

Solid oral dosage form comprising antibodies for sustained release in the lower gastrointestinal tract

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FIELD OF THE INVENTION

The present invention relates to a solid oral dosage form for sustained release in the lower gastrointestinal tract, comprising antibodies or functional fragments thereof specific to tumor necrosis factor alpha (TNF α) in a depot layer (2) covering an inert core unit (1), a sustained release layer (3) covering the depot layer, and a delayed release layer (4) covering the sustained release layer, preferably prepared by drug layering; an oral multiparticulate drug delivery system comprising a plurality of the solid oral dosage forms; and the use of the solid oral dosage form in the targeted local treatment in the lower gastrointestinal tract of a patient.

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BACKGROUND OF THE INVENTION

Solid dosage forms such as pellets, mini-tablets, tablets, granules, capsules or tablets and the like are widely used in pharmaceutical industry. They typically comprise at least one active ingredient, and one or more carriers and other excipients. Advantages of such solid dosage forms include less storage space, ease of handling, and improved stability. Moreover, tablets or capsules provide the most widely used dosage unit for applying drugs to a patient in a non-invasive manner. For small molecule drugs there exists a long-established practice of preparing solid dosage forms. For antibodies and functional fragments thereof on the other hand, although they are finding an ever-increasing use as active ingredients in therapeutic or diagnostic applications, the formulation into solid dosage forms is more challenging.

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As an alternative to systemic treatment, the use of solid dosage forms intended for oral administration and targeting parts of the gastrointestinal (GI) tract has many potential advantages and therefore has become an interesting alternative in recent years, since it allows for the targeted local treatment of symptoms of diseases in parts of the GI

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tract, as for example immune checkpoint inhibitor (ICPI) induced colitis, ICPI induced enterocolitis, ICPI induced diarrhoea, inflammatory bowel disease (IBD), colorectal cancer, diarrhea or microbial infections. However, the use of antibodies and functional fragments of antibodies in solid dosage forms for such targeted local treatment in the GI tract faces various challenges.

Colitis is as a disorder characterized by inflammation of the large intestine/colon. Enteritis is defined as a disorder characterized by inflammation of the small intestine. Enterocolitis is as a disorder characterized by inflammation of both the small intestine and the large intestine/colon, i.e. a combination of enteritis and colitis. Symptoms characterizing ICP inhibitor-induced colitis include diarrhoea, abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits, fever, abdominal distention, obstipation and constipation (Brahmer et al., Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology (ASCO) Practice Guideline, J Clin Oncol. (2018) 10;36(17):1714-1768). Symptoms characterizing ICP inhibitor-induced enterocolitis include the symptoms listed above for ICP inhibitor-induced colitis.

With respect to ICPI induced colitis, ICPI induced enterocolitis and ICPI induced diarrhoea, it is important that patients can be treated for ICPI induced colitis, ICPI induced enterocolitis or ICPI induced diarrhoea with an antibody or functional antibody fragment while still undergoing cancer treatment with ICPI via intravenous route. This requires an alternative route of administration, both to allow parallel intravenous cancer treatment (for example, the standard therapy for treatment of severe ICPI induced colitis or ICPI induced enterocolitis using anti-TNF α specific antibodies at present involves regular systemic administration of an anti-TNF α antibody by intravenous infusion, which requires interruption of ICPI treatment), and to ensure targeted local delivery to keep systemic exposure to the antibody and potential side effects resulting therefrom to an absolute minimum. While this is beneficial for all patients, it is particularly important for patients with ICPI-induced colitis, ICPI induced enterocolitis or ICPI induced diarrhoea who are already heavily burdened by cancer therapy.

A problem associated with solid oral dosage forms comprising antibodies and functional fragments of antibodies is the size of the antibodies and antibody fragments

compared to small drug molecules, which, when combined with functional coatings like sustained release coatings and/or delayed release coatings, can greatly affect the release behaviour.

- 5 The targeted release of therapeutic antibodies or functional fragments thereof from a solid dosage form in a specific part of the GI tract over a defined window of time is particularly desirable for diseases of the lower GI tract and in particular ICPI induced colitis, ICPI induced enterocolitis, ICPI induced diarrhoea and IBD. However, a targeted release of antibodies or functional fragments thereof from a solid dosage form
- 10 in a specific part of the GI tract over a defined window of time can also be very challenging.

Thus, there is a need for a solid oral dosage form comprising therapeutic antibodies, preferably specific to tumor necrosis factor alpha (TNF α), or functional fragments

15 thereof, for release in a defined part of the GI tract and in particular the lower GI tract, that ensures targeted release over a defined window of time.

SUMMARY OF THE INVENTION

After testing various solid dosage form designs, excipients, manufacturing methods

20 and processing conditions the present inventors found an advantageous solid oral dosage form comprising an antibody or a functional fragment thereof, preferably specific to tumor necrosis factor alpha (TNF α), as an active ingredient. The solid oral dosage form of the present invention comprises an inert core unit (1), a depot layer (2) comprising the antibody or functional fragment thereof, a sustained release layer (3),

25 and a delayed release layer (4). The ingredients and composition of the depot layer, sustained release layer and delayed release layer are carefully selected to ensure the desired release profile of the antibody or functional fragment thereof after oral administration.

30 The present inventors unexpectedly found that the sustained release layer on its own, did not provide for consistent results regarding sustained antibody release from the depot layer. Surprisingly, only in combination with the final outer delayed release layer, a consistent and sufficiently high release rate (e.g. about 80 % antibody released within

26 hours in a release test) was achieved. This is surprising, since the delayed release layer is supposed to only prevent drug release until the pH trigger. Thus, the final solid oral dosage form found by the present inventors works due to the combinatorial effect of the layers and of the carefully selected and calibrated components in the different layers, enabling the targeted release of the antibody or functional fragment thereof in a desired manner. It has been found that a favorable release profile can be obtained when the delayed release layer comprises an anionic polymer and the sustained release layer comprises a cationic polymer. In addition, the formulation of the present invention was shown to be stable for 12 months. Unexpectedly, the antibody activity was stable even after storage at 25°C/60% RH for one year.

The solid oral dosage form of the present invention prevents release of the antibody or functional fragment thereof before a target site in the gastrointestinal (GI) tract of a patient. Thereby, the solid oral dosage form advantageously ensures a controlled and sustained release from the solid oral dosage form in the lower part of the GI tract, particularly starting preferably in the terminal ileum or the ileocolonic region, and over a clearly defined period of time, e.g. over the course of a day, ensuring the release of the majority of the antibody or functional fragment thereof from the solid oral dosage form in the target region of the GI tract and before it is expelled via the anus. Thus, the solid oral dosage form ensures that an optimal amount of the antibody or functional fragment thereof in active form can be released from the solid oral dosage form in a controlled manner. The solid oral dosage form is preferably prepared by drug layering, using carefully chosen combinations of excipients that ensure a fast and straight forward preparation of the solid oral dosage form, while preserving stability and activity of the antibodies or functional fragments thereof.

Thus, the present invention provides a novel solid oral dosage form, comprising as an active agent an antibody or functional fragment thereof, preferably specific to TNF α , in a depot layer (2) covering an inert core unit (1), a sustained release layer (3) covering the depot layer and a delayed release layer (4) covering the sustained release layer, thereby ensuring carefully calibrated delayed and sustained release from the solid oral dosage form starting at a defined location in the lower GI tract. The present invention relates to the subject matter defined in the following items 1 to 131:

- [1] A solid oral dosage form comprising
- i) an inert core unit (1);
 - ii) a depot layer (2) covering the inert core unit (1) and comprising an antibody or a functional fragment thereof, as an active agent; and optionally a stabilizer, a buffer and/or a polymeric binder;
 - iii) a sustained release layer (3), covering the depot layer (2) and comprising at least one cationic polymer; and optionally a plasticizer and/or an anti-tacking agent; and
 - iv) a delayed release layer (4) covering the sustained release layer (3) and comprising at least one anionic polymer and optionally a plasticizer.
- [2] A solid oral dosage form comprising
- i) an inert core unit (1);
 - ii) a depot layer (2) covering the inert core unit (1) and comprising an antibody or a functional fragment thereof as an active agent; a stabilizer; a buffer; and a polymeric binder;
 - iii) a sustained release layer (3), covering the depot layer (2) and comprising at least one cationic polymer; a plasticizer; and an anti-tacking agent; and
 - iv) a delayed release layer (4) covering the sustained release layer (3) and comprising at least one anionic polymer and a plasticizer.
- [3] The solid dosage form of item 1 or 2, wherein the at least one anionic polymer is selected from the group consisting of polymers comprising carboxylic acid groups; poly(methacrylic acid, methyl methacrylate) 1:1; poly(methacrylic acid, ethyl acrylate) 1:1; poly(methacrylic acid, methyl methacrylate) 1:2; poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1; carboxymethyl cellulose; and combinations thereof.
- [4] The solid dosage form of any one of items 1 to 3, wherein the at least one cationic polymer is selected from the group consisting of chitosan; cellulose; ammonio methacrylate copolymers; poly(ethyl acrylate, methyl methacrylate,

trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1; poly(2-N,N-dimethylaminoethylmethacrylate); poly-L-lysine; polyethylenimine; Poly(amidoamine).

[5] A solid oral dosage form comprising

- i) an inert core unit (1);
- 5 ii) a depot layer (2) covering the inert core unit (1) and comprising an antibody or a functional fragment thereof, preferably specific to tumor necrosis factor alpha (TNF α), as an active agent; a stabilizer, preferably sucrose; a buffer; and a polymeric binder, preferably hypromellose (HPMC);
- 10 iii) a sustained release layer (3), covering the depot layer (2) and comprising an ammonio methacrylate copolymer, preferably poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1; a plasticizer; and an anti-tacking agent; and
- 15 iv) a delayed release layer (4) covering the sustained release layer (3) and comprising poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof, preferably poly(methacrylic acid, methyl methacrylate) 1:2; an anti-tacking agent, preferably glycerol monostearate (GMS); and a plasticizer, preferably triethyl citrate (TEC).
- 20 [6] The solid oral dosage form according to any one of the preceding items, wherein the solid oral dosage form is a pellet, granule, bead, sphere, mini-sphere, tablet or mini-tablet, preferably a pellet.
- [7] The solid oral dosage form of any one of the preceding items, which is gastric resistant.
- 25 [8] The solid oral dosage form according to any one of the preceding items, for targeted release of the antibody or functional fragment thereof starting in the terminal ileum, the ileocolonic region, the ascending colon or transverse colon, preferably in the terminal ileum, the ileocolonic region or the ascending colon, more preferably in the terminal ileum or the ileocolonic region.
- 30 [9] The solid oral dosage form according to any one of the preceding items, for targeted release of the antibody or functional fragment thereof in the terminal ileum,

the ileocolonic region, the ascending colon, the transverse colon, and/or the sigmoid colon.

[10] The solid oral dosage form according to any one of the preceding items, for targeted sustained release of the antibody or functional fragment thereof starting in the
5 terminal ileum and continuing at least through the sigmoid colon.

[11] The solid oral dosage form according to any of the preceding items, wherein the inert core unit (1) is an inert pellet, mini-tablet, tablet, granule, core, bead, mini-sphere or sphere, preferably a pellet.

[12] The solid oral dosage form according to any of the preceding items, wherein the
10 inert core unit (1) comprises a monosaccharide, disaccharide, oligosaccharide, polysaccharide, silica, tartaric acid, calcium carbonate, or a combination thereof as a main component.

[13] The solid oral dosage form according to any of the preceding items, wherein the inert core unit (1) consists of a monosaccharide, disaccharide, oligosaccharide,
15 polysaccharide, silica, tartaric acid, calcium carbonate, or a combination thereof.

[14] The solid oral dosage form according to any of the preceding items, wherein the inert core unit (1) is a pellet, preferably comprising, or consisting of, a sphere; consists of a water insoluble or water swellable material; and/or is of uniform composition.

[15] The solid oral dosage form according to any of items 1 to 13, wherein the inert
20 core unit (1) comprises, or consists of, a pellet, e.g. a sphere, and optionally a seal coating covering the sphere, the seal coating preferably consisting of a water-insoluble material.

[16] The solid oral dosage form according to any of the preceding items, wherein the inert core unit (1) comprises a monosaccharide, disaccharide, oligosaccharide,
25 polysaccharide, silica, tartaric acid or a combination thereof as main or only component(s).

[17] The solid oral dosage form according to any of the preceding items, wherein the inert core unit (1), preferably is a pellet and, comprises, or consists of, microcrystalline cellulose, sucrose, starch, mannitol, calcium carbonate, silica, tartaric acid, lactose,
30 carboxymethylcellulose, crosslinked sodium carboxymethylcellulose, or a combination thereof.

[18] The solid oral dosage form according to any of the preceding items, wherein the inert core unit (1) comprises, or consists of, microcrystalline cellulose.

[19] The solid oral dosage form according to any of the preceding items, wherein the inert core unit (1) is pharmaceutically inactive.

5 [20] The solid oral dosage form according to any of the preceding items, wherein the inert core unit (1) comprises no active agents.

[21] The solid oral dosage form according to any of the preceding items, wherein the inert core unit (1) is a pellet with a sphericity degree of at least 0.6, preferably at least 0.7, more preferably at least 0.8, even more preferably at least 0.9, even more
10 preferably at least 0.95.

[22] The solid oral dosage form according to any of the preceding items, wherein the inert core unit (1) is a pellet with a median particle size of 50-5000 μm , preferably 100-3000 μm , more preferably 200-2000 μm , even more preferably 300-1500 μm , even more preferably 400-1400, even more preferably 700-1400, even more preferably 500-
15 1000, most preferably 500-700, 600-800, or 700-1000 μm .

[23] The solid oral dosage form according to any of the preceding items, wherein the inert core unit (1) is a pellet with a particle size distribution such that at least 85 % of the pellets have a particle size of 50-3000 μm , preferably 100-1500 μm , more preferably 350-1400 μm , even more preferably 500-1400 μm , even more preferably
20 700-1400, even more preferably 500-1000 μm , e.g. 500-700 μm or 700-1000 μm .

[24] The solid oral dosage form according to any of the preceding items, wherein the inert core unit (1) is a pellet with a particle size distribution such that at least 85 % of the pellets have a particle size of 700-1400 μm , preferably of 700-1000 μm .

[25] The solid oral dosage form according to any of the preceding items, wherein the
25 depot layer (2) was deposited on the inert core unit (1) by drug layering, preferably using spray coating, more preferably fluidized-bed spray coating.

[26] The solid oral dosage form according to any of the preceding items, wherein the stabilizer in the depot layer (2) is selected from sucrose, maltose, lactose, trehalose, glycerol, maltitol, isomalt, mannitol, sorbitol, xylitol and combinations thereof, preferably sucrose, maltose, lactose, glycerol, maltitol, isomalt, and combinations
30 thereof, more preferably sucrose.

[27] The solid oral dosage form according to any of the preceding items, wherein the buffer (i.e. buffer salt or salts and/or free base) in the depot layer (2) is selected from the group consisting of L-histidine buffer, citrate buffer, hydroxymethylaminomethane (TRIS) buffer, succinate buffer, phosphate buffer, acetate buffer, or salts thereof, and combinations thereof; preferably L-histidine buffer, citrate buffer, TRIS buffer, and combinations thereof; more preferably L-histidine buffer, citrate-TRIS buffer, and a combination thereof.

[28] The solid oral dosage form according to any of the above items, wherein the buffer (i.e. buffer salt and/or free base) in the depot layer (2) comprises, or consists of, L-histidine, preferably L-histidine monohydrochloride and/or free base.

[29] The solid oral dosage form according to any of the preceding items, wherein the polymeric binder in the depot layer (2) is selected from hypromellose (HPMC); methylcellulose (MC); polyvinylpyrrolidone (PVP); polyvinylalcohol (PVA); hydroxypropyl cellulose (HPC); macrogol poly(vinylalcohol) grafted copolymer (e.g. Kollidon® IR); and combinations thereof; preferably HPMC or MC; more preferably HPMC.

[30] The solid oral dosage form according to any of the preceding items, wherein the polymeric binder in the depot layer (2) is suitable for an immediate release drug coating.

[31] The solid oral dosage form according to any of the preceding items, wherein the polymeric binder in the depot layer (2) is hypromellose (HPMC); preferably hypromellose 2910, more preferably hypromellose 2910 2.6-3.6 mPas, even more preferably hypromellose 2910 3 mPas.

[32] The solid oral dosage form according to any of the preceding items, wherein the depot layer (2) comprises an anti-tacking agent.

[33] The solid oral dosage form according to item 32, wherein the anti-tacking agent is selected from mesoporous silica, colloidal silica dioxide, stearic acid, magnesium stearate, glycerol monostearate (GMS) and talc, preferably mesoporous silica.

[34] The solid oral dosage form according to any of the preceding items, wherein the depot layer (2) comprises a coalescence enhancer.

[35] The solid oral dosage form according to any of the preceding items, wherein the depot layer (2) comprises a surfactant, preferably a nonionic surfactant.

[36] The solid oral dosage form according to item 35, wherein the surfactant is selected from the group consisting of polysorbate 20, polysorbate 28, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85, poloxamer 124, poloxamer 181, poloxamer 188, poloxamer 237, poloxamer 331, 5 poloxamer 338 and poloxamer 407, and combinations thereof.

[37] The solid oral dosage form according to item 35, wherein the surfactant is polysorbate 20, 28, 40, 60, 65, 80, 81 and 85; preferably polysorbate 80.

[38] The solid oral dosage form according to any of the preceding items, wherein the depot layer (2) comprises or consists of antibody or functional fragment thereof 10 preferably specific to TNF α as an active agent, sucrose, L-histidine (salt and/or free base), preferably L-histidine monohydrochloride and/or free base, hypromellose (HPMC), preferably hypromellose 2910 2.6-3.6 mPas, mesoporous silica, polysorbate 80, and residual water.

[39] The solid oral dosage form according to any of the preceding items, wherein the 15 solid oral dosage form comprises 0.05-30 wt.-%, preferably 0.1-25 wt.-%, more preferably 0.1-20 wt.-%, even more preferably, 0.2-20 wt.-%, even more preferably, 0.2-15 wt.-%, even more preferably 0.5-12 wt.-%, even more preferably 0.5-10 wt.-%, even more preferably 0.8-12 wt.-%, even more preferably 8-12 wt.-%, even more preferably 8-10 wt.-%, e.g. about 9.5 wt.-%, of the antibody or functional fragment 20 thereof preferably specific to TNF α .

[40] The solid oral dosage form according to any of the preceding items, wherein the depot layer (2) comprises 0.2-75 wt.-% antibody or functional fragment thereof, 0.5-65 wt.-% binder, 2-80 wt.-% sucrose, 0.1-10 wt.-% L-histidine (salt and/or free base) and optionally 0.05-10 wt.-% other buffers, 0.2-15 wt.-% anti-tacking agent, 0.01-1 wt.-% 25 surfactant, and/or up to 10 wt.-% water, relative to the total weight of the depot layer; preferably 1-45 wt.-% antibody or functional fragment thereof, 2-35 wt.-% binder, 10-70 wt.-% sucrose, 0.2-5 wt.-% L-histidine and optionally 0.1-4 wt.-% other buffers, 1-5 wt.-% anti-tacking agent, 0.05-0.5 wt.-% surfactant, and/or up to 7 wt.-% water, relative to the total weight of the depot layer; more preferably 10-35 wt.-% antibody or 30 functional fragment thereof, 10-30 wt.-% binder, 30-60 wt.-% sucrose, 0.3-4 wt.-% L-histidine and optionally 0.2-3 wt.-% other buffers, 1.5-3 wt.-% anti-tacking agent, 0.1-0.3 wt.-% surfactant, and/or up to 6 wt.-% water, relative to the total weight of the depot layer; even more preferably 25-35 wt.-% antibody or functional fragment thereof, 15-

25 wt.-% binder, 40-55 wt.-% sucrose, 0.4-3 wt.-% L-histidine and optionally 0.5-2.5 wt.-% other buffers, 1.5-2.5 wt.-% anti-tacking agent, 0.2-0.3 wt.-% surfactant, and/or up to 5 wt.-% water, relative to the total weight of the depot layer.

[41] The solid oral dosage form according to any of the preceding items, wherein the solid oral dosage form, comprises, or consists of,

- a) in the inert core unit (1), microcrystalline cellulose; and/or
- b) in the depot layer (2), antibody or functional fragment thereof preferably specific to TNF α , sucrose, L-histidine, preferably L-histidine monohydrochloride and/or free base, hypromellose (HPMC), preferably hypromellose 2910 2.6-3.6 mPas, mesoporous silica, and/or polysorbate 80; and/or
- c) in the sustained release layer (3), poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (e.g. Eudragit® RS 30D), triethyl citrate (TEC) and/or mesoporous silica; and/or
- d) in the delayed release layer (4), poly(methacrylic acid, methyl methacrylate) 1:2, TEC, polysorbate 80, and/or glycerol monostearate (GMS); and/or
- e) residual water in the inert core unit and/or any of the layers.

[42] The solid oral dosage form of any of the preceding items, wherein the inert core unit (1) is a pellet with a particle size distribution such that at least 85 % of the pellets have a particle size of 700-1400 μm , preferably 700-1000 μm .

- [43] The solid oral dosage form of any of the preceding items, wherein the inert core unit comprises 5-75 wt.-%, preferably 15-65 wt.-%, more preferably 15-60 wt.-%, even more preferably 20-60 wt.-%, even more preferably 25-30 wt.-%, microcrystalline cellulose, relative to the total weight of the solid oral dosage form.

- [44] The solid oral dosage form of any of the preceding items, wherein the depot layer (2) comprises, relative to the total weight of the solid oral dosage form, 0.05-30 wt.-% antibody or functional fragment thereof, 0.03-30 wt.-% binder, 0.1-40 wt.-% sucrose, 0.005-5 wt.-% L-histidine (salt and/or free base) and optionally 0.001-5 wt.-% other buffers, 0.005-8 wt.-% anti-tacking agent, and/or 0.0005-2 wt.-% surfactant; preferably 0.1-20 wt.-% antibody or functional fragment thereof, 0.1-25 wt.-% binder, 0.5-35 wt.-% sucrose, 0.01-3 wt.-% L-histidine and optionally 0.01-3 wt.-% other buffers, 0.01-5 wt.-% anti-tacking agent, and/or 0.001-1 wt.-% surfactant; more

preferably 0.5-20 wt.-% antibody or functional fragment thereof, 0.5-15 wt.-% binder, 1-25 wt.-% sucrose, 0.05-2 wt.-% L-histidine and optionally 0.05-1.5 wt.-% other buffers, 0.05-1.5 wt.-% anti-tacking agent, and/or 0.005-0.3 wt.-% surfactant; even more preferably 2-20 wt.-% antibody or functional fragment thereof, 5-15 wt.-% binder, 5 10-25 wt.-% sucrose, 0.1-2 wt.-% L-histidine and optionally 0.5-1.5 wt.-% other buffers, 0.5-1.5 wt.-% anti-tacking agent, and/or 0.05-0.3 wt.-% surfactant; even more preferably 8-12 wt.-% antibody or functional fragment thereof, 6-8 wt.-% binder (preferably hypromellose (HPMC)), 15-18 wt.-% sucrose, 0.15-1 wt.-% L-histidine and optionally 0.6-0.9 wt.-% other buffers, 0.6-0.8 wt.-% anti-tacking agent (preferably 10 mesoporous silica), and/or 0.05-0.1 wt.-% surfactant (preferably polysorbate 80).

[45] The solid oral dosage form of any of the preceding items, wherein the sustained release layer (3) comprises, relative to the total weight of the solid oral dosage form, 1-10 wt.-% ammonio methacrylate copolymer, 0.1-5 wt.-% plasticizer, and/or 0.05-7 wt.-% anti-tacking agent; preferably 3-6 wt.-% ammonio methacrylate copolymer, 0.2- 15 2 wt.-% plasticizer, and/or 0.1-3 wt.-% anti-tacking agent; more preferably 3.3-4.5 wt.-% ammonio methacrylate copolymer, 0.5-1.5 wt.-% plasticizer, and/or 0.2-1 wt.-% anti-tacking agent; even more preferably 3.6-4.2 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (e.g. Eudragit® RS 30D), 0.6-1 wt.-% plasticizer (preferably triethyl citrate (TEC)) and/or 0.3-0.5 wt.-% 20 anti-tacking agent.

[46] The solid oral dosage form of any of the preceding items, wherein the delayed release layer (4) comprises, relative to the total weight of the solid oral dosage form, 10-40 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 0.5-10 wt.-% plasticizer, 0.1-3.5 wt.-% surfactant, and/or 0.5-10 wt.-% anti-tacking agent (preferably glycerol 25 monostearate (GMS)); preferably 15-35 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 1-5 wt.-% plasticizer, 0.2-2 wt.-% surfactant, and/or 1-5 wt.-% anti-tacking agent (preferably glycerol monostearate (GMS)); more preferably 18-30 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 1.5-3 wt.-% plasticizer, 0.5-1.3 wt.-% surfactant, and/or 1.5-3 wt.-% anti-tacking agent (preferably glycerol monostearate 30 (GMS)); even more preferably 21-26 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 2.0-2.6 wt.-% plasticizer, 0.7-1.1 wt.-% surfactant, and/or 2.0-2.6 wt.-% anti-tacking agent (preferably glycerol monostearate (GMS)).

- [47] The solid oral dosage form of any of the preceding items, comprising up to 7 wt.-%, preferably up to 6 wt.-%, more preferably up to 5 wt.-%, e.g. 5 wt.-%, water in the inert core unit and/or any of the layers, relative to the total weight of the solid oral dosage form.
- 5 [48] The solid oral dosage form according to any of items 1 to 41, wherein the solid oral dosage form (relative to the total weight of the solid oral dosage form) comprises, or consists of,
- a) in the inert core unit (1), 5-75 wt.-%, preferably 15-65 wt.-%, more preferably 20-60 wt.-%, even more preferably 25-30 wt.-%, microcrystalline cellulose; and/or
- 10 b) in the depot layer (2), 0.05-30 wt.-% antibody or functional fragment thereof, 0.03-30 wt.-% binder, 0.1-40 wt.-% sucrose, 0.005-5 wt.-% L-histidine (salt and/or free base) and optionally 0.001-5 wt.-% other buffers, 0.005-8 wt.-% anti-tacking agent, and/or 0.0005-2 wt.-% surfactant; preferably 0.1-20 wt.-% antibody or functional fragment thereof, 0.1-25 wt.-% binder, 0.5-35 wt.-% sucrose, 0.01-3 wt.-% L-
- 15 histidine and optionally 0.01-3 wt.-% other buffers, 0.01-5 wt.-% anti-tacking agent, and/or 0.001-1 wt.-% surfactant; more preferably 0.5-20 wt.-% antibody or functional fragment thereof, 0.5-15 wt.-% binder, 1-25 wt.-% sucrose, 0.05-2 wt.-% L-histidine and optionally 0.05-1.5 wt.-% other buffers, 0.05-1.5 wt.-% anti-tacking agent, and/or 0.005-0.3 wt.-% surfactant; even more preferably 2-20 wt.-%
- 20 antibody or functional fragment thereof, 5-15 wt.-% binder, 10-25 wt.-% sucrose, 0.1-2 wt.-% L-histidine and optionally 0.5-1.5 wt.-% other buffers, 0.5-1.5 wt.-% anti-tacking agent, and/or 0.05-0.3 wt.-% surfactant; even more preferably 8-12 wt.-% antibody or functional fragment thereof, 6-8 wt.-% binder (preferably hypromellose (HPMC)), 15-18 wt.-% sucrose, 0.15-1 wt.-% L-histidine and
- 25 optionally 0.6-0.9 wt.-% other buffers, 0.6-0.8 wt.-% mesoporous silica, and/or 0.05-0.1 wt.-% polysorbate 80; and/or
- c) in the sustained release layer (3), 1-10 wt.-% ammonio methacrylate copolymer, 0.1-5 wt.-% plasticizer, and/or 0.05-7 wt.-% anti-tacking agent; preferably 3-6 wt.-% ammonio methacrylate copolymer, 0.2-2 wt.-% plasticizer, and/or 0.1-3 wt.-%
- 30 anti-tacking agent; more preferably 3.3-4.5 wt.-% ammonio methacrylate copolymer, 0.5-1.5 wt.-% plasticizer, and/or 0.2-1 wt.-% anti-tacking agent; even more preferably 3.6-4.2 wt.-% poly(ethyl acrylate, methyl methacrylate,

- trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (e.g. Eudragit® RS 30D), 0.6-1 wt.-% triethyl citrate (TEC) and/or 0.3-0.5 wt.-% mesoporous silica; and/or
- d) in the delayed release layer (4), 10-40 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 0.5-10 wt.-% plasticizer, 0.1-3.5 wt.-% surfactant, and/or 0.5-10 wt.-% anti-tacking agent (preferably glycerol monostearate (GMS)); preferably 15-35 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 1-5 wt.-% plasticizer, 0.2-2 wt.-% surfactant, and/or 1-5 wt.-% anti-tacking agent (preferably glycerol monostearate (GMS)); more preferably 18-30 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 1.5-3 wt.-% plasticizer, 0.5-1.3 wt.-% surfactant, and/or 1.5-3 wt.-% anti-tacking agent (preferably glycerol monostearate (GMS)); even more preferably 21-26 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 2.0-2.6 wt.-% plasticizer, 0.7-1.1 wt.-% surfactant, and/or 2.0-2.6 wt.-% glycerol monostearate (GMS); and/or
- e) up to 5 wt.-%, e.g. 5 wt.-%, water in the inert core unit and/or any of the layers.
- [49] The solid oral dosage form according any of the preceding items, wherein sustained release layer (3) comprises, apart from ammonio methacrylate copolymer, no other sustained release polymer; preferably poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1; poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.2 (e.g. Eudragit® RL 30D); or a combination thereof, and preferably no other sustained release polymer.
- [50] The solid oral dosage form according any of the preceding items, wherein sustained release layer (3) comprises poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 and preferably no other sustained release polymer.
- [51] The solid oral dosage form according any of the preceding items, wherein the plasticizer in the sustained release layer (3) is triethyl citrate (TEC), polyethylene glycol, acetyl triethyl citrate, butyl citrate, polysorbate, polypropylene glycol, dibutyl sebacate (DBS), or a combination thereof, preferably triethyl citrate (TEC).
- [52] The solid oral dosage form according any of the preceding items, wherein the anti-tacking agent in the sustained release layer (3) is mesoporous silica, colloidal

silica dioxide, stearic acid, magnesium stearate, glycerol monostearate (GMS), or talc, preferably mesoporous silica.

[53] The solid oral dosage form according to any of the preceding items, wherein the solid oral dosage form comprises 0.5-15 wt.-%, preferably 1-10 wt.-%, more preferably 3-5 wt.-%, even more preferably 3.5-4.5 wt.-%, even more preferably 3.8-4.1 wt.-%, e.g. 4 wt.-%, ammonio methacrylate copolymer, preferably poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1.

[54] The solid oral dosage form according to any of the preceding items, wherein the sustained release layer (3) comprises 60-90 wt.-%, preferably 65-85 wt.-%, more preferably 70-80 wt.-%, even more preferably 72-78 wt.-%, ammonio methacrylate copolymer, preferably poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1, relative to the total weight of the solids (i.e. not including water) in the sustained release layer (3).

[55] The solid oral dosage form according to any of the preceding items, wherein the sustained release layer (3) comprises 2-40 wt.-%, preferably 5-30 wt.-%, more preferably 15-25 wt.-%, even more preferably 17-23 wt.-%, even more preferably 20 wt.-%, plasticizer, relative to the total weight of the ammonio methacrylate copolymers in the sustained release layer (3).

[56] The solid oral dosage form according to any of the preceding items, wherein the sustained release layer (3) comprises 1-30 wt.-%, preferably 2-25 wt.-%, more preferably 5-15 wt.-%, even more preferably 8-12 wt.-%, even more preferably 10 wt.-%, anti-tacking agent, relative to the total weight of the ammonio methacrylate copolymers in the sustained release layer (3).

[57] The solid oral dosage form according to any of the preceding items, wherein the sustained release coating comprises 5-25 wt.-%, preferably 10-20 wt.-%, more preferably 12-18 wt.-%, even more preferably 13-17 wt.-%, even more preferably 14-15 wt.-%, plasticizer, relative to the total weight of the solids (i.e. not including water) in the sustained release layer (3).

[58] The solid oral dosage form according to any of the preceding items, wherein the sustained release coating comprises 5-12 wt.-%, preferably 6-9 wt.-%, more preferably 6-8.5 wt.-%, even more preferably 6.5-8.0 wt.-%, even more preferably 6.9-7.8 wt.-%,

even more preferably 7.0-7.5 wt.-%, anti-tacking agent, relative to the total weight of the solids (i.e. not including water) in the sustained release layer (3).

[59] The solid oral dosage form according to any of the preceding items, wherein the sustained release layer (3) comprises no coalescence enhancer.

5 [60] The solid oral dosage form according to any of items 1 to 58, wherein the sustained release layer (3) comprises a coalescence enhancer.

[61] The solid oral dosage form according to item 60, wherein the coalescence enhancer is propylene glycol monolaurate (e.g. Lauroglycol™ 90).

10 [62] The solid oral dosage form according to any of the preceding items, wherein the weight of the sustained release layer (3), relative to combined weight of the inert core unit (1) and the depot layer (2), is 4-8 wt.-%, preferably 5-7 wt.-% more preferably about 6 wt.-%.

15 [63] The solid oral dosage form according to any of the preceding items, wherein the sustained release layer (3) was applied by spray coating, preferably fluidized-bed spray coating.

[64] The solid oral dosage form according to item 63, wherein the weight gain of the solid oral dosage form after sustained release coating and drying, but before applying any further layer, is 4-8 wt.-%, preferably 5-7 wt.-%, more preferably about 6 wt.-%.

20 [65] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) comprises no polymers that are not enteric polymers.

25 [66] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) comprises, apart from poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof, no other delayed release polymers.

[67] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) comprises poly(methacrylic acid, methyl methacrylate) 1:2, and preferably no other delayed release polymer.

30 [68] The solid oral dosage form according any of the preceding items, wherein the plasticizer in the delayed release layer (4) is triethyl citrate (TEC), polyethylene glycol,

acetyl triethyl citrate, butyl citrate, polypropylene glycol, dibutyl sebacate (DBS), or a combination thereof, preferably triethyl citrate (TEC).

[69] The solid oral dosage form according any of the preceding items, wherein the anti-tacking agent in the delayed release layer (4) is mesoporous silica, colloidal silica
5 dioxide, stearic acid, magnesium stearate, glycerol monostearate (GMS), or talc, preferably glycerol monostearate (GMS).

[70] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) comprises a surfactant, preferably a nonionic surfactant.

[71] The solid oral dosage form according to item 66, wherein the surfactant is
10 selected from the group consisting of polysorbate 20, polysorbate 28, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85, poloxamer 124, poloxamer 181, poloxamer 188, poloxamer 237, poloxamer 331, poloxamer 338 and poloxamer 407, and combinations thereof.

[72] The solid oral dosage form according to item 70, wherein the surfactant is
15 polysorbate 20, 28, 40, 60, 65, 80, 81 and 85; preferably polysorbate 80.

[73] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) comprises no coalescence enhancer.

[74] The solid oral dosage form according to any of the preceding items, wherein the solid oral dosage form comprises 5-40 wt.-%, preferably 10-40 wt.-%, more preferably
20 10-35 wt.-%, even more preferably 15-35 wt.-%, even more preferably 15-30 wt.-%, even more preferably 18-30 wt.-%, even more preferably 20-30 wt.-%, e.g. 22-25 wt.-%, poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof (preferably poly(methacrylic acid, methyl methacrylate) 1:2).

[75] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) comprises 65-95 wt.-%, preferably 70-90 wt.-%, more preferably 75-85 wt.-%, e.g. about 80 wt.-%, poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof (preferably
25 poly(methacrylic acid, methyl methacrylate) 1:2), relative to the total weight of the solids (i.e. not including solvents) in the delayed release layer (4).
30

[76] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) comprises 1-30 wt.-%, preferably 2-25 wt.-%, more preferably 5-15 wt.-%, even more preferably 8-12 wt.-%, even more preferably 10 wt.-%, plasticizer, relative to the total weight of the delayed release polymers in the delayed release layer (4).

[77] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) comprises 1-30 wt.-%, preferably 2-25 wt.-%, more preferably 5-15 wt.-%, even more preferably 8-12 wt.-%, even more preferably 10 wt.-%, anti-tacking agent, relative to the total weight of the delayed release polymers in the delayed release layer (4).

[78] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) comprises 0.1-15 wt.-%, preferably 0.5-10 wt.-%, more preferably 1-6 wt.-%, even more preferably 2-5 wt.-%, even more preferably 3-4.5 wt.-%, even more preferably 3.5-4 wt.-%, surfactant, relative to the total weight of the delayed release polymers in the delayed release layer (4).

[79] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) comprises 1-25 wt.-%, preferably 4-15 wt.-%, more preferably 5-12 wt.-%, even more preferably 6-10 wt.-%, even more preferably 7-9 wt.-%, even more preferably about 8 wt.-%, plasticizer, relative to the total weight of the solids (i.e. not including solvents) in the delayed release layer (4).

[80] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) comprises 1-25 wt.-%, preferably 4-15 wt.-%, more preferably 5-12 wt.-%, even more preferably 6-10 wt.-%, even more preferably 7-9 wt.-%, even more preferably about 8 wt.-%, even more preferably about 7.5 wt.-%, anti-tacking agent, relative to the total weight of the solids (i.e. not including solvents) in the delayed release layer (4).

[81] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) comprises 0.1-15 wt.-%, preferably 0.5-10 wt.-%, more preferably 1-5 wt.-%, even more preferably 2-4 wt.-%, even more preferably 2.5-3.5 wt.-%, even more preferably 3-3.5 wt.-%, even more preferably about 3-3.2 wt.-%, surfactant, relative to the total weight of the solids (i.e. not including solvents) in the delayed release layer (4).

[82] The solid oral dosage form according to any of the preceding items, wherein the solid dosage form, in the delayed release layer (4), comprises 7-13 mg/cm², preferably 8-12 mg/cm², more preferably 9-11.5 mg/cm², even more preferably about 9.5 mg/cm², or about 11.50 mg/cm², poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof (preferably poly(methacrylic acid, methyl methacrylate) 1:2).

[83] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) was applied by spray coating, preferably fluidized-bed spray coating.

[84] The solid oral dosage form according to any of the preceding items, wherein the solid oral dosage form comprises an amount of the antibody or functional fragment thereof that allows the administration of a therapeutically effective dose of the antibody or functional fragment thereof as a single unit dose.

[85] The solid oral dosage form according to any of the preceding items, wherein the solid oral dosage form (relative to the total weight of the solid oral dosage form) comprises, or consists of,

- a) in the inert core unit (1), 57.5-58.2 wt.-% microcrystalline cellulose; preferably 57.65-58.05 wt.-% microcrystalline cellulose (e.g. cellets 700);
- b) in the depot layer (2), 0.65-0.95 wt.-% antibody or functional fragment thereof, 0.44-74 wt.-% hypromellose (HPMC) (e.g. Pharmacoat 603), 1.24-1.60 wt.-% sucrose, 0.06-0.10 wt.-% L-histidine (e.g. L-Histidine and/or L-Histidine HCL buffer salts solid), 0.04-0.08 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 µm and/or an average pore volume of 1.58-1.62 cm³/g, e.g. Syloid 244FP), and 0.006-0.014 wt.-% polysorbate 80; preferably 0.75-0.85 wt.-% antibody or functional fragment thereof, 0.54-64 wt.-% hypromellose (HPMC) (e.g. Pharmacoat 603), 1.34-1.50 wt.-% sucrose, 0.07-0.09 wt.-% L-histidine (e.g. L-Histidine and/or L-Histidine HCL buffer salts solid), 0.05-0.07 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 µm and/or an average pore volume of 1.58-1.62 cm³/g, e.g. Syloid 244FP), and 0.008-0.012 wt.-% polysorbate 80;

- c) in the sustained release layer (3), 3.8-4.2 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (e.g. Eudragit® RS solids), 0.65-0.95 wt.-% triethyl citrate (TEC) and 0.30-0.50 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP); preferably 3.9-4.1 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (e.g. Eudragit® RS solids), 0.75-0.85 wt.-% triethyl citrate (TEC) and 0.35-0.45 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP);
- d) in the delayed release layer (4), 23.1-23.7 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2 (e.g. Eudragit® S100 solids), 2.19-2.49 wt.-% triethyl citrate (TEC), 0.79-1.09 wt.-% polysorbate 80, and 2.19-2.49 wt.-% glycerol monostearate (GMS); preferably 23.25-23.55 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2 (e.g. Eudragit® S100 solids), 2.29-2.39 wt.-% triethyl citrate (TEC), 0.89-0.99 wt.-% polysorbate 80, and 2.29-2.39 wt.-% glycerol monostearate (GMS); and/or
- e) 4.7 wt.-% to 5.3 wt.-% water; preferably 4.9 wt.-% to 5.1 wt.-% water in the inert core unit and/or any of the layers.
- [86] The solid oral dosage form according to any of items 1-84, wherein the solid oral dosage form (relative to the total weight of the solid oral dosage form) comprises, or consists of,
- a) in the inert core unit (1), 26.85-27.45 wt.-% microcrystalline cellulose; preferably 27.0-27.3 wt.-% microcrystalline cellulose (e.g. cellets 700);
- b) in the depot layer (2), 9.23-9.73 wt.-% antibody or functional fragment thereof, 6.7-7.1 wt.-% hypromellose (HPMC) (e.g. Pharmacoat 603), 16.62-17.12 wt.-% sucrose, 0.79-1.09 wt.-% L-histidine (e.g. L-Histidine and/or L-Histidine HCL buffer salts solid), 0.54-0.84 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP), and 0.06-0.10 wt.-% polysorbate 80; preferably 9.38-9.58 wt.-% antibody or functional fragment thereof, 6.8-7.0 wt.-% hypromellose (HPMC) (e.g. Pharmacoat 603), 16.72-17.02 wt.-% sucrose, 0.89-0.99 wt.-% L-histidine (e.g. L-

Histidine and/or L-Histidine HCL buffer salts solid), 0.64-0.74 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP), and 0.07-0.09 wt.-% polysorbate 80;

- 5 c) in the sustained release layer (3), 3.74-4.14 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (e.g. Eudragit® RS solids), 0.64-0.94 wt.-% triethyl citrate (TEC) and 0.29-0.49 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP); preferably 3.84-4.04
10 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (e.g. Eudragit® RS solids), 0.74-0.84 wt.-% triethyl citrate (TEC) and 0.34-0.44 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP);
- 15 d) in the delayed release layer (4), 22.63-23.23 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2 (e.g. Eudragit® S100 solids), 2.14-2.44 wt.-% triethyl citrate (TEC), 0.77-0.107 wt.-% polysorbate 80, and 2.14-2.44 wt.-% glycerol monostearate (GMS); preferably 22.78-23.08 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2 (e.g. Eudragit® S100 solids), 2.24-2.34 wt.-% triethyl citrate
20 (TEC), 0.87-0.97 wt.-% polysorbate 80, and 2.24-2.34 wt.-% glycerol monostearate (GMS); and/or
- e) 4.03 wt.-% to 4.63 wt.-% water; preferably 4.23 wt.-% to 4.43 wt.-% water in the inert core unit and/or any of the layers.

[87] The solid oral dosage form according to any of items 1-84, wherein the solid oral
25 dosage form (relative to the total weight of the solid oral dosage form) comprises, or consists of,

- a) in the inert core unit (1), 24.92-25.52 wt.-% microcrystalline cellulose, preferably 25.07-25.37 wt.-% microcrystalline cellulose (e.g. cellets 700);
- 30 b) in the depot layer (2), 9.0-9.5 wt.-% antibody or functional fragment thereof, 6.54-6.94 wt.-% hypromellose (HPMC) (e.g. Pharmacoat 603), 16.23-16.73 wt.-% sucrose, 0.76-1.06 wt.-% L-histidine (e.g. L-Histidine and/or L-Histidine HCL buffer salts solid), 0.52-0.82 wt.-% mesoporous silica (e.g. having average particle size

- of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP), and 0.06-0.10 wt.-% polysorbate 80; preferably 9.16-9.36 wt.-% antibody or functional fragment thereof, 6.64-6.84 wt.-% hypromellose (HPMC) (e.g. Pharmacoat 603), 16.33-16.63 wt.-% sucrose, 0.86-0.96 wt.-% L-histidine (e.g. L-Histidine and/or L-Histidine HCL buffer salts solid), 0.62-0.72 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP), and 0.07-0.09 wt.-% polysorbate 80;
- 5 c) in the sustained release layer (3), 3.6-4.0 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (e.g. Eudragit® RS solids), 0.61-0.91 wt.-% triethyl citrate (TEC) and 0.28-0.48 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP); preferably 3.7-3.9 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (e.g. Eudragit® RS solids), 0.71-0.81 wt.-% triethyl citrate (TEC) and 0.33-0.43 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP);
- 10 d) in the delayed release layer (4), 24.5-25.1 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2 (e.g. Eudragit® S100 solids), 2.33-2.63 wt.-% triethyl citrate (TEC), 0.85-1.15 wt.-% polysorbate 80, and 2.33-2.63 wt.-% glycerol monostearate (GMS); 24.65-24.95 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2 (e.g. Eudragit® S100 solids), 2.43-2.53 wt.-% triethyl citrate (TEC), 0.94-1.04 wt.-% polysorbate 80, and 2.43-2.53 wt.-% glycerol monostearate (GMS); and/or
- 15 e) 4.65 wt.-% to 5.25 wt.-% water; preferably 4.85 wt.-% to 5.05 wt.-% water in the inert core unit and/or any of the layers.
- [88] The solid oral dosage form according to any of items 1-84, wherein the solid oral dosage form (relative to the total weight of the solid oral dosage form) comprises, or
- 20 consists of,
- 30 a) in the inert core unit (1), 25.06-25.66 wt.-% microcrystalline cellulose, preferably 25.21-25.51 wt.-% microcrystalline cellulose (e.g. cellets 700);

- b) in the depot layer (2), 8.76-9.26 wt.-% antibody or functional fragment thereof, 6.38-6.78 wt.-% hypromellose (HPMC) (e.g. Pharmacoat 603), 15.57-16.17 wt.-% sucrose, 0.73-1.03 wt.-% L-histidine (e.g. L-Histidine and/or L-Histidine HCL buffer salts solid), 0.51-0.81 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP), and 0.06-0.10 wt.-% polysorbate 80; preferably 8.91-9.11 wt.-% antibody or functional fragment thereof, 6.48-6.68 wt.-% hypromellose (HPMC) (e.g. Pharmacoat 603), 15.72-16.02 wt.-% sucrose, 0.83-0.93 wt.-% L-histidine (e.g. L-Histidine and/or L-Histidine HCL buffer salts solid), 0.61-0.71 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP), and 0.07-0.09 wt.-% polysorbate 80;
- c) in the sustained release layer (3), 3.48-3.88 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (e.g. Eudragit® RS solids), 0.59-0.89 wt.-% triethyl citrate (TEC) and 0.27-0.47 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP); preferably 3.58-3.78 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (e.g. Eudragit® RS solids), 0.69-0.79 wt.-% triethyl citrate (TEC) and 0.32-0.42 wt.-% mesoporous silica (e.g. having average particle size of 3.4-3.6 μm and/or an average pore volume of 1.58-1.62 cm^3/g , e.g. Syloid 244FP);
- d) in the delayed release layer (4), 25.41-26.01 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2 (e.g. Eudragit® S100 solids), 2.42-2.72 wt.-% triethyl citrate (TEC), 0.88-1.18 wt.-% polysorbate 80, and 2.42-2.72 wt.-% glycerol monostearate (GMS); 25.56-25.86 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2 (e.g. Eudragit® S100 solids), 2.52-2.62 wt.-% triethyl citrate (TEC), 0.98-1.08 wt.-% polysorbate 80, and 2.52-2.62 wt.-% glycerol monostearate (GMS); and/or
- e) 4.60 wt.-% to 5.2 wt.-% water; preferably 4.80 wt.-% to 5.00 wt.-% water in the inert core unit and/or any of the layers

[89] The solid oral dosage form according to any of the preceding items, wherein the functional antibody fragment is a Fab fragment, a F(ab')₂ fragment, a Fab' fragment,

an scFv, a dsFv, a VHH, a diabody, a triabody, a tetrabody, an Fc fusion protein or a minibody.

[90] The solid oral dosage form according to any of the preceding items, wherein the antibody or functional fragment thereof is selected from antibodies specific to tumor
5 necrosis factor alpha (TNF α) and functional fragments thereof, antibodies specific to α 4 β 7 integrin and functional fragments thereof, antibodies specific to CD3, CD4 or CD20 and functional fragments thereof, antibodies specific to interleukin 6 (IL-6), interleukin 12 (IL-12), interleukin 13 (IL-13), interleukin 23 (IL-23) or to their receptors and functional fragments thereof, antibodies specific to CXCL10/IP-10 and functional
10 fragments thereof, and antibodies specific to p40 protein subunit and functional fragments thereof.

[91] The solid oral dosage form according to any of the preceding items, wherein the antibody or functional fragment thereof is suitable for use in the treatment of immune
checkpoint inhibitor (ICPI) induced colitis, ICPI induced enterocolitis, ICPI induced
15 diarrhoea and/or an inflammatory bowel disease (IBD), like Crohn's disease or ulcerative colitis.

[92] The solid oral dosage form according to any of the preceding items, wherein the antibody or functional fragment thereof is an antibody specific to tumor necrosis factor alpha (TNF α) or functional fragment thereof.

20 [93] The solid oral dosage form according to item 92, wherein the antibody specific to TNF α or functional fragment thereof is an anti-TNF α antibody.

[94] The solid oral dosage form according to any of the preceding items, wherein the antibody or functional fragment thereof is an anti-TNF α antibody or functional fragment thereof with a TNF α binding domain comprising (i) a V_L domain comprising a CDR1
25 region having an amino acid sequence as shown in SEQ ID NO:1, a CDR2 region having an amino acid sequence as shown in SEQ ID NO:2, and a CDR3 region having an amino acid sequence as shown in SEQ ID NO:3, and/or (ii) a V_H domain comprising a CDR1 region having an amino acid sequence as shown in SEQ ID NO:4, a CDR2 region having an amino acid sequence as shown in SEQ ID NO:5, and a CDR3 region
30 having the amino acid sequence as shown in SEQ ID NO:6.

[95] The solid oral dosage form according to any of the preceding items, wherein the antibody or functional fragment thereof is an anti-TNF α antibody or functional fragment

thereof with a TNF α binding domain comprising, or consisting of, (i) a V_L domain having an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:8, and/or (ii) a V_H domain having an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:7.

- 5 [96] The solid oral dosage form according to any of items 1-93, wherein the antibody or functional fragment thereof is an anti-TNF α antibody or functional fragment thereof with a TNF α binding domain comprising (i) a V_L domain comprising a CDR1 region having an amino acid sequence as shown in SEQ ID NO:9, a CDR2 region having an amino acid sequence as shown in SEQ ID NO:10, and a CDR3 region having an amino acid sequence as shown in SEQ ID NO:11, and/or (ii) a V_H domain comprising a CDR1 region having an amino acid sequence as shown in SEQ ID NO:12, a CDR2 region having an amino acid sequence as shown in SEQ ID NO:13, and a CDR3 region having the amino acid sequence as shown in SEQ ID NO:14.

- 15 [97] The solid oral dosage form according to any of items 1-93, wherein the antibody or functional fragment thereof is an anti-TNF α antibody or functional fragment thereof with a TNF α binding domain comprising, or consisting of, (i) a V_L domain having an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:16 or in SEQ ID NO:17, and/or (ii) a V_H domain having an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:15.

- 20 [98] The solid oral dosage form according to any of items 1-93, wherein the antibody or functional fragment thereof is an anti-TNF α antibody comprising a Fc region having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:18, in SEQ ID NO:19, in SEQ ID NO:20, in SEQ ID NO:21, or in SEQ ID NO:22, preferably in SEQ ID NO:18.

- 25 [99] The solid oral dosage form according to any of items 1-93, wherein the antibody or functional fragment thereof is an anti-TNF α antibody comprising, or consisting of, (i) a light chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:23, and (ii) a heavy chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:26.
- 30

[100] The solid oral dosage form according to any of items 1-93, wherein the antibody or functional fragment thereof is an anti-TNF α antibody comprising, or consisting of (i)

a light chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:24 or in SEQ ID NO:25, and (ii) a heavy chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:27.

5 [101] The solid oral dosage form according to any of items 1-93, wherein the antibody or functional fragment thereof is an anti-TNF α antibody comprising, or consisting of (i) a light chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:23, and (ii) a heavy chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:28, in SEQ ID NO:29, or in SEQ ID NO:30.

[102] The solid oral dosage form according to any of items 1-93, wherein the antibody or functional fragment thereof is an anti-TNF α antibody comprising, or consisting of (i) a light chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:24 or in SEQ ID NO:25, and (ii) a heavy chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:31, in SEQ ID NO:32, or in SEQ ID NO:33.

[103] The solid oral dosage form according to any of items 1-93, wherein the antibody or functional fragment thereof is an anti-TNF α antibody comprising, or consisting of (i) a light chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:23, and (ii) a heavy chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:34.

[104] The solid oral dosage form according to any of items 1-93, wherein the antibody or functional fragment thereof is an anti-TNF α antibody comprising, or consisting of (i) a light chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:24 or in SEQ ID NO:25, and (ii) a heavy chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:35.

[105] The solid oral dosage form according to any of items 1-91, wherein the antibody or functional fragment thereof is selected from infliximab, adalimumab, etanercept, certolizumab pegol, golimumab, visilizumab, eldelumab, abrilumab, canakinumab,

tocilizumab, ustekinumab, natalizumab, etrolizumab, priliximab, vedolizumab and functional fragments thereof.

[106] The solid oral dosage form according to any of items 1-92, wherein the anti-TNF α antibody or functional fragment thereof is selected from infliximab, adalimumab, etanercept, certolizumab pegol and golimumab or a functional fragment thereof.

[107] The solid oral dosage form according to any of the preceding items, allowing a sustained release of the antibody or functional fragment thereof over a time period of at least 5 h, preferably at least 10 h, more preferably at least 12 h, even more preferably at least 15 h, even more preferably at least 20 h, most preferably at least 24 h, upon continuously immersing the solid oral dosage form in an aqueous solution under continuous agitation at a pH of 6.5-7.5, preferably about 6.8.

[108] The solid oral dosage form according to any of the preceding items, wherein, upon continuously immersing the solid oral dosage form in an aqueous solution under continuous agitation and at a pH of 6.5-7.5, preferably pH of 6.5-7.0, more preferably a pH of 6.8, a sustained release, preferably with a substantially constant release rate, of at least 60 %, preferably of at least 80 %, more preferably at least 90 %, of the antibody or functional fragment thereof in the solid oral dosage form over 4-30h, preferably 8-28h, more preferably 16-26h, even more preferably 24 h, is achieved.

[109] The solid oral dosage form according to any of the preceding items, wherein water content in the solid oral dosage form is less than 10 wt.-%, preferably less than 8 wt.-%, more preferably less than 5 wt.-%, or less than 3 wt.-%, less than 1.5 wt.-% or less than 1 wt.-%, relative to the total weight of the solid oral dosage.

[110] The solid oral dosage form according to any of the preceding items wherein the fraction of total content of antibody or functional fragment thereof present in the solid oral dosage form as dimers and other aggregates does not exceed 15 %, preferably 12 %, more preferably 10 %, even more preferably 8 %, even more preferably 7 %, even more preferably 5 %, even more preferably 3 %.

[111] The solid oral dosage form according to any of the preceding items wherein the fraction of total content of antibody or functional fragment thereof present in the solid oral dosage form as fragments of the full-length antibody or functional fragment thereof does not exceed 15 %, preferably 12 %, more preferably 10 %, even more preferably 8 %, even more preferably 7 %, even more preferably 5 %, even more preferably 3 %.

[112] The solid oral dosage form according to any of the preceding items, wherein the depot layer (2) has an average thickness of 1-300 μm , preferably 2-200 μm , more preferably 5-200 μm , even more preferably 10-200 μm , e.g. 100-200, or 150 μm .

5 [113] The solid oral dosage form according to any of the preceding items, wherein the sustained release layer (3) has an average thickness of 5-50 μm , preferably 10-45 μm , more preferably 15-35 μm , even more preferably 18-30 μm , even more preferably 20-30 μm , e.g. 24 or 25 μm .

10 [114] The solid oral dosage form according to any of the preceding items, wherein the sustained release layer (3) has a fixed average thickness of 5-50 μm , preferably 10-45 μm , more preferably 15-35 μm , even more preferably 18-30 μm , even more preferably 20-30 μm , e.g. 24 or 25 μm ; preferably irrespective of the thickness the depot layer (2) and/or amount of antibody or functional fragment thereof in the depot layer (2).

15 [115] The solid oral dosage form according to any of the preceding items, wherein the delayed release layer (4) has an average thickness of 10-300 μm , preferably 50-180 μm , more preferably 60-160 μm , even more preferably 80-150 μm , even more preferably 90-130 μm , even more preferably 95-120 μm , e.g. 105 or 120 μm .

20 [116] The solid oral dosage form according to any of the preceding items, wherein the average thickness of the sustained release layer (3) is constant, irrespective of the amount of antibody or functional fragment thereof in the solid oral dosage form and/or the thickness of the depot layer.

25 [117] Solid oral dosage form according to any of items 1 to 116 for use in the targeted local treatment of a gastrointestinal disease, preferably immune checkpoint inhibitor (ICPI) induced colitis, ICPI induced enterocolitis, ICPI induced diarrhoea, an IBD, colorectal cancer, small intestine cancer, celiac disease, a gastrointestinal infections (e.g. Clostridium difficile infection), more preferably ICPI induced colitis, ICPI induced enterocolitis, ICPI induced diarrhoea, or an IBD.

[118] Solid oral dosage form for use according to item 117, wherein the gastrointestinal disease is IBD, preferably Crohn's disease or ulcerative colitis.

30 [119] Solid oral dosage form for use according to item 117, wherein the gastrointestinal disease is ICPI induced colitis, ICPI induced enterocolitis, or ICPI induced diarrhoea, preferably ICPI induced colitis.

[120] Solid oral dosage form according to any of items 117 to 119 for use in the targeted local treatment in the terminal ileum, the ileocolonic region, the ascending colon, transverse colon, the descending colon and/or the sigmoid colon of a patient, preferably a human patient.

- 5 [121] An oral multiparticulate drug delivery system, comprising a plurality of solid oral dosage forms of any one of items 1 to 116, preferably wherein the oral multiparticulate drug delivery system is a sachet/stick pack, a straw device (XStraw®), capsule, or tablet/mini-tablet, more preferably a capsule; preferably wherein the oral multiparticulate drug delivery system comprises a total amount of the antibody or
10 functional fragment thereof suitable for oral administration to a human patient.

- [122] An oral multiparticulate drug delivery system comprising a plurality of solid oral dosage forms of any of items 1 to 116, wherein each solid oral dosage form unit preferably has a predetermined axis and a predetermined cross-sectional profile, wherein at least 80 % by number of those solid oral dosage forms, preferably 90 %,
15 more preferably 95 %, have a median aspect ratio between 0.7 and 1.7, the aspect ratio being defined as solid oral dosage form length along the predetermined axis divided by the smallest cross-sectional dimension.

- [123] The oral multiparticulate drug delivery system according to item 121 or 122, wherein the median aspect ratio is above 0.8, preferably above 0.9, and below 1.6,
20 preferably below 1.5, more preferably 1.4, even more preferably below 1.3, even more preferably below 1.2, most preferably about 1.

- [124] The oral multiparticulate drug delivery system according to any of items 121 to 123, allowing the recovery of at least 60 %, preferably at least 80 %, more preferably at least 85 %, even more preferably at least 93 %, even more preferably at least 95 %,
25 even more preferably at least 97 %, even more preferably at least 98 %, of the antibody or functional fragment thereof from the solid oral dosage forms.

- [125] The oral multiparticulate drug delivery system according to any of items 121 to 124, allowing the recovery of at least 60 %, preferably at least 80 %, more preferably at least 85 %, even more preferably at least 93 %, even more preferably at least 95 %,
30 even more preferably at least 97 %, even more preferably at least 98 %, of the antibody or functional fragment thereof from the solid oral dosage forms, within 4 h, or 6 h, or 8 h, or 10 h, or 12 h, or 14 h, or 16 h, or 18 h, or 20 h, or 22 h, or 24 h, or 26 h, or 28 h,

or 30 h, of continuously immersing the solid oral dosage form in an aqueous solution under continuous agitation (sustained release), at a pH of 6.5 to 7, preferably at a pH of about 6.8.

5 [126] The oral multiparticulate drug delivery system according to any of items 121 to 125, wherein the oral multiparticulate drug delivery system is prepared from a plurality of solid oral dosage form by compression or encapsulation, preferably encapsulation.

[127] A method for targeted local treatment of a gastrointestinal disease, comprising administering to a patient in need thereof a pharmaceutically effective amount of the solid oral dosage form of any of items 1-116 or the oral multiparticulate drug delivery
10 system of any of items 121-126.

[128] The method of item 127, wherein the gastrointestinal disease is immune checkpoint inhibitor (ICPI) induced colitis, ICPI induced enterocolitis, ICPI induced diarrhoea, or an inflammatory bowel disease (IBD).

[129] The method of item 127 or 128, wherein the patient is a human patient and
15 wherein optionally the solid oral dosage form or the oral multiparticulate drug delivery system is administered orally every 24-48 h, preferably every 24 h.

[130] Use of the solid dosage form of any of items 1 to 116 in the preparation of a medicament for the treatment of a gastrointestinal disease.

[131] Use according to item 130, wherein the gastrointestinal disease is IBD,
20 preferably Crohn's disease or ulcerative colitis.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Multi-layered solid oral dosage form of the present invention, comprising an inert core unit (1); a depot layer (2) comprising the antibody or functional fragment
25 thereof; the sustained release layer (3); and the delayed release layer (4).

Figure 2: Illustration showing the oral multiparticulate drug delivery system comprising the multi-layer solid oral dosage form; a description of the different layers in a single solid oral dosage form; and a scanning electron microscope (SEM) image of a final
30 single solid oral dosage form.

Figure 3: (A) Drug loading confirmation (Bradford determination) for Example 1 drug coated intermediate (comprising inert core and depot layer) after 1 h incubation in pH 6.8 phosphate buffer. (B) Dissolution kinetics (Bradford determination) for Example 1 Eudragit® RS intermediate (comprising inert core unit, depot layer and sustained release layer) in pH 6.8 phosphate buffer. (C) Dissolution kinetics for Example 1 Eudragit® S coated final formulation [that is, Example 1 intermediate of (B) coated with delayed release layer] assessed using the dissolution assay.

Figure 4: Dissolution kinetics for Example 2 and Example 3 assessed using the dissolution assay.

Figure 5: Scanning electron microscope (SEM) image of cross-section of Eudragit® RS intermediate formulation (comprising inert core unit, depot layer and sustained release layer) with lower drug load.

Figure 6: Scanning electron microscope (SEM) image of cross-section of Eudragit® RS intermediate formulation (comprising inert core unit, depot layer and sustained release layer) with higher drug load.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a novel solid oral dosage form comprising i) an inert core unit (1); ii) a depot layer (2) covering the inert core unit (1) and comprising an antibody or a functional fragment thereof, preferably specific to tumor necrosis factor alpha (TNF α), as an active agent; a stabilizer, preferably sucrose; a buffer; and a polymeric binder, preferably hypromellose (HPMC); iii) a sustained release layer (3), covering the depot layer (2) and comprising an ammonio methacrylate copolymer, preferably poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1; a plasticizer; and an anti-tacking agent; and iv) a delayed release layer (4) covering the sustained release layer (3) and comprising poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof, preferably poly(methacrylic acid, methyl methacrylate) 1:2;

an anti-tacking agent, preferably glycerol monostearate (GMS); and a plasticizer, preferably triethyl citrate (TEC).

The term "solid oral dosage form" as used herein may be understood to be equivalent to "solid oral pharmaceutical dosage form" or "pharmaceutical composition formulated into a solid oral dosage form", is suitable for oral administration and includes for example a pellet, bead, sphere, mini-sphere, tablet, mini-tablet and the like. In one embodiment of the present invention the solid oral dosage form is a pellet, sphere, mini-sphere, bead, granule, tablet or mini-tablet. In a preferred embodiment of the present invention the solid oral dosage form is a pellet. The size of the solid oral dosage form is not particularly limited and may be characterized by a maximal diameter of between 100-4000 μm , preferably 300-3000 μm , more preferably 500-2500 μm , even more preferably 700-2000 μm , e.g. about 1200-1600 μm .

Multiple solid oral dosage forms of the present invention may be combined into a single-unit formulation in the form of an "oral multiparticulate drug delivery system", also known as "oral multiparticulate dosage form". The oral multiparticulate drug delivery system may be for example in the form of a hard gelatin capsule, tablet, sachet, caplet, or pill.

The term "inert core unit" as used herein is known to the skilled person. The term "inert core unit" as used herein may be understood to mean inert pellet, mini-tablet, tablet, granule, core, bead, mini-sphere or sphere, which consists of one or more of soluble or insoluble inert materials and the like, which are all pharmacologically inactive and do not interact with the active ingredient in the solid oral dosage form, that is, the antibody or functional fragment thereof.

The inert core unit may be optionally seal coated, for example to increase the strength of the core to withstand the mechanical pressures during processing.

The term "inert" as used herein preferably means that the inert core unit (1), that is including all its ingredients, is pharmacologically inactive and does not interact with the antibody or functional fragment thereof in the depot layer (2). This preferably means that the inert core unit (1) does not contain any active ingredients and does not reduce

stability and activity of the antibody or functional fragment thereof in the depot layer (2) during preparation of the solid oral dosage form, its storage and later administration and dissolution.

- 5 The term "about", as used herein, indicates the value or range of a given quantity can include quantities ranging within 10 % of the stated value or range, or optionally within 5 % of the value or range, or in some embodiments within 1 % of the value or range. Generally, unless otherwise indicated, "wt.-%" as used herein, refers to the weight percent of a substance relative to the total weight of the solid oral dosage form. In
10 some cases where indicated, "wt.-%" may refer to the weight percent of a substance relative to the weight of a specific layer of the solid oral dosage form.

- The inert core unit (1) may be an inert pellet, mini-tablet, tablet, granule, core, bead, mini-sphere or sphere e.g. prepared from one or a mixture of excipients for example
15 by compression or extrusion-spheronization. In a preferred embodiment the inert core unit (1) is a pellet. The pellet, for example, may comprise, or consist of, a water insoluble or water swellable material and/or may be of uniform composition. In one embodiment of the present invention, the inert core unit (1) comprises a monosaccharide, disaccharide, oligosaccharide, polysaccharide, silica, tartaric acid,
20 calcium carbonate, or a combination thereof as a main component. In another embodiment the inert core unit (1) consists of a monosaccharide, disaccharide, oligosaccharide, polysaccharide, silica, tartaric acid, calcium carbonate, or a combination thereof.

- 25 In a specific embodiment of the present invention, the inert core unit (1), e.g. a pellet, comprises, or consists of, microcrystalline cellulose, sucrose, starch, mannitol, calcium carbonate, silica, tartaric acid, lactose, or a combination thereof, preferably microcrystalline cellulose. In a further embodiment, the inert core unit (1), e.g. a pellet, comprises microcrystalline cellulose, sucrose, starch, mannitol, calcium carbonate,
30 silica, tartaric acid, lactose, or a combination thereof, preferably microcrystalline cellulose as a main component. "Main component" in this context refers to an inert core unit (1) comprising at least 50 wt.-%, preferably at least 70 wt.-%, more preferably at least 90 wt.-%, even more preferably at least 95 wt.-%, of said component. As used in

the context of the inert core unit above, "wt.-%" refers to the weight percent of a substance relative to the weight of the inert core unit (1).

In one embodiment the inert core unit (1) is a pellet. The pellet may have a median
5 particle size of 50-5000 μm , preferably 100-3000 μm , more preferably 200-2000 μm ,
even more preferably 300-1500 μm , even more preferably 400-1400, even more
preferably 700-1400, even more preferably 500-1000, most preferably 500-700, 600-
800, or 700-1000 μm . In another embodiment, the inert core unit (1) is a pellet with a
10 particle size distribution such that at least 85 % of the pellets have a particle size of
50-3000 μm , preferably 100-1500 μm , more preferably 350-1400 μm , even more
preferably 500-1400 μm , even more preferably 700-1400, even more preferably 500-
1000 μm , e.g. 500-700 μm or 700-1000 μm . According to a preferred embodiment of
the present invention the inert core unit (1) is a pellet with a particle size distribution
such that at least 85 % of the pellets have a particle size of 700-1400 μm , preferably
15 700-1000 μm .

The shape of the inert core unit (1), preferably a pellet, is not particularly limited. In one
embodiment, the inert core unit (1) is a pellet with a sphericity degree of at least 0.6,
preferably at least 0.7, more preferably at least 0.8, even more preferably at least 0.9,
20 even more preferably at least 0.95. In a preferred embodiment the inert core unit (1) is
a pellet comprising, or consisting of, a sphere. The term "sphere" as used herein
preferably refers to a particle with a sphericity degree of at least 0.8. The pellet, for
example, may comprise, or consist of, a sphere, which preferably consists of a water
insoluble or water swellable material and/or is of uniform composition.

25 The pellet or the sphere may be coated with a coating deposited on the sphere, e.g. a
seal coated, the seal coating preferably consisting of a water-insoluble material.
According to one embodiment, the inert core unit (1) comprises, or consists of, a pellet
e.g. a sphere, and optionally a seal coating covering the sphere, the seal coating
30 consisting of a water-insoluble material.

The pellet (or the sphere) may consist of microcrystalline cellulose, sucrose, starch,
mannitol, calcium carbonate, silica, tartaric acid, lactose or a combination thereof. In a
preferred embodiment the inert core unit (1) is a pellet, e.g. a sphere, and consists of

microcrystalline cellulose, sucrose, starch, mannitol, calcium carbonate, silica, tartaric acid, lactose or a combination thereof. In a preferred embodiment, the inert core unit (1) is a pellet, preferably in the form of a sphere, and consists of microcrystalline cellulose. Examples of commercially available inert core units include CELLETS®
5 (Pharmatrans-Sanaq AG) and SUGLETS® sugar spheres (Colorcon® Ltd).

The solid oral dosage form comprises a depot layer (2) covering the inert core unit (1) and comprising an antibody or a functional fragment thereof as an active agent; a stabilizer; a buffer; and a polymeric binder. The term "depot layer" as used herein refers
10 to a coating or coat, which comprises at least one active agent in the form of an antibody or functional fragment thereof, and which covers the inert core unit.

The term "cover" or "covering" as used herein in the context of a "layer" of the solid oral dosage form of the present invention means that the layer is positioned on top of the
15 inert core unit or layer being covered, such that there is no other layer in between (i.e. between the covering layer and the inert core unit or layer being covered) or such that there is one or more additional layers in between, preferably such that there is no other layer positioned in between. Preferably, a layer of the solid oral dosage form of the present invention continuously covers the inert core unit or the layer being covered,
20 such that there are no gaps in the covering layer. This may be particularly relevant for the sustained release layer and the delayed release layer, since otherwise the integrity of these layers may be compromised.

Preferably, the depot layer (2) is positioned on top of the inert core unit (1), such that
25 there is no other layer in between (i.e. between the depot layer and the inert core unit). Preferably, the depot layer (2) of the solid oral dosage form of the present invention continuously covers the inert core unit (1), such that there are no gaps in the depot layer.

30 A specific layer can be separated from the inert core unit, or further layers of the solid oral dosage form that have been applied separately, by its distinct physicochemical properties. Consequently, the depot layer (2), the sustained release layer (3), and/or the delayed release layer (4) can be separated from the inert core unit and the further

layers that have been applied separately after applying the depot layer, by its distinct physicochemical properties.

5 According to one embodiment of the present invention, the depot layer (2) of the solid oral dosage form of the invention has an average thickness of 1-300 μm , preferably 2-200 μm , more preferably 5-200 μm , even more preferably 10-200 μm , e.g. 100-200, or 150 μm .

10 According to another embodiment of the present invention, the sustained release layer (3) has an average thickness of 5-50 μm , preferably 10-45 μm , more preferably 15-35 μm , even more preferably 18-30 μm , even more preferably 20-30 μm , e.g. about 24 or 25 μm . According to another embodiment of the present invention, the thickness of the sustained release layer (3) is constant and not dependent on the amount of active agent and/or thickness of the depot layer (2). According to another embodiment, the
15 sustained release layer (3) has a fixed average thickness of 5-50 μm , preferably 10-45 μm , more preferably 15-35 μm , even more preferably 18-30 μm , even more preferably 20-30 μm , e.g. 24 or 25 μm ; preferably irrespective of the thickness the depot layer (2) and/or amount of antibody or functional fragment thereof in the depot layer (2).

20 According to a preferred embodiment of the present invention, the delayed release layer (4) has an average thickness of 10-300 μm , preferably 50-180 μm , more preferably 60-160 μm , even more preferably 80-150 μm , even more preferably 90-130 μm , even more preferably 95-120 μm , e.g. 105 or 120 μm .

25 According to a specific embodiment of the invention, the solid oral dosage form according to any of the of embodiments described above, the average thickness of the sustained release layer (3) is constant, irrespective of the amount of antibody or functional fragment thereof in the solid oral dosage form and/or the thickness of the depot layer.

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The thickness of a layer may be determined using scanning electron microscopy (SEM), based on e.g. 10, or 15, or 20, or 30, or 50 different measurement points in the layer.

The term "antibody", in the context of the present invention, refers to "immunoglobulin" (Ig), which is defined as a protein belonging to the class IgG, IgM, IgE, IgA, or IgD (or any subclass thereof), and includes all conventionally known antibodies and functional fragments thereof. The antibody or functional fragment thereof used for the present invention is an active agent, i.e. the antibody or functional fragment thereof is incorporated into the solid oral dosage form due to the pharmacological activity of the antibody or functional fragment thereof in a patient.

In the context of the present invention, a "functional fragment" of an antibody/immunoglobulin is defined as antigen-binding fragment or other derivative of a parental antibody that essentially maintains the properties of such a parental antibody. An "antigen-binding fragment" of an antibody/immunoglobulin is defined as a fragment (e.g., a variable region of an IgG) that retains the antigen-binding region. An "antigen-binding region" of an antibody typically is found in one or more hypervariable region(s) of an antibody, i.e., the CDR-1, -2, and/or -3 regions. "Antigen-binding fragments" according to the invention include the domain of a F(ab')₂ fragment and a Fab fragment. "Functional fragments" of the invention include Fab fragment, F(ab')₂ fragment, Fab' fragment, scFv, dsFv, VHH, diabody, triabody, tetrabody, Fc fusion protein and minibody. The F(ab')₂ or Fab domain may be engineered to minimize or completely remove the intermolecular disulphide interactions that occur between the CH1 and CL domains. The antibodies or functional fragments thereof used for the present invention may be part of bi- or multifunctional constructs.

Fab fragments can be obtained as the purified digestion products after digestion of an antibody with a cysteine proteinase like papain (EC 3.4.22.2). F(ab')₂ fragments can be obtained as the purified digestion products after digestion of an antibody with pepsin (EC 3.4.23.1) or IdeS (Immunoglobulin degrading enzyme from *Streptococcus pyogenes*; EC 3.4.22). Fab' fragments can be obtained from F(ab')₂ fragments in mild reducing conditions, whereby each F(ab')₂ molecule gives rise to two Fab' fragments. An scFv is a single chain Fv fragment in which the variable light ("VL") and variable heavy ("VH") domains are linked by a peptide bridge.

A "diabody" is a dimer consisting of two fragments, each having variable regions joined together via a linker or the like (hereinafter referred to as diabody-forming fragments),

and typically contain two VLs and two VHs. Diabody-forming fragments include those consisting of VL and VH, VL and VL, VH and VH, etc., preferably VH and VL. In diabody-forming fragments, the linker joining variable regions is not specifically limited, but preferably short enough to avoid noncovalent bonds between variable regions in the same fragment. The length of such a linker can be determined as appropriate by those skilled in the art, but typically 2-14 amino acids, preferably 3-9 amino acids, especially 4-6 amino acids are used. In this case, the VL and VH encoded on the same fragment are joined via a linker short enough to avoid noncovalent bonds between the VL and VH on the same chain and to avoid the formation of single-chain variable region fragments so that dimers with another fragment can be formed. The dimers can be formed via either covalent or noncovalent bonds or both between diabody-forming fragments.

Moreover, diabody-forming fragments can be joined via a linker or the like to form single-chain diabodies (sc(Fv)₂). By joining diabody-forming fragments using a long linker of about 15-20 amino acids, noncovalent bonds can be formed between diabody-forming fragments existing on the same chain to form dimers. Based on the same principle as for preparing diabodies, polymerized antibodies such as trimers or tetramers can also be prepared by joining three or more diabody-forming fragments.

In one embodiment, the functional fragment in the solid oral dosage form of the invention is a Fab fragment, a F(ab')₂ fragment, a Fab' fragment, an scFv, a dsFv, a VHH, a diabody, a triabody, a tetrabody, an Fc fusion protein or a minibody. Preferred functional fragments used in the present invention are Fab fragments, F(ab')₂ fragments, Fab' fragments, scFv and diabodies.

The antibody or functional fragment thereof used in the solid oral dosage form of the present invention is not particularly limited. In one embodiment, the antibody or functional fragment thereof is an antibody. In another embodiment of the present invention, the antibody or functional fragment thereof is functional fragment as defined above. The antibody or functional fragment thereof may further comprise one or more modifications, e.g. in the form of added or substituted residues, that improve stability, specificity or targeting. These may include any such modifications that are known in the art.

- The antigen against which the antibody or functional fragment is directed i.e. the immunogen, peptide, protein, or other molecular structure to which the antibody or functional fragment thereof can specifically bind, is not limited. The terms "specific to", "specifically bind" or "specific binding" in this context are known to the skilled person.
- 5 In its most general form (and when no defined reference is mentioned), "specific to" or "specific binding" refers to the ability of the antibody or functional fragment thereof to discriminate between the target of interest and an unrelated biomolecule (e.g. for antibodies specific to human TNF α to discriminate between human TNF α and an unrelated biomolecule), as determined, for example, in accordance with specificity
- 10 assay methods known in the art. Such methods comprise, but are not limited to, Western blots and enzyme-linked immunosorbent assay (ELISA) tests. For example, a standard ELISA assay can be carried out. Typically, determination of binding specificity is performed by using not a single reference biomolecule, but a set of about three to five unrelated biomolecules, such as milk powder, BSA, transferrin or the like.
- 15
- In one embodiment of the present invention the antibody or functional fragment thereof is suitable for use in the treatment of an inflammatory condition in the GI tract such as immune checkpoint inhibitor (ICPI) induced colitis, ICPI induced enterocolitis, ICPI induced diarrhoea, or inflammatory bowel disease (IBD, e.g. Crohn's disease or
- 20 ulcerative colitis). In a further embodiment of the present invention the antibody or functional fragment thereof is suitable for use in the local treatment in the (terminal) ileum and/or large intestine of the gastrointestinal tract of a patient, in particular at the mucosa.
- 25 In a further embodiment of the present invention the antibody or functional fragment thereof is selected from antibodies specific to tumor necrosis factor alpha (TNF α) and functional fragments thereof, antibodies specific to $\alpha 4\beta 7$ integrin and functional fragments thereof, antibodies specific to CD3, CD4 or CD20 and functional fragments thereof, antibodies specific to interleukin 6 (IL-6), interleukin 12 (IL-12), interleukin 13
- 30 (IL-13), interleukin 23 (IL-23) or to their receptors and functional fragments thereof, antibodies specific to CXCL10/IP-10 and functional fragments thereof, and antibodies specific to p40 protein subunit and functional fragments thereof. In yet another embodiment of the present invention the antibody or functional fragment thereof is selected from infliximab, adalimumab, etanercept, certolizumab pegol, golimumab,

visilizumab, eldelumab, abrilumab, canakinumab, tocilizumab, ustekinumab, natalizumab, etrolizumab, priliximab, vedolizumab and functional fragments thereof.

In a preferred embodiment of the solid oral dosage form of the present invention, the
5 antibody or functional fragment thereof is an antibody specific to tumor necrosis factor
alpha (TNF α) or a functional fragment thereof (that is, an anti-TNF α antibody or
functional fragment thereof). The antibody specific to TNF α or functional fragment
thereof is not particularly limited. In one embodiment, the antibody specific to TNF α or
functional fragment thereof is an antibody. In another embodiment, the antibody
10 specific to TNF α or functional fragment thereof is functional fragment as defined above.
The antibody specific to TNF α or functional fragment thereof may further comprise one
or more modifications, e.g. in the form of added or substituted residues, that improve
stability, specificity or targeting. These may include any such modifications that are
known in the art.

15 The terms "anti-TNF α antibody", "TNF α antibody" and "antibody specific to TNF α " as
used herein are interchangeable, and preferably mean that the anti-TNF α antibody is
able to specifically bind to TNF α , that is it preferably refers to the ability of the antibody
to specifically bind to TNF α , more preferably human TNF α (e.g. identifiable by the
20 uniprot identifier P01375). The terms "specific to", "specifically bind" or "specific
binding" in this context are known to the skilled person (see above). In one
embodiment, "specific binding" in the context of TNF α refers *inter alia* to the ability of
the antibody or fragment to discriminate between human TNF α and human TNF β .

25 In one embodiment of the present invention the anti-TNF α antibody or functional
fragment thereof is suitable for use in the treatment of immune checkpoint inhibitor
(ICPI) induced colitis, ICPI induced enterocolitis, ICPI induced diarrhoea, and/or an
inflammatory bowel disease (IBD), e.g. Crohn's disease or ulcerative colitis. In another
embodiment of the present invention the antibody or functional fragment thereof is
30 suitable for use in the local treatment in the ileum (preferably in the terminal ileum) or
large intestine of the gastrointestinal tract of a patient, in particular at the mucosa. In a
preferred embodiment of the present invention, the anti-TNF α antibody or functional
fragment thereof is an afucosylated antibody, meaning it is devoid of the core fucose.

Several monoclonal antibodies against TNF α (that is specific to TNF α) have been described in the prior art. Meager et al. (Hybridoma, 6, 305-311, 1987) describe murine monoclonal antibodies against recombinant TNF α . Fendly et al. (Hybridoma, 6, 359-370, 1987) describe the use of murine monoclonal antibodies against recombinant TNF α in defining neutralizing epitopes on TNF. Furthermore, in international patent application WO 92/11383, recombinant antibodies, including CDR-grafted antibodies, specific for TNF α are disclosed. U.S. Pat No. 5,919,452 discloses anti-TNF α chimeric antibodies and their use in treating pathologies associated with the presence of TNF α . Further anti-TNF α antibodies are disclosed in Stephens et al. (Immunology, 85, 668-674, 1995), GB-A-2 246 570, GB-A-2 297 145, US 8,673,310, US 2014/0193400, EP 2 390 267 B1, US 8,293,235, US 8,697,074, WO 2009/155723 A2 and WO 2006/131013 A2.

Currently approved anti-TNF α antibodies include (i) infliximab, a chimeric IgG anti-human monoclonal antibody (Remicade®); (ii) etanercept, a TNFR2 dimeric fusion protein, with an IgG1 Fc (Enbrel®); (iii) adalimumab, a fully human monoclonal antibody (mAb) (Humira®), (iv) certolizumab, a PEGylated Fab fragment (Cimzia®) and (v) golimumab, a human IgG1K monoclonal antibody (Simponi®). Moreover, various biosimilars are in development. Therefore, in some embodiments of the present invention, the anti-TNF α antibody or functional fragment thereof is selected from infliximab, adalimumab, etanercept, certolizumab pegol and golimumab or a functional fragment thereof.

In a preferred embodiment of the present invention, the antibody or functional fragment thereof is an anti-TNF α antibody or functional fragment thereof with a TNF α binding domain comprising (i) a V_L domain comprising a CDR1 region having an amino acid sequence as shown in SEQ ID NO:1, a CDR2 region having an amino acid sequence as shown in SEQ ID NO:2, and a CDR3 region having an amino acid sequence as shown in SEQ ID NO:3, and/or (ii) a V_H domain comprising a CDR1 region having an amino acid sequence as shown in SEQ ID NO:4, a CDR2 region having an amino acid sequence as shown in SEQ ID NO:5, and a CDR3 region having the amino acid sequence as shown in SEQ ID NO:6.

In another preferred embodiment of the present invention, the antibody or functional fragment thereof is an anti-TNF α antibody or functional fragment thereof with a TNF α binding domain comprising, or consisting of, (i) a V_L domain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:8, and/or (ii) a V_H domain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:7.

In yet another preferred embodiment of the present invention, the antibody or functional fragment thereof is an anti-TNF α antibody or functional fragment thereof with a TNF α binding domain comprising (i) a V_L domain comprising a CDR1 region having an amino acid sequence as shown in SEQ ID NO:9, a CDR2 region having an amino acid sequence as shown in SEQ ID NO:10, and a CDR3 region having an amino acid sequence as shown in SEQ ID NO:11, and/or (ii) a V_H domain comprising a CDR1 region having an amino acid sequence as shown in SEQ ID NO:12, a CDR2 region having an amino acid sequence as shown in SEQ ID NO:13, and a CDR3 region having the amino acid sequence as shown in SEQ ID NO:14.

In yet another preferred embodiment of the present invention, the antibody or functional fragment thereof is an anti-TNF α antibody or functional fragment thereof with a TNF α binding domain comprising, or consisting of, (i) a V_L domain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:16 or in SEQ ID NO:17, and/or (ii) a V_H domain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:15.

In yet another preferred embodiment of the present invention, the antibody or functional fragment thereof is an anti-TNF α antibody comprising a Fc region having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:18, in SEQ ID NO:19, in SEQ ID NO:20, in SEQ ID NO:21, or in SEQ ID NO:22, preferably in SEQ ID NO:18.

In yet another preferred embodiment of the present invention, the antibody or functional fragment thereof is an anti-TNF α antibody comprising, or consisting of, (i) a light chain having, or consisting of, an amino acid sequence in accordance with the

amino acid sequence as shown in SEQ ID NO:23, and (ii) a heavy chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:26.

- 5 In yet another preferred embodiment of the present invention, the antibody or functional fragment thereof is an anti-TNF α antibody comprising, or consisting of (i) a light chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:24 or in SEQ ID NO:25, and (ii) a heavy chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:27.

- 10 In yet another preferred embodiment of the present invention, the antibody or functional fragment thereof is an anti-TNF α antibody comprising, or consisting of, (i) a light chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:23, and (ii) a heavy chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:28, in SEQ ID NO:29, or in SEQ ID NO:30.

- 15 In yet another preferred embodiment of the present invention, the antibody or functional fragment thereof is an anti-TNF α antibody comprising, or consisting of, (i) a light chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:24 or in SEQ ID NO:25, and (ii) a heavy chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:31, in SEQ ID NO:32, or in SEQ ID NO:33.

- 20 In yet another preferred embodiment of the present invention, the antibody or functional fragment thereof is an anti-TNF α antibody comprising, or consisting of, (i) a light chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:23, and (ii) a heavy chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:34.

- 25 In yet another preferred embodiment of the present invention, the antibody or functional fragment thereof is an anti-TNF α antibody comprising, or consisting of, (i) a

light chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:24 or in SEQ ID NO:25, and (ii) a heavy chain having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:35.

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The amount of the antibody or functional fragment thereof is not particularly limited. Preferably, the depot layer (2) comprises an amount of the antibody or functional fragment thereof that allows the administration of a therapeutically effective dose of the antibody or functional fragment thereof as a single unit dose (e.g. in the form of a

10 multiparticulate drug delivery system comprising a plurality of the solid oral dosage forms of the present invention. In one embodiment, the depot layer (2) comprises 0.2-75 wt.-%, preferably 1-45 wt.-%, more preferably 10-35 wt.-%, even more preferably 20-35 wt.-%, even more preferably 25-35 wt.-% antibody or functional fragment thereof preferably specific to TNF α , relative to the total weight of the solids (i.e. not including

15 solvents, preferably water) in the depot layer (2). According to another preferred embodiment, the solid oral dosage form of the present invention comprises 0.05-30 wt.-%, preferably 0.1-25 wt.-%, more preferably 0.1-20 wt.-%, even more preferably 0.2-20 wt.-%, even more preferably 0.2-15 wt.-%, even more preferably 0.5-12 wt.-%, even more preferably 0.5-10 wt.-%, even more preferably 0.8-12 wt.-%, even more

20 preferably 8-12 wt.-%, even more preferably 8-10 wt.-%, e.g. about 9 wt.-%, or about 9.25 wt.-%, or about 9.5 wt.-%, of the antibody or functional fragment thereof preferably specific to TNF α .

In one embodiment of the present invention, the solid oral dosage form of the present

25 invention comprises an amount of the antibody or functional fragment thereof that allows the oral administration of a therapeutically effective dose of the antibody or functional fragment thereof as a single unit dose, for example in the form of a tablet or preferably a capsule comprising multiple solid oral dosage forms (e.g. in the form of multiple pellets). A "therapeutically effective dose" is the amount of the at least one

30 antibody or functional fragment thereof required to provide the desired therapeutic effect. The exact amount may vary for different antibodies or functional fragments thereof and/or for individual patients, but can be determined by one skilled in the art.

The depot layer (2) comprises a stabilizer. The nature of the stabilizer is not particularly limited and includes all stabilizers ensuring stability and activity of antibodies and functional fragments thereof, e.g. antibodies and functional fragments thereof specific to TNF α , while not compromising the integrity of the depot layer (2). In one embodiment of the present invention, the stabilizer is selected from sucrose, maltose, lactose, trehalose, glycerol, maltitol, isomalt, mannitol, sorbitol, xylitol and combinations thereof, preferably sucrose, maltose, lactose, glycerol, maltitol, isomalt, and combinations thereof. According to a preferred embodiment the stabilizer in the depot layer (2) is sucrose. The amount of stabilizer in the depot layer (2) is not particularly limited as long as it ensures stability of low and high concentration of antibody or functional fragment thereof, while not compromising the integrity of the depot layer. In one embodiment of the present invention, the depot layer (2) comprises 2-80 wt.-%, preferably 10-75 wt.-%, more preferably 20-70 wt.-%, even more preferably 30-60 wt.-%, even more preferably 35-60 wt.-%, even more preferably about 40-55 wt.-%, stabilizer (preferably sucrose), relative to the total weight of the solids (i.e. not including solvents, preferably water) in the depot layer (2). In another embodiment the weight ratio of antibody or functional fragment thereof to stabilizer (e.g. sucrose) is 1 : 2 to 1 : 1.5, preferably 1 : 9 to 1 : 1.7, e.g. about 1 : 1.77.

The depot layer (2) comprises a buffer. The nature of the buffer is not particularly limited and includes all buffers that ensure stability and activity of antibodies and functional fragments thereof, while not compromising the integrity of the depot layer (2). In one embodiment of the present invention, the buffer (i.e. buffer salt or salts and/or free base) in the depot layer (2) is selected from the group consisting of L-histidine buffer, citrate buffer, hydroxymethylaminomethane (TRIS) buffer, succinate buffer, phosphate buffer, acetate buffer, or salts thereof, and combinations thereof; preferably L-histidine buffer, citrate buffer, TRIS buffer, and combinations thereof; more preferably L-histidine buffer, citrate-TRIS buffer, and a combination thereof. According to a preferred embodiment the buffer (i.e. buffer salt and/or free base) in the depot layer (2) comprises, or consists of, L-histidine, preferably L-histidine monohydrochloride and/or free base.

The buffer may be present in the depot layer (2) in any amount that ensures stability and activity of antibodies and functional fragments thereof during and after preparation

of the solid oral dosage form, while not compromising the integrity of the depot layer (2). In one embodiment of the present invention, the depot layer (2) comprises 0.1-10 wt.-%, preferably 0.2-6 wt.-%, more preferably, 0.3-5 wt.-%, more preferably 0.5-4.5 wt.-%, even more preferably 1-4 wt.-%, more preferably about 2-3.5 wt.-%, buffer, relative to the total weight of the solids (i.e. not including solvents, preferably water) in the depot layer (2). In a further embodiment of the present invention, the depot layer (2) comprises 0.1-10 wt.-%, preferably 0.2-5 wt.-%, more preferably 0.3-4 wt.-%, even more preferably 0.35-3.5 wt.-%, more preferably about 0.4-3 wt.-%, L-histidine salt and/or free base, and optionally 0.3-6 wt.-%, preferably 0.5-4 wt.-%, more preferably 1-3.5 wt.-%, even more preferably 1.5-3 wt.-%, more preferably about 1.5-3.5 wt.-%, other buffer salts, relative to the total weight of the solids (i.e. not including solvents, preferably water) in the depot layer (2). In another embodiment the weight ratio of antibody or functional fragment thereof to buffer, preferably L-histidine buffer (salt and/or free base), is 100 : 1 to 1 : 1, preferably 50 : 1 to 3 : 1, more preferably 30 : 1 to 5 : 1; even more preferably 15 : 1 to 7 : 1; e.g. about 10 : 1. In another embodiment the weight ratio of antibody or functional fragment thereof to L-histidine buffer is 100 : 1 to 20 : 1, preferably 80 : 1 to 40 : 1, more preferably 60 : 1 to 50 : 1, and optionally the weight ratio of antibody or functional fragment thereof to other buffers is 25 : 1 to 5 : 1, preferably 16 : 1 to 10 : 1, more preferably 14 : 1 to 12 : 1.

20

Polymeric binders (also referred to herein as "binders") suitable for the depot layer (2) of the solid oral dosage form of the present invention comprise hypromellose (HPMC); methylcellulose (MC); polyvinylpyrrolidone (PVP); hydroxypropyl cellulose (HPC); macrogol poly(vinylalcohol) grafted copolymer (e.g. Kollidon® IR); and combinations thereof; preferably hypromellose or MC. In a preferred embodiment of the present invention, the polymeric binder in the depot layer (2) of the solid oral dosage form is hypromellose. Hypromellose is also known as hydroxypropyl methylcellulose (HPMC) and is available in different at different degrees of substitution (DS), molar substitution (MS) and viscosities. According to a preferred embodiment of the present invention, the polymeric binder in the depot layer (2) is hypromellose 2910, preferably hypromellose 2910 2.6-3.6 mPas, more preferably hypromellose 2910 3 mPas.

30

The amount of polymeric binder in the depot layer (2) is not particularly limited as long as a stable depot layer can be easily formed. In one embodiment of the present

invention, the depot layer (2) comprises 0.5-65 wt.-%, preferably 2-35 wt.-%, more preferably 10-30 wt.-%, even more preferably 15-25 wt.-%, e.g. about 20 wt.-%, polymeric binder (preferably hypromellose), relative to the total weight of the solids (i.e. not including solvents, preferably water) in the depot layer (2). In another embodiment
5 the weight ratio of antibody or functional fragment thereof to polymeric binder (e.g. hypromellose) is 1.2 : 1 to 1 : 1.5, preferably 1.3 : 1 to 1 : 1.4, e.g. about 1.35 : 1.

Preferably the polymeric binder in the depot layer (2) is suitable for an immediate release drug coating. Thus, the depot layer (2), without any additional layer (that is the
10 sustained and delayed release layers) gives rise to an immediate release of the antibody or functional fragment thereof from the dosage form. As used herein, the term "immediate release" is meant to describe a depot layer in which more than 60 %, preferably more than 70 %, more preferably more than 80 %, even more preferably more than 90 %, most preferably 95 %, of the antibody or functional fragment thereof
15 is released from the depot layer (2) after 2 h, preferably after 1 h, even more preferably after 0.5 h, of exposure to an aqueous environment. The term an "aqueous environment" as used in the context of the present invention may refer to a solution or suspension of which a large part is water. This includes intestinal fluid.

20 To measure the amount of antibody or functional fragment thereof released from a depot layer (2) as the outermost coating of a solid dosage form into an aqueous solution, the depot layer (drug layer) deposited on an inert core can be immersed in a defined volume of aqueous solution (preferably buffered) for a defined period of the time under continuous agitation of the aqueous (preferably buffered) solution and the
25 resulting concentration of the at least one antibody or functional fragment thereof in the aqueous solution can be determined and compared to the initial amount applied during the layering process, considering the process efficiency and weight gain. Similarly, the release from a solid dosage form with additional coatings deposited onto the depot layer (2), e.g. a sustained release coating and/or a delayed release coating,
30 can be determined. Means to determine an antibody concentration in an aqueous solution are known in the art and include for example measuring the absorbance at 280 nm or using a colorimetric, reagent-based protein assay like the Bradford assay or by ELISA.

According to one embodiment of the present invention, the depot layer (2) of the solid oral dosage form of the present invention comprises an anti-tacking agent. The anti-tacking agent that may be used in the depot layer (2) is not particularly limited. In one embodiment of the present invention, the anti-tacking agent in the depot layer (2) is selected from colloidal silica dioxide, mesoporous silica, glycerolmonostearate (GMS), stearic acid, magnesium stearate and talc, preferably mesoporous silica or GMS, more preferably mesoporous silica. The amount of anti-tacking agent in the depot layer (2) is not particularly limited. In one embodiment of the present invention, the depot layer (2) comprises 0.2-15 wt.-%, preferably 0.5-10 wt.-%, more preferably 1-5 wt.-%, even more preferably 1.5-3 wt.-%, even more preferably 1.5-2.5 wt.-%, e.g. about 2 wt.-%, anti-tacking agent, relative to the total weight of the solids (i.e. not including solvents, preferably water) in the depot layer (2). In another embodiment the weight ratio of anti-tacking agent to polymeric binder (e.g. hypromellose) in the depot layer (2) is 1 : 15 to 1 : 5, preferably 1 : 12 to 1 : 8, e.g. about 1 : 10.

According to a preferred embodiment of the present invention, the anti-tacking agent in the depot layer (2) is mesoporous silica, preferably mesoporous silica with an average particle size of 1-10 μm , preferably of 2-5 μm , more preferably 3-4 μm , even more preferably about 3.5 μm and/or an average pore volume of 1.50-1.70 cm^3/g , preferably 1.55-1.65 cm^3/g , more preferably 1.58-1.62 cm^3/g , even more preferably about 1.60 cm^3/g .

According to a further embodiment, the depot layer (2) of the solid oral dosage form of the invention does not comprise a plasticizer. According to another embodiment, the depot layer (2) of the solid oral dosage form of the invention comprises a coalescence enhancer, e.g. propylene glycol monolaurate (e.g. Lauroglycol™ 90).

According to yet another embodiment of the present invention, the depot layer (2) of the solid oral dosage form of the invention comprises a surfactant. The surfactant in the depot layer (2) is not particularly limited, however preferably it is a nonionic surfactant. According to one embodiment of the present invention, the surfactant in the depot layer (2) is selected from the group consisting of polysorbate 20, polysorbate 28, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, polysorbate 81,

polysorbate 85, poloxamer 124, poloxamer 181, poloxamer 188, poloxamer 237, poloxamer 331, poloxamer 338 and poloxamer 407, and combinations thereof.

According to a preferred embodiment of the solid oral dosage form, the surfactant in the depot layer (2) is polysorbate 20, 28, 40, 60, 65, 80, 81 and 85. In a particularly preferred embodiment, the surfactant in the depot layer (2) is polysorbate 80. In one embodiment of the present invention, the depot layer (2) comprises 0.01-2 wt.-%, preferably 0.02-1 wt.-%, more preferably 0.03-0.8 wt.-%, even more preferably 0.05-0.5 wt.-%, even more preferably 0.1-0.3 wt.-%, even more preferably 0.2-0.3 wt.-%, surfactant, relative to the total weight of the solids (i.e. not including solvents, preferably water) in the depot layer (2).

The depot layer (2) may optionally comprise at least one further excipient. The term "excipient," as used herein, refers to a non-therapeutic agent added to the formulation to provide for example a desired consistency, viscosity, or stabilizing effect. According to one embodiment of the present invention the at least one further excipient is selected from pharmaceutically acceptable excipients like antioxidants, humectants, protective colloids, dyes, protease inhibitors, and combinations thereof. In another embodiment, the depot layer (2) does not comprise any further excipients.

20

According to a preferred embodiment of the present invention, the depot layer (2) of the solid oral dosage form of the invention comprises, or consists of, antibody or functional fragment thereof e.g. specific to TNF α , as an active agent; stabilizers, preferably sucrose; buffer, preferably L-histidine, more preferably L-histidine monohydrochloride and/or free base; polymeric binder, preferably hypromellose (HPMC), more preferably hypromellose 2910 2.6-3.6 mPas; anti-tacking agent, preferably mesoporous silica; surfactant, preferably polysorbate 80; optionally further buffers like citrate-TRIS; and optionally residual solvent (preferably water). According to another preferred embodiment of the present invention, the depot layer (2) of the solid oral dosage form of the invention comprises, or consists of, antibody or functional fragment thereof e.g. specific to specific to TNF α , as an active agent; sucrose; L-histidine, preferably L-histidine monohydrochloride, and/or L-histidine free base; Hypromellose (HPMC), preferably hypromellose 2910 2.6-3.6 mPas; mesoporous silica; polysorbate 80; and optionally residual water.

30

According to another preferred embodiment of the present invention, the depot layer (2) of the solid oral dosage form of the invention comprises, or consists, of 0.2-75 wt.-% antibody or functional fragment thereof, 0.5-65 wt.-% binder, 2-80 wt.-% sucrose, 5 0.1-5 wt.-% L-histidine (salt and/or free base), 0.1-10 wt.-% other buffers, 0.2-15 wt.-% anti-tacking agent, 0.01-1 wt.-% surfactant, and/or up to 10 wt.-% water, relative to the total weight of the depot layer; preferably 1-45 wt.-% antibody or functional fragment thereof, 2-35 wt.-% binder, 10-70 wt.-% sucrose, 0.2-2 wt.-% L-histidine, 0.5-4 wt.-% other buffers, 1-5 wt.-% anti-tacking agent, 0.05-0.5 wt.-% surfactant, and/or 10 up to 7 wt.-% water, relative to the total weight of the depot layer; more preferably 10-35 wt.-% antibody or functional fragment thereof, 10-30 wt.-% binder, 30-60 wt.-% sucrose, 0.3-0.8 wt.-% L-histidine, 1.5-3 wt.-% other buffers, 1.5-3 wt.-% anti-tacking agent, 0.1-0.3 wt.-% surfactant, and/or up to 6 wt.-% water, relative to the total weight of the depot layer; even more preferably 25-35 wt.-% antibody or functional fragment 15 thereof, 15-25 wt.-% binder, 40-55 wt.-% sucrose, 0.4-0.6 wt.-% L-histidine, 1.5-2.5 wt.-% other buffers, 1.5-2.5 wt.-% anti-tacking agent, 0.2-0.3 wt.-% surfactant, and/or up to 5 wt.-% water, relative to the total weight of the depot layer (2).

In the solid oral dosage of the present invention, the depot layer (2) can be deposited 20 on the inert core unit (1) by drug layering, preferably using spray coating, more preferably fluidized-bed spray coating. Drug layering using solution/suspension layering allows the preparation of solid dosage forms with uniform size distribution and smooth surface morphology. Solution/suspension layering (or coating) involves depositing a substance dissolved or dispersed in a solvent on the surface of a 25 substrate. An example of spray coating is fluidized-bed spray coating / air-suspension coating. In fluidized-bed spray coating one or more substances are dissolved or dispersed in a liquid carrier in the form of a solvent. This solution or dispersion is then sprayed onto a substrate, e.g. an inert core (sucrose or microcrystalline cellulose spheres, etc.) suspended in a fluidized bed of a fluidized-bed spray coater. Method for 30 drug layering of a layer containing an antibody or functional fragment as an active ingredient onto an inert core are known in the art. Such a method can be found for example in WO 2019/057562. Methods for applying a functional coating e.g. by fluidized-bed spray coating are disclosed for example in WO 2004/062577, EP 1 684 729, WO 2005/046561 or WO2005/115340.

The inert core unit may be covered with the depot layer (2) using spray coating. For example, a fluidized-bed spray coater or a pan coater can be used. According to a preferred embodiment a fluidized-bed spray coater is used. The use of a fluidized-bed spray coater for spray coating an inert core unit is known in the art. It is beneficial for the at least one antibody or functional fragment thereof in the solid oral dosage form prepared by the inventive method, if parameters and conditions used during spray coating are carefully controlled. The fluidized-bed spray coater that may be used is not particularly limited. Fluidized-bed spray coater are known in the art and include for example fluidized-bed equipment developed and commercialized by GEA Group, Glatt GmbH, Freund-Vector Corporation and Inora Pharmaceutical Machinery Co. The depot layer coating liquid comprising the antibody or functional fragment thereof may be sprayed onto the inert core unit using a bottom-spray fluidized-bed spray coater. Alternatively, the depot layer coating liquid may be sprayed onto the inert core unit using a top-spray fluidized-bed spray coater.

It is to be understood that throughout the present disclosure, whenever referring to dissolution of, or recovery of antibodies or functional fragments thereof from, a solid dosage form/multiparticulate drug delivery system (as in the section just above and below), e.g. by continuously immersing a solid dosage form/multiparticulate drug delivery system in an aqueous (buffered) solution under continuous (constant) agitation, for example the following standard testing setup, or a related standard testing setup known to the person skilled in the art, can be used: The release of the at least one antibody or functional fragment thereof can be evaluated using a standard dissolution apparatus I (baskets), II (paddle), III (reciprocating cylinder) or apparatus IV (flow through cell), where the buffer (i.e. aqueous buffer solution) is equilibrated at 37°C. The buffer volume used for dissolution testing can be adapted for instance using mini-vessels in the apparatus I or II to allow reduction of volume required and to be more bio-relevant. Release of antibodies or functional fragments thereof during dissolution can be quantified offline by an ELISA method.

The solid oral dosage form of the present invention comprises a sustained release layer (3), covering the depot layer (2) and comprising an ammonio methacrylate copolymer, preferably poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl

methacrylate chloride) 1 : 2 : 0.1; a plasticizer; and an anti-tacking agent. The term "sustained release" is known in the art. As used herein, the term "sustained release" may be used to describe a continuous release of the antibody or functional fragment thereof from the solid oral dosage form over several hours, e.g. at a constant or nearly constant release rate, e.g. when immersed in an aqueous (buffered) solution under continuous agitation. According to one embodiment, the term "sustained release" is used to describe a continuous release of the antibody or functional fragment thereof from the solid oral dosage form, preferably at a nearly constant release rate, over several hours in a suitable aqueous environment. According to another embodiment, the term "sustained release" is used to describe a release of the antibody or functional fragment thereof from the solid oral dosage form, such that a substantial fraction of antibody or functional fragment thereof is release from the solid oral dosage form upon exposure to an aqueous environment over a prolonged time period, e.g. over at least 6 h, preferably at least 10 h, more preferably at least 14 h, even more preferably at least 18 h, e.g. at least 24 h.

The term "cover" or "covering" as used in this context is to be understood as defined above. Preferably, the sustained release layer (3) is positioned on top of the depot layer (2) being covered, such that there is no other layer in between (i.e. between the sustained release layer and the depot layer). Preferably, the sustained release layer of the solid oral dosage form of the present invention continuously covers the depot layer, such that there are no gaps in the sustained release layer (3).

The term "ammonio methacrylate copolymer" is known in the art. For example, the term "ammonio methacrylate copolymer" may refer to poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) (also known as poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride)). In a preferred embodiment the ammonio methacrylate copolymer is selected from poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (also known as ammonio methacrylate copolymer type B, or as poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1, or as poly[ethyl propenoate-co-methyl 2-methylprop-2-enoate-co-N,N,N-trimethyl-2-[(2-methylprop-2-enoyl)oxy]ethan-1-aminium chloride] 1 : 2 : 0.1, or as Eudragit® RS, e.g. commercially available as Eudragit® RS 30D); poly(ethyl

acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.2 (also known as ammonio methacrylate copolymer type A, or as poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.2, or as poly[ethyl propenoate-co-methyl 2-methylprop-2-enoate-co-N,N,N-trimethyl-2-[(2-methylprop-2-enoyl)oxy]ethan-1-aminium chloride] 1 : 2 : 0.2, or as Eudragit® RL, e.g. commercially available as Eudragit® RL 30D); or a combination thereof.

According to a preferred embodiment, the solid oral dosage form of the present invention comprises apart from ammonio methacrylate copolymer, no other sustained release polymer. According to another preferred embodiment the solid oral dosage form of the present invention comprises poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1; poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.2; or a combination thereof, and preferably no other sustained release polymer. According to another preferred embodiment of the present invention, the sustained release layer (3) comprises, apart from poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1; poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.2 (e.g. Eudragit® RL 30D); or a combination thereof, no other sustained release polymer (preferably no other polymer).

According to a particularly preferred embodiment of the present invention, the sustained release layer (3) comprises poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 and preferably no other sustained release polymers. According to another particularly preferred embodiment of the present invention, the sustained release layer (3) comprises poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 and preferably no other polymers.

The plasticizer in the sustained release layer (3) is not particularly limited. The plasticizer in the sustained release layer (3) may be selected for example from triethyl citrate (TEC), polyethylene glycol, acetyl triethyl citrate, butyl citrate, polysorbate, polypropylene glycol, dibutyl sebacate (DBS), and combinations thereof. Preferably, the plasticizer in the sustained release layer (3) of the oral dosage form of the present invention is triethyl citrate (TEC).

The anti-tacking agent in the sustained release layer (3) is not particularly limited. The anti-tacking agent in the sustained release layer (3) may be selected for example from mesoporous silica, colloidal silica dioxide, stearic acid, magnesium stearate glycerol monostearate (GMS), and talc. Preferably, the anti-tacking agent in the sustained release layer (3) of the oral dosage form of the present invention is mesoporous silica. Preferably the mesoporous silica has an average particle size of 1-10 μm , preferably of 2-5 μm , more preferably about 3-4 μm , even more preferably 3.5 μm and/or an average pore volume of 1.50-1.70 cm^3/g , preferably 1.55-1.65 cm^3/g , more preferably 1.58-1.62 cm^3/g , even more preferably about 1.60 cm^3/g .

The amount of ammonio methacrylate copolymer in the sustained release layer (3) is not particularly limited. According to one embodiment the solid oral dosage form of the present invention comprises 0.2-25 wt.-%, preferably 0.5-15 wt.-%, more preferably 1-10 wt.-%, even more preferably 3-5 wt.-%, even more preferably 3.5-4.5 wt.-%, even more preferably 3.8-4.1 wt.-%, e.g. 4 wt.-%, ammonio methacrylate copolymer (preferably poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1). According to another embodiment of the present invention the sustained release layer (3) comprises 60-90 wt.-%, preferably 65-85 wt.-%, more preferably 70-80 wt.-%, even more preferably 72-78 wt.-%, ammonio methacrylate copolymer (preferably poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1), relative to the total weight of the solids (i.e. not including solvents, preferably water) in the sustained release layer (3).

The amount of plasticizer in the sustained release layer (3) is not particularly limited. According to one embodiment of the present invention, the sustained release layer (3) comprises 2-40 wt.-%, preferably 5-30 wt.-%, more preferably 15-25 wt.-%, even more preferably 17-23 wt.-%, even more preferably 20 wt.-%, plasticizer, relative to the total weight of the ammonio methacrylate copolymers in the sustained release layer (3). According to another embodiment of the present invention the sustained release coating comprises 2-30 wt.-%, preferably 5-25 wt.-%, more preferably 10-20 wt.-%, even more preferably 12-18 wt.-%, even more preferably 13-17 wt.-%, even more

preferably 14-16 wt.-%, or 15-16 wt.-% plasticizer, relative to the total weight of the solids (i.e. not including solvents, preferably water) in the sustained release layer (3).

The amount of anti-tacking agent in the sustained release layer (3) is not particularly limited. According to one embodiment of the present invention, the sustained release layer (3) comprises 1-30, wt.-%, preferably 2-25 wt.-%, more preferably 5-15 wt.-%, even more preferably 8-12 wt.-%, even more preferably 10 wt.-%, anti-tacking agent, relative to the total weight of the ammonio methacrylate copolymers in the sustained release layer (3). According to another embodiment of the present invention, the sustained release coating comprises 2-15 wt.-%, preferably 5-12 wt.-%, more preferably 6-9 wt.-%, even more preferably 6-9 wt.-%, even preferably 6.5-8.5 wt.-%, even more preferably 7-8 wt.-%, even more preferably about 7.5 wt.-% anti-tacking agent, relative to the total weight of the solids (i.e. not including solvents, preferably water) in the sustained release layer (3).

The sustained release layer (3) may or may not comprise a coalescence enhancer. According to a preferred embodiment of the present invention, the sustained release layer (3) comprises no coalescence enhancer. According to another embodiment of the present invention, the sustained release layer (3) comprises a coalescence enhancer, e.g. propylene glycol monolaurate (e.g. Lauroglycol™ 90).

According to a preferred embodiment, the sustained release layer (3) consists of ammonio methacrylate copolymer (preferably poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1), plasticizer (preferably TEC) and anti-tacking agent (preferably mesoporous silica), and optionally residual solvent (preferably water).

According to a specific embodiment, the weight of the sustained release layer (3), relative to combined weight of the inert core unit (1) and the depot layer (2), is 4-8 wt.-%, preferably 5-7 wt.-% more preferably about 6 wt.-%.

The sustained release layer (3) may be applied to the inert core unit (1) covered (coated) with the depot layer (2) using drug layering. According to a preferred embodiment, the sustained release layer (3) of the solid oral dosage form of the

present invention can be deposited on the depot layer (2) by drug layering, preferably using spray coating, more preferably fluidized-bed spray coating. Method for drug layering of a sustained layer onto a depot layer containing an antibody or functional fragment as an active ingredient and covering an inert core are known in the art. Such
5 a method can be found for example in WO 2019/057562. According to a specific embodiment, the weight gain of the solid oral dosage form after sustained release coating by drug layering and subsequent drying, but before applying any further layer, is 4-8 wt.-%, preferably 5-7 wt.-%, more preferably about 6 wt.-%.

10 Finally, the solid oral dosage form of the present invention comprises a delayed release layer (4) covering the sustained release layer (3) and comprising poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof, preferably poly(methacrylic acid, methyl methacrylate) 1:2; an anti-tacking agent,
15 preferably glycerol monostearate (GMS); a plasticizer, preferably triethyl citrate (TEC), and preferably a surfactant.

The term "delayed release" is known in the art. A delayed release layer within the meaning of the present invention is a layer/coating that prevents the release of the
20 antibody or functional fragment thereof from the solid oral dosage form, until a specific event, preferably in the form of a pH trigger in solution, occurs. For example, a delayed release layer can be designed to focus the delivery of the antibody or functional fragment thereof entirely in the large intestine, beginning at the cecum, and continuing through the ascending, transverse, and descending colon, and ending in the sigmoid
25 colon. Alternatively, for example, a delayed release coating can be designed to begin the delivery of the antibody or functional fragment thereof in the ileum and end the release in the sigmoid colon.

The term "cover" or "covering" as used in this context is to be understood as defined
30 above. Preferably, the delayed release layer (4) is positioned on top of the sustained release layer (3) being covered, such that there is no other layer in between (i.e. between the delayed release layer and the delayed release layer). Preferably, the delayed release layer of the solid oral dosage form of the present invention

continuously covers the sustained release layer, such that there are no gaps in the delayed release layer.

The solid oral dosage form of the present invention is for oral administration, and comprises as an outer layer (is coated/coated with) a delayed release layer that prevents the release of the composition preferably before the terminal ileum, or before the ileocolonic region, alternatively before the ascending colon or before the transverse colon, of the gastrointestinal tract. The ileocolonic region is the region of the gastrointestinal tract where the small intestine merges with the large intestine. The large intestine is the penultimate section of the gastrointestinal tract and can be further subdivided into cecum, colon and rectum. The colon is further subdivided into ascending, transverse, descending colon and the sigmoid colon. The terminal ileum is the penultimate section of the small intestine and is directly adjacent to the cecum.

The approach for applying the delayed release layer is not particularly limited as long as it does not affect the stability and activity of the at least one antibody or functional fragment thereof in the depot layer coating. Methods for applying delayed release coatings are known in the art. In one embodiment of the present invention the delayed release coating is applied by spray coating, preferably fluidized-bed spray coating, e.g. as described above.

The delayed release polymer in the delayed release layer (4) is selected from poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof. Poly(methacrylic acid, methyl methacrylate) 1:2 is also known as methacrylic acid-methyl methacrylate copolymer (1:2), or as poly(methacrylic acid-co-methyl methacrylate) 1:2, or as Eudragit® S. Poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1 is also known as poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1, or as Eudragit® FS. Poly(methacrylic acid, methyl methacrylate) 1:1 is also known as methacrylic acid-methyl methacrylate copolymer (1:1), or as poly(methacrylic acid-co-methyl methacrylate) 1:1, or as Eudragit® L.

According to one embodiment the delayed release layer (4) comprises no polymers that are not enteric polymers. The term "enteric polymer" is known in the art and may refer to a polymer that does not dissolve in the gastric environment. According to another embodiment of the present invention the delayed release layer (4) comprises,
5 apart from poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof, no other delayed release polymers. According to a preferred embodiment of the present invention, the delayed release layer (4) comprises, poly(methacrylic acid, methyl methacrylate) 1:2, and preferably no
10 other delayed release polymer.

According to one embodiment of the present invention, the solid oral dosage form comprises 5-40 wt.-%, preferably 10-40 wt.-%, more preferably 10-35 wt.-%, even more preferably 15-35 wt.-%, even more preferably 15-30 wt.-%, even more preferably
15 18-30 wt.-%, even more preferably 20-30 wt.-%, even more preferably 21-26 wt.-%, e.g. about 22-25 wt.-%, poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof (preferably poly(methacrylic acid, methyl methacrylate) 1:2). According to another embodiment of the present invention, the
20 delayed release layer (4) comprises 50-97 wt.-%, preferably 65-95 wt.-%, more preferably 70-90 wt.-%, even more preferably 75-85 wt.-%, e.g. about 80 wt.-%, poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof (preferably poly(methacrylic acid, methyl methacrylate) 1:2),
25 relative to the total weight of the solids (i.e. not including residual solvent, e.g. ethanol and/or water) in the delayed release layer (4).

According to another embodiment of the present invention, the solid dosage form (in the delayed release layer) comprises 7-12 mg/cm², preferably 8-11 mg/cm², more
30 preferably 9-10 mg/cm², even more preferably about 9.5 mg/cm², poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof (preferably poly(methacrylic acid, methyl methacrylate) 1:2).

The plasticizer in the delayed release layer (4) is not particularly limited. The plasticizer in the delayed release layer (4) may be selected for example from triethyl citrate (TEC), polyethylene glycol, acetyl triethyl citrate, butyl citrate, polysorbate, polypropylene glycol, dibutyl sebacate (DBS), or a combination thereof. Preferably the plasticizer in the delayed release layer (4) is triethyl citrate (TEC). According to one embodiment of the present invention, the delayed release layer (4) comprises 1-30 wt.-%, preferably 2-25 wt.-%, more preferably 5-15 wt.-%, even more preferably 8-12 wt.-%, even more preferably about 10 wt.-%, plasticizer, relative to the total weight of the delayed release polymers in the delayed release layer (4). According to another embodiment of the present invention, the delayed release layer (4) comprises 1-25 wt.-%, preferably 4-15 wt.-%, more preferably 5-12 wt.-%, even more preferably 6-10 wt.-%, even more preferably 7-9 wt.-%, even more preferably about 8 wt.-%, plasticizer, relative to the total weight of the solids (i.e. not including residual solvents, e.g. ethanol and/or water) in the delayed release layer (4).

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The anti-tacking agent in the delayed release layer (4) is not particularly limited. The anti-tacking agent in the delayed release layer (4) may be selected for example from mesoporous silica, colloidal silica dioxide, stearic acid, magnesium stearate, glycerol monostearate (GMS), or talc. Preferably the anti-tacking agent in the delayed release layer (4) is glycerol monostearate (GMS). According to one embodiment of the present invention, the delayed release layer (4) comprises 1-30 wt.-%, preferably 2-25 wt.-%, more preferably 5-15 wt.-%, even more preferably 8-12 wt.-%, even more preferably about 10 wt.-%, anti-tacking agent, relative to the total weight of the delayed release polymers in the delayed release layer (4). According to another embodiment of the present invention, the delayed release layer (4) comprises 1-20 wt.-%, preferably 4-15 wt.-%, more preferably 5-12 wt.-%, even more preferably 6-10 wt.-%, even more preferably 7-9 wt.-%, even more preferably about 8 wt.-%, anti-tacking agent, relative to the total weight of the solids (i.e. not including residual solvents, e.g. ethanol and/or water) in the delayed release layer (4).

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The delayed release layer (4) of the solid oral dosage form of the present invention optionally may further comprise a surfactant. The surfactant in the delayed release layer (4) is not particularly limited, however preferably it is a nonionic surfactant. The solid oral dosage form in the delayed release layer (4) may comprise a surfactant

selected from the group consisting of polysorbate 20, polysorbate 28, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85, poloxamer 124, poloxamer 181, poloxamer 188, poloxamer 237, poloxamer 331, poloxamer 338 and poloxamer 407, and combinations thereof.

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According to a preferred embodiment of the present invention, the surfactant in the delayed release layer (4) is polysorbate 20, 28, 40, 60, 65, 80, 81 and 85; preferably polysorbate 80. According to one embodiment of the present invention, the delayed release layer (4) comprises 0.1-15 wt.-%, preferably 0.5-10 wt.-%, more preferably 1-10 6 wt.-%, even more preferably 2-5 wt.-%, even more preferably 3-4.5 wt.-%, even more preferably 3.5-4 wt.-%, even more preferably about 4 %, surfactant, relative to the total weight of the delayed release polymers in the delayed release layer (4). According to another embodiment of the present invention, the delayed release layer (4) comprises 0.1-15 wt.-%, preferably 0.5-10 wt.-%, more preferably 1-5 wt.-%, even more 15 preferably 2-4 wt.-%, even more preferably 2.5-3.5 wt.-%, even more preferably 3-3.5 wt.-%, even more preferably about 3-3.2 wt.-%, surfactant, relative to the total weight of the solids (i.e. not including solvent) in the delayed release layer (4).

According to a preferred embodiment of the solid oral dosage form of the present 20 invention, the delayed release layer (4) consists of poly(methacrylic acid, methyl methacrylate) 1:2, poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof (preferably poly(methacrylic acid, methyl methacrylate) 1:2); anti-tacking agent (preferably glycerol monostearate (GMS)); plasticizer (preferably triethyl citrate (TEC)); surfactant 25 (preferably polysorbate 80), and optionally residual solvent (e.g. ethanol and/or water).

In one embodiment of the present invention the residual solvent content of the solid oral dosage form (e.g. residual solvent, preferably water, content after preparation of the solid oral dosage form), relative to the total weight of the solid oral dosage form, is 30 less than 15 wt.-%, preferably less than 10 wt.-%, more preferably less than 8 wt.-%, even more preferably less than 7 %, even more preferably less than 6 %, even more preferably no more than 5 %, e.g. about 5 %, or alternatively no more than about 4 wt.-% or no more than about 3 wt.-%. In another embodiment of the present invention the residual water content of the solid oral dosage form, relative to the total weight of the

solid oral dosage form, is less than 15 wt.-%, preferably less than 10 wt.-%, more preferably less than 8 wt.-%, even more preferably less than 7 %, even more preferably no more than 5 %, e.g. about 5 %, or alternatively no more than about 4 wt.-%, or no more than about 3 wt.-%, or no more than about 2 wt.-%.

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In a preferred embodiment of the present invention the solid oral dosage form comprises, or consists of, a) in the inert core unit, microcrystalline cellulose; and/or b) in the depot layer, antibody or functional fragment thereof e.g. specific to TNF α , sucrose, L-histidine preferably L-histidine monohydrochloride and/or free base, hypromellose (HPMC), preferably hypromellose 2910 2.6-3.6 mPas, mesoporous silica, and/or polysorbate 80; and/or c) in the sustained release layer, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1, triethyl citrate (TEC) and/or mesoporous silica; and/or d) in the delayed release layer, poly(methacrylic acid, methyl methacrylate) 1:2, TEC, polysorbate 80, and/or glycerol monostearate (GMS); and/or e) residual water in the inert core unit and/or any of the layers.

In a preferred embodiment of the solid oral dosage form of the present invention, the inert core unit comprises 5-75 wt.-%, preferably 15-65 wt.-%, more preferably 15-60 wt.-%, even more preferably 20-60 wt.-%, even more preferably 25-30 wt.-%, microcrystalline cellulose, relative to the total weight of the solid oral dosage form.

In another preferred embodiment of the solid oral dosage form of the present invention, the depot layer (2) comprises, relative to the total weight of the solid oral dosage form, 0.05-30 wt.-% antibody or functional fragment thereof, 0.03-30 wt.-% binder, 0.1-40 wt.-% sucrose, 0.005-5 wt.-% L-histidine (salt and/or free base) and optionally 0.001-5 wt.-% other buffers, 0.005-8 wt.-% anti-tacking agent, and/or 0.0005-2 wt.-% surfactant; preferably 0.1-20 wt.-% antibody or functional fragment thereof, 0.1-25 wt.-% binder, 0.5-35 wt.-% sucrose, 0.01-3 wt.-% L-histidine and optionally 0.01-3 wt.-% other buffers, 0.01-5 wt.-% anti-tacking agent, and/or 0.001-1 wt.-% surfactant; more preferably 0.5-20 wt.-% antibody or functional fragment thereof, 0.5-15 wt.-% binder, 1-25 wt.-% sucrose, 0.05-2 wt.-% L-histidine and optionally 0.05-1.5 wt.-% other buffers, 0.05-1.5 wt.-% anti-tacking agent, and/or 0.005-0.3 wt.-% surfactant; even more preferably 2-20 wt.-% antibody or functional fragment thereof, 5-15 wt.-% binder,

10-25 wt.-% sucrose, 0.1-2 wt.-% L-histidine and optionally 0.5-1.5 wt.-% other buffers, 0.5-1.5 wt.-% anti-tacking agent, and/or 0.05-0.3 wt.-% surfactant; even more preferably 8-12 wt.-% antibody or functional fragment thereof, 6-8 wt.-% binder, 15-18 wt.-% sucrose, 0.15-1 wt.-% L-histidine and optionally 0.6-0.9 wt.-% other buffers, 0.6-
5 0.8 wt.-% anti-tacking agent (preferably mesoporous silica), and/or 0.05-0.1 wt.-% surfactant (preferably polysorbate 80).

In another preferred embodiment of the solid oral dosage form of the present invention, the sustained release layer (3) comprises, relative to the total weight of the solid oral
10 dosage form, 1-10 wt.-% ammonio methacrylate copolymer, 0.1-5 wt.-% plasticizer, and/or 0.05-7 wt.-% anti-tacking agent; preferably 3-6 wt.-% ammonio methacrylate copolymer, 0.2-2 wt.-% plasticizer, and/or 0.1-3 wt.-% anti-tacking agent; more preferably 3.3-4.5 wt.-% ammonio methacrylate copolymer, 0.5-1.5 wt.-% plasticizer, and/or 0.2-1 wt.-% anti-tacking agent; even more preferably 3.6-4.2 wt.-% poly(ethyl
15 acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 (e.g. Eudragit® RS 30D), 0.6-1 wt.-% plasticizer (preferably triethyl citrate (TEC)) and/or 0.3-0.5 wt.-% anti-tacking agent.

In another preferred embodiment of the solid oral dosage form of the present invention, the delayed release layer (4) comprises, relative to the total weight of the solid oral
20 dosage form, 10-40 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 0.5-10 wt.-% plasticizer, 0.1-3.5 wt.-% surfactant, and/or 0.5-10 wt.-% anti-tacking agent (preferably glycerol monostearate (GMS)); preferably 15-35 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 1-5 wt.-% plasticizer, 0.2-2 wt.-% surfactant, and/or 1-
25 5 wt.-% anti-tacking agent (preferably glycerol monostearate (GMS)); more preferably 18-30 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 1.5-3 wt.-% plasticizer, 0.5-1.3 wt.-% surfactant, and/or 1.5-3 wt.-% anti-tacking agent (preferably glycerol monostearate (GMS)); even more preferably 21-26 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 2.0-2.6 wt.-% plasticizer, 0.7-1.1 wt.-% surfactant, and/or 2.0-2.6
30 wt.-% anti-tacking agent (preferably glycerol monostearate (GMS)).

In another preferred embodiment of the present invention, the solid oral dosage form comprises up to 8 wt.-%, up to 7 wt.-%, or up to 6 wt.-%, or up to 5.5 wt.-%, preferably

up to 5 wt.-%, e.g. about 5, or 4.5, or 4, or 3 wt.-%, water in the inert core unit and/or any of the layers, relative to the total weight of the solid oral dosage form.

In yet another preferred embodiment of the present invention the solid oral dosage form, relative to the total weight of the solid oral dosage form, comprises, or consists of, a) in the inert core unit, 5-75 wt.-%, preferably 15-65 wt.-%, more preferably 20-60 wt.-%, even more preferably 25-30 wt.-%, microcrystalline cellulose; and/or b) in the depot layer, 0.05-30 wt.-% antibody or functional fragment thereof, 0.03-30 wt.-% binder, 0.1-40 wt.-% sucrose, 0.005-5 wt.-% L-histidine (salt and/or free base) and optionally 0.001-5 wt.-% other buffers, 0.005-10 wt.-% anti-tacking agent, and/or 0.0005-2 wt.-% surfactant; preferably 0.1-20 wt.-% antibody or functional fragment thereof, 0.1-25 wt.-% binder, 0.5-35 wt.-% sucrose, 0.01-3 wt.-% L-histidine and optionally 0.01-3 wt.-% other buffers, 0.01-5 wt.-% anti-tacking agent, and/or 0.001-1 wt.-% surfactant; more preferably 0.5-20 wt.-% antibody or functional fragment thereof, 0.5-15 wt.-% binder, 1-25 wt.-% sucrose, 0.05-2 wt.-% L-histidine and optionally 0.05-1.5 wt.-% other buffers, 0.05-1.5 wt.-% anti-tacking agent, and/or 0.005-0.3 wt.-% surfactant; even more preferably 2-20 wt.-% antibody or functional fragment thereof, 5-15 wt.-% binder, 10-25 wt.-% sucrose, 0.1-2 wt.-% L-histidine and optionally 0.5-1.5 wt.-% other buffers, 0.5-1.5 wt.-% anti-tacking agent, and/or 0.05-0.3 wt.-% surfactant; even more preferably 8-12 wt.-% antibody or functional fragment thereof, 6-8 wt.-% binder, 15-18 wt.-% sucrose, 0.15-1 wt.-% L-histidine and optionally 0.6-0.9 wt.-% other buffers, 0.6-0.8 wt.-% mesoporous silica, and/or 0.05-0.1 wt.-% polysorbate 80; and/or c) in the sustained release layer, 1-10 wt.-% ammonio methacrylate copolymer, 0.1-5 wt.-% plasticizer, and/or 0.05-7 wt.-% anti-tacking agent; preferably 3-6 wt.-% ammonio methacrylate copolymer, 0.2-2 wt.-% plasticizer and/or 0.1-3 wt.-% anti-tacking agent; more preferably 3.3-4.5 wt.-% ammonio methacrylate copolymer, 0.5-1.5 wt.-% plasticizer, and/or 0.2-1 wt.-% anti-tacking agent; preferably 3.6-4.2 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1, 0.6-1 wt.-% triethyl citrate (TEC) and/or 0.3-0.5 wt.-% mesoporous silica; and/or d) in the delayed release layer, 10-40 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 0.5-5 wt.-% plasticizer, 0.1-3.5 wt.-% surfactant, and/or 0.5-8 wt.-% glycerol monostearate (GMS); preferably 15-35 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 1-4 wt.-% plasticizer, 0.2-2 wt.-% surfactant, and/or 1-5 wt.-% glycerol monostearate (GMS); more preferably 18-30 wt.-% poly(methacrylic acid,

methyl methacrylate) 1:2, 1.5-3 wt.-% plasticizer, 0.5-1.3 wt.-% surfactant, and/or 1.5-3 wt.-% glycerol monostearate (GMS); even more preferably 21-26 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 2.0-2.6 wt.-% plasticizer, 0.7-1.1 wt.-% surfactant (e.g. polysorbate 80), and/or 2.0-2.6 wt.-% glycerol monostearate (GMS);
5 and/or e) up to 5.5 wt.-%, or up to 5 wt.-%, e.g. 5 wt.-%, water in the inert core unit and/or any of the layers.

The activity and stability of the antibody or functional fragment thereof, e.g. the anti-TNF α antibody or functional fragment thereof, in the solid oral dosage form of the
10 present invention is high. The stability and activity of an antibody or fragment thereof can be estimated for example by determining the fraction of an antibody or functional fragment thereof present as dimers and other aggregates. According to one embodiment of the present invention, the fraction of total content of antibody or functional fragment thereof present in the solid oral dosage form as dimers and other
15 aggregates does not exceed more than 15 %, preferably 12 %, more preferably 10 %, even more preferably 8 %, even more preferably 7 %, even more preferably 5 %, e.g. 3 %. Methods to determine the fraction of a polypeptide present as dimers and other aggregates are known in the art, and include for example Size Exclusion Chromatography (SEC). According to another embodiment the fraction of total content
20 of antibody or functional fragment thereof present in the solid oral dosage form as fragments of the full-length antibody or functional fragment thereof does not exceed 15 %, preferably 12 %, more preferably 10 %, even more preferably 8 %, even more preferably 7 %, even more preferably 5 %, e.g. 3 %.

25 The solid oral dosage form of the present invention preferably is gastric resistant. According to one embodiment of the present invention, the solid oral dosage form of the present invention is for targeted release of the antibody or functional fragment thereof starting in the terminal ileum, the ileocolonic region, the ascending colon or transverse colon, preferably in the terminal ileum, the ileocolonic region or the
30 ascending colon, more preferably in the terminal ileum or the ileocolonic region. According to another embodiment of the present invention, the solid oral dosage form of the present invention is for targeted release of the antibody or functional fragment thereof in the terminal ileum, the ileocolonic region, the ascending colon, the transverse colon, descending colon and/or the sigmoid colon. According to yet another

embodiment of the present invention, the solid oral dosage form of the present invention is for targeted sustained release of the antibody or functional fragment thereof starting in the terminal ileum and continuing at least through the descending colon, preferably the sigmoid colon.

5

The solid oral dosage form of the present invention is suitable for targeted sustained release in the lower GI tract. Preferably, the solid oral dosage form of the present invention, upon immersion in an aqueous solution at a pH 6.0 under continuous agitation (e.g. for 2 h), does not release any relevant amount of antibody or functional fragment thereof (e.g. releases less than 1 wt.-%, or less than 0.5 wt.-%, or less than 0.1 wt.-% of the total antibody or functional fragment thereof load). According to one embodiment of the invention, the solid oral dosage form according to any of the embodiments described above allows a sustained release of the antibody or functional fragment thereof over a time period of at least 5 h, preferably at least 10 h, more preferably at least 12 h, even more preferably at least 15 h, even more preferably at least 20 h, most preferably at least 24 h, upon continuously immersing the solid oral dosage form in an aqueous solution under continuous agitation at a pH of 6.5-7.5, preferably a pH of about 6.8. According to another embodiment of the invention, upon continuously immersing the solid oral dosage form according to any of the embodiments described above in an aqueous solution under continuous agitation and at a pH of 6.5-7.5, preferably pH of 6.5-7.0, more preferably a pH of 6.8, a sustained release, preferably with a substantially constant release rate, of at least 80 %, preferably at least 90 %, 95%, or 98 %, of the antibody or fragment thereof in the solid oral dosage form over 4-30h, preferably 8-28h, more preferably 16-26 h, even more preferably 24 h, is achieved.

In a further aspect the present invention is directed to the solid oral dosage form as defined in any of the embodiments above for use in the treatment of a disease in the gastrointestinal tract, preferably in the ileum (preferably the terminal ileum), the ileocolonic region, the ascending colon, transverse colon, the descending colon and/or the sigmoid colon of a patient, preferably a human patient. Such diseases include e.g. immune checkpoint inhibitor (ICPI) induced colitis, ICPI induced enterocolitis, ICPI induced diarrhoea, IBD, cancer (such as colorectal cancer or small intestine cancer), celiac disease, infections (such as Clostridium difficile infection) of the small intestine

30

and the colon, and diarrhea. In a preferred embodiment of the present invention, the solid oral dosage form of the present invention is for use in the treatment of ICPI induced colitis, ICPI induced enterocolitis, or ICPI induced diarrhoea, preferably ICPI induced colitis. In another preferred embodiment of the present invention, the solid oral dosage form of the present invention is for use in the treatment of an IBD, e.g. Crohn's disease or ulcerative colitis.

In another aspect, the present invention is directed to an oral multiparticulate drug delivery system, comprising a plurality of solid oral dosage forms of any of the embodiments described above, preferably wherein the oral multiparticulate drug delivery system is a sachet/stick pack, a straw device (xStraw®), capsule, or tablet/mini-tablet, more preferably a capsule; preferably wherein the oral multiparticulate drug delivery system comprises a total amount of the antibody or functional fragment thereof suitable for oral administration to a human patient.

According to a further embodiment, the oral multiparticulate drug delivery system of the invention comprises a plurality of solid oral dosage forms of any of the embodiments described above, wherein each solid oral dosage form preferably has a predetermined axis and a predetermined cross-sectional profile, wherein at least 80 % by number of those solid oral dosage forms, preferably 90 %, more preferably 95 %, have a median aspect ratio between 0.7 and 1.7, the aspect ratio being defined as solid oral dosage form length along the predetermined axis divided by the smallest cross-sectional dimension. According to another embodiment the median aspect ratio is above 0.8, preferably above 0.9, and below 1.6, preferably below 1.5, more preferably 1.4, even more preferably below 1.3, even more preferably below 1.2, most preferably about 1. For further details regarding aspect ratio, predetermined axis, predetermined cross-sectional profile and span (including definitions and embodiments), it is referred to the disclosure of EP 2 512 453. It is to be understood that the above definitions and embodiments regarding aspect ratio and span of the solid oral dosage form equally apply to the inventive solid oral dosage forms according to any one of the embodiments above. Further embodiments for the oral multiparticulate drug delivery system may be found in EP 2 512 453 and are applicable to the present invention independent of whether these embodiments are disclosed in EP 2 512 453 as referring to spheronized/non-spheronized solid dosage forms.

According to yet another embodiment of the present invention, the oral multiparticulate drug delivery system of the invention allows the recovery of at least 60 %, preferably at least 80 %, more preferably at least 85 %, even more preferably at least 93 %, even
5 more preferably at least 95 %, even more preferably at least 97 %, even more preferably at least 98 %, of the antibody or functional fragment thereof from the solid oral dosage forms.

According to yet another embodiment of the present invention, the oral multiparticulate
10 drug delivery system of the invention allows the recovery of at least 60 %, preferably at least 80 %, more preferably at least 85 %, even more preferably at least 93 %, even more preferably at least 95 %, even more preferably at least 97 %, even more preferably at least 98 %, of the antibody or functional fragment thereof from the solid oral dosage forms, within 4 h, or 6 h, or 8 h, or 10 h, or 12 h, or 14 h, or 16 h, or 18 h,
15 or 20 h, or 22 h, or 24 h, or 26 h, or 28 h, or 30 h, of continuously immersing the solid oral dosage form in an aqueous solution under continuous agitation (sustained release), at a pH of 6.5 to 7, preferably at a pH of about 6.8.

According to yet another embodiment of the present invention, the oral multiparticulate
20 drug delivery system of the invention is prepared from a plurality of solid oral dosage forms by compression or encapsulation, preferably encapsulation.

In a further aspect, the present invention is directed to the use of the solid oral dosage form as described in any of the embodiments above in the preparation of a medicament
25 for the treatment of a gastrointestinal disease. The medicament may comprise the oral multiparticulate drug delivery system as described in any of the embodiments above. According to one embodiment the gastrointestinal disease is immune checkpoint inhibitor (ICPI) induced colitis, ICPI induced enterocolitis, ICPI induced diarrhoea, or IBD (e.g. Crohn's disease or ulcerative colitis).

30 In yet a further aspect, the present invention is directed to a method for targeted local treatment of a gastrointestinal disease, comprising administering to a patient in need thereof a pharmaceutically effective amount of the solid oral dosage form of any of the embodiments described above or the oral multiparticulate drug delivery system of any

- of the embodiments described above. The patient preferably is a human patient. According to one embodiment, the method is for the treatment of the GI disease in the ileum (preferably the terminal ileum), the ileocolonic region, the ascending colon, transverse colon, the descending colon and/or the sigmoid colon of the patient.
- 5 According to another embodiment of the method, the gastrointestinal disease is an inflammatory bowel disease (IBD), e.g. Crohn's disease or ulcerative colitis. According to a preferred embodiment of the method, the gastrointestinal disease is immune checkpoint inhibitor (ICPI) induced colitis, ICPI induced enterocolitis, or ICPI induced diarrhoea, preferably ICPI induced colitis.

Table 1: Overview of the sequences of the sequence listing.

SEQ ID NO:	Description of the amino acid sequence
1	CDR L1 of clone 16-22-H05
2	CDR L2 of clone 16-22-H05
3	CDR L3 of clone 16-22-H05
4	CDR H1 of clone 16-22-H05
5	CDR H2 of clone 16-22-H05
6	CDR H3 of clone 16-22-H05
7	V _H of humanized IgG of clone 16-22-H05
8	V _L of humanized IgG of clone 16-22-H05
9	CDR L1 of clone 17-22-B03
10	CDR L2 of clone 17-22-B03
11	CDR L3 of clone 17-22-B03
12	CDR H1 of clone 17-22-B03
13	CDR H2 of clone 17-22-B03
14	CDR H3 of clone 17-22-B03
15	V _H of humanized IgG of clone 17-22-B03
16	V _L of humanized IgG of clone 17-22-B03 (sc08)
17	V _L of humanized IgG of clone 17-22-B03 (sc02)
18	Fc region of Ab-REW (including hinge region)
19	Fc region of Ab-YTE-DLE-PVAdeltaG (including hinge region)
20	Fc region of Ab-A-DLE-PVAdeltaG (including hinge region)
21	Fc region of Ab-A-AEA-PVAdeltaG (including hinge region)
22	Fc region of Ab-AA (including hinge region)
23	Light chain of humanized IgG of clone 16-22-H05
24	Light chain of humanized IgG of clone 17-22-B03 (sc08)
25	Light chain of humanized IgG of clone 17-22-B03 (sc02)
26	Heavy chain of Ab-REW (based on clone 16-22-H05)
27	Heavy chain of Ab-REW (based on clone 17-22-B03)
28	Heavy chain of Ab-YTE-DLE-PVAdeltaG (based on clone 16-22-H05)
29	Heavy chain of Ab-A-DLE-PVAdeltaG (based on clone 16-22-H05)
30	Heavy chain of Ab-A-AEA-PVAdeltaG (based on clone 16-22-H05)
31	Heavy chain of Ab-YTE-DLE-PVAdeltaG (based on clone 17-22-B03)
32	Heavy chain of Ab-A-DLE-PVAdeltaG (based on clone 17-22-B03)
33	Heavy chain of Ab-A-AEA-PVAdeltaG (based on clone 17-22-B03)
34	Heavy chain of Ab-AA (based on clone 16-22-H05)
35	Heavy chain of Ab-AA (based on clone 17-22-B03)

EXAMPLES

Materials and methods applied in the examples5 1 Manufacturing process1.1 *Drug layering*

Drug loaded multiparticulate pellets were prepared by layering (depositing) a depot layer solution containing the anti-TNF α antibody onto starting cellet seeds in a Mini-Glatt fluidized bed (Glatt GmbH, Binzen, Germany) equipped with a Wurster column (bottom spray assessment). For the preparation of the depot layer formulation, hydroxypropyl methylcellulose (HPMC) was slowly added to a histidine buffer solution (pH 5.5) under paddle stirring homogenization until full dissolution of the HPMC solids into the buffered media. Thereafter, Syloid 244 FP was slowly added and dispersed in the HPMC-pH 5.5 histidine buffer media by paddle stirring. The resulting HPMC coating dispersion was then blended with the required mass of the anti-TNF antibody drug substance (DS), which was available as a buffered solution in pH 5.5 histidine buffer, further comprising sucrose as stabilizer and polysorbate 80 as surfactant. The anti-TNF- α antibody coating formulation was layered on inert pellets (cellets[®]) to achieve the desired loading at an inlet air temperature of 38–44 °C and a product temperature of 31–35 °C. The antibody layered pellets were dried for 20 - 24 h in a drying oven with air circulation at 40 °C.

1.2 *Sustained release coating*

A Eudragit RS30D ready to use aqueous dispersion comprising 30% Eudragit[®] RS solids was used for the sustained release coating onto the antibody layered pellets. Before the coating step with Eudragit RS, the 30% polymer dispersion was homogenized and transferred to a beaker glass through a sieve to prevent particle agglomeration. Purified water was added followed by Triethyl citrate (plasticizer) and homogenized by magnetic stirring for 15 minutes. Thereafter, Syloid 244 FP (anti-tacking agent) was added and the final Eudragit RS dispersion was set to target concentration of 20 % total solids. The final aqueous coating dispersion of Eudragit RS was sprayed onto the anti TNF- α antibody drug layered pellets (cellets) using the

Micro-kit of the Glatt fluidized bed by bottom spray at 29–31 °C inlet air temperature and 26–28 °C product temperature. After completing the spraying of the Eudragit RS coating formulation, a Syloid 244 FP aqueous suspension was sprayed in order to decrease stickiness of the pellets. After this step, a post-coating thermal treatment (in process curing) was performed in the fluidized bed equipment for 30 minutes at 52–55 °C inlet air temperature to a target product temperature of 45–46 °C, while spraying water to create a moist environment.

1.3 *Delayed release coating*

Anti TNF- α antibody sustained release pellets (coated with Eudragit RS) were further coated with Eudragit S as delayed release polymer. The Eudragit S coating formulation was produced by fully dissolving the Eudragit[®] S polymer in 96 % ethanol under magnetic stirring at room temperature. Triethyl citrate was added to the organic (ethanolic) solution and homogenised by magnetic stirring. As next step, a Glycerol monostearate (GMS) aqueous emulsion (used as anti-tacking agent) was prepared by dissolving polysorbate 80 (Tween 80) in purified water by magnetic stirring followed by addition of GMS. The mixture was then heated up to 75 °C under continuous magnetic stirring and kept at this temperature for 15 minutes to achieve a homogenous emulsion. Thereafter, the GMS emulsion was cooled down to room temperature under continuous magnetic stirring. The GMS emulsion was slowly added to the Eudragit S organic solution resulting in the final Eudragit S coating formulation. The coating process was conducted by bottom spray using the Micro-kit of the Glatt fluidized bed at an inlet air temperature of 27–32 °C and 26.0–29 °C product temperature. After spraying the target amount of the Eudragit S polymer, a post-coating pre-drying step was carried out in process in the fluidized bed equipment for 30 minutes at 40 °C. The drying process was continued for 2 - 4 h in a drying oven with air circulation at 40 °C.

2 Dissolution Methods

2.1 *Dissolution assay*

Dissolution with 75 rpm agitation speed at 37 °C.

Media:

a) 0.1 N HCl;

b) potassium phosphate buffer with sodium chloride, pH 6.0. Salts were mixed so that the ionic strength of the medium was equivalent to the ionic strength of biorelevant Hanks buffer (H.M. Fadda, and A.W. Basit, J. Drug Del. Sci. Tech. 2005; 15(4): 273-280).

- 5 *Procedure:* Into each vessel, one dosage unit was placed and agitated for 2 h in 0.1 N HCl, followed by 2 h dissolution in medium b). After that, the pH of the dissolution medium was set to pH 6.8. To obtain profiles, samples were analyzed by HPLC and total protein was quantified using the Bradford method as detailed below.

10 2.2 *Antibody release using Bradford determination*

Dissolution of anti-TNF α antibody layered pellets, and sustained release coated pellets was performed by rotational mixing in phosphate buffer pH 6.8. Briefly, pellets were weighed in 5 mL cryotubes to which 4 mL phosphate buffer pH 6.8 was added. The tubes were then rotated at 15 rpm in a bench-top rotating device. The amount of coated
15 pellets used per tube was calculated in order to yield a theoretical 0.8 mg/mL antibody drug substance (DS) concentration in the buffer at 100% release, considering the theoretical antibody loading. At defined time points (15min; 30min; 1h; 2h; 4h; 6h and 24h), 100 μ L supernatant were sampled. The samples were then centrifuged for 5 min at 3000 rpm and the supernatant was used for further analysis. The volume of sample
20 taken was not replaced with fresh buffer during the course of the experiments.

Total protein quantification was done by colorimetry following the Bradford method with a Coomassie Plus assay (Thermo Scientific). Quantification was done using a freshly prepared standard calibration curve in 10 mM phosphate buffer pH 6.8. The calibration
25 curve was built with anti-TNF α antibody standards between 0.03 and 1.0 mg/mL.

Results

Formulation of a multilayer solid oral dosage form for delayed and sustained release

- 30 A drug product was developed comprising an anti-TNF α antibody as a multiparticulate formulation with a multilayer coating concept using cellets[®] as inert core units, which are coated with a depot layer formulation comprising the anti-TNF α antibody as active

ingredient (full antibody moiety), sucrose (stabilizer), Histidine/Histidine HCl (buffer agent) and Pharmacoat 603 (hypromellose) as film forming polymer (polymeric binder). The anti-TNF α antibody layered cellets[®] were further coated with an inner layer comprising Eudragit[®] RS (sustained release polymer) and an outer layer of Eudragit[®] S (delayed release polymer). The different layers were applied by drug layering using fluidized-bed spray coating.

- The following multilayer pellet design was thus defined during formulation development
- inert core unit (cellets[®]);
 - anti-TNF α antibody depot layer (Hypromellose as film forming polymer; aqueous);
 - sustained release layer (Eudragit[®] RS as film forming polymer; aqueous); and
 - delayed release layer (Eudragit[®] S as film forming polymer; organic).
- The resulting multi-layer solid oral dosage form is shown in Figures 1 and 2. Figure 5 shows a SEM image of a cross-section of the final drug product. The final drug product had the following ingredients in the individual layers as shown in Table 2 below.

Table 2: Ingredients in the layers of coated pellets

Depot layer	Sustained release layer	Delayed release layer
Antibody DS	Eudragit RS	Eudragit S
Syloid 244 FP	Syloid 244 FP	Triethyl citrate
Histidine monohydrochloride monohydrate	Triethyl citrate	Glycerol monostearate (GMS)
L-Histidine (free base)		Polysorbate 80
Sucrose		
Polysorbate 80		
Hypromellose (Pharmacoat 603)		

During drug product development, the solid dosage form was formulated with different loads of anti-TNF α -antibody in the depot layer and different functional coatings in solid oral dosage form were explored.

One approach for producing multiparticulates with different antibody loads is to use for the solid oral dosage forms in the multiparticulates the same depot layer formulation for differently loaded drug product (e.g. same concentration of anti-TNF α antibody and excipient in the depot layer coating formula), and adjusting during coating the amount required for the envisaged anti-TNF α antibody loading. Such an approach results in a thinner depot layer for a lower load in comparison to a thicker layer for a higher drug load. The other functional coating layers comprising Eudragit[®] RS (inner coating) and Eudragit[®] S (outer coating) were both kept unchanged independently of the target level of anti-TNF α antibody loading intended after drug layering.

10

Anti-TNF α antibody loaded cellets[®] were produced by applying the depot layer coating formulation until the target loading (of the anti-TNF α antibody) was achieved. 100 % recovery of anti-TNF α antibody could be confirmed (assay via Bradford) from the anti-TNF α antibody loaded pellets comprising the depot layer, but no sustained or delayed release layer (see e.g. Figure 3A for Example 1 drug layered intermediate).

15

Next the Eudragit[®] RS-based sustained coating was applied on top of the depot layer by spray coating. The quality and homogeneity of coating of the Eudragit[®] RS layer was confirmed by the SEM analysis of the Eudragit[®] RS intermediate, shown in Figure 5 for lower drug loading, and in Figure 6 for a higher drug loading.

20

As a final step the Eudragit[®] S-based delayed release layer was applied on top of the sustained release layer by spray coating.

During the evaluation of the anti-TNF α antibody loaded examples comprising the sustained release layer, it was unexpectedly found that the level of drug released from the anti-TNF α antibody layered cellets[®] further coated with the sustained release layer comprising Eudragit[®] RS, but not yet containing the Eudragit[®] S delayed release layer, was unreliable, in some cases achieving only ca. 12 % drug release within 24-26 hours (hr) in a release test simulating the GI environment as described above (Figure 3B).

25
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However, surprisingly after applying the final outer delayed release layer comprising Eudragit[®] S (Example 1 final), the amount of drug released consistently increased to levels interesting for commercial use of expensive drug product in the release test and

with a consistent and sufficiently high release rate (about 80 % antibody released within 26 hours in the release test, see Figures 3C and 4). This was surprising since the delayed release layer is supposed to only prevent drug release until the pH trigger.

- 5 These findings suggest that the anti-TNF α antibody multi-layer coating system proposed by the inventors is not solely driven by the isolated properties of the excipients used in the different coating layers, or by the isolated properties of the functional polymers, but rather by the combinatory effect of the whole formulation leading to a drug delivery system suitable for the targeted release of the large antibody moiety. Thus, these unexpected results suggest (without being bound to any particular theory) that the antibody containing final solid oral dosage form found by the inventors (e.g., Figure 1) works due to the combinatorial effect of the components in the different layers enabling the release of the large antibody moiety in a desired manner.
- 10
- 15 The example compositions of the final solid oral dosage form, having the layer structure as shown in Figure 1, is shown in Tables 3/4 and 5/6 below.

- For the final (multi-layer) combination of the anti-TNF α antibody depot layer and the functional polymeric layers, as evident for example from Figures 3C and 4 assessed using the dissolution assay, the release after 2 hours at pH 6.0 was 0 %. Slow release started after 1h – 2.5 hours at pH 6.8. After 26 hours approximately 80 % of the antibody had been released.
- 20

- Ultimately, the final (multi-layer) combination of the anti-TNF α antibody depot layer and the functional polymeric layers as proposed by the inventors and as shown in Figure 2 prevented the early (and undesired) drug release in media simulating the acidic environment of the stomach (2 hours in 0.1 N HCl), as well as the release during the passage through the upper small intestine (no release during two hours in buffer pH 6.0) and allowed a sustained release of the antibody in media with pH 6.8 or higher, simulating the pH conditions of the ileum where drug release is envisaged to start and to continue in a sustained manner along the gut.
- 25
- 30

Table 3: Composition of Example 1 (values in percentage are weight percentages of constituents, relative to the total weight of the final composition of Example 1)

Example 1		5
Eudragit RS weight gain after sustained release coating (target Eud RS: 6.0 %)		
Eudragit S100 after delayed release coating (target Eud S: 9.5 mg/cm ²)		
Composition Example 1		10
cellets (microcrystalline cellulose)	57.85 %	
anti-TNF α antibody drug substance (solid)	0.80 %	
L-Histidine/ L-Histidine HCL buffer salts (solid)	0.08 %	
Pharmacoat 603	0.59 %	15
Syloid 244FP	0.46 %	
Sucrose	1.42 %	
Polysorbate 80	0.94 %	
Eudragit RS (solid)	4.00 %	20
Triethyl citrate (TEC)	3.14 %	
Eudragit S100	23.40 %	
Glycerol monostearate (GMS)	2.34 %	
Humidity (measured by LoD)	4.99 %	25
TOTAL	100 %	

Table 4: Composition of Example 1 (values in percentage are weight percentages of constituents in individual layers, relative to the total weight of the final composition of Example 1)

Example 1		5
Eudragit RS weight gain after sustained release coating (target Eud RS: 6.0 %)		
Eudragit S100 after delayed release coating (target Eud S: 9.5 mg/cm ²)		
Composition Example 1		
Inert core		
cellets (microcrystalline cellulose)	57.85	%
Drug layer (depot layer)		
anti-TNF α antibody drug substance (solid)	0.80	%
L-Histidine/ L-Histidine HCL buffer salts (solid)	0.08	%
Pharmacoat 603	0.59	%
Syloid 244FP	0.06	%
Sucrose	1.42	%
Polysorbate 80	0.01	%
Sustained release layer		
Eudragit RS (solid)	4.00	%
Triethyl citrate (TEC)	0.80	%
Syloid 244FP	0.40	%
Delayed release layer		
Eudragit S100	23.40	%
Glycerol monostearate (GMS)	2.34	%
Polysorbate 80	0.94	%
Triethyl citrate (TEC)	2.34	%
Humidity (measured by LoD)	4.99	%
TOTAL	100	%

Table 5: Composition of Examples 2, 3 and 4 (values in percentage are weight percentages of constituents, relative to the total weight of the final composition of Example 2, 3 and 4, resp.)

Examples 2, 3 and 4			
Eudragit RS weight gain after sustained release coating (target Eud RS: 6.0 %)		(target Eud RS: 6.0 %)	
Eudragit S100 after delayed release coating (target Eud S: 9.5 mg/cm ²)		(target Eud S: 11.50 mg/cm ²)	
Composition	Example 2	Example 3	Example 4
Cellets (microcrystalline cellulose)	27.16 %	25.22 %	25.36 %
anti-TNF α antibody drug substance (solid)	9.48 %	9.26 %	9.01 %
L-Histidine/ L-Histidine HCL buffer salts (solid)	0.94 %	0.91 %	0.88 %
Pharmacoat 603	6.90 %	6.74 %	6.58 %
Syloid 244FP	1.08 %	1.05 %	1.03 %
Sucrose	16.87 %	16.48 %	15.87 %
Polysorbate 80	1.00 %	1.07 %	1.11 %
Eudragit RS (solid)	3.94 %	3.80 %	3.68 %
Triethyl citrate (TEC)	3.08 %	3.24 %	3.31 %
Eudragit S100	22.93 %	24.80 %	25.71 %
Glycerol monostearate (GMS)	2.29 %	2.48 %	2.57 %
Humidity (measured by LoD)	4.33 %	4.95 %	4.90 %
TOTAL	100 %	100 %	100 %

Table 6: Composition of Examples 2, 3 and 4 (values in percentage are weight percentages of constituents in individual layers, relative to the total weight of the final composition of Example 2, 3 and 4, resp.)

Examples 2, 3 and 4			
Eudragit RS weight gain after sustained release coating (target Eud RS: 6.0 %)			(target Eud RS: 6.0 %)
Eudragit S100 after delayed release coating (target Eud S: 9.5 mg/cm ²)			(target Eud S: 11.50 mg/cm ²)
Composition	Example 2	Example 3	Example 4
Inert core			
Cellets (microcrystalline cellulose)	27.16 %	25.22 %	25.36 %
Drug layer (depot layer)			
anti-TNF α antibody drug substance (solid)	9.48 %	9.26 %	9.01 %
L-Histidine/ L-Histidine HCL buffer salts (solid)	0.94 %	0.91 %	0.88 %
Pharmacoat 603	6.90 %	6.74 %	6.58 %
Syloid 244FP	0.69 %	0.67 %	0.66 %
Sucrose	16.87 %	16.48 %	15.87 %
Polysorbate 80	0.08 %	0.08 %	0.08 %
Sustained release layer			
Eudragit RS (solid)	3.94 %	3.80 %	3.68 %
Triethyl citrate (TEC)	0.79 %	0.76 %	0.74 %
Syloid 244FP	0.39 %	0.38 %	0.37 %
Delayed release layer			
Eudragit S100	22.93 %	24.80 %	25.71 %
Glycerol monostearate (GMS)	2.29 %	2.48 %	2.57 %
Polysorbate 80	0.92 %	0.99 %	1.03 %
Triethyl citrate (TEC)	2.29 %	2.48 %	2.57 %
Humidity (measured by LoD)	4.33 %	4.95 %	4.90 %
TOTAL	100 %	100 %	100 %

Stability tests

Formulations in accordance with Example 4 were stored at either 2-8°C or at 25°C/60%RH for 12 months. At various time points the potency of the antibody in the formulation was tested by determining the relative potency (against nominal antibody content) of the anti-TNFalpha antibody, using a cell-based assay adapted for the antibody.

Exemplary potency assay:

A549 cells are seeded prior to the assay. A dilution series of the analyte is incubated with a constant dose of TNFalpha. After allowing the formation of analyte-TNFalpha complexes, the A549 cells are subsequently stimulated with the mixture and the stimulation abrogated by fixing the cells with Paraformaldehyde. The phosphorylated NF-kB S536 is labeled by consecutive staining of the cells with a phosphor-specific NF-kB S536 antibody and a HRP-labeled detection antibody. The amount of HRP is detected by the conversion of a chemiluminescent substrate by HRP and the generation of a luminescent signal which can be captured on specialized instruments.

Results:

time point (months after start of incubation)	relative potency (%)	
	storage at 2-8°C	storage at 25°C/60%RH
0 (initial)	97	
1	103	102
3	100	103
6	103	98
9	104	94
12	103	95

As can be seen, the antibody retains its activity over a period of at least 12 months at both 2-8°C and 25°C/60% RH. The stability at 25°C is very remarkable and surprising for an antibody drug.

Claims

1. A solid oral dosage form comprising
 - 5 i) an inert core unit (1);
 - ii) a depot layer (2) covering the inert core unit (1) and comprising an antibody or a functional fragment thereof, as an active agent; and optionally a stabilizer, a buffer and/or a polymeric binder;
 - 10 iii) a sustained release layer (3), covering the depot layer (2) and comprising at least one cationic polymer; and optionally a plasticizer and/or an anti-tacking agent; and
 - iv) a delayed release layer (4) covering the sustained release layer (3) and comprising at least one anionic polymer and optionally a plasticizer.
2. A solid oral dosage form comprising
 - 15 i) an inert core unit (1);
 - ii) a depot layer (2) covering the inert core unit (1) and comprising an antibody or a functional fragment thereof as an active agent; a stabilizer; a buffer; and a polymeric binder;
 - 20 iii) a sustained release layer (3), covering the depot layer (2) and comprising at least one cationic polymer; a plasticizer; and an anti-tacking agent; and
 - iv) a delayed release layer (4) covering the sustained release layer (3) and comprising at least one anionic polymer and a plasticizer.
3. The solid dosage form of claim 1 or 2, wherein the at least one anionic polymer is selected from the group consisting of polymers comprising carboxylic acid groups; poly(methacrylic acid, methyl methacrylate) 1:1; poly(methacrylic acid, ethyl acrylate) 1:1; poly(methacrylic acid, methyl methacrylate) 1:2; poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1; carboxymethyl cellulose; and combinations thereof.

4. The solid dosage form of any one of claims 1 to 3, wherein the at least one cationic polymer is selected from the group consisting of chitosan; cellulose; ammonio methacrylate copolymers; poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1; poly(2-N,N-dimethylaminoethylmethacrylate); poly-L-lysine; polyethylenimine; Poly(amidoamine)
5. A solid oral dosage form comprising
- i) an inert core unit (1);
 - ii) a depot layer (2) covering the inert core unit (1) and comprising an antibody or a functional fragment thereof, as an active agent; a stabilizer; a buffer; and a polymeric binder;
 - iii) a sustained release layer (3), covering the depot layer (2) and comprising an ammonio methacrylate copolymer; a plasticizer; and an anti-tacking agent; and
 - iv) a delayed release layer (4) covering the sustained release layer (3) and comprising poly(methacrylic acid, methyl methacrylate) 1:2, poly(methacrylic acid, methyl methacrylate) 1:1, or a combination thereof; an anti-tacking agent; and a plasticizer.
6. The solid dosage form of any one of the preceding claims, wherein the sustained release layer does not comprise an anionic polymer; and/or wherein the delayed release layer does not comprise a cationic polymer.
7. The solid oral dosage form of any of the preceding claims, wherein the inert core unit (1) is an inert pellet comprising, or consisting of, microcrystalline cellulose.
8. The solid oral dosage form of any of the preceding claims, wherein the stabilizer in the depot layer (2) is selected from sucrose, maltose, lactose, trehalose, glycerol, maltitol, isomalt, mannitol, sorbitol, xylitol, and combinations thereof, preferably sucrose.
9. The solid oral dosage form of any of the preceding claims, wherein the buffer in the depot layer (2) is selected from the group consisting of L-histidine buffer,

citrate buffer, hydroxymethylaminomethane (TRIS) buffer, succinate buffer, phosphate buffer, acetate buffer, and combinations thereof.

10. The solid oral dosage form of any of the preceding claims, wherein in the depot layer (2) the stabilizer is sucrose; and/or the buffer is L-histidine or a salt thereof;
5 and/or the polymeric binder in the depot layer (2) is hypromellose (HPMC).
11. The solid oral dosage form of any of the preceding claims, wherein the depot layer (2) comprises an anti-tacking agent and/or a surfactant.
12. The solid oral dosage form of claim 11, wherein the anti-tacking agent is mesoporous silica, and/or the surfactant is polysorbate 80.
- 10 13. The solid oral dosage form according to any of the preceding claims, wherein sustained release layer (3) comprises poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1 and no other sustained release polymer.
14. The solid oral dosage form of any of the preceding claims, wherein in the
15 sustained release layer (3) the plasticizer is triethyl citrate (TEC); and/or the anti-tacking agent is mesoporous silica.
15. The solid oral dosage form of any of the preceding claims, wherein in the delayed release layer (4) the plasticizer is triethyl citrate (TEC); and/or the anti-tacking agent is glycerol monostearate (GMS).
- 20 16. The solid oral dosage form of any of the preceding claims, wherein the delayed release layer (4) comprises, poly(methacrylic acid, methyl methacrylate) 1:2, and no other delayed release polymers.
17. The solid oral dosage form of any of the preceding claims, wherein the delayed release layer (4) comprises a surfactant.
- 25 18. The solid oral dosage form of claim 17, wherein the surfactant in the delayed release layer (4) is polysorbate 80.
19. The solid oral dosage form of any of the preceding claims, wherein the inert core unit (1) is a pellet with a particle size distribution such that at least 85 % of the pellets have a particle size of 700-1400 μm .

20. The solid oral dosage form of any of the preceding claims, wherein the inert core unit comprises 15-60 wt.-% microcrystalline cellulose, relative to the total weight of the solid oral dosage form.
21. The solid oral dosage form of any of the preceding claims, wherein the depot layer (2) comprises 0.1-20 wt.-% antibody or functional fragment thereof, 0.1-25 wt.-% binder, 0.5-35 wt.-% sucrose, 0.01-2 wt.-% L-histidine and optionally 0.01-3 wt.-% other buffers, 0.01-5 wt.-% anti-tacking agent, and/or 0.001-1 wt.-% polysorbate 80, relative to the total weight of the solid oral dosage form.
22. The solid oral dosage form of any of the preceding claims, wherein the sustained release layer (3) comprises 3-6 wt.-% ammonio methacrylate copolymer, 0.2-2 wt.-% plasticizer and/or 0.1-3 wt.-% anti-tacking agent, relative to the total weight of the solid oral dosage form.
23. The solid oral dosage form of any of the preceding claims, wherein the delayed release layer (4) comprises 15-35 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 1-4 wt.-% plasticizer, 0.2-2 wt.-% surfactant, and/or 1-5 wt.-% glycerol monostearate (GMS), relative to the total weight of the solid oral dosage form.
24. The solid oral dosage form of any of the preceding claims, comprising up to 5 wt.-% water in the inert core unit and/or any of the layers, relative to the total weight of the solid oral dosage form.
25. The solid oral dosage form according to any of the preceding claims, wherein the solid oral dosage form comprises, or consists of,
- a) in the inert core unit (1), 57.65-58.05 wt.-% microcrystalline cellulose;
 - b) in the depot layer (2), 0.75-0.85 wt.-% antibody or functional fragment thereof, 0.54-64 wt.-% hypromellose (HPMC), 1.34-1.50 wt.-% sucrose, 0.07-0.09 wt.-% L-histidine, 0.05-0.07 wt.-% mesoporous silica, and 0.008-0.012 wt.-% polysorbate 80;
 - c) in the sustained release layer (3), 3.9-4.1 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1, 0.75-0.85 wt.-% triethyl citrate (TEC) and 0.35-0.45 wt.-% mesoporous silica;

- d) in the delayed release layer (4), 23.25-23.55 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 2.29-2.39 wt.-% triethyl citrate (TEC), 0.89-0.99 wt.-% polysorbate 80, and 2.29-2.39 wt.-% glycerol monostearate (GMS); and
- 5 e) 4.9 wt.-% to 5.1 wt.-%, water in the inert core unit and/or any of the layers.

26. The solid oral dosage form according to any of the preceding claims, wherein the solid oral dosage form comprises, or consists of,

- a) in the inert core unit (1), 57.85 wt.-% microcrystalline cellulose;
- 10 b) in the depot layer (2), 0.80 wt.-% anti-TNF α antibody or functional fragment thereof, 0.59 wt.-% hypromellose (HPMC), 1.42 wt.-% sucrose, 0.08 wt.-% L-histidine, 0.06 wt.-% mesoporous silica, and 0.01 wt.-% polysorbate 80;
- 15 c) in the sustained release layer (3), 4.00 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1, 0.80 wt.-% triethyl citrate (TEC) and 0.40 wt.-% mesoporous silica;
- 20 d) in the delayed release layer (4), 23.40 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 2.34 wt.-% triethyl citrate (TEC), 0.94 wt.-% polysorbate 80, and 2.34 wt.-% glycerol monostearate (GMS); and
- e) 4.99 wt.-% water in the inert core unit and/or any of the layers.

27. The solid oral dosage form according to any of claims 1 to 24, wherein the solid oral dosage form comprises, or consists of,

- a) in the inert core unit (1), 27.0-27.3 wt.-% microcrystalline cellulose;
- 25 b) in the depot layer (2), 9.38-9.58 wt.-% antibody or functional fragment thereof, 6.8-7.0 wt.-% hypromellose (HPMC), 16.72-17.02 wt.-% sucrose, 0.89-0.99 wt.-% L-histidine, 0.64-0.74 wt.-% mesoporous silica, and 0.07-0.09 wt.-% polysorbate 80;
- 30 c) in the sustained release layer (3), 3.84-4.04 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1

: 2 : 0.1, 0.74-0.84 wt.-% triethyl citrate (TEC) and 0.34-0.44 wt.-% mesoporous silica;

d) in the delayed release layer (4), 22.78-23.08 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 2.24-2.34 wt.-% triethyl citrate (TEC), 0.87-0.97 wt.-% polysorbate 80, and 2.24-2.34 wt.-% glycerol monostearate (GMS); and

e) 4.23 wt.-% to 4.43 wt.-%, water in the inert core unit and/or any of the layers.

28. The solid oral dosage form according to any of claims 1 to 24, wherein the solid oral dosage form comprises, or consists of,

a) in the inert core unit (1), 27.16 wt.-% microcrystalline cellulose;

b) in the depot layer (2), 9.48 wt.-% anti-TNF α antibody or functional fragment thereof, 6.90 wt.-% hypromellose (HPMC), 16.87 wt.-% sucrose, 0.94 wt.-% L-histidine, 0.69 wt.-% mesoporous silica, and 0.08 wt.-% polysorbate 80;

c) in the sustained release layer (3), 3.94 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1, 0.79 wt.-% triethyl citrate (TEC) and 0.39 wt.-% mesoporous silica;

d) in the delayed release layer (4), 22.93 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 2.29 wt.-% triethyl citrate (TEC), 0.92 wt.-% polysorbate 80, and 2.29 wt.-% glycerol monostearate (GMS); and

e) 4.33 wt.-% water in the inert core unit and/or any of the layers.

29. The solid oral dosage form according to any of claims 1 to 24, wherein the solid oral dosage form comprises, or consists of,

a) in the inert core unit (1), 25.07-25.37 wt.-% microcrystalline cellulose;

b) in the depot layer (2), 9.16-9.36 wt.-% antibody or functional fragment thereof, 6.64-6.84 wt.-% hypromellose (HPMC), 16.33-16.63 wt.-% sucrose, 0.86-0.96 wt.-% L-histidine, 0.62-0.72 wt.-% mesoporous silica, and 0.07-0.09 wt.-% polysorbate 80;

- 5 c) in the sustained release layer (3), 3.7-3.9 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1, 0.71-0.81 wt.-% triethyl citrate (TEC) and 0.33-0.43 wt.-% mesoporous silica;
- d) in the delayed release layer (4), 24.65-24.95 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 2.43-2.53 wt.-% triethyl citrate (TEC), 0.94-1.04 wt.-% polysorbate 80, and 2.43-2.53 wt.-% glycerol monostearate (GMS); and
- 10 e) 4.85 wt.-% to 5.05 wt.-%, water in the inert core unit and/or any of the layers.

30. The solid oral dosage form according to any of claims 1 to 24, wherein the solid oral dosage form comprises, or consists of,

- a) in the inert core unit (1), 25.22 wt.-% microcrystalline cellulose;
- 15 b) in the depot layer (2), 9.26 wt.-% anti-TNF α antibody or functional fragment thereof, 6.74 wt.-% hypromellose (HPMC), 16.48 wt.-% sucrose, 0.91 wt.-% L-histidine, 0.67 wt.-% mesoporous silica, and 0.08 wt.-% polysorbate 80;
- c) in the sustained release layer (3), 3.80 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1, 0.76 wt.-% triethyl citrate (TEC) and 0.38 wt.-% mesoporous silica;
- 20 d) in the delayed release layer (4), 24.80 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 2.48 wt.-% triethyl citrate (TEC), 0.99 wt.-% polysorbate 80, and 2.48 wt.-% glycerol monostearate (GMS); and
- 25 e) 4.95 wt.-%, water in the inert core unit and/or any of the layers.

31. The solid oral dosage form according to any of claims 1 to 24, wherein the solid oral dosage form comprises, or consists of,

- a) in the inert core unit (1), 25.21-25.51 wt.-% microcrystalline cellulose;
- 30 b) in the depot layer (2), 8.91-9.11 wt.-% antibody or functional fragment thereof, 6.48-6.68 wt.-% hypromellose (HPMC), 15.72-16.02 wt.-%

- sucrose, 0.83-0.93 wt.-% L-histidine, 0.61-0.71 wt.-% mesoporous silica, and 0.07-0.09 wt.-% polysorbate 80;
- 5 c) in the sustained release layer (3), 3.58-3.78 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1, 0.69-0.79 wt.-% triethyl citrate (TEC) and 0.32-0.42 wt.-% mesoporous silica;
- 10 d) in the delayed release layer (4), 25.56-25.86 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 2.52-2.62 wt.-% triethyl citrate (TEC), 0.98-1.08 wt.-% polysorbate 80, and 2.52-2.62 wt.-% glycerol monostearate (GMS); and
- e) 4.80 wt.-% to 5.00 wt.-%, water in the inert core unit and/or any of the layers.
32. The solid oral dosage form according to any of claims 1 to 24, wherein the solid oral dosage form comprises, or consists of,
- 15 a) in the inert core unit (1), 25.36 wt.-% microcrystalline cellulose;
- b) in the depot layer (2), 9.01 wt.-% anti-TNF α antibody or functional fragment thereof, 6.58 wt.-% hypromellose (HPMC), 15.87 wt.-% sucrose, 0.88 wt.-% L-histidine, 0.66 wt.-% mesoporous silica, and 0.08 wt.-% polysorbate 80;
- 20 c) in the sustained release layer (3), 3.68 wt.-% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1, 0.74 wt.-% triethyl citrate (TEC) and 0.37 wt.-% mesoporous silica;
- 25 d) in the delayed release layer (4), 25.71 wt.-% poly(methacrylic acid, methyl methacrylate) 1:2, 2.57 wt.-% triethyl citrate (TEC), 1.03 wt.-% polysorbate 80, and 2.57 wt.-% glycerol monostearate (GMS); and
- e) 4.90 wt.-%, water in the inert core unit and/or any of the layers.
33. The solid oral dosage form of any of the preceding claims, wherein the antibody or functional fragment thereof is an antibody specific to tumor necrosis factor alpha (TNF α) or a functional fragment thereof.
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34. The solid oral dosage form of claim 33, wherein the antibody specific to TNF α or functional fragment thereof is an anti-TNF α antibody or functional fragment thereof with a TNF α binding domain comprising (i) a V_L domain comprising a CDR1 region having an amino acid sequence as shown in SEQ ID NO:1, a CDR2 region having an amino acid sequence as shown in SEQ ID NO:2, and a CDR3 region having an amino acid sequence as shown in SEQ ID NO:3, and/or (ii) a V_H domain comprising a CDR1 region having an amino acid sequence as shown in SEQ ID NO:4, a CDR2 region having an amino acid sequence as shown in SEQ ID NO:5, and a CDR3 region having the amino acid sequence as shown in SEQ ID NO:6.
35. The solid oral dosage form of claim 33, wherein the antibody specific to TNF α or functional fragment thereof is an anti-TNF α antibody or functional fragment thereof with a TNF α binding domain comprising, or consisting of, (i) a V_L domain having an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:8, and/or (ii) a V_H domain having an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:7.
36. The solid oral dosage form of claim 33, wherein the antibody specific to TNF α or functional fragment thereof is an anti-TNF α antibody comprising an Fc region having, or consisting of, an amino acid sequence in accordance with the amino acid sequence as shown in SEQ ID NO:18, in SEQ ID NO:19, in SEQ ID NO:20, in SEQ ID NO:21, or in SEQ ID NO:22, preferably in SEQ ID NO:18.
37. The solid oral dosage form of any of the preceding claims, wherein the solid oral dosage form is prepared by drug layering using spray coating.
38. Solid oral dosage form of any of the preceding claims for use in the targeted local treatment of immune checkpoint inhibitor (ICPI) induced colitis, ICPI induced enterocolitis, ICPI induced diarrhoea, or an inflammatory bowel disease (IBD).
39. An oral multiparticulate drug delivery system, comprising a plurality of solid oral dosage forms of any of the preceding claims.
40. The oral multiparticulate drug delivery system according to claim 39, wherein the oral multiparticulate drug delivery system is a capsule.

41. A method for targeted local treatment of a gastrointestinal disease, comprising administering to a patient in need thereof a pharmaceutically effective amount of the solid oral dosage form of any of claims 1 to 37 or the oral multiparticulate drug delivery system of claim 39 or 40.
- 5 42. The method of claim 41, wherein the gastrointestinal disease is immune checkpoint inhibitor (ICPI) induced colitis, ICPI induced enterocolitis, ICPI induced diarrhoea, or an inflammatory bowel disease (IBD).