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(72) Feltaláló(k):
BARONI, Sergio, I-24030 Villa D'adda (IT)
BELLINVIA, Salvatore, 6850 Mendrisio (CH)
VITI, Francesca, 6872 Salorino (CH)

(73) Jogosult(ak):
Nogra Pharma Limited, Dublin 2 (IE)

(74) Képviselő:
Danubia Szabadalmi és Jogi Iroda Kft., Budapest

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(54) **ANTISENSE COMPOSITIONS AND METHODS OF MAKING AND USING SAME**

ANTISENSE-ZUSAMMENSETZUNGEN UND VERFAHREN ZUR HERSTELLUNG UND VERWENDUNG DAVON

COMPOSITIONS ANTISENS ET PROCÉDÉS DE PRÉPARATION ET D'UTILISATION DE CELLES-CI

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(73) Proprietor: **Nogra Pharma Limited**
Dublin 2 (IE)

(72) Inventors:
- **BARONI, Sergio**
  I-24030 Villa d'Adda (IT)
- **BELLINVIA, Salvatore**
  6850 Mendrisio (CH)
- **VITI, Francesca**
  6872 Salorino (CH)

(74) Representative: **Tomkins & Co**
5 Dartmouth Road
Dublin 6 (IE)

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Description

BACKGROUND

[0001] Ulcerative colitis and Crohn's disease are the major forms of chronic inflammatory bowel diseases (IBD) in humans. Intestinal bowel disease is an inappropriate immune response that occurs in genetically susceptible individuals as the result of a complex interaction among environmental factors, microbial factors and the intestinal immune system. It has been demonstrated that the excessive immune response to mucosal antigens inappropriately controlled by the normal counter-regulatory mechanisms leads to chronic intestinal inflammation.

[0002] Crohn's Disease is a chronic, relapsing inflammatory disease of the gastrointestinal tract, characterized by segmental transmural inflammation and granulomatous changes. Typical presentations include the discontinuous involvement of various portions of the gastrointestinal tract and the development of complications including strictures, abscesses or fistulas. Because its cause is unknown, medical management of Crohn's disease is largely empirical and is designed to reduce inflammation. Medical therapy includes corticosteroids, antibiotics, immunosuppressant drugs, and anti-TNFα agents. Due to the therapeutic failures and serious side effects of present therapies, alternatives are needed.

[0003] An important role in the pathogenesis of IBD is played by TGF-ß1, a multifunctional cytokine capable of regulating the growth, differentiation, and function of immune and non-immune cells. A diminished ability to mount an efficient counter-regulatory TGF-ß1 response to inflammatory stimuli is believed to be relevant in the pathogenesis of disease such as IBD. TGF-ß1 acts as a potent negative regulator of mucosal inflammation and that the inhibition of its activity results in the development of colitis which shows immunomorphological similarities with Crohn's disease or ulcerative colitis.

[0004] In the inflamed intestine of patients with IBD there is marked over expression of Smad7 (a protein that serves as substrates for TGF-ß1 receptors) and a reduction of Smad 3 phosphorylation, a crucial step in the TGF-ß1 mediated signal transduction. Thus, in IBD, high levels of Smad7 may lead to a defective TGF-ß1 signaling resulting in an overexpression of pro-inflammatory molecules genes and TGF-ß1 does not exert its anti-inflammatory role.

[0005] Antisense oligodeoxynucleotide drugs are short chains of DNA nucleotides that inhibit protein translation by specifically binding to a small segment of messenger RNA (mRNA) responsible for driving the production of disease-causing proteins. The sequence of an antisense drug is designed to be complementary to its mRNA target such that, upon hybridization, the resulting double-stranded segment is recognized by the cell as abnormal and is destroyed, thereby preventing translation of the message into the protein product.

[0006] Antisense therapeutics, however, are typically administered parenterally which can lead to adverse reactions due to systemic effects. Such administration may also be unable to localize at the site of needed treatment. Therefore, there is a need for a topical-like application of antisense treatments for the treatment of IBD and related diseases using tablet based formulations.

SUMMARY

[0007] This disclosure is directed to pharmaceutical tablet formulations for oral administration of antisense oligonucleotides as set out in the appended claims.

[0008] In an embodiment, a pharmaceutical tablet formulation for oral administration of an antisense oligonucleotide is provided that comprises an intra-granular phase, wherein the intra-granular phase includes an antisense oligonucleotide represented by SEQ ID NO 1, or a pharmaceutically acceptable salt thereof (such as a sodium salt), and a pharmaceutically acceptable filler, and an extra-granular phase, comprising a disintegrant; and an enteric coating comprising an ethylacrylate-methacrylic acid copolymer, wherein when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37°C in a phosphate buffer with a pH of 6.6 not more than about 50% of the amount of the antisense oligonucleotide is released from the pharmaceutical tablet formulation over a period of 30 minutes and when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37°C in diluted HCl with a pH of 1.0 substantially none of the amount of antisense oligonucleotide is released from the pharmaceutical tablet formulation over a period of 120 minutes, and wherein the formulation delivers the antisense compound to the terminal ileum and right colon of a patient.

[0009] Contemplated oligonucleotides include those represented by SEQ ID NO 1, wherein at least one, or in certain embodiments, all, the internucleotide linkages are O, O- linked phosphorothioates.

[0010] The present disclosure provides for a tablet that includes a disclosed antisense oligonucleotide, and comprises an enteric coating. Such a tablet includes a filler, a disintegrant, and may include a lubricant. For example, provided herein is an oral dose form as set out in the claims, such as a tablet, that comprises about 35mg to about 500mg of the antisense oligonucleotide, e.g. 40 mg of an oligonucleotide represented by SEQ ID NO 1 or a pharmaceutically acceptable salt thereof.

[0011] In an embodiment, provided herein is a tablet for oral use comprising: 0.5% to 10% by weight of an antisense

oligonucleotide represented by SEQ ID NO 1 or a pharmaceutically acceptable salt thereof; 30% to 50% by weight mannitol; and 10% to 30% by weight microcrystalline cellulose.

[0012] For example, the disclosure provides a pharmaceutically acceptable tablet for oral use as set out in the claims, comprising an intra-granular phase and extra-granular phase, wherein for example, the intra-granular phase comprises 5% to 10%, by weight (for example about 8% by weight) of an antisense oligonucleotide represented by SEQ ID NO 1 or a pharmaceutically acceptable salt thereof, about 40% by weight mannitol, about 8% by weight microcrystalline cellulose, about 5% by weight hydropropylmethyl cellulose, and about 2% by weight sodium starch glycolate, and for example, the extra-granular phase comprises about 17% by weight microcrystalline cellulose, about 2% by weight sodium starch glycolate, and about 0.4% by weight magnesium stearate, where the tablet comprises an enteric coating.

[0013] Also provided herein are pharmaceutical tablet formulations for use in treating Crohn's disease, ulcerative colitis, and chronic inflammatory bowel disease. The pharmaceutical tablet formulation may be administered to a patient in need thereof. For example, upon orally administering the pharmaceutical tablet formulation, to a patient, the pharmaceutical formulation, substantially delivers the antisense compound to the terminal ileum and right colon of the patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014]

FIGURE 1 depicts the molecular structure of an antisense compound, disclosed herein as AS 1.

FIGURE 2 is a schematic of the manufacturing process for AS 1.

FIGURE 3 is a bar graph depicting the particle size distribution for the 3.5mg dose strength of AS1.

FIGURE 4 is a bar graph depicting the particle size distribution for the 35mg dose strength of AS1.

FIGURE 5 is a bar graph depicting the particle size distribution for the 250mg dose strength of AS1.

FIGURE 6 is a line graph presenting the dissolution profiles (as a percentage of tablet dissolved) for three tablets with different dose strengths of AS1 in three different media (pH 1.0, pH 6.6, and pH 7.2).

FIGURE 7 depicts the dissolution profile of a batch described herein.

DETAILED DESCRIPTION

[0015] The present disclosure is generally directed to pharmaceutical compositions as set out in the claims that include an antisense oligonucleotide, such as that depicted in FIGURE 1. Contemplated compositions include oligonucleotides that act against Smad7, and are administered orally. Disclosed compositions, when administered orally, deliver an effective amount of an antisense oligonucleotide to the intestinal system of a patient, specifically an effective amount of an antisense oligonucleotide is delivered to the terminal ileum and right colon of a patient.

[0016] Contemplated antisense oligonucleotides include those comprising SEQ ID NO: 1 GTC* GCC CCT TCT CCC C*GC AGC, where C* represents 5-methyl-2'-deoxycytidine. In some embodiments, at least one of the internucleotide linkages of a contemplated antisense oligonucleotide is a *O*,*O*-linked phosphorothioate, for example, each of the 20 internucleotide linkages of SEQ ID NO: 1 may be a *O*,*O*-linked phosphorothioate. In some embodiments, contemplated compositions disclosed herein may include a pharmaceutically acceptable salt, e.g. a sodium salt of the antisense oligonucleotide of SEQ ID NO: 1, that optionally may include 1 to 20 *O*,*O*-linked phosphorothioate internucleotide linkages. Contemplated salts of oligonucleotides include those that are fully neutralized, e.g., each phosphorothioate linkage is associated with an ion such as Na^+. Oligonucleotides may include naturally occurring nucleobases, sugars, and covalent internucleoside (backbone) linkages as well as non-naturally occurring portions. An exemplary antisense oligonucleotide, referred herein as AS 1, is shown in FIGURE 1.

[0017] Contemplated herein are compositions suitable for oral delivery of an antisense oligonucleotide specifically tablets, that include an enteric coating, e.g., a gastro-resistant coating, such that the compositions may deliver the antisense compound to the terminal ileum and right colon of a patient. For example, such administration may result in a topical effect, substantially topically applying the antisense compound directly to an affected portion of the intestine of a patient. Such administration, may, in some embodiments, substantially avoid unwanted systemic absorption of the antisense compound.

[0018] For example, a tablet for oral administration is provided that comprises granules (e.g., is at least partially formed from granules) that include a disclosed antisense compound, e.g., AS1, and pharmaceutically acceptable excipients.

Such a tablet is coated with an enteric coating. Contemplated tablets include pharmaceutically acceptable a filler and a disintegrant and may include pharmaceutically acceptable excipients such as lubricants, as well as coloring agents, release agents, coating agents, sweetening, flavoring such as wintergreen, orange, xylitol, sorbitol, fructose, and maltodextrin, and perfuming agents, preservatives and/or antioxidants.

[0019] Contemplated pharmaceutical formulations include an intra-granular phase that includes a contemplated antisense compound, e.g. that depicted in SEQ ID NO. 1, or a pharmaceutically acceptable salt, e.g. AS1, and a pharmaceutically acceptable filler. For example, AS1 and a filler may be blended together, with optionally other excipients, and formed into granules. In some embodiments, the intra-granular phase may be formed using wet granulation, e.g. a liquid (e.g., water) is added to the blended antisense compound and filler, and then combination is dried, milled and/or sieved to produce granules. One of skill in the art would understand that other processes may be used to achieve an intra-granular phase.

[0020] Contemplated formulations include an extra-granular phase, which may include one or more pharmaceutically acceptable excipients, and which may be blended with the intra-granular phase to form a disclosed formulation.

[0021] A disclosed formulation includes an intra-granular phase that includes a filler. Exemplary fillers include, but are not limited to, cellulose, gelatin, calcium phosphate, lactose, sucrose, glucose, mannitol, sorbitol, microcrystalline cellulose, pectin, polyacrylates, dextrose, cellulose acetate, hydroxypropylmethyl cellulose, partially pregelatinized starch, calcium carbonate, and others including combinations thereof.

[0022] In some embodiments, a disclosed formulation may include an intra-granular phase and/or an extra-granular phase that includes a binder, which may generally function to hold the ingredients of the pharmaceutical formulation together. Exemplary binders include but are not limited to, the following: starches, sugars, cellulose or modified cellulose such as hydroxypropyl cellulose, lactose, pregelatinized maize starch, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, low substituted hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl cellulose, sugar alcohols and others including combinations thereof.

[0023] Contemplated formulations, include an intra-granular phase and an extra-granular phase. The formulations of the invention include a disintegrant such as but not limited to, starch, cellulose, crosslinked polyvinyl pyrrolidone, sodium starch glycolate, sodium carboxymethyl cellulose, alginates, corn starch, crosmellose sodium, crosslinked carboxymethyl cellulose, low substituted hydroxypropyl cellulose, acacia, and others including combinations thereof. For example, an intra-granular phase and an extra-granular phase may include a disintegrant.

[0024] In some embodiments, a contemplated formulation includes an intra-granular phase comprising a disclosed antisense compound and excipients chosen from: mannitol, microcrystalline cellulose, hydroxypropylmethyl cellulose, and sodium starch glycolate or combinations thereof, and an extra-granular phase comprising one or more of: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate or mixtures thereof.

[0025] In some embodiments, a contemplated formulation may include a lubricant, e.g. an extra-granular phase may contain a lubricant. Lubricants include but are not limited to talc, silica, fats, stearin, magnesium stearate, calcium phosphate, silicone dioxide, calcium silicate, calcium phosphate, colloidal silicon dioxide, metallic stearates, hydrogenated vegetable oil, corn starch, sodium benzoate, polyethylene glycols, sodium acetate, calcium stearate, sodium lauryl sulfate, sodium chloride, magnesium lauryl sulfate, talc, and stearic acid.

[0026] The pharmaceutical formulation as set out in the claims comprises an enteric coating. Generally, enteric coatings create a barrier for the oral medication that controls the location at which the drug is absorbed along the digestive track. Enteric coatings may include a polymer that disintegrates a different rates according to pH. Enteric coatings may include for example, cellulose acetate phthalate, methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxylpropylmethyl cellulose phthalate, methyl methacrylate-methacrylic acid copolymers, ethylacrylate-methacrylic acid copolymers, methacrylic acid copolymer type C, polyvinyl acetate-phthalate, and cellulose acetate phthalate.

[0027] Exemplary enteric coatings include Opadry® AMB, Acryl-EZE®, Eudragit® grades. In some embodiments, an enteric coating may comprise 5% to 10%, 5% to 20%, 8 to 15%, 8% to 18%, 10% to 12%, or 12 to 16%, of a contemplated tablet by weight. Enteric coatings include an ethylacrylate-methacrylic acid copolymer.

[0028] For example, a tablet is provided that comprises or consists essentially of 0.5% to 70%, e.g. 0.5% to 10%, or 1% to 20%, by weight of an antisense oligonucleotide or a pharmaceutically acceptable salt thereof (e.g. AS1). Such a tablet may include for example, 0.5% to 60% by weight of mannitol, e.g. 30% to 50% by weight mannitol, e.g. about 40% by weight mannitol; and/or 20% to 40% by weight of microcrystalline cellulose, or 10% to 30% by weight of microcrystalline cellulose. For example, a disclosed tablet may comprise a intra granular phase that includes 30% to 60%, e.g. 45% to 65% by weight, or alternatively, 5 to 10% by weight AS1, 30% to 50%, or alternatively, 5% to 15% by weight mannitol, 5% to 15% microcrystalline cellulose, 0% to 4%, or 1% to 7% hydroxypropylmethylcellulose, and 0% to 4%, e.g. 2% to 4% sodium starch glycolate by weight.

[0029] Exemplary formulations include dosage forms that include or consist essentially of 35mg to 500mg of AS1, for example, tablets that include about 35 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 150 mg, 200 mg, or 250 mg of AS 1 are contemplated herein.

[0030] In an exemplary embodiment, a pharmaceutically acceptable tablet for oral administration is provided that

includes an intra-granular phase that may comprise about 50% by weight AS1 (or salt thereof), about 11.5% by weight mannitol, about 10% by weight microcrystalline cellulose, about 3% by weight hydropropylmethylcellulose, and about 2.5% by weight sodium starch glycolate; and an extra-granular phase that may comprise about 20% by weight microcrystalline cellulose, about 2.5% by weight sodium starch glycolate, and about 0.5% by weight magnesium stearate. The tablet also includes an enteric coating as set out in the claims.

[0031] In another exemplary embodiment, a pharmaceutically acceptable tablet for oral administration is provided that includes or consists essentially of: an intra-granular phase that may comprise or consist essentially of 5% to 10%, e.g., about 8% by weight AS1 (e.g. wherein the internucleotide linkages are each O,O-linked phophorothioates, and/or salt thereof, e.g. a sodium salt), about 40% by weight mannitol, about 8% by weight microcrystalline cellulose, about 5% by weight hydropropylmethylcellulose, and about 2.% by weight sodium starch glycolate; and an extra-granular phase that may comprise about 17% by weight microcrystalline cellulose, about 2% by weight sodium starch glycolate, and about 0.4% by weight magnesium stearate.

[0032] Disclosed tablets also include an enteric coating as set out in the claims, e.g., a disclosed tablet may include about 13%, about 15%, 16%, 17% by weight of an enteric coating, e.g. AcyrlEZE®.

[0033] The rate at which point the coating dissolves and the active ingredient is released is its dissolution rate. In an embodiment, a contemplated tablet may have a dissolution profile, e.g. when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in a phosphate buffer with a pH of 7.2, of about 50% to about 100% of the oligonucleotide releasing after about 120 minutes to about 240 minutes, for example after 180 minutes. The contemplated tablet has a dissolution profile, when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37°C in diluted HCl with a pH of 1.0, where substantially none of the oligonucleotide is released after 120 minutes and a dissolution profile, when tested in USP/EP Type 2 apparatus (paddle) at 100 rpm and 37°C in a phosphate buffer with a pH of 6.6, of 10% to 30%, or not more than about 50%, of the oligonucleotide is released after 30 minutes.

[0034] Disclosed formulations, when orally administered to the patient may result in minimal plasma concentration of the oligonucleotide in the patient. Disclosed formulations, when orally administered to a patient, topically deliver to the terminal ileum and right colon of a patient, e.g. to an affected or diseased intestinal site of a patient.

[0035] Also provided herein pharmaceutical tablet formulations as set out in the claims for use in treating Crohn's disease, ulcerative colitis, and/or chronic inflammatory bowel disease.

EXAMPLES

[0036] The examples that follow are intended in no way to limit the scope of this invention but are provided to illustrate the methods of the present invention. Many other embodiments of this invention will be apparent to one skilled in the art.

Example 1 -Tablets

[0037] Wet granules were prepared by dispensing each intra-granular component into an appropriate container. All of the intra-granular materials were screened through a 710μm sieve and blended in a food processor bowl for around 5 minutes. Water granulating fluid was added slowly using a syringe. The wet mass was passed through 2.00mm hand screen and dried in an oven at 40°C for up to 90 minutes. After drying, the granules were screened through 1.00mm hand screen. A mortar and pestle was employed to reduce the size of the coarse granules. The granules were blended with the extra-granular excipients except magnesium stearate using a Turbula blender for 10 minutes at 42rpm. Magnesium stearate was added to the blend and further mixed for 2 minutes at 42rpm. Formulations were compressed on a Manesty F3 single punch compression machine. An overall manufacturing process flow diagram for the AS1 tablets may be seen in FIGURE 2.

[0038] The mannitol based 250mg dose strength formulation made at a 50g batch size had a moisture content of the dry mix of 5.21 % and a moisture content of the dried granules of 6.42%. The mannitol based 250mg dose strength formulation had 5.0g of water added, a granulation time of 4 minutes, and a drying time of 60 minutes.

[0039] The mannitol based 35mg dose strength made at a 100g batch size had a moisture content of 2.35% for the dried granules, 28g of water was added, 6 minutes of granulation time, and had a drying time of 65 minutes.

[0040] The compression IPC results for the mannitol based 250mg dose strength formulations are as follows: average weight of 453.0mg, a hardness of 18.0Kp, a thickness of 3.82mm, a friability of 0.23%, and a disintegration of 17 minutes.

[0041] Table 1A includes tablet compositions for three dose strengths: 3.5mg, 35mg, and 250mg. Tablet weight was 500mg for all formulations.

Table 1A:

Materials	3.5mg (%w/w)	35mg (%w/w)	250mg (%w/w)
Intra-granular			

(continued)

Materials	3.5mg (%w/w)	35mg (%w/w)	250mg (%w/w)
AS1 active	0.7	7.0	50.0
Mannitol	57.8	51.5	11.5
Microcrystalline cellulose	10.0	10.0	10.0
Hydroxypropylmethyl cellulose	6.0	6.0	3.0
Sodium starch glycolate	2.5	2.5	2.5
Extra-granular			
Microcrystalline cellulose	20.0	20.0	20.0
Sodium starch glycolate	2.5	2.5	2.5
Magnesium stearate	0.5	0.5	0.5
Total	100.0	100.0	100.0

Table 1B indicates composition of core batches of these three dose strengths:

Materials %w/w	Batch 1	Batch 2	Batch 3
Batch Size (units)	630	862	376
Intra-granular			
AS1 active	7.0	50.0	62.5 (corrected to potency, equiv. to 40% w/w pure AS1)
Mannitol	51.5	11.5	1.7
Microcrystalline cellulose	10.0	10.0	7.3
Hydroxypropylmethyl cellulose	6.0	6.0	3.0
Sodium starch glycolate	2.5	2.5	2.5
Extra-granular			
Microcrystalline cellulose	20.0	20.0	20.0
Sodium starch glycolate	2.5	2.5	2.5
Magnesium stearate	0.5	0.5	0.5
Total	100.0	100.0	100.0

Example 2 - Powder Characterization

[0042] Formulations were assessed for particle size distribution, density, Carr's index and angle of repose. Particle size analysis indicated that particles are bigger in size (335μm) for 3.5mg dose strength formulation, whereas 35mg and 250mg dose strength formulations exhibited usual particle size distribution. FIGURE 3 depicts the particle size distribution for the 3.5mg dose strength with the composition indicated in Table 1. FIGURE 4 depicts the particle size distribution of the 35mg dose strength with the composition indicated in Table 1. Finally, FIGURE 5 depicts the particle size distribution for the 250mg dose strength with the composition as indicated in Table 1. Table 2 presents the powder characterization results for the three dose strengths.

Table 2:

Properties	**3.5mg**	**35mg**	**250mg**
Angle of repose (°)	39.5	36.5	35.0
Poured bulk density ($g.cm^{-3}$)	.069	0.62	0.63

(continued)

Properties	3.5mg	35mg	250mg
Tapped bulk density ($g.cm^{-3}$)	0.75	0.72	0.72
Carr's compressibility index (%)	8.0	13.9	12.5
Median particle size (μm)	335	219	199

Example 3 - Enteric Coating

[0043] A 20% coating solution was prepared for Acryl-EZE® coatings. The required quantities of water and Acryl-EZE® were dispensed in appropriate containers. While mixing, Acryl-EZE® was added slowly to the vortex. The dispersion was stirred for 45mins and passed through a 500μm sieve. The spraying was continued until a weight gain of 10% or 16% was obtained.

Example 4 - 40 mg Tablets

[0044] A batch formula for 40 mg tables of AS1 is depicted below:

Materials	%w/w	g
Intra-granular		
AS1 active	8.02% (*)	188.66
Mannitol	40.47% (*)	952
Microcrystalline cellulose	8.29%	195
Hydroxypropylmethylcellulose	4.97%	117
Sodium starch glycolate	2.07%	48.75
Extra-granular		
Microcrystalline cellulose	16.58%	390
Sodium starch glycolate	2.07%	48.8
Magnesium stearate	0.42%	9.8
Opadry ® AMB	3.32%	78
AcrylEZE®	13.79%	324.5
Total	100.0	100.0
* Correction to potency is applied to account for API moisture and purity; mannitol is adjusted accordingly.		

Example 5 - 200mg Tablet Formulation

[0045] An AS 1 tablet at 200mg dose strength was manufactured generally following the procedure in Example 1, as shown in Table 4. The tablet weight for all the formulations was 500mg.

Table 4: Composition of the formulation at 200mg dose strength

Materials	200mg Dose Strength (%w/w)
Intra-granular	
AS1 active	62.5
Mannitol	1.7
Microcrystalline cellulose	7.3
Hydroxypropylmethyl cellulose	3.0

(continued)

Materials	200mg Dose Strength (%w/w)
Intra-granular	
Sodium starch glycolate	2.5
Extra-granular	
Microcrystalline cellulose	20.0
Sodium starch glycolate	2.5
Magnesium stearate	0.5

Example 6 - HPLC Dissolution Method

[0046] This analytical test procedure describes a dissolution analysis of AS1 enteric coated tablets by HPLC. Dissolution is preformed following the Ph. Eur. Procedure for delayed release solid dosage forms, using Method A. Apparatus used was Ph. Eur. /USP apparatus 2 (paddle).

[0047] The dissolution conditions for the HPLC are as follows: the media consists of pH 1.0 HCl (120 mins), pH 6.6 (30 mins), pH 7.2 (60 mins); a temperature of 37°C; a rate of 100 rpm; sample to recycle 7.5ml, sample size 0.8ml; sample times 120 min in pH 1.0 HCl, 15, 30 min pH 6.6, 15, 30, 45, 60 min pH 7.2; and a 45μm Disteck in-line filter.

[0048] Media was adjusted in each vessel during the dissolution at each state as follows: the initial volume 750ml pH 1.0 HCl; at 120 mins, 200ml of 0.2 M Na_3PO_4 and 30ml 1.0 M pH 6.7 Na_2HPO_4 was added followed by the adjustment of the pH to pH 6.60±0.05 with 2.0 M NaOH; at 150 mins, followed by the adjustment of the pH to 7.20±0.05 with 2.0 M NaOH.

[0049] The chromatographic conditions are as follows: a Dionex HPLC analytical column, DNAPac-100, 4 x 250 mm; a flow rate of 2.0 ml/min; a column temperature of 80°C; detection of UV at 260nm; an injection volume of 100 μl; a needle wash of water; a mobile phase of A) 10% v/v acetonitrile in 100mM Tris (pH 8.0) and B) 10% v/v acetonitrile in 100 mM Tris and 2M LiCl (pH 8.0); an HPLC run time of 15 mins; and an elution period of AS1 at approximately 6 minutes. The gradient is presented in Table 6.

Table 6:

Time (min)	Flow (ml/min)	%A	%B	Curve
Initial	2.0	70	30	-
6.0	2.0	0	100	6
10.0	2.0	0	100	6
11.0	2.0	70	30	6

[0050] Preparation of 35mg Tablets working standard solutions: 12.5mg of AS1 reference standard was placed into 50ml volumetric flask and dissolved with water to make 50ml solution. 7ml of the solution was diluted with water to make a 50ml solution yielding a final concentration of AS1 of 0.035 mg/ml.

[0051] Preparation of 250mg tablets working standard solutions: 12.5mg of AS1 is placed in a 50ml volumetric flask and dissolved with water to 50ml volume yielding a final concentration of AS1 of 0.25 mg/ml.

[0052] Table 5 presents the dissolution results for the 35mg, 250mg, and 200mg batches, with a 12% weight gain Acryl-EZE® coating. FIGURE 6 is a graph of the dissolution profiles for tablets with three dose sizes of AS 1 formulations in three different mediums.

Table 5:

	% AS1 Dissolved			
Time (min):	**120**	**150**	**180**	**210**
Media:	**pH 1.0**	**pH 6.6**	**pH 7.2**	**pH 7.2**
35mg (batch 1)	0.0	51.0	80.0	81.0
250mg (batch 2)	0.0	62.0	78.0	78

(continued)

	% AS1 Dissolved			
Time (min):	**120**	**150**	**180**	**210**
Media:	**pH 1.0**	**pH 6.6**	**pH 7.2**	**pH 7.2**
200mg (batch 3)	0.0	46.0	97.0	98.0

[0053] Tablets with 16% coating of Acryl-EZE® are made using tablets as described above in Batch 1, and the final coating is conducted until the weight gain of the tablets into the coating pan is 16% of the starting value. FIGURE 7 depicts the dissolution profile.

Example 7 - In vivo oral dosing of AS1

[0054] The objectives of the study were to identify the potential effects of AS 1 on cardiovascular, respiratory, and central nervous systems of conscious, unrestrained, cynomolgus monkeys when administered a single dose by oral administration or intravenous administration. The intravenous administration in this study was included to investigate potential effects associated with systemic exposure. The intravenous dose formulation was administered as bulk powder and for oral administration as enteric coated tablets contained within gelatin capsules. Four experimentally non-naive cynomolgus male monkeys, 3.6 to 3.8 years of age, and weighing 3.4 to 3.9 kg were assigned to a single group.

Table 7:

No. of Animals (male)	Dosing Days	Nominal Dose Level (mg/kg)	Dose Volume (ml/kg)	Dose Concentration (mg/ml)	Dose Route
4	1	0	N/A	N/A	Oral
	4	~13.4-14.9	N/A	N/A	Oral
	7	-87.1-97.1	N/A	N/A	Oral
	12	0	1	0	IV
	14	3		3	IV
	19	10		10	IV

[0055] All dose levels represent the quantity of AS1, corrected for purity. The control oral doses was two capsules containing placebo tablets. Approximate dose level, achieved by administration of two capsules, each containing a tablet with 26.1 mg AS 1 per tablet (corrected for purity), and based on body weights that ranged from 3.5 to 3.9 kg on Day 4. Approximate dose level, achieved by administration of two capsules, each containing tablet with 169.9mg AS1 per tablet (corrected for purity), and based on body weights that ranged from 3.5 to 3.9 kg on Day 4.

[0056] Blood samples for toxicokinetic analysis were collected prestudy and 1 and 6 hours post dose for oral doses and 5 minutes, 1 and 6 hours post dose for intravenous doses. The samples were processed to plasma under refrigerated conditions and the plasma was stored at -70°C until analyzed. The samples were analyzed using the AS 1 specific hybridization assay.

[0057] On Day 1, all animals received the oral control article dose, followed by doses of AS 1 on Days 4 and 7 via oral gavage. For the oral doses, the placebo and AS 1 containing tablets were contained within appropriate size gelation capsules to facilitate administration via the oral route. On Day 12, all animals received the intravenous control dose (phosphate-buffered saline) by slow push injection, followed by intravenous doses of AS 1 on Days 14 and 19.

[0058] Cardiovascular data and body temperature data were recorded via telemetry at frequent intervals prior to and for 24 hours following each dose administration. Respiratory function was assessed by measurement of blood gas parameters in arterial samples collected prior to dosing and 1, 6, and 24 hours following each dose, as well as by determining respiration rate (visually) at those same time points. Neurologic function was assessed by performing a comprehensive neurologic examination of all animals prior to the study within approximately 24 hours after the end of the telemetry recording period following the last oral dose of test article and again within approximately 24 hours after the end of the telemetry recording period following the last intravenous dose. Animals were also observed for clinical signs (mortality/morbidity, cage side observations, food consumption, and body weight).

[0059] Despite a very low LLOQ for the assay (0.5 ng/ml), AS1 was not detected in any plasma samples following oral doses up to nearly 100 mg/kg. In contrast, mean maximum plasma concentrations following IV injections were 28,309 and 180,352 ng/ml for the 3 and 10 mg/kg doses, respectively. Clearance of AS1 from the plasma following IC dosing exhibited kinetics similar to what has been reported for structurally related oligonucleotides (i.e., an approximate 0.5-hour half-life).

Example 8 - 28 Day In-Vivo Study of AS1 Administered Orally

[0060] The purpose of this study was to evaluate the potential toxicity and toxicokinetics of AS 1 when administered once daily orally to mice for 28 days followed by a 28 day recovery period. The AS 1 formulation was prepared as a formulation containing a gastro-protective coating in the form of small coated beads AS 1 was layered onto inert beads which were then coated with Eudragit® S 100 to mimic the oral formulations suitable for human use. Three groups administered different dose levels were used (30 mg/kg/day (low); 100 mg/kg/day; 300 mg/kg/day).

[0061] There were no gender-related differences in plasma or tissue levels. Despite a very low LLOQ for the assay, AS1 was detected in only two plasma samples from very low dose (30 mg/kg/day) animals collected on Day 1 and not in any samples collected on Day 28. At the higher dose levels of 100 and 300 mg/kg/day, AS1 was quantifiable in most plasma samples, and the levels were generally dose related. However, even at the highest dose level, the plasma levels did not exceed 21 ng/ml in any animal (in samples collected at various times between 0.5 and 24 hours post-dose). AS1 concentrations were very high in gastrointestinal (GI) tissues, with mean maximal concentrations at the highest dose level (following the first dose) of approximately 536, 857, 825, 538, 137 and 127 μg/gram of tissue for large intestine, small intestine, forestomach, glandular stomach, esophagus and rectum, respectively.

[0062] Extensive clearance from the GI tract tissues was evident by 24 hours after the first dose. There was no apparent accumulation of AS 1 with daily dosing.

[0063] Maximal mean concentrations in the two major organs of systemic uptake, kidney and liver, following the first dose of 300 mg/kg were only 4.0 and 2.3 μg/gram, which is over 100 times lower than the range of concentrations measured in GI tissues.

[0064] Following the lowest dose of 30 mg/kg, the highest kidney and liver mean concentrations were only 0.4 and 0.3 μg/gram. There was no evidence for accumulation of AS 1 in internal organs over the 28 day dosing period.

[0065] Systemic exposure to AS1 in mice was very low following oral administration of high doses (up to 300 mg/kg/day) of AS1, delivered in gastro-protected formulation and there was no accumulation in GI tissues or internal tissues when administered daily for 28 consecutive days.

Example 9 - Therapeutic effect of AS1 on Colitis

[0066] To examine the therapeutic effect of AS 1 on the course of the intestinal inflammation in the TNBS-induced colitis model, mice were treated with a single dose of AS1 or Smad7 sense oligonucleotide one day following intra-rectal administration of TNBS. Single doses of 125 or 250 μg/mouse ameliorated weight loss and markedly reduced the severity histological manifestations of colitis.

[0067] AS1 (given as a single 125 μg dose one day after TNBS-colitis induction) significantly reduced the colonic production of the monomeric p40 subunit, a component of IL-12 and IL-23 cytokines, demonstrating inhibition of colonic production of these pro-inflammatory cytokines.

[0068] All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

[0069] While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

Claims

1. A pharmaceutical tablet formulation for oral administration of an antisense oligonucleotide comprising:

an intra-granular phase comprising an antisense oligonucleotide represented by SEQ ID NO 1 or a pharma-

ceutically acceptable salt thereof and a pharmaceutically acceptable filler;
an extra-granular phase comprising a disintegrant; and
an enteric coating comprising an ethylacrylate-methacrylic acid copolymer, wherein when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37°C in a phosphate buffer with a pH of 6.6 not more than about 50% of the amount of the antisense oligonucleotide is released from the pharmaceutical tablet formulation over a period of 30 minutes and when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37°C in diluted HCl with a pH of 1.0 substantially none of the amount of antisense oligonucleotide is released from the pharmaceutical tablet formulation over a period of 120 minutes, and
wherein the formulation delivers the antisense compound to the terminal ileum and right colon of a patient.

2. The pharmaceutical tablet formulation of claim 1, wherein the internucleotide linkages of SEQ ID NO 1 are O,O-linked phosphorothioates.

3. The pharmaceutical tablet formulation of claims 1 or 2, wherein the antisense oligonucleotide is the sodium salt of SEQ ID NO 1.

4. The pharmaceutical tablet formulation of any one of claims 1-3, wherein the intra-granular phase further comprises a disintegrant and/or the extra-granular phase further comprises a lubricant.

5. The pharmaceutical tablet formulation of claim 4, wherein the lubricant is sodium starch glycolate.

6. The pharmaceutical tablet formulation of any one of claims 1-5, wherein the filler is mannitol, and/or the disintegrant is sodium starch glycolate.

7. The pharmaceutical tablet formulation of any one of claims 1-6, wherein the intra-granular phase further comprises a component chosen from microcrystalline cellulose, sodium starch glycolate, hydroxypropylmethyl cellulose, and mixtures thereof and/or the extra-granular phase further comprises a component chosen from microcrystalline cellulose and magnesium stearate, and mixtures thereof.

8. The pharmaceutical tablet formulation of any one of claims 1-7 wherein said enteric coating is 8% to 18%, by weight of the tablet.

9. The pharmaceutical tablet formulation of claim 1 comprising:

0.5% to 10% by weight of an antisense oligonucleotide represented by SEQ ID NO 1 or a pharmaceutically acceptable salt thereof;
30% to 50% by weight mannitol; and
10% to 30% by weight microcrystalline cellulose.

10. The pharmaceutical tablet formulation of claim 1 comprising 35mg to 500mg of an antisense oligonucleotide represented by SEQ ID NO 1 or a pharmaceutically acceptable salt thereof.

11. The pharmaceutical tablet formulation of claim 1 comprising:

an intra-granular phase comprising:

5% to 10% by weight antisense oligonucleotide represented by SEQ ID NO 1 or a pharmaceutically acceptable salt thereof;
about 40% by weight mannitol,
about 8% by weight microcrystalline cellulose,
about 5% by weight hydroxypropylmethyl cellulose, and
about 2% by weight sodium starch glycolate; and
an extra-granular phase comprising:

about 17% by weight microcrystalline cellulose,
about 2% by weight sodium starch glycolate, and
about 0.4% by weight magnesium stearate.

12. The pharmaceutical tablet formulation of claim 10, having about 40 mg of the antisense oligonucleotide.

13. The pharmaceutical tablet formulation of any one of claims 1-12 for use in treating Crohn's disease, ulcerative colitis or chronic inflammatory bowel disease.

14. The pharmaceutical tablet formulation of claim 1, wherein the pharmaceutical tablet formulation comprises 0.5% to 70% by weight of an antisense oligonucleotide represented by SEQ ID NO: 1 or a pharmaceutically acceptable salt thereof; 0.5% to 60% by weight mannitol; 20% to 40% by weight microcrystalline cellulose.

15. The pharmaceutical tablet formulation of claim 14, wherein the pharmaceutical tablet formulation comprises 5% to 20% by weight of the enteric coating.

16. The pharmaceutical tablet formulation of claim 14, wherein the pharmaceutical tablet formulation comprises 8% to 18% by weight of the enteric coating.

17. The pharmaceutical tablet formulation of claim 14, wherein the pharmaceutical tablet formulation comprises 8% to 15% by weight of the enteric coating.

18. The pharmaceutical tablet formulation of claim 14, wherein the pharmaceutical tablet formulation comprises 12% to 16% by weight of the enteric coating.

19. The pharmaceutical tablet formulation of claim 14, wherein the pharmaceutical tablet formulation comprises about 13%, about 15%, about 16%, or about 17% by weight of the enteric coating.

Patentansprüche

1. Pharmazeutische Tablettenformulierung zur oralen Verabreichung eines Antisense-Oligonukleotids, welche Folgendes aufweist:

   eine intragranuläre Phase, welche ein Antisense-Oligonukleotid aufweist, welches durch SEQ ID NO 1 oder ein pharmazeutisch verträgliches Salz davon und einen pharmazeutisch verträglichen Füllstoff dargestellt wird; eine extragranuläre Phase, die ein Zerfallsmittel aufweist; und
   einen darmlöslichen bzw. magensaftresistenten Überzug, der ein Ethylacrylat-Methacrylsäure-Copolymer aufweist, wobei bei einem Test in einer USP/EP-Typ 2-Apparatur (Paddle) mit 100 U/min und 37 °C in einem Phosphatpuffer mit einem pH-Wert von 6,6 nicht mehr als ungefähr 50 % der Menge des Antisense-Oligonukleotids aus der pharmazeutischen Tablettenformulierung über eine Periode von 30 Minuten freigegeben wird, und wobei bei einem Test in einer USP/EP-Typ 2-Apparatur (Paddle) bei 100 U/min und 37 °C in gelöstem HCl mit einem pH-Wert von 1,0 im Wesentlichen nichts von der Menge des Antisense-Oligonukleotids aus der pharmazeutischen Tablettenformulierung über eine Periode von 120 Minuten freigegeben wird, und
   wobei die Rezeptur die Antisense-Verbindung zum terminalen bzw. endständigen Ileum und dem rechten Colon eines Patienten liefert.

2. Pharmazeutische Tablettenformulierung nach Anspruch 1, wobei die Internukleotid-Verknüpfungen der SEQ ID NO 1 O,O-verknüpfte Phosphorothioate sind.

3. Pharmazeutische Tablettenformulierung nach Anspruch 1 oder 2, wobei das Antisense-Oligonukleotid das Natriumsalz von SEQ ID NO 1 ist.

4. Pharmazeutische Tablettenformulierung nach Anspruch 1-3, wobei die intragranuläre Phase weiter ein Sprengbzw. Zerfallsmittel aufweist und/oder wobei die extragranuläre Phase weiter ein Gleitmittel aufweist.

5. Pharmazeutische Tablettenformulierung nach Anspruch 4, wobei das Gleitmittel Natriumstärkeglykolat ist.

6. Pharmazeutische Tablettenformulierung nach einem der Ansprüche 1-5, wobei der Füllstoff Mannit ist und/oder wobei das Zerfallsmittel Natriumstärkeglykolat ist.

7. Pharmazeutische Tablettenformulierung nach einem der Ansprüche 1-6, wobei die intragranuläre Phase weiter eine

Komponente aufweist, die aus mikrokristalliner Cellulose, Natriumstärkeglykolat, Hydroxypropylmethylcellulose und Mischungen davon ausgewählt ist und/oder wobei die extragranuläre Phase weiter eine Komponente aufweist, die aus mikrokristalliner Cellulose und Magnesiumstearat und Mischungen davon ausgewählt ist.

8. Pharmazeutische Tablettenformulierung nach einem der Ansprüche 1-7, wobei die magensaftresistente Beschichtung 8 Gewichts-% bis 18 Gewichts-% der Tablette ausmacht.

9. Pharmazeutische Tablettenformulierung nach Anspruch 1, die Folgendes aufweist:

0,5 - 10 Gewichts-% eines Antisense-Oligonukleotids, welches von SEQ ID NO 1 oder einem pharmazeutisch verträglichen Salz davon dargestellt wird;
30 - 50 Gewichts-% Mannit; und
10 - 30 Gewichts-% mikrokristalline Cellulose.

10. Pharmazeutische Tablettenformulierung nach Anspruch 1, die 35 mg bis 500 mg eines Antisense-Oligonukleotids aufweist, welches durch SEQ ID NO 1 oder ein pharmazeutisch verträgliches Salz davon dargestellt wird.

11. Pharmazeutische Tablettenformulierung nach Anspruch 1, die Folgendes aufweist:

eine intragranuläre Phase, die Folgendes aufweist:

5 - 10 Gewichts-% Antisense-Oligonukleotid, welches durch SEQ ID NO 1 oder ein pharmazeutisch verträgliches Salz davon dargestellt wird;
ungefähr 40 Gewichts-% Mannit,
ungefähr 8 Gewichts-% mikrokristalline Cellulose,
ungefähr 5 Gewichts-% Hydroxypropylmethylcellulose, und
ungefähr 2 Gewichts-% Natriumstärkeglykolat; und
eine extragranuläre Phase, die Folgendes aufweist:

ungefähr 17 Gewichts-% mikrokristalline Cellulose,
ungefähr 2 Gewichts-% Natriumstärkeglykolat und
ungefähr 0,4 Gewichts-% Magnesiumstearat.

12. Pharmazeutische Tablettenformulierung nach Anspruch 10, die ungefähr 40 mg Antisense-Oligonukleotid hat.

13. Pharmazeutische Tablettenformulierung nach einem der Ansprüche 1-12 zur Verwendung bei der Behandlung von Morbus Crohn, Colitis ulcerosa oder chronischer entzündlicher Darmerkrankungen.

14. Pharmazeutische Tablettenformulierung nach Anspruch 1, wobei die pharmazeutische Tablettenformulierung 0,5 - 70 Gewichts-% eines Antisense-Oligonukleotids aufweist, welches durch SEQ ID NO: 1 oder ein pharmazeutisch verträgliches Salz davon dargestellt wird; weiter 0,5 bis 60 Gewichts-% Mannit; 20 bis 40 Gewichts-% mikrokristalline Cellulose.

15. Pharmazeutische Tablettenformulierung nach Anspruch 14, wobei die pharmazeutische Tablettenformulierung 5 bis 20 Gewichts-% eines magensaftresistenten Überzugs aufweist.

16. Pharmazeutische Tablettenformulierung nach Anspruch 14, wobei die pharmazeutische Tablettenformulierung 8 bis 18 Gewichts-% des magensaftresistenten Überzugs aufweist.

17. Pharmazeutische Tablettenformulierung nach Anspruch 14, wobei die pharmazeutische Tablettenformulierung 8 bis 15 Gewichts-% des magensaftresistenten Überzugs aufweist.

18. Pharmazeutische Tablettenformulierung nach Anspruch 14, wobei die pharmazeutische Tablettenformulierung 12 bis 16 Gewichts-% des magensaftresistenten Überzugs aufweist.

19. Pharmazeutische Tablettenformulierung nach Anspruch 14, wobei die pharmazeutische Tablettenformulierung ungefähr 13 Gewichts-%, ungefähr 15 Gewichts-%, ungefähr 16 Gewichts-% oder ungefähr 17 Gewichts-% des magensaftresistenten Überzugs aufweist.

Revendications

1. Formule de comprimé pharmaceutique pour l'administration orale d'un oligonucléotide anti-sens, comprenant :

   une phase intra-granulaire comprenant un oligonucléotide anti-sens représenté par SEQ ID NO 1 ou un sel de celui-ci acceptable du point de vue pharmaceutique et une substance de remplissage acceptable du point de vue pharmaceutique ;
   une phase extra-granulaire comprenant un désintégrant ; et
   un revêtement entérique comprenant un copolymère d'acide méthacrylique et d'acrylate d'éthyle, où lors d'un test dans un appareil USP/EP de Type 2 (à pales) à 100 tours/minute et à 37 °C dans un tampon de phosphate ayant un pH de 6,6 pas plus qu' environ 50 % de la quantité d'oligonucléotide anti-sens est libérée par la formule de comprimé pharmaceutique sur une période de 30 minutes, et lors d'un test dans un appareil USP/EP de Type 2 (à pales) à 100 tours/minute et à 37 °C dans du HCl dilué ayant un pH de 1,0 sensiblement aucune quantité d'oligonucléotide anti-sens n'est libérée par la formule de comprimé pharmaceutique sur une période de 120 minutes, et
   où la formule délivre le composé anti-sens à l'iléon terminal et au colon droit d'un patient.

2. Formule de comprimé pharmaceutique selon la revendication 1, dans laquelle les liaisons inter-nucléotides de SEQ ID NO 1 sont des phosphorothioates à liaisons O,O.

3. Formule de comprimé pharmaceutique selon la revendication 1 ou 2, dans laquelle l'oligonucléotide anti-sens est le sel de sodium de SEQ ID NO 1.

4. Formule de comprimé pharmaceutique selon l'une quelconque des revendications 1 à 3, dans laquelle la phase intra-granulaire comprend en outre un désintégrant et/ou la phase extra-granulaire comprend en outre un lubrifiant.

5. Formule de comprimé pharmaceutique selon la revendication 4, dans laquelle le lubrifiant est du glycolate d'amidon sodique.

6. Formule de comprimé pharmaceutique selon l'une quelconque des revendications 1 à 5, dans laquelle la substance de remplissage est du mannitol, et/ou le désintégrant est du glycolate d'amidon sodique.

7. Formule de comprimé pharmaceutique selon l'une quelconque des revendications 1 à 6, dans laquelle la phase intra-granulaire comprend en outre un composant choisi parmi la cellulose microcristalline, le glycolate d'amidon sodique, la hydroxypropyl-méthyl-cellulose et leurs mélanges et/ou la phase extra-granulaire comprend en outre un composant choisi parmi la cellulose microcristalline et le stéarate de magnésium et leurs mélanges.

8. Formule de comprimé pharmaceutique selon l'une quelconque des revendications 1 à 7, dans laquelle le revêtement entérique constitue 8 % à 18 % en poids du comprimé.

9. Formule de comprimé pharmaceutique selon la revendication 1, comprenant :

   0,5 % à 10 % en poids d'un oligonucléotide anti-sens représenté par SEQ ID NO 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique ;
   30 % à 50 % en poids de mannitol ; et
   10 % à 30 % en poids de cellulose microcristalline.

10. Formule de comprimé pharmaceutique selon la revendication 1, comprenant 35 mg à 500 mg d'un oligonucléotide anti-sens représenté par SEQ ID NO 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique.

11. Formule de comprimé pharmaceutique selon la revendication 1, comprenant :

    une phase intra-granulaire comprenant :

    5 % à 10 % en poids d'oligonucléotide anti-sens représenté par SEQ ID NO 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique ;
    environ 40 % en poids de mannitol,
    environ 8 % en poids de cellulose microcristalline,

environ 5 % en poids de hydroxypropyl-méthyl-cellulose, et
environ 2 % en poids de glycolate d'amidon sodique ; et
une phase extra-granulaire comprenant :

environ 17 % en poids de cellulose microcristalline,
environ 2 % en poids de glycolate d'amidon sodique, et
environ 0,4 % en poids de stéarate de magnésium.

12. Formule de comprimé pharmaceutique selon la revendication 10, contenant environ 40 mg de l'oligonucléotide anti-sens.

13. Formule de comprimé pharmaceutique selon l'une quelconque des revendications 1 à 12, pour utilisation dans le traitement de la maladie de Crohn, des rectocolites hémorragiques ou des affections de l'intestin inflammatoires chroniques.

14. Formule de comprimé pharmaceutique selon la revendication 1, dans laquelle la formule de comprimé pharmaceutique comprend 0,5 % à 70 % en poids d'un oligonucléotide anti-sens représenté par SEQ ID NO: 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique ; 0,5 % à 60 % en poids de mannitol ; 20 % à 40 % en poids de cellulose microcristalline.

15. Formule de comprimé pharmaceutique selon la revendication 14, dans laquelle la formule de comprimé pharmaceutique comprend 5 % à 20 % en poids du revêtement entérique.

16. Formule de comprimé pharmaceutique selon la revendication 14, dans laquelle la formule de comprimé pharmaceutique comprend 8 % à 18 % en poids du revêtement entérique.

17. Formule de comprimé pharmaceutique selon la revendication 14, dans laquelle la formule de comprimé pharmaceutique comprend 8 % à 15 % en poids du revêtement entérique.

18. Formule de comprimé pharmaceutique selon la revendication 14, dans laquelle la formule de comprimé pharmaceutique comprend 12 % à 16 % en poids du revêtement entérique.

19. Formule de comprimé pharmaceutique selon la revendication 14, dans laquelle la formule de comprimé pharmaceutique comprend environ 13 %, environ 15 %, environ 16 % ou environ 17 % en poids du revêtement entérique.

FIGURE 1

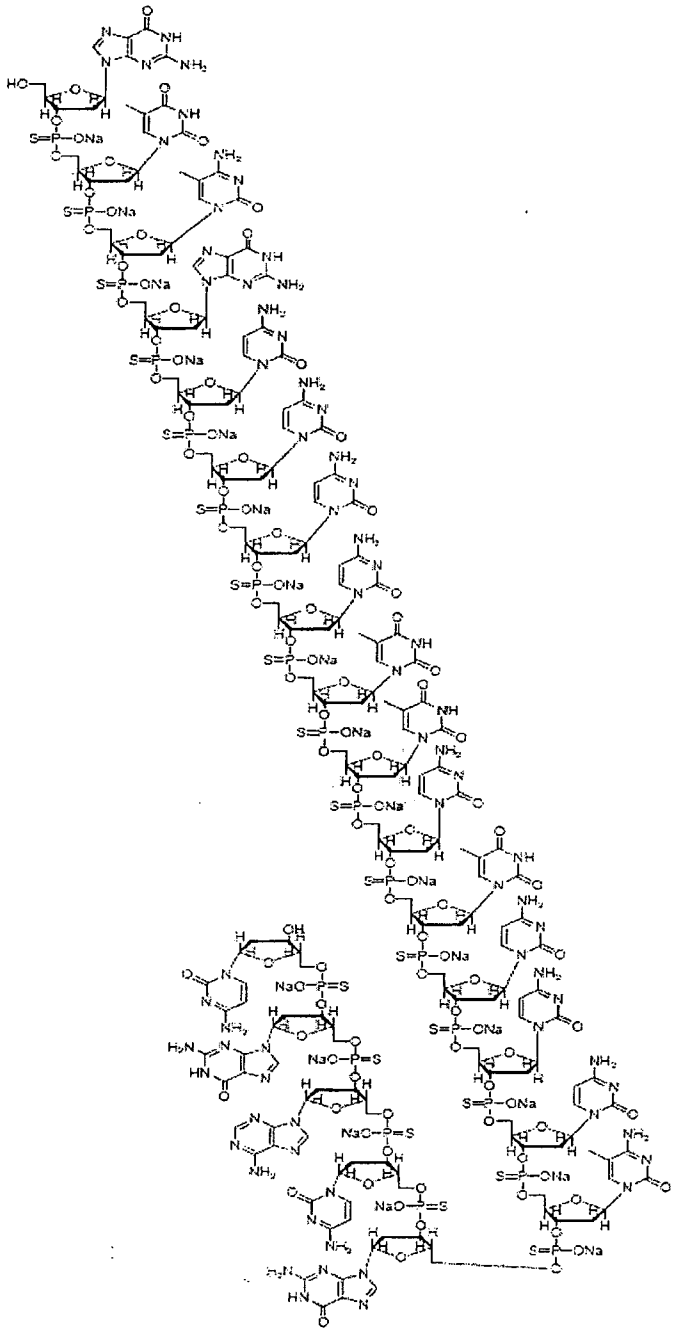


FIGURE 2

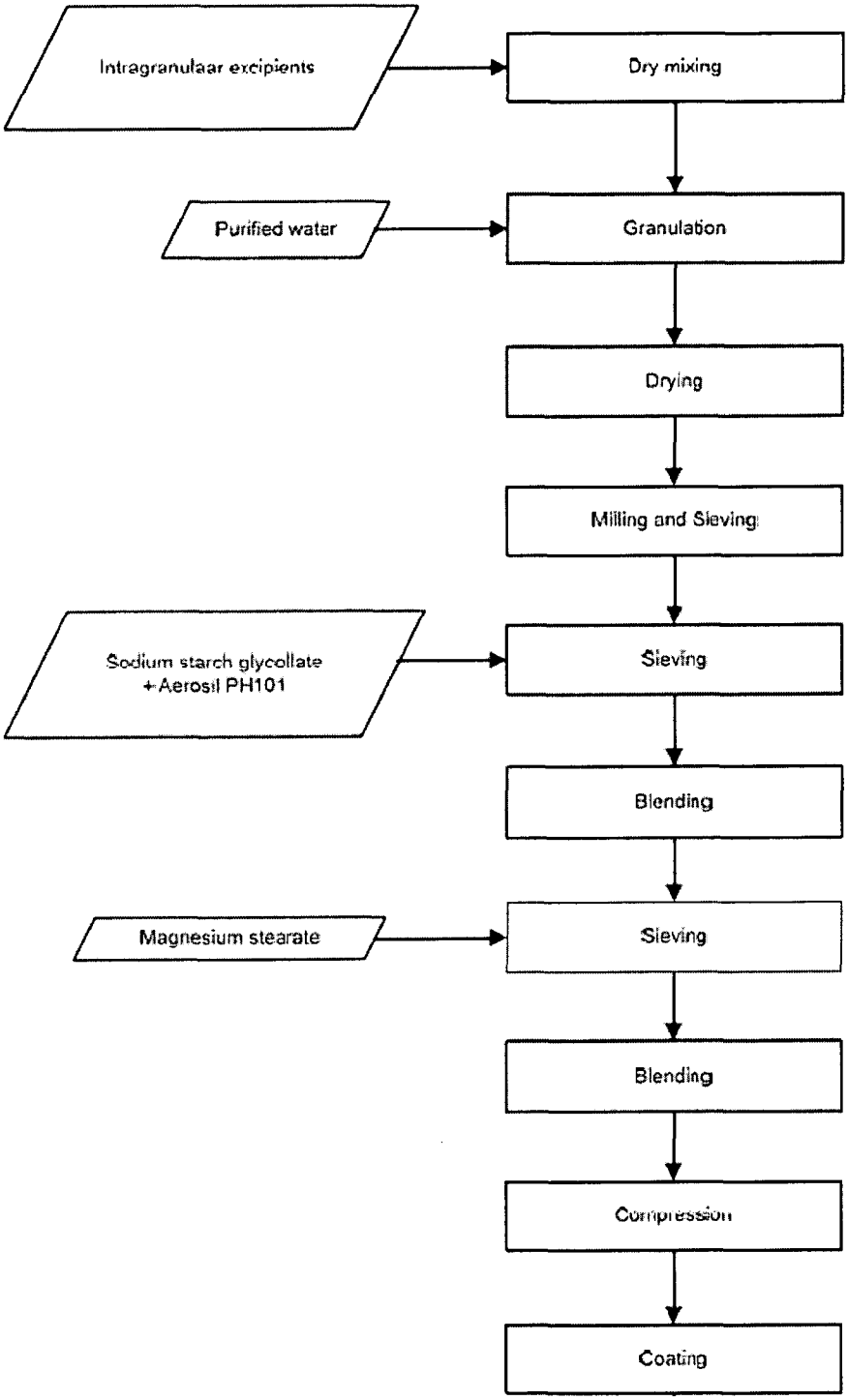

Intragranulaar excipients
Dry mixing
Purified water
Granulation
Drying
Milling and Sieving
Sodium starch glycollate
+Aerosil PH101
Sieving
Blending
Magnesium stearate
Sieving
Blending
Compression
Coating

FIGURE 3

FIGURE 4

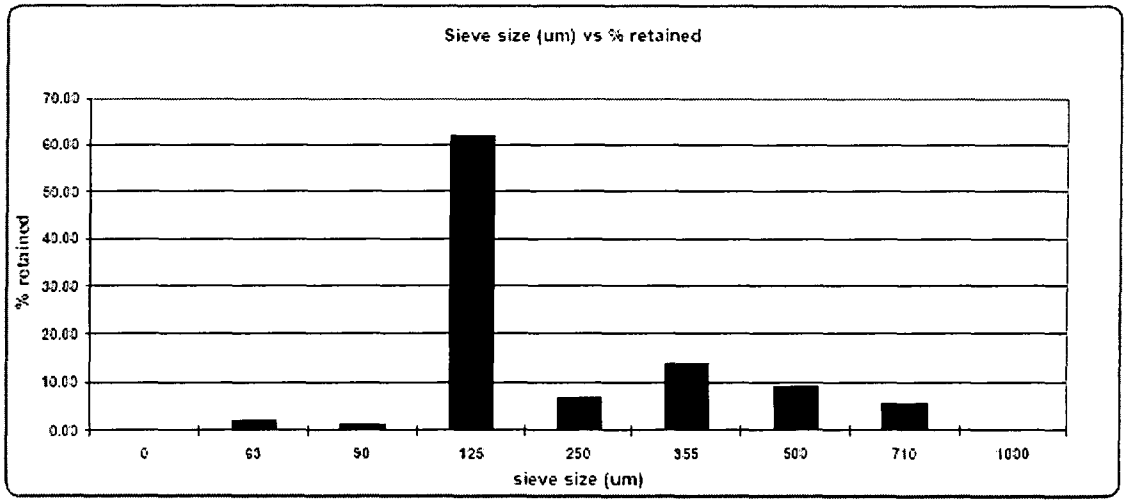


FIGURE 5:

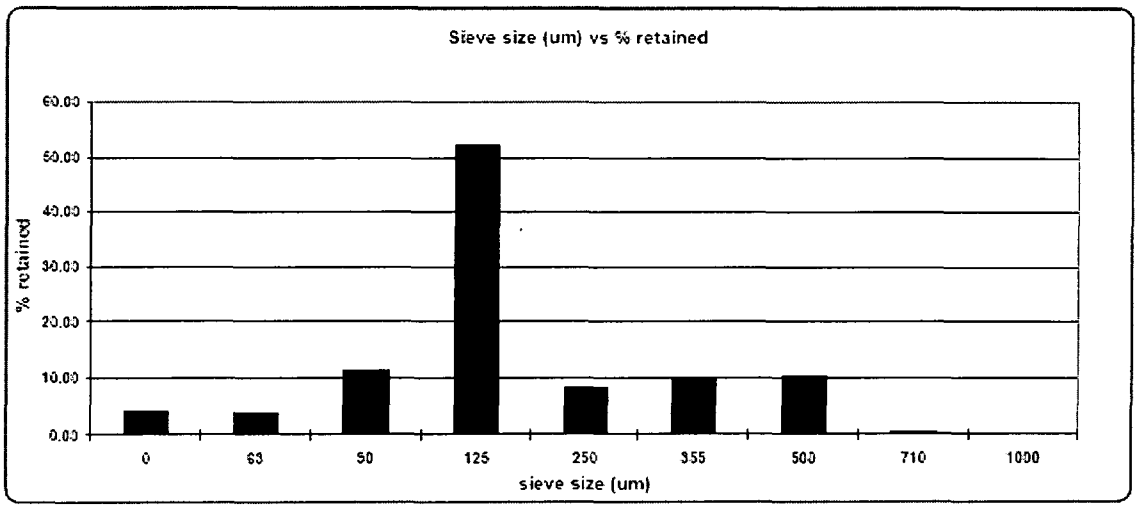


FIGURE 6:

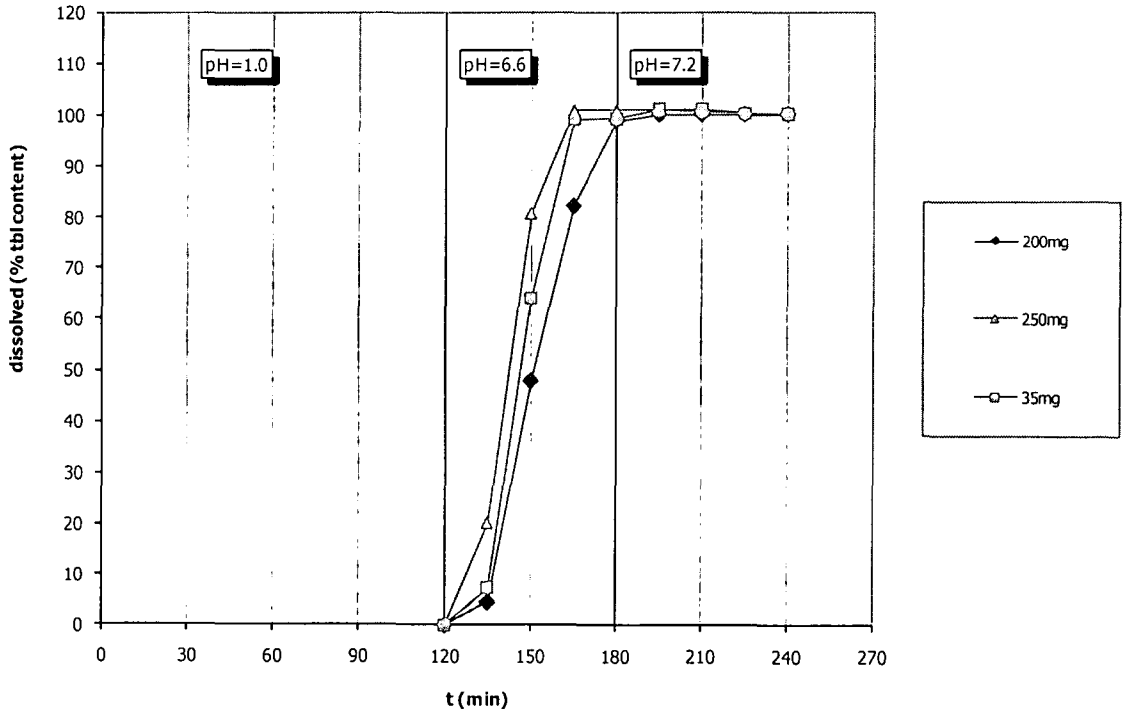
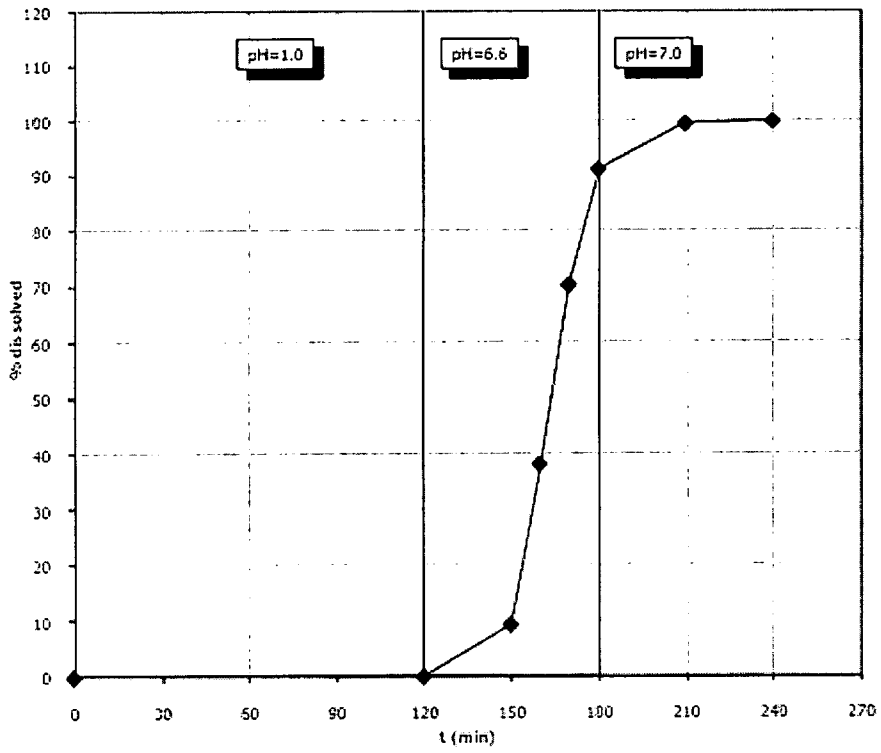


FIGURE 7


pH=1.0
pH=6.6
pH=7.0
% dissolved
t (min)
0
10
20
30
40
50
60
70
80
90
100
110
120
0
30
60
90
120
150
180
210
240
270

ANTISZENSZ KÉSZÍTMÉNYEK ÉS ELJÁRÁSOK ELŐÁLLÍTÁSUKRA ÉS ALKALMAZÁSUKRA

Szabadalmi igénypontok

1. Gyógyászati tablettakészítmény antiszensz oligonukleotid orális beadására, amely tartalmaz:
intragranuláris fázist, amely a SEQ ID NO 1 szerinti szekvenciájú antiszensz oligonukleotidot vagy gyógyászatilag elfogadható sóját és gyógyászatilag elfogadható töltőanyagot tartalmaz,
extragranuláris fázist, amely szétesést elősegítő anyagot tartalmaz, és
bélben oldódó bevonatot, amely etilakrilát-metakrilsav-kopolimert tartalmaz, ahol USP/EP 2-es típusú készülékkel (lapátos, „paddle") 100 rpm-en, 37°C-on, foszfátpufferben, 6,6-os pH-n tesztelve a gyógyászati tablettakészítményből az antiszensz oligonukleotid mennyiségének 50%-a vagy kisebb százaléka szabadul fel 30 perc alatt, és USP/EP 2-es típusú készülékkel (lapátos) 100 rpm-en, 37°C-on, higított HCl-ban, 1,0 pH-n tesztelve a gyógyászati tablettakészítményből az antiszensz oligonukleotid mennyiségének lényegében 0%-a szabadul fel 120 perc alatt, és
ahol a készítmény az antiszensz oligonukleotidot páciens csípőbelének terminális szakaszára és a jobb oldali vastagbelébe juttatja.

2. Az 1. igénypont szerinti gyógyászati tablettakészítmény, ahol a SEQ ID NO 1 szerinti szekvenciában lévő internukleotid kötések O,O-kapcsolt foszforotioátok.

3. Az 1. vagy 2. igénypont szerinti gyógyászati tablettakészítmény, ahol az antiszensz oligonukleotid a SEQ ID NO 1 szerinti vegyület nátriumsója.

4. Az 1-3. igénypontok bármelyike szerinti gyógyászati tablettakészítmény, ahol az intragranuláris fázis szétesést elősegítő anyagot is tartalmaz és/vagy az extragranuláris fázis csúsztatóanyagot is tartalmaz.

5. A 4. igénypont szerinti gyógyászati tablettakészítmény, ahol a csúsztatóanyag nátrium-keményítő-glikolát.

6. Az 1-5. igénypontok bármelyike szerinti gyógyászati tablettakészítmény, ahol a töltőanyag mannit és a szétesést elősegítő anyag nátrium-keményítő-glikolát.

7. Az 1-6. igénypontok bármelyike szerinti gyógyászati tablettakészítmény, ahol az intragranuláris fázis a következők közül választott komponenst is tartalmaz: mikrokristályos cellulóz, nátrium-keményítő-glikolát hidroxipropilmetil-cellulóz és ezek bármilyen keveréke, és/vagy az extragranuláris fázis mikrokristályos cellulóz és magnézium-sztearát és ezek bármilyen keveréke közüli választott komponenst is tartalmaz.

8. Az 1-7. igénypontok bármelyike szerinti gyógyászati tablettakészítmény, ahol a bélben oldódó bevonat a tabletta tömegének 8-18%.

9. Az 1. igénypont szerinti gyógyászati tablettakészítmény, amely tartalmaz:
0,5-10 tömeg% SEQ ID NO 1 szerinti szekvenciájú antiszensz oligonukleotidot vagy annak gyógyászatilag elfogadható sóját,
30-50 tömeg% mannitot és
10-30 tömeg% mikrokristályos cellulózt.

10. Az 1. igénypont szerinti gyógyászati tablettakészítmény, amely tartalmaz 35-500 mg SEQ ID NO 1 szerinti szekvenciájú antiszensz oligonukleotidot vagy annak gyógyászatilag elfogadható sóját.

11. Az 1. igénypont szerinti gyógyászati tablettakészítmény, amely tartalmaz:
intragranuláris fázist, amely:
5-10 tömeg% SEQ ID NO 1 szerinti szekvenciájú antiszensz oligonukleotidot vagy annak gyógyászatilag elfogadható sóját,
mintegy 40 tömeg% mannitot,
mintegy 8 tömeg% mikrokristályos cellulózt,
mintegy 5% hidroxipropilmetil-cellulózt és
mintegy 2 tömeg% nátrium-keményítő-glikolátot tartalmaz, és
extragranuláris fázist, amely
mintegy 17 tömeg% mikrokristályos cellulózt,
mintegy 2 tömeg% nátrium-keményítő-glikolátot és
mintegy 0,4 tömeg% magnézium-sztearátot tartalmaz.

12. A 10. igénypont szerinti gyógyászati tablettakészítmény, amely mintegy 40 mg antiszensz oligonukleotidot tartalmaz.

13. Az 1-12. igénypontok bármelyike szerinti gyógyászati tablettakészítmény Crohn-betegség, fekélyes vastagbélgyulladás vagy krónikus gyulladásos bélbetegség kezelésében történő alkalmazásra.

14. Az 1. igénypont szerinti gyógyászati tablettakészítmény, ahol a gyógyászati tablettakészítmény tartalmaz 0,5-70 tömeg% SEQ ID NO 1 szerinti szekvenciájú antiszensz oligonukleotidot vagy annak gyógyászatilag elfogadható sóját, 0,5-60 tömeg% mannitot, 20-40 tömeg% mikrokristályos cellulózt.

15. A 14. igénypont szerinti gyógyászati tablettakészítmény, ahol a gyógyászati tablettakészítmény 5-20 tömeg% bélben oldódó bevonatot tartalmaz.

16. A 14. igénypont szerinti gyógyászati tablettakészítmény, ahol a gyógyászati tablettakészítmény 8-18 tömeg% bélben oldódó bevonatot tartalmaz.

17. A 14. igénypont szerinti gyógyászati tablettakészítmény, ahol a gyógyászati tablettakészítmény 8-15 tömeg% bélben oldódó bevonatot tartalmaz.

18. A 14. igénypont szerinti gyógyászati tablettakészítmény, ahol a gyógyászati tablettakészítmény 12-16 tömeg% bélben oldódó bevonatot tartalmaz.

19. A 14. igénypont szerinti gyógyászati tablettakészítmény, ahol a gyógyászati tablettakészítmény mintegy 13 tömeg%, mintegy 15 tömeg%, mintegy 16 tömeg% vagy mintegy 17 tömeg% bélben oldódó bevonatot tartalmaz.