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(71) Applicant *(for all designated States except US)*: **COSMO S.P.A.** [IT/IT]; Via Colombo, 1, I-20020 Lainate (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **AJANI, Mauro** [IT/IT]; Via Colombo, 1, I-20020 Lainate (IT). **MORO, Luigi** [IT/IT]; Via Colombo, 1, I-20020 Lainate (IT). **VILLA, Roberto** [IT/IT]; Via Colombo, 1, I-20020 Lainate (IT).

(74) Agents: **MINOJA, Fabrizio** et al.; Bianchetti Bracco Minoja S.R.L., Via Rossini 8, I-20122 Milano (IT).

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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE ORAL ADMINISTRATION OF HEPARIN OR DERIVATIVES THEREOF

(57) Abstract: Pharmaceutical compositions suitable for the oral administration of heparin or derivatives thereof, particularly controlled-release oral pharmaceutical compositions containing heparin with different molecular weight, for the treatment of inflammatory bowel diseases and related conditions, are disclosed.

PHARMACEUTICAL COMPOSITIONS FOR THE ORAL ADMINISTRATION OF HEPARIN OR DERIVATIVES THEREOF

The present invention relates to pharmaceutical compositions suitable for the oral administration of heparin or derivatives thereof for the treatment of inflammatory bowel diseases.

More particularly, the invention relates to controlled-release oral pharmaceutical compositions containing heparin (either unfractioned or low molecular weight heparins) capable of selectively releasing the active ingredient in the intestine.

Chronic inflammatory bowel diseases (IBD), such as ulcerative colitis and Crohn's disease, involve therapeutical problems which have still to be satisfactorily solved. The use of the medicaments available to date, such as aminosalicylates and pro-drugs thereof, steroids, immunosuppressive agents, is often restricted by the important side effects involved as well as by the sometime insufficient effectiveness.

Safer, more effective medicaments than those presently available are therefore particularly needed.

Recently, the use of heparin has been suggested in the IBD parenteral treatment: in fact, although IBD etiology has still to be clarified, its pathogenesis is somewhat clearer, and this can account for the use of heparin in this disease.

In particular, the thrombophilic state frequently observed in ulcerative colitis favours intravasal district coagulation, which is confirmed by the presence of sub-mucosal microthrombosis and by vasculytic phenomena on the mesenteral vessels; furthermore, important inflammatory conditions are

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always present, which can be related with an alteration of both the immune system and the Th1/Th2 balance, which are mediated by interleukins (IL-1), TNF and numerous other pro-inflammatory cytokines.

All these considerations suggest the presence of vascular damage associated with, or consequent to, inflammatory conditions on an immune base, in the pathogenesis of ulcerative colitis.

Clinical studies have confirmed the therapeutical activity of heparin administered parenterally, usually through subcutaneous injection, in the treatment of IBD (Aliment. Pharmacol.Ther. 1997;11:1037-1040; Inflammatory Bowel Diseases, 1997;3(2): 87-94; Gastroenterology, 1996;110:A872; Gastroenterology, 1996;110. A 900; Gastroenterology, 1996;110. A908, Gut, 1995;137(S2):F194; Am. J. Gastroenterol. 1995;90:220-223).

In these clinical studies, heparin was always administered intravenously or subcutaneously, namely through the conventional administration routes of choice for heparins and other glycosaminoglycan derivatives, which usually are not absorbed orally. Studies have been carried out for alternative administration routes to the injective one, such as the oral administration, which is by far suitable for self-medication for use in the antithrombotic therapy. However, heparin and low molecular weight derivatives thereof, when administered orally, are absorbed in insufficient amounts to attain an effective concentration and usually only in the first tract of intestine.

On the other hand, considering the chronic nature of IBD, the oral administration would be much preferable, as the treatment is usually long-term.

Formulations studied to increase heparin absorption in the gastro-intestinal tract are described in WO-A-01/34114 and WO-A-00/48589.

According to the invention, controlled-release formulations containing

heparin or low molecular weight derivatives thereof have now been found, which can be administered through the oral route and are particularly suitable for the treatment of IBD, in that they provide the gradual release of heparin in the intestinal tract in corrispondence with the inflammed intestinal mucosa and therefore a rapid, effective therapeutical response.

The formulations of the invention have also the advantage of preventing or slowing down any degradation and depolymerization of the molecule by the digestive juices, in the first tract of the transit of the medicament to reach the intestinal tract, where its therapeutical action has to be exerted.

The controlled-release compositions of the invention consist of a multi-matrix structure comprising:

a) a matrix consisting of amphiphilic compounds and lipophilic compounds, with melting point lower than 90°C, in which the active ingredient is at least partially englobated;

b) an outer hydrophilic matrix, in which the amphiphilic/lipophilic matrix is dispersed;

c) optionally, other excipients.

"Heparin" herein means both unfractioned heparins of various origin, and low molecular weight heparins, typically ranging from 1,000 to 10,000 Da, such as enoxaparin, fraxiparin, dalteparin, parneparin, their salts and/or derivatives and the like, and other glycosaminoglycans such as heparan sulfates, dermatan sulfates and hyaluronates. Preferably, the compositions of the invention contain optionally salified heparins (sodium or calcium heparin) or low molecular weight heparins.

The compositions of the invention, containing heparin or low molecular weight heparins or other glycosaminoglycans, can be prepared with a method comprising the following steps:

a) First, heparin is embedded in by kneading or mixing or is coated

with amphiphilic compounds, which will be precised below. Mixing can be carried out without using solvents or with small amounts of water-alcoholic solvents.

b) The matrix from a) is added in a low melting lipophilic excipient or mixture of excipients, with heating to soften and/or melt the excipient in which the active ingredient is thus dispersed. The inert matrix resulting from cooling to room temperature can be reduced in size to obtain inert matrix granules containing the active ingredient particles.

c) The granules of inert+amphiphilic matrix are then mixed with one or more hydrophilic excipients which swell in the presence of water, thus increasing their volume to form a hydrated, highly viscous layer in which the solvent progress is slowed down. The mixture of powders and matrix granules is then subjected to compression or compaction so that, when the tablet is contacted with biological fluids, a swollen, highly viscous layer forms, which coordinates the solvent molecules and acts as a barrier against the penetration of the aqueous fluid inside the new structure. Said barrier antagonizes the starting "burst effect" deriving from the dissolution of the medicament present inside the inert matrix, which is in turn inside the hydrophilic matrix.

Amphiphilic compounds for use according to the invention comprise polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidyl-ethanolamine), ceramides, glycol alkyl ethers such as diethylene glycol monomethyl ether (Transcutol®), polyoxyethylated castor oil, polysorbates, phosphoacetylcholine, sodium laurylsulfate, fatty acids sucroesters, polyethylene glycols.

The lipophilic matrix consists of compounds selected from unsaturated and/or hydrogenated fatty acids and salts, esters or amides thereof; fatty acids mono-, di- or triglycerids of polyoxyethylated derivatives thereof, waxes, cholesterol derivatives, long chain alcohols or mixtures thereof, whose

melting point ranges from 40° to 90°C.

If desired, a fatty acid calcium salt dispersed in an hydrophilic matrix prepared with alginic acid can be englobated inside the lipophilic matrix, to markedly increase the hydrophilic matrix viscosity, due to penetration of the solvent until contacting the lipophilic matrix granules dispersed therein.

According to an embodiment of the invention, a pharmaceutical composition for the oral administration of heparin is obtained, by preparing first an inert, amphiphilic matrix with high content in heparin, typically ranging from 5 to 95% w/w, through dispersion of heparin in amphiphilic compounds, such as lecithin, other polar lipids of type II, surfactants or diethylene glycol monoethylene; the resulting mixture is then mixed or kneaded, usually while hot, with lipophilic compounds suitable to form an inert matrix, for example saturated or unsaturated fatty acids, such as palmitic, stearic, myristic or oleic acids, cetyl alcohol, glyceryl behenate, glyceryl palmitostearate, or mixtures thereof with other fatty acids having shorter chain, or salts or derivatives of the cited fatty acids, alone or in combination with waxes, ceramides, cholesterol derivatives or other apolar lipids in various ratios, selected so that the melting or softening points of the lipophilic compounds mixtures range from 40° to 90°C.

The resulting lipophilic/amphiphilic matrix is then reduced into granules by an extrusion and/or granulation process, or by other known processes which keep the macro-homogeneous matrix dispersion structure of the starting mix.

The hydrophilic matrix to add subsequently consists of hydrogels, i.e. substances which, when passing from the anhydrous to the hydrated state, undergo the so-called molecular relaxation, characterized by a marked increase in volume and weight following coordination of a large number of water molecules by the polar groups present in the polymeric chains of the

hydrogels.

Examples of hydrogels for use according to the invention are compounds selected from acrylic or methacrylic acids polymers or copolymers, alkyl vinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celuloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid.

Hydrophilic compounds having bio-adhesive properties can further be used advantageously.

The granules of lipophilic/amphiphilic matrix containing the active ingredient are mixed with the above cited hydrophilic compounds in weight ratios typically ranging from 100:0.5 to 100:20 (lipophilic matrix: hydrophilic matrix). Part of the heparin can optionally be mixed with the hydrophilic compounds to obtain compositions in which the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or mini-matrices.

The compression of the mixture consisting of lipophilic/amphiphilic matrix, hydrogel-forming compound and optional active ingredient not embedded in the lipophilic matrix, as well as any functional excipients, produces a structure macroscopically homogeneous throughout its volume, namely a matrix containing a dispersion of the lipophilic and amphiphilic granules in a hydrophilic matrix.

Oral solid forms such as tablets, capsules, matrix granules or mini-matrices obtainable according to the invention can be optionally subjected to conventional coating processes with gastro-resistant films, such as methacrylic acids polymers (Eudragit®) or cellulose derivatives, such as cellulose acetophthalate and hydroxypropyl methylcellulose phthalate.

The compositions of the invention ensure the controlled release of the heparin or heparin derivative into the last part of small intestine and colon,

wherein the antithrombotic, antiinflammatory, immunomodulating and endothelium-regulating activities of heparin on the intestinal mucosa and sub-mucosa provide an effective treatment of both active phases and relapses of ulcerative colitis, Chron's disease, sigmoiditis, proctitis and aspecific bowel inflammatory diseases.

For the envisaged therapeutical uses, suitable doses of heparin can range from 5 to 1000 mg per single administration, one to three times a day, with a daily dosage preferably ranging from 5 to 1000 mg.

The following examples illustrate the invention in greater detail.

Examples 1-7

Heparin tablets for the controlled-release in the colon

Quali-quantitative composition for each tablet

Components	Um	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7
Active ingredient								
Unfractioned heparin	mg	50	150	250	500	700	85	1000
Lipophilic component								
Cetyl alcohol	mg	15				20		
Stearic acid	mg		65					140
Glyceryl behenate	mg			100				
Hydrogenated castor oil	mg				54			
Glyceryl palmitostearate	mg						12	
White wax	mg							10
Carnuba wax	mg					20	1	
Amphiphilic component								
Soy lecithin	mg	10						
Phosphoacetylcholine			10					
Sodium laurylsulfate				25				10
Polysorbate					10		1	10
Poe castor oil						15	1	
Hydrophilic polymer								
Sodium carboxymethylcellulose	mg	50				10		
Hydroxypropyl methylcellulose	mg		150				20	
Hydroxypropyl cellulose	mg			200				200
Hydroxyethyl cellulose	mg				168			
Hydroxymethyl cellulose	mg					200		
Glidant								
Talc	mg	10	12	10	15	15	1. 5	20
Anhydrous colloidal silica	mg	20	28	10	5	5	0. 5	10
Lubricant								
Magnesium stearate	mg	10	10	10			1	15
Hydrogenated castor oil	mg				30	30	2	
Diluent								
Mannitol	mg	550						
Mocrocrystalline cellulose	mg		225		200			
Lactose monohydrate	mg			345				
Dibasic calcium phosphate	mg		200		218			
Calcium carbonate	mg					150		
Coating								
Acrylic polymers	mg	32	32	32	32	32	3. 2	32
Talc	mg	15	15	15	15	15	1. 5	15
Triethyl citrate	mg	3. 2	3. 2	3. 2			0. 3	3. 2
Dibutyl phthalate	mg				3. 2	3. 2		
Titanium dioxide	mg	6	6	6	6	6	0. 6	6
Iron oxide	mg	3	3	3	3	3	0. 3	3
Polyethylene glycol 600	mg	1	1	1	1	1	0. 1	1

Examples 8-14

Heparin tablets for the controlled-release in the colon

Examples 8-14

Quali-quantitative composition per each tablet

Components	Um	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12	Ex. 13	Ex. 14
Active ingredient								
LMW heparin (MW range 2000-10000)	mg	100	15	250	500	700	8. 5	1000
Lipophilic component								
Cetyl alcohol	mg	50				20		
Stearic acid	mg		6. 5					140
Glyceryl behenate	mg			100				
Hydrogenated castor oil	mg				54			
Glyceryl palmitostearate	mg						1. 2	
White wax	mg							10
Carnauba wax	mg					20	0. 1	
Amphiphilic component								
Soy lecithin	mg	10						
Phosphoacetylcholine			1					
Sodium laurylsulfate				25				10
Polysorbate					10		0. 1	10
Poe. castor oil						15	0. 1	
Hydrophilic polymer								
Sodium carboxymethylcellulose	mg	50				10		
Hydroxypropyl methylcellulose	mg		15				2	
Hydroxypropyl cellulose	mg			200				200
Hydroxyethyl cellulose	mg				168			
Hydroxymethyl cellulose	mg					200		
Glidant								
Talc	mg	10	1. 2	10	15	15	0. 15	20
Anydrous colloidal silica	mg	20	2. 8	10	5	5	0. 05	10
Lubricant								
Magnesium strearate	mg	10	1	10			0. 05	15
Hydrogenated castor oil	mg				30	30	0. 2	
Diluent								
Mannitol	mg	550						
Microcrystalline cellulose	mg		22. 5		200			
Lactose monohydrate	mg			345				
Dibasic calcium phopshate	mg		20		218			
Calcium carbonate	mg					150		
Coating								
Acrylic polymers	mg	32	3. 2	32	32	32	0. 32	32
Talc	mg	15	1. 5	15	15	15	0. 15	15
Trietyl citrate	mg	3. 2	0. 3	3. 2			0. 05	3. 2
Dibutyl phthalate	mg				3. 2	3. 2		
Titanium dioxide	mg	6	0. 6	6	6	6	0. 06	6
Iron oxide	mg	3	0. 3	3	3	3	0. 03	3
Polyethylene glycol 600	mg	1	0. 1	1	1	1	0. 02	1

Example 15

2 Kg of sodium Parnaparin are mixed with 100 g of stearic acid, 150 g of sodium laurylsulfate and 40 g of magnesium stearate before being compacted by compression. The resulting slugs are forced through a granulator fitted with a mesh screen suited to break the compacted granules to 2 mm maximum size; then 500 g of hydroxypropyl methylcellulose, 1000 g of microcrystalline cellulose, 1000 g of lactose, 130 g of colloidal silica and 80 g of magnesium stearate are added. After thoroughly mixing, the powders are tabletted with a biconvex tooling to unitary weight of about 500 mg. The resulting cores are then placed in a coating pan and coated with a gastro-protective film containing methacrylic copolymers of type A and B, titanium dioxide, talc, triethyl citrate, iron oxides and polyethylene glycol. The resulting tablets showed the characteristic slow dissolution profile, releasing the active ingredient linearly and progressively in about 8 hours.

Example 16

1.2 Kg of sodium Parnaparin are mixed with 50 g of stearic acid, 100 g of sodium cholate and kneaded with a solution containing an acrylic polymer. After granulation through a 3 mm screen and subsequent drying, 200 g of high viscosity hydroxypropyl methylcellulose, 50 g of carboxyvinyl polymer, 500 g of lactose, 500 g of microcrystalline cellulose, 80 g of colloidal silica and 70 g of magnesium stearate are added. After thoroughly mixing, the powders are tabletted to unitary weight of about 250 mg using a rotary tabletting machine. The resulting cores, after gastro-resistent film-coating with acrylic copolymers of type A and B, titanium dioxide, talc, triethyl citrate, iron oxides and polyethylene glycol, showed a progressive dissolution curve in simulated enteral juice with about 30% of active ingredient released in the first 2 hours, and at least 80% in the first 8 hours.

Example 17

600 g of sodium Parnaparin are mixed with 20 g of stearic acid, 10 g of wax, 25 g of soy lecithin and kneaded with a solution containing a medium-viscosity cellulose derivative. After granulation through a 2 mm screen and subsequent drying, 200 g of sodium carboxymethyl cellulose, 400 g of lactose, 550 g of microcrystalline cellulose, 50 g of colloidal silica and 30 g of magnesium stearate are added. After thoroughly mixing, the powders are tabletted to unitary weight of about 200 mg using a rotary tabletting machine. The resulting cores, after gastro-resistent film-coating with acrylic copolymers of type A and B, titanium dioxide, talc, triethyl citrate, iron oxides and polyethylene glycol, showed a progressive dissolution curve in simulated enteral juice with less than 40% of active ingredient released in the first 2 hours, and at least 80% in the first 8 hours.

CLAIMS

1. Oral pharmaceutical compositions for the controlled release of heparin or derivatives thereof, comprising:

a) a matrix consisting of amphiphilic compounds and lipophilic compounds with melting point lower than 90°C in which the active ingredient is at least partially dispersed;

b) an outer hydrophilic matrix in which the lipophilic/amphiphilic matrix is dispersed;

c) optionally, other excipients suitable for solid pharmaceutical forms.

2. Compositions as claimed in claim 1, wherein the amphiphilic compounds are polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolamine), ceramides, glycol alkyl ethers such as diethylene glycol monomethyl ether (Transcutol®), polyoxyethylenated castor oil, sodium laurylsulfate, polysorbates, phosphoacetylcholine.

3. Compositions as claimed in claim 1 or 2, wherein the lipophilic matrix consists of compounds selected from unsaturated and/or hydrogenated fatty acids, the salts, esters or amides thereof, fatty acids mono-, di- or triglycerids, polyoxyethylated derivatives thereof, waxes, cholesterol derivatives, long chain aliphatic alcohols.

4. Compositions as claimed in any one of claims 1 to 3, wherein the hydrophilic matrix consists of hydrogel-forming compounds.

5. Compositions as claimed in claim 1, wherein the hydrophilic matrix consists of compounds selected from acrylic or methacrylic acids polymers or copolymers, alkyl vinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, natural or synthetic gums.

6. Compositions as claimed in any one of the above claims, in the solid

form with gastro-resistant coating.

7. Compositions as claimed in claim 6, wherein the gastro-resistant coating consists of methacrylic acid polymers or cellulose derivatives.

8. Compositions as claimed in any one of claims 1 to 7, wherein the active ingredient is contained entirely in the inert/amphiphilic matrix and the pharmaceutical form to administer is in the form of tablets, capsules or mini-matrices.

9. Compositions as claimed in any one of claims 1 to 8, wherein the active ingredient is dispersed both in the hydrophilic matrix and in the lipophilic/amphiphilic matrix, in the form of tablets, capsules or mini-matrices.

10. Compositions as claimed in any one of the above claims, wherein the compounds which form the hydrophilic matrix have bio-adhesive properties.

11. Compositions as claimed in any one of the above claims, wherein the active ingredient is selected from heparin, sodium heparin, calcium heparin, sodium parnaparin, heparin with molecular weight ranging from 1,000 to 10,000 Da, heparan sulfates, dermatan sulfates, hyaluronates.

12. Compositions according to claim 11, wherein the active ingredient is sodium parnaparin.

13. A process for the preparation of the compositions of claims 1 to 12, which comprises:

a) kneading or mixing the heparin with the inert and amphiphilic compounds in the absence of solvents or in water-alcoholic solvents;

b) mixing the granules from step a) with the hydrophilic excipients and subsequent compression and compaction;

c) optionally, gastro-protective film-coating of the oral solid forms from step b).

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/28 A61K9/20 A61K31/727 A61K31/728

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 48589 A (MARTIN MARY L ;CUMMING KENNETH IAIN (IE); EMISPHERE TECH INC (US)) 24 August 2000 (2000-08-24) page 25; table 10 claims 1-11	1-13
A	WO 00 76481 A (CIP NINETY TWO 92 S A ;AJANI MAURO (PA); VILLA ROBERTO (PA); FOSSA) 21 December 2000 (2000-12-21) page 7; example 1 claim 1	1-13

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

☒ Patent family members are listed in annex.

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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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Muller, S

INTERNATIONAL SEARCH REPORT

Information on patent family members

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