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(54) Title: CONTROLLED RELEASE ORAL SOLID FORMS CONTAINING MESALAZINE AS ACTIVE AGENT

(57) Abstract: The invention discloses a composition and a method for producing oral solid mesalazine forms with controlled release for the administration of said active agent into the colon.

# CONTROLLED RELEASE ORAL SOLID FORMS CONTAINING MESALAZINE AS ACTIVE AGENT

## Field of the invention

Controlled release oral solid forms for the administration of mesalazine into the colon consist of capsules filled with mesalazine-containing cores; said cores are singularly provided with a coating layer soluble at pH > 6.5 which is thinner than formulations of the prior art.

## State of the art

The use of mesalazine (5-amino-salicylic acid) in the treatment of Crohn's disesase or irritable bowel syndrome has been known for a long time. It is desirable that the administration of said active agent is intended for the region concerned by said pathology, so as to provide and control the optimal local concentration and also to avoid systemic side effects. To this purpose mesalazine formulations have been developed in recent years, which are provided with particular coatings releasing the active agent only in the desired area.

Anionic polymers have been used for several years to coat tablets and other forms for oral administration with delayed or controlled release of the active agent. In particular, the use of copolymers of methacrylic acid and of its methyl ester have been known to this purpose since 1974. Said copolymers are available as Eudragit L and Eudragit S. Eudragit L dissolves at pH values higher than 5.5, whereas Eudragit S dissolves at pH values higher than 7.

Patent application no. EP 0 040 590 describes oral pharmaceutical preparations which can release the drug selectively into the colon. The active agent is coated with a 3-60 μm layer of a mixture of an acrylic anionic polymer soluble at pH 5.5 such as for instance Eudragit L, in amounts between 10% and 85%, and of an acrylic polymer substituted by quaternary ammonium, insoluble in water, such as for instance Eudragit RS or RL, in amounts between 15% and 90%. Mesalazine is listed among the active agents.

Patent no. EP 0 097 651 relates to a solid form for oral administration, such as a capsule or a tablet, containing a pharmacologically active agent for the treatment of colon pathologies, such as for instance mesalazine. Said solid form is coated with an anionic polymer, insoluble both in the stomach and in the small intestine

where pH is lower than 7, though soluble in the large intestine where pH is higher than 7. The preferred polymer is reported to be Eudragit S. The coating should have such a thickness to allow the solid form to reach the colon in its whole state and to dissolve only there. Such thickness should therefore be of at least 60 μm. The coating is applied onto the finished form and not necessarily on the single particles it contains.

Patent no. EP 0 572 486 claims an oral form suitable for the selective administration of a drug into the intestine, comprising a plurality of granules of active agent within a capsule. Both the granules and the capsule are coated with the same or different materials which are soluble in the intestine, and in particular in the ileum or colon depending on the coating. This patent makes reference to EP 0 097 651, already discussed above, and states that the new system is advantageous with respect to the one described in said patent since it enables a more gradual release of mesalazine into the colon, thus avoiding possible local irritations due to a too rapid release. Both Fig. 1 and Example 2 of this patent point out that granules should be protected by a layer corresponding to 16% of their weight (as dry substance) in order to obtain the desired effect.

Patent no. IT 1246382 includes various sustained release formulations for oral administration with controlled release. In particular, it describes compositions coated with a membrane whose solubility is pH-dependant, such as Eudragit S, and with an insoluble membrane, though permeable to intestinal fluids such as for instance ethyl cellulose. In order to obtain the desired effect both membranes should be applied one after the other, because using a mixture of both components to coat the active agent would result in a too rapid dissolution of the solid form in the colon.

Patent application no. EP 0 629 398 relates to pharmaceutical compositions which can provide a controlled release of the active agent into the desired zone of the intestinal tract (duodenum, small intestine, colon, rectum) by a suitable choice of coatings, and also controlling the dissolution rate of said drug. Eudragit L and Eudragit S are quoted among the large number of coatings taken into consideration.

Patent EP 0 658 103 claims pearls having a fungicidal action, characterized in that

they consist of a core with a diameter of 600-700 μm, which is coated in its turn with a layer of hydrophilic polymer, the latter being in its turn coated with a layer of "seal-coating" polymer. The preparation of said pearls consists in spraying a 600-700 μm sugar sphere with a solution of the fungicide and of the hydrophilic polymer in an organic solvent, and after a drying phase the granule thus obtained is sprayed with a solution of the "seal-coating" polymer. The latter is polyethylene glycol 20.000 and its purpose is to avoid that the pearls stick one to the other. Hydroxypropylcellulose and Eudragit E are quoted among hydrophilic polymers.

Patent application no. WO 96/36321 relates to formulations with controlled release of bisacodile in an administration form without edges (sphere or ellipsis) coated with two overlapping layers, one of a polymer soluble at pH = 5-6.1, the other one of a polymer soluble at pH = 6.8-7.2.

**Summary of the invention**

An oral solid formulation for the selective administration of mesalazine into the colon has now been surprisingly found, together with a method for producing said formulation.

The present invention relates to a solid formulation for oral administration of mesalazine, consisting of a capsule containing mesalazine-loaded cores which can release the active agent selectively into the colon. A further object of the present invention is a method for producing said formulation.

**Description of the invention**

The object of the present invention is a solid form for the selective oral administration of mesalazine into the colon, comprising a plurality of mesalazine-loaded cores contained in a capsule dissolving in the stomach, said mesalazine-loaded cores being singularly provided with a coating layer which comprises a substance soluble only at pH > 6.5 and whose thickness lower than 40 μm.

The present oral solid dosage form can be prepared as follows: (a) the cores are wetted with a solution of a binder; (b) the wetted cores are powdered with mesalazine, (c) coated with a solution containing the substance soluble only at pH > 6.5, (d) dried, and (e) introduced into capsules.

Preferably, said cores are sugar spheres as defined in the monograph "Sugar spheres", USP/NF, 24$^{th}$ edition; they have diameters of 0.3 mm -0.7 mm,

preferably 0.5 mm - 0.6 mm.

The binder used in phase (a) is preferably chosen from the group comprising copolymers of methacrylic acid, e.g. Eudragit S 100; the binder is used in solution with a suitable organic solvent: solvents which are preferably used in the present invention are ethanol and acetone or mixtures thereof, more preferably the solvent is ethanol/acetone 80:10.

When the above described sugar spheres are used as a core, the amount of powdered mesalazine is such to provide a mesalazine/sugar spheres weight ratio of at least 85:15.

At the end of phase (b), mesalazine-loaded cores are obtained (herein also defined as granules), wherein the drug is incorporated onto the core within a binding layer. The thus obtained loaded cores can optionally be dried before performing the phase (c).

The substance soluble only at pH > 6.5 used in phase (c) is preferably a copolymer of methacrylic acid, which can be mixed with a suitable plasticizing agent and talc.

Suitable copolymers of methacrylic acid which can be used as coatings in the present invention are for instance the above-mentioned products known on the market with the mark Eudragit, in particular Eudragit S 100, Eudragit L 100, mixtures thereof and the like.

The plasticizer is chosen from the group comprising diethyl phtalate, dibutyl phtalate, triethyl citrate and polyethylene glycol. It is used in amounts between 5% and 30% by weight with respect to the acrylic copolymer.

Talc has an anti-aggregating function, i.e. it prevents granules from sticking to one another during the coating process. It is used in a percentage between 30% and 80% by weight with respect to the copolymer, preferably between 40% and 70% by weight, still more preferably 60% by weight.

This coating mixture can optionally comprise further additives such as for instance coloring agents.

In phase (c) the cores are preferably coated with a suspension of the above copolymer in ethanol, which is sprayed with or without air. This operation is carried out in a turning tray or in a fluidized bed. The drying phase (d) is performed in such

conditions as to eliminate the solvent of the coating solution, e.g. at 45°C for 6 hours.

In phase (e) the cores are introduced into capsules, preferably hard gelatin capsules.

As previously mentioned, the thickness of the coating layer is lower than 40 μm. Preferably, the coating thickness is lower than 30 μm, more preferably lower than 25 μm, still more preferably the thickness is of about 20 μm. The thickness of the coating according to the present invention is drastically lower than the one characterizing similar formulations described in the prior art. The above-mentioned patent no. EP 0 097 651 points out the fact that the coating thickness should be of at least 60 μm so that the formulation can reach the target area, i.e. the colon, in its whole state. Therefore, contrarily to the teachings of the prior art, it has been found that granules coated with a protective layer whose thickness is extremely lower than this of the prior art can also provide a satisfying protection of the core as far as the target area.

The substantial reduction of the thickness of the protective layer according to the invention, is preferably accomplished when the mesalazine powders used in the present invention have particle-size distribution in compliance with the following table:

| particle size | Distribution |
|---|---|
| Lower than 10 μm | <20% |
| Lower than 50 μm | >40% |
| Lower than 150 μm | >80% |

More preferably, the particle-size distribution of mesalazine powders is in compliance with the following table:

| particle size | Distribution |
|---|---|
| Lower than 10 μm | <15% |
| Lower than 50 μm | >70% |
| Lower than 150 μm | >90% |

The low thickness of the coating layer according to the present invention causes a weight percentage of the substance coating the granules of maximum 10% by

weight with respect to the total weight of the granule. The above-mentioned patent no. EP 0 572 486 points out that the percentage of substance coating the granules should be at least of 16% by weight (calculated on dry weight) with respect to the granule weight, in order for the active agent to be released by said granule in a pH-dependent manner. Contrarily to the statements of the prior art, the granules according to the invention show a maximum of 10% by weight of coating substance with respect to their total weight (values calculated on dry weight), though being able to release the active agent in a pH-dependent manner.

From what has been previously said it can be inferred that the capsules of the present invention have the indubitable advantage with respect to those in the prior art of containing a lower amount of coating substance, though maintaining the same features of solution zone and mode, and therefore the same release profile for the active principle, as the oral forms described in the prior art.

The invention will now be disclosed in further detail by the following examples, which should be considered as illustrative and non limitative of the present invention.

EXAMPLE 1

400 mg formulation

In a suitable Pellegrini-type turning tray mesalazine is applied to sugar spheres by using a process in which the wetting phase with a 10% solution of Eudragit S 100 in ethanol/acetone 80:10 is followed by a powdering phase with mesalazine powder. The wetting phase is carried out by means of a spraying device without air (Graco pump). The capacity of the turning tray requires two different layering phases for each batch. After about 1/3 of mesalazine application the batch is divided into three portions and the process is continued onto each portion as before. Eventually, the product is dried in the running tray at 40°C for 10 hours, thus obtaining a mesalazine-loaded core with the following composition:

| | |
|---|---|
| Sugar spheres | 9.8% |
| Mesalazine | 83.0% |
| Eudragit S 100 | 7.2% |

The cores are then coated within the turning tray with a dispersion so as to obtain the following final composition, in which the compounds with the asterisk are those

constituting the core:

| | |
|---|---|
| Sugar spheres* | 8.9% |
| Mesalazine* | 75.5% |
| Eudragit S 100* | 6.5% |
| Eudragit S 100 | 4.3% |
| Eudragit L 100 | 1.1% |
| Talc | 3.2% |
| Diethyl phtalate | 0.5% |

The dispersion is prepared by introducing diethyl phtalate and the various Eudragit's in ethanol, then talc is dispersed into it and the whole is homogenized. The dry content of the coating suspension is 10%.

The cores are coated with the suspension by means of a continuous spray system using air at a temperature of 65°C. The product thus obtained is then dried at 40°C for about 3 hours.

The coated cores are then introduced into oblong capsules of hard gelatin, size 0, containing a dose of mesalazine of 400 mg.

EXAMPLE 2

<u>500 mg formulation</u>

Operating as described in example 1 a mesalazine-loaded core is prepared with the following composition:

| | |
|---|---|
| Sugar spheres | 8.4% |
| Mesalazine | 84.2% |
| Eudragit S 100 | 7.4% |

The cores are then coated within the turning tray with a dispersion so as to obtain the following final composition, in which the compounds with the asterisk are those constituting the core:

| | |
|---|---|
| Sugar spheres* | 7.6% |
| Mesalazine* | 76.1% |
| Eudragit S 100* | 6.6% |
| Eudragit S 100 | 4.6% |
| Eudragit L 100 | 0.8% |
| Talc | 3.0% |
| Diethyl phtalate | 1.3% |

The coated cores are then introduced into oblong capsules of hard gelatin, size 00, containing a dose of mesalazine of 500 mg.

EXAMPLE 3

*In vitro* dissolution test

The formulations of examples 1 and 2 undergo *in vitro* tests using the following method:

| | |
|---|---|
| Device | Apparatus 4 according to US Pharmacopoeia, 24$^{th}$ edition (flow cell corresponding to *"flow through apparatus"* according to European pharmacopoeia, suppl. 2000) |
| Flow | 16.7 ml/min |
| Method | 2 hours at pH 1.2<br>1 hour at pH 6.5<br>1 hour at pH 6.8<br>1 hour at pH 6.9<br>1 hour at pH 7.0<br>until 8$^{th}$ hour at pH 7.5 |

The results are shown in the following tables.

Table 1

Dissolution degree of the formulation in example 1 as a function of time and pH

| Hour | Dissolved active agent (%) | Standard deviation index |
|---|---|---|
| 2nd | 0.08 | 61.46 |
| 3rd | 0.1 | 52.93 |
| 4th | 0.2 | 31.71 |
| 5th | 1.3 | 8.30 |
| 6th | 12.3 | 2.77 |
| 6.5th | 28.1 | 2.58 |
| 7th | 41.7 | 4.06 |
| 8th | 65.3 | 3.66 |

As is evident from the above-listed data, no significant dissolution occurs at pH lower than 6.5.

Table 2

Dissolution degree of the formulation in example 2 as a function of time and pH

| Hour | Dissolved active agent (%) | Standard deviation index |
|---|---|---|
| 2nd | 0.06 | 55.63 |
| 3rd | 0.09 | 47.58 |
| 4th | 0.15 | 40.24 |
| 5th | 1.22 | 12.34 |
| 6th | 9.87 | 4.98 |
| 6.5th | 25.73 | 3.91 |
| 7th | 40.54 | 2.41 |
| 8th | 66.37 | 2.67 |

As is evident from the above-listed data, no significant dissolution occurs at pH lower than 6.5.

EXAMPLE 4

Test on mesalazine bioavailability

The formulation of example 1 is tested in a bioavailability assay carried out on

male healthy volunteers taking as reference Asacol® produced by SmithKline Beecham. The objective of the assay is to show that a formulation according to the invention can release the active agent mesalazine into the distal tract of the intestine, thus obtaining an activity and safety profile which is at least similar to the one obtained with an equivalent product on the market.

Plasma levels are analyzed so as to show the low absorption of mesalazine released by the formulation according to the invention, and said levels indicate that in the proximal region of the intestine no release takes place.

Urine is analyzed in order to confirm this low systemic adsorption. The fecal levels are controlled to verify that the release of mesalazine occurs on the target area.

Analogously, data referring to N-acetyl 5-aminosalicylic acid (NAS), the main metabolite of mesalazine, are detected.

The following Table 3 shows the obtained results.

Table 3

| Formulation | | Plasma | | | | Urines Total recovery (mg) | Feces Total recovery (mg) |
|---|---|---|---|---|---|---|---|
| | | $C_{max}$ (ng/ml) | $T_{max}$ (hours) | AUC (0-t) (ng/ml·hour) | Appearance time (hour) | | |
| Asacol® | | | | | | | |
| mesalazine | mean | 540.95 | 8.92 | 1903.30 | 6.33 | 0.56 | 75.50 |
| | CV(%) | 141.57 | 25.06 | 76.93 | 33.89 | 101.80 | 80.57 |
| NAS | mean | 858.32 | 10.25 | 5883.67 | 5.75 | 79.91 | 85.86 |
| | CV(%) | 86.31 | 25.69 | 42.07 | 22.40 | 50.73 | 51.70 |
| Ex.1 | | | | | | | |
| mesalazine | mean | 372.62 | 6.00 | 1261.92 | 4.00 | 0.29 | 66.29 |
| | CV(%) | 75.68 | 28.43 | 58.94 | 26.11 | 140.72 | 61.22 |
| NAS | mean | 571.50 | 6.67 | 4253.98 | 3.50 | 56.33 | 94.96 |
| | CV(%) | 46.78 | 24.21 | 35.71 | 33.36 | 43.36 | 65.19 |

The formulation according to the invention provides plasma parameters which are drastically lower than one of the commercially available pharmaceutical forms. This means that, thanks to the characteristics of the invention, systemic absorption of mesalazine is reduced, which is positive from a toxicological point of view, since it is known that mesalazine is toxic for kidneys, and from a therapeutic point of view, since the target area to which the present formulation is directed is colon, where mesalazine should act locally. Urine concentration confirms the systemic data, whereas feces concentration points out that the action of both formulations in the colon is equivalent.

EXAMPLE 5

Measurement of film thickness by means of porosimetry

Film thickness is measured with the following method. A mercury porosimeter is used to evaluate the volume of 500 granules. Assuming that all these granules are approximately spherical, it is possible to calculate the average volume of each granule. If said analysis is carried out before and after coating, the thickness of the coating layer can be calculated. The obtained data are shown in Table 4.

Table 4

| | Uncoated granule | Coated granule |
|---|---|---|
| Average weight (mg) | 1.402 | 1.582 |
| Average volume ($mm^3$) | 1.042 | 1.156 |
| Average radius (μm) | 629 | 651 |
| Average thickness of the coating (μm) | - | 22 |

EXAMPLE 6:

Particle size of mesalazine powder

Different mesalazine powders coming from various suppliers and batches are characterized as far as the distribution of their particle sizes is concerned by means of a mercury porosimetry (Porosimetro 2000+ Micropores Unit 120 Carlo Erba Instruments, software Milestone 200, version 3.02) according to the following method.

Sample preparation and treatment

An amount of powder between 100 mg and 150 mg, precisely weighed, is introduced into the dilatometer containing mercury reaching 1 cm from the bottom of the capillary. The sample is then degassed under vacuum for 30 minutes and filled with mercury reaching a 70 mm height, then brought back to atmospheric pressure.

First mesoporosity run with disintegration of crystal agglomerates contained in the sample

The dilatometer, weighed with mercury and sample, is introduced into the mesopore unit. The central unit is set on the following parameters:

| | |
|---|---|
| pressure limit | 400 bar |
| Decrease | 1 |
| pump speed | 1 |

The analysis is set according to the following parameters:

| | |
|---|---|
| Instrumental parameters | |
| Type of porosimeter | Po-2000 |
| Capillary radius | 1.5 mm |
| Volume of dilatometer | 15 $cm^3$ |
| Macropore connection | Auto |
| Macropore unitary pressure | kPa |
| Parameter collection | |
| Phase time | 5 seconds |
| Maximum pressure | 400 bar |
| Pump speed | 1 |
| Analytic conditions | |
| Wetting angle | 141.3 deg |
| Hg surface tension | 480 Dyn/com |
| Mercury height | 70 mm |
| Hg density | 13.65 $g/cm^3$ |
| Parameter calculation and report | |
| Type of report | Summary |
| Calculation pattern | Cylindrical |

Upon analysis start the porosimeter has carried out a pressure increment stroke

as far as 400 bar, followed by the extrusion phase which brings the system back to atmospheric pressure. The oil which is left on the mercury meniscus is sucked and the sample is placed under vacuum for 10 minutes. The difference in the height of the mercury column is registered with respect to the beginning of the first run (it is due to the breaking of the agglomerates). The sample is brought to atmospheric pressure noting down a further lowering of the mercury column due to the penetration into the macropores.

Second mesoporosity run and determination of particle size

Proceeding as in 2., after the intrusion and extrusion, it is possible to detect the inflexion point of the volume/pressure curve corresponding to the pore radius (cut-off point). The lower calculation limit for particle-size distribution is determined on the basis of this value. The apparatus then calculates the typical physical parameters of the sample taking as reference mercury volumes and the pressure at which intrusion has taken place.

The results are shown in the following Table 5.

Table 5

| | Batch | | | | | |
|---|---|---|---|---|---|---|
| Particle-size distribution % under size | A | B | C | D | E | F |
| 10 μm | 3.7 | 5.7 | 7.2 | 9.9 | 1.8 | 28.3 |
| 50 μm | 76.0 | 82.7 | 82.8 | 83.8 | 37.6 | 84.1 |
| 100 μm | 91.4 | 92.2 | 91.6 | 91.9 | 91.2 | 89.6 |
| 150 μm | 94.7 | 93.9 | 95.0 | 96.3 | 96.1 | 93.1 |

EXAMPLE 7

Specific area of mesalazine powders

Different mesalazine powders coming from various suppliers and batches are characterized as far as their specific area is concerned using Sorptomatic 1990 (Fisons) with software Milestone 200 Fisons. About 8 g of powder, precisely weighed in a burette, are degassed at 40°C for at least 17 hours using a turbomolecular pump, reaching a residual pressure lower than 0.01 Pascal. The burette is placed in liquid nitrogen. Upon reaching the balance temperature a precise amount of nitrogen gas is introduced into the burette, just to enable a mono-layer absorption on the sample surface. After a first analysis, a second one is carried out using helium instead of nitrogen, in the same conditions. The specific area is automatically calculated by the instrument.

The results are shown in table 6.

Table 6

| Batch | Specific area ($m^2/g$) |
|---|---|
| A | 0.43 |
| B | 0.61 |
| C | 0.48 |
| D | 0.68 |
| E | 0.17 |
| F | 1.17 |

EXAMPLE 8

Solubility of the coating at pH lower than 7

The casting method is used to evaluate solubility at various pH values of coating layers having different compositions. Several coating solutions based on Eudragit S 100, Eudragit L 100 with 10% plasticizer (diethyl phtalate) are prepared and poured into Petri dishes. The solvent is then evaporated at ambient temperature to enable film building. Film thickness is in the range between 30 μm and 50 μm. Films are detached from the dishes and their solubility is tested at pH 6.5, 6.8 and 7.4, at 37°C in a dissolution apparatus type 2, US Pharmacopoeia 24$^{th}$ edition. Films are applied onto the blade with adhesive tape and the test is carried out at 30 rpm in 900 ml of buffer according to US Pharmacopoeia. Films are observed after 4 hrs and 21 hrs. Already at pH 6.7 it is possible to observe a softening of the protective layer. The results are shown in Table 7.

Table 7

| Film | Eudragit S/Eudragit L ratio | pH 6.5 | | pH 6.8 | | pH 7.4 | |
|---|---|---|---|---|---|---|---|
| | | 4 h | 21 h | 4 h | 21 h | 4 h | 21 h |
| A | 80:20 | Unchanged | Unchanged | soluble | soluble | soluble | soluble |
| B | 100:0 | Unchanged | Unchanged | Unchanged | Unchanged | soluble | soluble |

CLAIMS

1. Oral solid form for the selective administration of mesalazine into the colon, comprising a plurality of mesalazine-loaded cores contained in a capsule which can dissolve in the stomach, said mesalazine-loaded cores being singularly provided with a coating layer which comprises a substance soluble only at pH > 6.5 and has a thickness lower than 40 μm.

2. Oral solid form according to claim 1, wherein the cores consist of sugar spheres with a diameter of 0.3-0.7 mm onto which mesalazine is layered by means of a binder chosen from the group comprising copolymers of methacrylic acid, and the coating layer contains a suitable copolymer of methacrylic acid which can dissolve only at pH > 6.5, talc and a plasticizing agent.

3. Oral solid form according to claim 2, in which the diameter of the sugar spheres is 0.5 mm - 0.6 mm.

4. Oral solid form according to claim 2-3, in which the binder is Eudragit S 100.

5. Oral solid form according to claim 2-4, in which the mesalazine/sugar spheres weight ratio is at least 85:15.

6. Oral solid form according to claims 2-5, in which the coating agent is Eudragit S 100, Eudragit L 100, or mixtures thereof.

7. Oral solid form according to claims 2-6, in which the plasticizer is chosen from the group comprising diethyl phtalate, dibutyl phtalate, triethyl citrate and polyethylene glycol.

8. Oral solid form according to claims 2-7, in which the plasticizer is used in amounts between 5% to 30% by weight with respect to the copolymer contained in the coating layer.

9. Oral solid form according to claims 2-8, in which talc is used in a percentage between 30% and 80% by weight with respect to the copolymer contained in the coating layer.

10. Oral solid form according to claims 2-8, in which talc is used in a percentage between 40% and 70% by weight with respect to the copolymer contained in the coating layer.

11. Oral solid form according to claims 2-8, in which talc is used in a percentage of 60% by weight with respect to the copolymer contained in the coating layer.

12. Oral solid form according to claims 1-11, in which the thickness of the coating layer is lower than 30 μm.

13. Oral solid form according to claim 12, in which the thickness of the coating layer is lower than 25 μm.

14. Oral solid form according to claim 13, in which the thickness of the coating layer is about 20 μm.

15. Oral solid form according to claims 2-14, in which the mesalazine layered onto the cores is a powder having the following particle-size distribution:

| particle size | Distribution |
|---|---|
| Lower than 10 μm | <20% |
| Lower than 50 μm | >40% |
| Lower than 150 μm | >80% |

16. Oral solid form according to claim 15, in which the size-particle distribution of mesalazine powder is the following:

| particle size | Distribution |
|---|---|
| Lower than 10 μm | <15% |
| Lower than 50 μm | >70% |
| Lower than 150 μm | >90% |

17. Method for the production of an oral solid form according to claims 1-16 comprising the following phases:

a) wetting cores with a solution of a binder;

b) powdering the wetted cores of a) with mesalazine;

c) coating the cores with a solution of a substance soluble only at pH > 6.5;

d) drying the coated cores

e) introducing the coated cores into capsules.

18. Method according to claim 17, wherein:

in phase a) said cores are sugar spheres having a diameter of 0.3 mm - 0.7 mm and the binder is a copolymer of methacrylic acid; in phase c) the substance which can dissolve only at pH > 6.5 is a copolymer of methacrylic acid, and the coating solution includes talc and a plasticizer; in phase e) the capsules are hard gelatin

capsules.

19. Method according to claim 18, in which the sugar spheres have a diameter of 0.5-0.6 mm.

20. Method according to claims 17-19, in which the solution of phase a) is a solution of Eudragit S 100 in a suitable organic solvent, or mixtures thereof.

21. Method according to claim 20, in which the solvent is chosen from the group comprising ethanol, acetone or mixtures thereof.

22. Method according to claim 21, in which the solvent is ethanol/acetone 80:10.

23. Method according to claims 18-22, in which the amount of mesalazine powdered in phase b) is in a mesalazine/sugar spheres weight ratio of at least 85:15.

24. Method according to claims 17-23, in which the coating solution of phase c) is a solution of Eudragit S 100, Eudragit L 100 or mixtures thereof.

25. Method according to claims 18-24, in which the plasticizer is chosen from the group comprising diethyl phtalate, dibutyl phtalate, triethyl citrate and polyethylene glycol.

26. Method according to claim 25, in which the plastizicer is used in an amount between 5% and 30% by weight with respect to the copolymer.

27. Method according to claims 17-26, in which the solution in c) is in ethanol.

28. Method according to claims 17-27, in which the solution in c) is sprayed with or without air.

29. Method according to claims 17-28, in which the drying phase d) is carried out at 45°C for 6 hours.

30. Method according to claims 17-29, in which the mesalazine powder used in phase b) has the following particle-size distribution:

| particle size | Distribution |
|---|---|
| Lower than 10 μm | <20% |
| Lower than 50 μm | >40% |
| Lower than 150 μm | >80% |

31. Method according to claim 30, in which the mesalazine powder has the following particle-size distribution:

| particle size | Distribution |
|---|---|
| Lower than 10 μm | <15% |
| Lower than 50 μm | >70% |
| Lower than 150 μm | >90% |

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/02539

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/50 A61K31/606

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, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

[X] Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 2 August 2001 | 10/08/2001 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Marttin, E |

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International Application No
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