

Capsule for delivery of a carrier system with a locally acting cargo to the intestines of a mammal.

Technical field

- 5 The present invention relates to a capsule comprising an effervescent couple for targeted delivery of a carrier system transporting a cargo to the small and/or large intestine of a mammal.

Background

- 10 In many circumstances, there is a need for administering an active agent locally to the small and/or large intestine. One such circumstance is inflammatory bowel disease (IBD) such as Crohn's disease and ulcerative colitis.
- Even for healthy subjects without a diagnosed gastrointestinal disorder there may be a desire to seed bacteria (probiotics) or spray nutritional supplements for the gut
- 15 microbiota over the complete inner surface of the large intestine. Under such circumstances the motivations could be to achieve a healthier gut microbiota, to provide an energy substrate to the enterocytes and/or to protect the enterocytes from oxidative stress.
- 20 Some orally administrated formulations for delivery of active agents consist of capsules with an enteric coating, which secures that the capsule remains intact until it reaches the desired part of the gastrointestinal tract. For agents with intended systemic effect, the actual uptake of the drug may very well occur over a small surface area surrounding the site where capsule dissolution occurs. For agents with intended local
- 25 effect, however, it is pivotal that as large surface area as possible is exposed to the active agent. In addition, it may, depending on the circumstances, also be desirable that the release kinetics of the capsule can be kept independent of the carrier system used for the active agent.
- 30 **Summary**
- The present disclosure concerns a capsule for delivery of a carrier system with a locally acting cargo to the intestines of a mammal. The present disclosure relates to the finding that carrier systems comprising microparticles (pellets) and effervescent reagent in an appropriate ratio allows for reproducible delayed release of a locally
- 35 acting active ingredient for local treatment, to an extended surface area.

In a first aspect, the present disclosure concerns a composition for oral administration of an active agent, the composition comprising

- a. microparticles having a size of 100 μm to 2000 μm , said microparticles comprising a polymer and an active agent,
- 5 b. an effervescent reagent,

wherein the w/w ratio of microparticles to effervescent reagent is between 7:1 and 1.5:1, and wherein said composition is encapsulated.

10 In a second aspect the present disclosure concerns a composition for oral administration of an active agent, the composition comprising

- a. microparticles having a size of 100 μm to 2000 μm , said microparticles comprising a polymer and an active agent,
- b. an effervescent reagent,

15 wherein the w/w ratio of microparticles to effervescent reagent is between 7:1 and 1.5:1, and wherein said composition is encapsulated, for use as a medicament.

20 In a third aspect the present disclosure concerns a composition for use in the treatment of an inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer, wherein the active agent comprises or consists of insulin or an analogue thereof

In a fourth aspect the present disclosure concerns a method of manufacturing the composition, the method comprising

- a. Mix polymer with active agent and optionally with lubricant
- 25 b. extruding and optionally spheronising microparticles comprising at least one polymer and having a size of 100 to 2000 μm ;
- c. mixing the microparticles with an active agent and an effervescent reagent thereby obtaining a mixture;
- d. encapsulating the mixture,
- 30 thereby obtaining a composition according to present disclosure.

In a fifth aspect the present disclosure concerns a method of manufacturing the composition, the method comprising

- a. suspending polymer, active agent and optionally lubricant in a solvent

- b. stirring until solvent has evaporated, collect and wash microparticles comprising at least one polymer and having a size of 100 to 2000 μm ;
 - c. mixing the microparticles with an active agent and an effervescent reagent thereby obtaining a mixture;
 - 5 d. encapsulating the mixture,
- thereby obtaining a composition according to present disclosure.

Description of Drawings

Figure 1. Implementation of excipients in capsules to promote disintegration (gelatine capsules). i: Microparticles, ii: Microparticles + citric acid + bicarbonate, iii: Microparticles + MgCl_2 . A. $t=0$. B. $t=3$ min static, C. $t=\text{additional } 6$ min static and 4 min orbital shaking. D. $t=0$. i: Microparticles, ii: Microparticles + citric acid + bicarbonate, iii: Microparticles + MgCl_2 . E. 1.5 min orbital shaking. F. Additional 4 min orbital shaking.

Figure 2. Implementation of excipients in capsules to promote disintegration (hydroxypropyl methylcellulose (HPMC) capsules). A. $t=0$. i: Microparticles, ii: Microparticles + citric acid + bicarbonate, iii: Microparticles + MgCl_2 . B. 2.5 min static. C. Additional 5 min orbital shaking.

Figure 3. Release study from capsules (normal, exothermic, effervescent) (gelatine capsules). Microparticles: 1% insulin, 99% microcrystalline cellulose, MCC. Capsules: Coni-Snap®, size 5. Normal: 50 mg microparticles. Effervescent (+ citric acid, bicarbonate in the figure legend): 50 mg microparticles + 40 mg citric acid + bicarbonate. Exothermic (MgCl_2 in the figure legend): 50 mg microparticles + 40 mg MgCl_2 . A. insulin release from pellets over 24 hours. B. close-up of Figure 3A, insulin release first 6 hours.

Figure 4. Implementation of excipients in capsules to promote disintegration. HPMC capsule with different amounts of effervescent powder. A. $t=0$. i: microparticles 225 mg, effervescent powder 45 mg (5:1). ii: microparticles 180 mg, effervescent powder 90 mg (2:1). iii: microparticles 135 mg, effervescent powder 135 mg (1:1). B. static: 1.5 min, orbital shaking: 3 min. C. additional orbital shaking: 2 min. D. Additional orbital shaking: 4 min.

Figure 5. Implementation of excipients in capsules to promote disintegration. HPMC capsule with different pellet sizes. A. different pellet sizes: 250-400 μm (iii), 400-710

μm (ii), 710-1000 μm (i). B. static: 2 min, orbital shaking: 1 min. C. Additional orbital shaking: 3 min. D. Additional orbital shaking: 1 min.

Figure 6. Implementation of excipients in capsules to promote disintegration. HPMC capsule with different pellet sizes. A. different pellet sizes: 400-700 μm , 700-1000 μm . B. static: 2.5 min, orbital shaking: 2 min. C. additional orbital shaking: 1 min.

Figure 7. Implementation of excipients in capsules to promote disintegration. HPMC capsules: coated S100 (4) vs. non-coated (3). pH: 7.3 (PBS). A. coated pellet (Eudragit S 100, right) and non-coated pellet (left). B. orbital shaking: 8 min. C. additional orbital shaking: 4 min.

Figure 8. Release study from microparticles. A. Insulin release from microparticles, respectively MCC:mannitol (2:1) /insulin, MCC:mannitol (5:1) /insulin and MCC /insulin (no mannitol) over 24 hours. B. Close-up of Figure 8A. C. MCC: mannitol (5:1) /insulin microparticle at respectively $t=0$ and after 1.5 hours.

Figure 9. Release profile of various APIs. A. Na-butyrate, B. caffeine, C. Insulin, D. Infliximab. MCC: microcrystalline cellulose.

Figure 10. A. Butyrate release profile with different pellet coatings, respectively non-coated, 5% RL, 8% RL and 8%RL+12%RS. B. Butyrate release from 8%RL+12%RS coated pellets either encapsulated in HPMC capsule (capsule + effervescent powder) or free pellets (loose).

Figure 11. Mitigation of effects of carrier properties: commercial Cellets (without stearate) vs Pellets (with stearate))

Figure 12. Pellet coverage area. Circle area covered after 15 minutes with and without effervescent powder. Comparison of diameter of circles around released pellets after 15 minutes.

Figure 13. Effect of amount of effervescent couple. Effervescent couple added: citric acid and Na-bicarbonate (3:1 molar ratio). Amount of effervescent couple: 0 mg, 20 mg, 45 mg, 90 mg. Amount of pellets kept constant at 225 mg.

Detailed description

Definitions

For the purposes of the present invention, the following terms may be considered to be substantially equivalent to 'sustained release': continuous release, controlled release, delayed release, depot, gradual release, long-term release, programmed release, prolonged release, proportionate release, protracted release, repository, retard, slow release, spaced release, time coat, timed release, delayed action, extended action, layered-time action, long-acting, prolonged action, repeated action, slowing acting, sustained action, sustained-action medications, and extended release. Further discussions of these terms may be found in Lesczek Krowczynski, Extended-Release Dosage Forms, 1987 (CRC Press, Inc.)

Sustained release, or controlled release, implies that the therapeutic bioactive agent is not released from the sustained release material sporadically in an unpredictable fashion and does not "burst" from the sustained release material upon contact with a biological environment (also referred to herein as first order kinetics) unless specifically intended to do so. However, the term "sustained release" as used herein does not preclude a "burst phenomenon" associated with deployment. In some example embodiments according to the present description an initial burst of at least one therapeutic bioactive agent may be desirable followed by a more gradual release thereafter. The release rate may be steady state (commonly referred to as "timed release" or zero order kinetics), that is the at least one therapeutic bioactive agent is released in even amounts over a predetermined time (with or without an initial burst phase) or may be a gradient release. A gradient release implies that the concentration of therapeutic bioactive agent released from the sustained release material changes over time.

As used herein "enteric coating", is a material, such as a polymer material or materials which encase the therapeutically active agent either as a dosage form or as particles. Typically, a substantial amount or all of the enteric coating material is dissolved before the therapeutically active agent is released from the dosage form, so as to achieve delayed dissolution of the therapeutically active agent in the intestine. Enteric coatings are discussed, for example, Loyd, V. Allen, Remington: The Science and Practice of Pharmacy, Twenty-first Ed., (Pharmaceutical Press, 2005; and P.J. Tarcha, Polymers

for Controlled Drug Delivery, Chapter 3, CRC Press, 1991. Methods for applying enteric coatings to pharmaceutical compositions are well known in the art, and include for example, U.S. Patent Publication No. 2006/0045822.

5 The term "effervescent couple" as well as the terms "effervescent reagents" and "effervescent powder" as used herein refer to a pair of pharmaceutically acceptable excipients, one of which is a basic ingredient and the other is an acidic ingredient. The basic ingredient liberates carbon dioxide when it comes in contact with the acidic ingredient and water.

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The terms "treatment" and "treating" as used herein refer to the management and care of a patient for the purpose of combating a condition, disease or disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient is suffering or is suspected of suffering, such as administration of the active compound for the purpose of: alleviating or relieving symptoms or complications;
15 delaying the progression of the condition, disease or disorder; curing or eliminating the condition, disease or disorder; and/or preventing the condition, disease or disorder, wherein "preventing" or "prevention" is to be understood to refer to the management and care of a patient for the purpose of hindering, reducing or delaying the
20 development of the condition, disease or disorder, and includes the administration of the active compounds to prevent or reduce the risk of the onset of symptoms or complications. The treatment may thus be a prophylactic treatment. The patient to be treated is preferably a mammalian, in particular a human being. The patients to be treated can be of various ages.

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An "Inflammatory bowel disease" or "IBD" is a group of inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn's disease and ulcerative colitis (UC). Accounting for far fewer cases are other forms of IBD, such as collagenous colitis, Lymphocytic colitis, Ischaemic colitis, Diversion colitis, Behçet's disease,
30 Indeterminate colitis, left sided colitis, and noninfective colitis.

For treatment or prevention of inflammatory bowel disease (IBD) such as Crohn's disease and ulcerative colitis, the active agent may be either locally acting insulin or an analogue thereof, or a locally acting monoclonal antibody directed against tumour
35 necrosis factor alpha.

“Inflammation-induced colorectal tumour and/or cancer” is a form of colorectal tumour and/or cancer that develops in subjects suffering from or suspected of suffering from IBDs. Inflammation-induced colorectal tumour and/or cancer appears to have a different aetiology, carcinogenesis pathway and clinical course than its sporadic counterpart. Therefore, different treatment approaches may be necessary.

A “unit” or “unit of insulin” or “U” or “IU” as used herein is defined as the biological equivalent of 34.7 µg pure crystalline insulin, which also corresponds to 6 µmol (provided that the molecular mass of insulin is considered to be 5800 Da. This corresponds to the old United States Pharmacopeia insulin unit, where one unit (U) of insulin was set equal to the amount required to reduce the concentration of blood glucose in a fasting rabbit to 45 mg/dl (2.5 mmol/L).

“Local administration” is used in the present disclosure to indicate that the compositions are delivered to a certain “localized” area of the body of a subject in need thereof and act locally at the site of administration. In particular, the present disclosure is directed to delivery to the intestines of a mammal, such as the small intestines, the large intestine or the colon. In the present disclosure, the term “local administration” refers to administration which is not systemic but instead limited to the site where the active agent is released. It refers to administration which has low or no systemic effects. One example of this could be the administration of insulin or an analogue thereof to the intestine, for example to the large intestine. Administration of the composition of the present disclosure, comprising insulin as active ingredient, will ensure that the insulin acts locally in the intestine, and does not affect the systemic blood glucose levels.

The “small intestine” (also referred to as the small bowel) is the specialized tubular structure between the stomach and the large intestine that absorbs the nutrition from food. It is approximately 5.5 m in length and is divided into three parts: the duodenum, jejunum and ileum.

The “large intestine” (also referred to as large bowel) is the last part of the gastrointestinal tract of the digestive system in vertebrates. It comprises cecum, colon, rectum, and anal canal. The large intestine is about 1.5 metres long, which is about one-fifth of the whole length of the gastrointestinal tract. The large intestine is the

portion of the digestive system most responsible for absorption of water from the indigestible residue of food.

5 As used herein the term "prebiotic" or "prebiotic nutrient" refers to a non-digestible food ingredient that beneficially affects a host when ingested by selectively stimulating the growth and/or the activity of one or a limited number of bacteria in the gastrointestinal tract. The prebiotic can be selected from the group consisting of fructo-oligosaccharide, gluco-oligosaccharide, galacto-oligosaccharide, polydextrose, isomalto-oligosaccharide, xylo-oligosaccharide, polydextrose and lactulose.

10 As used herein the term "probiotics" refers to micro-organisms, or processed compositions of micro-organisms which beneficially affect a host. As used herein "probiotic" also includes bacteria, bacterial homogenates, bacterial proteins, bacterial extracts, bacterial supernatants, and mixtures thereof, that perform beneficial functions
15 for the host when given at a therapeutic dose. Therefore, yeasts, moulds and bacteria may be included. Non-limiting examples of probiotics useful herein, comprise strains of Bifidiobacterium, Lactobacillus, and Enterococcus.

20 As used herein the term "subject" refers to an individual the species of mammals disclosed herein. A "patient" is a subject, which is suffering from, suspected of suffering from or who has been diagnosed with a particular disorder.

Composition

25 The composition of the current disclosure is for delivery of a carrier system with a locally acting cargo to the intestines of a mammal.

30 In one embodiment the carrier system of the current disclosure comprises active agent embedded into a microparticle. In one embodiment the microparticle is a pellet. In one embodiment the microparticle is loaded into a carrier system. In one embodiment the microparticle is loaded into a carrier system together with an effervescent reagent. In one embodiment the carrier system is encapsulated. In one embodiment the carrier system is comprised in a capsule.

In one embodiment, the composition of the present disclosure comprises

- a. microparticles having a size of 100 μm to 2000 μm , said microparticles comprising a polymer and an active agent,
 - b. an effervescent reagent,
- wherein the w/w ratio of microparticles to effervescent reagent is between 7:1 and 1.5:1, and wherein said composition is encapsulated.

In one embodiment, the composition of the present disclosure comprises

- a. microparticles having a size of 100 μm to 2000 μm , said microparticles comprising a polymer and an active agent,
 - b. an effervescent reagent,
- wherein the w/w ratio of microparticles to effervescent reagent is between 7:1 and 3:1, and wherein said composition is encapsulated.

Effervescent reagent

Effervescent gas production has been suggested as a mean for facilitating capsule and tablet disintegration. However, until now the hydration and subsequent disintegration of a capsule with a wall consisting of polymer networks of proteins (e.g. gelatine) or polysaccharides (e.g. cellulose) is a protracted process even in the presence of effervescent gas.

The inventors of the present disclosure have demonstrated that effervescent gas production in combination with microparticles of sufficient size is an effective mean for facilitating disintegration of an encapsulated carrier system, thereby resulting in effective release of active agent as well as increased coverage.

The inventors of the present disclosure have demonstrated that incorporation of an effervescent reagent and microparticles into capsules is an effective strategy both for accelerating capsule breakage and for increasing the microparticle coverage area (Example 2 and Example 11). The inventors have moreover demonstrated that the present disclosure is effective for delivery of both small molecule drugs, antibodies, peptides and tracers (Example 8).

The inventors of the present disclosure have moreover demonstrated that the ratio of effervescent reagent to microparticles (pellets) (Example 4) as well as the size of the microparticles (Example 5) is of importance for the capsule breakage time.

The inventors have surprisingly found that a w/w ratio of 7:1 to 1.5:1 between the amounts of microparticles having a size of 100 μm to 2000 μm and effervescent reagent results in faster capsule breakage and faster release of microparticles than other ratios comprising a higher proportion of effervescent reagent, such as

5 1:1 microparticles to effervescent reagent.

The inventors have demonstrated that larger sized microparticles (710-1000 μm) accelerate capsule breakage more efficiently than microparticles of smaller size (250-400 μm and 400-710 μm). This opens the possibility of manufacturing different

10 capsules filled with pellets having either large or small pellet diameters respectively. When two such capsules each containing either pellets with a large diameter or pellets with a small diameter is ingested this will result in capsule breakage at different anatomical positions in the intestine in a predictable manner. Thus, the capsule filled with pellets of a large diameter would break first whereas the capsule filled with pellets

15 with a smaller diameter would break later. In this way a larger surface area would be covered in a predictable manner.

The inventors of the present disclosure have demonstrated that the presence of effervescent reagent not only accelerates capsule breakage, but also improves insulin release % (Example 3).

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Ideally, the effervescent gas production is initiated when the carrier system reaches its intended destination in the intestines. One way to achieve this could be to employ an enteric coating in combination with an encapsulation layer. Upon dissolution of the

25 enteric coating, water will be able to permeate through the material of the encapsulation layer, to dissolve the effervescent reagent, and initiate release of effervescent gas. Subsequently the effervescent gas will facilitate rapid disintegration of the encapsulated carrier system and subsequently provide for dispersion of microparticles over the mucosa.

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The inventors of the present disclosure have demonstrated that enteric coating (Eudragit® S) extends the time until capsule breakage at pH 7.3.

In one embodiment effervescent gas is produced by an effervescent reagent. In one

35 embodiment the effervescent reagent is an effervescent couple. In one embodiment

the effervescent couple is a pair of pharmaceutically acceptable excipients, wherein one is a basic ingredient and the other is an acidic ingredient. In one embodiment the basic ingredient liberates carbon dioxide when it comes in contact with the acidic ingredient and water. In one embodiment the effervescent reagent produces carbon
5 dioxide when in contact with water.

In one embodiment the effervescent reagent comes in contact with water upon rupture of the encapsulation layer. In one embodiment the effervescent reagent is activated upon rupture of the encapsulation layer. In one embodiment the effervescent gas is
10 generated upon rupture of the encapsulation material. In one embodiment the effervescent gas functions as a propulsion agent. In one embodiment the effervescent gas facilitates rapid disintegration of an encapsulated carrier system. In one embodiment generated effervescent gas provides for effective release of microparticles comprising active agent. In one embodiment generated effervescent gas provides for
15 increased coverage of the surface of the targeted intestine. In one embodiment an effervescent reagent facilitates efficient coverage of the surface of the intestine. In one embodiment the microparticles will gradually release the embedded active agent to the intestinal mucosa.

20 In one embodiment the effervescent reagent is an effervescent couple comprising or consisting of

- a. a base, such as a base selected from the group consisting of sodium bicarbonate, potassium bicarbonate and sodium carbonate, and
- 25 b. an acid, such as an acid selected from the group consisting of citric acid, maleic acid and tartaric acid.

In one embodiment the effervescent reagent comprises or consists of an acid and a base at a molar ratio of 1 mol acid to between 1 and 6 moles of base, such as a molar
30 ratio of 1 mol acid to 1 moles of base, such as a molar ratio of 1 mol acid to 2 moles of base, such as a molar ratio of 1 mol acid to 3 moles of base, such as a molar ratio of 1 mol acid to 4 moles of base, such as a molar ratio of 1 mol acid to 5 moles of base, such as a molar ratio of 1 mol acid to 6 moles of base.

In one embodiment the effervescent reagent comprises or consists of citric acid and bicarbonate at a molar ratio of 1 mol citric acid to between 1 and 6 moles sodium bicarbonate, such as a molar ratio of 1 mol citric acid to 1 moles sodium bicarbonate, such as a molar ratio of 1 mol citric acid to 2 moles sodium bicarbonate, such as a
5 molar ratio of 1 mol citric acid to 3 moles sodium bicarbonate, such as a molar ratio of 1 mol citric acid to 4 moles sodium bicarbonate, such as a molar ratio of 1 mol citric acid to 5 moles sodium bicarbonate, such as a molar ratio of 1 mol citric acid to 6 moles sodium bicarbonate.

10 In one embodiment the effervescent reagent comprises or consists of citric acid and bicarbonate at a molar ratio of 1 mol citric acid to 3 moles sodium bicarbonate.
A molar ratio of 1 mol citric acid to 3 moles sodium bicarbonate corresponds to a w/w ratio of citric acid to sodium bicarbonate of 1:1.3.

15 In one embodiment the effervescent reagent comprises or consists of citric acid and bicarbonate at a w/w ratio of 1 citric acid to 1.3 sodium bicarbonate.

In one embodiment the effervescent reagent comprises or consists of a base and an acid at a molar ratio of 1 mol of base to between 1 and 6 moles of acid, such as a
20 molar ratio of 1 mol of base to 1 mol of acid, such as a molar ratio of 1 mol of base to 2 moles of acid, such as a molar ratio of 1 mol of base to 3 moles of acid, such as a molar ratio of 1 mol of base to 4 moles of acid, such as a molar ratio of 1 mol of base to 5 moles of acid, such as a molar ratio of 1 mol of base to 6 moles of acid.

25 In one embodiment the effervescent reagent comprises or consists of sodium bicarbonate and citric acid at a molar ratio of 1 mol of sodium bicarbonate to between 1 and 4 moles of citric acid, such as a molar ratio of 1 mol sodium bicarbonate to 1 mol citric acid, such as a molar ratio of 1 mol sodium bicarbonate to 2 moles citric acid, such as a molar ratio of 1 mol sodium bicarbonate to 3 moles citric acid, such as a
30 molar ratio of 1 mol sodium bicarbonate to 4 moles citric acid.

A molar ratio of 3 moles sodium bicarbonate to 1 mol citric acid corresponds to a w/w ratio of sodium bicarbonate to citric acid of 1:0.77.

In one embodiment the effervescent reagent comprises or consists of bicarbonate and citric acid at a w/w ratio of 1 sodium bicarbonate to 0.77 citric acid.

5 In one embodiment the ratio of microparticles to effervescent reagent is between 6:1 and 4:1, such as about 5:1.

In one embodiment the ratio of microparticles to effervescent reagent is between 7:1 and 1.5:1, such as between 6:1 and 4:1, such as 1.6:1, such as 2.5:1, such as 3:1, such as 5:1.

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In one embodiment the ratio of microparticles to effervescent reagent is between 7:1 and 3:1.

Microparticles

15 The term 'microparticles' and the term 'pellet' as used herein are used interchangeably.

In one embodiment the microparticles of the current disclosure comprise a polymer and an active ingredient. In one embodiment the microparticles further comprise one or more diluents. In one embodiment the microparticles further comprise one or more
20 additives. In one embodiment the microparticles further comprise one or more coatings.

The release kinetics and in particular the dissolution rate of active ingredient from microparticles is affected by the composition of the microparticles.

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Polymer

In one embodiment the microparticles of the current disclosure comprise a polymer. In one embodiment the polymer is a sustained release polymer. In one embodiment the microparticles comprise polymeric material. In one embodiment the polymeric material is a sustained release polymer.

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In one embodiment the polymer is selected from the group consisting of microcrystalline cellulose (MCC), an acrylic polymer such as Eudragit RL (CAS no.: 51822-44-7) and Eudragit RS (CAS no.: 33434-24-1), polyethylene oxide, starch, a starch derivative, alginate, pullulan, scleroglucan, povidone, a povidone derivative,
35 natural gums, gelatine, chitosan, polyvinyl alcohol, and combinations thereof.

EUDRAGIT® RL and EUDRAGIT® RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups (Eudragit RL: 10% quaternary ammonium groups, Eudragit RS: 5% quaternary ammonium groups, Santos et al, 2021). The ammonium groups are present as salts and give rise to permeability of the films. EUDRAGIT® RL and EUDRAGIT® RS are freely permeable (RL) and slightly permeable (RS), respectively, independent of pH. The polymers swell in water and digestive juices, in a pH-independent manner. In the swollen state, they are permeable to water and to dissolved active compounds.

Eudragit RL is a low permeability polymer comprising Poly(ethyl acrylate, methyl methacrylate, and a low amount (10%) of methacrylic acid ester with quaternary ammonium groups). Eudragit RL is typically used for sustained-release formulations due to its ability to control the drug release rate by modulating the permeability. The drug release can furthermore be tailored by adjusting the ratio of Eudragit RL to other polymers or excipients in the formulation. Eudragit RL is insoluble in the gastrointestinal tract but swells and becomes permeable in an aqueous environment.

Eudragit® RS is a standard permeability polymer, with a composition similar to Eudragit® RL, that is a polymer comprising Poly(ethyl acrylate, methyl methacrylate, and a low amount (5%) of methacrylic acid ester with quaternary ammonium groups). Eudragit RL is typically used for sustained-release formulations. Due to its lesser content of quaternary ammonium groups compared to Eudragit RL, Eudragit RS has a lower permeability. This means that drug release from Eudragit RS might be slower than from Eudragit RL. Eudragit RS is insoluble in the gastrointestinal tract but swells and becomes permeable in an aqueous environment.

The CAS number of monomeric Eudragit RS (ethyl prop-2-enoate;methyl 2-methylprop-2-enoate;trimethyl-[2-(2-methylprop-2-enoyloxy)ethyl]azanium;chloride) is 33434-24-1. The CAS number of monomeric Eudragit RL (*N,N*-dimethylmethanamine;2-methylprop-2-enoic acid) is 51822-44-7.

Starch is a polymeric carbohydrate consisting of numerous glucose units joined by glycosidic bonds. Starch includes amylose, amylopectin and maltodextrin, including digestible maltodextrin and resistant maltodextrin. Starch derivatives include modified

starch, such as dextrin, acid-treated starch, base-treated starch, starch acetate, bleached starch.

5 Alginate is a naturally occurring, linear co-polymer composed of mannuronate and guluronate. Alginates includes alginate, alginate derivatives such as amphiphilic alginate derivatives which have been derivatized with hydrophilic moieties (e.g. alkyl chains), and alginate compositions, including alginate in combination with chitosan (Wang et al, 2016).

10 Povidone (polyvinylpyrrolidone, PVP) is a synthetic polymer used in the pharmaceutical industry as vehicle for dispersing and suspending drugs. It also acts as a disintegrant and tablet binder. Povidone has the molecular formula of $(C_6H_9NO)_n$. Povidone formulations are widely used in the pharmaceutical industry due to their ability to dissolve in both water and oil solvents. Povidone derivatives include crospovidones (PVPP) and copovidones.

15 In one embodiment the concentration of polymer in the microparticles is 94 to 98.9% (w/w), such as 97-98% (w/w). In one embodiment the concentration of polymer in the microparticles is 75 to 99% (w/w), such as 80 to 99% (w/w), such as 82 to 99% (w/w), such as 84 to 99% (w/w), such as 86 to 99% (w/w), such as 88 to 99% (w/w), such as 90 to 99% (w/w), such as 91 to 99% (w/w), such as 92 to 99% (w/w), such as 93 to 99% (w/w), such as 94 to 99% (w/w), such as 95 to 99% (w/w), such as 96 to 99% (w/w), such as 97 to 99% (w/w), such as 98 to 99% (w/w).

20 In one embodiment the concentration of polymer in the microparticles is 75 to 80% (w/w), such as 80 to 85% (w/w), such as 85 to 90% (w/w), such as 90 to 95% (w/w), such as 95 to 99% (w/w).

In one embodiment the concentration of polymer in the microparticles is 97.5%.

30 In one embodiment the microparticles comprise one or more polymers.

In one embodiment the one or more polymers are selected from the group consisting or comprising of microcrystalline cellulose (MCC), an acrylic polymer such as Eudragit RL (CAS no.: 51822-44-7) and Eudragit RS (CAS no.: 33434-24-1), polyethylene oxide,

starch, a starch derivative, alginates, povidone derivatives, natural gums, gelatine, chitosan, polyvinyl alcohol, and combinations thereof.

5 In one embodiment the concentration of microcrystalline cellulose (MCC) in the microparticles is 94 to 98.9% (w/w), such as 97-98% (w/w). In one embodiment the concentration of polymer in the microparticles is 75 to 99% (w/w), such as 80 to 99% (w/w), such as 82 to 99% (w/w), such as 84 to 99% (w/w), such as 86 to 99% (w/w), such as 88 to 99% (w/w), such as 90 to 99% (w/w), such as 91 to 99% (w/w), such as 92 to 99% (w/w), such as 93 to 99% (w/w), such as 94 to 99% (w/w), such as 95 to 10 99% (w/w), such as 96 to 99% (w/w), such as 97 to 99% (w/w), such as 98 to 99% (w/w).

15 In one embodiment the concentration of microcrystalline cellulose (MCC) in the microparticles is 97.5%.

In one embodiment the microparticles comprise two polymers, such as two polymers A and B, wherein the two polymers A and B are at a ratio of at least 1:1, such as 2:1, such as 3:1, such as 4:1, such as 5:1, such as 6:1, such as 7:1, such as 8:1.

20 In one embodiment the microparticles comprise two polymers, such as two polymers A and B, wherein the two polymers A and B are at a ratio of at least 1:1, such as 1:2, such as 1:3, such as 1:4, such as 1:5, such as 1:6, such as 1:7, such as 1:10.

25 In one embodiment the microparticles comprise microcrystalline cellulose and Eudragit® RL.

In one embodiment the microparticles comprise microcrystalline cellulose and Eudragit® RL at a ratio of at least 3:1, such as 4:1, such as 5:1, such as 6:1, such as 7:1, such as 8:1.

30 In one embodiment the microparticles comprise microcrystalline cellulose and Eudragit® RL at a ratio of 4:1.

35 In one embodiment the microparticles comprise 78.16% microcrystalline cellulose, 19.54% Eudragit RL, 1.3% insulin, and 1.0% magnesium stearate.

Diluent

The release kinetics and in particular the dissolution rate of active ingredient from microparticles is affected by the composition of the microparticles.

- 5 One strategy for controlling the dissolution rate could be to exchange part of insoluble microcrystalline cellulose with a soluble diluent.

10 The inventor of the present disclosure has demonstrated (Example 7) that a higher ratio of insoluble polymer to soluble diluent results in higher release of active ingredient. The inventor of the present disclosure has moreover demonstrated (Example 7) that a higher ratio of insoluble polymer to soluble diluent results in faster release of active agent.

15 In one embodiment the microparticles comprise a diluent. In one embodiment the diluent is selected from the group consisting of lactose, dicalcium phosphate, starch and a sugar alcohol such as mannitol, xylitol and sorbitol, and combinations thereof.

In one embodiment the diluent is mannitol.

20 In Example 7 it is demonstrated, that microparticles prepared from MCC release 80% of insulin within 24 hours. It is moreover demonstrated that the release of insulin is faster, if the microparticles further comprise a soluble diluent such as mannitol. It is demonstrated that a ratio of MCC to mannitol on 2:1 leads to a release of 80% of insulin within 1 hour, and 90% within 6 hours, and that microparticles comprising a ratio
25 of MCC to mannitol on 5:1 release of 80% of insulin within 4 hours and 90% within 6 hours. Finally in Example 7 it is demonstrated that microparticles comprising mannitol as diluent, show full release of insulin within 24 hours.

30 In one embodiment the microparticles comprise microcrystalline cellulose and mannitol at a ratio of 2:1 (w/w) to 6:1 (w/w), such as at a ratio of 5:1 (w/w).

The present disclosure suggests that a mean for controlling the release rate of active ingredient, as well as controlling the total release of active ingredient, may be the ratio of polymer to diluent. The present disclosure suggests that higher ratio of diluent may

lead to faster release of active ingredient. The present disclosure moreover suggests, that higher ratio of diluent may lead to higher release of active ingredient.

Additives

5 In one embodiment the microparticles comprise one or more additives.

Additives can be lubricants, binders, disintegrants, plasticizers, glidants, surfactants, colorants, flavoring agents, antioxidants and preservatives.

10 In one embodiment the microparticles comprise one or more additives, such as lubricants, binders, disintegrants, plasticizers, glidants, surfactants, colorants, flavoring agents, antioxidants and preservatives.

15 In one embodiment the microparticles are manufactured using an extrusion method. If the microparticles are produced in an extrusion method, it may be advantageous to include an additive such as a lubricant.

In one embodiment the microparticles further comprise a lubricant.

20 In one embodiment the lubricant is selected from the group consisting of magnesium stearate, stearic acid and talc, and/or combinations thereof.

In one embodiment the concentration of additives in the microparticles is 0.1 to 2% (w/w), such as about 1% (w/w).

25

Preparation of microparticles

The microparticles of the current disclosure can be prepared by any standard method known in the art. Examples of methods for preparation of microparticles include extrusion methods and solvent evaporation methods.

30

In one embodiment the microparticles are produced by an extrusion method. In one embodiment, the extrusion methods comprise the steps of mixing of ingredients, extrusion, spheronization, and drying. In one embodiment the extrusion method is carried out using a Celeva Multi lab extruder. In one embodiment the extrusion method

is carried out using a Celeva Multi lab extruder equipped with a mixer/granulator. In one embodiment the Celeva Multi lab extruder is further equipped with a Spheronizer. In one embodiment the microparticles are manufactured using an extrusion method as described in Example 1. The review by Muley et al., 2016 is referred to for further
5 information about extrusion methods.

In one embodiment the microparticles comprise polymer, active agent and lubricant. In one embodiment the polymer is a sustained release polymer. In one embodiment the sustained release polymer is one or more polymers such as Eudragit® RL, Eudragit®
10 RS, microcrystalline cellulose and/or polyethylene oxide. In one embodiment the lubricant is magnesium stearate, stearic acid and talc, or combinations thereof.

In one embodiment the microparticles are produced by a solvent evaporation method. In one embodiment the solvent evaporation method is carried out using a solvent
15 evaporation setup. In one embodiment the solvent evaporation method comprises the steps of suspending active agent and polymer in a suitable solvent, and stirring until the solvent has evaporated. In one embodiment the polymer is a sustained release polymer as defined elsewhere in the application. In one embodiment the solvent is an organic solvent. In one embodiment the solvent is a low-boiling organic solvent. In one
20 embodiment the solvent is acetone.

The method of choice for preparing the microparticles may depend on the desired size or shape of the microparticles. Typically microparticles prepared by solvent evaporation are smaller than microparticles prepared by extrusion methods. In one embodiment the
25 microparticles are spherical. In one embodiment the microparticles are pellets.

In one embodiment the microparticles have a size of 100 µm to 2000 µm, , such as of 150 µm to 2000 µm, such as of 200 µm to 2000 µm, such as of 250 µm to 2000 µm, such as of 300 µm to 2000 µm, such as of 350 µm to 2000 µm, such as of 400 µm to
30 2000 µm, such as of 245 µm to 2000 µm, such as of 500 µm to 2000 µm, 550 µm to 2000 µm, such as a size of 600 µm to 2000 µm, such as a size of 650 µm to 2000 µm, such as a size of 700 µm to 2000 µm, such as a size of 700 µm to 2000 µm, such as a size of 700 µm to 1900 µm, such as a size of 700 µm to 1000 µm, such as a size of 700 µm to 1100 µm, such as a size of 800 µm to 2000 µm, such as a size of 900 µm to
35 2000 µm, such as a size of 1000 µm to 2000 µm, such as a size of 1200 µm to 2000

μm, such as a size of 1300 μm to 2000 μm, such as a size of 1400 μm to 2000 μm, such as a size of 1500 μm to 2000 μm.

5 In one embodiment the microparticles have a size of 150 μm to 2000 μm, such as 150 μm to 1500 μm, such as 150 μm to 1000 μm, such as 150 μm to 800 μm, such as 150 μm to 700 μm, such as 150 μm to 600 μm, such as 200 μm to 600 μm.

10 In one embodiment the microparticles have a size of 250 μm to 1000 μm, such as 250 μm to 400 μm, such as 400 μm to 700 μm, such as 700 μm to 1000 μm.

Typically, microparticles prepared by solvent evaporation are smaller than microparticles prepared by extrusion methods. Typically microparticles prepared by extrusion methods are larger than microparticles prepared by solvent evaporation methods.

15 In one embodiment the microparticles prepared by solvent evaporation methods have a size of 250 to 400 μm.

20 In one embodiment the microparticles prepared by extrusion methods have a size of 400 to 1000 μm, such as 400 to 710 μm, such as 710 to 1000 μm.

Microparticles disclosed herein of a size between 150 μm to 2000 μm may not be able to penetrate the intestinal mucosa, thus ensure local treatment and local action of the active agent.

25 As demonstrated in Example 5, the capsule breakage time and the release speed of the microparticles is related to the size of the microparticles. Thus the skilled person will choose a size or a combination of sizes depending on the desired release speed.

Coating

30 The composition of the current disclosure is for delivery of a carrier system with a locally acting cargo to the intestines of a mammal.

In one embodiment, the composition of the present disclosure further comprises at least one coating layer.

35

Coating can be performed by spraying the coat solution onto the pellets using any coating method known in the art. An example of a suitable method is the Mini-Glatt fluid bed coater system, or the FC-LAB Micro FLO-COATER® system.

- 5 Examples of suitable coatings include Poly(ethyl acrylate, methyl methacrylate, 2-trimethylammonioethyl methacrylate chloride, 10% quaternary ammonium groups) (Eudragit RL) and Poly(ethyl acrylate, methyl methacrylate, 2-trimethylammonioethyl methacrylate chloride, 5% quaternary ammonium groups) (Eudragit RS).
- 10 In one embodiment the at least one coating layer coats the microparticles. Adding a coat to the microparticles makes it possible to delay the release from the microparticles even further thereby extending the delayed release already provided by the capsule coat. Examples of coated microparticles are given in the Examples of WO 2020/115277 A1.
- 15 In one embodiment the at least one coating layer coating the microparticles is an enteric coating.

In one embodiment the microparticles of the current disclosure are coated in at least one coating layer coating.

20

In one embodiment the microparticles of the current disclosure are coated with at least one enteric coating.

- 25 In one embodiment the microparticles are coated with Eudragit RL. In one embodiment the microparticles are coated with Eudragit RS. In one embodiment the microparticles are coated with a mixture of Eudragit RL and Eudragit RS. In one embodiment the microparticles are coated with both Eudragit RL and Eudragit RS. In one embodiment the microparticles are coated first with a layer of Eudragit RL and then with a layer of Eudragit RS.

30

The coatings introduce a weight gain to the pellets.

- In one embodiment the coating introduces a theoretical weight gain of at least 2%, such as 4%, such as 6%, such as 8%, such as 10%, such as 12%, such as 14%, such as 20%, such as 25%. In one embodiment coating with Eudragit RL introduces a
- 35

theoretical weight gain of at least 2%, such as 4 %, such as 6%, such as 8%, such as 10%, such as 12%, such as 14%, such as 20%. In one embodiment coating with Eudragit RS introduces a theoretical weight gain of at least 2%, such as 4%, such as 6%, such as 8%, such as 10%, such as 12%, such as 14%, such as 20%,

5

In one embodiment the release of active ingredient is delayed.

In one embodiment the release of active ingredient is delayed of 5 min, such as 15 min, such as 30 min, such as 1 hour. In one embodiment the release of active ingredient is delayed of 15 min, such as 30 min, such as 1 hour, such as 2 hours, such as 3 hours, such as 4 hours, such as 5 hours.

10

In one embodiment the microparticles of the current disclosure are coated with at least one enteric coating, to delay the release of active ingredient. In one embodiment the at least one coating layer which covers the microparticles is a pH sensitive coating, such as a coating that dissolves at pH 5.5 or higher, such as a coating that dissolves at pH 5.5 to 8, such as a coating that dissolves at pH 6 or higher, such as a coating that dissolves at pH 7 or higher.

15

In one embodiment the at least one coating layer covering the microparticles is Eudragit® S 100 (CAS no: 25086-15-1).

20

The coating material can be the same as described herein below in the section "Coating".

25

Active ingredient

The composition of the present invention allows for administration of various active ingredients, including biologics, small molecule drugs and tracers.

In one embodiment the active agent is selected from the group consisting of biologics, therapeutic peptides, small molecule drugs, bacteria, probiotics, prebiotics, bacteriophages and natural products.

30

In one embodiment the natural products are bilberry extracts. In one embodiment the natural products is butyric acid, or butyrates, such as salts of butyric acid and/or esters of butyric acid, such as sodium butyrate.

5 In one embodiment the active agent is a biologic, such as a biologic selected from the group consisting biologics such as a monoclonal antibody, a protein or a peptide, or derivatives thereof.

10 In one embodiment the active agent is a therapeutic antibody, such as Adalimumab, Golimumab or Infliximab.

In one embodiment the active agent is a therapeutic peptide.

15 In one embodiment the active agent is a biologic therapeutic peptide, such as a biologic therapeutic peptide selected from the group consisting of a protease, a peptidase, a disaccharidase, an oligo-saccharidase, a lipase, a growth factor, an extracellular matrix protein such as a laminin, a collagen, a glycosaminoglycan, a proteoglycan, a mucin, and analogues thereof.

20 In one embodiment the active agent is a small molecule, such as caffeine.

In one embodiment the active agent is a tracer molecule, such as caffeine.

25 In one embodiment the active agent is a small molecule drug, such as Na-butyrate.

In one embodiment the concentration of active agent in the composition is at the most 4% (w/w), such as at the most 3.5% (w/w), such as at the most 3% (w/w), such as at the most 2.5% (w/w), such as at the most 2% (w/w), such as at the most 1.5% (w/w), such as at the most 1.3% (w/w).

30 In one embodiment the active agent is insulin or an analogue thereof. In one embodiment the insulin analogue is selected from the group consisting of insulin aspart, insulin lispro, insulin glulisine, insulin glargine, insulin detemir, and insulin degludec. In one embodiment the insulin analogue is an insulin derivative.

35

Encapsulation

In one embodiment, the composition of the present disclosure is encapsulated in an encapsulating layer.

In one embodiment the encapsulating layer comprises an encapsulating polymer
5 selected from the group consisting of gelatine, alginate, alginate derivatives, cellulose, methacrylate acid copolymers such as Eudragit® L100 (CAS no.: 25086-15-1), Eudragit® S100 (CAS no.: 25086-15-1), Eudragit® L-30D (CAS no.: 100218-76-6 or 25212-88-8), Eudragit® FS 30D (CAS no.: 26936-24-3), and Eudragit® L100-55 (CAS
10 no.: 25212-88-8), cellulose acetate phthalate, cellulose acetate trimellitate, polyvinyl acetate phthalate, hydroxyethylcellulose phthalate, hydroxypropyl methylcellulose phthalate, or shellac, or an aqueous dispersion thereof. In one embodiment the encapsulation layer is an edible biopolymer, such as starch, carrageenan, pullulan, scleroglucan, cellulose or chitin.

15 An example of an encapsulating layer is alginate, which has been used in combination with Chitosan for microencapsulation of icariin for colonic targeting and treatment of colitis in a rat model (Wang et al 2016).

In one embodiment, the encapsulating layer is alginate.
20

Coating

The composition of the current disclosure is for delivery of a carrier system with a locally acting cargo to the intestines of a mammal.

25 To ensure delivery to the intestines of a mammal, the carrier system can be coated.

Coating materials for targeted release of a solid dosage form, in particular for targeted release in the ileum or the large intestine, upon oral administration are known in the art. They can be subdivided into coating materials that disintegrate above a specific pH,
30 coating materials that disintegrate after a specific residence time in the gastrointestinal tract and coating materials that disintegrate due to enzymatic triggers specific to the microflora of a specific region of the intestines. Coating materials of these three different categories for targeting to the large intestine have been reviewed for example in Bansal et al. (Polim. Med. 2014, 44, 2, 109-1 18). These uses of such coating

materials have also been described for example in WO 2007/122374 A2, WO 01/76562 A1, WO 03/068196 A1, WO 2008/135090 A1 and GB 2367002 A.

5 In one embodiment the carrier system is coated with an enteric coating. The enteric coating can be chosen to only dissolve only under specific conditions e.g., with respect to pH or the presence of a large number of bacteria. Thus, when the specified conditions are met, the enteric coat dissolves, the carrier system breaks and the microparticles comprising active agent are released.

10 Dissolution of the coat and capsule breakage depends on the properties of the enteric coating. The dissolution process itself progresses in a time dependent manner which may be relatively long (hours) e.g., for coats which are designed to dissolve in the large intestine. To achieve a higher precision in the anatomical targeting of pharmaceuticals aiming at topical treatment in the intestines it would be desirable with a more abrupt
15 capsule breakage occurring just prior to or at the entry to the targeted intestinal segment.

For targeted delivery to the intestines of a mammal through the oral route, the delivery system must pass the stomach. The pH of the fluid in the stomach is low, typically
20 around 1.5 to 3.5. For the targeted delivery to pass through the stomach, it may be advantageous that the carrier system is protected in a way which prevents it from dissolving in the stomach. One strategy could be to coat the carrier system with at least one layer of coating, which does not dissolve before reaching the intestines.

25 In one embodiment, the composition of the present disclosure further comprises at least one coating layer.

In one embodiment, the composition of the present disclosure further comprises at least one coating layer which covers the encapsulating layer.

30 In one embodiment, the at least one coating layer is an enteric coating.

In one embodiment, the composition of the present disclosure further comprises at least one coating layer, such as two layers, such as 3 layers, which covers the
35 encapsulating layer.

The pH in the proximal small intestine is typically 6-7, and the pH in the distal small intestine and at the beginning of the colon is typically 7-7.5.

For targeted delivery to the small intestine, dissolution of coating should occur at pH>6.

5 For targeted delivery to the colon, dissolution should occur at pH>7.0.

In one embodiment the composition of the present disclosure is for delivery to the small intestine.

10 In one embodiment the composition of the current disclosure is coated in a coating allowing for small intestinal release. In one embodiment the coating dissolves at pH>6.

In one embodiment the composition of the present disclosure is for delivery to the large intestine. In one embodiment the composition of the current disclosure is coated in a
15 coating allowing for large intestinal release. In one embodiment the coating dissolves at pH>7.

In one embodiment the composition of the present disclosure is for delivery to the colon. In one embodiment the composition of the current disclosure is coated in a coating allowing for release to the colon. In one embodiment the coating dissolves at
20 pH>7.

An example of a polymer that can be used for targeted delivery to the intestines of a mammal is Eudragit® S. Eudragit® S is a pH sensitive polymer, comprising methacrylic acid and methyl methacrylate copolymer (1:2 ratio). Eudragit® S is used for
25 enteric coatings to protect the coated species from the acidic environment of the stomach. Eudragit® S dissolves at a pH above 7, which typically occurs in the distal small intestine and colon, which makes it suitable for targeted drug release in these regions. The formal name of Eudragit® S is Poly(methacrylic acid-co-methyl methacrylate copolymer (1:2)). The CAS number of Eudragit® S is 25086-15-1.

30

In one embodiment the at least one coating layer is a pH sensitive coating, such as a coating that dissolves at pH 5.5 or higher, such as a coating that dissolves at pH 5.5 to 8, such as a coating that dissolves at pH 6 or higher, such as a coating that dissolves
35 at pH 7 or higher.

In one embodiment the at least one coating layer is an enteric coating.

5 In one embodiment the at least one coating layer is a coating that dissolves at conditions found in the intestine of a mammal, such as at conditions found in the intestine of a primate.

10 In one embodiment the at least one coating layer is a coating that dissolves at conditions found in the small intestine of a mammal, such as at conditions found in the small intestine of a human.

In one embodiment the at least one coating layer is a coating that dissolves at conditions found in the large intestine of a mammal, such as at conditions found in the large intestine of a human.

15 *Use as medicament*

In one embodiment, the composition of the present disclosure is for use as a medicament.

20 In one embodiment the composition of the present disclosure is administered to an subject in need thereof.

In one embodiment the composition does not cause cell proliferation in the small intestine.

25 In one embodiment the composition of the present disclosure is for local treatment.

In one embodiment the composition does not promote penetration of biological tissue or biological barriers.

30 In one embodiment the composition does not promote penetration of biological barriers, such as the gastrointestinal barrier, such as the gastrointestinal mucosa.

In one embodiment the composition of the present disclosure is for local treatment of the intestines, such as the small intestine and/or the large intestine.

35

In one embodiment the active ingredient is insulin or analogues thereof.

In one embodiment the active ingredient is an antibody specific to tumour necrosis factor alpha (TNFa) or functional fragments and derivatives thereof.

5

In one embodiment the insulin has low or no systemic effects.

In one embodiment the insulin does not affect systemic blood glucose levels.

10 *Modified release*

In one embodiment, the composition of the present disclosure is a modified-release composition.

15 Multiple factors affect the release rate of active ingredient from the composition of the present disclosure. Strategies for modifying the release rate of the composition of the current disclosure includes coating of the microparticles, as well as incorporation of soluble diluents to the microparticles.

In one embodiment, the composition of the present disclosure releases the active agent at least 1 hour after administration, such as at least 2 hours after administration,
20 such as at least 3 hours after administration, such as at least 4 hours after administration, such as 6 to 8 hours after administration, such as 10 to 20 hours after administration.

25 In one embodiment, the composition of the present disclosure is an extended-release composition.

Delivery of drug compounds

In one embodiment the composition of the present disclosure is for use in a method for delivery of drug compounds to the intestines. In one embodiment the composition of
30 the present disclosure is for use in a method for healing colonic mucosa in a subject suffering from or suspected of suffering from an inflammatory bowel disease, wherein the active agent comprises or consists of insulin or an analogue thereof.

35 In one embodiment the composition of the present disclosure is for use in a method for preventing or healing colonic mucosa in a subject suffering from or suspected of

suffering from inflammation-induced colorectal tumour and/or cancer, wherein the active agent comprises or consists of insulin or an analogue thereof.

5 In one embodiment the insulin analogue is selected from the group consisting of insulin aspart, insulin lispro, insulin glulisine, insulin glargine, insulin detemir, and insulin degludec.

10 In one embodiment the composition comprises between 100 IU and 1000 IU, such as between 200 IU and 1000 IU, such as between 300 IU and 1000 IU, such as between 400 IU and 1000 IU, such as between 500 IU and 1000 IU, such as between 600 IU and 1000 IU, such as between 700 IU and 1000 IU, such as between 800 IU and 1000 IU of insulin or an analogue thereof.

15 In one embodiment the composition comprises between 1 mg and 35 g of insulin or an analogue thereof, such as between 3 mg and 35 g of insulin, such as between 10 mg and 35 g of insulin or an analogue thereof, such as between 50 mg and 35 g of insulin or an analogue thereof, such as between 100 mg and 35 g of insulin or an analogue thereof, such as between 1 g and 35 g of insulin or an analogue thereof, such as between 10 g and 35 g of insulin or an analogue thereof, such as between 20 g and 35 g of insulin or an analogue thereof.

25 In one embodiment the total dose of insulin per day is between 100 IU and 1000 IU, such as between 200 IU and 1000 IU, such as between 300 IU and 1000 IU, such as between 400 IU and 1000 IU, such as between 500 IU and 1000 IU, such as between 600 IU and 1000 IU, such as between 700 IU and 1000 IU, such as between 800 IU and 1000 IU of insulin or an analogue thereof.

30 In one embodiment the composition of the present disclosure releases the active agent in the intestine of the individual in need thereof.

In one embodiment the composition of the present disclosure releases the active agent in the small intestine of the individual in need thereof.

35 In one embodiment the composition of the present disclosure releases the active agent in the large intestine, such as in the colon, of the individual in need thereof.

Inflammatory bowel diseases

Crohn's disease and ulcerative colitis, two varieties of inflammatory bowel disease (IBD), both tend to arise in early adulthood, but can in fact arise at any age from early childhood onward. Their diagnosis is often delayed despite their prominent
5 manifestations, including diarrhoea, abdominal pain, and, in ulcerative colitis, perianal bleeding. Crohn's disease can affect the entire gastrointestinal tract transmurally, from the mouth to the anus, while ulcerative colitis mainly affects the colonic mucosa. The clinical picture is rounded out by extra-intestinal manifestations in the joints, eyes, and skin, which can arise before the bowel disease does.

10 In one embodiment the composition of the present disclosure is for use in a method of treatment or prevention of an inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer, wherein the active agent comprises or consists of insulin or an analogue thereof.

15 Inflammatory bowel diseases (IBDs) are common, with prevalence as high as 1 in 198 persons (ulcerative colitis) and 1 in 310 persons (Crohn's disease). Both young and elderly are affected and once diagnosed IBD is a chronic condition characterized by alternating episodes of inflammation with acute symptoms and remission which is
20 asymptomatic. In the long-term perspective especially ulcerative colitis (UC) is a known risk factor for development of colorectal tumours and cancer. Crohn's disease and ulcerative colitis, two varieties of inflammatory bowel disease (IBD), both tend to arise in early adulthood, but can in fact arise at any age from early childhood onward. Their diagnosis is often delayed despite their prominent manifestations, including diarrhoea,
25 abdominal pain, and, in ulcerative colitis, perianal bleeding. Crohn's disease can affect the entire gastrointestinal tract transmurally, from the mouth to the anus, while ulcerative colitis mainly affects the colonic mucosa.

30 In one embodiment the inflammatory bowel disease is selected from the group consisting of ulcerative colitis, diversion colitis, Behçet's disease, indeterminate colitis, left sided colitis, microscopic colitis such as collagenous colitis or lymphocytic colitis, Crohn's disease, noninfective colitis, pouchitis, immunotherapy-related colitis and immune-checkpoint induced-colitis.

35 A subject suffering from or suspected of suffering from an IBD usually presents periods

of disease, when the symptoms of the IBD are present, and periods of remission, when no symptoms are present. After a period of remission, the symptoms may return and there can be re-occurrence or relapse.

- 5 In one embodiment the present disclosure relates to compositions comprising a therapeutically effective amount of insulin or a pharmaceutically acceptable salt thereof for use in a method of treatment of inflammatory bowel disease, wherein the composition is administered to a subject in need thereof. In some embodiments of the present disclosure, the inflammatory bowel disease is selected from the group
- 10 consisting of ulcerative colitis, microscopic colitis such as collagenous colitis or lymphocytic colitis, diversion colitis, Behçet's disease, indeterminate colitis, left sided colitis, noninfective colitis, Crohn's disease and pouchitis.
- Pouchitis is the inflammation of the ileal pouch (an artificial rectum surgically created out of ileal gut tissue in patients who have undergone a colectomy), which is created in
- 15 the management of patients with ulcerative colitis, indeterminate colitis, familial adenomatous polyposis (FAP), or, in some cases other colitis. Subjects with pouchitis typically present symptoms associated with IBDs, in particular bloody diarrhoea, extreme cramping and abdominal pain.
- 20 Ulcerative colitis is normally continuous from the rectum up the colon. The disease is classified by the extent of involvement, depending on how far up the colon the disease extends, into (a) distal colitis, which includes proctitis, proctosigmoiditis and left-sided colitis, and (b) extensive colitis, which includes pancolitis. For the purpose of this disclosure, the term "ulcerative colitis" refers to any one of the forms in which the
- 25 disease presents itself, in particular the above mentioned forms.

Inflammation-induced colorectal tumour and/or cancers

- Inflammation-induced colorectal tumour and, also called colitis-associated cancer (CAC), is the subtype of colorectal cancer that is associated with IBDs, is difficult to
- 30 treat, and has high mortality.

In one embodiment the composition of the present disclosure is for use in a method of treatment or prevention of cancer.

With the widespread use of immune checkpoint inhibitors for treatment of various types of cancer, immune-related adverse events, are becoming increasingly common. One example of an immune-related adverse event is immunotherapy-induced colitis.

5 In one embodiment the immunotherapy-related colitis is immunotherapy-induced colitis.

In one embodiment, the composition comprising insulin or an analogue thereof is for use in the treatment of Immunotherapy-related colitis.

10 In one embodiment, the composition comprising insulin or an analogue thereof is for use in the treatment of immunotherapy-induced colitis.

In some embodiments of the present disclosure, the composition is administered to a subject who has been diagnosed with an inflammatory bowel disease and/or

15 inflammation-induced colorectal tumour and/or cancer.

One aspect of the present disclosure relates to a method for treatment of an inflammatory bowel disease in a subject in need thereof, the method comprising administration of the composition comprising a therapeutically effective amount of

20 insulin or a pharmaceutically acceptable salt thereof as disclosed herein.

Skin cancer

Inflammatory bowel disease (IBD) is a chronic autoimmune condition that is associated with increased risk of development of skin cancer. Proposed mechanisms predisposing

25 IBD patients to skin cancer include chronic inflammation, cellular damage, and underlying immune dysfunction leading to altered tumour surveillance. Use of immunosuppressants in IBD patients has been shown to lead to a 4–7-fold increased risk of skin cancer and approximately half of IBD patients are exposed to these medications within 5 years of diagnosis.

30

In one embodiment the composition is for use in the prevention of skin cancer. In one embodiment the composition is for reducing the risk of developing skin cancer. In one embodiment the skin cancer is nonmelanoma skin cancers (NMSCs) or melanoma.

Delivery of probiotics and or prebiotics

Even for healthy subjects without a diagnosed gastrointestinal disorder there may be a desire to seed bacteria (probiotics) or spray nutritional supplements for the gut microbiota (prebiotics) over the complete inner surface of the large intestine. The
5 motivations are multiple e.g. to achieve a healthier gut microbiota, to provide an energy substrate to the enterocytes and/or to protect the enterocytes from oxidative stress.

10 In one embodiment the composition of the current disclosure relates to a dietary supplement.

In one embodiment the active ingredient of the dietary supplement is a prebiotic nutrient.

15 In one embodiment the composition of the present disclosure is for oral administration of an active agent, wherein the active agent is a prebiotic.

Prebiotic nutrients are non-digestible food ingredients that beneficially affects a host when ingested, by selectively stimulating the growth and/or the activity of bacteria in the gastrointestinal tract. Non-limiting examples of prebiotic nutrients include butyrate
20 and bilberry extracts, as well as dietary fibers such as fructo-oligosaccharide, gluco-oligosaccharide, galacto-oligosaccharide, polydextrose, isomalto-oligosaccharide, xylo-oligosaccharide, polydextrose and lactulose.

25 In one embodiment the active ingredient of the dietary supplement is a probiotic.

In one embodiment the composition of the present disclosure is for oral administration of an active agent, wherein the active agent is a probiotic.

30 Probiotics are live microorganisms intended to maintain or improve the microflora in the gastrointestinal tract. Examples of probiotics include yeasts, moulds and bacteria. Non-limiting examples of probiotics, comprise strains of Bifidiobacterium, Lactobacillus, and Enterococcus.

35 In one embodiment the composition of the present disclosure is for oral administration of a dietary supplement to a subject.

In one embodiment the composition of the present disclosure is for use in a method for delivery of dietary supplements to the intestines of a subject.

5 In one embodiment the composition of the present disclosure is for use in a method for delivery of probiotics to the intestines of a subject.

In one embodiment the composition of the present disclosure is for use in a method for delivery of prebiotics to the intestines of a subject.

10 For example, the prebiotics can comprise sodium butyrate and/or bilberry extracts.

Administration

15 In one embodiment the composition is administered to the individual in need thereof at the most four times a day, such as at the most three times a day, such as at the most two times a day, such as at the most once a day, such as at the most once each 48 hours.

In one embodiment the composition is a capsule.

20 In one embodiment one capsule is administered to the individual in need thereof at the most four times a day, such as at the most three times a day, such as at the most two times a day, such as at the most once a day, such as at the most once each 48 hours.

25 In one embodiment one or more capsules are administered to the individual in need thereof at the most four times a day, such as at the most three times a day, such as at the most two times a day, such as at the most once a day, such as at the most once each 48 hours.

30 In one embodiment one or more capsules are administered to the individual in need thereof once a day.

In one embodiment one or more capsules are administered to the individual in need thereof once a day.

35 In one embodiment two capsules are administered at the same time to the individual in

need thereof once a day.

In one embodiment three capsules are administered at the same time to the individual in need thereof once a day.

5

In one embodiment the composition is administered in the morning. In one embodiment the composition is administered in the evening.

10 In one embodiment the composition of the present disclosure is administered to an individual in need thereof three times daily, such as twice daily, such as once daily, such as each other day.

15 In one embodiment the composition is administered to an individual in need thereof over a period of at least 3 weeks, such as over a period of at least 4 weeks, such as over a period of at least 5 weeks, as over a period of at least 6 weeks, as over a period of at least 7 weeks, such as lifelong.

20 In one embodiment the composition comprises insulin or an analogue thereof and it is administered to an individual in need thereof during the remission phase of the inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer for a period between 3 weeks and 3 months, such as between 3 weeks and 4 months, such as between 3 weeks and 5 months, such as between 3 weeks and 6 months, such as between 3 weeks and 7 months, such as between 3 weeks and 8 months, such as between 3 weeks and 9 months, such as between 3 weeks and 10 months, such as between 3 weeks and 11 months, such as between 3 weeks and 12 months, such as between 3 weeks and 18 months, such as between 3 weeks and 24 months.

25 In one embodiment of the present disclosure, the active ingredient is insulin or an analogue thereof.

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In one embodiment the composition comprising insulin or an analogue thereof is administered to a subject suffering from or suspected of suffering from an inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer during the acute phase and/or during relapse of the disease.

In one embodiment the composition comprising insulin or an analogue thereof is administered to a subject suffering from or suspected of suffering from an inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer during the acute phase and/or during relapse of the disease.

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In one embodiment the composition comprising insulin or an analogue thereof is administered to a subject suffering from or suspected of suffering from an inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer during the remission phase of the disease.

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In one embodiment the composition comprising insulin or an analogue thereof is administered to a subject suffering from or suspected of suffering from an inflammatory bowel disease during the acute phase and/or during relapse of the disease.

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In one embodiment the composition comprising insulin or an analogue thereof is administered to a subject suffering from or suspected of suffering from an inflammatory bowel disease during the remission phase of the disease.

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In one embodiment the composition comprising insulin or an analogue thereof is administered to a subject suffering from or suspected of suffering from inflammation-induced colorectal tumour and/or cancer during the acute phase and/or during relapse of the disease.

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In one embodiment the composition comprising insulin or an analogue thereof is administered to a subject suffering from or suspected of suffering from during the remission phase of the disease.

In one embodiment the composition comprising insulin or an analogue thereof is administered to a subject suffering from or suspected of suffering from mild to moderate ulcerative colitis.

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In one embodiment the composition comprising insulin or an analogue thereof is administered to a subject suffering from or suspected of suffering from mild to moderate ulcerative colitis during the acute phase and/or during relapse of the disease.

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In one embodiment the composition comprising insulin or an analogue thereof is administered to a subject suffering from or suspected of suffering from mild to

moderate ulcerative colitis during the remission phase of the disease.

In one embodiment the composition comprising insulin or an analogue thereof is administered to a subject in need thereof, wherein the subject presents one or more of the following symptoms: abdominal pain, vomiting, chronic diarrhoea, rectal bleeding, severe internal cramps/muscle spasms in the region of the pelvis, weight loss, deep geographic and serpiginous ulcers, continuous ulcer, transmural inflammation, mucosal inflammation, stenosis, granulomas on biopsy (for example non-necrotizing non-peri-intestinal crypt granulomas), high levels of faecal calprotectin, anaemia, thrombocytosis, architectonic abnormalities of the rectal tissue on histological examination, fistulae or abscesses to any segment of the gastrointestinal tract, toxic megacolon.

In one embodiment the composition comprising insulin or an analogue thereof is administered to a subject who has been diagnosed with an inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer.

Manufacture

In one embodiment, the composition of the present disclosure is manufactured in a method comprising

- a. Mixing polymer with active agent and optionally with lubricant
- b. extruding and optionally spheronising microparticles comprising at least one polymer and having a size of 100 to 2000 μm ;
- c. mixing the microparticles with an active agent and an effervescent reagent thereby obtaining a mixture;
- d. encapsulating the mixture, thereby obtaining the composition of the present disclosure.

In one embodiment the microparticles are manufactured using a method as described in Example 1. In one embodiment the microparticles are manufactured using an extrusion method as described in Example 1.

In one embodiment, the composition of the present disclosure is manufactured in a method comprising

- a. Suspending polymer, active agent and optionally lubricant in a solvent

- b. Stirring until solvent has evaporated, collect and wash microparticles comprising at least one polymer and having a size of 100 to 2000 μm ;
- c. mixing the microparticles with an active agent and an effervescent reagent thereby obtaining a mixture;
- 5 d. encapsulating the mixture, thereby obtaining the composition of the present disclosure.

In one embodiment the microparticles, the polymer, the active agent, and the effervescent reagent used in the manufacture as are as defined elsewhere in the description.

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In one embodiment, the method of manufacturing the composition of the present disclosure further comprising adding at least one coating layer, wherein the at least one coating layer is as defined elsewhere in the description.

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Examples

Example 1. Preparation of pellets (microparticles) and analysis of insulin release and capsule breakage.

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Materials and methods:

Materials: Recombinant human insulin (Bioton SA), Recombinant monoclonal antibody against, Tumor necrosis factor alpha (Infliximab; Sigma), Cellets (IPC Process-Center), Caffeine (AppliChem), Microcrystalline cellulose (MCC, Avicel PH-101), Magnesium stearate (MS), MgCl_2 , NaHCO_3 , Citric acid, Na-butyrate (Sigma).

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Insulin pellets.

Insulin (80 mg) was dissolved in 5.3 mL 10 mM HCl. Magnesium stearate (50 mg) was mixed with 1.625 g of MCC in a mortar. When properly mixed, another 1.625 g of MCC was added and further mixed before additional 1.625 g of MCC was added and mixed. The powder mixture was wetted by slow addition of 5.0 mL of the insulin solution resulting in a liquid addition of 1.0 mL/g. The homogeneous wet insulin-containing powder mixture was extruded with 1 mm die and an extrusion speed of 300-500 RPM with the Caleva Multi Lab instrument. The extrudate was refed to the extruder until the extrudate looked properly compressed. The final, still wet, extrudate was immediately

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spheronized for 5 minutes with a speed of 3000 RPM and the pellets dried overnight under vacuum.

Composition after drying: Insulin 75 mg (1.5%), MCC: 4875 mg (97.5%), MS: 50 mg (1.0%).

- 5 The pellets were sieved through relevant pore diameters, and fractions collected from 250 µm to 1400 µm. In some instances, mannitol was mixed with the MCC / MS mixture before addition of insulin solution. In those instances mannitol was added to the MCC /MS mixture, e.g. in a ratio of MCC: mannitol 2:1 and 5:1, this was done without changing the composition in terms of insulin % and MS %.

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Na-butyrate pellets.

- Equal amounts (w/w) of MCC and Na-butyrate was mixed with 1% Mg-stearate and extruded followed by spheronization (as described above for insulin) and sieved to achieve a pellet size of approximately 1000 µm. The pellets were further coated (8% theoretical weight gain) with Poly(ethyl acrylate, methyl methacrylate, 2-trimethylammonioethyl methacrylate chloride, 10% quaternary ammonium groups) (Eudragit RL) and further coated (12% theoretical weight gain) with Poly(ethyl acrylate, methyl methacrylate, 2-trimethylammonioethyl methacrylate chloride, 5% quaternary ammonium groups) (Eudragit RS). The coating was performed using a FC-LAB Micro FLO-COATER®.
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- 20

Caffeine pellets.

- MCC and Caffeine was mixed in a 4:1 ratio followed by the addition of 1% Mg-stearate. Pellets were produced by the extrusion / spheronization method (as described above for insulin) aiming at pellet size of 1000 µm.
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Infliximab pellets.

- Infliximab was purchased from Sigma and mixed in a 1:1000 ratio with MCC followed by the addition of 1,23% Mg-stearate. Pellets were produced by the extrusion / spheronization method (as described above for insulin) aiming at pellet size of 1000 µm.
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- HMPC and gelatine capsules were filled with pellets, sodium hydrogen bicarbonate, citric acid and closed. The effervescent couple was mixed in a molar ratio of 1:3 (citric acid versus NaHCO₃). For enteric coating, the capsules were dip coated in a 10% (w/v)
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Poly(methacrylic acid-co-methyl methacrylate copolymer (1:2)) (also marketed under the brand name Eudragit® S100) solution in isopropanol:H₂O (98:2 v/v). Firstly, the cap of the capsules was immersed in the coating liquid and allowed to dry before the body of the capsule was immersed. The dipping procedure was repeated to ensure an intact coating.

Analysis of insulin release from pellets:

The pellets were placed in a glass tube and shielded with a grid. Phosphate buffered saline (PBS pH 7.0) was filled into the tube and a magnet bar was placed above the grid thus preventing the magnet bar from directly touching the pellets which were shielded by the grid (Knopp et al, 2022). The system was placed in a magnetic stirrer. The buffer was sampled over time and samples analysed quantitatively by HPLC for the amounts of intact insulin.

Analysis of capsule breakage:

Petri dishes were filled with PBS (pH 7.4) and a capsule added to each dish. Three dishes at a time were mounted on a heated rotating table. A GoPro camera was mounted above the rotating table and the entire experiments were recorded with the GoPro camera. The temperature of the heated table was set to 37 °C. The capsules were added (one for each petri dish) and the experiment commenced with a static incubation period 1 (between 1.5 to 3 minutes, depending on the experiments) without orbital shaking after which the rotation (approximately 15-20 rpm) of the table was initiated. When all capsules were disrupted, and the pellets released, the experiment was terminated.

Example 2. Effervescent agent increases the area covered by pellets following gelatine capsule breakage.

Gelatine capsules (size 2) were filled with microcrystalline cellulose insulin containing pellets. In addition, MgCl₂ was added to some capsules as an exothermic agent, which was anticipated to accelerate melting of the gelatine capsule. Alternatively, an effervescent couple of citric acid and sodium hydrogen bicarbonate (NaHCO₃) was added in the molar ration of 1:3. The capsules were placed in petri dishes on a heated rotating table. A static incubation of 3 minutes resulted in the hydration and breakage of all three capsules (control, NaHCO₃/citric acid, MgCl₂) without any difference in the time required to reach capsule breakage (Figure 1B). To simulate peristaltic bowel

movements, the incubation was continued with gentle orbital shaking for 4 minutes. This resulted (Figure 1C,F) in a clear difference with a larger area covered by the pellets in the capsule containing the effervescent couple. Moreover, by gentle manual tilting of the petri dishes at the end of the orbital shaking it was observed that the pellets from the control capsules and the MgCl_2 containing capsules adhered more tightly to the hydrated gelatine mesh compared with the pellets released from the capsule containing the effervescent couple. Based on this initial experiments it was decided to proceed with an experimental design where the experiment is initiated by a short static period followed by a longer period with gentle orbital shaking.

In a follow-up experiment an HPMC capsule was used instead of a gelatine capsule. The HPMC capsule hydrated more slowly than the gelatine capsule and after 2.5 minutes of static incubation all three capsules (control (i), NaHCO_3 /citric acid (ii), MgCl_2 (iii)) were still intact with no visible pellet release (Figure 2B). Bubbles were visible, coming from the NaHCO_3 /citric acid containing capsule. A further 5 minutes incubation with orbital shaking resulted in capsule breakage and release of pellets only from the NaHCO_3 /citric acid containing capsule (Figure 2C). The released pellets covered most of the area of the petri dish. The two other capsules remained intact, and no released pellets were visible from these capsules.

Example 3. Effervescent couple does not affect insulin release.

The effect of either the citric acid and sodium hydrogen bicarbonate effervescent couple or the MgCl_2 exothermic agent on insulin release from microcrystalline cellulose pellets was investigated. As seen in Figure 3 the % insulin release was not affected by the effervescent couple as measured by HPLC analysis. In contrasts, MgCl_2 addition led to a decrease in the % release of insulin (Figure 3A,B).

Example 4. Determination of optimal ratio between effervescent couple and pellets in HPMC.

The effect of changing the ratio of effervescent couple on HPMC capsule breakage time was investigated. It was found that a 5:1 w/w ratio between the amounts of pellets (of size 710 μm -1000 μm) and the amounts of the effervescent couple was optimal. This 5:1 ratio resulted in the fastest capsule breakage and pellet release compared to

the other ratios tested (2:1 and 1:1). This was not due to incomplete dissolution of the effervescent couple as the use of 135 mg effervescent couple in a 1:1 ration led to the highest amounts of CO₂ bubbles released. Thus, even though a high amounts of CO₂ was produced with the 1:1 ratio, the capsule breakage was inefficient compared to the use of only 45 mg effervescent couple (5:1 ratio) (Figure 4). This was further confirmed in a more quantitative experiment (Figure 13) where the time to first liberated pellet was measured as a function of effervescent couple added (citric acid and Na-bicarbonate; 3:1 molar ratio). In this experiment the amounts of pellets were kept constant at 225 mg. With 20 mg effervescent couple there is not a significant difference in the time to first released pellet when comparing to capsules without effervescent couple. With 45 mg effervescent couple added there is a significantly reduced time to first liberated pellet but increasing the amounts of effervescent couple to 90 mg does not lead to a significant decrease in time to first liberated pellet compared to the addition of 45 mg of effervescent couple.

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Example 5. Larger pellet size accelerates capsule breakage more efficiently compared with smaller pellet sizes.

HPMC capsules were filled with pellets of different pellet sizes (710 µm – 1000 µm, 400 µm - 710 µm and 250 µm – 400 µm) and the effervescent couple (NaHCO₃ and citric acid). The weight of the pellets and the amounts of effervescent couple was kept constant. A static 2 minutes incubation on the heated rotating table was followed by gentle orbital shaking. After 1 minutes of orbital shaking i.e., 3 minutes total incubation time, the capsule with the largest pellet diameter broke and began releasing pellets (Figure 5B). The capsules with intermediate pellet size (400 µm - 710 µm) broke after further 3 minutes orbital shaking (6 minutes in total, Figure 5C) while the capsule with the smallest pellet size began releasing after further 1 minutes of orbital shaking (after 7 minutes total incubation time, Figure 5D). The experiment was repeated (Figure 6) with two different pellet sizes, respectively 400-700 µm and 700-1000 µm, with similar results i.e., the capsule with pellets having the largest pellet diameter broke before the capsule with pellets of the smaller pellet diameter.

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Example 6. Ejection of pellets from capsules coated with enteric coat of Poly(methacrylic acid-co-methyl methacrylate copolymer (1:2)) (Eudragit® S100)

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An HPMC capsule coated with the enteric coat, poly(methacrylic acid-co-methyl methacrylate copolymer (1:2)), dissolved more slowly at pH 7.3 than an uncoated HPMC capsule (Figure 7B). However, by addition of the effervescent couple the pellets were seen being actively ejected together with CO₂ bubbles from the capsule after 10 – 12 minutes of incubation (Figure 7C).

The tested capsules comprised 180 mg pellets (400-710 µm) and 90 mg effervescent couple (citric acid: sodium hydrogen bicarbonate, molar ratio 1:3).

Example 7. Recovery studies.

Recovery studies were done for three different types of microparticles, respectively microparticles comprising MCC:mannitol (2:1) /insulin, MCC:mannitol (5:1) /insulin and MCC /insulin. The recovery studies were conducted by stirring the microparticles in a release medium.

MCC /insulin microparticles (Microparticles consisting of MCC and insulin) showed release of 60% insulin within 6 hours, and release of 80% insulin within 24 hours (Figure 8). MCC:mannitol (2:1) /insulin microparticles (Microparticles consisting of MCC, mannitol and insulin) showed release of 80% insulin within 1 hour and 90% within 6 hours. MCC:mannitol (5:1) /insulin microparticles (Microparticles consisting of MCC, mannitol and insulin) showed release of 80% insulin within 4 hours and 90% within 6 hours. MCC:mannitol (5:1) /insulin microparticles display full release of insulin within 24 hours.

Example 8. Test of a selection of ingredients which can be used with the invention.

Na-butyrate.

Commercial usage: Sodium butyrate is sold as a nutraceutical compound to retail customers. The products are provided as enteric coated capsules and as granulates.

Analysis of Manufactured pellets: In PBS buffer at pH 7.0, 50% percent of the Na-butyrate is released after one hour with Eudragit RS (poly(ethyl acrylate, methyl methacrylate, 2-trimethylammonioethyl methacrylate chloride, 5% quaternary ammonium groups) coated pellets (Figure 9A).

Caffeine.

Commercial usage: Caffeine is a natural extract of the coffee bean. It occurs in coffee and as additive to soft drinks. Caffeine is also marketed in tablets for retail sale. In medical and pharmaceutical research caffeine can be used as a tracer in experiments measuring the release of water-soluble compounds from tablets and capsules for oral administration.

Analysis of manufactured pellets: In PBS buffer pH 7.0, 50% percent of the caffeine is released after 20 minutes (Figure 9B).

Insulin.

Commercial usage: Insulin is an approved drug for treatment of diabetes. Insulin comes as a solution to be administered intravenously or subcutaneously. Insulin is also being developed as a topical treatment in the colon for treatment of inflammatory bowel disease.

Analysis of manufactured pellets: In PBS buffer, 50% percent of the insulin is released after 2 hours (Figure 9C).

Infliximab.

Commercial usage. Infliximab is the trade name for a monoclonal antibody which can bind to tumour necrosis factor alpha (TNF-alfa). Infliximab is an approved drug which is administered intravenously to patients to suppress inflammation in some autoimmune diseases such as rheumatoid arthritis and inflammatory bowel diseases.

Analysis of manufactured pellets: In PBS buffer, 40% percent of the infliximab antibody is released after one hour. After one hour the release continues almost linearly until 80% has been released after thirty-two hours of incubation (Figure 9D).

Example 9. Na butyrate – effect of coating

A) As an example, 275 mg Na-butyrate / MCC pellets (1:1 ratio) can be filled into a size 2 capsule. The release of Na-butyrate from uncoated pellets is fast (Figure 10A), with 85% being released in six minutes. The maximal recovery of Na-butyrate is 90%.

To achieve a delayed release of Na-butyrate compatible with topical treatment the pellets were coated first with (8% theoretical weight gain) poly(ethyl acrylate, methyl methacrylate, 2-trimethylammonioethyl methacrylate chloride, 10% quaternary ammonium groups) (Eudragit RL) and further coated (12% theoretical weight gain) with poly(ethyl acrylate, methyl methacrylate, 2-trimethylammonioethyl methacrylate chloride, 5% quaternary ammonium groups) (Eudragit RS). Pellets coated with both polymers, Eudragit RL and Eudragit RS, displayed a delayed release profile of the Na-butyrate after ninety minutes. The delayed release coat with Poly(ethyl acrylate, methyl methacrylate, 2-trimethylammonioethyl methacrylate chloride, 10% quaternary ammonium groups) (Eudragit RL) did not on its own yield pellets with delayed release properties since the profile of pellets with this coat was only shifted marginally compared with the uncoated pellets.

B) The Na-butyrate release profile of pellets manufactured with the double coat (of Example 9A) were tested either as loose pellets or as pellets filled into a capsule together with the effervescent couple of citric acid and sodium bicarbonate (3:1 molar ratio). The release profile (Figure 10B) was shifted to the right by approximately 15 minutes for the pellets in the capsule. Thus, the encapsulation delays the release of Na-butyrate from the pellets until capsule breakage has occurred. There are no signs of premature leakage of Na-butyrate from the capsule, which in this experiment is an uncoated HPMC capsule. In our experiments such capsules typically sheds the first pellet after 4-5 minutes when the effervescent couple is also included in the capsule.

Example 10. Addition of an effervescent couple to the capsule mitigates the impact of pellet-carrier chemical composition on release kinetics.

Capsules filled with either commercially available microcrystalline cellulose pellets (350 μm) manufactured without glidant or filled with in house manufactured pellets (350 μm) containing microcrystalline cellulose with addition of glidant (stearate) were tested in release studies where the time to first released pellet was measured (Figure 11). Without effervescent couple there was a significant difference in the time to the first released pellet observed between MCC pellets (shed after approximately 6 minutes) and MCC+stearate pellets (shed after approximately 9 minutes). Addition of an effervescent couple (Citric acid and sodium bicarbonate; 3:1 molar ratio) decreased the release time for the first liberated pellet for both pellet types. Moreover, no significant difference in pellet release times were observed in the presence of the effervescent couple. Thus,

addition of the effervescent couple yields release kinetics which is independent on the composition of the carrier material.

Example 11. Area covered by pellets as a function of time

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A) HPMC capsules filled with MCC pellets with a diameter of 350 μm with or without the addition of the effervescent couple of citric acid and sodium bicarbonate (3:1 molar ratio) were followed by video recording for 15 minutes.

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After 5 minutes it can clearly be seen that the addition of the effervescent couple leads to more consistent pellet release as all three capsules with an effervescent couple has shed between 39 and 70 pellets. Without effervescent couple one capsule did not shed any pellets after 5 minutes and another capsule shed very few (10) and the last capsule shed 50 pellets. Due the high variability the difference of the means of the shed pellets is not statistically significant.

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B) After 15 minutes of incubation all capsules have shed clouds of pellets. To quantify the area covered, circles were drawn around the pellet clouds using the selection tool in Adobe Photoshop. The circles were drawn to include 90 percent of the released pellets and thereby excluding single pellets which had moved, as outliers, away from the main pellet cloud. Subsequently the area (in pixels) of the circles were measured. The addition of the effervescent couple led to the coverage of a 40% larger surface area (Figure 12 B, $p < 0,05$, unpaired t-test) when the effervescent couple is added. The mean circle area was determined to be 5487 pixels without effervescent couple and 7670 pixels with effervescent couple in the capsule.

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Claims

1. A composition for oral administration of an active agent, the composition comprising
 - a. microparticles having a size of 100 μm to 2000 μm , said microparticles comprising a polymer and an active agent,
 - b. an effervescent reagent,wherein the w/w ratio of microparticles to effervescent reagent is between 7:1 and 1.5:1, and wherein said composition is encapsulated.
2. The composition according to claim 1, wherein said composition is a modified-release composition.
3. The composition according to claim 2, wherein said composition releases the active agent at least 1 hour after administration, such as at least 2 hours after administration, such as at least 3 hours after administration, such as at least 4 hours after administration, such as 6 to 8 hours after administration, such as 10 to 20 hours after administration.
4. The composition according to any one of the preceding claims, wherein the microparticles have a size of 150 μm to 2000 μm , such as 150 μm to 1500 μm , such as 150 μm to 1000 μm , such as 150 μm to 800 μm , such as 150 μm to 700 μm , such as 150 μm to 600 μm , such as 200 μm to 600 μm .
5. The composition according to any one of the preceding claims, wherein the microparticles have a size of 100 μm to 2000 μm , such as 150 μm to 2000 μm , such as of 200 μm to 2000 μm , such as of 250 μm to 2000 μm , such as of 300 μm to 2000 μm , such as of 350 μm to 2000 μm , such as of 400 μm to 2000 μm , such as of 245 μm to 2000 μm , such as of 500 μm to 2000 μm , 550 μm to 2000 μm , such as a size of 600 μm to 2000 μm , such as a size of 650 μm to 2000 μm , such as a size of 700 μm to 2000 μm , such as a size of 700 μm to 2000 μm , such as a size of 700 μm to 1900 μm , such as a size of 700 μm to 1000 μm , such as a size of 700 μm to 1100 μm , such as a size of 800 μm to 2000 μm , such as a size of 900 μm to 2000 μm , such as a size of 1000 μm to 2000 μm , such as a size of 1200 μm to 2000 μm , such as a size of 1300 μm to 2000

μm, such as a size of 1400 μm to 2000 μm, such as a size of 1500 μm to 2000 μm.

- 5 6. The composition according to any one of the preceding claims, wherein the microparticles have a size of 250 μm to 1000 μm.
- 10 7. The composition according to any one of the preceding claims, wherein the effervescent reagent is an effervescent couple comprising or consisting of
- a. a base, such as a base selected from the group consisting of sodium bicarbonate, potassium bicarbonate and sodium carbonate, and
- b. an acid, such as an acid selected from the group consisting of citric acid, maleic acid and tartaric acid.
- 15 8. The composition according to any one of the preceding claims, wherein the effervescent reagent comprises or consists of citric acid and bicarbonate at a molar ratio of 1 mol citric acid to 3 moles sodium bicarbonate.
- 20 9. The composition according to any one of the preceding claims, wherein the ratio of microparticles to effervescent reagent is between 7:1 and 1.5:1, such as between 6:1 and 4:1, such as 1.6:1, such as 2.5:1, such as 3:1, such as 5:1.
- 25 10. The composition according to any one of the preceding claims, wherein the ratio of microparticles to effervescent reagent is between 7:1 and 3:1.
- 30 11. The composition according to any one of the preceding claims, wherein the ratio of microparticles to effervescent reagent is between 6:1 and 4:1, such as about 3:1.
12. The composition according to any one of the preceding claims, wherein the microparticles have a size of 710 μm to 1000 μm, wherein the effervescent reagent is citric acid and sodium hydrogen carbonate, and wherein the ratio of microparticles to effervescent reagent is 5:1.
- 35 13. The composition according to any one of the preceding claims, wherein the polymer is selected from the group consisting of microcrystalline cellulose, an

- acrylic polymer such as Eudragit® RL and Eudragit® RS, polyethylene oxide, starch such as amylose, amylopectin and maltodextrin, a starch derivative such as dextrin, acid-treated starch, base-treated starch, starch acetate, bleached starch, alginates, pullulan, scleroglucan, povidone derivatives such as
- 5 crospovidones (PVPP) and copovidones, natural gums, gelatine, chitosan, polyvinyl alcohol, and combinations thereof.
14. The composition according to any one of the preceding claims, wherein the concentration of polymer in the microparticles is 94 to 98.9% (w/w), such as 97-
- 10 98% (w/w).
15. The composition according to any one of the preceding claims, wherein the microparticles comprise a diluent, such as a diluent selected from the group consisting of lactose, dicalcium phosphate, starch and a sugar alcohol such as
- 15 mannitol, xylitol and sorbitol, and combinations thereof.
16. The composition according to any one of the preceding claims, wherein the microparticles comprise microcrystalline cellulose and mannitol at a ratio of 2:1 (w/w) to 6:1 (w/w), such as at a ratio of 5:1 (w/w).
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17. The composition according to any one of the preceding claims, wherein the microparticles comprise microcrystalline cellulose and Eudragit® RL at a ratio of 4:1.
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18. The composition according to any one of the preceding claims, wherein the microparticles comprise one or more additives.
19. The composition according to any one of the preceding claims, wherein the concentration of additives in the microparticles is 0.1 to 2% (w/w), such as
- 30 about 1% (w/w).
20. The composition according to any one of the preceding claims, wherein the microparticles comprise a lubricant, such as a lubricant selected from the group consisting of magnesium stearate, stearic acid and talc, and combinations
- 35 thereof.

21. The composition according to any one of the preceding claims, wherein the active agent is selected from the group consisting of biologics, therapeutic peptides, small molecule drugs, bacteria, probiotics, prebiotics, bacteriophages and natural products.
22. The composition according to any one of the preceding claims, wherein the active agent is a biologic therapeutic peptide, such as a biologic therapeutic peptide selected from the group consisting of a protease, a peptidase, a disaccharidase, an oligo-saccharidase, a lipase, a growth factor, an extracellular matrix protein such as a laminin, a collagen, a glycosaminoglycan, a proteoglycan, a mucin, and analogues thereof.
23. The composition according to any one of the preceding claims, wherein the active agent is a biologic, such as a biologic selected from the group consisting of such as a monoclonal antibody, a vaccine, a modified or unmodified mRNA with vaccine properties.
24. The composition according to any one of the preceding claims, wherein the active agent is a therapeutic peptide.
25. The composition according to any one of the preceding claims, wherein the active agent is a therapeutic peptide, such as insulin or analogues thereof.
26. The composition according to any one of the preceding claims, wherein the active agent is insulin or an analogue thereof, such as an analogue selected from the group consisting of insulin aspart, insulin lispro, insulin glulisine, insulin glargine, insulin detemir, and insulin degludec.
27. The composition according to any one of the preceding claims, wherein the active agent is a therapeutic antibody, such as Adalimumab, Golimumab or Infliximab.
28. The composition according to any one of the preceding claims, wherein the active agent is a small molecule drug, such as Na-butyrate.

29. The composition according to any one of the preceding claims, wherein the active agent is tracer molecule, such as caffeine.
- 5 30. The composition according to any one of the preceding claims, wherein the active agent is a small molecule, such as caffeine.
31. The composition according to any one of the preceding claims, wherein the concentration of active agent in the composition is at the most 6% (w/w), such
10 as at the most 5% (w/w), such as at the most 4% (w/w), such as at the most 3.5% (w/w), such as at the most 3% (w/w), such as at the most 2.5% (w/w), such as at the most 2% (w/w), such as at the most 1.5% (w/w), such as at the most 1.3% (w/w), such as at the most 1% (w/w), such as at the most 0.5% (w/w).
- 15 32. The composition according to any one of the preceding claims, wherein the composition is encapsulated in an encapsulating layer.
33. The composition according to any one of the preceding claims, wherein the
20 encapsulating layer comprises an encapsulating polymer selected from the group consisting of gelatine, cellulose, methacrylate acid copolymers such as Eudragit® L100 (CAS no.: 25086-15-1), Eudragit® S100 (CAS no.: 25086-15-1), Eudragit® L-30D (CAS no.: 100218-76-6 or 25212-88-8), Eudragit® FS 30D (CAS no.: 26936-24-3), and Eudragit® L100-55 (CAS no.: 25212-88-8),
25 cellulose acetate phthalate, cellulose acetate trimellitate, polyvinyl acetate phthalate, hydroxyethylcellulose phthalate, hydroxypropyl methylcellulose phthalate, chitosan, pullulan, scleroglucan, alginate, an alginate derivative, or shellac, or an aqueous dispersion thereof.
- 30 34. The composition according to any one of the preceding claims, wherein the composition further comprises at least one coating layer.
- 35 35. The composition according to any one of the preceding claims, wherein the at least one coating layer covers the microparticles.

36. The composition according to any one of the preceding claims, wherein the at least one coating layer is an enteric coating, such as Eudragit® S 100.
- 5 37. The composition according to any one of the preceding claims, wherein the at least one coating layer covers the encapsulating layer.
- 10 38. The composition according to any one of the preceding claims, wherein the at least one coating layer is a pH sensitive coating, such as a coating that dissolves at pH 5.5 or higher, such as a coating that dissolves at pH 5.5 to 8, such as a coating that dissolves at pH 6 or higher, such as a coating that dissolves at pH 7 or higher.
- 15 39. The composition according to any one of the preceding claims, wherein the at least one coating layer is an enteric coating.
- 20 40. The composition according to any one of the preceding claims, wherein the at least one coating layer is a coating that dissolves at conditions found in the intestine of a mammal, such as at conditions found in the intestine of a primate.
- 25 41. The composition according to any one of the preceding claims, wherein the at least one coating layer is a coating that dissolves at conditions found in the large intestine of a mammal, such as at conditions found in the large intestine of a human.
- 30 42. The composition according to any one of the preceding claims, wherein the at least one coating layer is alginate or an alginate derivative.
43. The composition according to any one of the preceding claims, wherein the at least one coating layer covers the microparticle.
- 35 44. The composition according to any one of the preceding claims, wherein the at least one coating layer covering the microparticle is Eudragit RL.
45. The composition according to any one of the preceding claims, wherein the at least one coating layer covering the microparticle is Eudragit RS.

46. The composition according to any one of the preceding claims, wherein the at least one coating layer covering the microparticle is a mixture of Eudragit RL and Eudragit RS.
- 5
47. The composition according to any one of the preceding claims, wherein the microparticles are coated with one or more layers of Eudragit RL and one or more layers of Eudragit RS.
- 10
48. The composition according to any one of the preceding claims, wherein the at least one coating layer covering the microparticle, introduces a theoretical weight gain of at least 2%, such as 4 %, such as 6%, such as 8%, such as 10%, such as 12%, such as 14%, such as 20%, such as 25%.
- 15
49. The composition according to any one of the preceding claims, wherein a coating layer of Eudragit RL introduces a theoretical weight gain of at least 2%, such as 4 %, such as 6%, such as 8%, such as 10%, such as 12%, such as 14%, such as 20%.
- 20
50. The composition according to any one of the preceding claims, wherein a coating layer of Eudragit RS introduces a theoretical weight gain of at least 2%, such as 4 %, such as 6%, such as 8%, such as 10%, such as 12%, such as 14%, such as 20%.
- 25
51. The composition according to any one of the preceding claims, wherein the at least one coating layer is an enteric coating that dissolves at conditions found in the intestine of a mammal, such as at conditions found in the small intestine and/or the colon of a human.
- 30
52. The composition according to any one of the preceding claims, wherein the microparticles are produced by extrusion and spheronisation, or by solvent evaporation.
- 35
53. The composition according to any one of the preceding claims, wherein the microparticles are spherical.

54. A method of manufacturing the composition of any one of the preceding claims, the method comprising
- a. mixing polymer with active agent and optionally with lubricant
 - 5 b. extruding and optionally spheronising microparticles comprising at least one polymer and having a size of 100 to 2000 μm ;
 - c. mixing the microparticles with an active agent and an effervescent reagent thereby obtaining a mixture;
 - d. encapsulating the mixture,
 - 10 thereby obtaining a composition according to any one of claims 1 to 53.
55. A method of manufacturing the composition of any one of the preceding claims, the method comprising
- a. suspending polymer, active agent and optionally lubricant in a solvent
 - 15 b. stirring until solvent has evaporated, collect and wash microparticles comprising at least one polymer and having a size of 100 to 2000 μm ;
 - c. mixing the microparticles with an active agent and an effervescent reagent thereby obtaining a mixture;
 - d. encapsulating the mixture,
 - 20 thereby obtaining a composition according to any one of claims 1 to 53.
56. The method according to claims 54 and 55, wherein the microparticles, the polymer, the active agent, and the effervescent reagent are as defined in any one of claims 7 to 12.
- 25
57. The method according to any one of claims 54 to 56, further comprising adding at least one coating layer, wherein the at least one coating layer is as defined in any one of claims 34 to 51.
- 30
58. The method according to claim 55, wherein the solvent is an organic solvent, such as a low-boiling organic solvent, such as acetone.
59. A composition according to any one of the preceding claims for use as a medicament.
- 35

60. The composition for the use according to claim 59, wherein said composition in administered to an individual in need thereof.
- 5 61. The composition for use according to any one of claims 59 and 60, wherein said composition releases the active agent in the intestine of the individual in need thereof.
- 10 62. The composition for use according to any one of claims 59 to 61, wherein said composition releases the active agent in the small intestine of the individual in need thereof.
- 15 63. The composition for use according to any one of claims 59 to 62, wherein said composition releases the active agent in the large intestine, such as in the colon, of the individual in need thereof.
- 20 64. A composition according to any one of claims 1 to 53, for use in the treatment of an inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer, wherein the active agent comprises or consists of insulin or an analogue thereof.
- 25 65. A composition according to any one of claims 1 to 53 use in healing colonic mucosa in a subject suffering from or suspected of suffering from an inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer, wherein the active agent comprises or consists of insulin or an analogue thereof.
- 30 66. The composition for use according to any one of claims 64 and 65, wherein the composition comprises between 100 IU and 1000 IU, such as between 200 IU and 1000 IU, such as between 300 IU and 1000 IU, such as between 400 IU and 1000 IU, such as between 500 IU and 1000 IU, such as between 600 IU and 1000 IU, such as between 700 IU and 1000 IU, such as between 800 IU and 1000 IU of insulin or an analogue thereof.
- 35 67. The composition for use according to any one of claims 64 to 66, wherein the composition comprises between 1 mg and 35 g of insulin or an analogue

- thereof, such as between 3 mg and 35 g of insulin, such as between 10 mg and 35 g of insulin or an analogue thereof, such as between 50 mg and 35 g of insulin or an analogue thereof, such as between 100 mg and 35 g of insulin or an analogue thereof, such as between 1 g and 35 g of insulin or an analogue thereof, such as between 10 g and 35 g of insulin or an analogue thereof, such as between 20 g and 35 g of insulin or an analogue thereof.
- 5
68. The composition for use according to any one of claims 64 to 67, wherein the total dose of insulin per day is between 100 IU and 1000 IU, such as between 200 IU and 1000 IU, such as between 300 IU and 1000 IU, such as between 400 IU and 1000 IU, such as between 500 IU and 1000 IU, such as between 600 IU and 1000 IU, such as between 700 IU and 1000 IU, such as between 800 IU and 1000 IU of insulin or an analogue thereof.
- 10
69. The composition for use according to any one of claims 64 to 68, wherein the composition is administered to the individual in need thereof at the most four times a day, such as at the most three times a day, such as at the most two times a day, such as at the most once a day, such as at the most once each 48 hours.
- 15
- 20
70. The composition for use according to any one of claims 64 to 69, wherein the composition is administered to the individual in need thereof three times daily, such as twice daily, such as once daily, such as each other day.
- 25
71. The composition for use according to any one of claims 64 to 70, wherein the composition is administered to the individual in need thereof over a period of at least 3 weeks, such as over a period of at least 4 weeks, such as over a period of at least 5 weeks, as over a period of at least 6 weeks, as over a period of at least 7 weeks, such as lifelong.
- 30
72. The composition for use according to any one of claims 64 to 71, wherein the composition is administered to the individual in need thereof during the remission phase of the inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer for a period between 3 weeks and 3 months, such as between 3 weeks and 4 months, such as between 3 weeks
- 35

5 and 5 months, such as between 3 weeks and 6 months, such as between 3 weeks and 7 months, such as between 3 weeks and 8 months, such as between 3 weeks and 9 months, such as between 3 weeks and 10 months, such as between 3 weeks and 11 months, such as between 3 weeks and 12 months, such as between 3 weeks and 18 months, such as between 3 weeks and 24 months.

10 73. The composition for use according to any one of claims 64 to 72, wherein the inflammatory bowel disease is selected from the group consisting of ulcerative colitis, diversion colitis, Behçet's disease, indeterminate colitis, left sided colitis, microscopic colitis such as collagenous colitis or lymphocytic colitis, Crohn's disease, noninfective colitis, pouchitis and immunotherapy-related colitis.

15 74. The composition for use according to any one of claims 64 to 73, wherein the composition is administered to a subject suffering from or suspected of suffering from an inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer during the acute phase and/or during relapse of the disease.

20 75. The composition for use according to any one of claims 64 to 74, wherein the composition is administered to a subject suffering from or suspected of suffering from an inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer during the remission phase of the disease.

25 76. The composition for use according to any one of claims 64 to 75, wherein the composition is administered to a subject suffering from or suspected of suffering from an inflammatory bowel disease during the acute phase and/or during relapse of the disease.

30 77. The composition for use according to any one of claims 64 to 76, wherein the composition is administered to a subject suffering from or suspected of suffering from an inflammatory bowel disease during the remission phase of the disease.

35 78. The composition for use according to any one of claims 64 to 77, wherein the composition is administered to a subject suffering from or suspected of suffering

from inflammation-induced colorectal tumour and/or cancer during the acute phase and/or during relapse of the disease.

- 5 79. The composition for use according to any one of claims 64 to 78, wherein the composition is administered to a subject suffering from or suspected of suffering from during the remission phase of the disease.
- 10 80. The composition for use according to any one of claims 64 to 79, wherein the composition is administered to a subject suffering from or suspected of suffering from mild to moderate ulcerative colitis.
- 15 81. The composition for use according to any one of claims 64 to 80, wherein the composition is administered to a subject suffering from or suspected of suffering from mild to moderate ulcerative colitis during the acute phase and/or during relapse of the disease.
- 20 82. The composition for use according to any one of claims 64 to 81, wherein the composition is administered to a subject suffering from or suspected of suffering from mild to moderate ulcerative colitis during the remission phase of the disease.
- 25 83. The composition for use according to any one of claims 64 to 82, wherein the composition is administered to a subject in need thereof, wherein the subject presents one or more of the following symptoms: abdominal pain, vomiting, chronic diarrhoea, rectal bleeding, severe internal cramps/muscle spasms in the region of the pelvis, weight loss, deep geographic and serpiginous ulcers, continuous ulcer, transmural inflammation, mucosal inflammation, stenosis, granulomas on biopsy (for example non-necrotizing non-peri-intestinal crypt granulomas), high levels of faecal calprotectin, anaemia, thrombocytosis, 30 architectonic abnormalities of the rectal tissue on histological examination, fistulae or abscesses to any segment of the gastrointestinal tract, toxic megacolon.
- 35 84. The composition for use according to any one of claims 64 to 83, wherein the composition is administered to a subject who has been diagnosed with an

inflammatory bowel disease and/or inflammation-induced colorectal tumour and/or cancer.

5 85. The composition for use according to any one of claims 64 to 84, wherein the composition does not cause cell proliferation in the small intestine.

86. The composition for use according to any one of claims 64 to 85, wherein the insulin has low or no systemic effects.

10 87. The composition for use according to any one of claims 64 to 86, wherein the insulin does not affect systemic blood glucose levels.