary defect of bile acid (BA) synthesis; progressive familial intrahepatic cholestasis (PFIC) including PFIC-1, PFIC-2, PFIC-3 and non-specified PFIC; benign recurrent intrahepatic cholestasis (BRIC) including BRIC1, BRIC2 and non-specified BRIC; autoimmune hepatitis; primary biliary cirrhosis (PBC); liver fibrosis; non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH); portal hypertension; general cholestasis; jaundice during pregnancy; jaundice due to drugs; intrahepatic cholestasis; extrahepatic cholestasis; primary sclerosing cholangitis (PSC); gall stones and choledocholithiasis; malignancy causing obstruction of the biliary tree; pruritus due to cholestasis or jaundice; pancreatitis; chronic autoimmune liver disease leading to progressive cholestasis; hepatic steatosis; alcoholic hepatitis; acute fatty liver; fatty liver of pregnancy; drug-induced hepatitis; iron overload disorders; hepatic fibrosis; hepatic cirrhosis; amyloidosis; viral

hepatitis; and problems in relation to cholestasis due to tumours and neoplasms of the liver, of the biliary tract and of the pancreas.

Disorders of fatty acid metabolism and glucose utilization disorders include, but are not limited to, hypercholesterolemia, dyslipidemia, metabolic syndrome, obesity, disorders of fatty acid metabolism, glucose utilization disorders, disorders in which insulin resistance is involved, and type 1 and type 2 diabetes mellitus.

IBAT inhibitors are often referred to by different names. As used herein, the term "IBAT inhibitors" should be understood as also encompassing compounds known in the literature as Apical Sodium-dependent Bile Acid Transporter Inhibitors (ASBTI's), bile acid transporter (BAT) inhibitors, ileal sodium/bile acid cotransporter system inhibitors, apical sodium-bile acid cotransporter inhibitors, ileal sodium-dependent bile acid transport inhibitors, bile acid reabsorption inhibitors (BARI's), and sodium bile acid transporter (SBAT) inhibitors.

IBAT inhibitors that can be used in combination with the bile acid sequestrant formulation disclosed herein include, but are not limited to, benzothiazepines, benzothiepines, 1,4-benzothiazepines, 1,5-benzothiazepines and 1,2,5-benzothiadiazepines.

Suitable examples of IBAT inhibitors that can be used in combination with the bile acid sequestrant formulation disclosed herein include, but are not limited to, the compounds disclosed in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/03818, WO 98/07449, WO 98/40375, WO 99/35135, WO 99/64409, WO 99/64410, WO 00/47568, WO00/61568, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68096, WO 02/32428, WO 03/061663, WO 2004/006899, WO 2007/009655, WO 2007/009656, DE 19825804, EP 864582, EP 489423, EP 549967, EP 573848, EP 624593, EP 624594, EP 624595, EP 624596, EP 0864582, EP 1173205 and EP 1535913.

Particularly suitable IBAT inhibitors are those disclosed in WO 01/66533, WO 02/50051, WO 03/022286, WO 03/020710, WO 03/022825, WO 03/022830, WO 03/091232, WO 03/106482 and WO 2004/076430, and especially the compounds selected from the group consisting of:
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]-benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*'-((S)-1-carboxyethyl)carbamoyl]-benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)-carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)-carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)-carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)carbamoyl]-benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1, 1-dioxo-3, 3-dibutyl-5-phenyl-7-methylthio-8- (*N*-{(R)-α-[*N*'-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)-carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N*'-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
or a pharmaceutically acceptable salt thereof.

Other particularly suitable IBAT inhibitors are those disclosed in WO99/32478, WO00/01687, WO01/68637, WO03/022804, WO 2008/058628 and WO 2008/058630, and especially the compounds selected from the group consisting of:
1-[4-[4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]butyl]4-aza-1-azoniabicyclo[2.2.2]octane methanesulfonate;
1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniazabicyclo[2.2.2]octane chloride;

1-[[5-[[3-[(3S,4R,5R)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy-D-glucitol; and potassium ((2R,3R,4S,5R,6R)-4-benzyloxy-6-{3-[3-((3S,4R,5R)-3-butyl-7-dimethylamino-3-ethyl-4-hydroxy-1,1-dioxo-2,3,4,5-tetrahydro-1H-benzo[b]thiepin-5-yl)-phenyl]-ureido}-3,5-dihydroxy-tetrahydro-pyran-2-ylmethyl)sulphate, ethanolate, hydrate.

An effective amount of the cholestyramine formulation according to the invention can be any amount containing more than or equal to about 100 mg of cholestyramine, such as more than or equal to about 250 mg, 500 mg, 750 mg, 1000 mg, 1250 mg, 1500 mg, 1750 mg or 2000 mg of cholestyramine. For example, the effective amount of cholestyramine can be between 100 mg and 5000 mg, such as between 250 mg and 2500 mg, between 250 mg and 2000 mg, between 500 mg and 2500 mg, between 500 mg and 2000 mg, or between 750 mg and 2000 mg.

A unit dose of the cholestyramine formulation according to the invention may comprise from 200 to 300 mg of cholestyramine, such as from 220 to 280 mg of cholestyramine, such as from 240 to 260 mg of cholestyramine. A unit dose preferably comprises about 250 mg of cholestyramine. The daily dose can be administered as a single dose or divided into one, two, three or more unit doses.

The frequency of administration of the formulation as disclosed herein can be any frequency that reduces the bile acid malabsorption condition without causing any significant adverse effects or toxicity to the patient. The frequency of administration can vary from once or twice a week to several times a day, such as once a day or twice a day. The frequency of administration can furthermore remain constant or be variable during the duration of the treatment.

Several factors can influence the frequency of administration and the effective amount of the formulation that should be used for a particular application, such as the severity of the condition being treated, the duration of the treatment, as well as the age, weight, sex, diet and general medical condition of the patient being treated.

The invention is further illustrated by means of the following examples, which do not limit the invention in any respect. All cited documents and references are incorporated herein by reference.

Abbreviations

HPLC	High Performance Liquid Chromatography
PTFE	Polytetrafluoroethylene
RH	Relative humidity
rpm	revolutions per minute
UHPLC	Ultra High Performance Liquid Chromatography
UV-Vis	Ultraviolet-visible spectroscopy

EXAMPLES

Example 1

Extrusion experiments

All experiments were performed on a 100-200 g scale. The dry ingredients (cholestyramine, the vinylpyrrolidone-based polymer and/or microcrystalline cellulose) were mixed in the amounts indicated below. Water was added in portions of 50-100 gram with 3 minutes of mixing between each addition. When an acrylate copolymer was included in the experiment, it was added as a 2% w/w dispersion in water (20 g acrylate copolymer (aqueous dispersion 30%) added up to 300 g water). A final portion of pure water was added, if necessary. In each experiment, the total amount of liquid added was between 1.7 and 2.3 times the amount of solid material (w/w).

The wet mass was transferred to an extruder equipped with a 1.5 mm screen, operated at 25 rpm (revolutions per minute) and the extrudate was collected on a stainless steel tray. Approximately 100 g of the extrudate was run in the spheronizer for 1 minute at a speed of 730 rpm. The spheronized material was then transferred to stainless steel trays, placed in a drying oven and dried for 16 hours at 50°C. The yield was calculated as the fraction of pellets that pass through a 1.6 mm sieve but are retained on a 1.0 mm sieve.

Friability testing was performed using the equipment and procedure described in European Pharmacopoeia 8.0, test 2.9.7. The pellets were sieved on a 500 µm sieve to remove any loose dust before weighing.

The results using copovidone and Eudragit® RL 30 D are shown in Table 1, and the results using povidone and other Eudragit® copolymers are shown in Table 2.

Table 1

Entry	Amount (% w/w)				Yield (%)	Friability (%)
	Cholestyramine	Copovidone	MCC	Eudragit® RL 30 D		
1	100	0	0	0	*	*
2	90	0	10	0	*	*
3	70	0	30	0	39	1.6
4	70	6	24	0	*	*
5	70	0	26	4	*	*
6	70	6	20	4	85	0.1
7	80	3	15	2	*	*
8	85	7.5	4.5	3	92	0.6
9	90	6	4	0	*	*
10	90	0	6	4	*	*
11	90	0	0	10	*	*
12	90	6	0	4	85	1.4
13	90	10	0	0	87	1.2
14	91	9	0	0	82	0.5
15	92	8	0	0	83	1.5
16	93	7	0	0	78	1.0
17	94	6	0	0	*	*
18	91	6	0	3	84	0.3
19	92	6	0	2	82	1.6
20	93	6	0	1	*	*
21	85	6	8	1	81	3.5
22	80	6	13	1	85	0.8
23	92	5	0	3	70	2.0
24	93	5	0	2	*	*
25	85	5	8	2	54	7.1
26	80	5	13	2	73	9.1

* = extrusion followed by spheronization did not lead to pellets.

Table 2

Entry	Amount (% w/w)				Yield (%)	Friability (%)
	Cholestyramine	Povidone	MCC	Eudragit®		
1	85	7.5	4.5	3% w/w FS 30 D	79	0.2
2	85	7.5	4.5	3% w/w L 30 D-55	24	0.8
3	85	7.5	4.5	3% w/w NE 30 D	88	0.5
4	85	7.5	4.5	3% w/w NM 30 D	96	0.9
5	85	7.5	4.5	3% w/w RS 30 D	82	0.8

Example 2

Preparation of pellets

Pellets with a composition according to Table 1, entry 8, were manufactured at a batch size of 200 g in the extrusion step and 100 g in the spheronization step. 170 g cholestyramine, 15 g copovidone and 9 g microcrystalline cellulose were charged into a planetary mixer. The mixer was operated at intermediate speed and the liquid was slowly added in portions with mixing between each addition. First 300 g water with 20 g Eudragit® RL 30 D (30% dry weight) was added in three equal portions, with mixing for 3 minutes between each addition. Finally 40 g pure water was added and mixing was performed for additionally 30 seconds. The wet mass was then transferred to the extruder. The extruder was equipped with a 1.5 mm screen, operated at 25 rpm and the extrudate was collected on a stainless steel tray. Approximately 100 g of the extrudate was run in the spheronizer for 1 minute at a speed of 730 rpm. The spheronized material was then transferred to stainless steel trays, placed in a drying oven and dried for 16 hours at 50°C. The dried pellets were sieved and the fraction between 1 mm and 1.4 mm or between 1 mm and 1.6 mm was collected.

Example 3

Formulations A-C for enzyme-controlled release

The cholestyramine pellets of Example 2 were formulated with a colon release coating based on Eudragit® FS 30 D and native high amylose maize starch.

The pellets composition for a unit dose comprising 250 mg cholestyramine is shown below.

Ingredient	Amount (mg/dose)
Cholestyramine	250
Copovidone (Kollidon® VA64 Fine)	22.1
Microcrystalline cellulose (Avicel® PH102)	13.2
Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2 (Eudragit® RL 30 D)	8.8
Total	294.1

For the coating, a glycerol monostearate (GMS) emulsion containing GMS, polysorbate 80 and triethyl citrate was prepared according to general instructions from Evonik. The emulsion was then mixed with Eudragit® FS 30 D (aqueous dispersion 30%). The composition of the Eudragit FS 30 D coating dispersion, based on dry weight, is shown below. The concentration, based on dry weight, is 19.8% (w/w).

Ingredient	Amount (w/w)
Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1 (Eudragit® FS 30 D)	90.4
Triethyl citrate	4.5
Glycerol monostearate 45-55 (Kolliwax® GMS II)	3.6
Polysorbate 80 (Tween® 80)	1.5

The pH of the dispersion was adjusted with a 0.3 M NaOH solution to 5.5. The dispersion was mixed with a suspension of native starch granules containing 12.9% starch, 0.1% Kolliphor® SLS fine and water. The Eudragit® dispersion was mixed with the starch suspension so that the ratio between polymer film and starch in the final film was 60% starch to 40% Eudragit® FS 30 D film. The composition of the coating, based on dry weight, is shown below. The concentration, based on dry weight of the applied dispersion, is 15% (w/w).

Ingredient	Amount (w/w)
Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1 (Eudragit® FS 30 D)	36.0
High amylose maize starch (Hylon® VII)	59.7
Triethyl citrate	1.8
Glycerol monostearate 45-55 (Kolliwax® GMS II)	1.4
Polysorbate 80 (Tween® 80)	0.6
Sodium lauryl sulphate (Kolliphor® SLS Fine)	0.5
NaOH	qs pH 5.5

The coating layer was applied using a Hüttlin Kugelcoater HKC005. The initial batch size was 75 g. The coating process was performed with an air inlet temperature of 47-52°C, resulting in a product temperature of 27-29°C. The air flow was adjusted to achieve an appropriate fluidization of the pellets during the coating.

The coating was applied to the cholestyramine pellets so as to obtain a weight gain of 84% (formulation A), 65% (formulation B) or 50% (formulation C). After the coating, the pellets were heat-treated at 40°C for 2 hours.

The coated pellets may be encapsulated in capsules, e.g. hard gelatine capsules. Details for the final formulations (on dry weight basis) are shown below:

	Formulation A	Formulation B	Formulation C
Dose weight:	541 mg	485 mg	441 mg
Cholestyramine:	250 mg (46%)	250 (52%)	250 (57%)
Coating:	247 mg (46%)	191 (39%)	147 (33%)

Example 4

Formulation D for pH- and diffusion-controlled release

The cholestyramine pellets of Example 2 were formulated with an inner barrier coating of hydroxylpropyl methylcellulose (HPMC), a colon release coating based on Eudragit® FS 30 D and

native high amylose maize starch and finally coated with fumed silica to prevent sticking of the pellets during storage.

The pellets composition for a unit dose comprising 250 mg cholestyramine is shown below.

Ingredient	**Amount (mg/dose)**
Cholestyramine	250
Copovidone (Kollidon® VA64 Fine)	22.1
Microcrystalline cellulose (Avicel® PH102)	13.2
Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2 (Eudragit® RL 30 D)	8.8
Total	294.1

For the inner barrier coating, a hydroxypropyl methylcellulose solution was prepared by suspending HPMC (Methocel E3, Colorcon) in hot water and then allowing the suspension to cool down so that the HPMC dissolved. The concentration of HPMC in the solution was 10% (w/w).

The coating solution was applied using a Vector FL-M-1 apparatus. The initial batch size was 500 g. The coating process was performed with an air inlet temperature of 57°C, resulting in a product temperature >40°C. The air flow was adjusted to achieve an appropriate fluidization of the pellets during the coating. The coating was applied to the cholestyramine pellets so as to obtain a weight gain of 3% (w/w). After the coating, the heating of the inlet air was switched off and the pellets were heat-treated in the coating equipment for 7 minutes.

For the colon release coating, a ready formulated mixture, PlasACRYL® T20 (aqueous dispersion 20%) containing glycerol monostearate (GMS), polysorbate 80 and triethylcitrat was mixed with Eudragit® FS30D (aqueous dispersion 30%) and water according to general instructions from Evonik. The composition of the Eudragit FS 30 D coating dispersion, based on dry weight, is shown below. The concentration, based on dry weight, is 20%.

Ingredient	Amount (w/w)
Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1 (Eudragit® FS 30 D)	90.9
PlasACRYL® T20	9.1

The pH of the dispersion was adjusted with a 0.3 M NaOH solution to 5.5. The dispersion was mixed with a suspension of native starch granules containing 12.9% starch, 0.1% Kolliphor® SLS fine and water. The Eudragit® dispersion was mixed with the starch suspension so that the ratio between polymer film and starch in the final film was 60% starch to 40% Eudragit® FS 30 D film. The composition of the coating, based on dry weight, is shown below. The concentration, based on dry weight of the applied dispersion, is 15% (w/w).

Ingredient	Amount (w/w)
Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1 (Eudragit® FS 30 D)	36.2
High amylose maize starch (Hylon® VII)	59.7
PlasACRYL® T20	3.6
Sodium lauryl sulphate (Kolliphor® SLS Fine)	0.5
NaOH	qs pH 5.5

The coating layer was applied using a Vector FL-M-1 apparatus. The coating process was performed with an air inlet temperature of 39-40°C, resulting in a product temperature of 25-26°C. The air flow was adjusted to achieve an appropriate fluidization of the pellets during the coating. The coating was applied to the cholestyramine pellets so as to obtain a weight gain of 50% (w/w).

Directly after the colon release coating, fumed silica was applied onto the coated pellets by spraying a 5% suspension of Aerosil® 200 in water onto the pellets. The coating was applied using the same equipment with an inlet temperature of 39-40°C, resulting in a product temperature of 30°C. The air flow was adjusted to achieve an appropriate fluidization of the pellets during the coating. The coating was applied to the cholestyramine pellets so as to obtain a weight gain of 1% (w/w).

The coated pellets were heat-treated at 40°C for 2 hours.

The coated pellets may be encapsulated in capsules, e.g. hard gelatine capsules. Details for the final formulations (on dry weight basis) are shown below:

Dose weight:	458.9 mg	
Cholestyramine:	250 mg	(54%)
Barrier coating:	*8.8 mg*	
Colon release coating:	*151.5 mg*	
Anti-sticking coating	*4.5 mg*	
Total coating:	164.8 mg	(36%)

Example 5

Sequestration assay

The sequestering capacities of formulations A, B and C were determined in a simplified assay, simulating the pH of the stomach and the small intestine. The sequestration was determined by measuring the decreasing amount of cholic acid in an aqueous solution. The USP Dissolution Apparatus 2 (paddle) Ph. Eur. 2.9.3 was used.

Sequestration at pH 5.5

An amount of formulation A, B or C corresponding to 250 mg cholestyramine was added to a vessel containing 500 mL of a buffered solution of cholic acid (0.192 mg/mL), pH 5.5 and the contents were stirred at 75 rpm for 6 hours. Samples of the solution were withdrawn at different time points and analysed for cholic acid by HPLC using a Thermo Hypersil Gold column, 50 mm x 2.1 mm, particle size 1.9 µm; column temperature 60 °C; mobile phase 30:70 acetonitrile: phosphate buffer (pH 3.0); flow rate 0.75 mL/min. 5 replicate samples were analysed for each formulation and the average values were calculated.

Sequestration at pH 6.8 or 7.4

An amount of formulation A, B or C corresponding to 250 mg cholestyramine was added to a vessel containing 250 mL 0.1 M hydrochloric acid solution (pH 1) and the contents were stirred at 75 rpm for 2 hours. 250 mL of a solution of cholic acid in potassium hydroxide/potassium phosphate buffer solution was then added to the vessel, giving a buffered solution of cholic acid (0.192 mg/mL) with

pH 6.8 or 7.4. After 1 minute of mixing, a first sample was removed. The pH was thereafter verified and if necessary adjusted to 6.8 or 7.4 by addition of the appropriate amount of 0.1 M potassium hydroxide solution. The solution was thereafter mixed for an additional 6 hours. Samples of the solution were withdrawn at different time points and analysed for cholic acid by HPLC using a Thermo Hypersil Gold column, 50 mm x 2.1 mm, particle size 1.9 µm; column temperature 60 °C; mobile phase 30:70 acetonitrile: phosphate buffer (pH 3.0); flow rate 0.75 mL/min. 5 replicate samples were analysed for each formulation and the average values were calculated.

The sequestration profiles for formulations A-C are shown in Figure 1. The pH of 5.5 is slightly lower than the pH normally observed in the duodenum, although it may occur in some patients and healthy persons. At this pH, sequestration is limited for all formulations (Figure 1A). Sequestration at pH 6.8 is representative for the conditions in the ileum. At this pH, formulation A gave 23% sequestration after 4 hours and formulation C gave 40% sequestration (Figure 1B). At pH 7.4, formulation C reached almost 100% sequestration within 2 hours. Whereas this pH is probably slightly higher than the pH normally observed in the distal ileum, the experiment shows that Eudragit® FS 30 D in the coating layer rapidly dissolves at this pH (Figure 1C).

The coated pellets of formulations A, B and C showed no or only minor disintegration at pH 5.5 or 6.8. Visual inspection of the pellets revealed that the coating was intact after stirring for 6 hours at pH 5.5 or after 2 hours at pH 1 followed by 4 hours at 6.8. In contrast, the uncoated pellets of Example 2, when stirred in a phosphate buffer (50 mM, pH 6.8) at 300 rpm (propeller stirrer), fully disintegrated within 1 minute and 25 seconds.

Example 6

***In vitro* determination of the sequestering capacity of formulations A-C under simulated conditions for the gastrointestinal tract**

The sequestering capacities of formulations A, B and C were studied in the Simulator of the Human Intestinal Microbial Ecosystem (SHIME®) as developed by ProDigest (Ghent, Belgium). The simulator was adapted to evaluate the sequestering capacity of binding bile salts under physiological conditions representative for fasted stomach, small intestine and proximal colon. The liquid media representative of the fasted stomach and small intestine have previously been described by Marzorati et al. (*LWT-Food Sci. Technol*. 2015, vol. 60, p. 544-551). The liquid medium for the proximal colon comprises a SHIME® matrix containing a stable microbial community representative for the human colon. A method for obtaining a stable microbial community of the human intestine is

described by Possemiers et al. (*FEMS Microbiol. Ecol*. 2004, vol. 49, p. 495-507) and references therein. The sequestration was determined by measuring the decreasing amount of bile acids in an aqueous solution. A 40:40:20 (w/w) mixture of cholic acid (CA), chenodeoxycholic acid (CDCA) and deoxycholic acid (DCA) was used as a representative mixture of human bile salts (Carulli et al., *Aliment. Pharmacol. Ther*. 2000, vol. 14, issue supplement s2, p. 14-18).

A comparative experiment was conducted to which pure cholestyramine powder was added. A control experiment to which no cholestyramine was added was conducted in order to monitor the degradation of the bile salts under the colonic conditions used in the assay.

Each experiment was performed in triplicate to account for biological variation.

Fasted stomach

Amounts of formulations A, B and C corresponding to 91 mg of cholestyramine and the pure cholestyramine (91 mg) were dosed to 14 mL fasted stomach liquid medium (pH 1.8). The digests were incubated for 1 hour at 37 °C.

Small intestine

After one hour of stomach incubation, 5.6 mL pancreatic juice (pH 6.8) containing the defined 40:40:20 mixture of bile salts (46.7 mM) was added. The small intestine digests were incubated for 2 hours at 37 °C and samples were taken after 0, 60 and 120 minutes.

Proximal colon

After two hours of small intestine incubation, 42 mL of a full SHIME® matrix (pH 6.0) originated from the ascending colon of a SHIME® system was added. The colon digests were incubated for 24 hours at 37 °C and samples were collected every hour for the first 6 hours and then at 19h and at 24h.

Sample analysis

The concentration of free bile salts in the samples was assessed by means of HPLC. A calibration curve was used to calculate the concentrations of CA, CDCA and DCA in the samples. One mL of each sample was centrifuged for 2 min at 5000 g. 500 µL of the supernatant was mixed with 500 µL of an 80:20 (v:v) mixture of methanol and phosphate buffer, vigorously vortexed, filtered through a 0.2 µm PTFE filter and injected in a Hitachi Chromaster HPLC equipped with a UV-Vis detector. The three bile salts were separated by a reversed-phase C18 column (Hydro-RP, 4 µm, 80 Å, 250 x 4.6 mm, Synergi). The separation was performed under isocratic conditions at room temperature, using a 80:20 (v:v)

mixture of methanol and phosphate buffer as the mobile phase. The analysis was performed at 0.7 mL/min during 23 minutes and the bile salts were detected at 210 nm. The injection volume was set at 20 µL for stomach and small intestine samples and 50 µL for colon samples.

The full SHIME® matrix that was used for the colonic incubations contains (degraded) bile salts originating from BD Difco™ Oxgall, a dehydrated fresh bile extract from bovine origin (Catalog Number 212820). Although the exact composition of this mixture is unknown, a higher quantity of free bile salts might be expected in the colon samples. The values of the background (i.e. blank sample where no mix of bile salts was added) were therefore subtracted from each sample in order to take into account the 'baseline' of free bile salts present in the total SHIME® matrix.

The table below shows the relative concentrations of CA, CDCA and DCA, respectively, after 2 hours of small intestinal incubations ("SI-2") and after 4 hours of colonic incubations ("C-4"), as well as the proportional reduction in the period therebetween.

Formulation	CA			CDCA			DCA		
	SI-2	C-4	Δ	SI-2	C-4	Δ	SI-2	C-4	Δ
Control	1	41	40	3	67	64	19	90	70
Cholestyramine	57	69	12	91	94	3	92	100	8
A	18	59	42	30	83	53	36	100	64
B	19	58	40	25	82	57	36	100	64
C	19	57	39	23	80	57	35	100	65

The relative concentrations of CA, CDCA and DCA (%) vs. incubation time are shown in Figures 2, 3 and 4, respectively. The graphs include the samples taken after 0 hours and 2 hours of small intestinal (SI) incubation, and after 0, 2, 4, 6, 19 and 24 hours of colonic (C) incubation.

The figures confirm the effect and extent of microbial salt metabolism in the gut (e.g. deconjugation, dehydrogenation and dehydroxylation) as observed by the significant decrease in bile salt levels in the control samples to which no cholestyramine was added.

It can be seen that the three formulations offered a protection of the active compound during the small intestinal incubation. Whereas pure (uncoated) cholestyramine led to a reduction of 57% of CA, 91% of CDCA and 92% of DCA already after 2 hours of small intestinal incubation (see the

comparative experiment), formulations A, B and C gave rise to much lower reduction of bile salts during this period. In contrast, the three formulations gave rise to very high removal of the bile salts during the colonic incubation (24 hours). Formulation C, which has the thinnest coating of the three tested formulations and gave rise to more sequestration than formulations A and B in the assay of Example 4, surprisingly did not show more or faster sequestration in the *in vitro* assay than formulations A and B. The sequestration of bile acids after 4 hours of colonic incubation was very similar for the three formulations (57-59% sequestration of CA; 80-83% sequestration of CDCA; and 100% sequestration of DCA).

Example 7

Stability test

Hard capsules comprising formulation C (250 mg cholestyramine) were stored at 25 °C/60% RH during 11 months.

After 0, 3, 6 and 11 months of storage, the capsules were analysed for cholestyramine and water content. Also, the sequestering capacity of the formulation was determined using the assay described in Example 5. The results are shown in the table below.

Analysis	**Units**	**Time (months)**			
		0	3	6	11
Cholestyramine content	mg/capsule	250	247	244	
	% of initial	100	98.8	97.6	
Water content	%	11.9	12.0	12.1	
Sequestration pH 5.5 (6h)	%	12	18	11	11
Sequestration pH 1 (2h) + pH 6.8 (4h)	%	41	32	32	34

CLAIMS

1. An oral formulation for targeted delivery of cholestyramine to the colon, comprising:
   a) a plurality of pellets comprising cholestyramine and
      i. at least 7% w/w of a vinylpyrrolidone-based polymer; or
      ii. a combination of at least 6% w/w of a vinylpyrrolidone-based polymer and at least 2% w/w of an acrylate copolymer; or
      iii. a combination of at least 5% w/w of a vinylpyrrolidone-based polymer and at least 3% w/w of an acrylate copolymer; or
      iv. a combination of at least 6% w/w of a vinylpyrrolidone-based polymer, at least 1% w/w of an acrylate copolymer and at least 10% w/w microcrystalline cellulose; or
      v. a combination of at least 5% w/w of a vinylpyrrolidone-based polymer, at least 2% w/w of an acrylate copolymer and at least 20% w/w microcrystalline cellulose; and
   b) a colon release coating around said pellets.

2. The formulation according to claim 1, wherein the colon release coating is elastic.

3. The formulation according to claim 1 or 2, wherein the colon release coating comprises starch.

4. The formulation according to any one of claims 1 to 3, wherein the starch is resistant starch type 2 (RS2).

5. The formulation according to any one of claims 1 to 4, wherein the colon release coating further comprises poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1.

6. The formulation according to any one of claims 1 to 5, wherein the diameter of the uncoated pellets is from 1000 to 1400 μm.

7. The formulation according to any one of claims 1-6, wherein the uncoated pellets also comprise microcrystalline cellulose.

8. The formulation according to any one of claims 1-7, wherein the uncoated pellets are free from microcrystalline cellulose.

9. The formulation according to any one of claims 1 to 8, wherein the uncoated pellets comprise at least 70% w/w cholestyramine.

10. The formulation according to any one of claims 1 to9, wherein the uncoated pellets comprise at least 80% w/w cholestyramine.

11. The formulation according to any one of claims 1 to 10, wherein the uncoated pellets comprise at least 85% w/w cholestyramine.

12. The formulation according to any one of claims 1 to 11, wherein the cholestyramine content of the final formulation (on dry weight basis) is at least 50% w/w.

13. The formulation according to any one of claims 1 to 12, wherein the cholestyramine content of the final formulation (on dry weight basis) is at least 55% w/w.

14. The formulation according to any one of claims 1 to 13 wherein the amount of coating layer in the final formulation (on dry weight basis) is less than 40% w/w.

15. The formulation according to any one of claims 1 to 14, wherein the amount of coating layer in the final formulation (on dry weight basis) is less than 35% w/w.

16. The formulation according to any one of claims 1 to 15, wherein more than 70% of the cholestyramine is released in the colon.

17. The formulation according to any one of claims 1 to 15, wherein less than 30% of the cholestyramine is released in the small intestine.

18. The formulation according to any one of claims 1 to 17, wherein the formulation is contained within a capsule.

19. The formulation according to any one of claims 1 to 17, wherein the formulation is contained within a sachet.

20. The formulation according to any one of claims 1 to 19 for use in the treatment or prevention of bile acid malabsorption.

21. The formulation for use according to claim 20, wherein the bile acid malabsorption is the result of ileal disease (Crohn's disease), ileal resection or ileal bypass, the result of overproduction of bile acids or defective feedback inhibition of hepatic bile acid synthesis, or the result of cholecystectomy, vagotomy, small intestinal bacterial overgrowth (SIBO), coeliac disease, pancreatic insufficiency (chronic pancreatitis, cystic fibrosis), pancreatic transplant, radiation enteritis, collagenous colitis, microscopic colitis, lymphocytic colitis, ulcerative colitis or irritable bowel syndrome (IBS-D).

22. The formulation according to any one of claims 1 to 19 for use in the treatment or prevention of bile acid diarrhoea.

23. The formulation according to any one of claims 1 to 19 for use in the treatment or prevention of bile acid diarrhoea upon oral administration of an IBAT inhibitor.

24. The formulation according to any one of claims 1 to 19 for use in the treatment or prevention of bile acid diarrhoea upon treatment of a cholestatic liver disease comprising oral administration of an IBAT inhibitor.

25. The formulation for use according to claim 23 or 24, wherein the IBAT inhibitor is

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)-carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; or

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N*'-(carboxymethyl)-carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
or a pharmaceutically acceptable salt thereof.

FIG. 1A

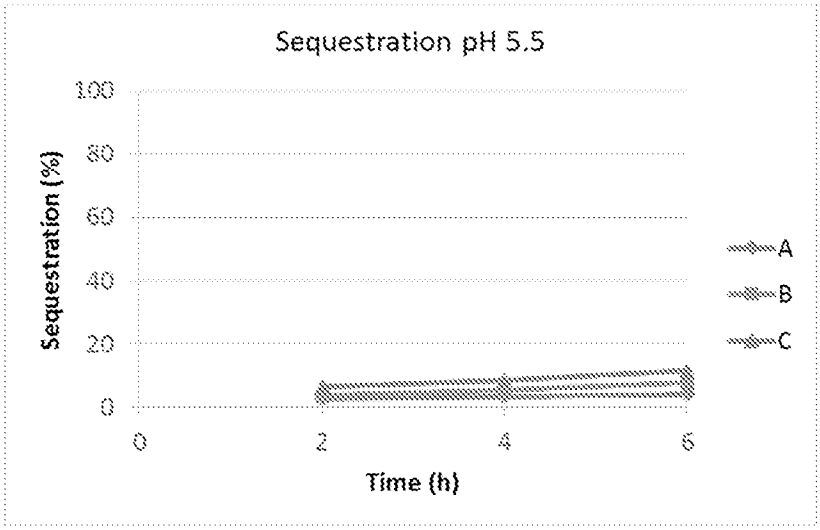


FIG. 1B

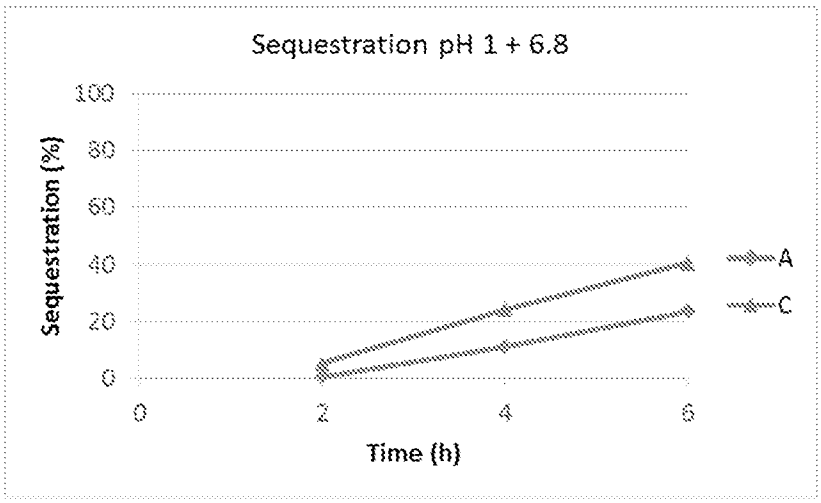


FIG. 1C

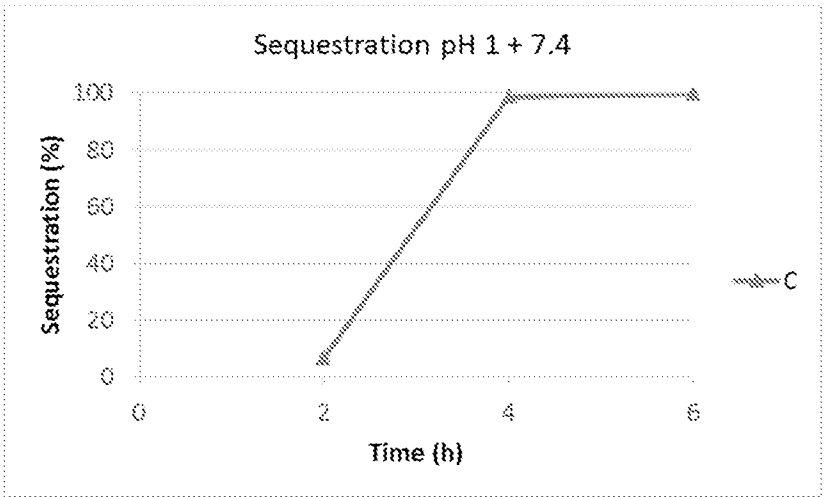


FIG. 2

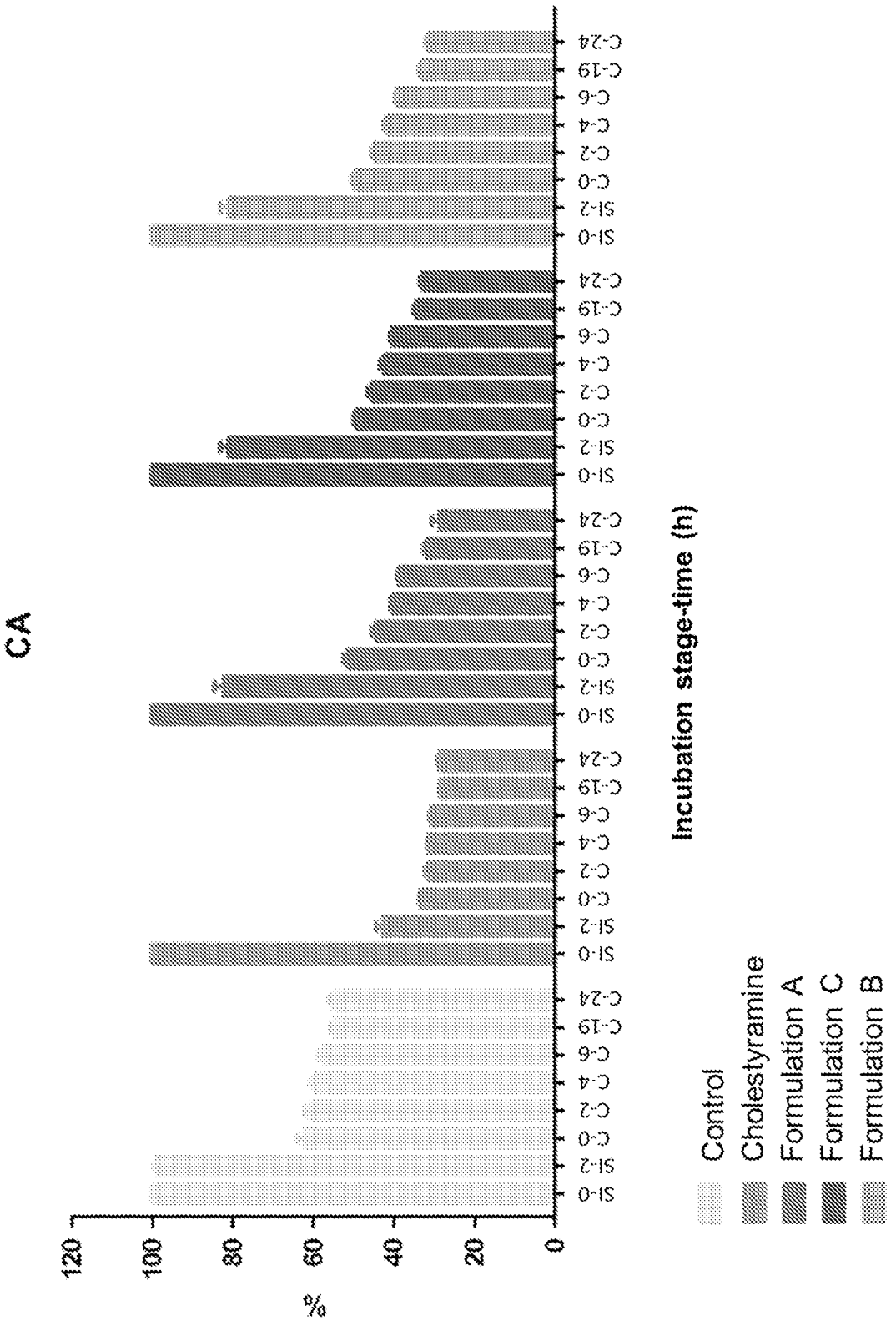

CA
%
120
100
80
60
40
20
0
Incubation stage-time (h)
Control
Cholestyramine
Formulation A
Formulation C
Formulation B
SI-0
SI-2
C-0
C-2
C-4
C-6
C-19
C-24

FIG. 3

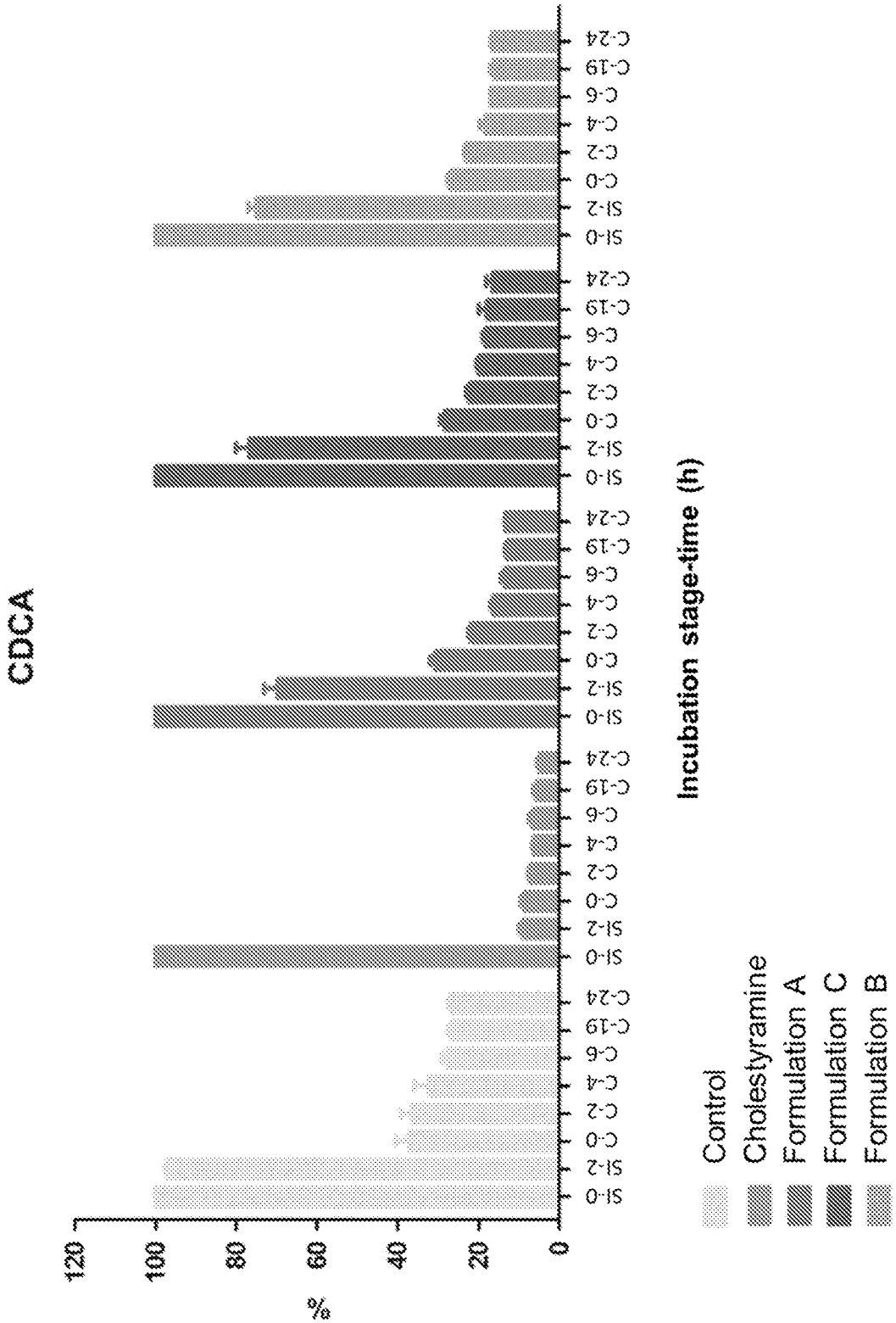
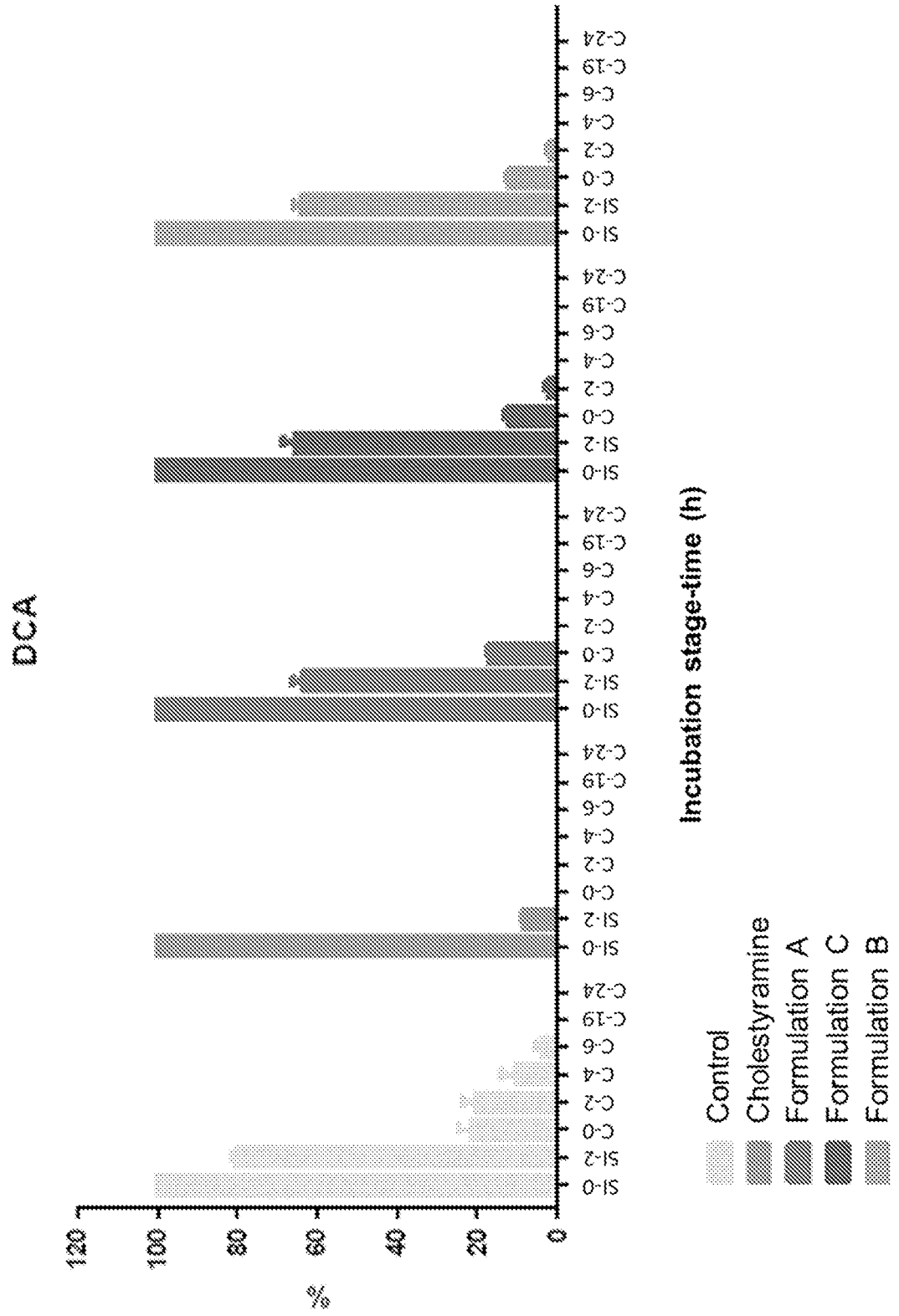

CDCA
%
120
100
80
60
40
20
0
Incubation stage-time (h)
Control
Cholestyramine
Formulation A
Formulation C
Formulation B
Sl-0
Sl-2
C-0
C-2
C-4
C-6
C-19
C-24

FIG. 4



SUBSTITUTE SHEET (Rule 26)

INTERNATIONAL SEARCH REPORT

International application No
PCT/SE2017/050127

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/50 A61K31/554 A61K31/785 A61P3/06 A61P1/12
ADD.

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)
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 practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 April 2017	08/05/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Marchand, Petra

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Form PCT/ISA/210 (second sheet) (April 2005)

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Information on patent family members

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